Published in final edited form as:

Org Lett. 2013 November 1; 15(21): . doi:10.1021/ol402815d.

A Simple, Scalable Synthetic Route to (+)- and (–)-Pseudoephedrine

Kevin T. Mellem and Andrew G. Myers

Department of Chemistry and Chemical Biology, Harvard University, Cambridge, MA 02138

Andrew G. Myers: myers@chemistry.harvard.edu

Abstract

A three-step synthesis of pseudoephedrine suitable for preparing multigram amounts of both enantiomers of the auxiliary from the inexpensive starting material benzil is described. The sequence involves synthesis of the crystalline mono-methylimine derivative of benzil, reduction of that substance with lithium aluminum hydride, and resolution of pseudoephedrine with mandelic acid.

Pseudoephedrine (**1**) is a useful chiral auxiliary for the synthesis of enantioenriched carboxylic acids, ketones, primary alcohols, and α -methyl α -amino acids, and in many instances it proves to be superior to the regulated substance pseudoephedrine in parallel transformations.¹ The primary disadvantage of pseudoephedrine relative to pseudoephedrine is that it is not yet commercially available. Previously, we reported a four-step synthesis of pseudoephedrine from the commercially available chiral amino alcohol 1,2-diphenyl-2-aminoethanol (the synthesis of (1*S*,2*S*)-pseudoephedrine, (–)-**1**, is depicted in Scheme 1).^{2,3} Here we report a shorter, more facile, and readily scalable procedure for the preparation of optically pure pseudoephedrine from the inexpensive starting material benzil (**2**).⁴

Wheatley and co-workers first described the preparation of methylimino benzil (**3**) by the condensation of methylamine and benzil in methanol–water at 50 °C, reporting a yield of 84%.⁵ In adapting this synthesis, we found that it is critical to use a fresh (commercial) 40 wt % solution of methylamine in water (such that the titer of the volatile methylamine reactant is accurate) and crystalline benzil as a co-reactant. After the reactants are combined, we heat the heterogeneous mixture in an oil bath while stirring until an internal temperature of 50 °C is achieved and all solids are dissolved. Heating is immediately discontinued at this point; upon cooling, we observed that the mono-imine crystallizes from the reaction mixture. The product is isolated in pure form by simple filtration (88% yield, 100–600-g scale, Table 1). Without careful control of the reaction time and temperature, further reaction to produce bis-methylimino benzil can occur. We have established that the

Correspondence to: Andrew G. Myers, myers@chemistry.harvard.edu.

Supporting Information Available Full experimental procedures, characterization data, and ¹H and ¹³C NMR spectra for all synthetic intermediates. This material is available free of charge via the Internet at <http://pubs.acs.org>.

crystalline methylimino benzil we obtain has (*Z*)-geometry by NOE and HMBC NMR correlations as well as X-ray crystallography (see Supporting information).

Two prior studies of the reduction of methylimino benzil explored the use of Raney nickel⁵ and sodium borohydride⁶ as reductants, and in each case ephenamine was reported to be the major or exclusive product. We are unaware of any reports of the reduction of methylimino benzil to form pseudoephenamine as the primary product. Initially, we attempted to achieve both an enantio- as well as diastereoselective reduction of mono-imine **3** by exploring various chiral reductants;⁷ however, in each instance we obtained only racemic ephenamine. Parenthetically, we found that mixtures of the four possible stereoisomeric amino alcohols are conveniently assayed by admixing an equimolar quantity of (*S*)-mandelic acid in CDCl₃ followed by ¹H NMR analysis (500 MHz). Multiple resonances are found to be well-resolved for each diastereomer (see Supporting Information). Although reduction of **3** to form racemic ephenamine was not our objective, in Scheme 2 we depict a convenient method by which we achieved this transformation with 19:1 dr.^{8,9}

Based upon the promising report of the reduction in the desired sense of achiral *N*-aryl and *N*-benzyl benzil mono-imines using lithium aluminum hydride (LAH),¹⁰ we investigated the use of this reagent for the reduction of methylimino benzil.¹¹ In an initial experiment, reduction of methylimino benzil with LAH in THF at −78 °C afforded a 4:1 mixture of diastereomeric amino alcohols favoring pseudoephenamine. Further investigations revealed that the diastereoselectivity of the reduction varied as a function of the rate of addition of LAH to the reaction mixture, and it was noted that addition of powdered LAH too quickly led to delayed exotherms. Controlled addition of LAH with a powder addition funnel prevented this and allowed an internal temperature of −70 °C to be maintained. It is useful to note that exotherms more commonly occur early in the course of the reaction; thus, the rate of LAH addition may be increased as the reaction progresses. Efficient mechanical stirring of the reaction is very important, especially on large scale, so as to prevent the aggregation of powdered LAH on the surface of the reaction mixture. In this manner, we routinely obtained racemic pseudoephenamine of 4.7–5.4:1 dr on 75–570 g scales in reproducibly high yield (>85%, see Table 2). As noted by Alcaide et al. in their study of the reduction of *N*-aryl and *N*-benzyl benzil mono-imines, the observed diastereoselectivity of the reduction is consistent with the polar Felkin-Ahn model.¹⁰

Direct resolution of pseudoephenamine from the mixture of diastereomers obtained in the LAH reduction was achieved with mandelic acid. We found that (*R,R*)-pseudoephenamine preferentially formed a highly crystalline salt with (*R*)-mandelic acid but not with (*S*)-mandelic acid.^{12,13} Beneficially, neither diastereomeric ephenamine mandelate salt crystallized in our experiments. Two procedures for the direct resolution of the LAH reduction products were developed, one with and one without stirring. Both methods yield highly diastereoenriched mandelate crystals (19:1 dr by ¹H NMR, with no trace of either ephenamine mandelate salt) with good recovery (defined as the percent of the theoretical amount of the targeted enantiomer of pseudoephenamine). Seed crystals are typically unnecessary for these resolutions, though they will effectively initiate resolution if crystal formation is sluggish.

In the first method, a solution of pseudoephenamine mandelate in methanol was allowed to stand at −20 °C for several days without stirring, producing orthorhombic crystals. One representative set of experiments demonstrating this protocol is illustrated in Scheme 3. In the optimized procedure, pseudoephenamine (10 g, 5.4:1 dr, racemic) is mixed with (*S*)-mandelic acid (1 equiv) in methanol (2.2 M in pseudoephenamine and ephenamine combined), and the mixture is warmed to 50 °C in a 100- mL round-bottom flask to effect dissolution of the solid materials.¹⁴ After cooling to room temperature and removing the stir

bar, the base of the flask is carefully scratched with a spatula, and the vessel is transferred to a $-20\text{ }^{\circ}\text{C}$ freezer to promote crystallization. After standing for several days (incubation times ranging from 2–10 days are typical), crystalline (*S,S,S*)-**5** of 19:1 dr is obtained by filtration using a Büchner funnel. The mother liquor is concentrated, and, after formation of the free base, resolution with the opposite enantiomer of mandelic acid is conducted. The pseudoephedrine mandelate salts obtained by this process serve as suitable seed crystals for later resolutions. Pseudoephedrine is isolated as the free base, and, after recrystallization from hot absolute ethanol, optically pure auxiliary is obtained (81% recovery, 99% ee, see Scheme 4).¹⁵ The mandelic acid is also easily recovered and recycled (see Supporting Information).

Conducting resolutions of pseudoephedrine on a larger scale (>300 g) required the development of a second protocol involving gentle stirring of the cooled solution of pseudoephedrine mandelate in methanol.¹⁶ Resolutions employing this method produce fine, powdery crystals and progress much more rapidly than those performed using the earlier protocol, with typical resolution times ranging from 2–12 hours. Several rounds of resolution were routinely conducted in the time it would take to conduct a single resolution using the first method. A series of iterative resolutions conducted on a single batch of 570 g of pseudoephedrine (4.7:1 dr, racemic) demonstrate the utility of the stirring protocol to produce highly enriched mandelate crystals (19:1 dr by ^1H NMR, see Scheme 5), providing approximately 100 g of each enantiomer of pseudoephedrine (92% ee). Recrystallization of the auxiliary from absolute ethanol provided more than 80 g of each enantiomer of 99% ee. This protocol is our preferred method of resolving pseudoephedrine, and we have routinely performed it on large amounts of material (>300 g), although it also works well on much smaller scales (<50 g).

When pseudoephedrine is appreciably contaminated with ephedrine (<2.5:1 dr), recoveries upon resolution with mandelic acid are low. To circumvent this problem, mixtures of low dr can be diastereomerically enriched by recrystallization from methanol in the presence of a seed crystal of optically pure pseudoephedrine (Scheme 6). The diastereomerically enriched pseudoephedrine can then be subjected to mandelic acid resolution as in Scheme 5. In addition, we have discovered that ephedrine is slowly converted to pseudoephedrine upon heating ($110\text{ }^{\circ}\text{C}$) in 9 N H_2SO_4 (Scheme 7).¹⁷ At equilibrium, the diastereomeric ratio of the amino alcohols is ~3:1 favoring pseudoephedrine. Recrystallization from methanol as in Scheme 6 provides diastereomerically enriched pseudoephedrine suitable for mandelic acid resolution. In this way, it is possible to convert the majority of the amino alcohols obtained in the reduction of methylimino benzil to optically pure pseudoephedrine.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We gratefully acknowledge the NSF (CHE-1152205) and NIH (CA-047148) for financial support of this research. We also wish to express our sincere appreciation to Dr. Shao-Liang Zheng of Harvard University for X-ray crystallographic analyses.

References

1. (a) Morales MR, Mellem KT, Myers AG. *Angew Chem Int Ed.* 2012; 51:4568–4571. (b) Medley JW, Movassaghi M. *Angew Chem Int Ed.* 2012; 51:4572–4576. (c) Hugelshofer CL, Mellem KT, Myers AG. *Org Lett.* 2013; 15:3134–3137.

2. For alternative syntheses of pseudoephedrine, see: Yamashita J, Kawahara H, Ohashi S, Honda Y, Kenmotsu T, Hashimoto H. Tech Rep Tohoku University. 1983; 48:211–219. Meyers AI, Marra JM. Tetrahedron Lett. 1985; 26:5863–5866. Lour R, Mi A, Jiang Y, Qin Y, Li Z, Fu G, Chan ASC. Tetrahedron. 2000; 56:5857–5863.
3. Currently, both enantiomers of 1,2-diphenyl-2-aminoethanol are available from Ace Synthesis, LLC at a cost of \$550 for 100 g.
4. Currently, benzil is available from Alfa Aesar at a cost of \$225 for 2.5 kg.
5. Wheatley WB, Fitzgibbon WE, Cheney LC. J Org Chem. 1953; 18:1564–1571.
6. Hahn WE, Bartnik R, Mloston G. Acta Poloniae Pharmaceutica. 1979; 36:619–620.
7. See, for example: Prasad KKK, Joshi NN. J Org Chem. 1996; 61:3888–3889. [PubMed: 11667247] Murata K, Okano K, Miyagi M, Iwane H, Noyori R, Ikariya T. Org Lett. 1999; 1:1119–1121. Touge T, Hakamata T, Nara H, Kobayashi T, Sayo N, Saito T, Kayaki Y, Ikariya T. J Am Chem Soc. 2011; 133:14960–14963. [PubMed: 21870824]
8. Reductive amination of benzil in the presence of methylamine and a platinum catalyst has been reported to form ephedrine: Skita A, Keil F. Manufacture of Aminoalcohols. UK Patent. 313,217. Jul 24.1930
9. While we recognize the importance of ephedrine in asymmetric synthesis, we have made no attempt to resolve the racemic substance. For a resolution of racemic ephedrine with penicillin, see reference 5.
10. Alcaide B, López-Mardomingo C, Pérez-Ossorio R, Plumet J. J Chem Soc, Perkin Trans 2. 1983:1649–1653.
11. For the use of LAH in the reduction of chiral benzil mono-imines, see: Haro-Ramos R, Jimenez-Tebar A, Pérez-Ossorio R, Plumet J. Tetrahedron Lett. 1979; 20:1355–1356. Alcaide B, Fernández de la Pradilla R, López-Mardomingo C, Pérez-Ossorio R, Plumet J. J Org Chem. 1981; 46:3234–3238. Alcaide B, Dominguez G, López-Mardomingo C, Pérez-Ossorio R, Plumet J. J Chem Soc, Perkin Trans 2. 1986:99–103.
12. For a comprehensive guide to the optical resolution of racemic compounds via formation of diastereomeric salts, see: Kozma D. CRC Handbook of Optical Resolutions via Diastereomeric Salt Formation. CRC Press Boca Raton 2002
13. For selected resolutions of structurally similar amino alcohols, see: Erlenmeyer E, Arnold A. Justus Liebigs Ann Chem. 1904; 337:307–328. Manske RHF, Johnson TB. J Am Chem Soc. 1929; 51:1906–1909. Weijlard J, Pfister K III, Swanezy EF, Robinson CA, Tishler M. J Am Chem Soc. 1951; 73:1216–1218. Saigo K, Sugiura I, Shida I, Tachibana K, Hasegawa M. Bull Chem Soc Jpn. 1986; 59:2915–2916.
14. We recommend the solution be filtered through a fritted funnel while warm if insoluble impurities are observed in the flask.
15. Crystallization of pseudoephedrine is an exothermic process, and concentrated solutions of the auxiliary in volatile solvents such as ethyl ether (employed in the workup of these reactions) can produce pressure buildup in a sealed vessel if spontaneous crystallization occurs.
16. See chapter 3 of reference 12 for a discussion of the effect of stirring on the resolution of diastereomeric salts.
17. A similar process has been reported to transform ephedrine to pseudoephedrine: Chou TQ. J Biol Chem. 1926; 70:109–114.

Scheme 1.

First-generation synthesis of pseudoephedrine.

Scheme 2.

Hydrogenation of methylimino benzil to form (±)-ephedrine.

^a dr refers to the ratio of (±)-**4** to (±)-**1**.

Scheme 3.

Resolution of (±)-pseudoephedrine with mandelic acid at -20 °C without stirring.

^a dr refers to the ratio of (+)- and (-)-**1** to (±)-**4**. ^b dr refers to the ratio of (S,S,S)- or (R,R,R)-**5** to (R,R,S)- or (S,S,R)-**5**, respectively.

Scheme 4.

Isolation of (+)-pseudoephedrine.

^a dr refers to the ratio of (*R,R,R*)-5 to (*S,S,R*)-5.

Scheme 5.

Resolution of $(\pm)$ -pseudoephedrine with mandelic acid at 4 °C with stirring.

Total pseudoephedrine recovery after isolation of the free auxiliary and recrystallization from ethanol: 91.12 g $(+)$ -**1** (99% ee) and 89.54 g $(-)$ -**1** (99% ee)

^a dr refers to the ratio of $(+)$ - and $(-)$ -**1** to $(\pm)$ -**4**. ^b dr refers to the ratio of (R,R,R) - or (S,S,S) -**5** to (S,S,R) - or (R,R,S) -**5**, respectively.

Scheme 6.
Diastereoenrichment of pseudoephedrine.
^a dr refers to the ratio of **(±)-1** to **(±)-4**.

Scheme 7.

Isomerization of ephenamine to pseudoephenamine.

^a dr refers to the ratio of **(±)-1** to **(±)-4**.

Table 1

Synthesis of methylimino benzil.

 2 3	
scale (g)	isolated yield (%)
100	88
300	92
600	91

Table 2

Synthesis of (±)-pseudoephedrine.

scale (g)	dr ^a	isolated yield (%)
75	5.4:1	86
290	5.0:1	92
570	4.7:1	96

^a dr refers to the ratio of (±)-1 to (±)-4.