A Simple Secondary Amine Synthesis: Reductive Amination Using Sodium Triacetoxyborohydride

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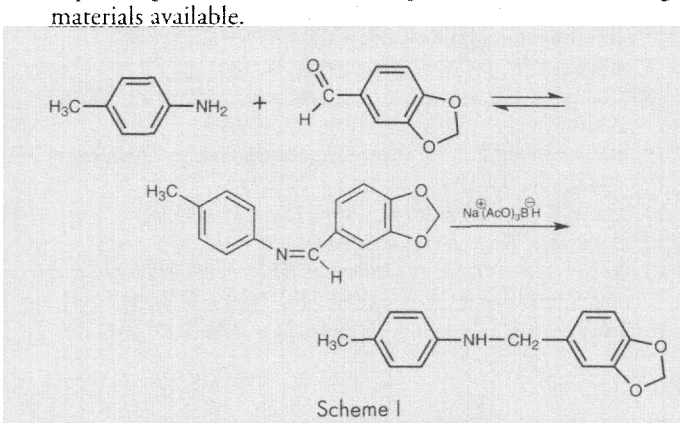
In modern organic synthesis, reductive amination is considered one of the principal ways to make secondary and tertiary amines (*1*). Given the importance of amines in modern organic chemistry and biochemistry, it is surprising to find that this particular synthetic method is often missing from the organic laboratory curriculum. A detailed experimental procedure for the synthesis of secondary amines for a second-semester organic chemistry class is described herein.

Traditional reducing agents for reductive amination have included hydrogen with metal catalysts (*2*), sodium cyanoborohydride (*3*), and sodium borohydride (*3*). However, they may require preformation and isolation of the imine, the possibility of toxic by-products (HCN in the case of sodium cyanoborohydride), or specialized equipment (hydrogenator). These complications have limited the application of reductive amination in the undergraduate laboratory. By using a selective reducing agent, sodium triacetoxyborohydride (*4*), undergraduates may conveniently sidestep many of these difficulties in the laboratory.

In this particular experiment, piperonal and *p*-toluidine will be allowed to form an imine, and this imine will be reduced in situ to form *N*-(*p*-tolyl)piperonylamine (Scheme I). Other amine plus aldehyde, amine plus ketone, and even amine plus ester combinations will participate in this process,[1] depending on the desired amine product and the starting materials available.



Scheme I

The use of a selective reducing agent will allow the reduction of the imine, but not the aldehyde.[2] This may facilitate discussion of functional group selectivity by the instructor. The entire reaction process can be monitored by TLC. The piperonal, *p*-toluidine, imine intermediate, and product all appear as unique spots by TLC (the order of migration of spots, from lowest to highest R_f values, is *p*-toluidine, imine intermediate, piperonal, and *N*-(*p*-tolyl)piperonylamine), and the reaction may be periodically monitored for completion using this method. Observation of the intermediate imine by TLC is a particularly valuable aspect to this laboratory, as students do not often "see" reaction intermediates.

Upon purification of the product, the instructor may choose to have students perform NMR (^{1}H and ^{13}C), IR, MS, or a melting or boiling point determination of the given amine product, depending on instrument availability. In the case described above, the ^{1}H NMR, IR, and melting point were taken (^{1}H NMR and IR spectra are appended;[W] melting points were generally within ±3 °C of that of the pure compound in our hands).

Experimental Procedure

A solution of carbonyl compound and primary amine is prepared by dissolving the appropriate amount of each reagent (approximately 1.3 mmol carbonyl compound, 1.9 mmol primary amine) in 35 mL of dichloromethane in a 125-mL Erlenmeyer flask. The sodium triacetoxyborohydride (approximately 2.0 mmol, 2 equivalents)[2] is then added to the solution, resulting in a slurry which is swirled occasionally (approximately three good "swirls" every five minutes).

TLC is utilized to monitor the reaction for completion. The ideal solvent system in our hands was dichloromethane. When the reaction is complete, approximately 1½ hours later, the remaining borohydride is destroyed by the addition of 25 mL of aqueous 5% sodium bicarbonate solution. After the foaming subsides, the solution is placed into a separatory funnel and the aqueous (upper) phase is removed. The organic layer is washed twice more with 20-mL portions of water. Without drying, the solvent is removed by evaporation using a rotary evaporator.

The resulting solid may then be recrystallized by dissolving in about 5 mL of hot ethanol[3] (95%) until a homogeneous solution is obtained. While keeping the solution hot, room temperature water is added dropwise with agitation until the solution becomes turbid. At this point, a few more drops of ethanol are added to redissolve the precipitate. The flask is cooled to room temperature, and then in an ice bath for several minutes until precipitation is complete. The solid is collected by suction filtration, washing with a small amount of ice-cold ethanol. The melting point of *N*-(*p*-tolyl)piperonylamine, the product in Scheme I, is 95–96 °C.

Acknowledgment

We would like to thank Butler University's 1998 spring organic chemistry classes for assisting with the preparation and testing of this lab.

[W]Supplemental Material

Supplemental material for this article is available in this issue of *JCE Online*.

Notes

1. Ninety-six successful substrate pairs are described in ref *4*.
2. Two equivalents of hydride was used in order to have the reaction go to completion in the desired period of time (1 to 1½ hours). The reaction does work with 1.4 equivalents of hydride in approximately three hours.
3. The product may also be recrystallized from hot hexanes.

Literature Cited

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2. For leading references, please see: Klyuev, M. V.; Khidekel, M. L. *Russ. Chem. Rev.* **1980**, *49*, 14. Freifelder, M. In *Practical Catalytic Hydrogenation*; Wiley-Interscience: New York, 1971; pp 333–345, 351–374.
3. For a review of these reductions, please see: Hutchins, R. O.; Hutchins, M. K. In *Comprehensive Organic Synthesis*; Trost, B. N.; Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 8, pp 25–78.
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Catalytic Asymmetric Epoxidation Using a Fructose-Derived Catalyst

W

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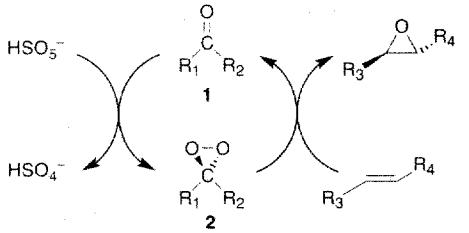
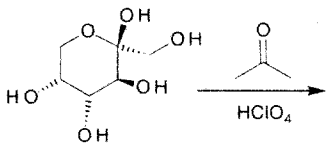
Modern epoxidation methods are able to convert achiral alkenes into products containing two adjacent stereocenters with very high enantioselectivities. Opening of the epoxides with nucleophiles permits rapid entry into complex organic systems, making this methodology one of the essential reactions of organic synthesis. Yet until very recently, epoxidation had received virtually no attention from the chemical education community. One report examining the kinetics of a catalytic epoxidation appeared in the mid-1980s (*1*), while another report featuring an epoxidation–rearrangement sequence appeared in 1996 (*2*). More recently, a very nice treatment of the Sharpless reaction explored both the regioselectivity and enantioselectivity of the epoxidation of geraniol (*3*). Unfortunately, while this procedure clearly demonstrates that asymmetric induction can be achieved, the mechanism of the reaction is not discussed. Indeed, the description of intermediates in titanium-catalyzed reactions is challenging at the undergraduate level (*4*).

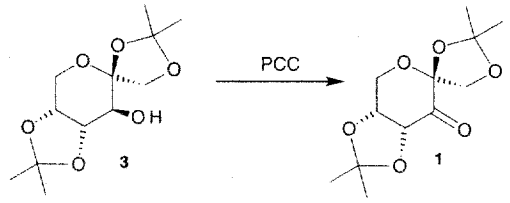
Another very versatile method for generating epoxides from alkenes is through the use of dioxiranes (*5*). Typically, the dioxirane is generated in situ from a ketone and an oxidizing agent (eq 1). The dioxirane then transfers an oxygen to the alkene. If the ketone is chiral, enantiomerically enriched products can result. This approach has proven to be exceptionally effective with trans or trisubstituted alkenes, even when they are nonallylic.



(1)

Recent work by Yian Shi and coworkers at Colorado State University has introduced a ketone catalyst derived from fructose (1) (*6*). In the winter of 1998, we introduced an experiment based upon Shi's report into our Techniques in Chemistry laboratory course for sophomore and junior chemistry majors.[1] The multistep experiment described here is highly modular and may be effectively used at a variety of levels. The complete experiment, as described here, is designed for more advanced students with significant synthetic experience. The synthesis of the ketone catalyst, 1, can be completed in two lab periods (eq 2).





(2)

CAUTION: Instructors should be aware that this synthesis makes use of potentially hazardous reagents (perchloric acid and pyridinium chlorochromate).

The catalytic epoxidation can be completed in a single period and would be appropriate for more junior students. Instructors contemplating this approach would want to prepare ketone 1 beforehand in sufficient quantities. The analysis portion of the experiment can be made as elaborate as desired. The full procedure, including modeling, would take at least three additional lab periods. Optical rotation can be used in place of the NMR shift experiment for determination of enantiomeric excess.

Several analytical methods are appropriately applied to the analysis of the reaction products. Some of these are detailed in the supplemental materials, including an NMR shift experiment.[W] We are strong advocates of the use of molecular modeling in the undergraduate curriculum (*7*), and there are a number of modeling studies that can be used to explain the observed enantiomeric enrichment. Some of these are presented in the supplemental materials.[W]