

## The Vespiary

Main Topics => Publications => Topic started by: slave2carbon on April 26, 2020, 12:59:21 AM

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Title: **Zn/HCl reduction of nitrostyrenes**

Post by: **slave2carbon** on **April 26, 2020, 12:59:21 AM**

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### Solvents and reagents

2.40 g beta-nitro-3,4,5-trimethoxystyrene; recrystallized once from 91% IPA, powdery and bright yellow in appearance  
10.11 g zinc powder, 300 mesh; technical grade, not activated, free-flowing but dull gray in appearance  
49 ml 31% HCl; technical grade, slight yellow tinge  
65 g KOH; technical grade  
98% H<sub>2</sub>SO<sub>4</sub>; reagent grade  
NaCl; table salt, non-iodized  
Chloroform; technical grade, synthesized from acetone/bleach, brine washed and fractionally distilled but may contain some acetone  
Methanol; technical grade, once distilled  
Toluene; technical grade, once distilled  
Acetone; technical grade, once distilled  
Water; distilled

### Procedure

Approximately 25 ml methanol was added to a beaker and then submerged in a salt water bath. The separatory funnel was charged with 33 ml HCl. Zinc and nitrostyrene were split into 5 roughly equal batches, 0.5 g and 2.0 g respectively. With rapid magnetic stirring the first batch of nitrostyrene was added by microspatula, followed immediately by the first batch of zinc. The stopcock was opened and HCl was added dropwise to the stirring mixture at a rate such that reaction temperature never exceeded 5 C. As HCl was added continuously, stopping only to moderate temperature or change salt water baths, the remaining 4 batches of nitrostyrene and zinc were added, in that particular order, over the course of about 30 minutes.

**Observations:** Grey solution of zinc, bubbling. Solution was kept grey at all times by zinc addition. Temperature was between -15 C and 5 C at all times, the average being closer to 0-5 C.

After all nitrostyrene, zinc, and HCl were added, the sides of the beaker were rinsed with 5 ml methanol and the mixture was allowed to stir for 5 minutes. The separatory funnel was charged with another 16 ml HCl. The HCl was added over the course of 5 minutes, maintaining a reaction temperature <5 C. The apparatus was transferred to a freezer and the reaction was allowed to stir for 16-17 hours.

**Observations:** After the first hour of stirring the solution was opaque white, no yellow nitrostyrene evident, with some unreacted zinc on the bottom. Cold temperatures slowed reaction considerably as effervescence was evident but it was not rapid by any means. At the 16-17th hour of stirring the opaque white appearance remained, only the vast majority of zinc had reacted and was no longer visible; only a small portion of zinc remained. Average temperature during these 16-17 hours of stirring was between -15 C and -20 C.

After 16-17 hours of stirring the reaction mixture was vacuum filtered through a fast filter paper into a chilled filtration flask. The filter paper was washed with 5 ml water, and the filtrate was transferred to a small beaker. The filtration flask was rinsed with 10 ml water and this was also added to the beaker. Less than 0.1 g unreacted zinc was recovered and discarded. The beaker containing the filtrate, clear with a slight pale gray tinge, was placed in a freezer for 1 hour while a 50% solution of 60 g KOH and 60 g water was prepared. The KOH solution was chilled to room temperature and then transferred to a separatory funnel, total volume approximately 90 ml. The reaction mixture was placed on a salt water bath and, with magnetic stirring, the KOH solution was added dropwise over the course of 30 minutes such that reaction temperature <5 C. Once all KOH had been added the beaker was allowed to warm to room temperature without further stirring.

**Observations:** Extremely exothermic and so this must be done slowly and carefully to prevent localized heating. Manual stirring was required for the bulk of this reaction. As KOH is added white wisps dissolve, eventually yielding a milky white solution, then yielding a thick milk white paste which must be stirred by hand or with overhead stirring, and then finally yielding a milky white solution. An amine aroma was evident after approximately 1/3 to 1/2 of the KOH solution was added. The reaction mixture thinned out, as previously described, after approximately 3/4 of the KOH solution was added. A strange light pinkish hue became evident as the last 1/4 of the KOH was added. After all KOH was added and the contents were allowed to warm to room temperature without stirring, small amounts of yellow-brown oil floating on top became visible. An amine smell was also evident. Total volume of the milky-white solution was approximately 200 ml.

The mixture was extracted from the beaker with 4 x 25 ml portions of toluene in the following manner. Toluene was added and then magnetic stirring was initiated at a rapid pace for 10 minutes. After 10 minutes of stirring the mixture was allowed to separate over a 10 minute period. The upper layer was removed via pipette and transferred to a round bottom flask.

**Observations:** Approximately 25 ml recovered in all 4 extractions. First extraction was champagne in color. After the first extraction the basic solution no longer had the odd pinkish hue, it was now milky white in appearance. The second extraction was light champagne in color. The third and fourth extractions were absolutely clear in color.

The combined organic extracts were set up for distillation and heated to 90 C on a hot water bath although nothing distilled/condensed. Apparently, no methanol was brought over in the toluene extraction process. This was unexpected as toluene and methanol are miscible, and so this step may not be necessary. The organic extracts were transferred to a separatory funnel and the round bottom flask was rinsed with 10 ml toluene, which was also added to the separatory funnel. A dilute solution of HCl was prepared, 40 ml ~5% w/w HCl. The combined organics were then extracted with 4 x 10 ml 5% w/w HCl.

**Observations:** First extraction yielded an opaque white/yellow upper layer, clear yellow bottom layer. Fourth extraction yielded opaque whiteish upper layer, clear bottom layer.

The HCl extracts were combined in the separatory funnel, clear yellow in appearance, and washed with 2 x 10 ml toluene.

**Observations:** Both washes yielded a clear-yellow upper layer, slightly darker clear-yellow bottom layer.

The combined HCl extracts were transferred to a small beaker, and the separatory funnel rinsed with a small portion of water which was also added to the beaker. A 50% solution of 5 g KOH and 5 g water was prepared and chilled to room temperature. With manual stirring, the KOH solution was added to the beaker containing the HCl extracts over the course of about 1 minute.

**Observations:** White-brown and opaque solution after addition of KOH.

The solution was transferred to a separatory funnel, the beaker rinsed with a small portion of chloroform and also added to the separatory funnel. The basic solution was extracted with 3 x 10 ml chloroform.

**Observations:** First extraction yielded opaque white upper layer, light yellow-orange bottom layer. Third extraction yielded opaque white upper

layer, clear bottom layer.

The combined chloroform extracts were washed with 1 x 10 ml ~5% w/w brine.

**Observations:** Clear upper layer, champagne slightly yellow bottom layer.

The chloroform extracts were transferred to a small beaker. A solution of 25 drops 98% w/w H<sub>2</sub>SO<sub>4</sub> in 5 ml methanol was prepared. With manual stirring, the chloroform extracts were made acidic to pH = 3-5, with respect to wetted pH paper, by dropwise addition of methanolic acid.

**Observations:** Free-flowing, creamy white, very fine precipitate formed in a yellow-orange solution.

All solvent was stripped over a hot water bath with magnetic stirring, ideally in a distillation apparatus but in this case directly from the beaker. A strange yellow-orange solid/paste resulted. The beaker was allowed to cool and then 20 ml acetone was added. The beaker was placed back on the hot water bath and stirred until the yellow-orange solid/paste fully dissolved, approximately 3 minutes. The reaction mixture was chilled in a freezer to -15 C and a fine precipitate was filtered through a slow filter paper. The beaker and solids were rinsed with 10 ml acetone. Creamy white solids were recovered on the filter paper. The filtrate was placed in the freezer and a second, smaller crop of crystals was recovered. The crystals were rinsed as before with 10 ml acetone, yielding a combined mass of 1.80 g (58% yield on nitrostyrene.)

The crude product was dissolved in a minimal amount of 70 C water, approximately 15 ml. The water took on a slight yellow hue. To the water was added two volumes, or 30 ml, of boiling 91% IPA. The beaker was cooled to room temperature and then placed in a freezer overnight. The contents of the beaker were vacuum filtered over a fast filter paper and the beaker and crystal cake washed with 10 ml acetone. The filtrate was returned to the freezer but there was not a second crop of crystals. The filtered solids were dried to yield 1.58 g glistening snow white crystals (88% recovery on crude, 51% yield on nitrostyrene.)

#### Other reaction notes

Stirring during zinc/HCl addition phases must be rapid to keep zinc in suspension. A large excess of base (2.5 molar equivalents with respect to HCl) is necessary to form a free-flowing basic solution that can be extracted. Strict temperature control is necessary during zinc/HCl addition and basification as side reactions readily occur. This means that any heating or distillation of the reaction mixture must be done after all KOH is added. Temperature control during basification may be revised from <5 C to <10 C to make the process a bit easier to control but if you have the time and patience, colder is better. Toluene is an ideal solvent for the initial extraction because of its density; DCM or chloroform will form terrible emulsions due to the extremely basic environment and due to the density of the amine/zinc salt solution with respect to DCM or chloroform. Xylene is also an ideal solvent if toluene is unavailable. IPA was avoided as a reaction/extraction solvent as it complicates the extraction and acid/base workup process due to co-solvent effects. IPA may also form explosive peroxides when distilling to dryness, as many secondary/tertiary alcohols are prone to do.

#### Other reaction notes, continued

Extracting the basic mixture with via pipette is much easier than extraction via separatory funnel. Chloroform was used in the latter stages of the acid/base workup because it is easy to synthesize and it has a low boiling point making it easy to strip; other solvents like DCM may also be ideal. Ideally at the conclusion of the acid/base workup one would dry the organic solvent over MgSO<sub>4</sub>, strip all solvent, vacuum distill the freebase oil, and then take up the oil in methanol/ethanol/etc. for acidification. Due to the small scale of this reaction and the relatively high boiling point of the freebase (180 C at 12 mm Hg per literature, corresponding to 320-330 C at atmospheric pressure) it is largely impractical unless one has a specialty small scale bulb-to-bulb vacuum distillation apparatus like a Kugelrohr. Acidic methanol was used rather than acidic chloroform simply to reduce the amount of chloroform used. While chloroform is easy to synthesize it's also annoying and time consuming to synthesize. Mescaline salts may be slightly soluble in chlorinated solvents and are readily soluble in methanol which is why solvent was evaporated entirely. Mescaline hydrochloride and sulfate are insoluble in acetone making it an ideal solvent for washing as it readily dissolves unreacted nitrostyrene (yellow solids), partially reduced nitro intermediates (white solids), polymerization products, etc. Zinc hydroxide is practically insoluble in water and so the easiest way to clean it from glassware is to use a dilute solution of HCl.

#### Ideas for improvement

Apparently this reaction can yield 80-90% under ideal conditions. This variant represents the best yield to date. The biggest takeaway from this "success" is that long reaction times are necessary. Previous trials included shorter reaction times of 4-8 hours which yielded little to no product. These trials were conducted at -15 to -20 C (freezer temperature) and subsequently at 5 C (refrigerator temperature.) While certain academic papers promise that these shorter reaction times yield completed reactions per HPLC, this has not been consistent with reality. The sequential addition of zinc, nitrostyrene, and acid to methanol has also yielded much better results than 1) forming a solution of methanol/nitrostyrene and then adding zinc and HCl or 2) forming a solution of methanol/nitrostyrene/HCl and then adding zinc. Ideas for improvement include the following:

- 1) Using slightly more HCl (to fully react the zinc and yield a more complete reduction of nitrostyrene) and slightly more methanol (to dilute the solution and slow the reaction on nitrostyrene, leading to less side products.)
- 2) Skip attempted distillation of methanol as there was no methanol in the toluene (again, entirely unexpected) or carry the attempted distillation out under gentle vacuum. The contents of the round bottom flask did darken slightly during heating on the hot water bath, potentially indicating a slight degradation of the freebase which may have reduced yield.
- 3) Improve acid/base workup. Finish HCl extraction with a single water wash. More thorough washing of HCl extracts with toluene, increasing from 2 x 10 ml to 3-4 x 10 ml. Ideally this will remove the yellow/orange color seen in the solvent evaporation process. Possibly eliminate the brine wash. Freebase is slightly water soluble and so this may be reducing yield.
- 4) Possibly run the reaction in a refrigerator at 5 C for 12-16 hours rather than a freezer at -15 to -20 C for 16-17 hours, if side reactions do not occur significantly.

#### Conclusion

This is a viable albeit difficult reaction which uses OTC reagents. I believe it works for all nitrostyrenes, and it is typically higher yielding on the 2C-H nitrostyrene precursor than this mescaline nitrostyrene precursor. That said, if you have access to NaBH<sub>4</sub> and CuCl<sub>2</sub> then absolutely do not bother with this reaction. The NaBH<sub>4</sub>/CuCl<sub>2</sub> reaction is faster and easier to carry out by an order of magnitude.

#### References and guidance

<https://anonym.to/?>

<https://chemistry.mdma.ch/hiveboard/palladium/pdf/An%20Experimental%20Evaluation%20of%20the%20Zinc%20Hydrochloric%20Acid%20Reduction%20of%20N>

DOI: 10.1055/s-0034-1379481

<https://anonym.to/?https://chemistry.mdma.ch/hiveboard/novel/000217679.html>

A number of posts on HyperLab

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Title: **Re: Zn/HCl reduction of nitrostyrenes**  
Post by: **xdragon** on **April 26, 2020, 04:59:46 AM**

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Wow! Thanks for your really detailed notes on this finicky reaction!

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Title: **Re: Zn/HCl reduction of nitrostyrenes**  
Post by: **carl** on **April 26, 2020, 05:21:05 AM**

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Uhm... why did you not post that directly into the publication section?  
This is a well written piece of work, very detailed, and complete with references and all.  
Do you want us to move it there?

I think it does belong there, its very good.  
Probably helpful for anyone who considers doing that reduction, especially helpful because it is really factual for an amateur chemist, and not possibly deliberately exaggerated like those papers claiming "80-90% yield" you also do mention.  
Having done that reduction myself and knowing these papers, using the same nitrostyrene as you, I never believed their claims to be actually truly this high.

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Title: **Re: Zn/HCl reduction of nitrostyrenes**  
Post by: **slave2carbon** on **April 26, 2020, 01:02:26 PM**

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Thanks. If you believe it is worthy of being moved to the publication section, please do so! :)

The claims of 80-90% also come from an experienced and respected bee who wishes to remain anonymous. Per correspondence with him/her it's very much a technique-dependent reaction. It does work as promised in theory, it just takes a lot of trial and error and modification of technique that the academic papers conveniently leave out. :)

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Title: **Re: Zn/HCl reduction of nitrostyrenes**  
Post by: **maker** on **April 26, 2020, 07:01:51 PM**

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Thank you sir. The write-up just felt right. We will see if this affects my future.

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Title: **Re: Zn/HCl reduction of nitrostyrenes**  
Post by: **slave2carbon** on **May 03, 2020, 11:09:39 PM**

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A small update, the reaction has been repeated twice more. Nothing remarkable as yields are still low. Reports are condensed since you get the idea.

Quote

**Trial #2**  
Beaker containing 40 ml methanol chilled on salt water bath. 2.43 g beta-nitro-3,4,5-trimethoxystyrene, 10.20 g zinc split into 6 portions. First portion nitrostyrene was added, followed by zinc. Addition of 40 ml 31% w/w HCl commenced, dropwise such that reaction temperature (RT) <5 C. All nitrostyrene, zinc, and HCl added with RT <5 C in about 25 minutes. Sides of flask rinsed with methanol. Stirred another 5 minutes, then another 20 ml HCl added to separatory funnel and added dropwise such that RT <5 C over a period of 10 minutes. By this point all yellow nitrostyrene had disappeared to yield an opaque white solution with some unreacted zinc (stirring momentarily paused to observe this.) Beaker transferred to freezer and stirred for 16 hours approximately -15 C. After 4 hours of stirring all zinc had disappeared. After 16 hours of stirring an opaque white solution was observed, slight yellow tinge due to unreacted HCl (technical grade HCl impurities.)  
  
Made basic with dropwise addition of approximately 3x molar excess of 50% KOH (73 g KOH + 73 g water) such that RT <5 C. Note that the addition took more time due to excess HCl used by comparison to previous trial. Total addition time was closer to 1.5 hours. Once all KOH had been added the solution was stirred until it had warmed to 10 C. Qualitatively speaking, larger amount of yellow-brown oil (with respect to previous trial) was visible and a strong amine smell evident.  
  
Extracted with 4 x 25 ml toluene as before (10 mins stir + 10 mins resolution of layers.) Extracts had a light champagne color. Extracts transferred to a distillation apparatus, placed on a hot water bath, and ~100 torr vacuum applied to distill 5 ml liquid at 55 C. Receiving flask contained toluene with a drop or two of water -- no methanol. Reaction flask had darkened from champagne to yellow-orange.  
  
Contents of reaction flask transferred back to separatory funnel, extracted with 4 x 10 ml 5% w/w HCl. The combined acidic extracts were washed with 3 x 10 ml toluene. Acidic extracts made basic with 50% KOH solution until strongly basic (5 g KOH + 5 g water, measured pH=14.) Mixture was now creamy white with yellow-brown tinge, no oil floating on top, amine smell evident but not overwhelming as before.  
  
Mixture extracted 4 x 10 ml chloroform, chloroform extracts washed with 1 x 10 ml 5% w/w brine. Made acidic with dilute methanolic H2SO4 until pH=5 by pH paper. Creamy white-yellow solution stripped of solvent on hot water bath. Orange-yellow paste/solid yielded as before. Residue was stirred under boiling acetone, placed in freezer, vacuum filtered, rinsed with acetone to yield creamy white solids. No second crop of crystals. Crude product (1.74 g, 55% crude yield on nitrostyrene) recrystallized from minimum amount of 70 C water + two volumes boiling 91% w/w IPA with respect to water used. Placed in freezer overnight, vacuum filtered, rinsed with acetone, dried. Total yield 1.45 g (83% recovery on crude, 46% yield on nitrostyrene) as shiny, snow white crystals.

Quote

**Trial #3**  
Same as trial #2. Made basic with 50% KOH as before. Qualitatively less yellow-brown amine oil visible than in trial #2, amine smell not as evident. Extracted with 4 x 25 ml toluene as before. No distillation or vacuum distillation was used, instead the toluene extracts were washed with 2 x 10 ml 10% w/w brine. Workup proceeded as before. Solvent stripped as before to yield orange-yellow solid/paste. Crude yield 49%, final yield 42%.

Going back to ideas presented in the first post:

Quote

1) Using slightly more HCl (to fully react the zinc and yield a more complete reduction of nitrostyrene) and slightly more methanol (to dilute the solution and slow the reaction on nitrostyrene, leading to less side products.)

Trial #2 showed a comparatively larger amount of amine following addition of base, with respect to trial #1 and trial #3. Unclear why this didn't occur in trial #3. Perhaps rate of addition of zinc/HCl was slightly too fast in trial #3. Will keep this in mind for future experiments.

Quote

2) Skip attempted distillation of methanol as there was no methanol in the toluene (again, entirely unexpected) or carry the attempted distillation out under gentle vacuum. The contents of the round bottom flask did darken slightly during heating on the hot water bath, potentially indicating a slight degradation of the freebase which may have reduced yield.

Brine washes in trial #3 didn't impact yield considerably and so solubility of freebase in brine can't be too great. As brine washes are faster and easier than distillations, this will be part of the workup going forward.

Quote

3) Improve acid/base workup. Finish HCl extraction with a single water wash. More thorough washing of HCl extracts with toluene, increasing from 2 x 10 ml to 3-4 x 10 ml. Ideally this will remove the yellow/orange color seen in the solvent evaporation process. Possibly eliminate the brine wash. Freebase is slightly water soluble and so this may be reducing yield.

It's hard to tell if the additional toluene washings improved the purity of the crude product as the crude product, immediately after stripping all solvent, is still the yellow-orange solid/paste. Since this seems to be a consistent phenomena I am assuming this is a polymerization product due to contamination of my chloroform with small amounts of acetone, which is reacting with a slight excess of sulfuric acid following addition of methanolic sulfuric acid. (pH strips aren't 100% accurate.) I believe rinsing chloroform with sulfuric acid prior to its use would wash out all acetone as a reddish polymerized upper layer. I may or may not do this in the future, as it really doesn't matter -- our product is insoluble in acetone and the acetone polymerization junk is itself soluble in acetone, so it's not harming purity or yield.

Quote

4) Possibly run the reaction in a refrigerator at 5 C for 12-16 hours rather than a freezer at -15 to -20 C for 16-17 hours, if side reactions do not occur significantly.

To be addressed.

Next trial will employ 1) slower and more careful addition of zinc/nitrostyrene/50 ml HCl over a 45-60 minute time span and 10 ml HCl addition over a 15 minute time span; 2) chilling of the basic reaction mixture during toluene extraction, rather than letting it warm to 10 C; 3) slightly longer stirring and extraction of the basic reaction mixture, something like 15 mins stirring + 15 mins resolution; and 4) slower, dropwise addition of KOH solution to acidic extracts over a salt water bath.

If yields do not improve then it will be assumed that the use of additional HCl with respect to trial #1 are unnecessary.

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Title: **Re: Zn/HCl reduction of nitrostyrenes**

Post by: **slave2carbon** on **May 08, 2020, 11:08:41 PM**

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Melting point was taken after two recrystallizations. The product appears as very fine fluffy needles, shiny and white. The literature reports MP 183 - 186 C for the dihydrate sulfate salt. Melting point was observed as 167 - 172 C. Not sure what to make of this. Maybe a miserable and painful attempt at microscale vacuum distillation through a short path apparatus is in order.