

REDUCTIVE AMINATION REVIEW

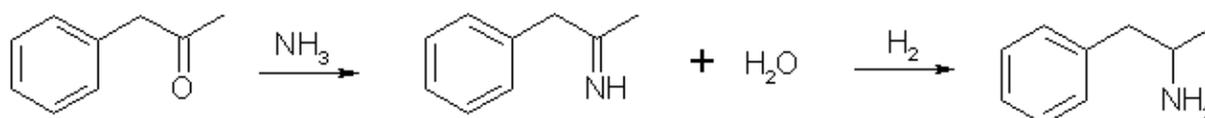
by Station

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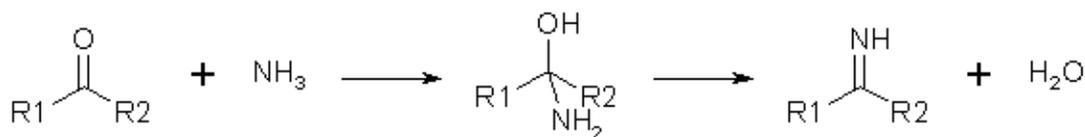
A note on nomenclature utilized in the various syntheses. The literature variously refers to amphetamine as beta-phenylisopropylamine, 1-phenyl-2-aminopropane, beta-aminopropylbenzene, deoxynorephedrine, desoxynorephedrine, PhCH₂CH(NH₂)CH₃ or PhCH₂CH(NH₂)Me. The dextro isomer of amphetamine is the d, (+), D or S isomer; the levo isomer is the l, (-), L or R isomer. The racemic mixture may be referred to as d,l, (+,-), DL or (R)(S).

REDUCTIVE AMINATION

Reductive amination is the process by which ammonia is condensed with aldehydes or ketones to form imines which are subsequently reduced to amines. Reductive amination is utilized to produce amphetamine from 1-phenyl-2-propanone and ammonia.



Ammonia reacts with aldehydes and ketones to form compounds called imines (a condensation reaction with the elimination of water). The first step is a nucleophilic addition to the carbonyl group followed by a rapid proton transfer. The resulting product, a hemiaminal, also sometimes called a carbinolamine, is generally unstable and cannot be isolated. A second reaction occurs in which water is eliminated from the hemiaminal and imine is formed.



The subsequent reduction of imine to amine is typically accomplished by treating with hydrogen and a suitable hydrogenation catalyst or treating with aluminum-mercury amalgam or via sodium cyanoborohydride.

REDUCTIVE AMINATION VIA CATALYTIC HYDROGENATION

Reductive amination via catalytic hydrogenation of a mixture of aldehyde or ketone and ammonia leads to a predominance of primary amine when excess ammonia is present. At least five equivalents of ammonia should be used; smaller amounts result in formation of more secondary amine.

A significant side reaction complicates the reductive amination method. As the primary amine begins to build up, it may react with the intermediate imine to form an imine which is reduced to secondary amine. The primary amine may also condense with the starting ketone to give an imine which is reduced to secondary amine. This side reaction may be minimized by using a large excess of ammonia in the reaction medium.

Another possible side reaction is reduction of the carbonyl group to a hydroxyl group (e.g., phenyl-2-propanone may be reduced to phenyl-2-propanol). Analysis was performed on the reaction medium from a room temperature reductive amination utilizing phenyl-2-propanone, methanol solvent, Raney nickel and a mixture of ammonia and hydrogen bubbled through the solution at a slight overpressure and on the amphetamine product which had been purified by repeated crystallization. (fn.1) Due to the small quantities of the impurities in the amphetamine, the reaction mixture, in which the impurities occurred in a much higher amount, was utilized for analysis. The major impurity found was the Schiff base (imine) of amphetamine and benzyl methyl ketone (phenyl-2-propanone), benzyl methyl ketone phenylisopropylimine. This compound is the condensation product of phenyl-2-propanone and amphetamine which had not been hydrogenated. The minor impurity, surprisingly, was benzyl methyl ketone benzylimine. This compound was found to be a by-product in the condensation of amphetamine with benzyl methyl ketone.

Reductive amination does not usually produce a very high yield of primary amine, although high yields have been reported for amphetamine. Raney nickel is particularly useful in this regard, particularly at elevated temperature and pressure.

Reductive aminations carried out at low pressure with Raney nickel are typically not very successful unless a large amount of catalyst is used. It should be noted that the presence of an ammonium salt is necessary in reductive amination with noble metals; in the absence of ammonium salts the catalysts are poisoned or inactivated.

Isolation of imine and its subsequent reduction are sometimes reported to be more effective than reductive amination, but typically the difficulties in obtaining imines in high yield and their instability argue against that procedure. Imines derived from ammonia tend to be unstable--they often rapidly hydrolyze even with water to generate carbonyl compound and are often prone to polymerization.

High Pressure Reductive Amination of 1-Phenyl-2-Propanone Utilizing Raney Nickel:

Organicum: Practical Handbook of Organic Chemistry (Addison-Wesley Publishing Co., Inc., 1973), English translation by B. J. Hazzard, 458-9 and 686.

In working with Raney nickel, Hazzard states that a highly basic catalyst (e.g., that of Urushibara prepared from 30% nickel alloy, see catalyst preparation below) gives the best results.

134.2 g. (1.0 mole) of phenyl-2-propanone is dissolved in 500 ml of methanol that has been saturated with ammonia at 10C (about 94 g. or 5.5 moles). After the addition of Raney nickel from 30 g. of alloy, hydrogenation is carried out in a shaking or stirring autoclave at 90C and 100 atm. After the uptake of hydrogen has ceased, the pressure is released, the catalyst is filtered off, and the solvent is distilled off. The residue is acidified with 20% hydrochloric acid to Congo Red (i.e., to pH 3; Congo Red is blue- violet at pH 3.0 and red at pH 5.0) and the non-basic impurities are extracted with ether. The ethereal extract is discarded and, with efficient cooling, the aqueous solution is made alkaline with 40% sodium hydroxide solution and is repeatedly extracted with ether. The extract is dried over potassium hydroxide. After the solvent has been evaporated off, the product is distilled through a 20-cm Vigreux column to obtain a 90% yield of DL-1-phenyl-2-aminopropane, b.p. 12mm. 92C.

Hazzard notes the amphetamine is better stored in the form of the hydrochloride. To obtain the hydrochloride, the amphetamine base was dissolved with cooling in an excess of absolute alcohol saturated with hydrogen chloride and precipitated with absolute ether to obtain the racemic DL amphetamine hydrochloride, mp 152C.

Preparation of alkaline highly active Raney Nickel (Urushibara nickel): In a vessel as large as possible (5 liters or larger), 50 g. of aluminum- nickel alloy containing 30-50% nickel is slurried in 500 ml water. Then solid sodium hydroxide is added without cooling at such a rate that the mixture just does not foam over. Caution: There is an induction period of 0.5-1 minute before the very violent reaction. The mixture boils vigorously. When the further addition of sodium hydroxide does not give rise to any appreciable reaction, which requires about 80 g., the mixture is allowed to sit for 10 minutes and then kept for 30 minutes on the water bath at 70C. The nickel settles to the bottom as a spongy mass. The supernatant aqueous layer is decanted off and, with shaking, the catalyst is washed by decantation two or three times with water and then two or three times with the solvent to be used for the hydrogenation. If the solvent is immiscible with water, a suitable intermediate washing liquid is used.

Although the catalyst can be stored for some time under a solvent, it is always desirable to prepare it directly before use, since storage leads to a marked fall in activity.

Low Pressure Reductive Amination of 1-Phenyl-2-Propanone Utilizing Raney Nickel:

Haskelberg, Aminative Reduction of Ketones. J. Am. Chem. Soc., 70 (1948) 2811-2; C.A. 43: 1349f (1949).

Phenylacetone (1-phenyl-2-propanone) was catalytically converted to beta-phenylisopropylamine (amphetamine) using ethanolic ammonia, hydrogen at about atmospheric pressure and Raney Nickel. A yield of 85% was obtained. Phenylacetone, 118 g. (0.89 mole) in 400 cc. 17% NH₃ in ethanol was hydrogenated with 22 g. Raney Nickel at a hydrogen pressure of 1 atm. or slightly above and a temperature of 20C or slightly above. After removal of the catalyst, the product was isolated by fractionation of the mixture. Beta- phenylisopropylamine was obtained in 85% yield, b.p. 10mm. 80C, hydrochloride m.p. 146. A higher-boiling by-product of 10.2 g. (8%) bis-(1- phenyl-propyl-2)-amine, C₁₈H₂₂N, b.p. 2mm. 154C was also obtained.

Mastagli et al., Study of the Aminolysis of Some Ketones and Aldehydes. Bull. soc. chim. France (1950) 1045-8; C.A. 45: 8970g (1951).

Primary amines were prepared by the ammonolysis of ketones. Reaction was carried out in methanol saturated with ammonia by the method of Haskelberg (see above). Where ammonolysis was not complete, the nonamine portion is a mixture of ketone and the corresponding alcohol (1- phenyl-2-propanol). 1-Phenyl-2-propanone (PhCH₂Ac) 15 g. (0.11 mole) in 60 cc. methanol saturated with NH₃ was hydrogenated over Raney nickel at 65C for 5 hours. An 86% yield of amphetamine (PhCH₂CH(NH₂)Me) was obtained, b.p. 12mm 92-95C.

Low Pressure Reductive Amination of 1-Phenyl-2-Propanone Utilizing Platinum Oxide:

Alexander et al., A Low Pressure Reductive Alkylation Method for the Conversion of Ketones to Primary Amines. J. Am. Chem. Soc., 70, 1315-6 (1948); C.A. 42: 5411d (1948).

Reductive amination was carried out in the presence of ammonium chloride, in the hopes that the more basic primary amine reaction product would react and form an alkylammonium ion, thereby tending to stop the process at the formation of primary amines. Nevertheless, considerable amounts of secondary amine were observed. The reaction medium was methanol saturated with ammonia and the catalyst was platinum oxide. A 52% yield of phenylisopropylamine was obtained.

An apparatus similar to the one described by Adams et al. (fn.2) was used for the reaction. The phenyl-2-propanone was redistilled before use. In a 300-ml reduction bottle containing 10 ml of distilled water, 0.2 g. of platinum oxide was prereduced to platinum by shaking in an atmosphere of hydrogen for 10 minutes (when an attempt was made to omit this step a long induction period occurred and reduction appeared to proceed much more slowly than normal).

Phenyl-2-propanone (40.2 g., 0.3 mole), ammonium chloride (20.0 g., 0.37 mole), 225 ml of absolute methanol saturated with ammonia, and 25 ml of aqueous ammonia were added and the mixture was reduced by shaking with hydrogen at one to three atmospheres. Hydrogenation was continued until a constant pressure reading indicated that reduction had ceased. Shaking was stopped, the bottle vented, and the catalyst allowed to settle. Filtration was through a Hirsch funnel into a round-bottomed flask, and the catalyst and salt which collected was rinsed down with water or methanol. The flask and contents were then removed to a hood and refluxed under a condenser for one hour to remove the excess ammonia (nitrogen entrainment can help here).

The solution was then cooled and acidified to Congo red paper with concentrated hydrochloric acid, forming an insoluble salt. The mixture was cooled, and the salts were filtered with suction and washed thoroughly with water and saved. The aqueous filtrate was extracted with three 25-ml portions of benzene. The benzene extracts were discarded (one likely side product here is phenyl-2-propanol, the result of direct reduction of the ketone starting material).

The aqueous filtrate was then recombined with the insoluble salts and made strongly basic with 50% sodium hydroxide solution. The two layers which formed were separated and the water layer was extracted three or four times with ether. The ether extracts and the oily layer were then combined, washed with water and dried over potassium hydroxide. The primary amine (amphetamine) was purified by distillation through a 13-cm column packed with glass helices and obtained in a 52% yield. Considerable amount of secondary amine was observed to remain in the boiling flask.

High Pressure Reductive Amination of 1-Phenyl-2-Propanone Utilizing Raney Nickel and Ammonium Acetate:

Green, Reductive Amination of Ketones. U.S. Pat. No. 3,187,047, June 1, 1965; C.A. 53: 9873f (1965).

A process for the reductive amination of ketones was described in which the NH₄ (ammonium) salt of an organic acid was used as the source of amine.

An autoclave was charged with 3 kg. 2,5-dimethoxyphenylacetone (2,5-dimethoxy-phenyl-2-propanone), 1.2 kg. AcONH₄ (ammonium acetate), 180 ml. AcOH (acetic acid), 9500 ml. MeOH (methanol), 300 ml. H₂O, and 500 g. Raney nickel catalyst. The autoclave was closed, heated to 90C, and H₂ (hydrogen) introduced to a pressure of 1200 psi. When the reaction was completed an analysis showed a 95% yield of 2,5-dimethoxyamphetamine, 3% distillation residues, and 2% acid insolubles.

REDUCTIVE AMINATION VIA DISSOLVING METAL REDUCTIONS

Dissolving metal reductions, in particular aluminum, continue to be utilized although not without their difficulties (such as trying to filter the aluminum hydroxide formed in the reaction).

Although molecular hydrogen is produced as the metal dissolves, this is generally considered to be a detriment to the reduction of the substrate. The actual reduction mechanism evidently does not involve molecular H₂ but is a result of an "internal electrolytic process." In one theory, electron transfer to a heteroatom results in a radical carbon which abstracts hydrogen from solution to complete reduction. (fn.3), (fn.4)

"Poisoning" via amalgamation is one approach used to minimize rapid dissolution of the metal and to abate formation of H₂. Aluminum-mercury amalgamation serves to give an activity somewhere between the extremes of the over-active metal and the inactive metal oxide. Amalgamation between aluminum and mercury has the additional benefit of preventing oxide formation on the surface of aluminum in contact with air. (fn.3)

ALUMINUM-MERCURY REDUCTION OF IMINE FROM PHENYL-2-PROPANONE AND AMMONIA:

Wassink et al., A Synthesis of Amphetamine. J. Chem. Ed., 51, 671 (1974). Amphetamine was obtained in a one step synthesis. Although the yield of the reaction was not as high with reduction utilizing ammonia instead of methylamine (30% yield versus 70%), the easiness of the procedure made the method worthwhile. Note that it may be possible to recover unreacted phenyl-2-propanone from the initial ether extract. A mixture of 40 g. (0.3 mole) phenyl-2-propanone, 200 ml ethanol, 200 ml 25% ammonia, 40 g. (1.5 mole) aluminum-grit and 0.3 g. (0.001 mole) mercuric chloride (HgCl₂) was warmed with vigorous stirring until reaction took place, after which warming was stopped immediately. Cooling was applied if the reaction became too violent. When the violence of the reaction had diminished, the mixture was refluxed with vigorous stirring for about 2 hours, concentrated in vacuo to 200 ml and poured into ice water, alkalized with 120 g. potassium hydroxide (KOH), and extracted with diethyl ether. The extractions were shaken with 20% HCl (pressure), the resulting water layer alkalized (e.g., with 50% sodium hydroxide) and then extracted with 150 ml ether. The organic layer was dried over Na₂SO₄ (sodium sulfate; KOH is probably a better choice), the ether evaporated and the residue distilled in vacuo. Yield: 12.5 g. (0.09 mole or 30% of theoretical yield). Preparation of amphetamine sulfate yielded 96-98% product with a purity of 99.2-99.8% according to the USP.

NOTES

- 1. Theeuwen et al., Impurities in Illicit Amphetamine. 7. Identification of Benzyl Methyl Ketone Phenylisopropylimine and Benzyl Methyl Ketone Benzylimine in Amphetamine. Forensic Science International, 15, 237-41 (1980).**

2. Adams et al., *Organic Syntheses* (John Wiley and Sons, Inc., 1941) p. 61.
 3. **Synthetic Reductions in Clandestine Amphetamine and Methamphetamine Laboratories: A Review**. *Forensic Science International*, 42, 183-99 (1989).
 4. Another theory utilizing implications of Feynman diagrams holds that if you add up all the probabilities of an electron appearing in the electron clouds for all the atoms in the universe, you find there is only one electron in the universe, only you can't tell if it's an electron going forward in time or a positron traveling backward in time.
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