



## Nitrostyrene reduction using NaBH<sub>4</sub>/CuCl<sub>2</sub>

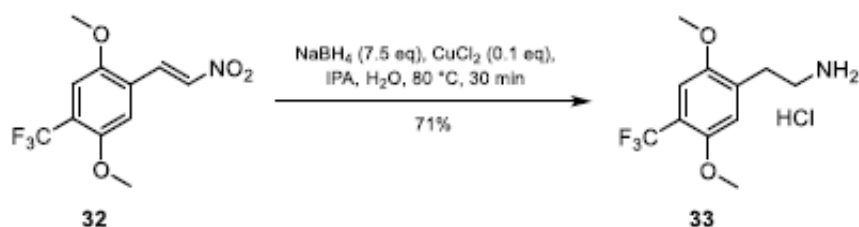
karlar - 11-7-2018 at 02:54

Just found this rather recent master thesis. Nothing too interesting, but what caught my eye was the method in which the author reduces his nitrostyrenes.

I have seen some similar methods in which NaBH<sub>4</sub> and a nickel salt has been used for reducing nitrostyrenes to phenethylamines, but I have not seen it being done in one pot previously.

Here is the method:

Quote:



Nitrostyrene **32** (2.77 g, 10 mmol) was added carefully in portions to a stirred suspension of NaBH<sub>4</sub> (2.84 g, 75 mmol) in IPA (32 ml) and water (16 ml) causing an exothermic reaction increasing the temperature of the mixture to 50-60°C. Thereafter a 2M solution of CuCl<sub>2</sub> (0.5 ml, 1 mmol) was added carefully dropwise causing further exothermicity. The reaction was then held at 80°C for 30 minutes using external heating. After reaching r.t, a 25% solution of NaOH (20 ml) was added under stirring and the phases were separated. The aqueous phase was thereafter extracted with IPA (3x30 ml). The extractions were combined, dried over MgSO<sub>4</sub> and filtered. A stoichiometric amount of 4M HCl in dioxane was added to the filtrate under stirring. The mixture was evaporated yielding a greyish sludge that was suspended in dry acetone and stirred for 1 h. The suspension was thereafter filtered and washed with dry acetone to yield **33** as a colorless amorphous solid (2.02 g, 71%).

Is anyone up for trying this method out? Would be interesting to see if its legit or not.

Attachment: [thesis.pdf](#) (3.1MB)

This file has been downloaded 2683 times

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Chemi Pharma - 11-7-2018 at 09:38

I have already documented here the reduction of nitrostyrenes with nickel boride (NaBH<sub>4</sub> + NiCl<sub>2</sub> in methanol): <http://www.sciencemadness.org/talk/viewthread.php?tid=80555&...> Have already documented the reduction of nitrocompounds with NaBH<sub>4</sub> and CuSO<sub>4</sub>·5 H<sub>2</sub>O in ethanol at 0°C either: <http://www.sciencemadness.org/talk/viewthread.php?tid=66278&...>

What worried me at your synthesys @Karlar, is the work up. First I don't understand why to use 25% NaOH, since there's no acid enviroment to neutralize when the reaction finish. I desagree any HCl will be produced in this reaction, like your equation said. Second the excess of borohydride must be neutralized with an acid, not with a base. Third, IPA isn't the right solvent to extract the aquous layer, but a non polar or aprotic solvent, like

ether or DCM. If the Ph of the reaction were acid, the amine will be dissolved at the aqueous layer, in the form of salt, if basic, the amine will be dissolved at the organic layer (ether, DCM).

Some kind of messy the recipe you brought about the work up. May be someone here could clear it for us.

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**wildfyr** - 11-7-2018 at 09:44

The aqueous phase is chock full of salts, IPA is perhaps immiscible under this condition. I agree that I would generally use one of the typical selection of aprotic water immiscible solvents (ether, toluene, DCM etc). At a glance, surely this product is soluble in some of them.

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**Sidmadra** - 16-7-2018 at 15:05

Quote: [Originally posted by Chemi Pharma](#) →

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The role of bases in borohydride extractions like this is to free the amine from the borate salts so it can be extracted into the organic layer. If you extract an amine with acid, the amine will be pulled into the aqueous phase with all the other junk as **wildfyr** mentioned.

IPA does work in this particular reaction because the amine in OP's post is a liquid so will dissolve in most organic solvents. A water solution saturated with Sodium Hydroxide would not be miscible with IPA.

Granted, it's not an ideal extraction solvent but it does work. I'm pretty sure this is taken from Erowid or one of those sites afterall.

[Edited on 16-7-2018 by Sidmadra]

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**Chemi Pharma** - 18-7-2018 at 11:06

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I apologize but I fully disagree with you @Sidmadra. The role of borohydrides extraction is to first neutralize the excess borohydride with an acid, to avoid free inflammable hydrogen to be liberated from the solution in the work up. The nitrocompound which has not been reduced would remained into the organic layer, with the other craps, and the aminocompound would remained at the aqueous layer.

Then, after that, you add a base to free the amine and extract it with a non polar or aprotic solvent like ether, DCM, toluene, etc., never with a polar solvent like IPA. Of Course IPA is miscible with water and lye, forming a homogeneous solution. Try this in your lab and see the results!

I don't think Erowid, even some of the bees have publicated something so stupid. Unless this text has been extracted from a newbie at the old Hive.

[Edited on 18-7-2018 by Chemi Pharma]

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**wildfyr** - 18-7-2018 at 12:22

I just experimentally checked the solubility, the isopropanol has to be a mistake. Its miscible with brine, and Chemi is right, also saturated NaOH. Almost any other immiscible solvent should work fine, though I would personally avoid EtOAc in the presence of an NaOH solution. Ether or toluene seem most obvious.

---

**happyfooddance** - 18-7-2018 at 12:39

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I don't know how you experimentally found this, but you didn't.

IPA is absolutely not miscible in either sat. NaCl or sat. NaOH. Maybe you don't know what "miscible" means? Soluble to a degree, yes, but they are not miscible.

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**wildfyr** - 18-7-2018 at 13:43

Fine, you caught me, I made a roughly 50:50 solution and it did not phase separate.

[Edited on 18-7-2018 by wildfyr]

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**DraconicAcid** - 18-7-2018 at 17:12

Quote: [Originally posted by wildfyr](#) ↗

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Bull. Isopropanol can easily be salted out of aqueous solution.

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**wildfyr** - 18-7-2018 at 19:06

I think we can agree its a pretty crappy choice for an LL extraction solvent.

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**happyfooddance** - 18-7-2018 at 19:55

Quote: [Originally posted by wildfyr](#) →

I think we can agree its a pretty crappy choice for an LL extraction solvent.

1. This is on a pretty small scale, so using IPA if it's already the reaction solvent, and is only gonna take 10 minutes on the rotovap anyway, doesn't sound like such a bad idea to me.

2. Your suggestion of ether doesn't seem so great, it's pretty non-polar and only has a hydrogen bond acceptor, and the product likewise: all hydrogen bond acceptors.

3. I used IPA once on a larger scale (3L) extraction of an organic that had been previously been attempted with a couple of the more usual suspects (to no avail). My bright idea was to salt it out and use IPA. It worked great and to my surprise my yield was better than expected, so... A lot of things are VERY soluble in IPA, and contrary to your opinion and your poorly conducted experiment, IPA is not very soluble in salt water or NaOH solutions.

4. IPA is cheap.

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**Sidmadra** - 19-7-2018 at 07:35

Quote: [Originally posted by Chemi Pharma](#) →

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Then, after that, you add a base to free the amine and extract it with a non polar or aprotic solvent like ether, DCM, toluene, etc., never with a polar solvent like IPA. Of Course IPA is miscible with water and lye, forming a homogeneous solution. Try this in your lab and see the results!

I don't understand what you disagree about. Borohydride reactions extracted with bases are pretty common.

But yes you are correct that when doing a base extraction of borohydride, the consequence is that the borohydride is not neutralized, since borohydride is partially stabilized in alkaline solutions. This may be considered hazardous depending on an individual labs protocol, because if put into a waste container, could result in buildup of hydrogen gas since the borohydride is not actually neutralized as it would be with an Acid. Regardless of how you look at it, there is still going to be either an A/B or a B/A extraction of some sort to separate the reacted and unreacted material, whether you use acid or base for the initial extraction step.

It is noteworthy is that it is easier to extract borohydride reactions with bases because bases tend to be cheaper and more easily available than acids. If you neutralize the initial borohydride with an acid, you will need a large molar excess due to the large excesses of Borohydride often used, not to mention the hydrogen gas build up. Whereas, if you save the acid for the final extraction step, you end up using less acid, and instead more base. Of course that depends on the scale an individual is working.

[Edited on 19-7-2018 by Sidmadra]

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**Melgar** - 19-7-2018 at 08:56

I'm pretty sure copper salts catalyze the decomposition of  $\text{NaBH}_4$ . That might be why no acid was used here.

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**stoichiometric\_steve** - 9-11-2018 at 14:24

Quote: [Originally posted by Chemi Pharma](#) →

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Not relevant.

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Not relevant either.

Quote: [Originally posted by Chemi Pharma](#) →

First I don't understand why to use 25%  $\text{NaOH}$ , since there's no acid environment to neutralize when the reaction finish.

Let me bring to your attention the ability of copper to form complexes with amines, which are the intended product of this reaction, and those complexes are broken up by adding  $\text{NaOH}$ , which in turn stabilizes residual  $\text{BH}_4^-$  and thus actually prevents having to deal with liberating  $\text{H}_2$  during workup.

I must insist that you reconsider spilling irrelevant matters over what can be valuable methods and subsequently discourage others trying them out, along with sparking useless discussions about tried and proven techniques.

Quote: [Originally posted by Chemi Pharma](#) →

May be someone here could clear it for us.

If you're ever unsure about trivial matters such as solvent miscibility and workups in particular again, please do your own research instead of requiring spoonfeeding which you like to accuse others of. Thank you.

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**Chemi Pharma** - 10-11-2018 at 05:36

Quote: [Originally posted by stoichiometric\\_steve](#) →

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If you're ever unsure about trivial matters such as solvent miscibility and workups in particular again, please do your own research instead of requiring spoonfeeding which you like to accuse others of. Thank you.

Dude, you really suck. I will not waste my time anymore arguing with people like you. Besides your colleague, you are another spoiled boy, and so is he, full of temper tantrums.

What is irrelevant to you is not always the same to others. See the amount of downloads that were made of the documents I brought.

I've been working with borohydride in my laboratory for over two years. I am more than accustomed with the work up via B-A-B or A-B-A and have never used isopropanol with borohydride because the literature say the yield is poor and you'd better use methanol, and to separate the amine the books say is better use apolar aprotic solvents like DCM or ether in terms of yield. So that's the reason for my questioning about the procedure given.

Do not want to come here in this space to give me a moral lesson, because you're nobody, just a brat wanting to appear in this Forum, just like your little friend.

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karlar - 11-11-2018 at 05:05

Quote: [Originally posted by Chemi Pharma](#) →

Quote: [Originally posted by Sidmadra](#) →

The role of bases in borohydride extractions like this is to free the amine from the borate salts so it can be extracted into the organic layer. If you extract an amine with acid, the amine will be pulled into the aqueous phase with all the other junk as **wildfy** mentioned.

IPA does work in this particular reaction because the amine in OP's post is a liquid so will dissolve in most organic solvents. A water solution saturated with Sodium Hydroxide would not be miscible with IPA.

Granted, it's not an ideal extraction solvent but it does work. I'm pretty sure this is taken from Erowid or one of those sites afterall.

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[Edited on 18-7-2018 by Chemi Pharma]

Sorry but what is so stupid about this procedure? Is it solely because of the IPA? There are more than one way to skin a cat you know.

Of course IPA is not the ideal solvent in this case but it obviously allows for a quick and easy workup using a solvent that is readily available to amateur chemists.

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**Chemi Pharma** - 11-11-2018 at 05:25

Sorry Karlar, all of this is about a fight I'm having with two rude members here, in this forum.

Off course, the use of isopropanol is valid. My question is if the yields sucks with this solvent, cause the litterature say you'd better use methanol in hydrogenations with borohydride.

Also has the problem with isopropanol miscibility with water. Cause this I asked if some other members here could help us to clarify this.

The paper you brought is a solid research, I'm not criticizing the paper, only asking if the researchers really used the better techniques in the work up and if this can not be improved with the use of another solvent, ok?

Again, sorry for the confusion some members of this Forum is doing in the thread you began.

---

**stoichiometric\_steve** - 12-11-2018 at 07:19

Quote: [Originally posted by Chemi Pharma](#) 

Again, sorry for the confusion some members of this Forum is doing in the thread you began.

You're the only one pulling stupid off topic shit here.

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**karlos<sup>3</sup>** - 2-12-2018 at 12:59

The reference here, I always wonder about their nitrostyrene addition.

Especially, why do they let their temperature rise so much, wouldn't it be much better to keep it colder to avoid polymerisation?

70% is not a very high yield I think, I think this can probably be increased if the nitroalkane is formed more carefully, or not?

Then warming of the reaction mixture, addition of the cupric chloride, etc, instead of allowing the exothermia to happen, would it not result in more product this way?

Quote: [Originally posted by stoichiometric\\_steve](#) →

...what can be valuable methods and subsequently discourage others trying them out, along with sparking useless discussions about tried and proven techniques.

...

I can confirm this is indeed a very valuable method, not just for nitrostyrenes but especially for nitropropenes. It is much discussed on another board dedicated to substances like the one produced in the reference. There it was tried by several people on nitropropenes (mostly plain 1-phenyl-2-nitropropene), and at least a single trial on a nitrostyrene as well, also tried it myself.

And the users report even higher yields on nitropropenes, a claim of encouraging 90% achieved included. Some substituted substrates were tried too, opposed to the reference in the OP, usually with the use of only 6eq. of NaBH<sub>4</sub>.

I can confirm from own experiments, that it is indeed possible to reduce a nitropropene into yields of above 80%.

But the reaction is done more harsh, as the nitropropene stands much better to be added fast enough to cause the reaction being at constant reflux during this, and it even proved to increase yield.

The workup is carried out else too, borohydride is quenched with AcOH as usual, IPA distilled off then, base added, so any copper complex is broken and it allows for simple steam distillation then to isolate the amine directly from the reaction flask.

Apparently it is not based on the reference here, but the older one using NaBH<sub>4</sub>/CuSO<sub>4</sub>, but since it is also carried out using CuCl<sub>2</sub> like here, I thought it would be interesting to add some real world knowledge on this reaction.

Actually, many of those who tried it out call it a superior reduction, compared to other methods it works without annoying metal salts in the work-up, without large volume of liquid, expensive, toxic or hard to get reagents and it is also pretty fast to do, and the possible yield is really outstanding.

It was even called the new gold standard for the reduction of nitropropenes to amine, and I agree on that, it is very valuable.

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**horribilis** - 27-10-2019 at 14:27

I am having issues with this reaction, running it on beta-nitro-3,4,5-trimethoxystyrene. I want to vacuum distill the freebase while avoiding distillation of IPA due to the potential risks of peroxides.

The post-reaction solution is made basic with concentrated (30-40% w/w) NaOH, forming two layers. I have attempted to extract both layers at once with toluene. I have also attempted to separate the IPA layer, extract the aqueous layer with toluene, and extract the separated IPA with toluene. In either case the yields are poor.

Is it reasonable to assume the solubility of the freebased amine in toluene is not great enough to pull it from the IPA? I have attempted it as written in the paper (make basic, separate IPA layer, extract with more IPA, dry combined IPA extracts over MgSO<sub>4</sub>, make acidic with H<sub>2</sub>SO<sub>4</sub> in dry IPA) but the crystals are dirty and don't clean up very well even with recrystallization -- this is why I would like to vacuum distill the freebase amine.

[Edited on 27-10-2019 by horribilis]

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**S.C. Wack** - 27-10-2019 at 15:44

Quote: [Originally posted by horribilis](#) →

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Extracting a polar cpd. from a polar solvent with a ~ nonpolar solvent is generally not going to go well.

---

**horribilis** - 27-10-2019 at 16:23

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Extracting a polar cpd. from a polar solvent with a ~ nonpolar solvent is generally not going to go well.



The impure salt could be converted back to the freebase and then vacuum distilled but this is more mechanical loss for a reaction run at the 1-2 gram scale. I wonder if running the reaction in toluene/water with PTC would work?

---

**S.C. Wack** - 27-10-2019 at 17:12

Not sure why you have to get toluene involved...it should have been better to extract with IPA and evaporate.

---

**horribilis** - 27-10-2019 at 17:52

Quote: [Originally posted by S.C. Wack](#) →

Not sure why you have to get toluene involved...it should have been better to extract with IPA and evaporate.

IPA may form explosive peroxides. <http://www.sciencemadness.org/talk/viewthread.php?tid=21495> I don't know if it's baseless paranoia or a valid concern when distilling to dryness? Another user has suggested peroxide test strips. Primary alcohols would be a safe solvent but NaBH<sub>4</sub> reacts with them?

[Edited on 28-10-2019 by horribilis]

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**SWIM** - 27-10-2019 at 18:38

I think I've seen a number of reductions done in alcohol with that reagent.

Not sure if I've seen nitro compounds to amines though.

I believe the reaction with alcohol is slow enough that it can be used as a solvent for some reductions.

I'll do some checking.

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**S.C. Wack** - 27-10-2019 at 19:00

(M)ethyl alcohol will not form a separate layer with NaOH. IPA will not form peroxides not already present when distilled or evaporated in vacuo, and I would think that peroxides in solvents would either decompose, not form, or react with other things when evaporated with many other cpds. besides the solvent. BTW it is said that even ethers full of peroxides can be distilled to dryness uneventfully if the heat source is not too strong.

[Edited on 28-10-2019 by S.C. Wack]

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**Mush** - 28-10-2019 at 13:50

Quote: [Originally posted by horribilis](#) →

Quote: [Originally posted by S.C. Wack](#) →

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[Edited on 28-10-2019 by horribilis]

May , but not in these reaction conditions.

NaBH<sub>4</sub> would react with the peroxide as per this paper:

<https://www.sciencedirect.com/science/article/abs/pii/S03603...>

Quote:

but the crystals are dirty and don't clean up very well even with recrystallization -- this is why I would like to vacuum distill the freebase amine.

There are other ways to clean amines. Use one of this method.

You can also check the purity by tlc with 2 different solvent systems and stains. Compare the 2 against each other. If u get 1 single spot you are good.

Shulgin distilled at 120-130 °C at 0.3 mm/Hg. If you are pro using such high vacuum then this is the way. IMO distillation can be replaced with other purification methods.

[Edited on 28-10-2019 by Mush]

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**horribilis** - 28-10-2019 at 16:07

Quote: [Originally posted by Mush](#) →

Quote: [Originally posted by horribilis](#) →

Quote: [Originally posted by S.C. Wack](#) →

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I did not think of that -- it now seems obvious that that a >6 molar excess of NaBH<sub>4</sub> would reduce peroxides.

