The Vespiary

Main Topics => General Chemistry => Topic started by: dingbow on July 30, 2011, 07:57:25 AM

Title: **Hofmann Rearrangement Yields**
Post by: **dingbow** on **July 30, 2011, 07:57:25 AM**

---

hello all,

After some experimentation with the rearrangement of an amide, I thought I might try my luck and see if I could get some guidance around increasing yields.

When I first attempted this reaction, yields were around 3-4% and the reaction did not run very clean at all and a lot of work up was required post reaction. After experimentation, I have finally ended up around the 25% mark with a much cleaner product, but this is still leaving me rather unsatisfied! Much amide is going to waste..

Anyway, the highest yielding reaction has been run something like this:
-add 1.2 molar excess of hypochlorite to an RB
-dissolve ~1 molar eq. of NaOH in RB
-Bring temperature down to 0-10ºc, then add all the amide
-add DH2O as required to allow good stirring
-maintian temp and stir for ~4hrs
-prepare a hot solution with 1 mole eq. of NaOH, and add to RB
-bring temp of reaction up to ~75ºc, maintain temp for ~20min
-extract with NP solvent, workup as usual

Now I recently tried to run it much like the below referenced patent, which basically encompassed 2 changes. One was to neutralise the excess hypochlorite with a 10% NaHSO3 solution, which actually gave a MUCH cleaner reaction (no polymerised looking goop to be seen) and the second change was dripping the reaction mixture onto a solution of hot NaOH. The latter change was not entirely possible, as the amide never fully dissolved like it does in the patent (even though I left it for 8hrs this time), so instead it was poured in portions from a beaker onto the hot NaOH solution. Now, whilst this was by far the cleanest reaction, the yield had in fact dropped from ~25% to ~10%. The other problem though, was that upon the completed reaction being let to stand, ~45% of the original amide crashed out and was recovered (some has always crashed out but I had not previously weighed it).

From this I concluded one of two things was happening, either the recovered amide had never been converted to the intermediate isocyanate, or alot of the formed isocyanate was reversing back to an amide during the rearrangement. I have no idea if the latter is even possible, but I made the assumption that the isocyanate was not forming explaining why it never completely dissolved in the solution.

So, can anyone provide some guiance on what could be done to bring up the yields :). I have seen on other forums claims of 60% being made, though I was unable to replicate it by following their procedure.

Any help is appreciated.

Reference: US Patent 7205440

Title: **Re: Hofmann Rearrangement Yields**
Post by: **jon** on **July 30, 2011, 09:39:19 AM**

---

i'm thinking if you can find a solvent for this you might be able to get better yeilds just a hunch.
there is an equilibrium between the isocyante and the cyanate.
i think if you dial in your temp a little higher to say 80 instead of 75 you can keep that equilibrium going.
i would use the rate of co2 generation as an indicator to what the optimal reaction temperature is.
what happens is the cyanate can polymerize into trimers.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **poisoninthestain** on **July 30, 2011, 06:46:57 PM**

EtOH or anothor polar alcohol of your choosing can better solvate the amide since the solubility of it in water is shotty. I have only experimented with EtOH and had a yield increase from 5-10% post workup. Temp control is the biggest factor i've found. With the colsolvent EtOH workup is a bit messier but worth it if you just got a buchner. sodium hypochlorite and calcium hypochlorite give roughly identical yields if done under proper conditions but the downside of bleach is that you gotta use a fresh bottle or yields are variable. Perhaps try a PTC found in your favorite fabric softener i've heard good things. This particular amide takes some tweaking to reach a 50% mark.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Enkidu** on **July 30, 2011, 07:42:33 PM**

Gene A. Hiegel, Tyrone J. Hogenauer
"Preparation of Methyl N-Substituted Carbamates from Amides through N-Chloroamides"
Synthetic Communications Volume 35, Issue 15, 2005 pp. 2091-2098 DOI: 10.1081/SCC-200066695

Quote

> Amides are chlorinated on the nitrogen using trichloroisocyanuric acid, and the N?chloroamides are then rearranged to the corresponding methyl N?substituted carbamates by sodium methoxide in methanol.

If anyone one has a paper like the one above that doesn't use an alkoxide (I thought I had one), please post it.

Also,

Quote

> Preparation and Diels-Alder reaction of a 2-amido substituted furan
>
> http://www.orgsyn.org/orgsyn/prep.asp?prep=v78p0202
>
> C. tert-Butyl N-(3-methyl-3-butenyl)-N-(2-furyl)carbamate. In a flame-dried, 500-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and reflux condenser are placed 4.0 g (21.8 mmol) of furan-2-ylcarbamic acid tert-butyl ester and 150 mL of toluene (Note 11) under an argon atmosphere. To this solution are added 3.1 g (76.4 mmol) of freshly ground powdered sodium hydroxide , 6.04 g (43.7 mmol) of potassium carbonate , and 1.48 g (4.4 mmol) of tetrabutylammonium hydrogen sulfate (Note 12). The solution is heated at 80°C for 25 min with vigorous stirring and then 3.9 g (26.2 mmol) of freshly distilled 4-bromo-2-methyl-1-butene is added as a solution in 10 mL of toluene over a 30-min period. After being heated at 80°C for 30 min, the solution is charged with an additional 0.98 g (6.6 mmol) of 4-bromo-2-methyl-1-butene . The mixture is heated at 80°C for an additional 1 hr. After the reaction is cooled to room temperature, it is quenched by the addition of 200 mL of water and the aqueous phase is extracted three times with 100-mL portions of dichloromethane . The combined organic phase is dried over magnesium sulfate and the solvent is removed

> with a rotary evaporator at aspirator vacuum. The crude residue is purified by silica gel chromatography (10% ethyl acetate-hexane) to give 5.0 g (91%) of tert-butyl N-(3-methyl-3-butenyl)-N-(2-furyl)carbamate as a colorless oil (Note 13).

The PTC isn't required, though you may have to tweak the ratios.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dingbow** on **July 31, 2011, 12:28:52 AM**

Quote from: jon on July 30, 2011, 09:39:19 AM

> i'm thinking if you can find a solvent for this you might be able to get better yeilds just a hunch...
> i think if you dial in your temp a little higher to say 80 instead of 75 you can keep that equilibrium going.
> i would use the rate of co2 generation as an indicator to what the optimal reaction temperature is.

Ive been thinking along the same lines, the problem is finding a suitable co-solvent. When I ran the reaction according to the patent I did actually dial in 80-85 degrees, since the patent said the higher temps were preferable to the rearrangement.

Quote from: poisoninthestain on July 30, 2011, 06:46:57 PM

> EtOH or anothor polar alcohol of your choosing can better solvate the amide since the solubility of it in water is shotty. ..Perhaps try a PTC found in your favorite fabric softener i've heard good things. This particular amide takes some tweaking to reach a 50% mark.

The reason I havent used alcohol as a co-solvent is because it would seem to me that it would be oxidised to chloroform and consume the hypochlorite. Interesting that you note a yield increase, i'll give this a run and see what happens.

I actually tried using benzalkonium chloride as a PTC, with no change in yield unfortunately. Havent tried fabric softener yet, maybe I should look into that..

Quote from: Enkidu on July 30, 2011, 07:42:33 PM

> If anyone one has a paper like the one above that doesn't use an alkoxide (I thought I had one), please post it.

See attached, example 4. They replace the alkoxide with soda ash, bubble in the chlorine.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dingbow** on **July 31, 2011, 12:44:10 AM**

Thought this was interesting, just reading the attached file to this post, they add the bisulfite seemingly after the rearrangement, where as in the US patent its clearly done before.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Enkidu** on **July 31, 2011, 04:45:01 AM**

Yeah, here's the one I have, which is a revision of the patent you posted. Of course there is a more facile method to prepare the N-chloroamide than working with Cl2.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **letters** on **August 03, 2011, 04:41:56 PM**

dioxane is the solvent of choice in hofmann rearrangements. THF can work sometimes if the intermediate chloramide is reactive enough to undergo rearrangement at THF's reflux temps

---

Title: **Re: Hofmann Rearrangement Yields**
Post by: **reDEEMed** on **August 03, 2011, 09:13:25 PM**

The method I was told to try by someone, I have yet to see posted anywhere. I'm running it now and will post my results. Being the first reaction of this nature I have ever ran I would be hard pressed to blame a bad yield on the parameters of the reaction, it's more likely due to my inexperience. However, I've had pretty good luck with every other reaction once I understood what it was doing and changed it around a little to suit my situation better.

The method I am trying now starts not unlike the op's. Reactants chilled to around -10c and the amide added after. The difference is I will never add heat and also I'm willing to give it a couple days. We'll see what happens.

Here it is as we speak. I don't think a single ice cube has melted and it's been almost 6 hours. Chemical wise I have all sorts of 'ines' and solvents too. I got plenty of amide to play with as well. I don't care about losing it, the experimentation is just too fucking awesome.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **jon** on **August 04, 2011, 12:29:47 AM**

hmmm drugs not food? man can't live on mda alone.
makes sense you want the chloramide to go to completion before you reflux it in base to the isoocyante.
remember bhopal?
methyl isocyanate nasty stuff.
25000 dead.
luckily it hydrolyses as fast as it's formed.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **reDEEMed** on **August 04, 2011, 01:20:03 AM**

You know better than to think I have any idea what I'm doing. The way this has went so far is, I have followed instructions to the letter, it has somehow failed everytime. I have then been able to apply that hands on knowledge to better understanding the reactions, make small but significant changes to better suit my situation and then I have pretty good luck. I'm doing the same thing this time, following instructions to the letter. We'll see what happens. I kept the food out of view from the camera. I eat people and I don't want any of you guys to recognize one of my meals.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **jon** on **August 04, 2011, 03:05:03 AM**

we don't care as long as it's mexican food we need the jobs.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **reDEEMed** on **August 04, 2011, 11:57:20 PM**

Does this look like amine to you guys in the bottom of the flask?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **akcom** on **August 05, 2011, 03:38:38 AM**

Looks like what I got when I tried (and failed) with OTC bleach. Finally resorted to generating my own solution with much better results

---

Title: **Re: Hofmann Rearrangement Yields**
Post by: **jon** on **August 05, 2011, 04:16:21 AM**

---

he failed to mention he only stirred it and never refluxed it.
the hoffman rxn can't go without heat.
ohh and letters did you know most detergents
(liquid detergents) contain dioxane...
so it must be a handy solvent.
so according to akcom your going to have to bubble cl2 gas into NaOH
Cl2 gas is no fun to work with.
you can neutralize the overflow with a sodium bisulfite solution, of course you need a trap in line to the wash solution.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Enkidu** on **August 05, 2011, 04:20:14 AM**

Yeah, that's a mixture of the amide and the N-chloroamide. The amine will be liquid.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **jon** on **August 05, 2011, 04:23:14 AM**

---

indeed a yellow liquid with a sweet odor and taste.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **reDEEMed** on **August 05, 2011, 01:25:47 PM**

Okay, so holding true to form, my first try using these notes I have has yielded nothing (with the exception of the beckmann which showed me much love). I will try again today using heat.

jon, I was expecting a red oil, based on the notes I have. If I got a yellow oil I would probably stick a straw down in it in the bottom of my flask and just drink it all, right then and there.

Sorry to take a thread about a general reaction and bend it specifically to suit my needs, but then again I assume me and the op are doing the same thing.

Edit: jon, I did mention that I wasn't using heat.
Quote from: reDEEMed on August 03, 2011, 09:13:25 PM

> The method I am trying now starts not unlike the op's. Reactants chilled to around -10c and the amide added after. The difference is I will never add heat and also I'm willing to give it a couple days. We'll see what happens.

akom, what do you make of what java said here?

http://www.psychonaut.com/post-34173.html?f=43&sid=312eea648a32530bbe629c0a8e1e46da&start=165#p216021
Quote

> .and now to the hoffman . as i blindly tried the reaction, as i coined it the "cold method", in the cold with 50 % yield with some slight heating at the end to put the base into solution....other wise the amine base i've noticed is that brown powder that sits at the end when the hoffman is allowed to return to RT.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **letters** on **August 05, 2011, 09:18:28 PM**

---

jon, i did not know commercial detergents contain dioxane. only bummer about dioxane is that it is next to impossible to distill it away from the reaction mixture in most cases, so it is not recyclable. THF can be used multiple times, since although it forms an azeotrope and is impossible to distill to dryness by itself, the wet THF that comes out of the rotavapor is suitable for reaction.
Regarding "active halogen" sources - bubbling Cl2 into NaOH just prior to reaction used to be the method of choice. I find that generating large amounts of chlorine needed for large scale is not my cup of tea. Liquid bromine is a suitable source and if the initial addition of amide to OBr(-) solution is slow enough yields are comparable. Still, liquid bromine is also not very nice to work with. it creeps through almost anything. normal glass joints do not hold bromine well.
There are other way to generate the active species insitu, all of them are easily accessible in the main journals. Think of the reagents used to halogenate aromatics nowadays. almost all of them are capable of producing the required oxidating species in the right conditions.
Since when i download articles they are tagged with an identifier i will not upload the refs, but here is a list of some interesting articles :
1. Amines Related to 2,5-Dimethoxyphenethylamine, Richard Baltzly, Johannes S. Buck, ,J. Am. Chem. Soc., 1940, 62 (1), pp 164–167, DOI: 10.1021/ja01858a047.
2. New Method for Direct Conversion of Amides to Amines. ,G. Marc Loudon et. al. J. Org. Chem., Vol. 44, No. 10, 1979, DOI: 0022-3263/79/1944-1746$01.00/0.
3. A Re-examination of Limitations of the Hofmann Reaction. Ernest Magnien, Richard Baltzly, J. Org. Chem., 1958, 23 (12), pp 2029–2032, DOI: 10.1021/jo01106a630.
4. Development of the Hofmann Rearrangement of Nr-Tosylasparagine through Calorimetric and NMR Analysis. Joseph S. Amato et. al., J. Org. Chem. 1998, 63, 9533-9534, 10.1021/jo980799l CCC: $15.00.
5. Nature of N-Bromosuccinimide in Basic Media: The True Oxidizing Species in the Hofmann Rearrangement. Chris H. Senanayake et. al., J. Am. Chem. SOC. 1994, 11 6, 7947-7948, 0002-7863/941/5 16-7947$04.50/0.
6. A Versatile Modification of the Hofmann Rearrangement. Radlick and Brown, Synthesis, 290-292, April, 1974.

Depending on the choice of amide and procedure, yields in a properly run rearrangement should exceed 80%. In the lit. you will many times see 60% and lower, this is due to no optimization done. Check out the industrial example in the articles, it gives a good insight into large scale.
Common yield killers in the hofmann -
instability of the reactants - your basically fucked unless you can find something mild enough, or choose a different route.
solubility issues - when the amide does not dissolve it can not react! when it dissolves it is either as a deprotonated species, or as is in an appropriate organic solvent. If there is not enough solvent, or no solvent at all, and the water solubility is low enough, the cyanate and amine will coextract each other into their phase and give you urea like products. this is very common when not using organic solvents!
inactivity of the oxidizing species - commercial bleach solution, even industrial ones are

sometimes no good. some of them are old, others contain stabilizers, and others contain inactive surfacatants which can retard the progress of reaction. When using OX(-) it is best to make your own.

another option to increase the yields is to generate the carbamate instead of free amine, and the find a suitable way to deprotect. methyl carbamate are very easy to make, but are also very hard to cleave. LiOH in the microwave works well, but thats out of reach for most amateur drug cookers. a right choice of alcohol as solvent can give you an easily cleaved carbamate. benzyl alcohol comes to mind. never tried it, but im sure any reaction protocol can be tweaked to work with it. the product would be the benzyl carbamate, or CBZ, which is easily cleaved via CTH. yields in the carbamate synthesis are usually stellar!

Title: **Re: Hofmann Rearrangement Yields**
Post by: **reDEEMed** on **August 05, 2011, 09:20:10 PM**

It sure looks like the same results to me and I have people telling me the precipitate is the shit it just needs to be extracted more thoroughly (shaken better) or allowed to sit and it will congeal into a single 'puddle'.

5.5gms of NaOH in 110mls of water were chilled to 0C. To this was added 11gms of amide and solution stirred until all of the amide was thoroughly mixed, it did not dissolve, of course. 138gms (145.25ml) of 6% bleach (chlorox) at room temperature was then added with stirring and heat started on 3. Solution went from grey to black to purple. Thirty eight minutes after heat was first applied the solution turned white (64C), four minutes after that light brown (milk coffee as it was once called), shortly after that (didn't record time) a dark crimson red. Finally, one hour fifteen minutes in the solution hit 80C. It was immediately removed from the hot plate and sat in a bucket of room temperature sand to cool.

It looks almost identical to what was given the first time. The only difference being a very slightly darker red at the end and a slightly darker precipitate. If there was any difference in the yield it was tiny, I would even say negligible.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **letters** on **August 05, 2011, 09:28:46 PM**

---

read the post above, and understand that you can not get good yields with fatty amides without a cosolvent! and yes, amides that have longish aliphatic chains and aromatic rings and what not can be considred fatty

---

Title: **Re: Hofmann Rearrangement Yields**
Post by: **reDEEMed** on **August 05, 2011, 09:33:33 PM**

At this point just plain yield would be great. Good yield can come later. I just want to see the expected result just one time. That's all I ask, one little time. I don't care if its 10 micrograms.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Waggledance** on **August 05, 2011, 11:11:19 PM**

Your previous posts tend to suggest you are following the procedures of patent

US7205440 by Wenzel *et al.* I would suggest that you follow this patent as closely as possible! Particularly example 6 on the table. However I can think of a much more suitable reagent to neutralize the OCl- ions that is readily available, in high concentrations, and reacts to form salt, water and oxygen. As a general rule it is more favorable to have as little unwanted species in solution as possible to reduce possible side reactions.

Learn as much as you can about equilibrium of chemical reactions and try and apply these principles to your reaction. I've seen letters mention it before, 80*C is too hot for the OCl- ion. Go find as many high conc NaOCl solutions as you can and try them all until you find one that works best beacuse generating it in the lab becomes tedious. If you do all of this then you should get a light orange to yellowy oil as jon described...don't drink it.

The carbamate can be fun but with the amide you are using you will find that the reaction involves a lot of experimentation and has very precise parameters, small deviations can fuck the whole thing. Not to mention that hydrolysis takes ages so unless you want your lab or house smelling like an asian takeaway shop for days I recommend you get a heating mantle.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **reDEEMed** on **August 06, 2011, 02:40:14 AM**

I think the biggest problem here is me posting about a particular experiment of mine in a thread about a general reaction. It makes it seem as if I am asking a question here when in fact I am not. I am simply playing around with no real concern for any yield at this point. I would like to see my target compound, yes, but I am not concerned with yield at this point. I cannot read about things I am not doing and retain it. The only way I can retain knowledge is to put my hands on it **and** read about. jon has already scolded me numerous times and tried to help, but at the time I had no hands on experience, so as valuable as the advice may have been, it was hard for me to apply that advice without doing what I have already been doing which is blindly follow a procedure that someone else put together. Now that I've ran it twice on opposite ends of the spectrum I feel as if I have some baseline to measure from now. Now I can take jon's advice and the other advice found in this thread and in various papers on the subject and and actually apply them for the good of all mankind. I won't post anymore in this thread unless I somehow can contribute to improving the procedure for the substrate I believe we are discussing here.

In other words, my bad.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **jon** on **August 06, 2011, 06:20:12 AM**

Quote

> I've seen letters mention it before, 80*C is too hot for the OCl- ion.

yes that is true at that point in the reaction you have the n-chloramide and naoh so if your stoichiometry is spot on the OCl- ion is irrelavant at this point the need for this specific temperature is to cause the protonation of the chloramide and maintain the isocyanate in an equilibrium at such a rate it can undergo hydrolysis.
if it's too cool you get cyanates floating around which tend to polymerize to biurets.
too hot is no good either.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Enkidu** on **August 06, 2011, 06:38:54 AM**

Of course, I you do get those ureas, just hydrolize.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Waggledance** on **August 07, 2011, 12:25:54 AM**

Quote from: Enkidu on August 06, 2011, 06:38:54 AM

> Of course, I you do get those ureas, just hydrolize.

Only had time to have a quick look but how to you propose this? Could extract a bunch of urease from yeast and feed into a cooled, extracted reaction, now that would be cool.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Enkidu** on **August 07, 2011, 04:25:03 AM**

Base will work, and I'm assuming acid will too? Acid = soluble amine salt

---

Title: **Re: Hofmann Rearrangement Yields**
Post by: **reDEEMed** on **August 07, 2011, 07:58:23 PM**

Quote from: akcom on August 05, 2011, 03:38:38 AM

> Looks like what I got when I tried (and failed) with OTC bleach. Finally resorted to generating my own solution with much better results

Could you elaborate on this at all?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **letters** on **August 09, 2011, 08:16:51 AM**

---

reDEEMed, if you read the refs ive attached, you will find examples of fresh preparations of NaOCl, by simply bubbling Cl2 gas into a cooled NaOH solution. there not much too it. you can generate the chlorine from many sources. gas obviously does not need to be dried, so its pretty straightforward.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **reDEEMed** on **August 09, 2011, 01:04:14 PM**

Edit: I'm combining two posts in to one here and doing away with the first post.

The only reference I was able to find for free download was number one, Amines related to dimethyloxyphenethylamines. Even under the request thread here it doesn't seem anyone is asking for them. I use three tools for finding refs, maybe I'm not using the right ones. I use library.nu for full texts, toodoc and google for specific papers. On google I just search like "limitations of hoffman reaction filetype:pdf" I couldn't find any of them for free. I did find some interesting ones that I will read until I can get the ones you mentioned.

One of the pdf's I got ended up being gold for me. Probably way too basic for you guys, but for me it has really cleared up things about the actual mechanism. I now understand what the isocyanate is and where it fits in (something I wasn't getting before). I'm gonna chew on this for a while and I think I'll be ready to read on some specific strategies and actually understand it.

So, if anyone can get any of those refs letters mentioned, please grab and attach them, thanks!

Title: **Re: Hofmann Rearrangement Yields**
Post by: **akcom** on **August 09, 2011, 05:28:28 PM**

March's Advanced Organic Chemistry is a good resource. They have a lot of info on the Hoffman mechanism and should allow you to understand why you allow the chloroamine to form at low temperatures, then drip into hot base. Sorry I didn't see the post earlier, but letters was correct. Just bubble chlorine gas into NaOH. Good ventilation is a must, outside if you can.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **reDEEMed** on **August 10, 2011, 12:49:16 PM**

---

akom, I have that one. IIRC that's the text I could not stop reading, very well written and easy to follow.

Letters, which of those refs specifically would you recommend for someone in my position who would like to try this again? I don't want to throw all of those on the request thread, although I guess I could if it came down to it. I'm ready to try it again. I just need to plan an approach that I can pull off. I have been reading about bubbling Cl through the solution for a few days, the problem I see is how do I bubble .412gms of Cl for every gram of amide? How in the hell is this measured, I don't see that anywhere. Also, isn't bulk gas like that made via electrolysis? I don't have what I need to do that atm.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **fries** on **August 10, 2011, 02:57:06 PM**

Quote from: jon on August 05, 2011, 04:16:21 AM

> the hoffman rxn can't go without heat.

I've run 3 Hoffmans, about 10g amide each, 1 hot and 2 cold. I got roughly the same yield from each, about 1g.

I have a question though, the original post that we saw this reaction in recommends a ratio of 20g amide to 10g NaOH to 10.5g NaOCL, or a molar ratio of 1:2.6:1.4. Most of the literature I've read on using bleach for this seems to recommend a molar ratio of about 1:2:1.1.

Does anyone know which of these ratios gives better yield? Does anyone know why the OP that I'm talking about might have wanted to use so much excess bleach and base?

On a side note, that same post also recommends at least an order of magnitude TOO MUCH HCl to salt the resultant amine. Is this just to throw noobs off and get them to ruin their product? For a 20g amide batch, which would give say 5g amine, he recommends 100ml conc. HCl. That is sure to ruin your day!

Title: **Re: Hofmann Rearrangement Yields**
Post by: **antibody2** on **August 10, 2011, 04:05:28 PM**

Quote from: reDEEMed on August 10, 2011, 12:49:16 PM

> how do I bubble .412gms of Cl for every gram of amide? How in the hell is this measured, I don't see that anywhere. Also, isn't bulk gas like that made via electrolysis? I don't have what I need to do that atm.

Try weighing your beaker of NaOH solution until it has gained enough weight after bubbling Cl2 through it. To generate Cl2, take a sidearm flask with household bleach in it and drip HCl into it. Do it outside on a windy day.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **reDEEMed** on **August 10, 2011, 09:34:05 PM**

Ahhh, so the chlorine is bubbled in to prepare the solution. For some reason I was thinking this was done during the reaction. That makes things easier since I can set up outside, do my bubbling, then move shit indoors to finish after I prepare my chlorine solution.

Thanks, antibody2. That answers a couple questions I had.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **akcom** on **August 11, 2011, 03:24:56 AM**

Formation of the o-methyl carbamate is affected by TCCA in methanol in good yields. Obviously FMOC can be cleaved to yield the amine in acid. Is acid catalyzed hydrolysis of the methyl carbamate an option?

edit: also, is anyone neutralizing their oxidant before performing the rearrangement? residual oxidant seems like a real yield killer to me...

Title: **Re: Hofmann Rearrangement Yields**
Post by: **java** on **August 11, 2011, 04:00:05 AM**

Quote from: akcom on August 11, 2011, 03:24:56 AM

> Formation of the o-methyl carbamate is affected by TCCA in methanol in good yields. Obviously FMOC can be cleaved to yield the amine in acid. Is acid catalyzed hydrolysis of the methyl carbamate an option?
>
> edit: also, is anyone neutralizing their oxidant before performing the rearrangement? residual oxidant seems like a real yield killer to me...

.......no doubt, however a reference would be advice to your statement....java

---

Title: **Re: Hofmann Rearrangement Yields**
Post by: **akcom** on **August 11, 2011, 04:15:49 AM**

---

unfortunately I have no references for o-methyl carbamate hydrolysis yielding an amine, thats why I'm here. PS does anyone else hate the new web based scifinder?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **java** on **August 11, 2011, 04:37:17 AM**

...read this, it may provide a clue, ...java

Theoretical studies on the acid hydrolysis of methyl carbamate†
Ikchoon Lee, Chang Kon Kim, Byung Choon Lee
Journal of Computational Chemistry
1987, Volume 8, Issue 6, pages 794–800
DOI: 10.1002/jcc.540080607

Title: **Re: Hofmann Rearrangement Yields**
Post by: **akcom** on **August 11, 2011, 04:55:07 AM**

Thank you, I saw this paper but did not have access to the reference. I've finally got a hang of the new scifinder, but the results are not impressive. More digging is required.

edit:
The important part of that article was a reference. I'd post it myself but its splattered with my ID.

Quote

> The Hydrolysis of Amides, Esters, and Related Compounds in Acid Solution. Part 11. Carbamates
> By V. C. Armstrong and R. B. Moodie
> Journal of the Chemical Society (B, Physical Organic) 1969 pg 934

Title: **Re: Hofmann Rearrangement Yields**
Post by: **java** on **August 11, 2011, 05:14:09 AM**

Quote

> The Hydrolysis of Amides, Esters, and Related Compounds in Acid Solution. Part 11. Carbamates
> By V. C. Armstrong and R. B. Moodie
> Journal of the Chemical Society (B, Physical Organic) 1969 pg 934

Title: **Re: Hofmann Rearrangement Yields**
Post by: **akcom** on **August 11, 2011, 05:47:57 AM**

Quote

> Allyl Cyanate-to-isocyanate Rearrangement for the Synthesis of Quaternary Stereocenter with Nitrogen Substituent
> Yoshiyasu Ichikawa, Eiji Yamauchi, Minoru Isobe
> Biosci. Biotechnol. Biochem. 2005, 69 (5) Pg 939-943

Last step is acid hydrolysis of an aliphatic methyl carbamate using 6N HCl. Viola. I need to TLC my aldehyde to make sure it hasn't degraded too much. Hopefully I'll have some results here shortly.

edit: for those of you isolating your chloroamine

Quote

> Properties of N-Chloroamines. At this point, it is important to state that all N-chloroamines are thermally unstable and can explode at elevated temperature. They can also react violently with amines, strong acids and bases, and easily oxidised organic material. N-Chlorosuccinimide has been reported to react violently with alcohols and benzylamine, 1,3-dichloro-5,5-dimethylhydantoin reacts violently with xylene, and trichloroisocyanuric acid has been reported to generate explosive nitrogen trichloride in concentrated acidic aqueous solution due to the attack of formed hypochlorous acid on the imine bond.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Waggledance** on **August 11, 2011, 07:09:00 AM**

Ever Tried TCCA in methanol? As far as I know you need completely anhydrous conditions or the reaction goes to shit and becomes rather violent! A lot of heat is evolved.

Edit: @Akcom, yea i think a few people on here are neutralizing, multiple mentions of bisulfite. Personally i would shy away from bisulfite as there are far more readily available chems that you can use, specifically there is one that reacts to form O2 and H2O, removing the addition of unnecessary reactants that could take part in side reactions..assuming NaOCl is being used!

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dingbow** on **August 11, 2011, 12:06:02 PM**

Quote from: letters on August 05, 2011, 09:18:28 PM

> 1. Amines Related to 2,5-Dimethoxyphenethylamine, Richard Baltzly, Johannes S. Buck, ,J. Am. Chem. Soc., 1940, 62 (1), pp 164–167, DOI: 10.1021/ja01858a047.
> 2. New Method for Direct Conversion of Amides to Amines. ,G. Marc Loudon et. al. J. Org. Chem., Vol. 44, No. 10, 1979, DOI: 0022-3263/79/1944-1746$01.00/0.
> 3. A Re-examination of Limitations of the Hofmann Reaction. Ernest Magnien, Richard Baltzly, J. Org. Chem., 1958, 23 (12), pp 2029–2032, DOI: 10.1021/jo01106a630.
> 4. Development of the Hofmann Rearrangement of Nr-Tosylasparagine through Calorimetric and NMR Analysis. Joseph S. Amato et. al., J. Org. Chem. 1998, 63, 9533-9534, 10.1021/jo980799l CCC: $15.00.
> 5. Nature of N-Bromosuccinimide in Basic Media: The True Oxidizing Species in the Hofmann Rearrangement. Chris H. Senanayake et. al., J. Am. Chem. SOC. 1994, 11 6, 7947-7948, 0002-7863/941/5 16-7947$04.50/0.
> 6. A Versatile Modification of the Hofmann Rearrangement. Radlick and Brown, Synthesis, 290-292, April, 1974.

Could anyone post these references up please? Especially number 2..

I have read that dioxane can be a good co-solvent, problem is its not very accessible to myself.

Redeemed, its not hard to get SOMETHING out of this reaction, if you follow the steps in my first post, you will get there.

Im thinking for my next run I will dissolve the amide in minimum amount EtOH and drip this into the basic NaOCl solution. What does everyone think?

I have tried 2 different bleach sources for those wondering, one was the 12% pool stuff and the other was 4.5% industrial cleaner sold at the local hardware store. They gave identical results.

Given that so much amide is coming out at the end of the reaction I assume the major problem here is generating the chloroamide.

Title: **Re: Hofmann Rearrangement Yields**

Post by: **fries** on **August 11, 2011, 12:40:26 PM**

Quote from: dingbow on August 11, 2011, 12:06:02 PM

> Given that so much amide is coming out at the end of the reaction...

I guess that is the answer to my question about excess NaOCl and base.

Redeemed, are you taking into account that your base is possibly the mono-hydrate? If not, that could be a reason it doesnt work so well...

Title: **Re: Hofmann Rearrangement Yields**
Post by: **java** on **August 11, 2011, 01:12:11 PM**

Quote from: dingbow on August 11, 2011, 12:06:02 PM

> Quote from: letters on August 05, 2011, 09:18:28 PM
>
> > 1. Amines Related to 2,5-Dimethoxyphenethylamine, Richard Baltzly, Johannes S. Buck, ,J. Am. Chem. Soc., 1940, 62 (1), pp 164–167, DOI: 10.1021/ja01858a047.
> > 2. New Method for Direct Conversion of Amides to Amines. ,G. Marc Loudon et. al. J. Org. Chem., Vol. 44, No. 10, 1979, DOI: 0022-3263/79/1944-1746$01.00/0.
> > 3. A Re-examination of Limitations of the Hofmann Reaction. Ernest Magnien, Richard Baltzly, J. Org. Chem., 1958, 23 (12), pp 2029–2032, DOI: 10.1021/jo01106a630.
> > 4. Development of the Hofmann Rearrangement of Nr-Tosylasparagine through Calorimetric and NMR Analysis. Joseph S. Amato et. al., J. Org. Chem. 1998, 63, 9533-9534, 10.1021/jo980799l CCC: $15.00.
> > 5. Nature of N-Bromosuccinimide in Basic Media: The True Oxidizing Species in the Hofmann Rearrangement. Chris H. Senanayake et. al., J. Am. Chem. SOC. 1994, 11 6, 7947-7948, 0002-7863/941/5 16-7947$04.50/0.
> > 6. A Versatile Modification of the Hofmann Rearrangement. Radlick and Brown, Synthesis, 290-292, April, 1974.
>
> Could anyone post these references up please? Especially number 2..

.....there is a format and a place to request references.....java

---

Title: **Re: Hofmann Rearrangement Yields**
Post by: **reDEEMed** on **August 11, 2011, 01:26:46 PM**

Monohydrate; no, I have only been following directions on a piece of paper, something I loathe to fucking do.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **akcom** on **August 11, 2011, 01:37:45 PM**

Quote from: Waggledance on August 11, 2011, 07:09:00 AM

> Ever Tried TCCA in methanol? As far as I know you need completely anhydrous conditions or the reaction goes to shit and becomes rather violent! A lot of heat is evolved.

I flame dried my flask and used dry methanol. Yields were quantitative. I don't have anything in my notes about the reaction being particularly exothermic though?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **reDEEMed** on **August 11, 2011, 01:57:04 PM**

Regarding Cl generation- Can excess Cl not be scrubbed so this can be done indoors? I live in a apartment complex and my only outdoors is on the balcony by the pool. The smell would be noticed and the girls would probably notice that I was not as interested in their tits and wonder what I was doing.

It seems to me that Cl is such a promiscuous reactive little shit it shouldn't be that hard to scrub.

Btw, I had two people recommend that I read what March's said about the Hoffman but after searching last night and this morning as well as using the pdf search function there is no mention of this reaction.

java, I have tried your cold method and some people who saw the pics said YES THATS IT!! Others say, nope you fail. So, I'm stuck as far as that goes and with under 100gms of amide left I'm not as keen on experimentation. These 80% yeilds I'm hearing about are what I want. Even if it means reading for another week and not getting a single flask dirty.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **reDEEMed** on **August 11, 2011, 02:04:38 PM**

Something that may be of some use.

Hauser,C;Renfrow,W
An Elementary Laboratory Experiment Involving the Hofmann Rearrangement. The Preparation of Methylamine Hydrochloride from Acetamide by means of Calcium Hypochlorite
J. Chem. Educ., 1937, Vol.14(11), pp.542-543 DOI: 10.1021/ed014p542

Quote

> The well-known Hoffman reaction by which an amide, in the presence of of chlorine or bromine and an alkali, is converted into a primary amine with one less carbon atom, is of considerable interest in organic chemistry. The reaction may be used in the "going down series", and it serves as a laboratory method for the preparation of a primary aliphatic amine. The reaction is of interest also because it involves a molecular rearrangement.

>>DOWNLOAD<< (https://www.thevespiary.org/talk/index.php?action=dlattach;topic=785.0;attach=2501)

Title: **Re: Hofmann Rearrangement Yields**
Post by: **fries** on **August 11, 2011, 03:48:27 PM**

Quote from: reDEEMed on August 11, 2011, 01:26:46 PM

> Monohydrate; no, I have only been following directions on a piece of paper, something I loathe to fucking do.

I'm not sure if that was a 'no, i dont have the monohydrate', but If you do have the monohydrate, then 1/3rd of the weight will be water. You will need to use 50% more by weight to get what you need. So 10g of NaOH anhydrate is +-15g of NaOH monohydrate.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **reDEEMed** on **August 11, 2011, 03:54:14 PM**

I would assume that I do have the monohydrate. I'm going to try bromine I think.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **fries** on **August 11, 2011, 04:47:25 PM**

Quote from: reDEEMed on August 11, 2011, 03:54:14 PM

> I would assume that I do have the monohydrate. I'm going to try bromine I think.

I'm talking about the NaOH, not the NaOCl...

Title: **Re: Hofmann Rearrangement Yields**
Post by: **reDEEMed** on **August 12, 2011, 02:45:08 AM**

Okay, this isn't making sense. I've found a ton of good refs and am slowly clawing my way through them. The thing that keeps popping up is the phrase 'heat is required'. jon said this already to me several times, but **lots** of people report this reaction running to completion with no heat. Java, you are pretty much credited with pushing experimentation of this reaction towards cold. What's going on here? Many many people say the cold method not only works, but yields are very acceptable as well. Is it possible that the mechanism of this reaction is not fully understood or is it something about our substrate that makes it do what is supposed to be impossible? Reading through the examples on orgsyn under the entry for phenylethylamine it says that the Hoffman degradation has been performed successfully on hydrocinnamide. This is not our substrate, but it's kinda close. Wtf does it all mean!! AAArrggghhh!

Edit: Essential reading found! The text is called 'Strategic Application of Named Reactions in Organic Chemistry'. Download it and hit the chapter on the Hoffman rearrangement.

http://ifile.it/qzc05h

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Waggledance** on **August 12, 2011, 05:51:04 AM**

Quote from: akcom on August 11, 2011, 01:37:45 PM

> Quote from: Waggledance on August 11, 2011, 07:09:00 AM
>
> > Ever Tried TCCA in methanol? As far as I know you need completely anhydrous conditions or the reaction goes to shit and becomes rather violent! A lot of heat is evolved.
>
> I flame dried my flask and used dry methanol. Yields were quantitative. I don't have anything in my notes about the reaction being
> particularly exothermic though?

Thats awesome man, I dried the methanol over molecular sieves and dried glass multiple times. Amide was dissolved in 200mL with heating, TCCA was added very slowly and after about half was added the reaction become extremely violent, lucky i used a 2L beaker otherwise it probably would have gone everywhere. I think the solution turned orange and smelt strongly of ammonia. My only explanation was that water had got in some how, maybe I didnt leave the methanol to dry for long enough....Didn't revisit it after that but may have to now.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **reDEEMed** on **August 12, 2011, 05:26:01 PM**

Another interesting read. I think this is the route I'm gonna go. It just seems easier to me to hit each point along the way if possible rather than have all these reactions happening one after another in a single pot when I barely understand the mechanism.

====

Gene A. Hiegel, Tyrone J. Hogenauer, and Justin C. Lewis
Synthetic Communicationsw, 35: 2099–2105, 2005 DOI: 10.1081/SCC-200066703
Preparation of N-Chloroamides Using Trichloroisocyanuric Acid

Quote

> Amides are efficiently converted to N-chloroamides by trichloroisocyanuric acid in methanol.

>>DOWNLOAD<< (https://www.thevespiary.org/talk/index.php/topic,785.msg10160.html#msg10160)

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Waggledance** on **August 12, 2011, 11:34:41 PM**

Quote from: reDEEMed on August 12, 2011, 05:26:01 PM

> Gene A. Hiegel, Tyrone J. Hogenauer, and Justin C. Lewis
> Synthetic Communicationsw, 35: 2099–2105, 2005 DOI: 10.1081/SCC-200066703
> Preparation of N-Chloroamides Using Trichloroisocyanuric Acid
>
> Quote
>
> > Amides are efficiently converted to N-chloroamides by trichloroisocyanuric acid in methanol.
>
> >>DOWNLOAD<< (https://www.thevespiary.org/talk/index.php/topic,785.msg10160.html#msg10160)

Thats the paper me and akcom at talking about, i'm going to revisit it but just remember that you need completely anhydrous conditions. Molecular sieves are probably your best bet for drying the methanol. If its not anhydrous i've found that it can become very violent so be careful!

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dingbow** on **August 13, 2011, 12:11:15 AM**

Quote from: java on August 11, 2011, 01:12:11 PM

> .....there is a format and a place to request references.....java

Apologies, will put it up on the other thread.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **reDEEMed** on **August 13, 2011, 01:06:36 AM**

My apologies for posting a ref the wrong way and one that was already here, but I didn't see it.

Okay, the formation of my N-Chloramide is almost complete. Up until now I had planned to evaporate the methanol and dry the chloramide so I could get an exact yield. But, now I'm wondering if I can put the methanol/chloramide solution into my addition funnel and drip it into hot base.

What do you guys think?

Title: **Re: Hofmann Rearrangement Yields**

Post by: **dingbow** on **August 13, 2011, 03:39:42 AM**

Quote from: reDEEMed on August 13, 2011, 01:06:36 AM

> Okay, the formation of my N-Chloramide is almost complete.

Did you get the cyanuric acid precipitate as per the reference?

Just read the reference you posted, this looks really promising... *Runs off to find some TCCA

EDIT: by the way, I have always used heat for the rearrangement. Incidently the time I got the highest yield of ~25%, I prepared a separate solution of ~70c base, dumped it all into the reaction and then heated to bring it to 70c.

EDIT: Just noticed the same reference, uses sodium bisulfite to convert the N-Chloramide back to the amide. Surely this would lower yields when the same reagent is used to quench excess hypochlorite that seems to be mentioned in the other refs? Could explain why I got so much amide precipitate last time I ran this.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **reDEEMed** on **August 13, 2011, 05:13:45 PM**

Yes, everything went the way I saw it going in my head before I started. I'm gonna say it was a success, we'll see how it goes adding this paste I now have to my Hoffman. Now I have to read more so I'm confident about the next step.

I know it has to irritate the fuck out of some of these dudes around here, I know they are just like "FUCKING DO IT ALREADY!!!" bwahahahaha

Edit:What happened to my beautiful amide!?!?!

Oh well...

Title: **Re: Hofmann Rearrangement Yields**
Post by: **akcom** on **August 13, 2011, 05:30:13 PM**

Did you dry your methanol before hand? My choroamine was a white sticky solid

---

Title: **Re: Hofmann Rearrangement Yields**
Post by: **reDEEMed** on **August 13, 2011, 05:33:52 PM**

Fuck no, that's what's going on, I know it is. God dammit.

Well, it shouldn't effect my next step, should it? Next time I will dry my methanol though. Fuck, I was in such a frenzy yesterday I made several stupid mistakes. Not the least of which cost me 10 grams of amide and almost killed me.

Edit: Regarding the use of PTCs-
Everything I've read about using fabric softeners has been negative. Not that any of those references have been specifically aimed at this exact situation, though. But almost without fail people called the quaternary ammonium salts used in fabric softeners useless because of their excessive chain length. Now, this means fuck all to me as I have no idea what that means and I currently don't have the spare brain power to dedicate to learning it. I did however wonder if anyone would be awesome enough to address that.

Something I did come across in reading about that is that most of these chemicals that are considered very good for use as a ptc are readily available in their pure form and not at all suspect. Why not just take a $100 and stock up on a few different ones?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dingbow** on **August 14, 2011, 12:41:11 AM**

Given that the hofmann is run in an aqueous solution, It shouldnt be an issue, but could explain why you have a paste.

Did you remove your MeOH under vacuum? Try recrystalise?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dingbow** on **August 14, 2011, 01:20:07 AM**

Quote from: akcom on August 13, 2011, 05:30:13 PM

> Did you dry your methanol before hand? My choroamine was a white sticky solid

Could you provide a brief outline of your procedure? Have you rearranged the chloroamide?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **reDEEMed** on **August 14, 2011, 06:15:47 PM**

Success is bitter and makes you grind your teeth incessantly.

Why does a marquis turn bright red, though?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Enkidu** on **August 14, 2011, 09:24:50 PM**

It's possible that you only have one stereoisomer of MDA.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **lugh** on **August 14, 2011, 11:03:54 PM**

The Marquis reagent can mean many things:

http://www.cognitiveliberty.org/shulgin/adsarchive/marquis.htm

http://www.erowid.org/chemicals/mdma/mdma_faq_testing_kits.shtml

http://en.wikipedia.org/wiki/Marquis_reagent

8)

Title: **Re: Hofmann Rearrangement Yields**
Post by: **WizardX** on **August 15, 2011, 12:25:24 AM**

Use TLC first, and then the Marquis reagent. This gives greater accuracy and identification.

Quote

> As the test is extremely sensitive, no estimate can be easily made as to the quantity of alkaloid present. **And of course, a dark color will tend to hide a light color.** As with all assays requiring subjective interpretation, experience is everything.
>
> -- Dr. Shulgin

Title: **Re: Hofmann Rearrangement Yields**
Post by: **reDEEMed** on **August 15, 2011, 02:26:09 AM**

Bottling up what I have to get a final number on yield of whatever it is I have and trying again.

Edit: Will do the chloramide conversion again, but with strict attention to anhydrous conditions, especially the methanol. Fuckin' shit, I heated up my flask and all that shit to around the temperature of the sun to dry it and forgot all about the methanol. This has impressed upon me the need to print out check lists, which I will do from now on.

I just put 20gms of amide in to try Java's cold method word for fucking word. Yes, I printed out a checklist.

Jeezus fucking christ can I borrow a dollar from one of you guys?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **fries** on **August 15, 2011, 07:53:16 AM**

---

how did you clean the result? What colour did it end up?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dingbow** on **August 15, 2011, 11:29:35 AM**

---

maybe obtain the MP of the hydrochloride you have obtained for assurance. Keen to hear what your yield was from amide to amine.

I'll give it a go either way, but first im going to try my hand at monomethylation..

Title: **Re: Hofmann Rearrangement Yields**
Post by: **fries** on **August 15, 2011, 12:39:23 PM**

Quote from: dingbow on August 15, 2011, 11:29:35 AM

> I'll give it a go either way, but first im going to try my hand at monomethylation..

I'd like to hear your results on that - I have paraformaldehyde, but nothing to reduce formaldehyde imine with...

Title: **Re: Hofmann Rearrangement Yields**

Post by: **reDEEMed** on **August 16, 2011, 05:29:44 PM**

Quote from: Wizard X on August 15, 2011, 12:25:24 AM

> Use TLC first, and then the Marquis reagent. This gives greater accuracy and identification.
>
> Quote
>
> > As the test is extremely sensitive, no estimate can be easily made as to the quantity of alkaloid present. **And of course, a dark color will tend to hide a light color.** As with all assays requiring subjective interpretation, experience is everything.
> >
> > -- Dr. Shulgin

I know it sounds stupid but I didn't know tlc was something you could do at home. Now that I'm reading more about doing it specifically at home I had to come back and thank you for stating what is no doubt the obvious to you guys, but news to me.

Thanks!

Edit: I'm going to follow this guide for making the plates http://www.scienceprojectlab.com/plates-for-cromatography-science-project.html

Any clue which solvent would be best for this? I'm not opposed to trying several, but thought someone might already know one that works well.

Edit 2: I'm the edit king, hands down. I just saw this and thought that others might find it useful. Especially when evaluating different methods of this reaction we're talking about.

Recommended methods for the identification and analysis of amphetamine, methamphetamine and their ring-substituted analogues in seized material

---

Title: **Re: Hofmann Rearrangement Yields**
Post by: **WizardX** on **August 17, 2011, 12:13:13 AM**

Quote from: reDEEMed on August 16, 2011, 05:29:44 PM

> I know it sounds stupid but I didn't know tlc was something you could do at home. Now that I'm reading more about doing it specifically at home I had to come back and thank you for stating what is no doubt the obvious to you guys, but news to me.
>
> Thanks!
>
> Edit: I'm going to follow this guide for making the plates http://www.scienceprojectlab.com/plates-for-cromatography-science-project.html
>
> Any clue which solvent would be best for this? I'm not opposed to trying several, but thought someone might already know one that works well.
>
> Edit 2: I'm the edit king, hands down. I just saw this and thought that others might find it useful. Especially when evaluating different methods of this reaction we're talking about.
>
> Recommended methods for the identification and analysis of amphetamine, methamphetamine and their ring-substituted analogues in seized material

Glad your learning! ;)

Look on Youtube for video examples of TLC.

http://www.youtube.com/results?search_query=thin+layer+chromatography&aq=0&oq=thin+layer

Thin Layer Chromatography Demonstrated by Mark Niemczyk, PhD
http://www.youtube.com/watch?v=w0FyQ_tO15U

Title: **Re: Hofmann Rearrangement Yields**
Post by: **reDEEMed** on **August 17, 2011, 05:02:42 AM**

I did figure one thing out about the crystal I had. it was much lighter than I thought. What I thought were solid point sized finger licks were nothing more than 10-20mg. I weighed out .100mg earlier today and I'm still fucked off my rocker.

BTW, any idea where I could get one of those uber smart fuckin' monkeys?

Edit: You know what occurs to me about blahblahblah's monkey method, it's actually worth stating as I believe from what I've read and heard that yields from the Hoffman go up with batch size and not linearly. Not only does it seem to scale up well, it seems to prefer it. This monkey and his several kilos of amide no doubt has a much easier time than those of us doing 10-20gms at a time. I'm going to do the next one with at least 40gms and see what's up with that. I plan on using a spider monkey as I feel the smaller monkey may have some synergistic effect on the smaller batch size.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Sedit** on **August 17, 2011, 09:27:37 PM**

I am experimenting and have been for a few months now with various papers to do Paper chromatography at home. I have been able to achieve pretty good results with a hydrophobic water color paper from the art store but I'm still having issues where there can be a heavy run together between compounds.

This may not be the paper but might have more to do with technique. I think the spot has to be super small on paper else the run together is much more noticeable. Also the RF values and the solvent systems I think need to be much different then when using Silica gel. All in all its not going bad and when I am able to produce repeatable decent results I will no doubt write a report here because I really want to see more people post analysis of there reactions more then just saying.... "WOW im HiGh"... ??? .

It will greatly enhance our cause and our site if this goes well.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **akcom** on **August 17, 2011, 11:26:43 PM**

Whatman filter paper is a decent substitute for TLC plates. Silica plates are not that expensive. 100 dollars gets you a fucking ton. You can use a nail filer for scoring them, although a real TLC plate scorer is the best option

---

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dingbow** on **August 18, 2011, 11:10:25 AM**

did you ever figure out your yield with the TCCA route, from amide to amine?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **reDEEMed** on **August 18, 2011, 02:56:07 PM**

No, I fucked that up. I will be trying again, though. Like an idiot I tried what came out, but not enough, thought it to be mostly inactive and dumped it :(Makes me sick because when I did that was the first time I got anything crystalline from the hoffman and I fucking chunked it. Part of the problem is my living situation, working in a kitchen. I need a dedicated lab area and I would hang on to things longer. I'm looking for a crib with a garage or work shed now, then the serious shit can start!

Title: **Re: Hofmann Rearrangement Yields**
Post by: **reDEEMed** on **August 23, 2011, 04:08:31 AM**

Okay, what's up with this? I have had several people vehemently insist that heat in the Hoffman is what is killing the yield. I've also had several people vehemently insist that you must have heat to effect the rearrangement. I have no idea, as I am but a lowly uneducated hick who does what smart people do and hope I have the same or atleast favorable results.

What some guys on Mattlock did
20gms of amide were placed in 250ml of -2C bleach and stirred until a uniform consistency was achieved. This was stirred in an ice/acetone bath for about 2 hours as the idiot doing it forgot all about the lye. Finally a solution of 200ml of water and 20gms of lye were added. The ice bath was replenished as needed for 24 hours to maintain 0-2C and stirring set as high as it could go without slinging the stir bar loose. The progression of colors in this reaction has thus far been very consistent, being loosely tied to temperature and time. As expected the color never changed during it's time in the ice, it never does. Usually upon hitting room temperature it will get white, then brown/tan and with heat it will go into darker brown and finally to red. None of this happened. Upon letting the solution warm up to room temperature on it's on it stayed the exact same color. After 18 hours or so it turned yellow and a brown precipitate began to show. After another full 24 hours (three days from start to finish) heat was added to bring it up to 60-63C and was held there for 30 minutes. After the 30 minutes it was allowed to cool on it's on. Then the yellow liquid was decanted off of the waxy brown chunk in the bottom of the flask. 150-200ml of fresh xylene were added to the solid and it was stirred vigorously for an hour. The resultant xylene was filtered and washed with HCl water as usual.

Now, what's weird.

6.18gms of unreacted amide were recovered, this has never happened. That means only 13.82gms of the amide participated in the reaction. The recovered amide was as white as the day it was born, and apparently unaltered. Sparkly, soft and white (like Sedit's girlfriend)
The xylene then shat out 4.3gms of amine for a total yield of 31.11%

I'm inclined to believe that the heat is definitely an issue, especially considering that blahblahblah's monkey is obviously a pro and he didn't use heat. I have also came to another conclusion, to hell with bleach. TCICA to get the chloramide before hand from now on.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dingbow** on **August 23, 2011, 10:18:52 AM**

I have yet to come across anyone posting an actual write up of this 'cold method' you speak of which doesnt use any heat, nor have I seen any patents or literature to state it either. Am I missing something here, who are these pros your referring to and where are their experiences noted?!

By the way when calculating yield, generally its calculated based on the amount of initial reactants used, regardless of whether you recovered any unreacted material at the end. Thus, your yield calculation should be based on 20g of starting amide, not 13.8. If you do this, the yield you achieved is lower then the 25% I achieved (I never measured the amount of amide I recovered in this run) with the well known method which involves heat. It took 6hrs to run my reaction, compared to your 3 days, this along with your current yield has me questioning this so called cold method.

I have acquired some TCCA to play with, i'll be removing the copper sulfate impurity shortly to give it a go. I just finished monomethylation which I'll post about shortly too.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **reDEEMed** on **August 23, 2011, 07:45:33 PM**

One person in particular who has chose to not join this conversation, so I'm not sayin' names, claims steady 70% yields using no heat over two days sometimes more.

What else can I say?

There it is.

ETA: as for yieid calculation- at the end of the day I got 6.18gms of amide back, so......

Edit2: Dnigbow, I have less than zero interest in a pissing contest. If you get better yields in 6 hours, then I commend you, well done. I am an experimenter, plain and simple. I change things and note what happens. You won't see people posting write ups about the 'cold method' because it's anti to the info in the patent. Heat is generally just an accelerant for a reaction, not always, but usually. I've said numerous times that I don't understand the mechanism here, what do you want me to say to justify my not using heat? The people who have taken me under their wing are not people who blow these boards up and participate in these conversations, therefore I won't be saying so and so told me this or that. If you'd like me to keep my results to myself you can always ignore me. But, I'm hoping someone sees something in my procedure and makes a connection of some sort and says 'AHA, the XXX, that seems to be using a greater percentage of your amide and shitting out what it doesn't use" I dunno, this is fun to me, 4.3 grams of amine is more than I need for a year, so I don't give two fucks. I'm here to figure out a mystery, now where's my dog????

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dingbow** on **August 25, 2011, 11:18:42 AM**

Quote from: reDEEMed on August 23, 2011, 07:45:33 PM

> One person in particular who has chose to not join this conversation, so I'm not sayin' names, claims steady 70% yields using no heat over two days sometimes more.

hmm have they actually posted their procedure on a forum or have they only passed on this information to you in private?

Dont take it the wrong way, im not interested in any pissing contest. The reason I started this thread was to try and get some help to increase yields in this reaction. I merely made the point around your yield calculation, so that when comparing yields amongst ourselves we are comparing apples with apples, otherwise determining the best reaction parameters becomes rather confusing.

Its akin to comparing molar/molar yields to weight/weight yields and hence why in the hive people would stipulate either m/m or w/w to avoid confusion.

Coming back again, im open minded to the cold method (or any method proposed), but given the lack of info its a bit hard to understand whats going on.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **reDEEMed** on **August 25, 2011, 04:09:58 PM**

It was passed on in private by more than one person and I have gotten the overwhelming impression that's how it should stay. I don't know why, but that's what I take away from it.

I think mostly anything that is gonna spoonfeed people these guys don't want it on their boards. I'm just guessing, but there again, that's my take away. I think talking about how the mechanism can run better cold would be okay.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **fries** on **August 25, 2011, 05:00:59 PM**

Here's my take on the cold method. I am no chemist, so i know this writeup is shit etc. This is just how i got it to work with very limited experience and equipment. I don't even have a thermometer that goes up higher than 40c.

Into a coke bottle is placed:
1. 20g Amide
2. 223ml of 4.7% NaOCl pre-cooled
3. 10g NaOH (15g monohydrate) in 200ml H2O pre-cooled

Shake the coke bottle like your life depends on it for about 5 minutes and place it in the freezer/fridge to get it nice and cold again. Shake it every 30 minutes or so, making sure never to let the temperature get too hot that the second part of the reaction starts happening. Keep doing this for a few hours, then leave the bottle in the fridge over night.

I usually lay the coke bottle on its side for the entire Hoffman, I think this allows greater surface area between the two phases.

Continue for a couple of shakes the next morning and then allow the mixture to rise to room temperature. Make sure your room isn't too cold, above 23c should be ok - otherwise it takes ages. I try to shake it as often as possible, every hour for a few minutes should be good.

Leave it at RT for about 24 hours. By this time all of the precipitate has turned into a dark brown oily mush that flows around the inside of the coke bottle (First picture). Add another 5g of NaOH and shake which instantly warms the mixture to about 30c. Leave it for another 2 hours and shake a few times (2nd and 3rd picture).

Extract with 3x100ml toluene, first extract is dark brown, almost black (4th picture), the combined extract is also almost black. Titrate with dilute HCl to get your orangish water layer (5th and 6th picture), wash with toluene, evap to get some reddish yellowy orange amine crystals, clean to get 4.5g purely white glimmering amine.

I know the yield isn't great, but you wanted a writeup on the cold method...

Title: **Re: Hofmann Rearrangement Yields**
Post by: **reDEEMed** on **August 25, 2011, 05:20:18 PM**

I usually get some nasty looking shit too, but one wash in acetone usually brightens it up quite a bit. What's weird about that last time when it gave back all the unreacted amide, the amine that came out was WHITE AS FUCK. This pic is as it came out, no wash.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **fries** on **August 26, 2011, 12:43:08 PM**

I find a simple acetone wash to be inadequate. Dissolve in ABSOLUTE MINIMUM volume of boiling alcohol, dump in 3/4 volumes of acetone and put in the fridge for a while. Then filter off your beautiful clean crystals. If you didn't use too much alcohol, the whole lot should turn into a crystal soup as soon as you dump in the acetone.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **jon** on **August 26, 2011, 08:25:18 PM**

thanks for the fries that's what i been saying for a long time.
that method seems to yeild no better than say 70-80 c.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **reDEEMed** on **August 26, 2011, 10:34:48 PM**

Well, I'm thankful mine has been very clean thus far and scary potent, so I hear on tv ;D

Title: **Re: Hofmann Rearrangement Yields**
Post by: **WazOne** on **August 27, 2011, 12:09:22 AM**

Run it cold over night. Work up is a bitch. So thats why heat was added. But it is not needed. 50+ % w/ consistent and thorough work up. Off white, a tone wash brings out the white.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **akcom** on **August 27, 2011, 02:22:15 AM**

As an aside, aldehyde was opened, left at RT in a closed container for 24hr, then transferred to a fridge. TLC 3 months later shows a major spot and a less polar very minor spot. NMR confirmed aldehyde is the major spot, minor spot unknown. Seems pretty stable.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dingbow** on **August 27, 2011, 09:51:43 AM**

Thanks fries, appreciate the write up. I might try and mish mash your method with mine, say run it in a bottle in the fridge with shaking overnight then heat it as per the 'usual' method.

Im going to try the TCCA method first though, should be done in a few days. If that works out, it could turn out better then the 'cold' or 'hot' method. Hopefully it works, I need more amine to try the monomethylation again...

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dingbow** on **August 27, 2011, 09:53:03 AM**

Quote from: akcom on August 27, 2011, 02:22:15 AM

> As an aside, aldehyde was opened, left at RT in a closed container for 24hr, then transferred to a fridge. TLC 3 months later shows a major spot and a less polar very minor spot. NMR confirmed aldehyde is the major spot, minor spot unknown. Seems pretty stable.

Interesting, did you have a control TLC result? My aldehyde has been sitting in dark RT conditions for months, hope it stays good!

Title: **Re: Hofmann Rearrangement Yields**
Post by: **fries** on **August 27, 2011, 06:00:41 PM**

Quote from: jon on August 26, 2011, 08:25:18 PM

> that method seems to yeild no better than say 70-80 c.

Yeah i know that, but its pretty simple and doesn't need any fancy schmancy stuff like decadent hot plates and thermometers :D

I don't find workup difficult, my only sep funnel is 100ml, so i'm separating layers more manually from beaker to beaker... just clean the result as i mentioned.

I'd love to know what Waz is doing right to get those 50% + w/w yields... running 200g batches or something?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **akcom** on **August 27, 2011, 10:24:14 PM**

Quote from: dingbow on August 27, 2011, 09:53:03 AM

> Quote from: akcom on August 27, 2011, 02:22:15 AM
>
> > As an aside, aldehyde was opened, left at RT in a closed container for 24hr, then transferred to a fridge. TLC 3 months later shows a major spot and a less polar very minor spot. NMR confirmed aldehyde is the major spot, minor spot unknown. Seems pretty stable.
>
> Interesting, did you have a control TLC result? My aldehyde has been sitting in dark RT conditions for months, hope it stays good!

Not sure what you mean by a control? A known authentic sample of aldehyde? The TLC was confirmed via NMR. Aldehyde was the major spot.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dingbow** on **August 28, 2011, 01:36:14 AM**

No I meant did you TLC your aldehyde as soon as you received it, to obtain its original purity for comparison to the aged sample? Or did you purify it then store it?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **akcom** on **August 28, 2011, 05:37:48 AM**

The aldehyde was stored as is. Its very possible the minor contamination was in the sample originally.

edit: should mention that the contamination was definitely not the carboxylic acid as it was less polar

---

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dingbow** on **August 28, 2011, 05:38:26 AM**

Alice just ran the TCCA method for prep of N-Chloroamides:

-Fully dissolved 10g amide into 100ml MeOH (took tiny bit of heat to speed things up)
-Added 4.1g TCCA, stirred for an hour (some evolution of heat occurred)
-Solid precipitate formed fairly quickly after addition of TCCA, assuming this precipitate is CYA
-CYA filtered
-Instead of boiling off solvent (pita to setup and timely) to obtain N-Chloroamide solid, I precipitated it by addition of H20, seemed to work great.

Few things work mentioning, my TCCA was a solid block that had copper sulfate mixed in. This was removed by powdering the block and stirring in H20, which dissolved the copper sulfate, then filtered and dried it as much as I could be bothered. MeOH was not dried. The final product obtained is a very clean white powder with no smell what so ever. Currently drying, so when thats done I will post yield.

I'll get a MP test for this substance too. Im pretty excited to see how this stuff goes in the rearrangement.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dingbow** on **August 29, 2011, 10:03:16 AM**

This stuff doesnt dry very easily and im not going to bother with recrystralisation at this point. I attempted a MP test though of this unpurified substance and its something like 67-72c. It seemed to decompose though, losing some mass and becoming yellow.

After vac filtration the weight was around 40g, after some drying time it came down to 25g, but also taking on a light yellow colour. A day later and its still damp and 25g.

It will used as is in a rearrangement.

Edit: FYI, 2.83g of CYA was filtered, a bit above the molar equivalent of TCCA that went in. The extra weight could possibly be some N-Chloroamide that had precipitated, I dont know - the CYA was dried to a crisp so I dont think it was moisture.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **reDEEMed** on **August 30, 2011, 12:56:02 AM**

Quote from: dingbow on August 28, 2011, 05:38:26 AM

> Alice just ran the TCCA method for prep of N-Chloroamides:

> -Fully dissolved 10g amide into 100ml MeOH (took tiny bit of heat to speed things up)
> -Added 4.1g TCCA, stirred for an hour (some evolution of heat occurred)
> -Solid precipitate formed fairly quickly after addition of TCCA, assuming this precipitate is CYA
> -CYA filtered
> -Instead of boiling off solvent (pita to setup and timely) to obtain N-Chloroamide solid, I precipitated it by addition of H20, seemed to work great.
>
> Few things work mentioning, my TCCA was a solid block that had copper sulfate mixed in. This was removed by powdering the block and stirring in H20, which dissolved the copper sulfate, then filtered and dried it as much as I could be bothered. MeOH was not dried. The final product obtained is a very clean white powder with no smell what so ever. Currently drying, so when thats done I will post yield.
>
> I'll get a MP test for this substance too. Im pretty excited to see how this stuff goes in the rearrangement.

Wow, I wonder why mine came out so gooey? If you're not drying your methanol either, I don't get that. Doesn't seem to matter to the rest of the rearrangement, though.

I can't tell you how many times I've run this reaction at this point, a lot! With stacks upon stacks of printed out patents and notes feverishly scribbled here and there. But the other day, having had enough and intrigued by the results blahblahblah's monkey got, I just said fuck it. I threw away every single note I had and I dumped in 40gms of amide. Having seen the changes in character this solution normally undergoes, I just watched it with no plan on what to do. I just played it by ear the entire way. I had a good feeling about it. Well, my first wash yielded 15gms of damn fine amine, with two more washes giving me another almost 10gms. It's only a matter of time before this rxn is my bitch.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **fries** on **August 30, 2011, 08:29:36 AM**

25g of amine from 40g amide sounds spectacular... Would you mind writing down/giving some of the details of the process you used?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dingbow** on **August 30, 2011, 10:57:42 AM**

Quote from: reDEEMed on August 30, 2011, 12:56:02 AM

> Wow, I wonder why mine came out so gooey? If you're not drying your methanol either, I don't get that. Doesn't seem to matter to the rest of the rearrangement, though.

Did you boil off your MeOH to obtain gooey chloroamide? Did you then have success with this in the rearrangement? How did you rearrange it?

I ask because im having trouble rearranging what I thought was the chloroamide. It went the usual milky white (albeit with more heat then usually required and longer time), so some form of reaction occurred, leaving a non water soluble crystaline powder in the reaction, that will not further convert to the amine.

I simply added the supposed N-Chloroamide to a solution of NaOH that was then heated.. so far I dont have amine though and its not looking good.

Quote from: akcom on August 13, 2011, 05:30:13 PM

> Did you dry your methanol before hand? My choroamine was a white sticky solid

Quote from: akcom on August 11, 2011, 03:24:56 AM

> Formation of the o-methyl carbamate is affected by TCCA in methanol in good yields. Obviously FMOC can be cleaved to yield the amine in acid. Is acid catalyzed hydrolysis of the methyl carbamate an option?
>
> edit: also, is anyone neutralizing their oxidant before performing the rearrangement? residual oxidant seems like

> a real yield killer to me...

Im a bit confused here, the attached reference from Redeemed says that the product of amide + TCCA in MeOH = N-Chloroamide, though these quotes mention chloroamines and carbamates.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **akcom** on **August 30, 2011, 05:32:32 PM**

The o-methyl carbamate is obtained only in the presence of strong base (sodium methoxide usually)

Title: **Re: Hofmann Rearrangement Yields**
Post by: **reDEEMed** on **August 30, 2011, 06:04:37 PM**

Quote from: dingbow on August 30, 2011, 10:57:42 AM

> Quote from: reDEEMed on August 30, 2011, 12:56:02 AM
>
> > Wow, I wonder why mine came out so gooey? If you're not drying your methanol either, I don't get that. Doesn't seem to matter to the rest of the rearrangement, though.
>
> Did you boil off your MeOH to obtain gooey chloroamide? Did you then have success with this in the rearrangement? How did you rearrange it?
>
> I ask because im having trouble rearranging what I thought was the chloroamide. It went the usual milky white (albeit with more heat then usually required and longer time), so some form of reaction occurred, leaving a non water soluble crystaline powder in the reaction, that will not further convert to the amine.
>
> I simply added the supposed N-Chloroamide to a solution of NaOH that was then heated.. so far I dont have amine though and its not looking good.

As funny as it is to you guys, the Hoffman as a whole did not produce shit for me several times. Now, looking back, I'm almost positive that it was my workup that was flawed. The very first time I had any success was when I used the TCICA first then rearranged the goo. That was the very first time I got bitter crystal. All I did was mix it with a minimum of water and dripped it in to 70C NaOH solution with stirring. IIRC I let it still for an hour or so. But, after the other day I wont bother with it again unless that can push yields toward quantitive.

Fries- I didn't write anything down or take any kind of notes. I came to conclusion that was not helping as yields were not getting any better. I just took what I knew from watching this reaction forty billion times and I watched it, with no heat to see how it would change. I already knew that the brown precipitate was my amine it just wasn't ready so to speak. One day I took the time with a flask of water and wrote out the temps on my hotplate, this has proven to be the most worthwhile thing I've done lol. Now I can wind off my dial to 50C or whatever and walk off and if I come back in an hour, it's 50C, not 48 not 52, 50! So I just started gently adding heat once the reaction had peaked at room temp and I was convinced that was all it was gonna do. I nudged on the heat to 50 and let it sit for a few hours, sure enough it pushed more of my shit back out of solution and into that brown precipitate. I did this again and again until I was at 65, not going past there. Actually I did bump it up to 70 briefly but no change seemed apparent in color, so I bumped back down. I can't say exactly how long I let it go, all day, not including the night in the fridge in the ice bath. After I was done heating I just let it cool on the hotplate to room temp. Once the hotplate was cool enough I turned stirring off which immediately caused buckets of that red oil to drop out of suspension.

This is just the beginning I really have the feeling I can get into the steady 70's or even 80's on yield. You already know what you want to see, throw those fucking notes away and make it show you what you want to see!!

Title: **Re: Hofmann Rearrangement Yields**
Post by: **fries** on **August 30, 2011, 09:52:30 PM**

Quote from: reDEEMed on August 30, 2011, 06:04:37 PM

> Fries- I didn't write anything down or take any kind of notes. I came to conclusion that was not helping as yields were not getting any better. I just took what I knew from watching this reaction forty billion times and I watched it, with no heat to see how it would change. I already knew that the brown precipitate was my amine it just wasn't ready so to speak. One day I took the time with a flask of water and wrote out the temps on my hotplate, this has proven to be the most worthwhile thing I've done lol. Now I can wind off my dial to 50C or whatever and walk off and if I come back in an hour, it's 50C, not 48 not 52, 50! So I just started gently adding heat once the reaction had peaked at room temp and I was convinced that was all it was gonna do. I nudged on the heat to 50 and let it sit for a few hours, sure enough it pushed more of my shit back out of solution and into that brown precipitate. I did this again and again until I was at 65, not going past there. Actually I did bump it up to 70 briefly but no change seemed apparent in color, so I bumped back down. I can't say exactly how long I let it go, all day, not including the night in the fridge in the ice bath. After I was done heating I just let it cool on the hotplate to room temp. Once the hotplate was cool enough I turned stirring off which immediately caused buckets of that red oil to drop out of suspension.
>
> This is just the beginning I really have the feeling I can get into the steady 70's or even 80's on yield. You already know what you want to see, throw those fucking notes away and make it show you what you want to see!!

So, just to get this strate... The above description was with the original household bleach and NaOH hoffman? It's not always clear in your posts when you're talking about TCCA or bleach.

"once the reaction had peaked at room temp" What do you mean by this - When it starts going brown? Or once everything has turned into oil? In my mind the raction has peaked once everything has turned into oil (like in my pictures a few posts ago). By this stage i'm not sure if there is anything left in my reaction to bother with heating. I once tried heating the reaction after it had reached this stage and it didn't give any better yield than the runs with no heating.

I'm wondering if your gradual or long period of heating have something to do with this working so well for you. Has anyone else seen this reaction been done at these temps over such a long period of time?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **reDEEMed** on **August 31, 2011, 01:17:17 AM**

That was with straight bleach. I added a little extra to make sure there was enough (like 20mls). When I say peaked, I simply mean that it had obviously plateaued, nothing more was going to happen. So at this point I nudge it forward with a little heat and continue to do this nudge wait for things stabilize nudge some more. I probably could have went further with this batch, but it was so obvious that I had a boatload of oil the excitement was killing me, so I ended it. All I know for sure is that for me, over analyzing was keeping me from seeing the obvious. I quite literally just watched the shit and then reacted to the visual cues the way my gut told me too. Just try it. Dump 40gms of amide in minimum and toss your notes. I think also there is definitely something to bigger batch size and how it relates to bigger percent yields.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dingbow** on **August 31, 2011, 02:02:22 PM**

Quote from: akcom on August 30, 2011, 05:32:32 PM

> The o-methyl carbamate is obtained only in the presence of strong base (sodium methoxide usually)

Yeah thats what I thought. I wonder if the dampness of my chloroamide was a problem as it would have contained some MeOH (it weighed more then twice what it should have). Could the MeOH have reacted with the NaOH solution to create the carbamate?

I'll try TCCA again, 2 slightly different methods. Once the chloroamide is formed, i'll halve it, evaporate the MeOH off one half like Redeemed did and precipitate out the other half with water like I did the last time. On the latter approach i'll wash the end product with water more and make sure its dry before the rearrangement.

Quote from: reDEEMed on August 30, 2011, 06:04:37 PM

> As funny as it is to you guys, the Hoffman as a whole did not produce shit for me several times. Now, looking back, I'm almost positive that it was my workup that was flawed. The very first time I had any success was when I used the TCICA first then rearranged the goo. That was the very first time I got bitter crystal. All I did was mix it with a minimum of water and dripped it in to 70C NaOH solution with stirring. IIRC I let it still for an hour or so. But, after the other day I wont bother with it again unless that can push yields toward quantitive.

Probably, the first few failures on the hofmann I had were work up related. The biggest help, especially with regard to yield was a post on PS where someone noted to extract the amine out of the hofmann whilst it was still warm, around 60c, whilst the amine had not yet gotten trapped into the solidified mass at the bottom.

Did you end up getting a yield figure on TCCA from amide to amine? Oh and was your chloroamide water soluble?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **reDEEMed** on **August 31, 2011, 05:26:18 PM**

No, I didn't give up. I just had to do something quick and I knew the bleach worked predictably so I used it. I will still be playing around, I just had some time constraints that made experimentation not feasible.

Java is the one who first mentioned extracting from 60C solution. If you're gonna copy anyone he's the one to copy. Dude is ridiculously on top of shit.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **jon** on **September 01, 2011, 09:45:41 AM**

---

also mda is volitile with steam you should hve luck with steam distillation to remove it from the heavy tars

---

Title: **Re: Hofmann Rearrangement Yields**
Post by: **fries** on **September 01, 2011, 10:45:11 AM**

---

dingbow, I think redeemed is saying the chloroamide is water soluble:
Quote from: reDEEMed on August 30, 2011, 06:04:37 PM

> All I did was mix it with a minimum of water and dripped it in to 70C NaOH solution with stirring. IIRC I let it still for an hour or so. But, after the other day I wont bother with it again unless that can push yields toward

> quantitive.

If this is correct (I have no idea, haven't read anything about it as I've not been interested in this route) then it wouldn't be chloroamide precipitating out when you add water.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **letters** on **September 01, 2011, 04:36:12 PM**

---

not sure which chloramide you guys are speaking of, but if it is the one derived from that aldehyde mentioned by twodogs, then it is not water soluble, at least not to any appreciable extent. it is however soluble in methanol, as well as various ethers.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **reDEEMed** on **September 01, 2011, 05:01:21 PM**

Ya know what, it was dissolved in methanol, not water. My bad.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dingbow** on **September 02, 2011, 05:10:42 AM**

---

oh you dissolved your chloroamide into MeOH and dripped that into the hofmann?? Interesting... alcohol was something I had considered as a co-solvent in the hofmann but didnt try it because it seemed it would react with the NaOCl. Though if you have the chloroamide, your past that stage, interesting!

Yeah I assumed the chloroamide was not water soluble, because the literature stated recrystalisation from benzene.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **reDEEMed** on **September 02, 2011, 06:24:26 AM**

I did it because it was already gooey and it was gooey because of something that happened in methanol lol. Flimsy logic, but that's all I got to work with.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **letters** on **September 02, 2011, 06:53:13 AM**

---

reacting the chloramide with methanol and naoh will yield a mixture of the methyl carbamate, primary amine and maybe some urea as well.
the chloramide you speak of does not react with methanol under neutral conditions.
there is no reason to get "gooey" chloramide, it is a solid, fully crystallizable.
and "Ya know what, it was dissolved in methanol, not water. My bad." is something i can not accept. the rhodium/barium style intended mistakes is something i really frown upon. if this was an honest mistake, ok. but ill be around watching, and will jump in whenever i see bullshit being written.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **reDEEMed** on **September 02, 2011, 04:59:57 PM**

It was an honest mistake, I tossed my notebook, the whole thing and that procedure is not something that's been on my mind lately. You don't have to worry about me writing 'bullshit' in this thread anymore because I'm done with it. My yields are now very very acceptable and I've said all I can say as to why that is.

I really have nothing more to add here.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dingbow** on **September 03, 2011, 03:26:25 AM**

Quote from: letters on September 02, 2011, 06:53:13 AM

> reacting the chloramide with methanol and naoh will yield a mixture of the methyl carbamate, primary amine and maybe some urea as well.
> the chloramide you speak of does not react with methanol under neutral conditions. there is no reason to get "gooey" chloramide, it is a solid, fully crystallizable.
> ...rhodium/barium style intended mistakes...

Right ok, so then the question is what ratios of carbamate, amine and urea do you get and if the major component is the amine, are the yields satisfactory.

Heres what i'll try:
-Form chloroamide via TCCA
-Filter CYA precipitate
-Split remaining chloroamide saturated MeOH solution into 3 equal portions
-evaporate one portion to dryness and rearrange without co-solvent
-precipitate one portion with water, thoroughly wash and dry then rearrange without co-solvent
-Drip last portion directly into hot NaOH solution.

by the way, what are 'rhodium/barium' style intended mistakes???

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dingbow** on **September 08, 2011, 07:54:28 AM**

So heres what I have done thus far;
-took a small amount of chloroamide saturated MeOH and tried to evaporate it.. decomposition seemed to occur so gave up on that.
-Took half of remaining saturated MeOH solution and ran it through rearrangement as is (Redeemed method), which resulted in the same as my first run, a white crystraline precipate that would not convert to amine. Not so surprising.

There seemed to be a fishy amine smell from the reaction though, so I proceeded to extract 2x from the reaction solution after filtering off the solids. The non polar extracts were then washed with dilute HCl solution, the washes evaporated to yield a TINY amount of amine.

This is somewhat encouraging, it shows the reaction can indeed produce the amine and hopefully can be tweeked to yield amine as the major component. From my reading, apparently the isocyanate can be trapped by the MeOH and convert to the carbamate, which could be my problem (especially given the weight of the chloroamide was double what should have been there @ 100% yield).

So, I have now recrystalised some chloroamide with xylene, which was obtained by precipitating it out of the MeOH with water, in the hope that its removed any last trace of

MeOH. Its dry now and I will attempt a rearrangement on it soon.

Actually I might recrystalise more chloroamide and see if it loses weight post recrystalisation.

PS; I tried doing a MP on the chloroamide again, it melted into this thick clear liquid and upon cooling did not change appearance but hardened. The weight of the product did not change, I reheated again and it went white, again not losing any weight but going by appearance it seems to be a different compound.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dingbow** on **September 14, 2011, 01:28:53 PM**

Recrystalised and completely dry chloroamide (supposedly) failed in rearrangement, yielding the same crystaline white powder as previous runs. Im starting to get the feeling I dont have the chloroamide at all to begin with and the minute amount of amine I yielded last time was as a result of some residual minor chloroamide mixed into this unknown white substance im getting out of the TCCA reaction.

Whilst doing some research I came across this:
hxxp://www.sciencemadness.org/talk/viewthread.php?tid=4201&page=3#pid138509

A hofmann rearrangement with TCCA in one step without isolation of the chloroamide, very interesting indeed... I'll be surely giving this a run.

What I also noted was the use of cooling in the formation of the chloroamide, as per the standard hofmann rearrangement using hypochlorite. Interestingly, the reference I have used thus far, DOI: 10.1081/SCC-200066703, makes no mention of the need to cool the reaction. This makes me wonder if heat is the issue in the TCCA reaction and whether it needs to be kept cool, I can certainly tell you the reaction is fast if all the TCCA is dumped in at once and is quite exothermic. If I succeed with running the procedure as outlined in the SM link, i'll try forming and isolating the chloroamide again by doing the following:

-Dissolve amide in MeOH and into RB
-Cool solution to 0-10c
-Dissolve TCCA in MeOH and into dropping funnel
-Drip TCCA solution into amide maintaining 0-10c

If both are a success, a comparison of the yields will tell us if its worthwhile isolating the chloroamide or whether the one step rearrangement is just as good and saves time and energy. Though I dont want to get too far ahead of myself..

Title: **Re: Hofmann Rearrangement Yields**
Post by: **b6baddawg** on **September 16, 2011, 03:14:58 AM**

---

reading that lots a bit confusing theres a few methods there.
AFAIK run like twodogs is good for 20% my dog never got more than 15, usually 5-10%
the tcca in methanol at the time was good to 35-40% cant remember what else added gave at best another 5%

the bisulphite hoffman ran dilute hit a sweet spot though

like in the patent, 3c is good temp to cool everything too prior to commencing
note heat is evolving as reaction commences, keep it down, had to add icecubes to keep temp below 3c. dont go too low and stop the reaction yet. after several hours the heat evolution ceases and solution temp drops.. NOW go to -9 -10c.
leave it stirring until the precipitate at the bottom turns from white to a yellow colour, might be 24 hour, might be 72hour (had a problem with naocl concentration which prolonged the reaction my dogs went longer due to this)
solution at this point should be golden yellow almost taking hint of orange.
allow to return to room temp on own accord.
add bisulphite to quench excess bleach. give a few hours for oil to fall out of solution.
separate the thick red sometimes slightly brown crude mda oil (you know how to work that up n recover unreacted amide yeah) its slightly yellow when done.

um the solution drip in the naoh 75c allow 15-20 mins from final addition before allowing to cool. n work up. screaming blinding white product
lie and say the yields shit, share the extra with friends
i just added the bits i thought might be missing from your practical whats killing yields
i hope that makes sense as in fills in a few gaps.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dingbow** on **September 16, 2011, 03:24:27 AM**

The hofmann with TCCA works!

I ran this:
-5g amide
-1.9g TCCA
-250ml 10% NaOH solution

I had a somewhat different experience then the post at SM, temperature control seems to be quite important.

My solution seemed to level out ~8c in an ice bath, there was no change in colouration with the addition of TCCA to the basic solution. This could possibly be because I cleaned my TCCA of any CuSO4 before use.

It took some time and heavy stirring to dissolve the TCCA, even then not all of it dissolved, especially the larger chunks, which is something to consider next time.

At ~8c there was no visible sign that any of the amide was converting to the chloroamide and dissolving. Raising the temperature had a dramatic impact on this though and the solution cleared and visually it looked like 90%+ of the amide had dissolved, I assume because it had converted to the chloroamide. From here more heat was applied and rearrangement occured quite nicely, albiet at ~75c, rather then the 65c noted on SM.

Final work up is yet to be complete, but visually it speaks for itself! For a 5g amide run, I have never seen so many droplets of oil swirling around the flask, not only that but the reacion is soo much cleaner then a hypochlorite hofmann. No tar was formed at all. I have some high expectations for the final yield, which I will post once work up is complete..

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dingbow** on **September 16, 2011, 03:26:56 AM**

---

thanks for the info b6baddawg. I managed ~25% on my best run with the twodogs method, allowing 4hrs for chloroamide formation, then heating quickly for rearrangement.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **WazOne** on **September 17, 2011, 01:58:35 AM**

> Quote from: fries on August 27, 2011, 06:00:41 PM
>
> > Quote from: jon on August 26, 2011, 08:25:18 PM
> >
> > > that method seems to yeild no better than say 70-80 c.
> >
> > Yeah i know that, but its pretty simple and doesn't need any fancy schmancy stuff like decadent hot plates and thermometers :D
> >
> > I don't find workup difficult, my only sep funnel is 100ml, so i'm separating layers more manually from beaker to beaker... just clean the result as i mentioned.
> >
> > I'd love to know what Waz is doing right to get those 50% + w/w yields... running 200g batches or something?

Shaking the fuck outta it.. And giving it the time it deserves to seperate. Remember once after waz added his 200ml of hcl to his xylene(40g batch) Based slowly over a few hours and let that sit till the next morning to find a good 5millimetres thick of honey coloured oil. Got 31g outta that batch.
Note: there has been times of complete failure.
The key is to be thorough and take your time.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dingbow** on **September 19, 2011, 01:23:47 PM**

Final workup on the TCCA hofmann has been completed and the yield from a 5g amide batch is 2.4g amine.HCl or 46% molar. The non polar solution containing the amine was only gassed once, so I would imagine there might be a bit more in it, but not much.

I was hoping for a higher yield, but this is the best I have so far achieved with the hofmann and it gives a much cleaner product. I think theres a few things to try differently and see how it affects yields.

i'll probably trying isolating the chloroamide one last time, this time keeping control of the reaction temperature.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dingbow** on **September 19, 2011, 01:38:56 PM**

One question though, looking at these two links:
hxxp://www.youtube.com/watch?v=mibv4bUarpE
hxxp://en.wikipedia.org/wiki/Hofmann_rearrangement

It seems to me that a hydroxide ion is necessary for the formation of the chloroamide. Given that "DOI: 10.1081/SCC-200066703" makes no use of NaOH in its reactions, does mean that the solvent is providing the hydroxide ion?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **atara** on **September 20, 2011, 06:57:20 PM**

Hydroxide isn't necessary -- you can run a water-free Hoffman using NCS or NBS (N-chloro/bromo succinimide) in methanol. You do need a base though, and strong nucleophiles are bad.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dingbow** on **September 21, 2011, 10:21:11 AM**

so the base is required for the deprotonation right, the reference I mention makes no use of a base so I dont understand how the chloroamide would be formed?!

Title: **Re: Hofmann Rearrangement Yields**
Post by: **reDEEMed** on **September 21, 2011, 10:32:22 AM**

I'm not sure if this is the video I watched or not, if it is, it will show you the role the base plays. I can't play it right now to verify, but I'm almost positive that's the one.

hxxp://www.youtube.com/watch?v=mibv4bUarpE

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dingbow** on **September 21, 2011, 11:24:26 AM**

Yeap, thats the one. As far as I can tell it clearly shows that deprotonation needs to occur before the chloroamide is formed, so im confused as to how its done in "DOI: 10.1081/SCC-200066703".

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dingbow** on **September 26, 2011, 11:27:47 AM**

I have now run the TCCA hofmann three times in total, with my last attempt yielding 3.9g amine.HCl from 5g amide, or 75% molar yield, in 2hrs total reaction time. I think at a larger scale, yields will improve slightly if only through minimised mechanical losses, but I think theres another few percent in the reaction parameters to be had.
VERY happy with this result :)

Through trial and error and some chance, the parameters of this reaction have become clearer. Temperature control is most important and interestingly for this particular amide, it seems that the temperatures requirements are quite different then was is written in any of the literature/references I have read to date.

I have abandoned the quest to isolate the chloroamide, this seems good enough to me. Monomethylation is the next goal. Thanks to everyones input, this thread has achieved what I wanted 8)

Title: **Re: Hofmann Rearrangement Yields**
Post by: **letters** on **September 26, 2011, 04:24:18 PM**

can you please input the exact methodology you used so it can be replicated and tested? 75% without a co-solvent seems like a fantasy, and if you are using methanol as a solvent, then most likely you are getting a mixture of carbamate and free amine. I am willing to test the exact conditions you use and report back to the community

---

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dingbow** on **September 27, 2011, 02:00:33 AM**

oh people are still interested in this, thought I was posting to myself :D

In the spirit of sharing information and giving back to the community (im not a follower of the secrecy thing), here it is:

5g amide Batch
1.2 molar equivalent of TCCA
10% 250ml NaOH solution

-Cool solution of NaOH down to ~20c, if necessary.
-Add TCCA, stir vigorously until FULLY dissolved, this is important. Some very slight foaming will occur. Do no proceed until it is all dissolved.
-Add amide, continue stirring vigorously, while SLOWLY raising the temp to around ~25-30c. You know the chloroamide is forming when the solution is becoming clearer over time, this took about an hour.
-Once the solution is free of any solids and appears a somewhat opaque but still clear solution, raise temperature rapidly to 75c. Once this temperature is reached, hold for 30min.

Extract and workup as usual.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **letters** on **September 27, 2011, 05:59:03 AM**

thanks. will try it as you suggest and report back.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **reDEEMed** on **September 27, 2011, 06:55:49 AM**

I don't think it's secrecy that keeps most people's lips sealed. I did at one time, but I have a different take on it now. I think it's more that people loathe the idea of someone who has not put forth any effort at all taking their hard work and reaping the benefits. Via pm I don't think I've came across a single person who was not willing to tell me anything they knew or had figured out. Of course there have been very few times when I asked anyone for that kinda help, but when I did, they were always very forthcoming and more than willing to share.

Anyway, I just thought I'd throw that out there lol.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dingbow** on **September 27, 2011, 07:26:40 AM**

I can understand where they are coming from, no one wants a repeat of the hive saga and the effects on the supply of certain materials occurring again.

Having said that, I think we all take from the community in some way, I certainly wouldn't be here if it weren't for certain members who opened up some possibilities to me and i'm sure many many others. For that reason I feel obliged to share, on a give and take basis, even though complete anonymity used to be what I thought completely necessary.

I also realise theres many lurkers who will simply leach, but that's the nature of the game and I would not want it to detract from the concept of sharing and community.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **fries** on **September 30, 2011, 04:18:33 PM**

Has anyone done any more runs with this tcca procedure? I'm wondering if yields are consistently good and if its easy to fuck up? If its robust and easy to get decent yields, i might give this one a go.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **b6baddawg** on **October 01, 2011, 06:17:40 AM**

ah yes youve ran a dilute hoffman dingbow, nice yield. ive not seen it run with tcca
can i ask did you notice byproduct formation, eg yellow/orange floaties? or tar?
im curious if after the tcca was dissolved with the naoh, before you added the amide did you cool the solution right down (2-5c) before beginning addition of amide and not raise temps till all was in solution?

if you scale that up have icecubes handy because amide addition is thermal as the scale increases and can become a yield killer.

(i base that suggestion on the hypochlorite not the tcca hoffman, i guess it will still apply)

the 2-5c comment is from various patents suggesting 0-5c as optimum addition of amide temperature. as i understand it with tcca the tcca must be dissolved slowly in solution at temp above 15c but am unsure if it can then be lowered as far as 0-5c afterwards and brought back up without smoking/runaway once the amide is in solution as the effect may be catalysed at 15c or thereabouts.
i hope that makes sense.
it will answer whether the amide all in solution in the dilute hoffman was what gave the good yield or the temps you used. the tcca yield i mentioned previously in a post had undissolved amide.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dingbow** on **October 02, 2011, 01:34:56 AM**

Quote from: b6baddawg on October 01, 2011, 06:17:40 AM

> can i ask did you notice byproduct formation, eg yellow/orange floaties? or tar?..
>
> ..im curious if after the tcca was dissolved with the naoh, before you added the amide did you cool the solution right down (2-5c) before beginning addition of amide and not raise temps till all was in solution?
>
> if you scale that up have icecubes handy because amide addition is thermal as the scale increases and can become a yield killer.
>
> ...the 2-5c comment is from various patents suggesting 0-5c as optimum addition of amide temperature..

There were floaties, but it was mostly amine. One one occasion yielding close to 50% the amine was so clean it appeared as light yellow blobs of oil. On the highest yielding occasion, the amine was darker probably from some slight tar. It all dissolved easily in the non polar extraction though. No solid tar ever obtained, like I used to get with the hypochlorite.

Nope, it was never cooled down that far. I used to cool it down to ~8c, that seemed to be an equilibrium temperature that was reached with the amide added, cooled on an ice bath.

Unfortunately for me I have gotten to your post too late, as I tried scaling it up a bit and had some major problems! I scaled up without increasing solvent volumes and it seemed to have a dramatic effect. After adding the amide and leaving the reaction to allow the chloroamide to form, I returned to see how it was going expecting to see a somewhat clearer solution. Instead what I saw was an orange/red milky solution with a lot of solids undissolved, the temperature had risen to ~28c from around ~18c when I first added the amide.

I continued as usual knowing things had not gone well. Let me tell you, I have never seen so much tar in my life! I lost count how many filtrations and separations I had to do, not to mention I had to do 2x A/B as the final non polar extract was as black as the night. The A/B helped a lot and I now have a non polar extract which is much cleaner, ready for final work up (yet to be done, will post yield when complete).

The previous 3 reactions with TCCA yielded such a clean product that the extract could be converted to the hydrochloride without any clean up, only a final recrystalisation. Oh well, lesson learnt. Im guessing the smaller solvent to amide ratio meant the net effect on the temperature of the reaction was rather quite large and killed it.

Correct, thats what all the patents say. I dont know if its because they all use hypochlorite? But even when I ran with the hypochlorite, I never got a clear solution to indicate full conversion to the chloroamide when I ran it that cold. I can tell you right now that with TCCA, <10c the chloroamide is way too slow to form and is completely unnecessary.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **b6baddawg** on **October 02, 2011, 05:45:27 AM**

---

i didnt see much point (for myself) running the dilute hoffman. by dilute i mean enough h20 as solvent to completely dissolve amide. for personal its a winner.
thats how you got the high yield i think dingbow.
naocl is comparable to tcca i think yieldwise when run dilute, difference is reaction time.
(thats speculation not tried and tested 100% fact)

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Enkidu** on **October 02, 2011, 05:56:48 AM**

DO NOT post in the PN thread on this topic.

The only reason that you get to play around with this is that people before you kept it quiet.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dingbow** on **October 12, 2011, 08:05:40 AM**

Yield of scaled up TCCA hofmann, an abysmal 18% molar. In hindsight I should have recycled/filtered the unconverted amide when I hit trouble, cleaned it and ran it again instead of attempting to re-arrange the whole mess.. oh well, live and learn, experimentation right?

b6baddawg, I believe the amide never dissolves in the water, it merely converts to the chloroamide, which is seemingly water soluble. This is a great indicator of how your hofmann is running, because if solids are visible you know your conversion to the intermediate is not complete.

Out of amide, what a bummer.

Letters, what happened to posting back your experience ? :)

Title: **Re: Hofmann Rearrangement Yields**
Post by: **letters** on **October 12, 2011, 11:31:33 AM**

sorry got caught up in other stuff. i got a very small yield, along the lines of what you got in your larger scale, however i used less dilute conditions. the only way for success at any reasonable scale with TCCA is with a cosolvent, just remember that THF will react with TCCA at and around r.t.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dingbow** on **October 12, 2011, 12:34:58 PM**

I think with careful temperature control, via external cooling and gradual addition of amide, this could be scaled to something reasonable.

Im curious enough to verify this with more experimentation, but thats probably some time away when more amide is available.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **fries** on **October 22, 2011, 11:44:20 PM**

I've just run a cold(ish) coke bottle style Hoffman with bleach, similar to my writeup a few posts ago with a couple of small tweaks. I used my last 25.5g of amide which i recrystallised twice, but it still looked a little bit dirty and could probably have gone for one more.

So far i have salted and dried 11.6g of dirty looking amine, with what looks like another 1g or so still drying. So, so far that's 43% molar yield dry, with a few more % on the way!

Title: **Re: Hofmann Rearrangement Yields**
Post by: **DopeBee** on **October 23, 2011, 01:05:17 AM**

I use boiling water to recrystallize the amide, as it is slightly soluble in boiling water.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **fries** on **October 23, 2011, 10:42:27 AM**

Total yield after drying was 12.5g, that's pretty close to 50%.

Edit: after recrystallisation i ended up with 12g of sparkling white amine, 45% molar yield.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **fries** on **October 24, 2011, 10:02:02 AM**

Here's what I did this time:

Into a coke bottle is placed:
1. 25.5g Amide, very clean, finely powdered.
2. 290ml of 4.7% NaOCl, pre-cooled to nearly 0c
3. 19.2g NaOH monohydrate in 260ml H2O, pre-cooled to nearly 0c

Mix all together in the coke bottle, shake really well for 5/10 minutes, place in fridge/freezer for a while, then shake again. Lots of shaking and keeping cold in the freezer/fridge for 24 hours. By now the amide had mostly turned into a very very fine white dust at the bottom of the coke bottle.

Allow the mixture to rise to room temperature. Make sure your room isn't too cold, above 23c should be ok - otherwise it takes ages. Try to shake it as often as possible, every hour for a few minutes should be good. As soon as the colour starts to change from yellow/white/green to red/brown, dump in another 10g NaOH monohydrate and shake till its dissolved (t+0). This should raise the temperature in the bottle a fair bit.

The next morning (t+9) I placed it on the warm radiator for 3/4 hours, then nearing the 24 hour point (t+18) i placed the bottle in a bath of hot water for a few hours, changing the water occasionally for more hot.

After 24 hours, i opened the bottle and noticed a smell of ammonia. The colour wasn't as dark as last time. I Extracted with 3x100ml toluene, titrated with about 20ml of 7% HCl and recieved my 45% yield.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **thescientist3000** on **March 07, 2012, 06:06:03 PM**

Hello.

Ferret followed Fries advice, and similar ratios. Here is ferret's update.
51gr amide
465ml of 6% NaOCl, pre-cooled in freezer for 30min
39gr NaOH, mixed in 520ml H2O. pre-cooled in freezer for 1hour.

Mixed amide into bleach first, and shook around for 20 minutes. The magnetic stirrer did not work for such a mix. This by itself took on a brownish color, before any base was added. Strange?

The NaOH solution was then added to the amide/bleach mix. There was a thick foam that was created on top of the liquid, also brown, maybe a little purple in color. This foam could be to a slushy consistency. It wasnt violent foaming or anything, very calm actually.

Color remains the same, and has been moved to the fridge instead of freezer after 30 mins. Shaking every once in a while.

Any recommendations for ferret on the color/foam?

How to proceed, long time cold method, or couple more hours cold, and move on to slow bumping of heat and ending at 60-65c max?

Bisulfite method?

Thanks.
TS3k

Title: **Re: Hofmann Rearrangement Yields**
Post by: **thescientist3000** on **March 08, 2012, 10:25:17 PM**

Cold temps kept it the dark color
50c- got lighter/white
60c- light yellow/orange, some dark oil droplets being thrown around
65c- darker yellow/orange, same or similar amount of oil, no more produced(possibly)
70c- darker orange
75c darker orange, temp shutoff

The ferret appeared to have a decent amount of this dark orange oil and thought success! NO, fail. Upon extraction, extraction is black. A/B lead to a very very small white/yellow oil, which pretty much gave nothing. Whered it all go?!?!?

Thoughts/impovements/questions:
1. One idea is to keep the temp under 60c or so. Once the oil droplets formed, it appears that no more oil was being created as the temp rose higher to 65-70-75c. The mix just appeared to get overall darker in color. Just an idea, shut off at 60c.
2. Aqueous layer was dripped on hot base, and extraction led to nearly nothing
3. Oil layer extraction, upon cooling had brownish particulate settle to bottom, this is supposedly unreacted amide and was filtered off.

All visual cues lead to success, somewhere along extraction, a/b perhaps something went wrong.   What if that black oil extraction was dried, and directly gassed instead? Ferret knows, scary looking shit extraction, but direct gassing would bring black crystals idk hahahaha!

Ferret doesnt know if anyone will respond, but there is her note. When will this hoffman be someones bitch!

Title: **Re: Hofmann Rearrangement Yields**
Post by: **DopeBee** on **March 09, 2012, 04:35:27 AM**

I posted this over at the silk road forums:
http://dkn255hz262ypmii.onion/index.php?topic=14484.0
Quote

> Recrystallize the product with hot xylene [or boiling water]. Dry the recrystallized product and grind in into an extremely fine dust in a coffee grinder. It is very important that is a very fine dust with small particle size.
> http://xfq5l5p4g3eyrct7.onion/upload/43ed083b3712d2bcf267a8e837c0ddee.jpg
>
> Add 2000ml water and 1200ml bleach into a clean 4-liter plastic milk jug. Add 100g sodium hydroxide and shake it up well. Cool it in a fridge for several hours. Add 100g of the finely powdered product from the previous step to the milk jug. Shake this mixture up and place it in the fridge for 72 hours, shaking it every few hours [or as much

> as possible as often as possible]. Take it out of the fridge and let if sit at room temp for 24 hours, again shaking it up whenever you get the chance. Then place it in a hot water bath for 6-12 hours. It should be a milky orange color with tarry MDA base floating in it. Use a separatory funnel to extract the MDA base with xylene or toluene and discard the water layer. Next add diluted HCl acid until the pH of the water layer is 1 and discard the oil layer this time. Evaporate the acidified water layer in a pyrex baking tray. A kilo of the original substrate will yield about 250g of MDA.
> http://xfq5l5p4g3eyrct7.onion/upload/41b65ce3728efeaaa9151285d87b1e22.jpg

---

Title: **Re: Hofmann Rearrangement Yields**
Post by: **jon** on **March 09, 2012, 05:34:38 AM**

---

i see what your doing with the cooler temperatures.
kinetic control allowing the chloramide to form at the lower temperatures first.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **thescientist3000** on **March 10, 2012, 01:34:48 AM**

Thanks.

S.R. forums, those look wild!! Little too wild for even a ferret.

What percent is the bleach used?
Judging by the ratios at hand, looks like you use a bit more sodium hydroxide than usual, which is said to increase yields a bit. Good move there ferret thinks.

H2o is also increased a bit more than anywhere else seen.

Order of addition here looks like to add amide last. Ferret seen elsewhere to add bleach/amide or base/amide and then the bleach or the base. Seems to not matter.

Cheers!

Title: **Re: Hofmann Rearrangement Yields**
Post by: **thescientist3000** on **March 10, 2012, 01:47:46 AM**

Almost forgot.

Water bath temp is not stated. Are you talking, like hot tap water, being replaced, or hotplate?

If you know temp, that would be very helpful.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **DopeBee** on **March 10, 2012, 03:15:18 AM**

Bleach was 6% namebrand stuff. I did this back in October and just put 8 milk jugs in an actual bathtub with hot tap water. As the water cools it is drained and refilled with new hot water. I think I may have left it in for even longer than 12 hours I can't remember exactly. Particle size is very important too, since the amide obviously doesn't dissolve much. I left one last milkjug in the fridge for a month to see what would happen. It eventually turned orange as well so it still reacts just much slower.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Carrion Fairy** on **April 12, 2012, 04:17:22 PM**

Interesting dopebee - How did you purify that gunk in the baking tray?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **DopeBee** on **April 13, 2012, 06:21:55 AM**

Acetone and a putty knife. :P

To re-x the brown sugar looking stuff heat up 1g H2O with 3g MDA.HCl on the stove (careful not to burn!). Once it liquifies take it off the heat and dump in cold acetone and let it cool at RT.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dingbow** on **April 18, 2012, 05:48:44 PM**

Quote from: dingbow on October 12, 2011, 12:34:58 PM

> I think with careful temperature control, via external cooling and gradual addition of amide, this could be scaled to something reasonable.
>
> Im curious enough to verify this with more experimentation, but thats probably some time away when more amide is available.

Been away for a while, but I did run another batch of amide and scaled up a TCCA hofmann (25g amide). Heres the procedude I used:
-used equimolar ammount of TCCA to amide
-1.5L h20 to 25g amide.
-Cool solution of NaOH down to 18c.
-Add TCCA, stir vigorously until FULLY dissolved, this is important. Some very slight foaming will occur. Do no proceed until it is all dissolved.
-Add amide in 5-10g portions, continue stirring vigorously, only add portions once the previous one is completely dissolved. Took something like 20-30min for each portion to dissolve. Also maintain 18c temperature, using ice bath if necessary.
-Once the solution is free of any solids and appears a somewhat opaque but still clear solution, raise temperature rapidly to 75c. Once this temperature is reached, hold for 30min.
-extract and work up as usual

I got something along the lines of 65% equimolar yield from memory, with the reaction being completed within 3hrs to reach extraction phase.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Sydenhams chorea** on **April 19, 2012, 04:42:12 PM**

---

from **Rec. Trav. Chim. Pays-Bas Belg. vol 50 (1931) p 305**:

Beta-2,4,5-trimethoxyphenethylamine from 2,4,5-trimethoxyphenylpropionamide (Hofmann reaction)

The amide, 7.5g, was suspended in 60ml water, a freshly prepared solution of 5g bromine in 50ml 25% KOH was added and the mixture heated to 60°C for 90 minutes. An oil gradually separated on the surface and, after cooling, a further 15g KOH were dissolved in the liquid, the latter extracted with ether and the extract dried over solid potash.

A small quantity of a colourless substance (unchanged starting material) separated out on the walls of the vessel from the initially clear solution. The clear filtrate was evaporated down and a pale yellow oil remained after the ether has been removed, which solidified to a white solid, mp 66-68°C [carbonate?]. This substance appeared to be beta-2,4,5-trimethoxyphenylethylamine, yield 4g.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Tsjanga** on **August 23, 2012, 11:41:30 AM**

Hmmm I allready fucked it up by step 1.....
Would love to try the TCCA route but I have to get to the amide first.... :-[
Used 2 different sources of hydroxylamine and Soda but still it isn't solidify just being a greenish blobbish layer and 1 watery layer.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **WazOne** on **August 23, 2012, 09:18:28 PM**

This doesnt relate to the hofmann. Try extra hydroxylamine and half again carbonate stir some more. Is the ph neutral?
Or decant water layer add 3 times the volume in ICE cold H2O and stir as quick as possible. The oxime should crash out.. Carry on from there.

The answers you seek or should I say the solution to your problem/s have been published already.
Hope none of the previous experiments were chucked out as its an easy Fix.

Cheers

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dingbow** on **September 01, 2012, 10:58:43 AM**

As has been mentioned, you do not need a solid oxime to continue. I have never obtained a solid oxime. Just extract the non aqueous and proceed, there have been posts made about this already, I described my procedure on PN.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Sneak** on **September 02, 2012, 12:06:56 AM**

After reading this thread i heard local wild life are quite excited to defrost some shit soon and report some results. They mentioned they need to create the oxime and amide first still. The method posted by fries in the coke bottle ran cold looks straight forward for a first time run for the rearrangement , the arrangement of animal's went on to explain then they are going to try a few other heated methods later depending on yields. 45% would be good enough for them. 3g street mda allows for many visually enhanced nights in the forrest. And lasts a good while. :)

It also beats fucking around with mercury they said.

This had made a lot of sense. Hope we can contribute!... They said, whilst merrily disappearing back into from whereth they cometh.

Thank you.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Tsjanga** on **September 02, 2012, 12:45:11 PM**

Quote from: dingbow on September 01, 2012, 10:58:43 AM

> As has been mentioned, you do not need a solid oxime to continue. I have never obtained a solid oxime. Just extract the non aqueous and proceed, there have been posts made about this already, I described my procedure on PN.

Allright!
Thank you dingbow, heard that the neighbors dog has a friend who told him that it worked.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **letters** on **September 04, 2012, 10:46:31 PM**

---

oxime can be made to generate small seed crystals when put under at least 4000 rpm for 5 minutes. These can then be used to crystallize large batches of oxime. With a seed crystal, the oximes crystallizes in minutes. Make sure to keep efficient stirring while adding the seed and while letting it crystalize, or it will make a brick that will be very hard to break.

regarding the hofmann/tcca - with a co-solvent yields are much better then 45%...

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Sneak** on **September 04, 2012, 11:32:00 PM**

How much better?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Tsjanga** on **September 05, 2012, 09:43:55 AM**

Quote from: letters on September 04, 2012, 10:46:31 PM

> regarding the hofmann/tcca - with a co-solvent yields are much better then 45%...

Can you explain it a bit more please?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **German** on **September 05, 2012, 09:25:43 PM**

The oxime can be solid or liquid it doesn't matter. Usually just washing with a bunch of water then cooling will turn from liquid to solid but I personally would pour it out before it had a chance to solidify because liquid is a hell of a lot easier to get out of a flask then a solid.

You're not getting a %45 yeild on the hoffman no matter what your solvent. Aint happening. I don't care about theory and I don't care about how much you got your unclean product to finally weigh in at, %45 isn't happening. As cheap and as few as all reagents are who cares anyways. If yeild is that big of deal get your %98 yeild with sodium azide in a few hours and hope you don't blow yourself up or poison yourself, otherwise I wouldn't get caught up in dramatically increasing yeild because it's futile.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **DopeBee** on **September 06, 2012, 03:09:09 AM**

Quote from: German on September 05, 2012, 09:25:43 PM

> You're not getting a %45 yeild on the hoffman no matter what your solvent. Aint happening. I don't care about theory and I don't care about how much you got your unclean product to finally weigh in at, %45 isn't happening.

(misinformation)
I get 70% yields.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **German** on **September 06, 2012, 04:22:47 AM**

Bullshit.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Sneak** on **September 06, 2012, 04:44:47 AM**

70%? That's a nice figure. How are you running that..?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **DopeBee** on **September 06, 2012, 06:17:42 AM**

(misinformation)

Right sorry I should've been clearer.
If I get 10% amine I'll get back 80% of my amide.
If I get 20% amine then I'll get back 70% amide.
So each reaction I only lose 10% of total weight which comes out to 70% total yield.
And since we're taking off a Carbon atom anyways, that's responsible for like 9% of the loss.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Quantum Dude** on **September 06, 2012, 04:41:08 PM**

Quote from: DopeBee on September 06, 2012, 06:17:42 AM

> Right sorry I should've been clearer.
> If I get 10% amine I'll get back 80% of my amide.
> If I get 20% amine then I'll get back 70% amide.
> So each reaction I only lose 10% of total weight which comes out to 70% total yield.
> And since we're taking off a Carbon atom anyways, that's responsible for like 9% of the loss.

For the record, the sludge you end up with during workup is FAR from being pure unreacted amide. You should do your math again because there is no way you have 70 % (w/w) MDA*HCl there.

Title: **Re: Hofmann Rearrangement Yields**

Post by: **German** on **September 08, 2012, 04:39:09 AM**

---

^^^ Yep what he said. You are making big assumptions about that sludge. Have you ever ran that "unreacted amide" through again? I have. A bunch. And you know what I've gotten back? ZERO. Thats not unreacted amide, it's reacted byproducts. The reason the yeild is for a fact so low and isn't increasing is because of all the side reactions going on. Who cares anyways, I'll take %25 on an easy OTC shake and bake over a %85 schedule 1 precusor route ending with heavy metals.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Sneak** on **September 08, 2012, 11:24:32 AM**

Yeh man exactly!!! 25%...Then make some more!

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Tsjanga** on **September 08, 2012, 03:32:37 PM**

So that means dingbow is wrong about his percentages?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **java** on **September 08, 2012, 03:38:39 PM**

.....dingbow never made such claims his comments can be found on this thread....his results are from a single run for which he states its been repeated with similar yields....java

---

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Quantum Dude** on **September 08, 2012, 04:00:53 PM**

For the sake of bringing back some actual CHEMISTRY in this thread I would like to point out that molar yields above 60 % are indeed feasible with the Hofmann rearrangement on Helionamide but one needs to understand the actual mechanism and kinetics of the reaction. There are some crucial steps that one needs to control experimentally in order to drive the reaction to the desired product. Its sure as hell more complicated than simply freezing and baking the amide in bleach Ill tell you that.

All that information is provided in this thread, one just needs to pick up some papers on the theory and dig through most of the crap within this thread.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **poisoninthestain** on **September 16, 2012, 09:31:15 PM**

All mp.'s below were taken on a melting block apparatus and observed over several runs:

arylamide post Beckmann rearrangement crude mp. 107-110C (usually brown is the most common impurity)
after recryst. from a EtOH:H2O system amide mp. approx. 117-126 as white crystals.

...and yes, as QD stated yields can exceed 60% molar but kinetics of the overall reaction rate are critical with enthalpy changes probably the most crucial.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **letters** on **September 16, 2012, 11:09:25 PM**

---

cyclic/acyclic, water-miscible, ether solvents work satisfactory. sulfolane is also a good hofmann co-solvent.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **fries** on **October 14, 2012, 10:39:50 PM**

Quote from: German on September 05, 2012, 09:25:43 PM

> You're not getting a %45 yeild on the hoffman no matter what your solvent. Aint happening. I don't care about theory and I don't care about how much you got your unclean product to finally weigh in at, %45 isn't happening.

Wait, what? You must be doing it wrong cause i got a good 45% yield after a few runs where i got <10%

Title: **Re: Hofmann Rearrangement Yields**
Post by: **fries** on **October 14, 2012, 10:48:43 PM**

Quote from: thescientist3000 on March 07, 2012, 06:06:03 PM

> Mixed amide into bleach first, and shook around for 20 minutes. The magnetic stirrer did not work for such a mix. This by itself took on a brownish color, before any base was added. Strange?

If you're getting brown then the temperature is getting too high. For me the colour was an off white colour until i removed it from the fridge to warm up, then it turns red/brown and goes darker as it gets warmer. I didn't use any serious heating and i doubt the temperature got above 50c.

As you probably know, i dint use a magnetic stirrer, shaking the coke bottel did a better job and kept it cooler.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **fries** on **October 14, 2012, 10:56:13 PM**

Quote from: thescientist3000 on March 08, 2012, 10:25:17 PM

> The ferret appeared to have a decent amount of this dark orange oil and thought success! NO, fail. Upon extraction, extraction is black. A/B lead to a very very small white/yellow oil, which pretty much gave nothing. Whered it all go?!?!?

Extraction was always black or very dark brown for me. Sounds like your a/b *might* be the problem. You have to titrate very carefully with a good ph meter and good stirring. I shook the coke bottle after every few drops of hcl were added, separated off the polar part, then took a ph reading of the non polar solution before adding more hcl. I found that over titrating, even a little, would ruin the whole batch and turn it all into red tar.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **LilDookie** on **October 15, 2012, 08:37:52 PM**

Quote from: fries on October 14, 2012, 10:39:50 PM

> Quote from: German on September 05, 2012, 09:25:43 PM
>
> > You're not getting a %45 yeild on the hoffman no matter what your solvent. Aint happening. I don't care about theory and I don't care about how much you got your unclean product to finally weigh in at, %45 isn't

> > happening.
>
> Wait, what? You must be doing it wrong cause i got a good 45% yield after a few runs where i got <10%

I agree. I have gotten as high as 50%, once. I'll be doing my first hofmann in a year soon. We'll see how well I do. I also agree with the poster who said brown/black means temp too high. I run mine so cold it'll have ice floating in it.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **DopeBee** on **October 16, 2012, 08:17:36 AM**

Who keeps deleting my posts?

.....stop the crap or get deleted permanently! what's with all those dead links?

Oh jeez sorry about that java... I didn't know the links were dead eh!
Here I've re-uploaded them to imageshack for you.

http://img267.imageshack.us/img267/7972/52270169.jpg
http://img191.imageshack.us/img191/34/82086418.jpg
http://img713.imageshack.us/img713/1192/99026897.jpg
http://img96.imageshack.us/img96/3998/44445470.jpg
http://img4.imageshack.us/img4/2056/33931074.jpg
http://img94.imageshack.us/img94/8577/88900480.jpg
http://img811.imageshack.us/img811/6919/21970114.jpg
http://img819.imageshack.us/img819/7964/72954742.jpg
http://img69.imageshack.us/img69/7030/43598446.jpg
http://img833.imageshack.us/img833/9062/79613375.jpg
http://img17.imageshack.us/img17/8443/19336278.jpg
http://img402.imageshack.us/img402/189/54032128.jpg
http://img401.imageshack.us/img401/6164/56497884.jpg
http://img594.imageshack.us/img594/7979/53427794.jpg
http://img109.imageshack.us/img109/1061/76114155.jpg
http://img546.imageshack.us/img546/2027/92413507.jpg
http://img267.imageshack.us/img267/9772/37201755.jpg
http://img9.imageshack.us/img9/6126/35575622.jpg
http://img213.imageshack.us/img213/8150/54466816.jpg
http://img141.imageshack.us/img141/7613/36746926.jpg
http://img22.imageshack.us/img22/7417/13043784.jpg

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dream0n** on **October 16, 2012, 01:21:15 PM**

You do? Is this a post saving server issue, or a java...script issue...

Title: **Re: Hofmann Rearrangement Yields**
Post by: **fries** on **October 16, 2012, 03:44:51 PM**

Quote from: LilDookie on October 15, 2012, 08:37:52 PM

> I agree. I have gotten as high as 50%, once. I'll be doing my first hofmann in a year soon. We'll see how well I do. I also agree with the poster who said brown/black means temp too high. I run mine so cold it'll have ice floating in it.

I got black when adding no external heat, ice cold for 24 hours then let it warm up to rt for about 10 hours.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Sneak** on **October 17, 2012, 08:15:16 AM**

Those are some great images dopebee. Cheers

Title: **Re: Hofmann Rearrangement Yields**
Post by: **uchiacon** on **December 27, 2012, 10:42:35 PM**

I'm having a very peculiar problem with my hofmann. My amide had not been recrystalized bc I didnt need to when I first attempted and succeeded with the reaction several months ago. is from the same bottle, same goes for all other reagents. I have tried 2 brands of bleach with the same result.

Here are the notes summarized. my bleach is 4.2% with 9g/L NaOH

10.1g amide, 5.05g NaOH in solution and 127g 4.2% bleach (which has 9g/L naoh) all mixed together and temperature raised to 70C. Turns brown, dark grey then black. Above 25C the black colour in the liquor PPTs out as a fine black particulate. Black does not respond to more heating or base.

Run cold: 325ml bleach and 19.2gNaOH in 260ml water and 25.5g amide; bleach and hydroxide added and cooled to 1-2C in freezer, amide added and shaken. About an hour in reaction is black. Same response as last time when heated above 25C

Above reaction rerun making sure bleach and hydroxide cooled to 0C. No change.

Above reaction rerun in an icebox with magstir underneath. Same problem.

Above reaction repeated, but addition of reagents changed. Bleach cooled, amide then added. Turns black in 30 min w/o hydroxide.

Before heating, the black colour in the liquor is from dissolved solids and there is a fine suspension of translucent clear colourless crystals. I am unsure what causes the black color, as there are no black particles currently in liquor.

After heating and going up to 80C, the black falls out of solution as a fine PPT and will settle quite quickly, leaving the liquor as clear as water.

What do?? I'm going to recrystallize but I do not think it will help... when I recrystallized amide in boiling water I a slightly lighter amide, but not much change at all. Certainly not white...

(I have notes I could contribute in regards to other parts of reactions but I dont know if it would be appreciated or wanted.)

Title: **Re: Hofmann Rearrangement Yields**
Post by: **poisoninthestain** on **December 29, 2012, 09:01:36 AM**

The black color is due to impurities from your amide that is not recrystallized. Dry IPA, MeOH, and EtOH work very well. This is one reason why your rxn mix was black regardless of rxn parameters. Garbage in, garbage out. The recrystallized looks remarkable compared to the crude amide. Check the mp on that amide.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **uchiacon** on **December 29, 2012, 09:05:59 AM**

Somehow what I ended up with wasn't an amide. Pretty basic test; heating with NaOH in a flask. Only a very faint ammonia smell... I never bothered to do it because the amide looked identical to what others reported and the pictures I saw along with the fact that it looked the same as the stuff I used months ago.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **LilDookie** on **December 29, 2012, 09:30:15 PM**

If you smelled ammonia then you had amide, no? Also, with the tiny amounts of amide you are using I wouldnt expect much from the Hofmann. Also I feel like you are heating too soon. I run the Hofmann at 0C for a full 24hrs then let it come up to room temp on its on then inch it up 10 degrees at a time till I hit 80C, it takes me almost 3 days to run but I always get 30+%

Edit: A better test rather than smell is to dangle a piece of wet litmus in the test tube.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **uchiacon** on **January 02, 2013, 12:50:12 PM**

I put a good 50-100mg of amide in the flask, dumped in a tiny amount of NaOH and a few droplets of water to make a slurry and then heating. Surely the ammonia smell would be stronger, its really barely noticeable. There are other smells(possibly something nasty) so I havent whiffed it since.

Surely the ammonia smell would be there, are clearly irrirating, if I had amide? You try with a tiny amount of yours and tell me the intensity of the vapours. I'm sure I have some amide, but over 30% would be doubtful. Additionally, my amide does not melt upon contacting a metal hotplate. It smokes a little bit and goes darker brown.

The only conclusion I can come to is that the dark colour of the xylene is indicating something not amide is forming. Quantum dude suggested that the heat of refluxing xylene (138-140C) is too high and that other compounds will be forming. Someone isolated the nitrile and reported it was a dark red oil. This explains the colour of the xylene mix once the temp got up to reflux, it was a dark cola brown with tones of red. (the oxime is clean and pure, does not dissolve in water as 1-2 of my earlier oximations did)

The first time I ran this reaction I used toluene for the beckmann. This worked pretty well iirc(but rxn mix was enough to push me towards , the reason for using toluene being that it was purer than the xylene and I assumed the difference in temperature during reflux wouldnt effect the reaction. Next time I plan to run it at 100 and 120C for 7-8hours, or until the amount of amide deposited on the bottom stops increasing.

Title: **Re: Hofmann Rearrangement Yields**

Post by: **LilDookie** on **January 03, 2013, 01:35:09 AM**

You shouldn't see the amide come out of solution when you're forming it. I want to say you aren't using enough solvent if you are seeing it come out of solution. Also, I push the Beckmann hard as fuck and have never had a problem, excepts almost having hot xylene come out of my reflux condenser. Mine is usually done in 6-7 hours. Regarding the ammonia smell when testing for amide, it has typically been faint for me as well, which is why I say dangle a piece of litmus wet with distilled water in the test tube instead.

I've been reading more about the Hofmann lately just to try and understand the mechanism better, but it's notoriously inefficient. I usually have what I would consider good luck with it, but I have a feeling I'm about to beat all my records, including 50% once. I also plan to run the reaction on some acetamide I have, to give methylamine. If I ever crack the code and have some major happening I'm not sure if I'll tell the world or not lol. I would say 9 times outta 10 I dont even use heat in the Hofmann. Regardless of what the published data and everyone says, I have real world experience that has shown no increase in yields by using heat and trying several different heat profiles, including pushing to 80 as fast as possible. It seems to me that with chemistry our individual mileage can vary greatly, so, grain of salt, dude.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Tsjanga** on **January 09, 2013, 09:25:58 PM**

Does somebody knows a guy who had success with TCCA route and lowering the solvents amount?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Tsjanga** on **January 15, 2013, 06:35:03 PM**

Just stumbled on an article about the formation of 2-chloro-4,5-methylenedioxyamphetamine when excess hypochlorite is used.
Somebody more info about this substance and is it possible to get it out of our desired product.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **fractal** on **January 16, 2013, 12:28:47 AM**

Having a large excess of sodium hydroxide present prevents this as free chlorine exists in equilibrium with sodium hypochlorite.

$Cl_2 + 2NaOH$? $NaCl + NaClO + H_2O$

You could separate by distillation though, I'd think the boiling points should be pretty different. I'd check with TLC to make sure before wasting time trying to get rid of something that's not there.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **fractal** on **January 16, 2013, 12:30:18 AM**

The ? mark was an equilibrium sign. Doesn't work for some reason.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **atara** on **January 16, 2013, 12:36:11 AM**

Quote

> is it possible to get it out of our desired product.

If you suspect your stuff is contaminated, reflux with NaOH should convert the 2-chloro to the 2-phenol, and the phenolate is then insoluble in most nonpolar solvents.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Tsjanga** on **January 16, 2013, 10:41:38 AM**

Thanks, was looking back at dingbow his posts and I think the 5.6 gr of TCCA with 5 gr amide is making a bit of Chloro...
Will work on the reflux NaOH thingie ;-)

Title: **Re: Hofmann Rearrangement Yields**
Post by: **uchiacon** on **January 20, 2013, 07:40:47 AM**

This is infinitely strange. I'm trying to isolate the problem in my synthesis but in doing so I'm seemingly creating more.

Hydroxylamine sulfate: nitromethane/sulfuric acid, refluxed for 3 hours, crashed out with IPA.

Aldoxime: hydroxylamine sulfate freebased with NaOH and then small amounts of sodium carbonate, yielding a reddish/orange liquor. IPA alcohol is mixed into this at high stir, then the hot mix is placed into the fridge to cool. Three layers form, the clear/slightly yellow IPA layer, the red layer (of what I assume is hydroxylamine, can be slush like if I cool it too long) and a white bottom layer of salts. Alcohol and red layer decanted off leaving the salt layer behind. This salt layer is discarded. Helional mixed in to form a yellow/orange waxy aldoxime, different from the crystalline slightly green aldoxime I was getting before when I wasn't freebasing hydroxylamine before the reaction.

Pump has crapped out so I can't currently run a reflux for the beckmann, but when I do I will try toluene and a longer run time (this is what I did the first run with success) and then xylene.

I have tried to recrystallize the "amide" I had left over from a while back that was yielding the black ppt when run in the hofmann: 50g dissolved in 300ml of boiling water and run through a vacuum filter. 300ml of methanol added, causing the solution to turn snow white the second the methanol mixed in. I hope it hasn't reacted with the methanol? It's a super, super fine suspension of some very white material. I really hope its clean amide and not some reactant byproduct.

If there's any glaring errors in my description, please point them out. Thanks

---

Title: **Re: Hofmann Rearrangement Yields**
Post by: **java** on **January 20, 2013, 06:08:28 PM**

.........get some of the precipitated material, and a MP, it should be around 130+/- i have seen white amide .....it will be pure......java

---

Title: **Re: Hofmann Rearrangement Yields**
Post by: **uchiacon** on **January 25, 2013, 10:03:00 AM**

Hey Guys,

I want to see if theres a way to skip the relatively messy aldehyde to amide steps we see in the commonly accepted method.
One of the two papers details a reaction that converts piperonal to methylenedioxybenzamide using copper sulfate 5hydrate as catalyst with hydroxylamine HCl and sodium acetate or carbonate to basify the hydroxylamine. Reaction is solventless, run at 110C for 2hrs.

With sodium acetate, it boasts a 98% yield of amide, with sodium carbonate coming in at 88%. Certainly seems very promising, especially since they use a methylenedioxy benzene compound for the tests.

I'll be looking into this. Does anyone see any glaringly obvious problems with this? I know it's going to be hard to purify my hydroxylamine, but that should be the only issue. I have the sulfate salt, so I'm thinking I'll basify and then titrate with HCl following by precipitation with alcohol and cooling(hopefully the sulfate ions won't cause an issue in the reaction?). Will use methanol so any residual will evaporate off during the reaction.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **uchiacon** on **January 27, 2013, 01:03:13 PM**

I've run this twice now. However, I tend to suffer from excitement so I have unfortunately muddled up the first two runs. I used sodium carbonate instead of sodium acetate.

My hydroxylammonium sulfate is undoubtedly contaminated with sulfuric acid and formic acid which is a real f*cking pain because I can't get rid of those contaminants easily with the solubility of the material itself in polar liquids. Maybe basifying before the reaction, then titrating with HCl or sulfuric acid until I get the salt and crash that out with IPA?

The first run I forgot to scale down the amount of copper sulfate catalyst I was using. I scaled down the reaction to 1/10 but I forgot to apply this to the catalyst molar amounts. 5mol % was the amount required, and from what I've read, thats simply :

x/3.1 = 0.05 , x being 0.155 mol of copper sulfate, then multiplied by 0.1.
19.2g aldehyde : 3.87g copper sulfate, etc etc. Please correct me if I'm wrong there...

First run was just a total messup. It was so strange, putting 38.7g copper sulfate into a beaker with about 40g of other reactants. How did they stir this, I thought. Yielded 8g of brown ppt from 19.2g aldehyde, but it didnt work in a hofmann. :(

Second run was better, but again I made an error by adding about 17g of sodium carbonate monohydrate(pool supply soda ash) instead of 13.6g. Reaction is going fine, transition from foaming blue with white particulate (carbonate) to green to terracotta brown.

1hr in, half way through, 100C, i started smelling ammonia. I didn't know that sodium carbonate could facilitate the hydrolysis of amides??

Dumped in toluene, filtered. Left with a terracotta filter cake with white grains in it, which when washed with water pretty much disappeared. Kept the toluene, discarded the water. Will evaporate off the toluene, see if any amide was in that. Its got a dark red/brown colour to it. Similar to the colour I was getting in my beckmann rearrangement with the xylene. I hope the perfumer's helional hasnt gone off in a few months..

This reaction is a bit of prick, but it would be so awesome if I could get it to work, even at 50% yield.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Tsjanga** on **January 30, 2013, 03:30:25 PM**

Quote from: uchiacon on January 25, 2013, 10:03:00 AM

> Hey Guys,
>
> I want to see if theres a way to skip the relatively messy aldehyde to amide steps we see in the commonly accepted method.
> One of the two papers details a reaction that converts piperonal to methylenedioxybenzamide using copper sulfate 5hydrate as catalyst with hydroxylamine HCl and sodium acetate or carbonate to basify the hydroxylamine. Reaction is solventless, run at 110C for 2hrs.
>
> With sodium acetate, it boasts a 98% yield of amide, with sodium carbonate coming in at 88%. Certainly seems very promising, especially since they use a methylenedioxy benzene compound for the tests.

Will have a look into this when I have some free time!
Great work!

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Tsjanga** on **February 03, 2013, 04:06:34 PM**

Quote from: Tsjanga on January 30, 2013, 03:30:25 PM

> Quote from: uchiacon on January 25, 2013, 10:03:00 AM
>
> > Hey Guys,
> >
> > I want to see if theres a way to skip the relatively messy aldehyde to amide steps we see in the commonly accepted method.
> > One of the two papers details a reaction that converts piperonal to methylenedioxybenzamide using copper sulfate 5hydrate as catalyst with hydroxylamine HCl and sodium acetate or carbonate to basify the hydroxylamine. Reaction is solventless, run at 110C for 2hrs.
> >
> > With sodium acetate, it boasts a 98% yield of amide, with sodium carbonate coming in at 88%. Certainly seems very promising, especially since they use a methylenedioxy benzene compound for the tests.
>
> Will have a look into this when I have some free time!
> Great work!

Have tried it, just getting some goo.
Have to get some work on it to tweak it.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **b6baddawg** on **February 07, 2013, 08:25:23 PM**

---

theres a 'one pot' to the amide using zinc nitrate hexahydrate. i dont have the paper but its worth reading that if it can be found if someones wanting to tweak the copper sulfate.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Tsjanga** on **March 04, 2013, 01:49:24 PM**

Quote from: b6baddawg on February 07, 2013, 08:25:23 PM

> theres a 'one pot' to the amide using zinc nitrate hexahydrate. i dont have the paper but its worth reading that if it can be found if someones wanting to tweak the copper sulfate.

Can you give us a hint?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Assyl Fartrate** on **March 04, 2013, 02:13:41 PM**

Quote from: b6baddawg on February 07, 2013, 08:25:23 PM

> theres a 'one pot' to the amide using zinc nitrate hexahydrate. i dont have the paper but its worth reading that if it can be found if someones wanting to tweak the copper sulfate.

Do you remember any of the specific examples used in the paper? As in, was the conversion of piperonal, helional, or anything similar performed?

Any recollection of what journal it's in and/or what time period?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **newbiechem** on **March 05, 2013, 04:04:26 AM**

---

i DOT NOT KNOW IF THIS IS CLOSE TO WHAT YA LOOKING FOR!!!!!

http://ntur.lib.ntu.edu.tw/bitstream/246246/171046/1/105.pdf

hope it is, and if its not, sorry! i tryed hehehe

peace

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Assyl Fartrate** on **March 05, 2013, 04:42:34 AM**

It's a different publication - no zinc nitrate hexahydrate - but that looks useful, nonetheless. Given the examples, it seems likely it would be viable with helional, and would provide good yields, too.

This was a good find, thanks for sharing. Given the possibility of nitrile synthesis as well, it could be synthetically useful for the clandestine chemist far beyond this topic alone.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **akcom** on **March 06, 2013, 03:00:07 AM**

There are a number of one pot reactions, they all seem to do the trick

---

Title: **Re: Hofmann Rearrangement Yields**

Post by: **dingbow** on **March 11, 2013, 04:39:41 AM**

TCCA run:
5g amide
equimolar TCCA (note I rinse my TCCA before use to get rid of some additives in this commercial product, which apparently can cause some hydrolysis to DCCA)
400ml H2o
5g NaOH

Using a lot of ice, 1L of h2o is cooled to approx 5c. 400ml is separated, NaOH added, then placed in RB. The remaining ice water is used in an ice bath, with the ice replenished as required (ice bath never went over 8c). TCCA is added and stirred vigorously until it is completely dissolved. Amide is added in one go, stirred until almost completely reacted/dissolved. The solution is now fairly clear. The ice bath is replaced with boiling water from a kettle and the hotplate is set to high, bringing the temp up to 75c as quickly as possible and holding it. Once the reaction reaches 70c, it was maintained for 20 minutes. Extracted with non polar whilst still hot. Yielded 3g impure amine.HCl, ~69% molar yield.

Reaction ran VERY clean, only a tiny amount of undissolved solids were seen and it was a dark golden colour. No A/B was required before gassing, though the HCl will need to be recrystalised for sure. End to end time taken including non polar extraction: 2.5hrs.

Im sure I would have gotten a bit more HCl if I had re-gassed the non polar again, as it was completely saturated on the first run, but didnt have the time to do it. The 18c reaction temperature I previously mentioned doesnt seem to give consistent results, as it failed on one run.

The above parameters have been repeated and gave consistent outcomes on two runs.

EDIT: equimolar amounts of TCCA is a bit confusing, its actually equimolar divide by 3. If using DCCA it would be equimolar divide by 2.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **newbiechem** on **March 12, 2013, 03:30:36 PM**

---

done EXACTLY as ding....
yiels of 10% on 10gr amide.....

ding you said 5gr naoh..... dont you mean 5% naoh solution?
will give that a shot

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dingbow** on **March 17, 2013, 12:52:19 PM**

Nope, 5g NaOH/400ml H2O
~0.3M

Extract varies from golden amber to red. No tar. Is your amide clean? Clean TCCA?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **b6baddawg** on **April 06, 2013, 04:35:17 PM**

---

assyl, tsjanga apoligies for the late reply. I cannot get access to the paper. its title is Tetrahedron Letters 51 (2010) 2724–2726. "Cost efficient synthesis of amides from oximes with indium or zinc catalysts".

In the paper theres a section with a modification,   15mol% zinc nitrate, 2 mol hydroxylamine, 2 mol sodium bicarbonate, 1L toluene, 1mol aldehyde. reflux 16 hours, then cool and filter to get good yields of the amide in 1 shot (80% is common).

It may -or not- be better to reduce the zinc load to 12% it could be even less. i dont recall for sure whether it was this specific reaction what benefited. id sub toluene for xylene too.

I tried toluene in the oxime>amide procedure using zinc nitrate and got orange goo. With xylene i got the amide.
Also using the general procedure in the oxime>amide using the catalyst load suggested by the paper the amide was a sandy colour. reducing the catalyst load a few % helped and white amide was obtained but it may have extended reaction time by an hour or so.

My results take with a pinch of salt, theyre from memory not notes and id hate to mislead anyone. The procedure and mods was suggested by someone else who preferred the one step aldehyde>amide.
I personally preferred the two step and went back to it for i could get 105% to the oxime mp @54c and 70-75% in the beckman to the amide, mp @115-118c without any bother or effort. I figured by the time i was consistantly maxing yields id never make up the amount lost from exploring and fine tuning the parameters. But thats just me, not the brightest spark.
Hopefully the reply was worth the wait, sorry about dangling a carrot on a stick.

EDITED to add a few replies to other questions.
The helionnal kept air free cool in the dark lasted a few years until used. Once opened i heard after several months the MP of the formed oxime was depressed slightly to usual, fresh heli as starting material.
The oxime and amide kept well over a year in the freezer until used without noticeable detioration
.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Tsjanga** on **April 07, 2013, 02:00:34 AM**

Quote from: b6baddawg on April 06, 2013, 04:35:17 PM

> assyl, tsjanga apoligies for the late reply. I cannot get access to the paper. its title is Tetrahedron Letters 51 (2010) 2724–2726. "Cost efficient synthesis of amides from oximes with indium or zinc catalysts".
>
> In the paper theres a section with a modification,   15mol% zinc nitrate, 2 mol hydroxylamine, 2 mol sodium bicarbonate, 1L toluene, 1mol aldehyde. reflux 16 hours, then cool and filter to get good yields of the amide in 1 shot (80% is common).
>
> It may -or not- be better to reduce the zinc load to 12% it could be even less. i dont recall for sure whether it was this specific reaction what benefited. id sub toluene for xylene too.
>
> I tried toluene in the oxime>amide procedure using zinc nitrate and got orange goo. With xylene i got the amide.
> Also using the general procedure in the oxime>amide using the catalyst load suggested by the paper the amide was a sandy colour. reducing the catalyst load a few % helped and white amide was obtained but it may have extended reaction time by an hour or so.
>
> My results take with a pinch of salt, theyre from memory not notes and id hate to mislead anyone. The procedure and mods was suggested by someone else who preferred the one step aldehyde>amide.
> I personally preferred the two step and went back to it for i could get 105% to the oxime mp @54c and 70-75%

> in the beckman to the amide, mp @115-118c without any bother or effort. I figured by the time i was consistantly maxing yields id never make up the amount lost from exploring and fine tuning the parameters. But thats just me, not the brightest spark.
> Hopefully the reply was worth the wait, sorry about dangling a carrot on a stick.
>
> EDITED to add a few replies to other questions.
> The helionnal kept air free cool in the dark lasted a few years until used. Once opened i heard after several months the MP of the formed oxime was depressed slightly to usual, fresh heli as starting material.
> The oxime and amide kept well over a year in the freezer until used without noticeable detioration
> .

Honey for you my friend! Very very nice!

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Sneak** on **April 07, 2013, 01:24:09 PM**

:)

Title: **Re: Hofmann Rearrangement Yields**
Post by: **syn** on **April 29, 2013, 05:20:04 AM**

Just wanted to update from my other post. I performed the hofmann rearrangement using 8% walmart brand bleach. A solution of 120g NaOH, 2L of dH_2O, and 1.2L of 8% NaClO were cooled to 2-3°C and 100g of amide was added. This was kept in an ice bath and shaken every so often for 48hrs. The reaction was then placed in hot water bath. The color went from greenish to orange to a brown/red. There appears to be a lot of unreacted amide on the bottom. I'll post yields if I get any but this appears to look like others reactions that didn't go so well. May just be something added to this particular brand of bleach that's not listed on the MSDS. If this doesn't pan out I'll be trying again with the 6% clorox. Will update.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **syn** on **May 02, 2013, 03:41:18 AM**

Extracted with xylene yesterday. All extractions were pooled and wash with dilute NaOH/dH2O. The basic solution was drained off and small amounts of HCl added. A massive amount of pinkish crystals formed. Looks like it worked out just fine=)

Title: **Re: Hofmann Rearrangement Yields**
Post by: **syn** on **May 05, 2013, 01:44:23 AM**

The pink crystals were dried and I gave them an acetone anhydrous wash. They completely dissolved. Not sure what could have went wrong here :-[

Title: **Re: Hofmann Rearrangement Yields**
Post by: **uchiacon** on **May 05, 2013, 02:01:56 AM**

This reaction can be a real bastard. I cracked it for the second time a few months ago but I've gone off MDA since and I don't believe selling it would be a good idea so not much has happened since.

Do the TCCA hoffman. Its far better.

Hmm what else... oh yeah, when making the aldoxime, basify the hydroxylammonium salt first and then extract with ethanol. (free base hydroxylamine was way more soluble in ethanol or methanol? but poorly soluble in isopropyl? Maybe the other way round. But this part is crucial and I believe it is beneficial.) Basify hydroxyl, extract it into a alcohol and leave salts behind, then use that to make the aldoxime by just mixing with the right amount He. You'll know which one is better because it will form a nice pink liquor without any layers. And he oxime is yellow wax iirc. Try ethanol and isopropyl and see which one dissolves more hydroxyl.

The amide must be needle like crystals. I didnt realize this and kept getting a brown powder that I thought was amide but only yielded black ppt on hoffman reaction. Purification of the amide... well some say its worth trying to get a whitish one but w/e its a bit of a bastard and 1-2 purifications in xylene or water work fine. I prefer water because xylene is oily and smelly.

The beckmann should be pushed as hard as possible. Chuck it in the flask, chuck in some xylene (tolly works too but not as well.) chuck in the catalyst and chuck on the condenser then chuck it on the hotplate stirrer and hopefully u remembered to chuck in the stir bar then chuck it up on high and chuck some sossies on the barbi m8

This drug is highly overrated dam I wish I had some methylpheniidate

---

Title: **Re: Hofmann Rearrangement Yields**
Post by: **uchiacon** on **May 05, 2013, 02:03:10 AM**

Quote from: syn on May 02, 2013, 03:41:18 AM

> Extracted with xylene yesterday. All extractions were pooled and wash with dilute NaOH/dH2O. The basic solution was drained off and small amounts of HCl added. A massive amount of pinkish crystals formed. Looks like it worked out just fine=)

lol probably your he oxime or hydroxyl amine

TCCA hoffman, bleach is only for the big boys

Title: **Re: Hofmann Rearrangement Yields**
Post by: **syn** on **May 05, 2013, 08:49:30 PM**

The amide I got was a brown powder, it looked like others photos I've seen after cleaning it. Considering a noticeable reaction occurred during the beckmann I'm thinking that the hofmann didn't occur. I know bleach works fine as others have reported they got good results. I will be doing this again using 6% name brand bleach as others have described and post results.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **uchiacon** on **May 07, 2013, 12:25:46 AM**

Quote from: syn on May 05, 2013, 08:49:30 PM

> The amide I got was a brown powder, it looked like others photos I've seen after cleaning it. Considering a noticeable reaction occurred during the beckmann I'm thinking that the hofmann didn't occur. I know bleach works fine as others have reported they got good results. I will be doing this again using 6% name brand bleach as others have described and post results.

Did it form needle like crystals upon recrystallization? They need to be needle like, not like a brown opaque powder. Purify it until you get needle like crystals or throw it out and get back to the drawing board.

needle crystals, not powder

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Tsjanga** on **June 29, 2013, 09:34:16 AM**

Anyone had tried FACILE ONE-POT CONVERSION OF ALDEHYDES INTO AMIDES?

As an illustrative example, our favorite aldehyde here (2.0 mmol) was added to a solution of hydroxylamine hydrochloride (3.8mmol) in DMSO (4mL), and the resulting reaction solution was stirred and heated for 30min in a sand bath maintained at 100C. Upon removal of the sand bath, but while still hot, aqueous sodium hydroxide (1mL of 5.68M, 5.68mmol) was slowly added to the reaction mixture over a 1-min period with stirring, followed by the slow and careful addition of 30% hydrogen peroxide (2.5 mL) over a 5-min period. After stirring for 1 min, the reac- tion mixture was extracted with ether (4x20mL), and the combined ether layers were washed with water (4x20mL) and dried (MgSO4).

Would make it much faster to work! Then we should be ready within 1 day when the tcca route is used.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **carl** on **June 29, 2013, 12:22:04 PM**

Dont use Et2O for extraction, use DCM instead, Et2O to wash your final product clean then.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Tsjanga** on **June 29, 2013, 01:18:36 PM**

Quote from: carl_nnabis on June 29, 2013, 12:22:04 PM

> Dont use Et2O for extraction, use DCM instead, Et2O to wash your final product clean then.

Allright, would this be a good way to achieve the amide?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **uchiacon** on **July 06, 2013, 05:43:38 AM**

Quote from: Tsjanga on June 29, 2013, 09:34:16 AM

> Anyone had tried FACILE ONE-POT CONVERSION OF ALDEHYDES INTO AMIDES?
>
> As an illustrative example, our favorite aldehyde here (2.0 mmol) was added to a solution of hydroxylamine hydrochloride (3.8mmol) in DMSO (4mL), and the resulting reaction solution was stirred and heated for 30min in a sand bath maintained at 100C. Upon removal of the sand bath, but while still hot, aqueous sodium hydroxide (1mL of 5.68M, 5.68mmol) was slowly added to the reaction mixture over a 1-min period with stirring, followed by the slow and careful addition of 30% hydrogen peroxide (2.5 mL) over a 5-min period. After stirring for 1 min, the reac- tion mixture was extracted with ether (4x20mL), and the combined ether layers were washed with water (4x20mL) and dried (MgSO4).
>
> Would make it much faster to work! Then we should be ready within 1 day when the tcca route is used.

I examined a method using coppersulfate in pretty dry conditions to go straight from aldehyde to amide. I may give this route a go that you suggest. I didnt flesh out the copper sulfate route properly though, although all it really did was make the oxime then reformat that to an amide in a one step.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Tsathoggua** on **July 07, 2013, 07:05:21 AM**

If it hasn't been said before, people should bee careful with hydroxylamine base. Its explosive. Nasty accidents have occured during heating and distillation of the substance, including some pretty ugly industrial fuckups.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **java** on **July 08, 2013, 12:41:45 AM**

... the thread is about Hofmann Rearrangement, make your inquiry in the proper thread....

Title: **Re: Hofmann Rearrangement Yields**
Post by: **java** on **July 08, 2013, 04:24:27 PM**

Reference Information

Practical Hofmann Rearrangement
Sang-sup Jew, Hyeung Geun Park
Arch. Pharm. Res.
1992, 15,4,pgs. 333-335

Abstract
Hofmann rearrangement of a series of primary aliphatic and aromatic carboxamides with HGO-NBS R'OH-DMF gives corresponding carbamates in excellent yields.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **java** on **July 08, 2013, 04:32:53 PM**

Reference Information

Approaches to ?-amino acids via rearrangement to electron-deficient nitrogen:Beckmann and Hofmann rearrangements of appropriate carboxyl-protected substrates
Sosale Chandrasekhar and V. Mohana Rao
Beilstein J. Org. Chem.
2012, 8, 1393–1399

Title: **Re: Hofmann Rearrangement Yields**
Post by: **b6baddawg** on **July 14, 2013, 06:56:53 PM**

Tried TccA as thus
20g TCCA (1 tablet 90% avalilable chlorine)
250g Naoh in 2500ml water
55g amide

The naoh was added to the water mixed n allowed to cool to 12-15c
The crushed TCCA was added in a few portions swirled occasionaly until dissolved.
The mixture was allowed to stand another hour in a waterbath while it 'cleared' somewhat
The amide was added in portions, 4-5 swirling until each portion almost completely dissolved.
A small amount remained undissolved.
The reaction was left stood and swirled occasionly in the waterbath over the next 2hours heated.
Left to cool somewhat.
extracted with 400ml xylene. the extracts filtered x2
HCL (aq) 3%ish added until ph7
the bottom layer tapped off and evaporated. crystals dcm washed.
Result 32.7g.

further notes. I broke my only thermometer so had no reliable temps to include after the initial reading.
I extracted too fast, maybe a bit more in there.
On adding the HCL (aq) to the xylene I should have give it more time. I just checked and could have got several mls more.
The resulting crystal is active at <0.1g I tried it at 0.1g. Onset was realising im having the best shit on toilet of my life lol
The amide used is over 4 years old kept in freezer. Must be stable stuff.
Never saw any 'oil' at any point.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Piglet** on **August 12, 2013, 10:23:49 PM**

Hypothetical question RE: Hoffman rearrangement yield Increase-

1)-could PTC ethyl-tri-octyl-ammonium possibly increase yield?
-the weak last position ethyl group is scavenged by the chloride/chlorine electronegativity?
My reference - hxxps://www.erowid.org/archive/rhodium/chemistry/isomerizafrole.html
[Phase Transfer Catalyzed Isomerization] section

2) Would running TCCA in ethanol advance or hinder this?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **CHEMICALCOWBOY36** on **August 15, 2013, 05:34:39 AM**

Quote from: Piglet on August 12, 2013, 10:23:49 PM

> Hypothetical question RE: Hoffman rearrangement yield Increase-
>
> 1)-could PTC ethyl-tri-octyl-ammonium possibly increase yield?
> -the weak last position ethyl group is scavenged by the chloride/chlorine electronegativity?
> My reference - hxxps://www.erowid.org/archive/rhodium/chemistry/isomerizafrole.html
> [Phase Transfer Catalyzed Isomerization] section
>
> 2) Would running TCCA in ethanol advance or hinder this?

First off are you the same piglet from DF?

Second yes from what I read on the Hoffman run in alcohol
Mainly methanol is what's used but it forms the methyl carbamate in 90%+ yields in most cases but then you have to preform a basic Hydrolysis to the achieve the sweet amine!!

Check out organic reactions vol 3

Title: **Re: Hofmann Rearrangement Yields**
Post by: **java** on **August 15, 2013, 11:39:12 AM**

Reference Information

Organic Reactions Vol 3
(Hofmann Rearrangement)

Title: **Re: Hofmann Rearrangement Yields**
Post by: **atara** on **August 15, 2013, 06:07:04 PM**

Quote from: java on July 08, 2013, 04:24:27 PM

> Reference Information
>
> **Practical Hofmann Rearrangement**
> Sang-sup Jew, Hyeung Geun Park
> Arch. Pharm. Res.
> 1992, 15,4,pgs. 333-335
>
> **Abstract**
> Hofmann rearrangement of a series of primary aliphatic and aromatic carboxamides with HGO-NBS R'OH-DMF gives corresponding carbamates in excellent yields.

In the literature it is common for the Hofmann rearrangement to be performed using succinimide, as NBS or NCS similar to this link. Has anyone tried making succinimide? Succinate is cheap and OTC , and the hassle of making succinimide could be worth it for the yield increase you might see, considering how precious the precursor is.

IIRC it's just succinate + ammonia, dried by heating under nitrogen.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **meme** on **August 15, 2013, 07:24:44 PM**

For that matter, bromine water might be better than bleach.

NaBr + H_2SO_4 + H_2O_2 ---+ then NaOH

Title: **Re: Hofmann Rearrangement Yields**
Post by: **eindreizig** on **August 19, 2013, 09:51:26 AM**

Just go buy NBS. It's stupid cheap and readily available.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **atara** on **August 28, 2013, 09:26:45 PM**

Quote from: eindreizig on August 19, 2013, 09:51:26 AM

> Just go buy NBS. It's stupid cheap and readily available.

Excellent advice for those who can, of course :p

Title: **Re: Hofmann Rearrangement Yields**
Post by: **carl** on **September 02, 2013, 11:08:09 PM**

Quote from: atara on August 15, 2013, 06:07:04 PM

> In the literature it is common for the Hofmann rearrangement to be performed using succinimide, as NBS or NCS similar to this link. Has anyone tried making succinimide? Succinate is cheap and OTC , and the hassle of making succinimide could be worth it for the yield increase you might see, considering how precious the precursor is.
>
> IIRC it's just succinate + ammonia, dried by heating under u.

According to the attached document N-halosaccharines work as halogenating agent and they are very similiar , maybe they could be used here too?

Quote

> Selective Monobromination of 1,3-Diones with N-Bromosaccharin/Mg(ClO4)2
> System in Solution and under Solvent-Free Conditions
>
> N-Bromosaccharin/Mg(ClO4)2 is an effective and regioselective system for ?-monobromination of 1,3-dicarbonyl compounds. A wide variety of ?-keto esters and 1,3-diketones in reaction with this system afforded a regioselectively ?-monobrominated products.

And they are this simple prepared:

Quote

> A Green Preparation of N-Chloro- and N-Bromosaccharin
>
> ABSTRACT
> The reaction of the sodium salt of saccharin, potassium chloride or bromide and oxone in water at room temperature for 24h produced pure N-chloro- and N-bromosaccharin in 58% and64% yield, respectively

---

Title: **Re: Hofmann Rearrangement Yields**
Post by: **pbinteger** on **September 22, 2013, 04:42:51 AM**

I just ran this series -- got back 45% dry, recrystallized hcl salt from 610g of very pure / dry amide. It should bee possible to optimize it even more.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dingbow** on **September 25, 2013, 12:18:07 AM**

Quote from: syn on May 05, 2013, 01:44:23 AM

> The pink crystals were dried and I gave them an acetone anhydrous wash. They completely dissolved. Not sure what could have went wrong here :-[

Assuming that your acetone was definitely dry, then the crystals you had were amide, not amine, which is highly soluble in acetone. Further indication to this is the fact that the amine does not appear as crystals, but a powder when turned into the HCl.

Your Hofmann failed, use TCCA.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **poisoninthestain** on **November 22, 2013, 02:51:27 AM**

I've found that after several trials TCCA has better yields and runs much cleaner with MUCH less tar formation than various sodium hypochlorite solutions (usually 6-12% w/w hypochlorite)....

...slow addition of hypochlorite via an addition funnel while cold, bisulfite quench, and/or slow addition of N-chloroamide solution to preheated NaOH solution seems to boost yield a bit...

...see United States patent US7205440 for details....

Title: **Re: Hofmann Rearrangement Yields**
Post by: **uchiacon** on **December 04, 2013, 11:54:10 PM**

When we go to heat up the TCCA hoffman, 2L of fluid can take a while to get up to 70/80C. Could a microwave facilitate this faster?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **b6baddawg** on **January 01, 2014, 09:53:46 PM**

Quote from: uchiacon on December 04, 2013, 11:54:10 PM

> When we go to heat up the TCCA hoffman, 2L of fluid can take a while to get up to 70/80C. Could a microwave facilitate this faster?

use a wallpaper stripper steamer and steam the sucker directly to @70c-75c it takes about um 10 perhaps 15mins to reach temp. that's with 4 litres or so liquid a time. no other external heat source is used in combination.
don't forget to remove the pipe when you turn the steamer off (suckback).

does it reduce yields this way? I have no idea, final yields appear in low 60 to high 60%s n some amide is recovered and reused next time. the recovered amide isn't considered in the final yield calculation.

Various quality-colour amides was used this way. Final product colour xtalised, recrushed n after wash almost always whitey white white

---

Title: **Re: Hofmann Rearrangement Yields**
Post by: **poisoninthestain** on **January 06, 2014, 01:43:58 AM**

The worst TCCA yield I've seen so far...typically one can reach up to 50% w/w yield if slow addition of TCCA occurs along with with a post rxn bisulfite quench...

3.8g 99% technical grade TCCA
10g amide
800ml H2O

NaOH 10g NaOH +10g NaOH at 45C not to exceed 70-80C

Powdered TCCA is added to prechilled 5-10C hydroxide solution and stirred until dissolution which is complete in approx. 20min. Amide is added while maintaining temperature parameters previously mentioned. Now, the amide-water suspension is mag. stirred for roughly 30min or until the amide appears to be dissolved into an almost turbid opaque solution that will seem almost clear at times with or without a yellow tinge. When this color change occurs the flask is heated to 70C and held there for 20-30min. At approx. 45C an additional eq. of NaOH may be added to hasten the steady rise in temp and also promote isocyanate hydrolysis.

Usually at 60-70C the reearrangement will occur resulting in a color change from yellow-orange-red varying greatly upon your reaction parameters. In this trial, as well as several others, the reaction was removed from external heating up noting the flask color begin to change from a yellow into an orange. While the flask is still warm the solution is extracted once with 100ml xylene and twice at rt. The extracts are then pooled together and filtered on a buchner. The negligable amounts of filtrand were discarded. The filtrate is left to sit in a sep. funnel for 72h at which point a dark precip will crash out which is vac. filtered and discarded.

The now less dark extract (hopefully) is washed twice with an equal part brine and dried over anhydrous K_2CO_3. The extract is typically honey yellow at this point which is then gassed, chilled, washed with dry acetone, and dried to yield a white brittle solid. Yield 20% w/w..as the hydrochloride. + to both Marquis and Mandelin reagents.

...i have yet to attempt hydrolysis of the urethane through MeOH and TCCA followed by addition to preheated NaOH and then steam distillation of the amine azeotrope as this seems the best way to go...

Title: **Re: Hofmann Rearrangement Yields**
Post by: **fractal** on **January 06, 2014, 02:59:59 AM**

A higher yield wasn't noted with TCCA through experimentation although the few times it was tried the product needed less clean up. The average yield achieved using sodium hypochlorite solution (6% store bought) is in the 75% (w/w) range consistently, usually on the higher end.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Richard Swagner** on **January 06, 2014, 08:26:19 PM**

Interesting, what were the conditions employed?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dingbow** on **January 10, 2014, 01:03:39 PM**

I attempted a 20g amide TCCA batch and it failed, again (10% yield, lots of tar etc). Being limited to a 1L RB, I was using the same water volume as the 10g batch that I have previously run very successfully.
If you have your process streamlined you can run a 10g batch in 2 hours, do 4 of them in a day and your looking at a decent yield. I usually get around 60-70% on 10g batches.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **uchiacon** on **January 15, 2014, 12:36:36 PM**

So amide is recycled by cooling the post reaction mix down and waiting for it to ppt out?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **thinkgeek** on **January 18, 2014, 03:28:47 AM**

---

dingbow is that the total reaction percentage?
or just the yield of the hofmann?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Tsjanga** on **January 18, 2014, 05:27:44 PM**

Quote from: thinkgeek on January 18, 2014, 03:28:47 AM

> dingbow is that the total reaction percentage?
> or just the yield of the hofmann?

It will be the yield of the hofmann.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **thinkgeek** on **January 18, 2014, 10:55:03 PM**

---

thanks tsjanga.. for someone catching up its hard to distinguish whats what.. i read this thread in 2 days .. trying to fit the pieces together..

Title: **Re: Hofmann Rearrangement Yields**
Post by: **fractal** on **January 19, 2014, 07:18:45 AM**

Quote from: uchiacon on January 15, 2014, 12:36:36 PM

> So amide is recycled by cooling the post reaction mix down and waiting for it to ppt out?

There should be no unreacted amide provided your numbers are correct.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **uchiacon** on **January 23, 2014, 02:02:16 AM**

Oh I was under the impression that it did not consume all the amide.

Using parameters:

-5g amide
-1.9g TCCA
-250ml 10% NaOH solution

This will allow as much of the amide to react as possible while not leaving amide to be recycled?

Title: **Re: Hofmann Rearrangement Yields**

Post by: **Tsjanga** on **January 23, 2014, 10:19:25 AM**

Quote from: thinkgeek on January 18, 2014, 10:55:03 PM

> thanks tsjanga.. for someone catching up its hard to distinguish whats what.. i read this thread in 2 days .. trying to fit the pieces together..

If it was easy the honey was already banned ;-)

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Solitarius** on **January 23, 2014, 03:01:56 PM**

Quote from: Tsjanga on January 23, 2014, 10:19:25 AM

> If it was easy the honey was already banned ;-)

I wonder why it has not been banned yet, 4years since it has been let loose.

Java has said that controlled deliveries are a possibility because of its publicity but i have not heard of any so far.

LE too busy with the big boys?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Tsjanga** on **January 23, 2014, 05:37:23 PM**

Quote from: Solitarius on January 23, 2014, 03:01:56 PM

> Quote from: Tsjanga on January 23, 2014, 10:19:25 AM
>
> > If it was easy the honey was already banned ;-)
>
> I wonder why it has not been banned yet, 4years since it has been let loose.
>
> Java has said that controlled deliveries are a possibility because of its publicity but i have not heard of any so far.
>
> LE too busy with the big boys?

It isn't used as big as other honey's I think that is the main thing.

But please let's get back on topic!

Title: **Re: Hofmann Rearrangement Yields**
Post by: **uchiacon** on **March 03, 2014, 07:07:37 AM**

Ok bruce

More notes on the oximation

Hydroxylamine HCl or equivalent sulfate salt dissolved in water. (60g to ~150ml) basified with carbonate until... basic, or fizzing stops. Excess is ok.

Solution then hit with 150ml of isopropanol (ethanol and methanol sovlate the ions too well, ethanol can be used but must be cooled a lot) and cooled in the freezer. Biphasic mix results. Take alcohol, discard aqueous and salt. Add aldehyde. Mix for a few hours. Then hit with excess of water. If you get a yellow opaque mix with a amber layer at the bottom(instead of solid oxime), add saturated salt solution and give a good mix. This will cause solidification.

Allow oxime to harden overnight then decant off water.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Solitarius** on **March 03, 2014, 11:22:15 AM**

Quote from: uchiacon on March 03, 2014, 07:07:37 AM

> Ok bruce
>
> More notes on the oximation
>
> Hydroxylamine HCl or equivalent sulfate salt dissolved in water. (60g to ~150ml) basified with carbonate until... basic, or fizzing stops. Excess is ok.
>
> Solution then hit with 150ml of isopropanol (ethanol and methanol sovlate the ions too well, ethanol can be used but must be cooled a lot) and cooled in the freezer. Biphasic mix results. Take alcohol, discard aqueous and salt. Add aldehyde. Mix for a few hours. Then hit with excess of water. If you get a yellow opaque mix with a amber layer at the bottom(instead of solid oxime), add saturated salt solution and give a good mix. This will cause solidification.
>
> Allow oxime to harden overnight then decant off water.

Were you getting a waxy yellow solid or the sugary crystals?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **uchiacon** on **March 03, 2014, 12:12:37 PM**

Waxy solid. It is initially the colour of pancake mix, tan colour, then I think it gets a surface oxidation when it dries.

The sugary crystals, I dont know if that is any good.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Solitarius** on **March 04, 2014, 03:11:53 AM**

I hate the pancake mix, its so sticky.

I have some aldoxime left out for a few weeks now.

It is a crumbly yellow solid that is not sticky anymore. No idea how it performs in the beckmann however, i may give it a try soon.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **AnyNameWillDo** on **June 19, 2014, 11:46:52 PM**

I was just wondering if anyone can offer any insight into what may have been messed up for someone to get these results on the oximation. 69.4 g hydroxylamine hcl was added to 127g h20, 96g aldehyde to 120g EtOH and 29.7g NaOH in 90g h20.

The basic solution was added to the hydroxylamine solution and stirred until clear. The aldehyde/EtOH was added dropwise with stirring and then diluted with about 50g more EtOH then stirred for 12 hours. When it was hit with ice cold water to precipitate the aldoxime, some very slightly greenish runny but thick oil came to the bottom. This didn't sound quite right already but they thought that maybe once they washed it up and tried to crystallize it it would end up looking better.

What they have now is still a slimy, sticky oil. They said the smell it leaves on their fingers or flasks is much closer to the smell of the final product but it still doesn't seem right at all. Finally, it was washed in a makeshift buchner funnel. At this point, it was supposed to be solidifying, but it's actually just very slowly dripping through the filter paper along with the water and getting mixed back together.

Is there something these guys did wrong? I mean, obviously, but does anyone have any idea what it might have been?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Sneak** on **June 28, 2014, 10:49:31 AM**

It is said further back in the thread that this green oil/slime is usable in the next stages. I think! Read back and check.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **superlative** on **June 28, 2014, 12:38:09 PM**

---

but its obviously not perfect.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **uchiacon** on **July 01, 2014, 12:20:22 PM**

If you are having problems change your procedure slightly

Honestly, if hydroxyl HCl isnt working for you, then basify it first, then extract with methanol or ethanol. Use that instead of the salt.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **fractal** on **July 01, 2014, 10:58:04 PM**

Quote from: superlative on June 27, 2014, 01:12:12 PM

> In my dreams i end up with this contact glue all the time. Trying different solvents, temps, amount of hydroxylamine/NaOh ratio to aldehyde, vinagre or salt washes doesnt change a thing. The colour sometimes changes from caramel to pancakemix. but never solidifies or crystallizes in any way. am i seeing the forest for all the trees?

Do you wash the formed oxime multiple times with dH2O until the washes are clear and allow the now whitish oxime to sit for a few days? It's much easier to work with the oxime as a liquid anyway. I would be happy never having it crystallize.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **AnyNameWillDo** on **July 14, 2014, 06:36:09 PM**

The second time I ran it I got the same sticky, gooey stuff. After pouring into a Pyrex pan and letting it dry for about 2 hours, I came back to very nice white chunky powder that snapped and crackled violently when placed on foil and a lighter held underneath it. Just as I'd hoped to see.

The next and most recent time I ran it, I ended up with a nice big white powder cake in the bottom of the flask without any work up or needing time in the freezer, etc. Still hit it with very cold water to precipitate all of it out but without really even changing my procedure I ended up with the nice solid immediately instead of messing with that sticky stuff.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dingbow** on **September 19, 2014, 06:49:04 AM**

Quote from: Sneak on June 28, 2014, 10:49:31 AM

> It is said further back in the thread that this green oil/slime is usable in the next stages. I think! Read back and check.

I have NEVER worked with solid oxime. I always have two layers from the oxime reaction, extract the oxime/etoh layer and proceed as usual. I have elsewhere that is due to the solubility of etoh being slightly different to meoh. With Meoh its apparently a lot easier to get solid oxime, I never tried though so dont know for sure.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **superlative** on **September 19, 2014, 04:51:47 PM**

So what is making the butter scotch colour? i never got white oxime. This bothers me alot more then solidifying.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **WazOne** on **September 19, 2014, 09:03:36 PM**

Add your hydroxylamine to your aldehyde ethanol. Start mixing adding carbonate solution SLOWLY. Should start fizzing keep the addition at a constant flow still going slow. Ph should be neutralized and you will have white snot like oxime flying around the flask and the solution will clear. Keep stirring untill the reaction is complete. Let the oxime settle decant liquid add 3 times volume of cold water and stir decant repeat... decant and let dry.
Its possible to get a range of colours and sometimes never the perfect reaction. In this case let it stir alot longer then let settle decant and add 4times volume of ice cold water and stir the oxime should solidify then.

Cheers

Title: **Re: Hofmann Rearrangement Yields**
Post by: **WazOne** on **September 19, 2014, 10:47:57 PM**

Hydroxylamine hcl solution ^^^^

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Username404** on **October 12, 2014, 08:40:21 PM**

Came across this reference where a 20kg hoffman rearrangement was performed.
It proceeded in 130kg of organic solvents along with 10kg of water, until here no problem. What I don't understand is what acts as a base. Iodosobenzene is the oxidant,

but as I see the only thing that can act as a base are the acetate groups, and I find them not basic enough to deprotonate the haloamide. Maybe the reaction goes through different intermediates than the hypochlorite hoffman. Any input is welcome.

Also see http://www.orgsyn.org/demo.aspx?prep=cv8p0132 for a similar example.

Edit: the idea is that if this reaction could be performed with TCCA in ethyl acetate saturated with water one would not need to worry about methyl carbamates and the reaction mixture could be gassed after drying the 5% water contained, therefore using a much smaller reaction volume (10X) than the original hypochlorite hoffman.

Edit2: Ok so looking more papers about this reaction it seems that the haloamide proton is taken by the acetate covalently bound to the hypervalent iodine species, eventhough it is not basic enough to take this proton in the usual hoffman. So it seems that a procedure without a strong base is only possible with this iodine species.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Deez** on **October 14, 2014, 08:07:27 AM**

I am reading a lot of posts where people are using a small amount of NaOH when using NaOCl..

The original:

To a solution of 10 grams of NaOH in 200ml of water in a 500ml flask is added 20 grams of amide and 250 grams of (3.45%) NaOCl. The mixture is then heated to 80C with stirring. At about 50-60 C the mixture can become white as the carbonate forms. At 70-80C an oil seperates. (this is crude product). The solution was cooled and extracted with Xylene. The solution was filtered and the filtrate washed with xylene and the xylene portions each added together. About 100ml of Muriatic acid was added to the xylene, shaken and separated. The aqueous solution was extracted with xylene and the xylene separated. The amine was then liberated from the aqueous portion with Sodium Hydroxide and worked up in the usual way to give product.

The improvements:

Now here is a little something I read on the wall of a stall in a proctologists office. My Dam Ass was really hurting so I needed it looked at.

Firstly, an excess of 2.5g additionally (12.5g) NaOH should be used initially, but not after cooled this solution is cooled to -4c along with the 250g of NaOCl which is stirred for an hour in an ice bath before the introduction of the highly recrystalized 20g of amide. The amide is added in 500mg portions over the course of 20 minutes. This is allowed to stir for 18 hours in ice cold conditions with maximum stirring.

Allow this to come to room temperature after 18 hours and then begin slowly adding heat over 45 minutes till 70c is reached. Once reached, this temp is held for 1 hour and then the heat is killed and the reaction is allowed to stir till the contents have retuned to room temp.

Instead of using Xylene, use DCM to extract the freebase. This will allow for easier stripping, preventing degradation of the amine due to the low heat used. Once the DCM has been extracted set up for high vacuum distillation using a short path distillation rig. Gather your freebase in an anhydrous non-polar solvent of your choosing if you intend on gassing with HCl. If titrating with HCl, anhydrous solvents are obviously not necessary.

IF you followed these steps and recrystalized each intermediate, you should be staring at 12g of after cleanup of the amine, 60% from amide. I have read this can be improved upon and get 80% but that may be on another stall wall at a different ass doctors office.

A high boiling buffer oil may also be of help when it comes time to distill the freebase under vacuum. IDK, never tried this because it's illegal and stuff. Never saw yields under 50% from wt/amide to amine. Never read of the heat going a degree above 70c.

For what it's worth.. hope this helps. All praise to the original dog lover who got this ball rolling and those that improved upon it and defaced the proctologists bathroom. From what I read, bioassay is the bees knees. :o::) ;D

AND GUYS, just because you can you use the aldoxime "as is" when it doesn't solidify doesn't mean you should. Follow WazOne's advice. Flood the reaction numerous times with H2O, letting each flood stir for a while before decanting. Then repeat, repeat, repeat. Add to a vacuum desiccator or just place the beaker in a dry area and voila, within 48 hours you should have solid aldoxime that is ready for RECRYSTALIZATION.

The use of ethanol/methanol is not causing the aldoxime to not solidify. You are doing water washes anywhere which will collect any residual alcohol in the flask/beaker.

Crap in, Crap out. You want higher yields in the end? Then spend the day or two it takes to clean up the intermediates. You will be amazed at how pretty the crystals are when you take your time to perform a long crystallization in xylene. I know not everyone has patience, but take pride in your work.

One final note: Actually two: The color of the aldoxime can be from degraded aldehyde used. As knows, this stuff degrades over time. You can be anal and vacuum the aldehyde or you can just recrystalize the solid aldoxime.

Secondly and lastly: Recrystalize hydroxylamine.hcl after its production at least once. There is residual HCl on the crystal shards and this will negatively affect the production of the aldoxamine causing you to compensate for the amount of base needed. Just recrystalize the stuff in Hot DH2O, let cool, crash out, collect, repeat.

If this isn't enough info to get your balls rollin' then consider crocheting as a hobby :p

---

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Sneak** on **October 14, 2014, 10:38:18 AM**

Thanks alot :)

Title: **Re: Hofmann Rearrangement Yields**
Post by: **morehepaplease** on **October 24, 2014, 04:23:36 AM**

Well I finally got around to steam distilling some crude base and it sucked a bit. :-\ I've been curious about this for a while and I feel like people pushed the subject around with no actual trials. Here's mine.

Ran a diluted hofmann with bleach and a bisulfite quench (which deez forgot to mention if we're talking about improvements). Everything ran well and the bulk of it sent on to hydrolysis (glowing success btw) whilst I stared at some, in my opinion, pretty good lookin' crude ::) ;D.

For my steam still set-up it was... a 2L erlenmyer with a one hole stopper on a hotplate, with a copper pipe going to another stopper, that's in a 3-way adapter with a glass tube going to the middle of a 1L rbf. The 1L has a hotplate stirrer with a hot ass water bath :). First steam distillation, I was satisfied with the rig.

Well I collected 600mL H2O and it doesn't look like there is a DROP of clean base in it. Tomorrow I'll extract the 600ml with some xylene and pass dry HCl gas through it.

Bottom line for me, damn. I was hoping for something dreamy... or easy to clean up... or higher yielding... maybe, just a good time. I've sucked the water off the other half and will put it under a hard vacuum tomorrow morning, at least find out what's in that half.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **CHEMICALCOWBOY36** on **October 24, 2014, 05:26:21 AM**

Quote from: morehepaplease on October 24, 2014, 04:23:36 AM

> Well I finally got around to steam distilling some crude base and it sucked a bit. :-\ I've been curious about this for a while and I feel like people pushed the subject around with no actual trials. Here's mine.
>
> Ran a diluted hofmann with bleach and a bisulfite quench (which deez forgot to mention if we're talking about improvements). Everything ran well and the bulk of it sent on to hydrolysis (glowing success btw) whilst I stared at some, in my opinion, pretty good lookin' crude ::) ;D.
>
> For my steam still set-up it was... a 2L erlenmyer with a one hole stopper on a hotplate, with a copper pipe going to another stopper, that's in a 3-way adapter with a glass tube going to the middle of a 1L rbf. The 1L has a hotplate stirrer with a hot ass water bath :). First steam distillation, I was satisfied with the rig.
>
> Well I collected 600mL H2O and it doesn't look like there is a DROP of clean base in it. Tomorrow I'll extract the 600ml with some xylene and pass dry HCl gas through it.
>
> Bottom line for me, damn. I was hoping for something dreamy... or easy to clean up... or higher yielding... maybe, just a good time. I've sucked the water off the other half and will put it under a hard vacuum tomorrow morning, at least find out what's in that half.

when should the bisulfite be added? Before or after heating? And is it sodium bisulfite or bisulfate?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Solitarius** on **October 24, 2014, 07:25:44 AM**

Quote from: TCdboy28 on October 24, 2014, 05:26:21 AM

> when should the bisulfite be added? Before or after heating? And is it sodium bisulfite or bisulfate?

Sodium bisulfite

Before heating, i'll try the bisulfite quench and see if my yield improves.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **superlative** on **October 24, 2014, 02:53:36 PM**

---

i dont see the point of adding bisulfite if you are steam distilling.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **fractal** on **October 24, 2014, 10:21:39 PM**

This really seams pointless to even do. Just grab a vigruex column for $20 and a used vacuum for a couple hundred bucks and do a fractional distillation. Beyond it being just as easy, you'll end up with something of higher purity.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Deez** on **October 27, 2014, 12:13:18 AM**

Quote from: morehepaplease on October 24, 2014, 04:23:36 AM

> Well I finally got around to steam distilling some crude base and it sucked a bit. :-\ I've been curious about this for a while and I feel like people pushed the subject around with no actual trials. Here's mine.
>
> Ran a diluted hofmann with bleach and a bisulfite quench (which deez forgot to mention if we're talking about improvements). Everything ran well and the bulk of it sent on to hydrolysis (glowing success btw) whilst I stared at some, in my opinion, pretty good lookin' crude ::) ;D.
>
> For my steam still set-up it was... a 2L erlenmyer with a one hole stopper on a hotplate, with a copper pipe going to another stopper, that's in a 3-way adapter with a glass tube going to the middle of a 1L rbf. The 1L has a hotplate stirrer with a hot ass water bath :). First steam distillation, I was satisfied with the rig.
>
> Well I collected 600mL H2O and it doesn't look like there is a DROP of clean base in it. Tomorrow I'll extract the 600ml with some xylene and pass dry HCl gas through it.
>
> Bottom line for me, damn. I was hoping for something dreamy... or easy to clean up... or higher yielding... maybe, just a good time. I've sucked the water off the other half and will put it under a hard vacuum tomorrow morning, at least find out what's in that half.

I think you may have misunderstood me. I would advise extracting the freebase, with DCM 3-4x, distill at atmospheric pressure then vacuum distill the freebase under high vacuum with a proper short path rig, (or larger based on your batch size).

Title: **Re: Hofmann Rearrangement Yields**
Post by: **morehepaplease** on **October 27, 2014, 07:02:31 AM**

Yeeeeeesh guys, I've got a goddamn vacuum :). Sucks the hell out of stuff. I just wanted to try something new.

I gassed the xylene extraction from the steam distillation. .2g ::). Seems to me like steam (low pressure at least) distillation isn't a viable option for reaction clean-up.

I don't use a column for the vac distillation. Seems fine :-X. Always gets recrystallized regardless.

On the bisulfite, Solitarius nailed it. Brewers bisulfite works too and it's cheap.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **CHEMICALCOWBOY36** on **October 29, 2014, 11:48:07 PM**

Quote from: superlative on October 24, 2014, 02:53:36 PM

> i dont see the point of adding bisulfite if you are steam distilling.

http://www.freepatentsonline.com/7205440.html

hey bees check this out it seem doing the sodium bisulfite quench is well worth it
but how do you remove it for the work up to get hcl salt?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Vesp** on **October 30, 2014, 12:34:26 AM**

Why have it be the HCl salt? Why not solvent extraction after the fact?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **morehepaplease** on **October 30, 2014, 07:07:22 PM**

After bisulfite addition let it settle. Then decant the top layer, hydrolyze it, and extract with your solvent of choice. Vacuum distill the bottom thick oily layer. The distilled base should be water white.

I think people prefer the HCl salt because the dose is lower so it *seems* stronger. I wish the standard conjugate acid didn't fume >:(. ...was conjugate acid the right term...? ...stoned up a bit :D.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **CHEMICALCOWBOY36** on **October 30, 2014, 10:52:43 PM**

Quote from: morehepaplease on October 30, 2014, 07:07:22 PM

> After bisulfite addition let it settle. Then decant the top layer, hydrolyze it, and extract with your solvent of choice. Vacuum distill the bottom thick oily layer. The distilled base should be water white.
>
> I think people prefer the HCl salt because the dose is lower so it *seems* stronger. I wish the standard conjugate acid didn't fume >:(. ...was conjugate acid the right term...? ...stoned up a bit :D.

ok what do you mean by hydrolyze tho?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **morehepaplease** on **October 31, 2014, 04:06:37 AM**

It's in your patent there bud ::) ;). Good read by the way.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **frank** on **November 26, 2014, 01:52:47 PM**

Has anyone thought about using Calcium Hypochlorite instead of NaOCl? The volume of the reaction could be reduced, making it more practical.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **fractal** on **November 26, 2014, 05:51:38 PM**

Yep, it works as far as running the reaction but not for reducing the solvent volume required. Reducing solvent volumes reduces yields do to the poor solubility of the amide. Keep in mind that the chloroamide is formed below 10°C too, this reduces the solubility of calcium hypochlorite by a decent amount. Cosolvent will help but further reduces the amount of calcium hypochlorite that is able to be dissolved. Not exactly limited to 6% stock solution to begin with as sodium hypochlorite is fairly easy to make in a higher concentration, just not able to store it that way.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **fractal** on **December 04, 2014, 09:50:52 PM**

Stop looking for a spoon feeding, if you don't understand what you're doing and can't follow directions you obviously get what you paid for.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **CHEMICALCOWBOY36** on **December 05, 2014, 08:52:02 PM**

Screw the bleach use TCCA for the win 8)

Title: **Re: Hofmann Rearrangement Yields**
Post by: **CHEMICALCOWBOY36** on **December 06, 2014, 08:30:52 PM**

Ok I need some help fellow bees after the 2 hours you let the cloramide form do you have to heat right away or can it sit for a while I was in the middle of an synthesis when something came up and I couldn't heat to 75°c and hold for an 30mins will this fuck up the hoffman if I dont heat right away ? Also can I heat later or have I royal fucked it up! If so this bee is going to cry yes yes I know you shouldn't rush but this bees roommate came home early so he had to shut down for a bit cuz said roommate doesnt know about this bees projects

Any help would greatly bee appreciated

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Username404** on **December 06, 2014, 08:33:14 PM**

If kept cool (<10) I'd expect it to last for atleast one day without too much drop in yields.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Username404** on **December 11, 2014, 05:17:20 PM**

So I recently acquired some TCCA. I checked the documentation and it contains 86% TCCA, 4% boric acid, and the other 10% is who knows what (no copper sulfate). Someone employed something similar with good results? Any idea if the boric acid is to interfere with the reaction other than requiring more base?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **morehepaplease** on **December 13, 2014, 08:20:39 PM**

---

plainview, I'm not a mod, but post shit about the beckmann in the beckmann thread ::). This thread is already extensive enough. Comments about oximations and beckmanns should go in the appropriate threads.

TCdboy, I let my chloroamide stir for 24-48 hours at 2-10*C before I quench and hydrolyze.

Lastly, I don't think 6% bleach exists as I've never seent it ;D. Only 8.25%. You know the label, it says, "Now 33% more concentrated!" And it's said that for years :P.

Never messed with TCCA, never had a problem with solvent volumes.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Impossible** on **February 05, 2015, 07:30:49 PM**

Did you wash the NP prior to titration? Or else have you steam distilled the freebase or performed any other purification techniques?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Scarecrow** on **February 18, 2015, 10:31:08 AM**

Ive run this a few times with dingbows workup with low yielding results. Im going to attempt this this week using the attached patent. Procedure will look something like this:

>.5 mol amide added to 500 ml water while stirring
>Cooled to 0 degrees.
>1mol equiv of 45% NaOH solution slowly added keeping temp low
>Chlorine source (they use hypochlorite in patent, in this case TCCA) metered in slowly (.33mol equiv, or did you say using a slight excess of amide for purity is better so perhaps .3mol)
>Leave for 4-6 hours stirring as cold as possible (patent gets best yields at around 4-6h, other members have told me 24-48h)
>.1mol excess (so .6mol) of 10% sodium bisulfite solution added between 5-10degrees while stirring (leave for 1 hour, this isnt in patent but from what ive been told is what should be done)
>500ml of water and 89g (61ml) of 45% NaOH solution is then prepared seperately and heated to boiling
>The sodium salt of the n-chloramide that has been bisulfite quenched (the solution that has been stirring cold) is then metered into the boiling NaOH solution slowly (90% yields are apparently obtained if this is metered in over a 6 hour period, perhaps poruing chloramide solution into addition funnel and letting it slowly drip?)
>During the metering in of the chloramide to the boiling hydroxide, water AND the resulting product (so steam distillation) are distilled off directly and continuously into a distillation reciever. The product solidifies as the lower phase (red amine base?), the water is seperated off and amine collected. (may end up just solvent extracting this)

Note - in two of the experiments the distillation was not done concurrently to the chloramide addition, and was distilled after the complete addition of the chloramide. The highest yielding of these two experiements was when the post chloramide addition reaction mixture was allowed to sit for twelve hours then distilled.

using steam distillation should also afford a more pure product than solvent extraction I believe.

Product obtained as a pink liquid (so yes amine base)

This can be more easily worked up too, or put in a distillation setup and vacuum distilled for maximum purity.

Do you think this is too complicated? Everyone seems to be dumping amide tcca and Naoh in, letting it cool and stir for 24 hours then heating it to 80 degrees for 30 minutes and claiming 70% yields lol

---

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Scarecrow** on **February 27, 2015, 03:06:49 AM**

Okay sorry for the double post but Ive run this and had excellent results I thought id share.

>37.7g (.182 mol) of bone dry recrystalized amide dissolved in 200ml of 10% NaOH solution (Ive found ethanol best recrystalization solvent to remove yellow tinge)
>14g of TCCA added (.06 mol, .33 mol equiv)
>Allowed to stir in salted ice bath for 8 hours, colour at end of reaction was foamy light yellow/white
>In a seperate flask, 400ml of 10% NaOH heated to 90* degrees with strong stirring.
>N-Chloramide solution added in small portions over 8 hour period
>After last addition of n-chloramide soluition, allowed to sit for 30* min, resulted in dark orange solution.
>Extracted with DCM, dried over MgSO4 and filtered to give a dark red DCM extract.
>DCM gassed with dry HCl, filtered, repeated 3 times.
>Crystals washed with acetone, left to dry in food dehydrator
>Yeild 28g of amine 67% molar yeild

Pure amide is very important for this reaction, recrystalization in ethanol works well.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **CHEMICALCOWBOY36** on **February 27, 2015, 08:20:01 AM**

Why did you deviate from the procedure ? If you see in the first boxes in it they say they have gotten a great 81% yield from 1 hour of stirring and then another 2.5 hours for adding to the base !
What do you think are the main sticking points to the yield?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Scarecrow** on **February 27, 2015, 09:40:58 AM**

I didnt deviate from the procedure.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Lipbalm** on **February 27, 2015, 05:34:57 PM**

%80 yeilds doing the Hoffman? I call bullshit. I call bullshit on anyone claiming they are getting over %50. The %40 area is pretty much max.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Scarecrow** on **February 28, 2015, 12:05:17 AM**

Try using TCCA and adding your chloramide solution to hot NaOH solution portionwise, I was stuck at around %40 for a while too

---

Title: **Re: Hofmann Rearrangement Yields**

Post by: **thewire** on **February 28, 2015, 07:05:44 PM**

> Process for generating an explosion
> US 3465674 A
>
> **N-halo amides react explosively with alkyl sulfoxides and active hydrogen compounds such as certain hydroxy compounds and amines. Delayed explosive decompositions occurring after a predetermined time can be produced by selection of components and variation of their proportions.**
> **It has now been found that when a di lower alkyl sulfoxide or an active hydrogen compound such as any of certain alcohols and amines is intimately contacted with an N-halo amide or N-halo imide, the halogen being bromine or chlorine, the mixture remains substantially unchanged in appearance and temperature for a measurable time ranging from a second or two to several minutes, and in some cases, as long as several hours or even days, then it suddenly decomposes explosively with flame formation and generation of considerable gas and vapor. By choice of particular components and proportions of these, the interval between contact and explosion can be adjusted to a predetermined desired length.**

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Scarecrow** on **March 02, 2015, 01:38:08 AM**

> woa

Title: **Re: Hofmann Rearrangement Yields**
Post by: **mulemaster** on **March 04, 2015, 02:18:32 PM**

> Scarecrow, is it possible to do the tcca hoffman without a fumehood, say inside a flat, without worries about smell?
> Another question regarding recrystalisation from etoh, how much amid is soluble in boiling etoh? I have only recrystalised from boiling water, but it seems to need much to solvate a decent amount of amide.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **AnyNameWillDo** on **March 04, 2015, 05:25:34 PM**

> I was wondering the same thing about smell yesterday. I finally picked up some xylene for the Beckmann and god almighty damn, I forgot how strongly that smells compared to naphtha and such. You guys must live on fuckin farms or something, I'm a bit bummed/nervous now trying to assess how to proceed. Especially imagining it being performed in a large beaker without reflux, just allowing it to evaporate over the course of the 5 hours like someone here recommended.
>
> Anyway, I know this thread isn't about the Beckmann but that then made me wonder about the Hofmann smell as well, once I figure out a way to manage the Beckmann.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **luminouspath** on **March 04, 2015, 05:43:51 PM**

> Stick a plastic tube in your condenser for the Beckmann and vent outside. As for the Hofmann, there is virtually no odor. Faintly of chlorine when forming the chloroamide and

then of MDA base when you heat it.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **AnyNameWillDo** on **March 04, 2015, 07:07:19 PM**

Awesome yes, thank you for that! Definitely going to give that a try and hope for the best with the stank. Also, got super excited imagining the MDA smell upon heating of the Hofmann. I need to just do this already.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Lipbalm** on **March 04, 2015, 09:35:12 PM**

A beaker without reflux??? Did flasks and condensers go up in price like %50000 in the last few days or something???? We are not talking expensive technical hard to get lab equipment here.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **AnyNameWillDo** on **March 04, 2015, 10:30:46 PM**

No, I had asked previously about it because of the fact that I had heard some things about 2-neck flasks being somewhat sketch, depending on where it comes from, some may view it with a degree of skepticism. Especially if one had recently bought a decent amount of other lab related equipment. So I just asked about that and someone said they just did it in a large beaker without condenser. Only thing I don't have is a multi-neck flask, thus no way of monitoring temperature while refluxing so I had just asked. Obviously it would be money well spent, this was just a concern I had.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Lipbalm** on **March 04, 2015, 11:18:36 PM**

You don't need to monitor temp. It is not that sensitive. Just crank it up until you get a good boil. Halfway up the reflux condenser is a good temp.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **unlikely_username** on **March 05, 2015, 06:48:12 AM**

@Lipbalm
40% is not the maximum yield for this reaction. I've been working on this with Scarecrow for a while and his results are legitimate. I haven't tried his exact procedure, but I do know that thorough recrystallization of the amide, longer chloramide formation, and good dilution have given me yields in the range of 60-70% of purified, dry product. I didn't stir the chloramide as long as he did, and I didn't add mine to a hot base solution as opposed to just boiling it one-pot, but I used a more thoroughly purified amide from what I could tell. I think a combination of very pure amide and including elements of Scarecrow's procedure are good ideas.

@Anynamewilldo
I couldn't tell you anything about the beckmann, but the hof is pretty smell-free, nor does it appear to be extremely temp sensitive IMO.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Lipbalm** on **March 05, 2015, 10:15:41 AM**

---

^^^ I notice you didn't mention the tcca. Is it entirely needed for %60+ yeilds then?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **luminouspath** on **March 05, 2015, 10:39:39 AM**

Quote

> ^^^ I notice you didn't mention the tcca. Is it entirely needed for %60+ yeilds then?

I'm getting 70% with NaOCl. Forming chloroamide at 4c for 34 hours. Heating to 70c over 3 hours, maintain for 1 hour and workup.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **unlikely_username** on **March 05, 2015, 10:25:22 PM**

I prefer to use TCCA, as I've had my best results with it. But the patent that Scarecrow adapted for his procedure called for hypochlorite, which he substituted TCCA in for, and other members have reported good success with hypochlorite.

I find TCCA to be more forgiving than hypochlorite, similarly priced if not cheaper, and I don't need to worry about the actual concentration of any industrial grade solution

---

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Uppy** on **March 14, 2015, 05:49:18 AM**

Just want to make sure I have it right, the amide is converted to the n-chloramide via (solventless) TCCA hoffman, the reaction contents are then rearranged with the hot NaOH solution producing the crude amine (including cl-mda?) which would then be extracted with a np solvent and either titrated or gassed to yield the final .hc l?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **unlikely_username** on **March 14, 2015, 02:34:19 PM**

Chloramide formation takes place in highly basic water, it is not solventless. The product is then rearranged in hot NaOH, the chloramide solution can be heated or it can be added slowly to a preheated NaOH solution as suggested by scarecrow. As long as you had very pure amide and you did not add an excess of chlorinating agent 2-Cl-MDA will not be a significant product, the amide group is more reactive. Yes, after rearrangement work up however you feel like.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Uppy** on **March 15, 2015, 06:53:59 PM**

Going through and doing the molar calculations on several runs (mostly Dingbow's) , it seems that .33 mol equiv of TCCA is the average amount used for batches ranging from 5g to 37.7g of amide. A few though are stated to use equimolar, equimolar/2 and 1.2mol equiv. while providing significant yields, but given the excess, a lot of this would probably be 2-CL-MDA I assume...My point being, stick with the .33 molar equivalent?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **unlikely_username** on **March 15, 2015, 11:03:52 PM**

I always use 0.33 equiv. When people refer to using 1-1.2 equiv they are often referring to the quantity of availible chlorine atoms, 3 moles per mole TCCA. So, Yes.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Impossible** on **March 16, 2015, 11:55:11 PM**

Has there been any reports on this route using the unsubstituted aldehyde(2-phenyl-2-propanal? I suck at IUPAC). I've read through the main threads on the Beckmann/Hoffmann route on psychonaught, the collective, and here, and noticed that there is no information whatsoever on anything but the reaction using helional as the substrate.

I ask because from what I understand, a lot of reaction optimization done in the academic field comes from comparing how certain substrates influence the way the reaction progresses. It seems counter-intuitive to do absolutely all the research on the substituted substrate and essentially ignore any possible effects of the methylenedioxy group.

Unless the unsubstituted version is actually hydratropic aldehyde, that would make sense given alternative procedures for it.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Username404** on **March 17, 2015, 12:34:30 AM**

5445-77-2 is not commercially available.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **unlikely_username** on **March 17, 2015, 12:53:34 AM**

That aldehyde isn't particularly available, however the carboxylic acid appears to be somewhat more available, though not extremely so. Theres actually even a route from it to amphetamine on the rhodium archive already (it's kinda overcomplicated though, they're going for optical purity).
alpha-Methylhydrocinnamic acid
https://www.erowid.org/archive/rhodium/chemistry/alpha-methylhydrocinnamic.html

The methylenedioxy group likely results in somewhat lower yields as it's kinda touchy, but the functional group you're shooting for is pretty far removed from the ring, don't think you'll see aromaticity playing much of a role here.

Here's a synthesis of the aldehyde if you're interested, not exactly OTC though:
http://www.orgsyn.org/demo.aspx?prep=cv7p0361

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Username404** on **March 17, 2015, 07:26:55 PM**

Sorry for the off topic but in case people didn't read the original post, that remebered me of its corresponding cinnamaldehyde, which is commercially available, dirt cheap, and twodogs proposed that it could be converted to p2p in 1 step with nickel, bleach and heat. No one reported back tho.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Lipbalm** on **March 18, 2015, 01:05:02 AM**

Quote from: Username404 on March 17, 2015, 07:26:55 PM

> Sorry for the off topic but in case people didn't read the original post, that remebered me of its corresponding cinnamaldehyde, which is commercially available, dirt cheap, and twodogs proposed that it could be converted to p2p in 1 step with nickel, bleach and heat. No one reported back tho.

Twodogs is the tits. Why has no one tried this? One step cinamaldehyde to p2p would be the biggest game changer in the drug game ever. Is this really feasible? Does it work in theory?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **unlikely_username** on **March 18, 2015, 02:42:57 AM**

If we continue this conversation further (and I'm definitely open to it!), we should do so in a new thread I think. That being said, I want to share what information I've gathered so far before I forget it. Going to continue this offtopic-ness for one last post. ;D

I'm interested in a-methylcinnamic acid more than a-methylcinnamaldehyde. a-methylcinnamic acid is going to tolerate reductions a lot better than the aldehyde, and once the alkene's been dealt with the corresponding amide can be formed with urea, similarly to the benzamide synth from scimad:
http://www.sciencemadness.org/talk/viewthread.php?tid=4201&page=4
I don't believe this to be specific to benzyllic carboxyllic acids as a similar synthesis has been described for acetamide.
The amide would then undergo the hoffman as usual.

The a-methylcinnamic acid appears to be commercially available based on a quick check of alibaba (they use the name 2-methyl-3-phenylacrylic acid I think, CAS 1199-77-5) and for reasonable prices.

The only problem that I can really see with this is reducing the alkene. Cinnamic acid --> hydrocinnamic acid is well described in the literature, but I have yet to come across anything that doesn't use palladium catalysis. If their use can be tolerated Pd/C in tetralin is supposed to work in ~70% yield after 1-1.5 hrs (5 gram scale), and PdCl2 in aqueous hydroxide solution w/formic acid is supposed to give near quantitative yields (although this second one was in microscale...).
http://pubs.acs.org/doi/abs/10.1021/ed039p209
https://www.erowid.org/archive/rhodium/chemistry/cth.cinnamic.html

I don't see much of a reason why these reductions shouldn't work with the addition of a methyl group, but palladium catalysts are expensive and not exactly OTC. I'm going to poke around for better routes in my free time at some point.

This has the potential to be a very OTC synthesis if the palladium hydrogenation can be substituted out, and even if it can't the catalyst isn't *extremely* suspicious and it's reusable, meaning it wouldn't need to be purchased often.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Lipbalm** on **March 18, 2015, 04:25:57 AM**

You know what, I now remember that I actually tried that 8 years ago. I forget what exactly what I was doing but I was messing around with Cassia Oil and cinnameldahyde and I believe I was trying to get to p2p. I forget the details but i remember moving on to toluene oxidation after not having much success. should be noted though I was in my infancy of learning chemistry (then again I still am lol).

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Impossible** on **March 18, 2015, 06:21:32 AM**

---

a-methylcinnamic acid should be fairly easy to prepare with yeast biocatalysts.

Acetobacter species are luckily one of the easiest to capture, identify, and isolate from wild cultures. Hillbillies do it all the time for making home made vinegar.

Hell, saccharomyces cerevisiae is capable of producing styrene oxide from styrene, in case the Acetobacter enzyme isn't promiscuous enough.

Both of these fermentations would be a hell of a lot easier than the l-PAC synthesis too. Possibly achievable with only minimal brewing experience/research. I've played with Acetobacter(only partially characterized, not sure what specific species) a few times using unnatural substrates, with decent success rates. Although they were all aliphatic/closely related to the natural substrate.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Scarecrow** on **March 18, 2015, 07:47:59 AM**

---

alpha-methyl-cinnamic acid can be catalytically hydrogenated to alpha-methyl-hydrocinnamic acid and then amidated with boric acid catalyst to 2-methyl-3-phenylpropanamide which can be used in the TCCA Hoffman to give racemic amphetamine. This could then be monomethylated to give racemic methamphetamine and separated with d-tartaric acid.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **pervopelle** on **March 24, 2015, 10:43:41 AM**

I figured I'd share my experiences with this reaction so far.

To date my friend have only dabbled in household bleach and have gotten yields that at times has made me question him and if he's done something wrong.

He's reliably been getting 28-32g of amine HCL salt from 100g of amide, having something like 30-40% of the amide crash out upon cooling of the reaction. The amide is then recrystallised and reused. Which in pretty much means a 50% yield!

It would seem that this reaction gives better yeilds as it is scaled up. First time it was attempted by an aquaintance 20g of amide was used and roughly 2g of amine salt was yielded. A later attempt making sure the reaction was only heated for 30 minutes yeilded 4 g of amine hydrochloride.

After looking at this thread and a document purchased off of a darknet market (could post it here as a write up) it was decided to try doing a 100g batch and let it stir with ice until the ice had melted and the reaction reached room temperature prior to heating. Every time this has been attempted yields have exceeded 25g amine hydrochloride.

I don't have time for more sharing right now!

Title: **Re: Hofmann Rearrangement Yields**
Post by: **mulemaster** on **March 24, 2015, 11:36:08 AM**

---

hi,

what is a good work up of the post Hofmann, i have used the TCCA route as per scarecrow in half the scale.
My amide is really voluminous so i added a little more water to the NaOH solution. AFter addition of TCCA everything went into solution (did not happen with my commercial NaOCl solution). I let the solution stir maybe 6 Hours in an icebath by the end of the time most of the ice have been molten. First the solution was a light yellow, but as i came home it has turned to a bright brown.
After this i added excess NaOH solution and heated all to 75-80 °C for half an hour and let it cool down again. Some tiny droplets of oil were floating on top of a brown solution. I extracted twice with DCM and then extracted the DCM twice with acidic (HCl) Water. Since the water was still very dark i tried to clean it with anoither DCM wash, but it did not help much. #
Now i distiled off the Water and Excess HCL and am left with a brown liquid that solidifies on cooling to a transparent hard cristaline solid! Taste is extremly bitter and i have hard time getting the hard solid out of my beaker. The crude solids are 9,1g.

Can i now clean it with aceton or something else? I dont want to waste any product that might be in there by some residual water. But i heated it to 140°C so i think all water must have boiled off and i am left with MDA 2CL-MDA and synthesis byproduct that survived the AB extraction.

All i want it clean the Product up so that it gets brighter....What is good solvent to recrystalise MDA*HCL from?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **unlikely_username** on **March 24, 2015, 11:28:15 PM**

@mulemaster
I answered your question in a different thread already, please try not to clutter up the board with duplicates of simple questions like this.
Not to be an asshole, but if you'd done any searching you'd have found that acetone is about as good a wash solvent as it gets.
So yes, cold acetone is going to work great.
No, unless you have a metric shitload of residual water in there you're not going to lose significant amounts of product. Besides, if you're worried about it boil off 2/3 of the gross acetone once you're done washing, stick it in the freezer and see what drops out. Sometimes you get a few tenths of a gram.
You could probably recrystallize from a minimal amount ethanol after, water probably works but it takes forever to dry.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Scarecrow** on **March 25, 2015, 03:48:11 AM**

In future I reccomend recrystalizing your amide in ethanol to remove any impurities.

Then after your DCM extracts vacuum distillation of MDA freebase to give a much more pure product. Anhydrous acetone will remove colour, and recrystalization will help. You could even try recrystalizing in xylene/toluene could be good.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **mulemaster** on **March 25, 2015, 07:38:07 AM**

I excuse myself for posting the same question in two threads. Scarecrow my Amide was allready very white, see picture in the Beckmann thread. Unfortunatly my air cadet vacuum pump is good for nothing else beside vacuum filtration. A reasonable vacuum pump is one of my next big investments in labware. Aceton wash is just not possible these crystals are so sticky, even if i try to powder it, with what ever god knows. I usually do aceton washes when i make amphetamine in the last step. But i asked more of a question like dissolve all the MDA*HCl in hot solvent X and crash it out with Y solvent or let it slowly cool down to get clean crystals.
Does anyone know the solubility of MDA*HCl in ethanol cold and boiling?
Fuck this next time i will be gassing for sure.

ps: now i got impatient waiting for my marquis reagent, i just droped a small amount maybe 80 mg, lets see where this gets me. :)

God damn this stuff is strong even in low doses, i havent been rolling like that for along time (im usually more into opiates)

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Lipbalm** on **March 26, 2015, 12:09:54 AM**

Quote from: mulemaster on March 25, 2015, 07:38:07 AM

> these crystals are so sticky

Food dehydrator man. Put in food dehydrator for a day or two then chop that shit up in a food processor (chopper). You will have incredibly light dry fine powder which you can clean however you like.

.... wear nitrile gloves when you mess with the final powder as any moisture (even that on your hands) will make it sticky again.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **poisoninthestain** on **March 27, 2015, 12:56:17 AM**

...both MDA and MDMA crystals regardless of polymorphs should not be sticky. Stickiness is usually the result of an excess of water present with acid resulting in polymerization(among other things). This is hardly a problem when one uses a gas generator and nearly impossible to fuck up if one fractionally distills under vacuum and then gasses. Garbage in, garbage out. Both MDA and MDMA hydrochorides will dry fast even without a vacuum dessicator(although I prefer one).

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Scarecrow** on **March 27, 2015, 03:13:24 PM**

Imo dump your sticky MDA in basic water then re-extract into DCM then extract into 2% HCl water and let evap and that should give you nice crystals. Or gas straight into your

DCM but that always gives me super fine crystals that need to be recrystalized. Still havent found the best recrystalization solvent for MDA yet I think even Xylene or Toluene could be good.

unlikely_username has a good suggestion, gassing HCl into 1L of IPA and keeping it aside.

Then you can say with your MDA, add it to basic water, extract into DCM, then let DCM evap then drop IPA onto freebase oil for yummy MDA xtals.

I dunno MDA doesnt seem to be that hot with people I know, people describe it almost as empathetic speed, doesnt floor you like MDMA does

---

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Kykeon** on **March 30, 2015, 08:10:11 PM**

I would like to share a very simple workup method that has worked well for me.

The post reaction mixture was extracted with toluene.
An excess of 3% HCl was added to the toluene extract and mixed well in a separatory funnel.
The aqueous phase was then separated and the water (as well as excess HCl) was evaporated with a little heat and a stream of air.
The dry residue was suspended in acetone and heated to boiling. With stirring, a very small amount of water were slowly dripped in until a homogenous solution were obtained.
The solution was then allowed to cool to room temperature and then placed in the freezer. This gave a precipitation that was filtered and washed thoroughly with cold acetone, which gave a fine colorless product.

The filtrate was evaporated and the resulting residue was recrystallized in the same way to give another crop of product.
(A third repeat gave only a very small amount of product, to save work one would save the filtrate after the second recrystallization and combine it with later runs)

Notes:

Over acidification does not seem to cause any problems in this reaction workup, I have acidified to pH~3 without any issues.

On the addition of water in the recrystallization, it is important that you do not add to much water, add it dropwise and let it stir for a couple of seconds between the additions until you get a homogenous solution.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **mulemaster** on **April 01, 2015, 06:28:14 AM**

---

i repeated the procedure of scarecrow with the exact same amide, except that i used a little less solvent during the chloramid formation. And rather that a slight yellow, occured, there where first spots of red in the solution and after some hours of stirring the whole solution was more red, then the orange brown i was used to ? I still added it to hot NaOH solution and let it stir a while, solution turned dark brown with brown whobbley pieces floating around. I still extracted it and god NOTHING.
I am pissed off because this was the rest of my amide and because it was my first that i

put so much work into it to get it as clean as it was. And last time, i easy got 9,1g crude MDA*HCL from 17g which seem spectecular.

One other point i modyfied the procedure by scarecrow in my first try it that way, that i used more solvent during cloramide formation at least two fold, because my amide was so voluminous. I think i added the TCCA more portionwise and a little bit more then required (0,4g) i also noticed a heavy chlorine smell in the first run, almost impossible to stay longer times in that room. The second time i smelled nothing at all?! ALso i did not ad the chloramide to hot NaOH solution. I rather dropped the solution into the chloramid and heated to 80*C for 1 hour. Then extracted, the DCM extract was also very brown in my first run, in my second it was almost same colour i put it in. I am quite sure the chloramide formation failed, indicative by the brown insolubles. I will use more solvent next time again, maybe a little excess of TCCA even if i risk 2-CL MDA formation.

I am now in the process of making new amide, i will try some more variations that i have stumbled upon.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Scarecrow** on **April 01, 2015, 07:25:03 AM**

If you 'dropped the solution into the chloramid and heated to 80*C', I can only assume you dropped NaOH into your chloramide solution. This will not work.

IT sounds like you were being sloppy with your technique. Weigh out the exact molar ratios of everything you need. Recrsytalzie your amide in ethanol.

Did you use 10% NaOH solution during your chloramide formation? You said you used double the amount of solvent, did you use double the amount of NaOH?

I reccomend writing out your modified procedure on paper to make sure it all makes sense before starting

---

Title: **Re: Hofmann earrangement Yields**
Post by: **mulemaster** on **April 05, 2015, 05:27:16 PM**

@Scarecrow: maybe my last post was a little confuse. now comes a long rant. :)

A busy bee made more Amide the last days and followed your procedure again with the exception that i added the TCCA first into the NaOH solution. Then maybe 30 minutes later the Amide (scale 2x). It dissolved in about maybe 2 hours to a transparent opaque solution. Probably Amide was not pure enough, slighly off white to yellow. Only made two recrystalisations.

Anyway, after another two hours my Opaque solution went to a reddish colour and then after a while, small white sediments started to form up, untill it became a shaving foam like consistency,my stirbar could not handle. Colour had still a tinge of red. This happend with my second hoffman too,which was a fail.

Is this a normal thing to happen? As i removed it from the ice bath it became more liquid again. I dropped this portionwise in 800ml 10% NaOH @ 90°C. Now its cooling down, looks much more like my first time, no whobbly/slimy particulates floating around like in second try. And i can see already oily drops floating on top of solution.

Will report yields later, unfortunatly i never gased, but i was unsatisfied with purity of wet

HCl method, so i will give it a try in Xylene.

Scarecrow, you have my fullest respect but your claim "If you 'dropped the solution into the chloramide and heated to 80*C', I can only assume you dropped NaOH into your chloramide solution.This will not work."

I have exactly done this for lazyness reasons and it yielded my one and only MDA i ever synthed.
My amide was perfectly white also. I also dont think 10% NaOH solution during chloramid formation is absolutly nessesary, because i dilluted it a little bit with water(still same molar amount inside). These were the two points i changed and i still got yield, not stellar on a molar basis but still ok for first try.

I think i have gathered a much better understanding of the reaction now, next time i will just wait untill amide has dissolved, add more NaOH and heat. One thing, i do not completly understand is the molar ratio of NaOH. Theoretical 1 mole per mole of amide and 1 mole per 1/3 mol TCCA. Also 1 mole for the deprotonation of the chloramide and 1 mol(?) for the decarboxylation of the carbamic acid. So why this much excess NaOH? 4 mole per mole of Amide should suffice, can someone explain.

Short update: gassing in DCM dried with CaCl2 failed somehow, must still have been too wet. Then i titrated the DCM to a PH of 2 and distilled of the water to be left with a grey cristaline powdery substance. MUCH cleaner then my first MDA that was still sticky and brown. Its also is very bitter as expected. Unfortunaty yields are poor with only 9,5g MDA*HCl from 76g Amide. Thats a shame.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Scarecrow** on **April 06, 2015, 04:15:29 AM**

> You are correct, 10% isnt absolutely neccesary anywhere between 5% and 10%, is acceptable. I also figure that the harsher conditions hydrolize the amide quicker, which is the whole reason why adding it slowly increases yeilds, so you can push equilibrium towards amide formation

>Yes it is normal for it to go foamy. If its stopping your stir bar add more water or NaOH solution to help dissolution/get a better stirrer

>If your having a problem with your amide dissolving, get your amide and grind/crush it to the finest powder you can before adding it to the reaction (do so portionwise), then if you are still dissatisfied add some more water and/or more NaOH solution.

Scarecrow, you have my fullest respect but your claim "If you 'dropped the solution into the chloramide and heated to 80*C', I can only assume you dropped NaOH into your chloramide solution.This will not work."

Sorry what I was trying to say was that if you slowly dripped naoh into chloramide solution over 8 hours then heated the whole thing to 80, it would be beside the point. Im thinking your saying you added your naoh portionwise over a small period of time then heated to 80* which yes does work. But this is different to slowly dropping chloramide into hot NaOH solution.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **unlikely_username** on **April 08, 2015, 02:22:45 AM**

I'd like to make a small note here since this has come up a couple times for me now.

For those of you who don't already know, isocyanuric acid is going to precipitate during the chloramide formation if you use TCCA (Tri-Chloro-isoCyanuric Acid), as it's almost insoluble in cold water.
It isn't a big deal, and it isn't your amide refusing to dissolve (although that also happens sometimes, rextalize and grind your amide people!).

If you want to minimize weird moments like this where you have no clue what's going on please read the papers that these procedures are based on so you can better understand why things are done the way they are done and what is and isn't supposed to happen.
For example, the paper discussing the formation of chloramides with TCCA mentions the precipitation of ICA as an indication that chloramide is being formed. If you're curious about what happens to the TCCA after the chlorine is removed and look up ICA you'd find that it has *very* low solubility in water.

@mulemaster
You'll be doing yourself a favor if you step the scale down to like 25g runs of amide until you get the hang of it. The larger the scale the harder it is to do things *just* right IMO (excluding microscale, smartass ::)). ~75g of amide was all I used in three runs, and the last one gave me more clean product than the first two combined and almost doubled.

And I don't know why you're trying to use NaOH in molar ratios? It's the concentration of the [OH-] ion that matters, and it isn't really consumed in the reaction (except maybe TCCA forms shortlived hypochlorite ions? dunno). You just want a pretty strongly basic solution.

I'm kinda against the idea of adding excess chlorinating agent. That's almost knowingly contaminating and/or destroying your product. High yields with stoichiometric quantities have been shown several times.

I also don't like the idea of gassing into DCM, it's too hydroscopic IMO. But the workup part of things really boils down to personal preference and personal experience. (IPA/HCl until slightly acidic, crash out with acetone and a freezer. Never had any problems and product cleans up to a shimmering clean white powder after acetone rinse. Just sayin... :P)

Title: **Re: Hofmann Rearrangement Yields**
Post by: **mulemaster** on **April 16, 2015, 02:25:01 PM**

Ok i have scaled the reaction down and had great success too great to be true, so i have my doubts about purity.

-500ml 10% NaOH @ 1°C in beaker with stirbar surrounded by an icebath
-addition of 20g dry, several times recrystalised and as fine powdered amide as possible, in 4-5 small portions
-30 minutes later addition of 7,4g finely powdered TCCA also in 3-4 portions (important first amide then TCCA, i think this is why i fucked up so often)

so not much happened at all, except the solution cleared up a little bit , no colour change or anything the like. Then maybe 4-5 hours later the white foam formed (the lower the NaOH solution to amide ratio the thicker this foam). I think this is ICA precipitating out of solution. Then stirred overnight, next morning temperature was 15°C and i heated it

surrounded by Al Foil to ~80°C for one hour.
Still no colour change but the solution cleared up again a little bit (mabye ICA is more soluble in hot water). After all cooled down i extracted with DCM twice and titrated the basic DCM phase untill ph 2 and boiled off the water to be left with a white crystaline powdery substance of 17g. This would translate to a yield of 81% molar which i dont think is possible with this synthesis, so some kind of impurity must have transfered through the basic A/B extraction. But on the other side i have allways done this extraction, sometimes yielding nothing from much larger batches. Any input what this impurity could be?

I will try to recreate this experiment today.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **unlikely_username** on **April 16, 2015, 05:36:46 PM**

17g+ is possible with 25g amide. I ended up with 17.1g the last time I did this, and I know other members have obtained higher yields than I have, I've only run the damn thing three or four times. ::)
That being said, we can still examine your reaction.

Interesting that you had no color change, but not necessarily damning. Color change is an unreliable indication of reaction activity, it's just a nice reference point when everything is working like it should be (not as common as I'd like).

I seem to recall adding the TCCA and then the amide, but the other way around should work just fine IMO. Who knows, maybe even better haha.

ICA is much more soluble in hot water than cold. I think it's also very weakly acidic. So some would definitely dissolve in a hot basic solution.

Off the top of my head I can think of a few possible contaminants, but I'd need a better idea of your workup before I could put anything out there:

Assuming you titrated the DCM with dilute HCl in water, about how much water was there when you were done?

About how much DCM was being titrated?

Did you wash the water layer with any kind of organic solvent to get rid of the dissolved DCM and associated impurities? Even a bit more DCM would've helped pull out any organic stuff that wasn't to comfortable in there in the first place. Backwashing extractions is somewhat important when your solvents exhibit a not inconsiderable degree of cosolubility.

Did you wash your product with cold acetone? Or even cold ether if you don't have acetone for some reason. This really cleans up the product.

And finally, I'm a big fan of of using the Marquis reagent test, it's not the most definitive test ever but it's helped me troubleshoot a couple reactions. It just takes some concentrate sulfuric acid and a bit of formaldehyde solution, you can find the exact amounts in the wikipedia entry, and it's pretty forgiving about minor concentration differences. Put a couple drops on a small amount of your product and see what color it turns. It should go pretty much instantly purple/black. When it's taken a while to turn that color, especially if I see other colors hang around first it's correlated to a weak batch of MDA. When it just turned orange (only happened once) it's been 2-Cl-MDA. I tested the amide once just for kicks and it turned pink.

Keep us updated.

Oh, side note here, I was somewhat mistaken about NaOH not being consumed in the reaction. The ICA is prone to forming the Disodium salt when presented with an excess of NaOH, so there's the possibility of your precipitate being disodium isocyanurate instead of just isocyanuric acid, in which case two moles of NaOH would have been consumed. See link below for a pretty detailed description of a lot of the associated chemistry:
http://www.sciencemadness.org/talk/files.php?pid=185660&aid=11296

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Burgi-Dunit-Again** on **April 19, 2015, 08:21:26 PM**

Just for the record, others have mentioned that use of some co-solvent like THF will help with solubility issues in this reaction, and though I have never tried, I would definitely imagine this to be true.

What I have tried is the use of DCCA (sodium dichloroisocyanurate) rather than TCCA. It is already a sodium salt, and so has excellent water solubility. It is also cheap and perhaps even more readily available than the trichloro compound. I think I got a kilo for 15 dollars. Its oxidizing ability is identical to the trichloro, just be sure to tailor the stoichiometry accordingly as there are of course only 2 electrophilic chlorines.

This modification works just as well, and while I have only run this reaction twice, I obtained satisfactory yields in each case, >60%.

Oh and also, I was always too lazy to make hydroxylamine and go through the trouble and harsh conditions of the Beckmann rearrangement. I just did Pinnick oxidation followed by activation with DIC and addition of superstoichiometric ammonium hydroxide. Works like a charm and much cleaner than the oxime -> beckmann process. No heating required 8)

Title: **Re: Hofmann Rearrangement Yields**
Post by: **iLENZi** on **April 19, 2015, 08:41:08 PM**

Quote from: Burgi-Dunit-Again on April 19, 2015, 08:21:26 PM

> Oh and also, I was always too lazy to make hydroxylamine and go through the trouble and harsh conditions of the Beckmann rearrangement. I just did Pinnick oxidation followed by activation with DIC and addition of superstoichiometric ammonium hydroxide. Works like a charm and much cleaner than the oxime -> beckmann process. No heating required 8)

Please, give the details for the Pinnick and activation. Scaleable for 1kg of the helional?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **mulemaster** on **April 21, 2015, 02:44:44 AM**

---

i am also very much interested in the Pinick oxidation, what reaction conditions did you employed and what yields did you get. If you have a reference you followed, i would be happy to read it too.
Are there other possible ways to the carboxylic acid? Because you could do a

halodecarboxylation to get to a haloalkane (Hunsdiecker reaction, Kochi reaction)

Title: **Re: Hofmann Rearrangement Yields**
Post by: **pyrrolidin** on **April 22, 2015, 09:21:09 PM**

Has anyone ever tried bis-(trifluoroacetoxy)iodobenzene as a reagent for the hofmann rearrangement? Apparently it gives high yields (>90% mostly) and reacts at RT.

The reagent can be prepared from iodobenzene and trifluoroacetic acid with oxone in 97% yield and with little experimental effort.
Of course non of this is OTC but the chems aren't watched at all so it shouldn't be a problem acquiring them.

Here is the experimental procedure for a very interesting amide/amine:
"I,I-Bis(trifluoroacetoxy)iodobenzene (5.20g, 12.8mmol) and H2O (15mL) were added sequentially to a stirred solution of amide (1.8g, 12.8mmol) in MeCN (15mL) at rt. After 8h the reaction mixture was acidified with 10M aq HCl (3mL) and washed with Et2O (2×5mL). The resultant aqueous solution was then neutralised (to pH 7–8) using 1.0M aq NaOH and washed with Et2O (5×10mL). The resultant aqueous solution was then basified (to pH 14) using 2.0M aq NaOH and extracted with CH2Cl2 (5×10mL). The combined organic extracts were dried and concentrated in vacuo to give amine as a colourless oil (1.50g, 96percent)"
(http://i.imgur.com/bzDYqO9.png)

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Lipbalm** on **April 22, 2015, 11:29:09 PM**

Quote from: pyrrolidin on April 22, 2015, 09:21:09 PM

> Has anyone ever tried bis-(trifluoroacetoxy)iodobenzene as a reagent for the hofmann rearrangement? Apparently it gives high yields (>90% mostly) and reacts at RT.

Chlorine Hoffmans are suppose to give high yeilds too and I read how those have been going :-)

Title: **Re: Hofmann Rearrangement Yields**
Post by: **pyrrolidin** on **April 23, 2015, 07:13:43 AM**

Quote from: Lipbalm on April 22, 2015, 11:29:09 PM

> Quote from: pyrrolidin on April 22, 2015, 09:21:09 PM
>
> > Has anyone ever tried bis-(trifluoroacetoxy)iodobenzene as a reagent for the hofmann rearrangement? Apparently it gives high yields (>90% mostly) and reacts at RT.
>
> Chlorine Hoffmans are suppose to give high yeilds too and I read how those have been going :-)

Well, the chlorine Hofmann is an ancient method that generally works but depending on substrate and exact conditions the yield varies greatly. The next problem is solubility issues as you are bound to the aqueous phase for the oxidiser. The next obvious try after chlorine Hofmann would be bromine/KOH in methanol/water. This would probably already increase the yields.

As you can see the substrate I posted has significant chemical similiarity with a wanted substrate on this forum, because of this I would argue it is reasonable to expect as good or better yields with the protocol I posted and also better reproducability since there are no temperature periods or homogenity issues due to low solubility of the amide in water.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **thewire** on **April 23, 2015, 06:09:53 PM**

TCCA-Mediated Hofmann Rearrangement

Synthesis of Methyl-1-(tert-butoxycarbonylamino)-2-vinylcyclopropanecarboxylate via a Hofmann Rearrangement Utilizing Trichloroisocyanuric Acid as an Oxidant

Zackary D. Crane *, Paul J. Nichols , Tarek Sammakia ‡, and Peter J. Stengel
Department of Process Chemistry, Array Bio Pharma Inc., 3200 Walnut Street, Boulder, Colorado 80301, United States
J. Org. Chem., 2011, 76 (1), pp 277–280
DOI: 10.1021/jo101504e

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Burgi-Dunit-Again** on **April 23, 2015, 07:22:58 PM**

Quote from: thewire on April 23, 2015, 06:09:53 PM

> TCCA-Mediated Hofmann Rearrangement

Is it just me or did this thread just go around in a big circle? Here's where I come in and say that DCCA works as well and without TCCA's solubility issues.

And for the Pinnick oxidation, Pinnick has some good articles on it ;), see: *Pinnick, H. Oxidation of ?,?-unsaturated aldehydes. Tetrahedron 1981, 37, 2091-2096.* Preferably hydrogen peroxide is used as the hypochlorous acid scavenger, unless you have 2-methyl-2-butene sitting around for some reason.

You can also get to the carboxylic acid just with aqueous hydrogen peroxide and a bit of acid catalyst at elevated temps as per "*Sato, Kazuhiko, et al. Tetrahedron Letters 41.9 (2000): 1439-1442.*"

But getting from a carboxylic acid to an amide will probably not be as easy as the oxime-beckmann procedure unless you have access to coupling reagents.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **thewire** on **April 23, 2015, 08:42:44 PM**

A Simple Method for the Synthesis of the Sterically Hindered Chloramines (with DCCA)
Jerzy Zakrzewski
pages 2135-2140

Synth. Commun., 18, 2135 (1988).

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Burgi-Dunit-Again** on **April 24, 2015, 01:05:41 AM**

I know this topic is about the hofmann rearrangement, but since everyone here seems to love theory, what really needs to be done to get this 'propanal of the ocean' controlled as soon as possible is the following:

Find a way to use TCCA / DCCA to get directly from the aldehyde to the nitrile: *Veisi, Hojat. "Direct oxidative conversion of alcohols, amines, aldehydes, and benzyl halides into the corresponding nitriles with trichloroisocyanuric acid in aqueous ammonia." Synthesis 15 (2010): 2631-2635.*

The nitrile is then easily hydrolyzed to the amide in situ with a bit of H2O2, recrystallized from water, and the DCCA used again in the usual manner to form the amine.

So there you have it. Two easy steps, two OTC reagents, and zero solvents.. to turn Uncle Sam's favorite cologne ingredient into the "hip" stimulant of our age.

The pollen's right there, who's going to bee the first to make the honey?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Impossible** on **April 24, 2015, 04:17:33 AM**

Workup is usually excluded from consideration as a real step in the majority of chemistry discussion/articles. We are really only focusing on improving the yield of the reaction itself, isolation and(for example) titration is left up to the individual.

The workup is often still included in a lot of posts, but it's not an expectation unless there is a significant issue with a standard methods.

Burgi-Dunit-Again could techincally say he will vacuum distill the base and lead it into an equimolar amount of HCl, forgoing the need for a solvent at at any point whatsoever.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Uppy** on **April 24, 2015, 04:23:13 AM**

Thanks for clarifying, that does make sense :)

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Scarecrow** on **April 25, 2015, 08:01:52 PM**

Quote from: Burgi-Dunit-Again on April 23, 2015, 07:22:58 PM

> Quote from: thewire on April 23, 2015, 06:09:53 PM
>
> > TCCA-Mediated Hofmann Rearrangement
>
> Is it just me or did this thread just go around in a big circle? Here's where I come in and say that DCCA works as well and without TCCA's solubility issues.
>
> And for the Pinnick oxidation, Pinnick has some good articles on it ;), see: *Pinnick, H. Oxidation of ?,?-unsaturated aldehydes. Tetrahedron 1981, 37, 2091-2096.* Preferably hydrogen peroxide is used as the hypochlorous acid scavenger, unless you have 2-methyl-2-butene sitting around for some reason.
>
> You can also get to the carboxylic acid just with aqueous hydrogen peroxide and a bit of acid catalyst at elevated temps as per "*Sato, Kazuhiko, et al. Tetrahedron Letters 41.9 (2000): 1439-1442.*"
>
> But getting from a carboxylic acid to an amide will probably not be as easy as the oxime-beckmann procedure unless you have access to coupling reagents.

Actually carboxylic acid to amide is not as difficult as you may think

http://www.sciencemadness.org/talk/viewthread.php?tid=4201&page=4

Oxidation of aldehyde to caboxylic acid and then boric acid/urea catalyzed amidation of ....heli..onic...acid?? or is it.. 2-methyl-3-(3,4-methylenedioxythingo)propanoic acid?

Probably shouldnt go into any more detail in this thread.

I think any suggestions on how to improve the Hoffman yeilds should be investigated in this thread including non-chlorine reagents Pyrolidin id be interested to see the patent for using the I,I-Bis(trifluoroacetoxy)iodobenzene reagent.

TCCA/DCCA I think is the most efficient OTC route at this point, using DCCA is a good improvement.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Burgi-Dunit-Again** on **April 25, 2015, 11:11:00 PM**

Quote from: Impossible on April 24, 2015, 04:17:33 AM

> Burgi-Dunit-Again could techincally say he will vacuum distill the base and lead it into an equimolar amount of HCl, forgoing the need for a solvent at at any point whatsoever.

Technically he could say whatever he pleases, regardless of its validity or practicality in real-life situations, though it would be against his moral code to intentionally disseminate false information to other well-meaning clandestine chemists. Sadly this is a liberty that other folks have in the past taken for one reason or another.

With regard to the carboxylic acid (and I promise this will be the last time I mention it here), the whole urea thing didn't work for me, and I suspected it was due to the methylenedioxy function's inherent fragility. That is purely speculation based on the flask full of charred black post-reaction gunk.

So back to the matter at hand: Hofmann Rearrangement! Hypervalent iodine reagents are definitely the more modern way of going about this. You guys should check out this paper if you haven't already: "*Miyamoto, Kazunori, et al. "A catalytic version of hypervalent aryl-?3-iodane-induced Hofmann rearrangement of primary carboxamides: iodobenzene as an organocatalyst and m-chloroperbenzoic acid as a terminal oxidant." Chem. Commun. 48.7 (2012): 982-984.*" Catalytic hofmann rearrangement at room temperature using an in-situ formed hypervalent iodine species from iodobenzene and mCPBA. Not exactly OTC but interesting chemistry nonetheless!

Perhaps a system like this could be devised in a hobby setting using some other acid and terminal oxidant with, say, iodotoluene to make it more OTC.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **AnyNameWillDo** on **April 30, 2015, 12:34:32 AM**

---

scarecrow, for what reason are you calling the use of DCCA as opposed to TCCA a great improvement? What benefit are you referring to?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Kykeon** on **April 30, 2015, 07:36:39 AM**

Quote from: AnyNameWillDo on April 30, 2015, 12:34:32 AM

> scarecrow, for what reason are you calling the use of DCCA as opposed to TCCA a great improvement? What benefit are you referring to?

Im also interested in hearing why DCCA would be better than TCCA.
I know DCCA is more soluble in water, but in my opinion the problem with the TCCA-Hoffman is not the solubility of TCCA, its the solubility of the amide.

My best yield with TCCA has been 71%, based on recrystallized and completely colorless amine.HCL.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Burgi-Dunit-Again** on **May 01, 2015, 05:23:59 AM**

Yes the amide solubility is the main issue and as such it's fastest when finely powdered. I like DCCA because I would rather worry about solubility of less things, but to each their own.

Really though, a co-solvent is the best way to counteract these solubility issues with amide/chloramide/whatever. Try THF or dioxane.

71% is very good. I think in many cases low yields and un-sumountable issues with solubility are just due to dirty amide. Recrystallization from water is good, but not necessarily a cure-all. It may be worth-while in some cases to recrystallize from both water and toluene-hexane.

Remember that recrystallization will only remove impurities from one 'side,' so to speak, of the solubility spectrum. It's often best to find a way to approach your compound from both ends.. e.g. silica plug then ether-hexane recrystallization etc. If that makes any sense.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Kykeon** on **May 01, 2015, 07:38:34 AM**

Yeah it makes perfect sense.

About the 71% yield it was at a 5g amide scale, when scaling up my yield drops.
The amide was recrystallized from water and ethanol. With this method I still get yellow visual bits of impurities in the amide.

The purest amide Ive obtained was when I dripped the post reaction mixture (one pot beckmann in DMSO) in iced brine, instead of extracting it.

Co-solvent is something I'd like to try, will probably try with dioxolane. Thanks for the tip.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **thewire** on **May 01, 2015, 05:22:37 PM**

New Strategies for the Hofmann Reaction
Dhananjay S. Rane 8z Man M. Sharma"

"*Using co-solvent*

Amide (0.1 mol) was dissolved in sulfolane (80 cm3). To it, freshly prepared hypochlorite solution (160 cm3, containing 0106 mol NaOCl and 0 2mol NaOH) was added. The stirring was continued until the reaction mixture attained room temperature. Then it was warmed with stirring to 45"C, when the heat of reaction was sufficient to maintain the temperature. When the exothermic reaction had ceased, the solution was warmed to 80°C and kept at that temperature for 1 h, after which the reaction mixture was cooled. The reaction mixture was extracted with dichloromethane (2 x 50 cm3). The combined extracts were washed twice, with water and then with hydrochloric acid (1 N, 100 cm3). The acid extracts were neutralised and the oil was extracted into dichloromethane. The dichloromethane solution was dried over anhydrousNa,S04. Thesolvent was recovered by distillation, leaving behind the oily residue of fatty amines."

For solubility issues:

"Jeffrey's modification ofthe Hofmann rea~tion'~.'has been extended for the preparation ofcarbamates. A slight excess of freshly prepared NaOCl solution was added to a methanolic solution of fatty amides with good stirring. The mode of mixing of the reactants is important for the preparation ofcarbamates." When a methanolic solution ofheptanamide was added to preformed NaOCl solution, the yield was found to be lower than with addition of NaOCl solution to amides (80% against 95%). Hence, for the preparation of carbamates, aqueous NaOCl solution was added to the methanolic amide solution immediately. For the preparation of methyl N-undecylcarbamates, excess of methanol was required, because undecylamide (C, ,) and lauramide (Clz)are precipitated by water. Table 4shows the yield ofcarbamates obtained from amides.
Thus, Jeffrey's modification gave excellent yields of amines as their carbomethoxy derivatives. Unfortunately no general method of hydrolysis has been recognised ***(there is one over here) http://cssp.chemspider.com/Article.aspx?id=734 (http://cssp.chemspider.com/Article.aspx?id=734)***."

Title: **Re: Hofmann Rearrangement Yields**
Post by: **oldman** on **May 18, 2015, 10:03:03 AM**

I dont think anyone has broched this subject yet but ....

Hoffman reactions do not like transition elements.
what do yo use for the beckmann reaction.

better yeilds can be found by oxidising the aldehyde
then forming the amide in another way.

This also allows you to do the whole process from the beginning to the end in cooking pots with out making hydroxylamine or forming oximes.

also of note is that the aldehyde of interest comes in two forms.
E and Z isomer.
only one isomer when made into an oxime will undergo beckmann.
The other will make a nice white crystal that is a condensation product of the amide and the aldehyde. this white crystal will make the acid when boiled with sodium hydroxide.

when the aldehyde is made from hydroformylation of the alkene you get the right isomer.

over time this changes to the other isomer that is not able to undergo beckmann.

as the USA is cracking down on china using the alkene they are now making there own aldehyde from the benzene ring up which makes a different isomer ratio than we are used to.

oxidation then forming the amide makes it so that this is not a problem.
also any aldehyde that has gone off over time has gone off to the oxidation product also allowing some one to store this product :)

this information cost a lot to obtain you are welcome.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **P!ssedSc!ent!st** on **June 01, 2015, 03:03:18 AM**

> Quote from: Burgi-Dunit-Again on April 23, 2015, 07:22:58 PM
>
> > Quote from: thewire on April 23, 2015, 06:09:53 PM
> >
> > > TCCA-Mediated Hofmann Rearrangement
>
> Is it just me or did this thread just go around in a big circle? Here's where I come in and say that DCCA works as well and without TCCA's solubility issues.
>
> And for the Pinnick oxidation, Pinnick has some good articles on it ;), see: *Pinnick, H. Oxidation of ?,?-unsaturated aldehydes. Tetrahedron 1981, 37, 2091-2096.* Preferably hydrogen peroxide is used as the hypochlorous acid scavenger, unless you have 2-methyl-2-butene sitting around for some reason.
>
> You can also get to the carboxylic acid just with aqueous hydrogen peroxide and a bit of acid catalyst at elevated temps as per "*Sato, Kazuhiko, et al. Tetrahedron Letters 41.9 (2000): 1439-1442.*"
>
> But getting from a carboxylic acid to an amide will probably not be as easy as the oxime-beckmann procedure unless you have access to coupling reagents.

Hey uh.
Why bother with the amide if you're at the carboxylic acid? Why not try the Hunsdeicker > bromopropane. Then it's as easy as MeAm.

Cool thing I saw on reddit ^

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Burgi-Dunit-Again** on **June 03, 2015, 06:00:32 PM**

I never had promising results aminating secondary haloalkanes with mediocre nucleophiles. If you got this to work, do tell :)

Title: **Re: Hofmann Rearrangement Yields**
Post by: **P!ssedSc!ent!st** on **June 04, 2015, 10:27:31 AM**

Just for fun tonight since I had a bit of "amide" that was beautiful crystal white and had been rextallized like 5 times from various solvents, water ethanol etc. But I had never taken a mp so I guess this was to see if what I had was actually amide. Lol

Anyway, since I passed by fries' work on this particular reread of this thread not too long ago, and just recently acquired a scale capable of measuring the measly quantity of 'amide' I had on hand, I decided or was time to use about 200mg of the 700mg I found and plug it into a scaled down version of fries wonderful coke-bottle hoffman - which I happened to have a cute little empty bottle (previously containing anise oil lol) just perfect for.

So.

200mg amide - finely crushed and powdered
2.23 ml 4.7% bleach (this was made from 5ml concentrated 8.25% bleach which was diluted with 1&3/4 it's own volume [2.8ml] dh2o - of course the full ~8ml wasn't all used)
150mg NaOH in 2ml dh2o

Bleach and NaOH soln were cooled in freezer until the bleach had ice in it, NaOH soln never got ice. Immediately after ice thawed, began adding reagents together

Since there was no order mentioned by fries, I chucked the 200mg amide in first, dropped the 2ml NaOH soln on that, agitated, dropped the 2.23ml bleach into it, capped the bottle & agitated the piss out of it for about 10 minutes, while popping it into an ice/salt bath every few minutes with continual agitation.
Finally another 5 minutes of shaking later I put the bottle in the ice bath and into the fridge.

And that's where it stands.

Will report back tomorrow :)

P.s. here's an unexciting picture of what the reaction vessel looks like shortly after a period vigorous masturbatoric shakings. A lightly cloudy, thin liquid sits in the bottom corner of mostly empty plastic bottle... At least I tried to make it poetic for you.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Kykeon** on **June 25, 2015, 09:32:14 PM**

Quote from: AnyNameWillDo on June 25, 2015, 07:11:02 PM

> So are there any tricks to getting the amide to dissolve?? Going off of another post here, a close friend had tried 20g sandy amide in 500ml h20/50g NaOH solution. (This seems like a pretty huge amount of h2o/NaOH for such a small amount of amide, no? Couldn't they maybe halve the amount?) They said the amide just spins and spins and never seemed to really get anywhere. It was in an ice bath and solution was at about 5 Celsius. They let it stir for a while and then fairly slowly, added 7g TCCA. Haven't heard back from them yet on results but it didn't seem promising considering the amide never seemed to dissolve at all.

Dont know how others have done it here but try 80ml water per gram amide, which

obviously is quite alot.
Stirred for 2h30min while keeping the temperature below 15C, then stored in a 8C fridge over night (needed sleep).
The amide used was recrystallized and finely powdered, yield on 5g scale was 71%.

Edit: I found that in the workup for the amide preparation via nitrile in DMSO, you dont need to extract the amide. Just stick the whole post reaction mixture in the freezer over night, the next day the amide should have precipitated.
An ethanol recrystallization on this material gave an amide much(!) cleaner than when extracting the post reaction mixture using DCM.
Yield on recrystallized amide was 76%, so I guess there might have been some amide left that did not precipitate.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **CHEMICALCOWBOY36** on **June 26, 2015, 05:21:26 AM**

Very interesting and great to hear fellow bee! Did you ever have any other crystals crash out besides the amide using this work up?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **CHEMICALCOWBOY36** on **June 26, 2015, 05:26:29 AM**

Quote from: oldman on May 18, 2015, 10:03:03 AM

> I dont think anyone has broched this subject yet but ....
>
> Hoffman reactions do not like transition elements.
> what do yo use for the beckmann reaction.
>
> better yeilds can be found by oxidising the aldehyde
> then forming the amide in another way.
>
> This also allows you to do the whole process from the beginning to
> the end in cooking pots with out making hydroxylamine or forming
> oximes.
>
> also of note is that the aldehyde of interest comes in two forms.
> E and Z isomer.
> only one isomer when made into an oxime will undergo beckmann.
> The other will make a nice white crystal that is a condensation product of
> the amide and the aldehyde. this white crystal will make the acid when boiled
> with sodium hydroxide.
>
> when the aldehyde is made from hydroformylation of the alkene you get the right
> isomer.
>
> over time this changes to the other isomer that is not able to undergo beckmann.
>
> as the USA is cracking down on china using the alkene they are now making there
> own aldehyde from the benzene ring up which makes a different isomer ratio
> than we are used to.
>
> oxidation then forming the amide makes it so that this is not a problem.
> also any aldehyde that has gone off over time has gone off to the oxidation
> product also allowing some one to store this product :)
>
> this information cost a lot to obtain you are welcome.

Can you back this up with data? As far as the no hydroxlamine ?

Also would any other season bee like to chime in on this two isomers bullcrap ?
Do you have any proof?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Kykeon** on **June 26, 2015, 11:44:21 AM**

Quote from: TCdboy28 on June 26, 2015, 05:21:26 AM

> Very interesting and great to hear fellow bee! Did you ever have any other crystals crash out besides the amide using this work up?

I dont know, but the m.p of the crude amide was "better" (closer to the one stated in an article) than the m.p of the crude amide from DCM extracton.
Im sure the 76% yield could be improved, the H2O2 I used was only 17.5% so I could probably have allowed the reaction to continue for another two hours or so. Since the reaction time needed increases with lower concentrations of reactants, in this case.

Another thing I tried which seemed to be working well was to perform the heating part of the hofmann in an large beaker and letting the water slowly evaporate during the course of the reaction (I probably heated it for 2-2.5 hours).
This will give you alot less volume to deal with during workup. So less volume of non-polar is needed, amongst other benefits.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **CHEMICALCOWBOY36** on **July 09, 2015, 01:09:26 AM**

Quote from: AnyNameWillDo on July 08, 2015, 11:45:00 PM

> Guys, I'm seriously fucking confused and getting frustrated now. I followed the lead of someone in here who had gotten 81% yield, I ran the hofmann with 20g amide and got back 16g after extracting with xylene, and then extracting that with 5% HCl and evaporating. This is right on par with, I believe it was mulemaster. Here's the thing.
>
> I've been fucking around with this stuff for a while now. I never titrated before but the way it came out was not looking like other mdxx I've ever had. After it evaporated I was left with a thin chunk of offwhite, yellowish dried paste looking stuff. I was a dumbass and when I chopped it up and tried to wash with acetone, I used WARM acetone. Warm as in, it had been in my trunk all day, and its summer. It wasn't a super hot day so I wouldn't say the acetone was HOT, but it was certainly farrr from cold acetone. Anyway, when I did this, the large majority of what was in the funnel dissolved into the acetone and went through. Is this extremely weird? I know it shouldn't be soluble in cold acetone, but is it that strange for it to dissolve in pretty warm acetone?
>
> Also, I (maybe foolishly) tried some of the stuff. I had maybe 80mg by the end of the day and had a nice experience. Wasn't speedy or anything at all, it was super mellow. No jaw clenching or anything, just super peaceful and felt like I was floating around on a cloud. So it seems it was active. I did feel some slightly discomfort in my kidney that night in bed, but I had felt that two days earlier because I was sort of binging on mxe trying to get rid of it and I think my kidney was just getting tired and telling me to chill the fuck out. Which I have since done!
>
> The "mda" which seemed to get my quite high, has this strange taste though! Instead of of an overwhelming bitterness like I was expecting, it has actually got more of a... Sharp, tart/sourness that hits initially and quickly fades to more of a bitter taste like I would be expecting. I just tried to recrystallize in 91% IPA, it dissolved in about the amount of IPA expected... I just tasted a small piece and it still has the sharp, tart burst when I placed a tiny bit onto my tongue.
>
> This is a damn long post but I am CONFUSED!! When I heated the hofmann, the place wreaked (in the best way possible) of mda freebase, but once I extracted the xylene extraction with 5% HCl, the resulting "crystals"/paste smelled much more like the H nectar?! Which makes no sense because the amide smells awesome, and heating the hofmann smelled GREAT, I was dancing in my shoes. Now I've got this shit that got me pretty high but I don't know what the fuck is going on with it...
>
> Does anyone have ANY idea what I'm talking about?? How did your stuff look when you titrated or gassed? Did it smell exactly as you had imagined? Taste exactly as you had imagined? Granted I have much more experience tasting mdma and only did mda once, but I can't imagine mda would have that tart/sour tinge upon intially

> placing it on my tongue. Yet, it got me high... What's going on?! I'm losing it over here.

First off can you edit your post for the H word please i would hate for another strike situation!

But to answer your question the same thing happened to me but my cat unfortunately had to stop experiment do some other factors but anyway do you have a test kit?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **lullu** on **July 09, 2015, 11:17:46 AM**

Quote from: AnyNameWillDo on July 09, 2015, 06:25:25 AM

> Is it correct that the freebase does not seperate from the water after being filtered? I mean, if it did, what would be the need for extracting with xylene or dcm, right? If it did, you'd just throw it into a sep funnel and seperate it that way.

No you would never to that, simple reason is that you want to reduce the mechanical loss.
Even in a perfect scenario you would have product somewhere in your funnel after partition.
So normally you should do multiple solvent extractions (read on Nernst's distribution law and play around with it to see why multiple instead of a big portion), after that one small portion to clean out the funnel afterwards.

You can get perfect yield in reactions but if you don't work up properly you will never see it.

I experienced this oiling out on aldehydes a few times and never found a solution for that, never on a recrystallized salt though.
but I think ORG talked about it somewhere maybe he has a few tricks under his sleeve.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Kykeon** on **July 09, 2015, 12:47:34 PM**

What do you mean you got 16g back after extracting with xylene? Could you write down your workup procedure? I have
a feeling that you might have messed something up there. And no the amine.HCl shouldnt be soluble in even warm acetone (perhaps very slightly).

You also mention that your amide smells awesome, if the amide is properly recrystallized it shouldnt smell much (it does smell a little but in my opinion the smell is neutral), if your amide is dirty that would explain your poor results in the hofmann.

Edit: Replies disappears...

Title: **Re: Hofmann Rearrangement Yields**
Post by: **unlikely_username** on **July 15, 2015, 01:38:43 AM**

I just made a fresh batch of Marquis and tested my amide again. Both very pure and fairly impure samples turned straight black. This directly contradicts what I said earlier about it turning pink and is more in line with the findings of others on this forum. The

amide should cause marquis to turn black.
This marquis was specifically made with 20mL Rooto Sulfuric Acid added to 1mL 37% formaldehyde solution (Tech.).
This preparation is more or less in line with DOJ standards to the best of my knowledge.

Quote from: unlikely_username on April 16, 2015, 05:36:46 PM

> 17g+ is possible with 25g amide. I ended up with 17.1g the last time I did this, and I know other members have obtained higher yields than I have, I've only run the damn thing three or four times. ::)
> That being said, we can still examine your reaction.
>
> Interesting that you had no color change, but not necessarily damning. Color change is an unreliable indication of reaction activity, it's just a nice reference point when everything is working like it should be (not as common as I'd like).
>
> I seem to recall adding the TCCA and then the amide, but the other way around should work just fine IMO. Who knows, maybe even better haha.
>
> ICA is much more soluble in hot water than cold. I think it's also very weakly acidic. So some would definitely dissolve in a hot basic solution.
>
> Off the top of my head I can think of a few possible contaminants, but I'd need a better idea of your workup before I could put anything out there:
>
> Assuming you titrated the DCM with dilute HCl in water, about how much water was there when you were done?
>
> About how much DCM was being titrated?
>
> Did you wash the water layer with any kind of organic solvent to get rid of the dissolved DCM and associated impurities? Even a bit more DCM would've helped pull out any organic stuff that wasn't to comfortable in there in the first place. Backwashing extractions is somewhat important when your solvents exhibit a not inconsiderable degree of cosolubility.
>
> Did you wash your product with cold acetone? Or even cold ether if you don't have acetone for some reason. This really cleans up the product.
>
> And finally, I'm a big fan of of using the Marquis reagent test, it's not the most definitive test ever but it's helped me troubleshoot a couple reactions. It just takes some concentrate sulfuric acid and a bit of formaldehyde solution, you can find the exact amounts in the wikipedia entry, and it's pretty forgiving about minor concentration differences. Put a couple drops on a small amount of your product and see what color it turns. It should go pretty much instantly purple/black. When it's taken a while to turn that color, especially if I see other colors hang around first it's correlated to a weak batch of MDA. When it just turned orange (only happened once) it's been 2-Cl-MDA. I tested the amide once just for kicks and it turned pink.
>
> Keep us updated.
>
> Oh, side note here, I was somewhat mistaken about NaOH not being consumed in the reaction. The ICA is prone to forming the Disodium salt when presented with an excess of NaOH, so there's the possibility of your precipitate being disodium isocyanurate instead of just isocyanuric acid, in which case two moles of NaOH would have been consumed. See link below for a pretty detailed description of a lot of the associated chemistry:
> http://www.sciencemadness.org/talk/files.php?pid=185660&aid=11296

Title: **Re: Hofmann Rearrangement Yields**
Post by: **AnyNameWillDo** on **July 28, 2015, 09:04:46 PM**

Is it considered normal for the reaction mixture to to still be a deep orange even after extracting twice and getting what 'appears' to be all of the fb out? I mean, there's really no way to see all of what would be in there and the reaction was never observed to go red and orange until heating and all of that lovely smell starts forming. That and the fact that the fb has that orange/red color to it led them to believe that the fact that the reaction mixture is still a deep orange after extracting meant they might be leaving a decent amount behind. Is it just something else in there that went orange/red as well or is this person doing sloppy workup?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **luminouspath** on **July 29, 2015, 02:55:47 AM**

It will stay orange no matter how many extractions you do. Side products I guess. The colour of your solvent after extraction is a more useful aid. If cost isn't an issue keep going until its obvious nothing is being pulled.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **unlikely_username** on **July 30, 2015, 01:57:09 PM**

Quote from: luminouspath on July 29, 2015, 02:55:47 AM

> It will stay orange no matter how many extractions you do. Side products I guess. The colour of your solvent after extraction is a more useful aid. If cost isn't an issue keep going until its obvious nothing is being pulled.

You'll want to factor in time and volume considerations as well ;)

In all honesty, I've almost never extracted anything worthwhile with more than three extractions. I sometimes like to check the third extraction on it's own to see if it might be worth extracting again, and I've found that sometimes the *third* extraction didn't provide anything worthwhile.
Sometimes you have to ask yourself if another 15-30 minutes of extra workup is worth an extra $5 worth of product, minus the cost of solvent used. The answer in that case would hopefully be no.
This is all obviously dependant on specific solvents and substrates, etc.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **P!ssedSc!ent!st** on **August 02, 2015, 03:44:13 PM**

Sooooooooo why is nobody posting attention to the bisulfite quench anymore? Didn't that seem to be the best way? Then to distill the amine as it's formed, as you meter-in the n-chloroamide solution to the hot NaOH soln.

Has any bee done this?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **syn** on **August 02, 2015, 07:45:29 PM**

Bisulphite quench is unnecessary, does absolutely nothing to improve yields. As to adding the solution to hot NaOH solution you're making things way harder than they have to be. Common sense says that the N-Chloroamide solution can just be made basic and hot and achieve the same results.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **P!ssedSc!ent!st** on **August 02, 2015, 11:31:32 PM**

Quote from: syn on August 02, 2015, 07:45:29 PM

> Bisulphite quench is unnecessary, does absolutely nothing to improve yields. As to adding the solution to hot NaOH solution you're making things way harder than they have to be. Common sense says that the N-Chloroamide solution can just be made basic and hot and achieve the same results.

I have learned that it is only necessary to quench with bisulfite of using bleach, not TCCA

I have yet to try adding the rxn mix to boiling NaOH soln. But it seems promising, as you can avoid shabbily and unevenly heating the mixture. Plus it's in the damn patent. Why not follow it?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **unlikely_username** on **August 03, 2015, 07:30:23 AM**

Quote from: P!ssedSc!ent!st on August 02, 2015, 11:31:32 PM

> Quote from: syn on August 02, 2015, 07:45:29 PM
>
> > Bisulphite quench is unnecessary, does absolutely nothing to improve yields. As to adding the solution to hot NaOH solution you're making things way harder than they have to be. Common sense says that the N-Chloroamide solution can just be made basic and hot and achieve the same results.
>
> I have learned that it is only necessary to quench with bisulfite of using bleach, not TCCA
>
> I have yet to try adding the rxn mix to boiling NaOH soln. But it seems promising, as you can avoid shabbily and unevenly heating the mixture. Plus it's in the damn patent. Why not follow it?

In my experience patents are often sort of bullshit, just an FYI.

You do not want to do a bisulfite quench if you're using pure amide and a known quantity of available chlorine. The idea behind the bisulfite quench is to remove excess chlorine, however, it is also quite happy to reduce your chloramide back to the amide, that particular reaction was actually used in one of the TCCA papers in this thread to prove the chloramide they had was the expected product by reducing it back to the original substrate.
tl;dr - don't try a bisulfite quench unless you actually know what it's supposed to do and have independently decided you need to do it in your particular situation and have calculated the proper quantity of bisulfite to use.

Quote from: syn on August 02, 2015, 07:45:29 PM

> Bisulphite quench is unnecessary, does absolutely nothing to improve yields. As to adding the solution to hot NaOH solution you're making things way harder than they have to be. Common sense says that the N-Chloroamide solution can just be made basic and hot and achieve the same results.

As for the dripping into a hot base solution, I believe there is a polymerization side reaction that can compete with the degradation, so keeping the concentration of the substrate low during the rearrangement could actually be beneficial.
https://en.wikipedia.org/wiki/Hofmann_rearrangement
https://en.wikipedia.org/wiki/Isocyanate

The isocyanate intermediate likes to form urethane linkages, this is undesirable to say the least, unless you want to make some kind of interesting MDA based memory foam? ;D

Title: **Re: Hofmann Rearrangement Yields**
Post by: **P!ssedSc!ent!st** on **August 04, 2015, 02:39:49 PM**

So uh.
Last night I combined 150ml h2o, 15g NaOH, chilled to below 10°, added 5g amide, bone dry, beautiful blinding white, followed after dissolution by 1.95g TCCA,
, stirred on high for 12.5 hours on ice salt bath. And maintained below 8° the entire time.

Woke up, lifted the beaker from the bath to find a HOLE IN THE FUCKIN BEAKER, WHERE THE RXN MIX THEN STARTS LEAKING OUT.

The whole must have been eaten through some weakness in the glass :(

Trying to salvage it now because tap water and salt prolly won't hurt it... Much... :/

Title: **Re: Hofmann Rearrangement Yields**
Post by: **d00 it now!** on **September 18, 2015, 10:33:21 PM**

Is there decomposition/polymerization issues with steam-distilling the amine post reaction? Why extract with DCM only to steam distill after? (suggested under vac? in this thread). Other popular amine's are very steam volatile, just wondering if there are specific reasons behind extracting for no reason really.

Quote

> The isocyanate intermediate likes to form urethane linkages, this is undesirable to say the least, unless you want to make some kind of interesting MDA based memory foam? ;D

Isocyanate's don't 'like' to form linkages with random compounds. Polyurethane's are catalyzed two-part reaction's, generally four part polyol, one part isocyanate catalyst (4:1 in retail applications you mix yourself, foams come pre-mix'ed in can, there are also 2-part spray can's you catalyze by pressing a big red button on the bottom releasing the isocyanate catalyst). Without the polyol, no foam, no polyurethane rubbery hard stuff, etc. No worries about any linkages, besides, polyurethanes vary greatly from fluffy foam, to rock hard foam, to UV resistant clear coat paints. You could get a rock at the bottom (no biggie in this case), or some foamy stuff, but IT WONT happen, not without a reasonably specific polyol. Even if a polyurethane is formed, it most likely won't be noticable at all. Polyurethane's have MANY variants that differ greatly, but basically no polyol, no polyurethane, no catalyzed cross-linked compounds via isocyanate.

https://en.wikipedia.org/wiki/Polyol <--- shit ref

http://www.azom.com/article.aspx?ArticleID=218 < --- much better

or for the more academically inclined reader

http://www.vanderbilt.edu/AnS/Chemistry/omrg/Articles/JPSa_2003_1114.pdf

---

Title: **Re: Hofmann Rearrangement Yields**
Post by: **BakingBrad** on **September 22, 2015, 04:36:39 PM**

So, anyone had any success with hydrolyzing the isocyanate? Any target temps or timelines?

Also, why does everyone keep the isocyanate formation cold?
Is there a side reaction if it's too high?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **P!ssedSc!ent!st** on **September 23, 2015, 02:49:24 AM**

---

heyyyyy SO UH upon xylene extraction i end up with a xylene whitish cloudy top layer with a middle layer of what looks like precipitate?! like a SHIT load of it. on top of th e

water layer. could this just be the mda freebase oil trapped in water in the xylene? could i use NaCl to fix this? i used 300ml xylene then 3x150 ml and still had the precip. lost more each time...but its worrying me...
i took a sample of it and waiting for it to dry so i can smell test to see if its amine or not...but beezz....i smelled it a second ago and its not an oil, its white and smells weird as hell....

Ok, so since no beez were available to assist, igor just plowed into the extraction, took a few samples of xylene, filters to remove the white crap, which on the Buchner was gooey and weird as hell - no smell discernible (isocyanate?)
After washing with brine and water and drying with mgso4 a 5ml sample was titrated with 2.5ml 3% muriatic sol. In water and the water layer dried to reveal crystals that appear familiar and smell nice.

The rest of the xylene was pooled and done the same way. The resulting xtals were rextalled once in h2o/acetone, dried finely powdered and waster thoroughly twice with ice cold anh. Acetone to yield 25g amine/38g amide starting material (Using scarecrows hoff. Protocol)

Title: **Re: Hofmann Rearrangement Yields**
Post by: **tyronious** on **October 19, 2015, 11:01:32 PM**

Out of curiosity, what are you all extracting with? One post mentioned xylene. Id imagine xylene or toluene are most common/available.

It seems like some issues would come up if extracting with ethyl acetate as it is easily hydrolized in basic conditions. Anyone running into this/care to share experiences?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **fractal** on **October 20, 2015, 12:02:41 AM**

That is most likely not amide you recovered PS provided you used the correct molar ratios.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **P!ssedSc!ent!st** on **November 01, 2015, 08:54:06 AM**

So I want attentive to my words.
The yield I got was not from the weird white precip. I assume that was ICA, it was
Filtered (painstakingly filtered) and the liquid
Was
Worked
Up
As usual.

It was performed again and yielded the exact same.

The Weird precip needs to be removed before extraction

Title: **Re: Hofmann Rearrangement Yields**
Post by: **unlikely_username** on **November 02, 2015, 02:31:25 PM**

Quote from: P!ssedSc!ent!st on November 01, 2015, 08:54:06 AM

> So I want attentive to my words.
> The yield I got was not from the weird white precip. I assume that was ICA, it was
> Filtered (painstakingly filtered) and the liquid
> Was
> Worked
> Up
> As usual.
>
> It was performed again and yielded the exact same.
>
> The Weird precip needs to be removed before extraction

I think it is a combination of ICA and sodium carbonate. The carbonate would form during the decarboxylation from co2 reacting with the excess of strong base available. Upon cooling it is quite likely to be very insoluble in a solution containing strong base. Maybe this could be mitigated by using potassium hydroxide instead? Question then is, is it worth the effort and how effective would it really be?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **brainchild** on **November 03, 2015, 11:13:39 AM**

I tried another work up. After the hofmann reaction is complete, i put the whole solution into a sep funnel. Mda freebase (slightly orange) has a relativly high density >1,2g/ml and drops to the bottom. I seperate the base, filter it with vacuum, wash with water trice, add hcl, wash with dcm twice. Destill off the water. Powder everything and boil it in acetone. Cool and filter of acetone. Product comes out strong and usually white. Yield is around 15-17g hcl per 40g clean amide. I have to say i also droped the amout of tcca to amide to 1:3.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Kykeon** on **November 03, 2015, 07:10:47 PM**

There is still some MDA left in the water phase.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Flasky Mountain Flask** on **November 04, 2015, 06:18:43 AM**

I searched around and haven't noticed anyone using calcium hypochlorite for the fruity substrate. Somebuddy posted a question about it earlier in this thread and it was not recommended in the response.

8.64g of a mixture containing 47.5% calcium hypochlorite was finely ground and repeatedly extracted with small amounts of boiling water then filtered. The filtered solution (containing the hypochlorite, estimated at around 200ml) was chilled to -10C. 68.9ml of 10% NaOH was chilled to -10C. Upon thawing of ice in each solution, 11.6g of the amide was ground under the NaOH solution until mostly dissolved. The NaOH/Amide solution was dripped into the stirring hypochlorite solution slowly over 8 hours with temperature maintained at 0-5C, and the combined solution was allowed to stir for an additional 10 hours at 15C.

125ml 10% NaOH was heated to 85C, and the chlorinated amide solution was slowly dripped into the stirring NaOH solution during 1 hour. The temperature was maintained at 85C for 5 hours. The mixture was allowed to cool and settle for 1 hour, then was extracted with xylene. Xylene was treated with excess of HCl, the aqueous phase was washed 2x with xylene, the aqueous phase was basified and extracted multiple times with xylene, which was dried and titrated with HCl and acetone-washed to yield 7.63g amine HCl (61.6% of theory).

During the formation of the chloroamide, a white precipitate. The reaction remains cream white until heat and excess base is applied. This turns the reaction orange-red.

The yield can be improved. 61% is ok and not using methanol is good.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **BakingBrad** on **December 01, 2015, 07:56:46 AM**

My friend attempted to distill off the amine as he was hydrolysing in the final step, and the red globby stuff stayed in the bottom of the flask.
He noted a small amount of clear oil on top of the distillate, was that the mda freebase?

He assumed that the red oil was the product, and washed that with Xylene.
He then gassed it with HCl gas and got a bit of precipitate.

Where does the MDA freebase go in an aqueous solution?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **unlikely_username** on **December 01, 2015, 11:32:10 AM**

The freebase is still slightly soluble/dispersed in the aqueous solution, also often absorbed into whatever droplets of hydrophobic gunk form.

You almost always want to extract your entire solution.

Extraction works based on relative solubility, not absolutes. The basic aqueous solution makes freebase dissolution *much* less favorable as any sort of ionization equilibrium is pushed towards the nonpolar/noncharged state due to the abundance of free (OH)-. The dissolution still occurs to an extent, and even nonpolar molecules can be dissolved in an aqueous solution to some extent.
When you shake or stir with an immiscible NP solvent this means it is much more favorable to interact with the NP molecules than the water molecules, and the product amine will tend to follow the NP solvent molecules into their phase.
This also brings any nonpolar gunk formed during the reaction over and this is why we then isolate the amine salt, the red droplets were not necessarily product.

If you fail to dry your extraction solvent with something like anhydrous $MgSO_4$ before attempting to use HCl(g) to precipitate it there is a decent chance that the residual water in your extraction solvent will prevent it from crystallizing. I personally find gassing to be a huge pain, and there are alternatives to that route if you are having problems.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **BakingBrad** on **December 03, 2015, 11:47:53 PM**

The red droplets were certainly not his product, they did not dissolve into the NP.
In the past, in less sucessful reactions, he got a brownish gunk. He thinks that it is brown because he didn't decant the solution off the precipitate from the first part of the reaction.
(he is using store bought sodium hypochlorite bleach... any clue what the impurity is? sodium oxide?)
He wishes he could buy TCCA; but the only vendor he has found only ships to business addresses, and he doesn't want his boss asking questions.

Thanks for that excellent explanation. I never really processed that an ionic charge was behind the amine's propensity to fall out of polar solutions.

He's had most success with adding the amide to the water, bleach, and lye (in molar amounts except the lye), then adding enough water to dissolve most of the amide and letting it set overnight. After doing this, he one time got a yellow solution, and another time got a clear solution.

Both were poured into a boiling flask (the second time, decanting off of the precipitate that formed during the first step) and heated on a mantle to 50C and held there for 30 or so minutes.
Then he jacked the heat up to about 80C and got a nice red globby precipitate (as most people speak of), and held the temp at 80C for about 30 minutes.

The second time, he set up a distillation apparatus and began distilling off water, as he heard that the freebase was steam-soluable. He did not notice any freebase amine distilling over, but he may have been mistaken.

Instead of extracting the distillate, he extracted what was left in the boiling flask when it cooled down, and got some amount of product.

-Do you think it is possible to burn/char the product (salt) when trying to distill off the water?
My friend was particularly sloppy once, and tried to distill the water off the amine salt, just to get a bunch of black char that tested positive on marq. (he was using a mantle and no vacuum) However, his amide also tests positive, so he doesn't use that as a gauge.
-Should he just salt using water and HCL then distill under vacuum? That seems like the most reasonable way to me. (I wouldn't know that much, though)

Title: **Re: Hofmann Rearrangement Yields**
Post by: **NotGuilty** on **December 22, 2015, 02:31:37 AM**

I've been working on this thing for almost 2 years now, finally got to the stage where after washing the Beckmann and sending it to a lab for GCMS it came back as >99% pure alpha-methyl-3,4-methylenedioxyphenylpropionamide, which I assume means I just have the Hoffmann left to go.

Will Xylene be sufficient for workup after the TCCA reaction? I can't get hold of anything approaching pure DCM without paying astronomical prices for tiny amounts and going through lots of hassle, whereas Xylene can be picked up like it's bottled water with no hassle.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **brainchild** on **December 22, 2015, 07:32:23 AM**

What was your way of purificating the Amide?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **NotGuilty** on **December 22, 2015, 11:40:44 AM**

After the reaction I let it sit somewhere totally undisturbed to cool down. When it's about 90 to 70C the amide started precipitating out and looked like a cola slurpee. Then I stirred it up some to cause more of it to precipitate being careful not to let it sit too long as it creates dirty crystals. Then I vacuum filter it asap and wash it with a lot of xylene. Then soak it in xylene, filter, and wash it again with xylene and lay it out to dry outside. If the amide is not a light tan or whitish when it's dry I put it in a filter and just keep pouring xylene through it and stirring a little each time.

I found a lab service in Spain that does GCMS for 50 EUR so i've been religiously testing all my results and things are looking good so far. I've stockpiled a lifetime supply of necter for the eventual ban so i'm happy to spend as much time as necessary getting this process perfect.

Will report back with how things go for the Hoffmann, going to try it with Xylene. I have a wholesale tek using NaOH but I want to perfect the TCCA route before I start throwing kg's of Amide into reactions as I have a real bottleneck making the Hydroxylamie from scratch so I don't want to waste precursor.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **pyrrolidin** on **December 22, 2015, 06:26:34 PM**

There is a procedure using acetone:chloroform 1:2 as a solvent with TCCA. The solubility issues of the amide are non-existent and after filtration of salts the N-chloroamides can be isolated in high yields and purity. I imagine, by dissolving these chloroamides in dioxane or THF and adding NaOH one could get a very clean conversion to the amine. A/B extract and done.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Lipbalm** on **December 22, 2015, 08:10:38 PM**

Quote from: NotGuilty on December 22, 2015, 11:40:44 AM

> I've stockpiled a lifetime supply of necter for the eventual ban s

Should have been banned 5 years ago. It seems they have instead adopted a "watch to see where it goes" approach.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **CHEMICALCOWBOY36** on **December 23, 2015, 02:19:41 AM**

Lipbalm how accurate is this info ? Not questioning you per se but is this info from a reliable source?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Lipbalm** on **December 23, 2015, 06:54:48 AM**

Quote from: TCdboy28 on December 23, 2015, 02:19:41 AM

> Lipbalm how accurate is this info ? Not questioning you per se but is this info from a reliable source?

The biggest domestic supplier was/is Vigon International. You could one-click order literally a ton of it on credit card from your online cart and have it shipped next day from NJ. Then 5 years ago they started demanding intent forms and all that jazz. They didn't do that just because they felt like it.... Strange thing is though although I'm sure they have been keeping tabs on it there hasn't really been any busts. Maybe they are just making sure it stays below a thresh-hold, I dunno.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **brainchild** on **December 23, 2015, 08:58:32 AM**

Quote from: NotGuilty on December 22, 2015, 11:40:44 AM

> After the reaction I let it sit somewhere totally undisturbed to cool down. When it's about 90 to 70C the amide started precipitating out and looked like a cola slurpee. Then I stirred it up some to cause more of it to precipitate being careful not to let it sit too long as it creates dirty crystals. Then I vacuum filter it asap and wash it with a lot of xylene. Then soak it in xylene, filter, and wash it again with xylene and lay it out to dry outside. If the amide is not a light tan or whitish when it's dry I put it in a filter and just keep pouring xylene through it and stirring a little each time.
>
> I found a lab service in Spain that does GCMS for 50 EUR so i've been religiously testing all my results and things are looking good so far. I've stockpiled a lifetime supply of necter for the eventual ban so i'm happy to spend as much time as necessary getting this process perfect.
>
> Will report back with how things go for the Hoffmann, going to try it with Xylene. I have a wholesale tek using NaOH but I want to perfect the TCCA route before I start throwing kg's of Amide into reactions as I have a real bottleneck making the Hydroxylamie from scratch so I don't want to waste precursor.

Have you tried a recrystalisation with water:ethanol 10:2, it seems more convenient and cheap compared to xylene. I really dont like to work work with xylene also ethanol is much more cheap for me.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **brainchild** on **December 23, 2015, 09:13:22 AM**

Quote from: pyrrolidin on December 22, 2015, 06:26:34 PM

> There is a procedure using acetone:chloroform 1:2 as a solvent with TCCA. The solubility issues of the amide are non-existent and after filtration of salts the N-chloroamides can be isolated in high yields and purity. I imagine, by dissolving these chloroamides in dioxane or THF and adding NaOH one could get a very clean conversion to the amine. A/B extract and done.

To be honest the one thing i like about the hofmann is the lack of need for expensive and possibly toxic solvents. Its easy to get rid off the post reaction solvents as its only basic water with cyanuric acid dissolved. Even the whole process from the aldehyde to final amine only needs 2 weight equivalent of xylene to oxime and some Dcm to extract the amine. Otherwise i only use cheap and non toxic solvents like ethanol, water and a little bit of acetone.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **P!ssedSc!ent!st** on **December 24, 2015, 08:19:14 AM**

So Igor used scarecrows method for the Hoffman on ~75g amide, added the cold n-chloramide soon over 16 hours, ended up with 14g decent purity amine material.

Longer is not always better - contrary to the patent.

Next time
Igor will
Just drip the chloroamide sold into the hot naoh over as long as it takes while maintaining he temp @90* and see how it goes.

Another important note: make Damn sure your amide is PERFECT.when you're done rextalling and it looks perfect, DO IT AGAIN.

Also: when using DCM to extract the amine you'll get a serious precip of ICA which will not vac filter easily - but it's necessary to vac filter it. Maybe try chilling the DCM extraction before filtering to prevent DCM evap and removal via vacuum. (It was warm when I worked last)

Washing the DCM/xylene extract with brine and then water twice usually does the best job of cleaning it. I've never tried toluene as ext solvent, maybe try and report back?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Flasky Mountain Flask** on **December 25, 2015, 06:55:34 AM**

From swapping out the calcium hypochlorite with sodium dichloroisocyanurate, there was noted a 15-20% increase in yields. (from 60% with Ca(ClO)2 to 80% with S-DCCA).

Another important thing noticed was that there was no difficulty dissolving anything (amide in warm NaOH THEN chilled; chlorine source is of course very water soluble), and during the formation of the chloroamide there was no precipitate. During the cleaving of the chloroamide, there was a small amount of red droplets precipitating which did not dissolve in the xylene during extraction. Also the amine came out a bit cleaner than with Ca(ClO)2.

After reading all the problems which appear in the use of TCCA, I suggest perhaps the use of S-DCCA would be preferable?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **BakingBrad** on **January 08, 2016, 03:56:38 AM**

Quote from: lysurgeon on December 25, 2015, 06:55:34 AM

> From swapping out the calcium hypochlorite with sodium dichloroisocyanurate, there was noted a 15-20% increase in yields. (from 60% with Ca(ClO)2 to 80% with S-DCCA).

A friend who is a chemist told me that NaDCC doesn't have solubility issues, especially if it's mixed into water beforehand.
He said that he ran 1g of amide with molar amount/2 of NaDCC in 250ml water (ph 10, NaOH) and he didn't get the usual red-brown coloration that he got with NaOCl.
He thinks that store bleach has higher Cl content than the package says, and the excess Chlorine causes some kind of side reaction. He thinks it might polymerize the isocyanoate, but he admits that he knows little about these things.

He claims that in the 1g Hofmann, the solution did not discolor during hydrolysis.
Instead, the amine separated out into it's own layer on top. He thinks that the side reaction with excess Cl modifies the solubility of the amine, causing a lot of it to get caught in the aqueous layer.

Excess Cl also seems to cause a gunk that does not dissolve properly in either water or xylene. Hence his hypothesis about polymerization.

So remember, DO YOU MOLAR CALCULATIONS. (and use a slight excess of amide)
If you can't learn how to do that, you probably shouldn't quit your day job.
If you fuck and add too much (like forgetting to divide by two with NaDCC) then you can add a molar amount of sodium metabisulfite.
It won't save it, but it may reverse it enough to make it salvageable.
Again, this is something you need molar calculations for.

===

Can anyone else give me some anecdotes?
Should the Chloro-amide be white or yellow before one heats it?
My friend said that yellow seems to mean that it is over-chlorinated, at least at his tiny scale.
He also said (as he has read in some papers) that the Chloro-amide only takes about an hour to form. (of course, there may be any number of issues with scaling)

Title: **Re: Hofmann Rearrangement Yields**
Post by: **P!ssedSc!ent!st** on **January 20, 2016, 08:52:36 PM**

---

does anyone know approximately what PH the hoff runs best at?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **poisoninthestain** on **January 23, 2016, 03:31:36 AM**

@BakingBrad

"Can anyone else give me some anecdotes?"

Trials with aq. NaClO were similar to your reports. OTC bleach can be problematic as you said especially if you haven't preformed it yourself due to OTC variablility in reported concentrations at times. This OTC bleach can also include added ingredients that may hinder the reaction. TCCA is a much better option and NaDCC even moreso. TCCA solubility sucks and unless excess NaOH or KOH is used CA will precip. Everything else is pretty on point.

"Should the Chloro-amide be white or yellow before one heats it?"

Doesn't matter IMO for the most part. Yields are pretty similar(5-10% maybe maximum) depending mostly on workup and unless the carbamate is formed with an alcohol between C-2 through C-3 in length it doesn't matter(but that's a topic for a different discussion). As a generality I'd say it's due to an excess of hypochorite ion (it's yellow if you check the MSDS).

Title: **Re: Hofmann Rearrangement Yields**
Post by: **BakingBrad** on **January 24, 2016, 11:00:53 AM**

What if one uses NaDCC and it still turns yellow?
The crystals are white.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **poisoninthestain** on **February 01, 2016, 10:13:06 AM**

It really doesn't matter IMO. The hypochlorite anion is yellow when NaDCC is in solution as hypochlorous acid is formed.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **P!ssedSc!ent!st** on **February 06, 2016, 06:42:57 PM**

---

does anyone think acetone would work as a cosolvent without producing any garbage?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **fractal** on **February 06, 2016, 07:27:45 PM**

Acetone reacts with hypochlorite, wouldn't work.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dongsdongs** on **February 07, 2016, 11:08:54 AM**

Anyone got a proper cosolvent?
Isopropyl doesnt work, the alcohol and water seperate out at a point, with the top layer bein clear and the bottom being white.
(With naDCC as the chlorine source)

Title: **Re: Hofmann Rearrangement Yields**
Post by: **unlikely_username** on **February 08, 2016, 01:55:03 PM**

Interestingly enough, I've heard acetone is a good solvent for halogenation type reactions. This was in the context of forming acid chlorides so in this case it was anhydrous, I don't know if aqueous conditions would make acetone more vulnerable. But the person I heard this from is one of the most skilled synthetic chemists I've met, so I wouldn't automatically rule out acetone.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **brainchild** on **February 23, 2016, 08:37:56 AM**

Quote from: unlikely_username on February 08, 2016, 01:55:03 PM

> Interestingly enough, I've heard acetone is a good solvent for halogenation type reactions. This was in the context of forming acid chlorides so in this case it was anhydrous, I don't know if aqueous conditions would make acetone more vulnerable. But the person I heard this from is one of the most skilled synthetic chemists I've met, so I wouldn't automatically rule out acetone.

Acetone forms chloroform with sodium hypochlorite in a reaction called the haloform reaction.

What kind of post hofmann reaction workup do you perform?
I have trouble with insolubles sometimes. Filtering does not seem to be the solution because it clogs up the filter and the base sticks to it. If one uses dcm, i have the impression some of this crap dissoves too. Recently xylene was tested, with the benefit of swimming on top of the reaction solution. Xylene was washed with brine. After this amine was extracted with HCl/ water. Washed with dcm twice and water distiled off.

After this dry fine powdered hydrochloride salt will be boiled with minimum amount of acetone usually yielding an white to off white powder. 50 % w/w yield hydrochloride from amide. Not the best yield but considering the first two steps to amide are high yielding, and starting chemicals + solvents are very cheap, its good enough. Also there is not much "work" to be done.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **atara** on **February 23, 2016, 07:22:18 PM**

> Quote from: Lipbalm on December 23, 2015, 06:54:48 AM
>
> > Quote from: TCdboy28 on December 23, 2015, 02:19:41 AM
> >
> > > Lipbalm how accurate is this info ? Not questioning you per se but is this info from a reliable source?
> >
> > The biggest domestic supplier was/is Vigon International. You could one-click order literally a ton of it on credit card from your online cart and have it shipped next day from NJ. Then 5 years ago they started demanding intent forms and all that jazz. They didn't do that just because they felt like it.... Strange thing is though although I'm sure they have been keeping tabs on it there hasn't really been any busts. Maybe they are just making sure it stays below a thresh-hold, I dunno.

About four years ago a paper came out about MDA made from ocean propanal with specific reference to 2-chloroMDA as an impurity that forms when NaOCl is used to do the Hofmann rearrangement. If we assume it takes a year for a bust to make it into the academic journals, then maybe the bust that led to that paper was what tipped them off.

It's possible that they haven't gone after it more because they know by looking at what hits the street that helional isn't where the big money is in molly. After all MDMA is still way more common that MDA, but right now the synthesis of MDMA from helional is only theoretical -- you can use that dehydrogenation route or monomethylate MDA, but there are good writeups for neither. Most MDMA probably goes via the Darzens intermediate which is made in third-world countries.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Tsathoggua** on **February 26, 2016, 11:35:09 AM**

Looking up 2-chloro-MDA, there appears to be a few forensic references etc. But I can see nothing like bioassays.

On a bare phenyl, 4-substitution alone in the case of amphetamines appears to have a distinct propensity towards producing a veritable smorgasbord of unpleasantries. PMA, PMMA, and even worse, the likes of para-chloro, bromo and iodoamphetamine, likewise also para-nitroamphetamine is one I'd want to avoid like a buboe ice lolly. 4-hydroxy is another iffy one, as serotonergic neurotoxins go, 4-methylthio results in a compound that is, I believe, not sharing those effects, but its a fairly strong MAOI (inhibiting MAO-a that is) so a very, very, very steep dose response curve and quite a potential for causing hyperpyrexia and hypertensive crises.

para-methylamphetamine and para-methylmethamphetamine, and likewise the cathinone/methcathinone analogs of those, sound horrifyingly poisonous substances, with the only results of human use T'sath has heard of, many in eastern europe, where these were abused with in some cases, horrendous sounding long term neurological deficits, with some victims ending up quite badly impaired.

This is mind you, a world away from para-monosubstitution, but this is a very new compound.

Whats known of toxicity or indeed, potential use of 2-chloro-MDA?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Kykeon** on **February 26, 2016, 12:55:42 PM**

There was a thread at hyperlabs a few months back where 2-Cl-MDA was bioassayed. Unfortunately it was moved to the hidden sections (I should have saved the thread when I had the chance), probably to avoid attention from RC manufacturers.

I sadly do not recall much of the thread, but I think that the effects were stated to be quite okey but I dont remember the dosages, probably above 100mg. Might be worth making some and evaluating.

Or, one could be creative and do an ullmann reaction and swap the halide with a methoxy to get 2-MMDA which seems more interesting.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **thewire** on **February 26, 2016, 02:14:28 PM**

The Shulgin Index page 238. (2-Cl-4,5-MDA, 2-Cl-4,5-MDMA, 2-Br-4,5-MDA, 2-I-4,5-MDA, 2-I-4,5-MDMA, 2-NO2-4,5-MDA...)

2-BR-4,5-MDA
https://www.erowid.org/library/books_online/pihkal/pihkal019.shtml
(https://www.erowid.org/library/books_online/pihkal/pihkal019.shtml)

Title: **Re: Hofmann Rearrangement Yields**
Post by: **NotGuilty** on **March 15, 2016, 12:35:27 PM**

Ok so i'm getting a lot better at the Hoffman, I have a few questions if you experts could be so kind as to impart some more knowledge. I have no formal training so all of my learning has been through forum posts, writing notes and slow experimentation.

After cleanup the average quantitative test results from the lab are landing around 59-73% pure, the remainder appears to be mostly unreacted precursor.

Is there anything I can do to clean the finished product after the Hoffman to >90% purity? I'm already washing a bunch with Xylene and gassing with Hcl but the impurity seems to survive.

At the moment the average yield from the entire process has risen to 12.5% amine per KG of Necter, up from 8.7% pure amine from the first KG. I'm hoping I can get higher in the future so I will report back once i've run another couple of KG's of Necter.

I've been following scarecrows method with TCCA, seems like temperature control is a real bitch with this reaction. I work in a super hot environment out in the desert due to safety reasons, and keeping this thing cold is a fricking nightmare. I'm too far from civilization to grab bags off ice from the store so I have to run a couple of ice machines simultaniously just to generate enough ice to hold down the temp. Is it worth investing in a cold plate or are there easier ways to keep this thing cool? I've noticed that for the best results you have to be EXACT with the temperature, even a couple of minutes of it running hot lowers yield significantly

Also, how much does the TCCA route scale? I'm currently yeilding about 40g of Amine each reaction, can this be pushed up to 250g or do I risk wasting amide by trying? Is there anything I should watch out for when I increase the scale?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Scarecrow** on **March 15, 2016, 01:11:59 PM**

Quote

> I've been following scarecrows method with TCCA, seems like temperature control is a real bitch with this reaction. I work in a super hot environment out in the desert due to safety reasons, and keeping this thing cold is a fricking nightmare. I'm too far from civilization to grab bags off ice from the store so I have to run a couple of ice machines simultaniously just to generate enough ice to hold down the temp. Is it worth investing in a cold plate or are there easier ways to keep this thing cool? I've noticed that for the best results you have to be EXACT with the temperature, even a couple of minutes of it running hot lowers yield significantly

I havent been able to get this procedure to yield from running it cold. I usually do the addition between 75-95 degrees.

Could you please inform me of the conditions you are using for the peroxide addition? Id be interested to know what temperature you are aiming to keep it at during the reaction which is requiring so much ice, you say keeping the temperature exact is important, what temperatures are you talking about? My suggestion is to perform the peroxide oxidation slower, and with weaker solution. Also make sure you are using equimolar hydroxylamine:helional when you are doing the first part of the reaction, as hydroxylamine releases alot of heat upon its decomposition.

Please be safe, good to know you are using ice.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **ricky** on **March 15, 2016, 03:52:58 PM**

I have used flourinated hydrocarbons (PFC's, not CFC's) in conjunction with a pressure regulating valve to get a condenser really cold. Only thing, you have to get a really good seal on it; I had the thing blow apart on me several times o.O

I don't know if something like that could help, but if you are good with hacking shit together, it wouldn't be too hard to go out and get an evaporating coil from Home Depot and rig up a refrigeration unit yourself.

Beats several thousand trips to the ice machine, at least x.X

Title: **Re: Hofmann Rearrangement Yields**
Post by: **magoo** on **March 16, 2016, 03:00:12 PM**

I've heard of a bee who is new to this whisper to me that for their 3rd tcca hoffman, ran with 50g brilliant white amide that was 1x xylene, 1x 10:2 ethanol/water, 2x water recrystallised, yielded after dcm extraction ~39g honey coloured freebase.

WTF?! How on earth did he get 78% out of the hoff?

the HCl product was reagent tested.
marqis=black instantly

mandelin=black instantly/smoke
mecke=very dark blue w slight green border
simons=no reaction
robatest= slow reaction, first light orange then deep purple

I was under the impression that the robatest should be pink/red/brown

An experienced 110kg bee flew away with 101mg pollen, returned and said it was brilliant but, almost too much, too long lol

---

Title: **Re: Hofmann Rearrangement Yields**
Post by: **unlikely_username** on **March 16, 2016, 04:46:58 PM**

@Magoo
What were your final yields of clean HCl salt? The initially isolated freebase is often heavily contaminated, depending on workup.

@notguilty
When you say "unreacted precursor" do you mean the aldehyde or the amide? Two entirely different potential issues.

To further purify your HCl salt you should try to clean it with cold anhydrous acetone, it's polar enough to take out all sorts of stuff but your ionic salt is not going to be very soluble. I've never needed to go further than an acetone wash or two. Save the solvent if you want, the small amount of product that dissolves can become worth recovering after a few runs.
After an initial cold acetone rinse you might try rextalling with hot anhydrous IPA or boiling in acetone. If you use IPA be prepared to strip your solvent. Acetone is nice because you can just freeze most of the product out, but it doesn't get hot enough to dissolve the product very well, it'd probably help more than just cold acetone rinses though.

You can increase the scale, this may result in somewhat decreased yields because fine control of conditions is harder. Temperature control especially becomes more difficult. EXOTHERMIA IS MUCH MORE DANGEROUS AT INCREASED SCALE. Sorry, but I didn't want anyone to miss that. It comes down to the square cube law, volume increases an order of magnitude faster than surface area, and temperature is controlled through the surface area. This means you can't heat or cool a larger volume anywhere near as fast, and they will not equilibrate with ambient conditions anywhere near as fast. Slight exothermia can turn into thermal runaway if scale is carelessly increased.
That being said, I believe scaling this up is fine if you have the equipment, I just want you to be aware that it can easily become complicated. Be prepared to troubleshoot. Never change conditions while also scaling up, limit potential issues to one variable at a time.

I use a mini fridge for the cold part of the hoffmann. Run a flat extension cord under the door for a stir plate. Pretty straightforward. For cooling the nitrile formation and oxidation you might be able to get away with a running water bath rather than ice since you don't want them cold anyway. Just keep enough ice on hand for emergencies and the occasional ice bath.

Imma go to bed now. Hope this helps.

Title: **Re: Hofmann Rearrangement Yields**

Post by: **brainchild** on **March 16, 2016, 05:19:09 PM**

@Magoo: please detail your workup method after you DCM extract the post reaction. I usually have also honey coloured amine swimming at the bottom (MDA base has a higher density then 10% NaOH/Water), lots of tiny droplets. But i have also some insoluble matter at the bottom of the beaker.
I use a 2 L Beaker with 1L 10% NaOH with 40g rather pure amide.
In my last run i used 50g amide in 1300ml 10% NaOH yielding 30g pure white amine*HCL, after acetone boil. I tried extract with xylene this time, so not to interfere with the insoluble matter on the ground of the beaker. But strange crystals formed when phases separated in the separatory funnel and also on the side of the beaker before separation. I never had this problem with DCM extraction. Human trials showed weaker batch then previous one.

@unlikely_username: what are the contaminations in the initially isolated freebase? And which of them can survive A/B extractions and several washes like described in my previous post.

ps: I usually extract the initial post hofmann reaction with DCM. In contrast to my description.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Zippy** on **March 16, 2016, 05:29:26 PM**

If you are getting such great yields then go the extra mile and distill the freebase and see how it ends up.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **brainchild** on **March 16, 2016, 06:11:38 PM**

I would if my vaccum pump be strong enough....

Title: **Re: Hofmann Rearrangement Yields**
Post by: **BakingBrad** on **March 17, 2016, 03:02:09 AM**

What's the BP of the freebase?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **magoo** on **March 17, 2016, 04:48:33 AM**

The bees lab skills are non existant, this is his introduction to real chemistry.
A bee must start somewhere on this long rewarding journey.
If any experienced bees can recommend any worthwhile learning resources, it would be appreciated

@unlikely_username
On the first tcca attempt 5g of brilliant white amide ran in 400ml water with 5g NaOH the reaction had light yellow blobs of oil stuck to inside of vessel, was extracted hot with Xylene, the combined extracts, when cooled had no ppt. The xylene soln. was then titrated with diluted HCl, aqueous layer was filtered then dried, leaving 3.2g MDA.HCl that smells very strongly of HCl.

The second tcca hoff attempt was 5g of sandy amide ran in 250ml 10% NaOH had a very visible blob of dark oil at bottom of RBF, was extracted cold with DCM, the combined extracts were left to dry until DCM evaporated, weighed .5mol equivalent of finely ground citric acid, added small amount of DCM to freebase, added citric acid to DCM soln., white chewing gum formed, was removed from soln. put in freezer for 30min, removed from freezer and placed with a warm air stream blowing across, within 20 mins went from soft chewing gum to very light yellow/off white hard solid of MDA.Citrate yeild 3.6g

The third attempt used 50g of sparkly white amide was run in 2500ml 10% NaOH had an almost clear layer of heavy oil, was extracted with DCM, was filtered warm, filter rinsed with warm DCM, which left ~300mg of white ppt(ICA??) on filter paper that had an odour of chlorine. Evaporated off DCM, leaving ~39g sweet smelling oil. Dissolved .5mol equivalant of citric acid in 100ml warm acetone, dripped the honey coloured freebase into warm acetone soln., turned into white chewing gum citrate before hitting the bottom, very exothermic, caused the acetone to boil :/
Yeilded 53g sticky citrate

He will probably wash with anhydrous acetone saturated with citric acid first, then try boiling acetone/IPA

ps: Only the second hoff attempt was done in glass w stirrer and careful temperature control, the others were done in a HDPE bottle w shaking and very lackadaisical temp control.

@zippy
Does it need to be distilled under vacuum?
He only has a water aspirator atm, a real vacuum pump is on the shopping list

@bakingbrad
He did not check the B.P. Shameful, i know, he will next time

---

Title: **Re: Hofmann Rearrangement Yields**
Post by: **BakingBrad** on **March 17, 2016, 04:56:24 AM**

Quote from: brainchild on March 16, 2016, 05:19:09 PM

> In my last run i used 50g amide in 1300ml 10% NaOH yielding 30g pure white amine*HCL, after acetone boil. I tried extract with xylene this time, so not to interfere with the insoluble matter on the ground of the beaker. But strange crystals formed when phases separated in the separatory funnel and also on the side of the beaker before separation. I never had this problem with DCM extraction. Human trials showed weaker batch then previous one.

What's you chlorine source? TCCA?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Zippy** on **March 17, 2016, 02:36:28 PM**

Yes you would distill it under vacuum. People keep talking about steam distillation here but I am not familiar with that technique.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Scarecrow** on **March 17, 2016, 06:51:52 PM**

Quote

> The third attempt used 50g of sparkly white amide was run in 2500ml 10% NaOH had an almost clear layer of

> heavy oil, was extracted with DCM, was filtered warm, filter rinsed with warm DCM, which left ~300mg of white ppt(ICA??) on filter paper that had an odour of chlorine. Evaporated off DCM, leaving ~39g sweet smelling oil. Dissolved .5mol equivalant of citric acid in 100ml warm acetone, dripped the honey coloured freebase into warm acetone soln., turned into white chewing gum citrate before hitting the bottom, very exothermic, caused the acetone to boil :/
> Yeilded 53g sticky citrate

"

Id reccomend using ether to extact your hoffman so you dont get ICA in your product

Scarescrow

Title: **Re: Hofmann Rearrangement Yields**
Post by: **magoo** on **March 18, 2016, 05:31:44 AM**

---

diethyl ether is significantly harder to obtain for this bee, is there a recommended way to remove ICA from the DCM?
I read that ICA is insoluble in acetone. Would it work if he dissolves the freebase in the minimum amount of acetone, then filters?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **ricky** on **March 18, 2016, 04:31:39 PM**

All these TLA's >.<

I assume that's some chlorinated byproduct from DCM and some reactive intermediate? >.>

Why not just make diethyl ether? It isn't hard, at all. Just don't light the place on fire :V

EtOH + H2SO4 === 140C ===> (C2H5)2O

Just don't go above that; I think at 160C you will start making mostly diethyl sulfate (a carcinogen).

Title: **Re: Hofmann Rearrangement Yields**
Post by: **brainchild** on **March 19, 2016, 07:44:28 AM**

Quote from: Scarecrow on March 17, 2016, 06:51:52 PM

> Quote
>
> > The third attempt used 50g of sparkly white amide was run in 2500ml 10% NaOH had an almost clear layer of heavy oil, was extracted with DCM, was filtered warm, filter rinsed with warm DCM, which left ~300mg of white ppt(ICA??) on filter paper that had an odour of chlorine. Evaporated off DCM, leaving ~39g sweet smelling oil. Dissolved .5mol equivalant of citric acid in 100ml warm acetone, dripped the honey coloured freebase into warm acetone soln., turned into white chewing gum citrate before hitting the bottom, very exothermic, caused the acetone to boil :/
> > Yeilded 53g sticky citrate
>
> "
>
> Id reccomend using ether to extact your hoffman so you dont get ICA in your product
>
> Scarescrow

Scarecrow, i also had the idea that some isocyanurate survives my clean up procedure. BUT is sodium isocyanurate even soluble in DCM?? I first highly doubt that, and after extracting the DCM with Acid water. Isocyanuricacid would be liberated but, its only soluble at 2g/L of water? Plus i wash the DCM Phase with brine and the Acid water phase with two times with DCM. Other possible side products of this reaction, could be the well know reaction between the reactive isocyanate intermediate whith amines, to form urea derivatives or build its own trimers of isocyanurates. I cant imagine the solubility of either.

@BakingBrad: Yes, TCCA

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Flasky Mountain Flask** on **March 19, 2016, 08:27:10 PM**

It seems like good practice to do multiple extractions to minimize impuritys.

Hoffman....>DCM/Ether/Tol....>drying sieve (silica gel swirled with solvent)....>aq. acid....>multiple nonpolar washes......>strong base.....>toluene....>drying sieve......>gas or titrate......>acetone wash......>re-crystallize

There's no substitute for a clean reaction workup. If you use DCM you really can't skip the drying step. DCM does dissolve some water, as well as whatever is dissolved in the water. using toluene or xylene would certainly bee cleaner for this purpose.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **brainchild** on **April 05, 2016, 11:48:42 AM**

Dcm dissolves only 0,24% of water, maybe a little more, if tiny droplets of emulsions form. You are certanly right, that multiple clean up steps are prefered. My only concern is not impuritys, its if they might be toxic to some degree. But i cannot imagine 10mg of a substance per dose being toxic, if i account for 10% impuritys. Which sounds high to me, but might be possible depending on cleanup. Breakage of the methylendioxy bridge should produce water soluble phenolic products, which should be washed away. Cl-Mda should not be produced in high enough quantity to have psychoactive effect.

I will try NaDcca next run i found more then a kg of it for 10 bucks at the hardware store by accident.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Tsathoggua** on **April 05, 2016, 01:35:00 PM**

Taking a little effort to ensure removal of the diol is advisable, as its likely to prove to be a monoaminergic neurotoxin, as are other dihydroxyamphetamines where the phenolic functions lie adjacent to each other on the ring, dopamine analogs expressing the same sort of substitution, and the likes of 5,6- and 6,7-dihydroxytryptamine are serotonergic neurotoxins too. Presumably due to the potential for generating ROS; and generally increasing focal oxidative stress.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **brainchild** on **April 05, 2016, 02:00:15 PM**

Yes, but are hydroxyamphtamines, extracted with dcm from strongly basic solutions? I imagine they form sodium salts, like other phenolic substances. Because these are my main concern when heating methylendioxy compounds in concentrated sodium hydroxide solutions. Maybe ill also try to lower the temperature in next run to 70 °C maximum after clhloramide formation. Because i can smell "that smell" of the desired product much earlier.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Tsathoggua** on **April 05, 2016, 02:42:33 PM**

Not sure on that brainchild. Do you mean mono-substituted or diol-type product such as may arise from cleavage of the benzodioxole ring?

On the one hand chances are that the phenolic groups will as said, form ionic sodium salts, not exactly lending itself to dissolution in nonpolars like dichlor, but if the amine is in freebase form then it may well have enough nonpolar character to permit its being extracted w/DCM all the same.

In the case of molecules bearing functional groups of opposing polarity, how does one then work out likely solvent affinities?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **brainchild** on **April 14, 2016, 11:02:20 AM**

I think when the MD bridge breaks compunds resembling dopamine would result.
Dopamine is at least insoluble in chloroform.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **ricky** on **April 14, 2016, 06:05:56 PM**

Hmm, I would guess the 1,3-Dioxane would need a stronger base than NaOH like sodium hydride or an alkoxide to cleave it. Acids would be easier and would form the aldehyde. A transacetylase I'd imagine, could form a chatecol derivative and strongly oxidizing conditions maybe either the lactone or cleavage to the alkane.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **magoo** on **May 13, 2016, 03:30:49 PM**

Has anyone removed the methylenedioxy ring on purpose?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **thewire** on **July 09, 2016, 08:36:24 PM**

Process for the preparation of cyclopropylamine
US 5032687 A

DE3836917A1, DE58908736D1, EP0367010A2, EP0367010A3, EP0367010B1

The present process for the preparation of cyclopropylamine by the so-called Hofmann degradation of cyclopropanecarboxamide is characterized in that the cyclopropanecarboxamide is employed in the form of a solution. The new process can be carried out at 5°-35° C. The cyclopropylamine is obtained after introducing the reaction

mixture into a concentrated alkali metal hydroxide solution.

Process for preparing amines
US 5410082 A

CA2123240A1, DE4315623A1, EP0628536A2, EP0628536A3, EP0628536B1

Process for preparing amines by reacting amides in aqueous-alkaline solutions and/or suspensions with halogens or hypohalites in the presence of alcohols, and converting the reaction products into the amines by hydrolysis, hydrogenation or reductive methods.

EXAMPLE 3
120 g of methanol, 70 g of water, 30 g (0.75 mol) of sodium hydroxide and 24.5 g (0.1 mol) of 2-benzyloxy 6-fuorobenzamide are initially introduced and heated to 40° C. Chlorine is passed in (4 l/h), the initially color less suspension assuming a brownish color after a short while, and it being possible to switch off the heating since the temperature is maintained owing to the reaction being exothermic. After 25 min, the reaction is concluded, as can be demonstrated by GC. A clear solution is obtained in place of the suspension which was present initially. The methanol is distilled off under a weak vacuum (50° C.), and the resulting suspension of 2-benzyloxy-6-fluoro-N-carboxymethoxyaniline is heated at 100° C. for 48 h. After the mixture has been cooled, 50 g of toluene are added, the phases are separated, and 2 g of MgSO4 and 1 g of active charcoal are added to the organic phase, which is stirred for some 7 hours. After filtration and removal of solvent on a rotary evaporator, 19.8 g (91 mmol, 91%) of 2-benzyloxy 6-fluoroaniline are obtained as a brownish, clear oil, which is of excellent purity (GC: >96%) for further reactlons.
2-Benzyloxy-6-fuoro-N-carbomethoxyaniline can be isolated by following the procedure already indicated in Example 1 but omitting the 48-hour hydrolysis of the intermediate, which is isolated and purifed by customary methods (in particular filtration and recrystallization).

EXAMPLE 5
190.0 g (1 mol) of 2,6-dichlorobenzamide are mixed together with 336.7 g (6 mol) of potassium hydroxide in 1000 g of water and 250 g of ethanol, and the suspension is heated to 50° C. Chlorine is passed in (6 l/h) at 55° C. for 4 h, excess halogen is then destroyed with sodium sulfite, and thereafter the mixture is heated at 99° C. for 36 h. After that, steam is passed into the mixture at 100° C. and the product is distilled off. The distillates are stirred in the cold at 0°—10° C., and 2,6-dichloroaniline is subsequently filltered off with suction. After drying, 147.3 g (0.909 mol, 91%) of 2,6-dichloroaniline are obtained as a colorless solid.

EXAMPLE 7
8.5 g (0.1 mol) of cyclopropanecarboxamide are introduced,

at 10° C, into 150 g of 30% sodium hydroxide
solution to which 20 g of benzyl alcohol have been
added. 17.6 g (0.11 mol) of bromine are added dropwise
at this temperature within 30 min. Subsequently, the
mixture is heated at 40° C. for 1 h in order to complete
the reaction, and excess bromine is destroyed using
sodium sulfite. After that, the mixture is boiled for 10 h
on a water separator, after which no further cyclopropylemine passes over.
The phases are separated, and
this is followed by drying with a little magnesium sulfate,
and 4.8 g (84 mmol, 84%) of cyclopropylamine are
distilled in a microdistillation apparatus at 48°—51° C.
;)

Title: **Re: Hofmann Rearrangement Yields**
Post by: **thewire** on **July 09, 2016, 11:51:11 PM**

Process for the preparation of amines
US 4198348 A
Abstract
There is described a process for the preparation of amines of the type RNH2, wherein R represents a hydrocarbon radical containing up to 18 carbon atoms, in particular an aliphatic, arylaliphatic, cycloaliphatic or aromatic radical, the said process being characterized by the fact that an amide having the formula RCONH2, wherein R has the aforesaid meaning, is reacted, at a pH less than or equal to 7, firstly with gaseous chlorine, in the absence or in the presence of a diluent, and the N-chloroamide thus formed is subsequently reacted with an alkali hydroxide and/or an earth alkali hydroxide.

EXAMPLE 1
A stream of gaseous chlorine is introduced at a speed
of 60 g/h into a solution of 127 g of hexahydrobenza
mide (1 mol) in 600 ml of CHC13, maintained at 0° C. 78
g of chlorine (1.099 mols), controlled by weighing, are
absorbed in 78 min.
The chlorinated product thus formed is poured onto
500 g of ground ice, the chloroform solution is sepa
rated and is washed with water until it becomes neutral.
A residue of 161 g of N-chlorohexahydrobenzamide
(quantitative yield) the active chlorine content of
which is 22% (theoretical 21.93%) is obtained by
evaporation of the solvent.
64.64 g (0.4 mol) of N-chlorohexahydrobenzamide
100%, obtained as set forth above, is added during an
hour to a solution of 32.32 g of 99% pure sodium hy
droxide (0.8 mol) dissolved in 400 ml of water and main
tained at a temperature comprised between 20" and 22°C.
The mixture thus obtained is kept under stirring for
one hour at 20° C., then it is heated for one hour at 80°
C., and the cyclohexylamine /water azeotropic mixture
thus obtained is distilled (distillation temperature 96" C.;
cyclohexylamine content in the azeotropic mixture:
44.4%).188 g containing 21% by weight of cyclohexylamine
are thus obtained, which corresponds to a yield of
***99.4%** of theory.*

EXAMPLE 2

Gaseous chlorine is introduced at a speed of 66 g/h into a suspension of 256 g of hexahydrobenzamide(2 mols) in 1700 ml of water maintained under stirring at 20° C. After 2 h and 28 min 163 g of chlorine have been obsorbed, corresponding to 2.3 mols. After separating the N-chlorohexahydrobenzamide from the suspension by ?ltration, it is washed with water until the acidity has been eliminated. 310 g of N-chlorohexahydrobenzamide (yield 95.75%) having a chlorine content of 21.1% (theoretical value a 21.93%) are thus obtained. 67.18 g (0.4 mol) of 96.22% pure N-chlorohexahydrobenzamide obtained as herein before described, are added during one hour to a sus pension of 46.79 g of 95% pure calcium hydroxide (0.6 mol) in 2500 ml of water maintained at a temperature of 20°-25° C.The mixture is stirred at 20°~25° C. until all active chlorine has disappeared, is heated for another 30 min at 80° C., then the cyclohexylamine is distilled in azeo tropic mixture with water at a temperature between 96° and 99° C., whereby 468 g of a solution containing 7.79% of cyclohexylamine, corresponding to a yield of 92% of theory, are obtained.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **RegularOldGuy** on **January 15, 2017, 01:17:14 PM**

Haven't seem much activity on this lately but thought I would post some of my results.

So far I have run this twice using 2 different methods, pretty happy with the yields given the simplicity of everything.

1st (b6baddawg method)
22g amide
10g TCCA
1100mL 10% NaOH

Dissolve the TCCA in NaOH solution while in ice bath, slowly added amide over the course of a few hours.
Attached reflux condenser and heated slowly to 90C, maintained for 1.5hr and cut heat, let cool down to room temp.
2 toluene pulls, washed with brine twice, dried over sodium sulfite.
Gassed, filtered, acetone wash, dual solvent recrystallization (acetone/methanol) to yield 14.3g of dry white crystal. **65%** by weight of starting amide.

2nd (Scarecrow method)
39.9g amide
14g TCCA
1000mL 10% NaOH

Combined 500mL of the NaOH solution with amide and TCCA whilst on icebath, let stir for approx 8hrs.
Heated remainder 500mL NaOH up to about 90C, added the solution from previous step over 2 hours and let it continue after last addition for another hour.
2 toluene pulls, washed with brine twice, dried over sodium sulfite.
Gassed, filtered, acetone wash, dual solvent recrystallization (acetone/methanol) to yield

28.3g of dry white crystal. **70%** by weight of starting amide.

Notes:
1st method was a bit easier effort wise.
Volume of NaOH solution makes a big difference in foaming/froth, the 400mL used in the 2nd was very thick after a bit.
Have some NaDCCA I am going to try next, DCCA was sourced from 'hockeypuck' style pellet.

Bioassay scheduled for today :P

Title: **Re: Hofmann Rearrangement Yields**
Post by: **thinkgeek** on **January 15, 2017, 07:31:46 PM**

---

props to regularoldguy for continuing research on this
its been a while since i have tried this synth..
what would you say your overall yield was on this ? from aldehyde to amine?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **RegularOldGuy** on **January 16, 2017, 12:06:53 AM**

Quote from: thinkgeek on January 15, 2017, 07:31:46 PM

> what would you say your overall yield was on this ? from aldehyde to amine?

Hmm, its kind of hard to tell at the moment, I did the oximations in several different batches and not been keeping track of how much in->out entire since all the different processes, once I finish everything up I should have a decent idea though, will report back on that. Stuff is so cheap though its not a huge deal.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **NotGuilty** on **January 16, 2017, 12:35:34 AM**

If you are going the TCCA route I recommend use overhead stirring with a regular hotplate. I've noticed it's way more consistently high-yielding than a stir-bar/hotplate combo.

With overhead stirring I get virtually the same yield on every batch and less formation of foam, with stir-bar it was slightly different yields every batch and I always had to be careful to break up the foam and pour chemicals into the whirlpool slowly.

What are you guys doing for workup after hot addition?

I was using Xylene and it was horrible, now I use DCM with much better success, is Toulene better than DCM? I know Ether is great but I don't want to fuck around with large quantities of it.

I'm doing 2-3 pulls with DCM, acid-base with Hcl and leave it in a bucket for a few days to form nice brownish rocks. Used to gas but sulphuric acid is watched-as-fuck here. Lab tests are coming back around 95% pure final product with no traces of DCM or residual Hcl. I used to take the extra step of acetone washing and recrystallization, then blending to yield a fluffy white powder but then people down the line complained and asked for the brownish rocks instead.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **RegularOldGuy** on **January 16, 2017, 01:37:36 AM**

I didn't have much of an issue keeping things moving, used a giant stirbar (can only fit in the 45/50 hole) which seems to help, more so the issue was solubility at the colder temps.

I'm pretty sick of the xylene smell so I wanted to avoid it, I mostly went with the toluene because I don't mind the smell as much as DCM and xylene and I have a jug of it that has been cleaned & recycled maybe 20 times over by now lol, still works great though.

Not seen anything brown come out yet, the first pull is pretty yellowish and the 2nd not as much, some of this comes over when filtering but doing the dual solvent recrystallize pulls any last bit of color out leaving the acetone a bit yellow but the crystals white.

For gassing I use CaCl2+HCl and a little aquarium pump to keep some air moving through the system, works great not had any issues with moisture.

Bioassay went great today, incredible experience. Thanks to everyone who contributed their notes and research which has helped me get to this point.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Scarecrow** on **January 16, 2017, 07:50:07 AM**

Quote from: NotGuilty on January 16, 2017, 12:35:34 AM

> If you are going the TCCA route I recommend use overhead stirring with a regular hotplate. I've noticed it's way more consistently high-yielding than a stir-bar/hotplate combo.
>
> With overhead stirring I get virtually the same yield on every batch and less formation of foam, with stir-bar it was slightly different yields every batch and I always had to be careful to break up the foam and pour chemicals into the whirlpool slowly.
>
> What are you guys doing for workup after hot addition?
>
> I was using Xylene and it was horrible, now I use DCM with much better success, is Toulene better than DCM? I know Ether is great but I don't want to fuck around with large quantities of it.
>
> I'm doing 2-3 pulls with DCM, acid-base with Hcl and leave it in a bucket for a few days to form nice brownish rocks. Used to gas but sulphuric acid is watched-as-fuck here. Lab tests are coming back around 95% pure final product with no traces of DCM or residual Hcl. I used to take the extra step of acetone washing and recrystallization, then blending to yield a fluffy white powder but then people down the line complained and asked for the brownish rocks instead.

What do you think the brown aromatic smelling byproduct is?

I recently ran a Hoffman, and I only had a 1L sep fun for 1.4L of liquid. So after cooling the post rxn hoffman, I poured half into the sep and extracted thrice with ether giving light yellow extacts. Then the second half, I noticed some red oil that had separated out to the bottom of the flask. I extracted once, and got a dark brown extract which had pulled the dark oil over with it, the next two extracts came out light yellow like the original extracts.

Anyway I tried to clean up the brown ether extract with brine and water to no avail, as in the past ive combined these with the cleaner ether extracts, but then have been unable to remove the brown from the product even with multiple acetone/ipa recrystalizations.

Since I dont know what this byproduct is, its hard to remove it from the ether. I may just have to acid extract and wash the acid extracts with some hexane and ethyl acetate.

Would be nice to know what it is though

Title: **Re: Hofmann Rearrangement Yields**
Post by: **NotGuilty** on **January 17, 2017, 12:28:23 PM**

Quote from: Scarecrow on January 16, 2017, 07:50:07 AM

> What do you think the brown aromatic smelling byproduct is?

I can't explain why but i've noticed that using aldehyde with a slightly lower density than normal results in a browner end product. Without fail, the lower the density of the aldehyde I use compared to the density in the literature of 1.162 g/ml the more brown the end product is, despite the intermediate steps being the same.

The thing that's most strange is that my amide appears to be great regardless of the density of the aldehyde, lately it's been coming out like beautiful white snow without even a tinge of yellow.

The lab that I use unfortunately cannot tell me what it is, they can only test for illicit substances, precursors they have a GC/MS sample to compare to, and other known chemicals that may harm an end user.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **NotGuilty** on **January 19, 2017, 01:14:59 AM**

A recent experiment:
A 25L stainless steel vessel was set up in a fridge with an overhead stirrer attached to a paint mixing paddle. The setup was tested with water first and the blades of the paddle cut to ensure liquid would not splash on high rates of stirring. After set up and testing the fridge was cooled to -2C

1800g of 98% pure Sodium Hydroxide was prepared into a 10% solution and the resulting 18L of liquid was poured into the vessel. Stirring was commenced and left to cool a little, about 30 minutes.

1500g of carefully purified and powdered amide was poured into the vessel through a funnel and left to stir until dissolution, about 2 hours.

616.2g of Chlorine (TCCA) is added in 12 portions with 6 minutes between additions. During each addition the stir speed is turned up high.

Exothermia begins during the last 3 additions and starts to develop rapidly, temperature of the fridge climbing from 0C to about 15C in about 10 minutes.

As an emergency measure ice is quickly crushed, poured in plastic bags and packed around the vessel. Temperature climbs to about 24C before beginning to drop slowly. The ice is replaced as needed and the temperature continues to slowly drop, reaching 9C after about 3 hours and 1C after about 5 hours.

After 5 hours it hasn't turned into that creamy milk that lets you know it's done so the vessel is then spun overnight for about 12 hours.

Upon coming back to the lab the Hoffmann has milked but it looks a bit dirty compared to smaller batches i've done. I also notice the chlorine has begun to attack the side of the vessel, i'm guessing a HDPE vessel might be better for this. Perhaps this may result in some loss of yield as Chlorine is reacting with the stainless steel instead of the amide, but i'm only a practitioner of chemistry and don't have any theoretical knowledge so i'm not sure on this.

Hot additions are commenced, splitting up the batch and doing a bit at a time as I don't have enough hotplate/stirrers to do it all at once. The n-chloramide solution is added slowly to 10% NaOH solution which was pre-heated to 90C. This is spun for 30 minutes and then combined in a seperate vessel to cool.

3 pulls are made with DCM before an acid-base. Crystallization is begun in buckets placed under dehydrators. Once it's done I will report back with yields, but it already looks like close to a KG, maybe a touch under around 900g.

Notes:
If anyone is going to try it be careful with the NaOH, it gets everywhere when you are using heaps of it. If you don't wear proper protective equipment just touching the inside of the fridge anywhere will begin to burn you.

Questions:
For the next run I might use HDPE in a salt water bath inside the fridge, can anyone advise me as to whether HDPE is appropriate for the beckmann/hoffmann?

Also, does anyone have any tips on scaling the hot additions? It took me almost an entire day doing it in portions in 5L beakers over 2 stirrers.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **RegularOldGuy** on **January 19, 2017, 06:21:30 AM**

Using a a peristaltic pump may be helpful for the additions, pretty cheap and not much that can really go wrong with them.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **NotGuilty** on **January 19, 2017, 09:08:48 AM**

Quote from: RegularOldGuy on January 19, 2017, 06:21:30 AM

> Using a a peristaltic pump may be helpful for the additions, pretty cheap and not much that can really go wrong with them.

Pardon my ignorance, but how would I use the pump to optimize the additions?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **NotGuilty** on **January 22, 2017, 09:12:41 AM**

Thought I would report back to let you guys know that yields were actually not that good after a proper cleanup including acetone wash.

675g of pure amine out of 1500g amide, or 45%.

I believe this could have been due to 3 factors:
1. The chlorine attacking the stainless steel vessel instead of reacting in the solution.
2. The temperature rising too high during the process

3. Using a paint mixing paddle instead of a teflon stir-bar which doesn't give as nice of a whirlpool

I've run another experiment of the same size with a HDPE bucket in a salt water bath (As much water as I could fit before boyency became an issue), with a teflon stir-bar. Hopefully yields will be better on this, i'm in the workup stage now.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **thinkgeek** on **January 26, 2017, 11:33:06 PM**

Quote from: NotGuilty on January 22, 2017, 09:12:41 AM

> Thought I would report back to let you guys know that yields were actually not that good after a proper cleanup including acetone wash.
>
> 675g of pure amine out of 1500g amide, or 45%.
>
> I believe this could have been due to 3 factors:
> 1. The chlorine attacking the stainless steel vessel instead of reacting in the solution.
> 2. The temperature rising too high during the process
> 3. Using a paint mixing paddle instead of a teflon stir-bar which doesn't give as nice of a whirlpool
>
> I've run another experiment of the same size with a HDPE bucket in a salt water bath (As much water as I could fit before boyency became an issue), with a teflon stir-bar. Hopefully yields will be better on this, i'm in the workup stage now.

well i think 45% is still pretty legit. thanks alot for sharing your research efforts..

Title: **Re: Hofmann Rearrangement Yields**
Post by: **d00 it now!** on **March 07, 2017, 03:19:37 AM**

Quote from: magoo on May 13, 2016, 03:30:49 PM

> Has anyone removed the methylenedioxy ring on purpose?

Yes. (Well, not the first time, that was a Eureka moment)

Just use too much sulfuric acid when salting the freebase amine. Bingo! Slightly pink primary amine, MP close to lit after typical work up. Bioassay confirms DEFINITELY NOT the 3,4-MD product. Can get messy, and undoubtedly some loss of product, but that being said I'm sure it could be optimized :)

Or you could just rearrange your Oxime w/ Sulfuric and in the process cleave that MD ring (The atypical procedure in Vogels for Oxime --> Amide) Can't confirm that this works, last time tried it just instantly created a polymerized mess.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **phantograx** on **March 29, 2017, 09:49:59 AM**

Quote from: d00d00d00 on March 07, 2017, 03:19:37 AM

> Just use too much sulfuric acid when salting the freebase amine. Bingo! Slightly pink primary amine, MP close to lit after typical work up. Bioassay confirms DEFINITELY NOT the 3,4-MD product. Can get messy, and undoubtedly some loss of product, but that being said I'm sure it could be optimized :)

So these results sound rather puzzling to me for several reasons.
Why would you perform this theoretical MD ring decomposition at the very last step after obtaining the amine? Do you think this could not be run after isolating the amide or even

to bring it back right to the beginning, on the aldehyde? If one was able to have total removal of the methylenedioxy group i would imagine running the known steps back to the amine would likely achieve higher yields due to a smaller more reactive starting compound of 2-methyl-3-phenylpropanal which bares resemblance to a-methylcinnamaldehyde less one double bond.

Also struggling to understand the proposed mechanism here, is the implication that a low ph addition causes total removal of the 3,4 substitutions or could we possibly be dealing with the potential for a 3,4-hydroxy compound which could be a source for the known neurotoxic compound 3,4-dihydroxyamphetamine https://en.wikipedia.org/wiki/Alpha-Methyldopamine (https://en.wikipedia.org/wiki/Alpha-Methyldopamine)

Title: **Re: Hofmann Rearrangement Yields**
Post by: **d00 it now!** on **March 30, 2017, 08:36:58 AM**

It wasn't an intended removal of the MD-ring. It happened as a result of using far too much H2SO4 titrating. Not claiming its ideal in any way shape or form. Just that it happened. Wet tests/bioassay was consistent with literature.

It may or may not be able to be done earlier on in the preparation, this is not known for certain. There is a very likely possibility that one of the earlier steps can be done with H2SO4 at the cost of the ring.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **dingbow** on **May 02, 2019, 02:53:26 PM**

Well, this certainly brings back memories and a few smiles :)

Title: **Re: Hofmann Rearrangement Yields**
Post by: **unlikely_username** on **May 02, 2019, 07:21:19 PM**

Quote from: dingbow on May 02, 2019, 02:53:26 PM

> Well, this certainly brings back memories and a few smiles :)

Right? It's a bit of a shame things died down.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **aes256** on **May 14, 2019, 07:06:31 AM**

Does anyone else get alarming odours coming from their Hofmann's when doing >= 5g of amide reactions? Maybe it's a result of excess TCCA..?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **fries** on **July 23, 2019, 01:45:01 PM**

Quote from: dingbow on May 02, 2019, 02:53:26 PM

> Well, this certainly brings back memories and a few smiles :)

Wow, 8 years on and this thread is still going :)

That was some great fun :D

Title: **Re: Hofmann Rearrangement Yields**
Post by: **sparklebags** on **September 25, 2019, 10:37:56 PM**

I have done a few Hoffmans, with success, but not getting the yields I should be. Here is a general idea of what I have been doing and what I think is wrong.

I make a solution of 10%NaOH, cool it to below 15* (maybe even down to 10*)
Add bone dry amide
Add 1/3 molar TCCA all at once
Let sit in ice bath stirring for 6 hrs
Divide into portions that are brought up to 90* on hot plates in flasks. Once 90* is reached, heat is discontinued but flasks remain on hot plates to cool
Portions are added back to original container for extraction with toluene.
Dried with Na2So4.
Gassed with HCL.
Yields have been around 30-40%.

My next attempt I plan to add the TCCA slower, perhaps let it mix for longer? I also think I am not heating enough. So I plan to bring it to 90*, let it stay there for 2hrs then discontinue heat. I also am unsure if I am extracting correctly. If I have say 10L of solution I have been using about 15% solvent (1.5L). I will do one 1 liter extraction, then a .5 liter extraction. Honestly, the 3rd extractions never yield anything so I stopped doing that. Perhaps some modification to my extraction is in order. I also though perhaps giving the solvent a longer dwell time but it seems to separate fairly quickly with a clear line. Lastly, I thought perhaps I could also use a brine solution to further assist in drying.I also have some 3A sieves I thought about using and I am not sure Na2SO4 is the best drying agent. Perhaps I can follow this one. Thanks for your input:

39.9g amide
14g TCCA
1000mL 10% NaOH

Combined 500mL of the NaOH solution with amide and TCCA whilst on icebath, let stir for approx 8hrs.
Heated remainder 500mL NaOH up to about 90C, added the solution from previous step over 2 hours and let it continue after last addition for another hour.
2 toluene pulls, washed with brine twice, dried over sodium sulfite.
Gassed, filtered, acetone wash, dual solvent recrystallization (acetone/methanol) to yield 28.3g of dry white crystal. 70% by weight of starting amide.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Ammaniac** on **September 27, 2019, 04:25:30 AM**

What procedure did you use to make your amide?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **sparklebags** on **September 27, 2019, 04:48:48 AM**

100g aldehyde was added to 500g of DMSO in a 5 liter flask. Heat was applied until temp. reached 70*c. Heat was discontinued and allowed to keep stirring on hot plate.

37g of NH20H-hcl was added slowly to maintain temp of 85*c-90*c. Essentially, the heat can be controlled via the addition. Once all was added, allowed to cool to 70*, ph brought to 10 and H2O2 addition began. Added 600ml of 29% H2O2 with ph kept at 10. Allowed to cool on stirrer. Filtered, washed with cold water. Yield approximately 70%.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **sparklebags** on **September 28, 2019, 03:20:04 PM**

Yields after the Hoffman increased to 60%. Heated for 3 hrs at 90*, allowed to cool overnight. Also used a slight excess of chlorine. I think with even longer heating yield could be increased even more.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **loft** on **January 27, 2020, 11:58:31 AM**

So it's been a while since this reaction was first discussed here and recently a new century had begun.

Are there any alternatives or new approaches to this low yielding reaction?
There is a review that might cover exactly this, however I'm unable to source it. If someone could give it a try?
https://www.eurekaselect.com/175956/article

Title: **Re: Hofmann Rearrangement Yields**
Post by: **carl** on **January 27, 2020, 09:12:06 PM**

Try NBS, that gives good yields.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **sparklebags** on **February 04, 2020, 06:27:43 PM**

NBS - in place of the TCCA? I actually have been getting pretty good yields with the Hoffmann ~ 70% of amide used. However, my amide formation has been giving me fits. If I do it in smallish batches in erlenmeyer flasks, I regularly get 70% of aldehyde used in return. If I try to combine multiple reactions into a larger vessel (say 15 gallon stainless pot) with overhead stirring I end up with as low as low as 50%. I keep the temp. the same, ph in check, add H2O2 into the vortex created by the stirrer. No clue why it lowers the yields so much - it def. cools off faster than glass, thus letting the reaction be ran faster. My only thoughts are - temp. is cooling too fast and H202 is boiling off on the surface due to larger area and scale of additions.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Corrosive Joeseph** on **February 13, 2020, 02:35:09 PM**

Quote from: loft on January 27, 2020, 11:58:31 AM

> So it's been a while since this reaction was first discussed here and recently a new century had begun.
>
> Are there any alternatives or new approaches to this low yielding reaction?
> There is a review that might cover exactly this, however I'm unable to source it. If someone could give it a try?
> https://www.eurekaselect.com/175956/article

It would appear that this paper cannot bee got..... I placed requests on two other forums after loft's post, but with no success. Also tried all my usual paper-retrieving 'tricks' and again, no dice..... The only saving grace is that the abstract page itself contains a list of the 101 references used to write the review, so maybe this will help anybody wanting to dig deep.

If the paper does surface in the future, I will post it, but for now....

/CJ

Title: **Re: Hofmann Rearrangement Yields**
Post by: **loft** on **February 13, 2020, 04:08:19 PM**

Thank you for trying Joe :)

Title: **Re: Hofmann Rearrangement Yields**
Post by: **atara** on **February 20, 2020, 05:50:53 AM**

People get good yields with the Hofmann, but not with the quick methods. You have to have clean reagents and there are advantages to using bromine compounds.

No reagent or alternative reaction is ever going to be as OTC as TCCA. Unless they start selling trimethylsilyl azide at Home Depot.

Sometimes I fantasize about finding a more OTC replacement for succinimide. Apparently N,N-diformylimide is very easy to synthesize (formamide + methoxide):

http://anonym.to/http://www.sciencemadness.org/talk/viewthread.php?tid=40900#pid358020

This gets even easier if you use KOMe from K2CO3/MeOH (both anhydrous):

http://www.sciencemadness.org/talk/viewthread.php?tid=76805

Title: **Re: Hofmann Rearrangement Yields**
Post by: **carl** on **February 20, 2020, 05:59:40 AM**

You thinking about using N-halodiformylamide as a reagent for the hofmann?

Saccharin is very OTC and can easily be halogenated as the sodium salt using oxone and a halogen salt in water, I tried that already for N-chlorosaccharin.
This should likely work too for the hofmann rearrangement I would assume.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **atara** on **February 20, 2020, 02:28:40 PM**

Yeah. The formyl groups might look unstable, but performic acid worked really well, so why not N-bromodiformylimide? It's worth trying if succinic acid is not available.

Saccharin is great, but is it OTC in sufficient quantity? A few milligrams of saccharin is enough to make coffee taste like Coca-cola.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **carl** on **February 20, 2020, 04:21:49 PM**

Quote from: atara on February 20, 2020, 02:28:40 PM

> Yeah. The formyl groups might look unstable, but performic acid worked really well, so why not N-bromodiformylimide? It's worth trying if succinic acid is not available.
>
> Saccharin is great, but is it OTC in sufficient quantity? A few milligrams of saccharin is enough to make coffee taste like Coca-cola.

Hmm.
I can try if I am able to make some N-halodiformylimide, I have done a bit of experimentation with sodium diformylamide already(and reported about it on here), so it might be interesting.
Would try it with oxone and KBr in water maybe, likewise to the N-halosaccharin preparation?

Well... sodium saccharin is not really on the shelves in the super market, but it can cheap and nonsuspiciously be found online.
I got myself 50g some time ago and it was really cheap too, something like 9€, and I've seen large bulk offers online too.
Much cheaper than succinimide, thats for sure!

We should also keep N-halophthalimides in mind, I've seen a paper where they used N-bromophthalimide for the hofmann.
And phthalimide forms salts easily with KOH in alcohol, then the same process using a halogen salt and oxone in water could be applied.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **atara** on **February 21, 2020, 04:39:40 AM**

Oxone/KBr seems fine. I would guess N-bromodiformylimide precipitates from water.

I suppose online saccharin is good enough. It doesn't seem especially easy to track.

Either one is also interesting for the reactions that require controlled halogenation, such as the oxidation of piperidine to 2,3,4,5-tetrahydropyridine.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **atara** on **February 23, 2020, 06:02:41 AM**

Regarding some points in your PM:

Quote

> And lastly, regarding your proposed N-halodiformylimide: do you really expect it to be barely or even insoluble in water?

I would guess that it will be much less soluble than the salts of diformylimide, and probably rather insoluble in saturated salt solutions. It should not be a very polar molecule due to symmetry, amide delocalization and the very close electronegativities of bromine (2.98) and nitrogen (3.04).

To reduce losses, I would expect it to partition into DCM or EtOAc so it can be extracted that way. Chloroform or ether probably should not be used here.

Quote

> Yet while formamide is rather easily made, there is a huge issue working that up... usually 5-7 distillations are needed to obtain it rather pure and without discolouration.

Good to know. I don't know what happens if you use impure formamide.

If we're being ambitious, suppose you perform the *whole* stupid process at once. Prepare solutions of formaldehyde, ammonia and methoxide in methanol. Add the formaldehyde to the methoxide solution and wait for the Tischenko reaction to complete (2 H2CO >> MeOCHO), then add the ammonia which will react with methyl formate to formamide and presumably again to diformylimide. It would be necessary to ensure all or nearly all of the formaldehyde has converted to methyl formate before adding ammonia in order to prevent the formation of hexamine.

Quote

> But honestly, I would rather put my bet on using Li-strips from batteries and make that gabriel reagent from it instead, seems easier and with less issues to work too, and the Li-diformylamide is a known and working salt too.

LiOMe may be more convenient and easier in this case. There are definitely some cases where you don't want lithium due to the "greasy"/"ester-like" nature of some lithium salts. Diformylimide is not lipophilic and the lithium salt acts like a salt.

Quote

> N-halosaccharines aren't much, but considered the huge volume of water needed for the halogenation of alkali metal saccharin salts, that limited solubility still results in a little loss, and seemingly for N-halosuccinimides even worse, with even more losses.

I would have to look more into it but at a glance I would be surprised if you need to use as much water for brominating diformylimide as you do for saccharin. Saccharin is pretty hydrophobic due to the aromatic ring. Diformylimide is small and charged which practically guarantees solubility unless the salt has especially low lattice energy.

Quote

> even if the N-halogenation of amides doesn't work well with it, even if the a-halogenation of ketones doesn't work well with it, hell, even if it isn't useful to halogenate 2C-H... I am sure it can do at least one of these reactions

I hadn't even thought of using it for 2C-H. Is NBS good for this rxn? Does it outperform the standard NH4Br/H2O2/HOAc?

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Scarecrow** on **February 23, 2020, 08:11:23 AM**

This is not particularly relevant to what you are discussing above, but is to the thread title.

The way I found best to do this was to make the isopropyl carbamate, isolate that, and then you can methylate your free hydrogen on the nitrogen with Methyl Tosylate or Iodide.

Then deprotect your carbamate to get MDMA. Or you can skip that and just hydrolize the carbamate to give you MDA in 80%+ yields

---

Title: **Re: Hofmann Rearrangement Yields**
Post by: **carl** on **February 23, 2020, 11:31:17 PM**

OT, but:

Quote from: atara on February 23, 2020, 06:02:41 AM

> Quote
>
> > even if the N-halogenation of amides doesn't work well with it, even if the a-halogenation of ketones doesn't work well with it, hell, even if it isn't useful to halogenate 2C-H... I am sure it can do at least one of these reactions
>
> I hadn't even thought of using it for 2C-H. Is NBS good for this rxn? Does it outperform the standard NH4Br/H2O2/HOAc?

NBS is very useful for that, it is rather quick and clean but since I haven't done another bromination on 2C-H and only did that once with NBS, I can't tell.
The advantage is you get the HCl salt(since you start with the HCl salt of 2C-H) and it doesn't need much purification since you simply filter it off in the end, without having to work with any obnoxious fumes.
And the HCl salt can be vaped very well, providing a short and intense trip.
If we can do that with N-bromosaccharin(how are we going to abbreviate that in the future if it proves to be as useful if we can expect it to be? NBSacc maybe?), well, in my opinion that would be a game changer.

If we can use that for the hofmann too, very nice!
Or for ketone halogenations too, that would enable everyone to cook up some cathinones and in consequence amino alcohols and amphetamines completely OTC... the implications are so huge.
And I know for sure that N-chlorosaccharin can be used to chlorinate ketones, I saw a reference about that.
Nothing speaks against them being of use for these things.

But enough rambling, I will report back when I received the methanol on its way and was able to make some new sodium diformylamide and was able to brominate it successful.

Title: **Re: Hofmann Rearrangement Yields**
Post by: **Corrosive Joeseph** on **April 19, 2020, 02:00:23 AM**

Quote from: loft on January 27, 2020, 11:58:31 AM

> So it's been a while since this reaction was first discussed here and recently a new decade had begun.
>
> Are there any alternatives or new approaches to this low yielding reaction?
> There is a review that might cover exactly this, however I'm unable to source it. If someone could give it a try?
> https://www.eurekaselect.com/175956/article

Quote from: Corrosive Joeseph on September 27, 2019, 12:46:42 AM

> I don't give up easy

Pradip Debnath
Recent Advances in the Hofmann Rearrangement and Its Application to Natural Product Synthesis
Current Organic Chemistry, 2019, 23(22), 2402-2435
DOI: 10.2174/1385272823666191021115508

is now attached....   ;)

/CJ

Title: **Re: Hofmann Rearrangement Yields**
Post by: **loft** on **April 19, 2020, 08:35:38 AM**

What more need be said? You are the best Joe :D

Title: **Re: Hofmann Rearrangement Yields**
Post by: **capableshark** on **April 19, 2020, 09:52:24 AM**

Quote from: Corrosive Joeseph on April 19, 2020, 02:00:23 AM

> Quote from: loft on January 27, 2020, 11:58:31 AM
>
> > So it's been a while since this reaction was first discussed here and recently a new decade had begun.
> >
> > Are there any alternatives or new approaches to this low yielding reaction?
> > There is a review that might cover exactly this, however I'm unable to source it. If someone could give it a try?
> > https://www.eurekaselect.com/175956/article
>
> Quote from: Corrosive Joeseph on September 27, 2019, 12:46:42 AM
>
> > I don't give up easy
>
> Pradip Debnath
> Recent Advances in the Hofmann Rearrangement and Its Application to Natural Product Synthesis
> Current Organic Chemistry, 2019, 23(22), 2402-2435
> DOI: 10.2174/1385272823666191021115508
>
> is now attached....   ;)
>
> /CJ

Good read!
Thanks :)

Title: **Re: Hofmann Rearrangement Yields**
Post by: **thewire** on **June 24, 2021, 03:40:15 AM**

Code: [Select]

```
10.1021/acs.oprd.6b00246

Abstract
A novel process has been described on 100 g scale for the preparation of gabapentin
lactam which is a penultimate intermediate for the preparation of gabapentin, comprising
a Hofmann reaction of 1,1-cyclohexanediacetic acid monoamide using chlorinating agents
such as trichloroisocyanuric acid, sodium dichloroisocyanurate, 1,3-dichloro-5,5-
dimethylhydantoin,
and N-chlorosuccinimide, which have not been employed so far for making this molecule.
Reactions done in aqueous alkali on the 1,1-cyclohexanediacetic acid monoamide led to a
solution of gabapentin sodium salt which on heating led to the formation of the
gabapentin lactam in good yield.
```

Title: **Re: Hofmann Rearrangement Yields**
Post by: **aes256** on **July 24, 2021, 05:49:17 PM**

Quote from: Scarecrow on February 23, 2020, 08:11:23 AM

> This is not particularly relevant to what you are discussing above, but is to the thread title.
>
> The way I found best to do this was to make the isopropyl carbamate, isolate that, and then you can methylate your free hydrogen on the nitrogen with Methyl Tosylate or Iodide.
>
> Then deprotect your carbamate to get MDMA. Or you can skip that and just hydrolize the carbamate to give you MDA in 80%+ yields

I take it you were able to overcome the troubles you faced with the carbamate documented in this thread https://www.thevespiary.org/talk/index.php?topic=14549.msg54163988