An Experimental Evaluation of the Zinc/Hydrochloric Acid Reduction of Nitrostyrenes

Abstract: *The reduction of nitrostyrenes using zinc and hydrochloric acid has been often reported and used in the synthesis of phenethylamines, despite the fact that there are very few reports of its use in the literature. An experimental evaluation of this reaction was performed, in order to find out the best conditions as far as time, effort, and cost. A reaction mechanism has also been proposed.*

Introduction:

The zinc/hydrochloric acid reduction of nitro-groups has been reported in the literature [1,2,3], however its use in the reduction of nitrostyrenes has only been reported by Leminger [4]. This reduction has been subsequently used by many to reduce various nitrostyrenes, typically in good yield. Anecdotal reports suggest that this reaction does not work on nitropropenes, despite its good results in the reduction of nitro groups and nitrostyrenes. The experiments that follow are an attempt to characterize the various factors that contribute to this reactions success in reducing nitrostyrenes, and also an attempt to create an idealized set of reactions that may be used in the future for consistent results.

Methods and Materials:

Nitrostyrene was prepared by a modified Henry reaction (for an example, see [5]), and used wet, directly after filtration and a short drying time. The actual procedure will be reported below. All reagents were of technical grade or higher, and fully anhydrous except where explicitly mentioned. The reactions were typically performed in an appropriately sized beaker, ranging from 100ml to 1000ml. The basic reaction methods are described in the table, while the reactions themselves will be further discussed in the results section. A magnetic stirrer was utilized to stir the reactions, typically at about 200rpm. An ice bath was used to chill the solutions.

The workup for all of the reductions was performed as follows:

A 50% solution of potassium hydroxide, containing an amount of potassium hydroxide approximately twice the molar equivalent of the hydrochloric acid present in the reaction was cooled to ~ -5*C, and slowly added to the hydrochloric acid-zinc-alcohol solution after the indicated total time, and stirred with a stir rod so as to evenly distribute the base and minimize localized heating. The temperature was monitored so as not to rise above 30-35*C. The solution was then further stirred in order to maximize the concentration of amine in the isopropyl alcohol layer, which upon standing separates and floats to the top. The aqueous and organic layers were then separated, and the aqueous layers again extracted with a small amount of isopropanol. These was also separated, and the organic layers were then combined, dried with magnesium sulfate, filtered, and allowed to evaporate under a fan. During this time, a theoretical equivalent of hydrochloric acid was added (any acid may be used). The product was typically washed with acetone until it was white and clean, and recrystallized if necessary, though this was in most cases unnecessary. The yield was based on the final cleaned product.

Nitrostyrene was prepared using the following procedure:

50mmol of aldehyde was dissolved in 40ml methanol and 125mmol of nitromethane. The solution was then stirred and cooled to ~0ºC. To this solution, 150mmol of potassium hydroxide in the minimum amount of cold (-5ºC – 5ºC) methanol was slowly added, with vigorous stirring, again ensuring that the temperature remains at about ~0ºC. Once the addition of the methanolic potassium hydroxide was completed, the solution was allowed to sit for another 30 minutes. The resultant mixture was then poured into 300ml of chilled (10ºC - 15ºC) 10% HCl solution, with vigorous stirring, followed by slow stirring as the nitrostyrene fell out of solution. The mixture was cooled (5ºC - 10ºC) and allowed to sit for another hour, to allow the precipitate to properly crystallize – typically as small, brightly colored, crystalline shards. Yields range from 65-95%, depending on the specific substrate. The nitrostyrene may then be recrystallized however this is unnecessary, and in fact, not recommend if being used for subsequently described reactions. The reasons for this will be described in the results section.

As the nitrostyrene was not weighed and used wet, the exact amounts produced by the reaction are unknown. However, the nitrostyrene was weighed upon the initial optimization of the reaction, and the results are given for reference:

3,4,5-trimethoxynitrostyrene – 90-95% yield

2,5-dimethoxynitrostyrene – 75-80% yield

4-hydroxy-3-methoxynitrostyrene – 65% yield

Results:

Nitrostyrene •	Zinc	31% Hydrochloric Acid	91% isopropanol	Average Temperature Of Reaction Mixture	General Procedure	Total Time of Reduction	Yield of Amine	Comments
~1.0-1.2g (from 1g aldehyde)	4g	24ml	12ml	12.5*C (10-15*C)	Chilled isopropanol and hydrochloric acid were mixed, cooled down to 10*C, and nitrostyrene added. The mixture was stirred on a magnetic stirrer, and zinc added very slowly, roughly .5g per half hour. The temperature was kept between 10*C and 15*C. The reaction was stirred until no more zinc seemed to dissolve. Workup as previously described.	~6 hours	~65-75%	This is the basic reaction that was found, which yields well enough, though not as well as it could. The reaction takes a long time, and there is nothing particularly worth noting. There always seems to be a bit of zinc remaining at the end.
~1.0-1.2g (from 1g aldehyde)	4g	35ml	12ml	12.5*C (10-15*C)	Chilled isopropanol and hydrochloric acid were mixed, cooled down to 10*C, and nitrostyrene added. The mixture was stirred on a magnetic stirrer, and zinc added very slowly, roughly .5g per half hour. The temperature was kept between 10*C and 15*C. The reaction was stirred until no more zinc seemed to dissolve. Workup as previously described.	~5 hours	~60-70%	The same reaction conditions as above were used, except using more acid. This had no direct effect on the reaction, but the zinc dissolved considerably faster and the effect on the yield can clearly be seen.
~1.0-1.2g (from 1g aldehyde)	4g	24ml	24ml	12.5*C (10-15*C)	Chilled isopropanol and hydrochloric acid were mixed, cooled down to 10*C, and nitrostyrene added. The mixture was stirred on a magnetic stirrer, and zinc added very slowly, roughly .5g per half hour. The temperature was kept between 10*C and 15*C. The reaction was stirred until no more zinc seemed to dissolve. Workup as previously described.	~6 hours	~65-75%	As the acid concentration in the previous reaction only seemed to affect the rate of Zn dissolution, more solvent was used to slow this reaction. As a result, the yield went up. There seems thus to be a correlation between rate of zinc dissolution and yield. It should be noted that nearly all the nitrostyrene dissolved at first. This may be a good thing.
~1.0-1.2g (from 1g aldehyde; dissolved in 10ml isopropanol, added in 3 portions)	4g	24ml (12ml initially, another 12 ml added in 4 portions after Zn)	12ml	10*C (5-15*C)	12ml of hydrochloric acid was added to 12ml of isopropanol and the solution chilled to 10*C. Nitrostyrene was dissolved in 10g of isopropanol, and roughly 1/3 of the solution added to the acid/alcohol mixture. Zinc was then added in about .5g amounts, every half hour, with a 3ml of hydrochloric acid added directly afterwards, followed by another portion of nitrostyrene. This was repeated until all of the nitrostyrene was exhausted, at which point the remainder of the zinc and acid were added. The reaction was magnetically stirred until all of the zinc dissolved.	~7 hours	~70-80%	The above reaction was attempted in portions, in order to keep the concentrations of the reactants relatively constant. This seems to have a small positive effect on the reaction. A reaction done in the past also used similar conditions. The reaction yielded 77%. Leminger used similar conditions, and in two separate reactions on other nitrostyrenes, achieved yields of 85% and 92%. Upon performing the reaction, it was noticed that the added solution of nitrostyrene lost color very quickly upon the addition of zinc. Thus, the correlation was made that this reaction is really series of small reductions, involving high acid concentrations, fast zinc additions, and dilute NS concentrations. In other words, a reaction that utilizes far less effort may yield as well, and also take less time.
~1.0-1.2g (from 1g aldehyde)	2.5g	30ml	12ml	5*C (3-7*C)	Chilled isopropanol and hydrochloric acid were mixed, cooled down to 3*C, and nitrostyrene added. The mixture was stirred on a magnetic stirrer, and zinc added very quickly, roughly 1g per 5-10 minutes. The temperature was kept between 3*C and 7*C. The reaction was stirred until the zinc dissolved. Workup as previously described.	~1.5 hours	~30-40% (did not fully reduce)	Based on the above proposition, this reaction was tried. The temperature was kept lower so as to try to eliminate any side reactions, which tended to leave an unclean product post-reaction. It was found that the solution lost color quite quickly, and that only 2.5g of Zn was needed to elicit this result. However, upon workup, it appeared that much of the product was unreduced, and as a result, a low yield of a very brown and unclean product was obtained. Subsequent washing with acetone and recrystallization yielded a product which was white/tan - however the extent of its purity was not confirmed.
~1.0-1.2g (from 1g aldehyde)	**5g**	**30ml (+5ml)**	**20ml (+5ml H2O)***	**5*C (3-7*C)**	**Chilled isopropanol and hydrochloric acid were mixed, followed by an additional 5ml of water. The solution was cooled down to 3*C, and nitrostyrene added. The mixture was stirred on a magnetic stirrer, and zinc added very quickly, roughly 1g per 5-10 minutes. The temperature was kept between 3*C and 7*C. After the zinc additions were complete, an additional 5ml of hydrochloric acid was added. The reaction was stirred until no more zinc seemed to dissolve. Workup as previously described.**	**~2 hours**	**~70-80%**	**Based on the result of the above reaction, which seemed to be very ideal, except for the reduction which didn't complete, the conditions were retried, this time adding more zinc after the solution lost its color. A lesser alcohol concentration was used so as to keep the nitrostyrene concentration relatively dilute, and also somewhat slow the Zn dissolution (by adding a bit more water). More Zn was also used to make up for the fast addition. The reaction quickly yielded a *very* clean and white product. Crystals formed during evaporation of isopropanol, opposed to a usual off-white/tan precipitate.**
~5-6g (from 5g aldehyde)	**25g**	**150ml (+25ml)**	**100ml (+25ml H2O)***	**5*C (3-7*C)**	**Chilled isopropanol and hydrochloric acid were mixed, followed by an additional 25ml of water. The solution was cooled down to 3*C, and nitrostyrene added. The mixture was stirred on a magnetic stirrer, and zinc added very quickly, roughly 5g per 5-10 minutes. The temperature was kept between 3*C and 7*C. After the zinc additions were complete, an additional 25ml of hydrochloric acid was added. The reaction was stirred until no more zinc seemed to dissolve. Workup as previously described.**	**~2.5 hours**	**~70-80%**	**The above reaction was found to be the best in terms of time, so it was scaled up. Product once again came out very nearly white-translucent; washing once with acetone is enough to get a completely pure product.**
~10-12g (from 10g aldehyde)	**50g**	**300ml (+50ml)**	**200ml (+50ml H2O)***	**12.5*C(10-15*C)**	**Chilled isopropanol and hydrochloric acid were mixed, followed by an additional 50ml of water. The solution was cooled down to 10*C, and nitrostyrene added. The mixture was stirred on a magnetic stirrer, and zinc added very quickly, roughly 10g per 5-10 minutes. The temperature was kept between 10*C and 15*C. After the zinc additions were complete, an additional 50ml of hydrochloric acid were added. The reaction was stirred until no more zinc seemed to dissolve. Workup as previously described.**	**~3 hours**	**~70-80%**	**The above reaction was once again scaled up. Unfortunately, temperature control on this large scale was not achievable using the available equipment. As a result, the product came up slightly more tan usual, but one acetone wash yielded in an absolutely white product. The time necessary for the reaction was also slightly elongated, however in comparison to the other reactions, which are nearly twice as long and yield about the same, though firstly through a product which needs a bit of cleaning. This is thus the ideal reaction, in the author's opinion.**

- Nitrostyrene was used while still damp, as previously (and subsequently) described.

<u>The bolded reactions are those utilizing the idealized reaction conditions.</u>

*** It may be advisable to use ice so as to keep the reaction colder.**

Discussion:

The first thing to discuss would be the choice of nitrostyrene preparation. The Henry reaction was found to be extremely high yielding on nearly all tested substrates, and given the fact that the time needed to prepare the nitrostyrene is a little less than an hour, this makes it the most ideal reaction for the preparation of nitrostyrenes. If temperature is kept fairly constant and cold, the products come out very clean, and can easily be used in the subsequent Zn/HCl reduction. The modified procedure mentioned above was the result of much testing, and works extremely well for 3,4,5-trimethoxynitrostyrene, as well as for 2,5-dimethoxynitrostyrene. The main advantages of this reaction are primarily its short time and cleanly produced product.

The reason for using the nitrostyrene wet, or more accurately damp, was because it was noted that the longer nitrostyrene sits, the more it polymerizes and the more it results in an inferior product after reduction. The water was found to not affect the reaction at all, and allowed for the entire synthesis of an amine from a corresponding benzaldehyde to be performed quite easily within just a few hours.

As far as choosing isopropanol for the reaction solvent, this solvent is most ideal because it allows for an extremely easy workup. The cost however, is that a slight amount of amine is lost during workup, though this is anticipated to be no more than ~5%. Given the ease of the workup, compared to a typical one involving multiple solvent mixtures and precipitate that is difficult to filter, the tradeoff is in the author's opinion very much worth it. The workup mentioned in the reaction also allows for maximum dilution of aqueous layers, so that the precipitated zinc hydroxide does not clog the separatory funnel. In other words, the workup is as simple as basifying separating, extracting once more, and separating once more. After that it's merely a matter of isolating the product. The final advantages of using this workup are that it is extremely quick, taking a few minutes at most, and also extremely cheap, involving non-toxic solvents and materials.

The reduction will now be discussed, and the following factors were noted to be the most influential:

- Time of Reaction: It was noted, based on the reaction mechanism found for the reduction of nitro groups by metals and acids [1], and experimental observations, that the bulk of the zinc used for the reduction goes toward the reduction of the nitro group. Experimentally, it was noticed that the color of the solution disappeared after about 3 of 4 equivalents of zinc were added – this of course indicating, that it is indeed the nitro group that it is first reduced. The reduction which used only a small amount of zinc also seemed to indicate this, as some sort of water-soluble material was isolated, but clearly not a phenethylamine. In any case, the results show the bulk of the time utilized by the reduction is for double bond. In addition to this, longer reaction times also seemed to lead to a product which was less pure, initially, however, it is unclear whether this can be attributed to time or other conditions. In summation, a long reaction time is NOT needed for a clean reduction, if the conditions are well kept.
- Concentration of Acid: The concentration of acid seems to be a critical factor in the reduction. This is made quite clear based on the reaction mechanism of nitro groups [1], but also in the fact that less acidic conditions promote the formation of oximes [5]. As a result, the concentration of acid should be kept well above the amount needed to dissolve all of the zinc throughout the entire length of the reaction. There seems to be no maximum concentration, however, the rate of dissolution of the zinc is affected, leading to the use of more zinc.
- Concentration of Solvent: This seems to have a minor effect on the reduction. It does however affect rate of zinc dissolution.
- Concentration of Nitrostyrene: This was initially thought to contribute to polymerization, however all indications show that as long as temperature is kept relatively low, this is but a minor factor.
- Amount of Zinc Added: The amount of zinc isn't very important past a certain point. At least 4g per 1g of nitrostyrene should be used in order to fully reduce the nitrostyrene to the amine, however above this doesn't seem to hurt the reaction. More zinc should be used if the concentration of acid is higher, as it dissolves much faster. This was exploited for the idealized reaction, which used a higher concentration of acid, and thus zinc.
- Rate of Zinc Addition: This seems to be the most critical factor. As the zinc is involved in electron transfers, which result in the reduction of the nitro group and possibly the indirect reduction the double bond as per the proposed reaction mechanism, the zinc should be kept in a very high concentration within the solution throughout much of the reaction. In other words, the zinc should be added at a fairly rapid rate in order to keep it in high concentration. This is especially important in the beginning of the reaction. In any case, adding the zinc quickly seems to have a few implications, which will be discussed with the proposed reaction mechanism.
- Temperature of Reaction: This has a relatively minor effect, as yields tend to remain roughly the same – though the product that is isolated is initially less pure. It is suspected that the nitrostyrene which does not get fully reduced somehow polymerizes and contaminates the product. Thus, the lower the temperature, the better.

Proposed Reaction Mechanism of Zn/HCl Reduction

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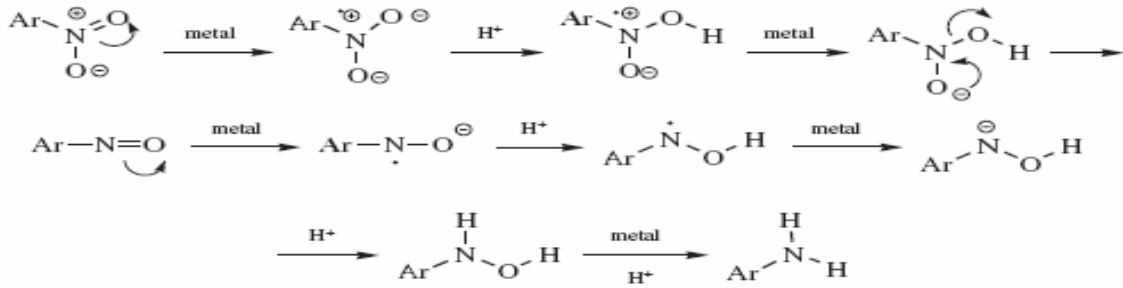
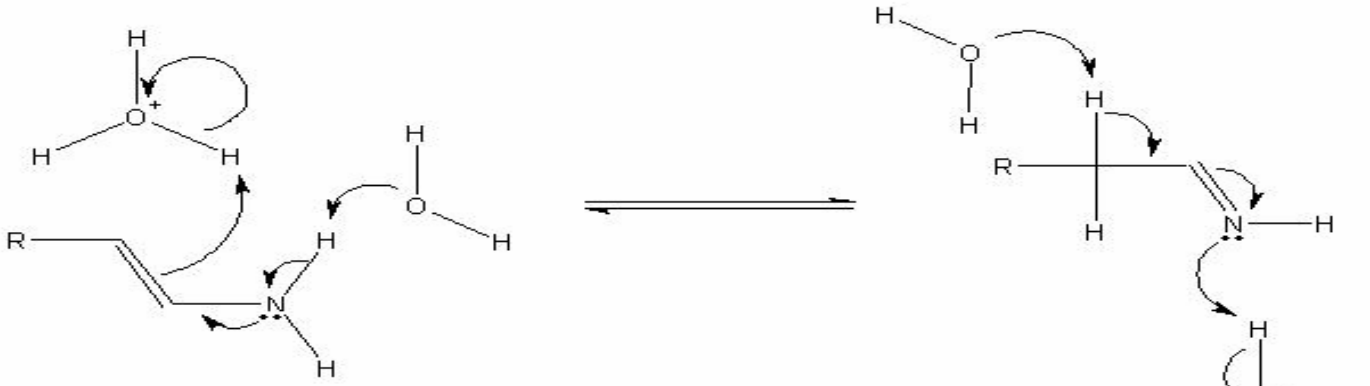
With metals and acid the following path has been suggested:[1218]



This should also be applicable to aliphatic nitro compounds, such as nitrostyrenes.

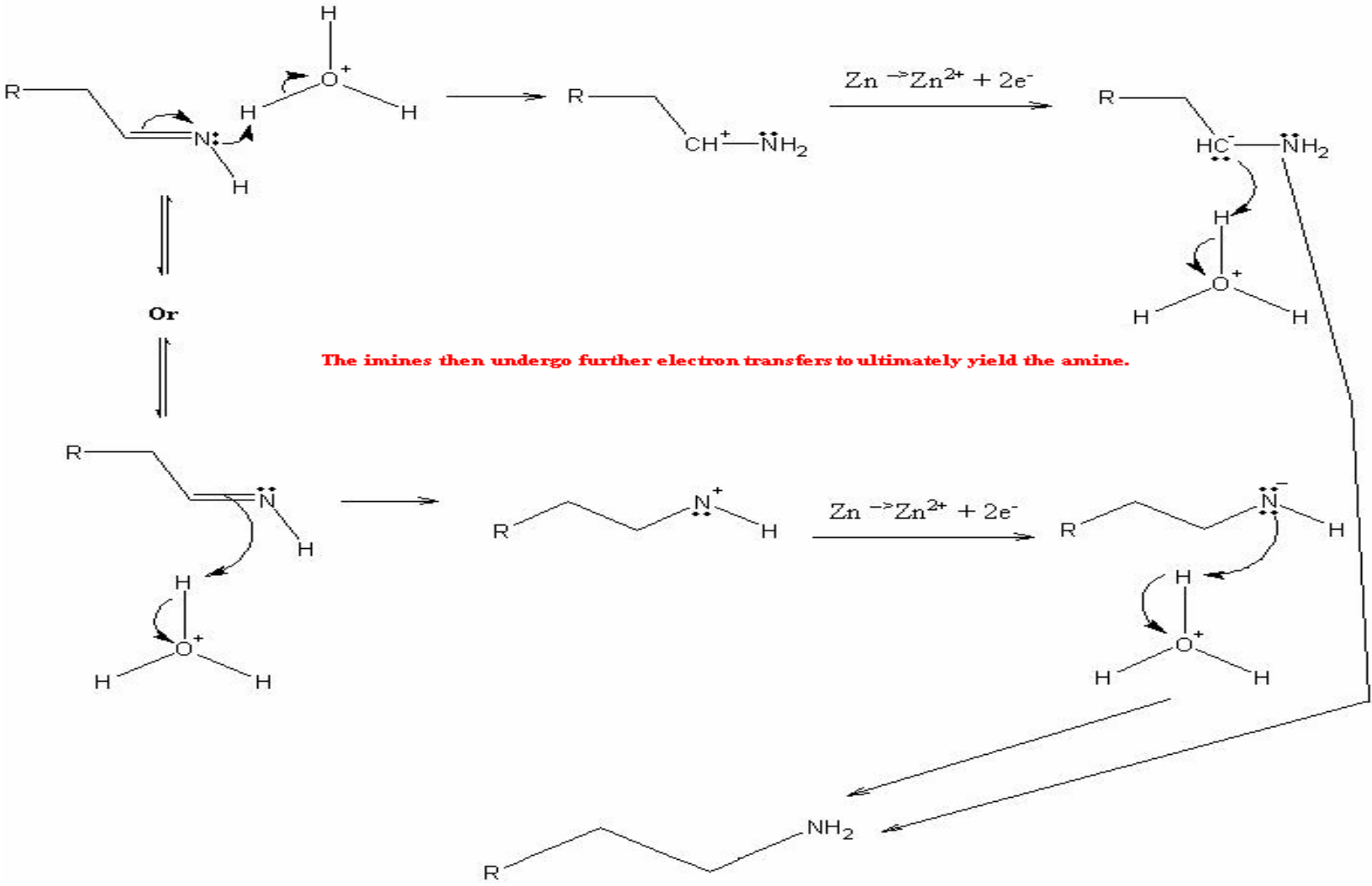
[1218] House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, p. 211.

It is expected that the nitro group would be the first reduced in the case of nitroalkenes.



Enamine - Imine Tautomerism

Reduction of the nitro group would lead to the enamines and their corresponding imines.



Or

The imines then undergo further electron transfers to ultimately yield the amine.

The proposed reaction mechanism, like the one for the nitro group, involves electron transfers. It was noted, that the bulk of the zinc went toward the reduction of nitro group, as suggested by the mechanism presented above. The last equivalent of zinc (the other three of four equivalents going towards the reduction of the nitro group) goes toward the reduction of the double bond. However, the author presupposes that the enamine double bond is not directly reduced, but rather that the reduction proceeds through the imine. This could also potentially explain the relatively long time needed to reduce the double bond after the nitro group is reduced.

The author believes that the enamine is in equilibrium with the imine, and it is the imine which is the most direct intermediate before the phenethylamine. The reaction may proceed through two routes – the formation of a carbanion, or the formation of an "imine anion." The author is leaning toward the carboanion.

The carboanion may be more likely for two reasons – one, the nitropropene does not get reduced due to this method; it is a well known fact that lesser substituted carbanions are more stable. Could this be the explanation for the failed nitropropene reduction? The second reason may be that in nitropropenes, the intermediate carbocation would also be more stable, being more heavily substituted, and as a result the equilibrium may favor the imine over the subsequent electron transfer. This would not occur in the case of nitrostyrenes. The author is not sure in either these matters, but thinks it may be a plausible start.

In any case, the proposed reaction mechanism would overlap with the found experimental conditions – those being: fast zinc addition, fairly high concentration of acid, and low temperature. The reaction mechanism may also explain why polymerization may occur, specifically in that a low concentration of zinc leads to the polymerization of nitrostyrenes and enamines. Whatever the case may be, the idealized reduction yields a very clean product, utilizing a very short reaction time, cheap reagents and a simple workup. Overall, this is the quickest and easiest reduction of nitrostyrenes that the author knows.

The idealized procedure, in detail, is as follows:

1g of aldehyde undergoes the Henry reaction as described above, and is lightly dried. Meanwhile, for every 1g of aldehyde, 30ml of 31% hydrochloric acid is added to 20ml of 91% isopropyl alcohol, followed by an additional 5ml water (it is advisable to use ice here). The solution is chilled to 5*C, the nitrostyrene added, and the resultant mixture stirred. Zinc is then added to the mixture at such a rate so as to keep the solution relatively gray – this is about 1g every 5-10 minutes. 5g of zinc is needed per 1g of aldehyde (for scaling the reaction upwards, 1/5 of the total amount of Zn is added every 5-10 minutes, or so as to keep the solution fairly gray). All of the zinc should be added within one hour, typically a little bit less. The temperature should be kept under 10*C during the entire reaction (the lower the better). Once the addition of the zinc is complete, an additional 5ml of 31% hydrochloric acid is added the solution, and this is stirred and allowed to sit until all or nearly all of the zinc dissolves. This takes about 2-3 hours, and though a longer reaction time will not adversely affect the reaction, it has been found to be unnecessary. (1)

A 50% solution of potassium hydroxide, containing an amount of potassium hydroxide approximately twice the molar equivalent of the hydrochloric acid present in the reaction is then cooled to ~ -5*C, and is slowly added to the hydrochloric acid-zinc-alcohol solution and stirred with a stir rod so as to evenly distribute the base and minimize localized heating. The temperature is monitored so as not to rise above 30-35*C. The solution is then further stirred in order to maximize the concentration of amine in the isopropyl alcohol layer, which upon standing separates and floats to the top. The aqueous and organic layers are then separated, and the aqueous layers again extracted with a small amount of isopropanol. These are also separated, and the organic layers are then combined, dried with magnesium sulfate, filtered, and allowed to evaporate under a fan. During this time, a theoretical equivalent of hydrochloric acid is added (any acid may be used). The product may then be washed with acetone until it is white and clean, and recrystallized if necessary, though this is in most cases unnecessary. The yield should be about 70-80% depending on how much nitrostyrene actually went into the reaction (assume 75%).

(1) – A slightly longer reaction time may be needed if a magnetic stirrer is not used, because the zinc does not contact the solution as well. In place of this, more acid and more zinc may be used. The most important factor is to keep the zinc concentration fairly high in the first hour or so of the reaction.

References:

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