



A Publication  
of Reliable Methods  
for the Preparation  
of Organic Compounds

## Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at [http://www.nap.edu/catalog.php?record\\_id=12654](http://www.nap.edu/catalog.php?record_id=12654)). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

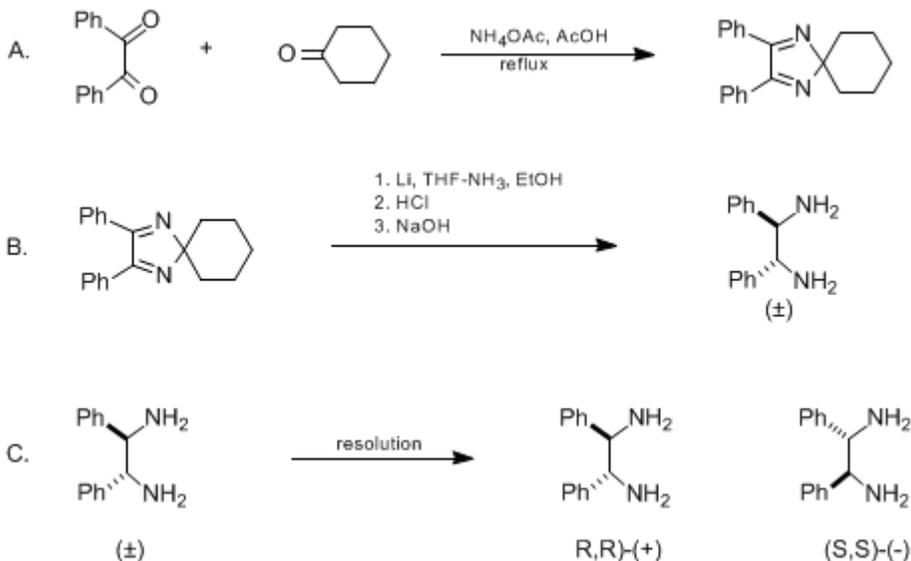
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*September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

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## (1R,2R)-(+)- AND (1S,2S)-(-)- 1,2-DIPHENYL-1,2-ETHYLENEDIAMINE

[1,2-Ethanediamine, 1,2-diphenyl-, [R-(R,R)]- and [S-(R,R)]-]



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### 1. Procedure

*CAUTION! Parts A and B of this procedure should be carried out in an efficient hood to avoid exposure to noxious vapors (acetic acid, ammonia).*

A. *2,2-Spirocyclohexane-4,5-diphenyl-2H-imidazole* (Note 1). A 2-L, three-necked, round-bottomed flask equipped with a mechanical stirrer and a reflux condenser is charged with 1.0 L of glacial acetic acid (Note 2), 158 g (0.75 mol) of benzil (Note 2), 400 g of ammonium acetate (Note 2) and 80 mL (0.77 mol) of cyclohexanone (Note 2). The mixture is stirred and heated at reflux temperature for 1.5 hr (Note 3) and then, while hot, poured into 3 L of vigorously stirred water. The mixture is left overnight to cool to ambient temperature, the crystals are collected by filtration, washed 4 times with 300 mL of water, crushed in a mortar and dried under reduced pressure to give 205–210 g (95–97%) of the imidazole as yellowish-green crystals, mp 105–106°C, lit.<sup>3</sup> mp 107–108°C (Note 4).

B. *(±)-1,2-Diphenyl-1,2-ethylenediamine*. A 2-L, four-necked, round-bottomed flask equipped with a mechanical stirrer, thermometer and dry ice condenser is charged with 72.0 g (0.250 mol) of 2,2-spirocyclohexane-4,5-diphenyl-2H-imidazole. The flask is flushed with argon, and 400 mL of tetrahydrofuran (Note 5) is added. The mixture is stirred until all solids dissolve, cooled to –78°C (dry ice/acetone bath) and treated with a stream of gaseous ammonia (Note 6) until the volume of liquid increases by about 400 mL (Note 7). One of the side necks is then equipped with a solids addition funnel and 6.94 g (1.00 mol) of lithium (Note 8) is slowly introduced by cutting the wire with scissors in a gentle stream of argon. The rate of lithium addition is such that the temperature does not rise above –65°C. Following the addition of lithium, the mixture is stirred for 30 min and 30 mL (1.0 mol) of ethanol (Note 9) is slowly added. The mixture is stirred for an additional 20 min and 70 g of ammonium chloride is added. The cooling bath is removed, the mixture is allowed to warm to 0°C, 400 mL of water is carefully introduced, and the phases are separated. The aqueous phase is washed 3 times with 300 mL of ether and the combined organic extracts are washed with brine, dried over anhydrous sodium sulfate,

filtered and concentrated with a rotary evaporator to about 200 mL. The solution is transferred to a 1-L, one-necked, round-bottomed flask equipped with a mechanical stirrer, cooled to 0°C and treated with 300 mL of 2 N aqueous **hydrochloric acid**. The biphasic mixture is vigorously stirred at ambient temperature for 1 hr, 500 mL of water is added and phases are separated. The organic phase is washed with 150 mL of water and the combined aqueous phases are extracted with 300 mL of **dichloromethane**. The aqueous solution is then carefully treated with 300 mL of 2 N aqueous **sodium hydroxide** and the mixture is extracted 4 times with 150 mL of **methylene chloride**. The combined organic extracts are washed with brine, dried over anhydrous **sodium sulfate**, and filtered. Removal of volatile material under reduced pressure (water aspirator) gives 47–50 g (89–94%) of racemic diamine as a pale yellow solid, mp 81–82°C, lit.<sup>4</sup> mp 82°C corr. (Note 10).

C. (*1S,2S*)-(-)- and (*1R,2R*)-(+)-1,2-Diphenyl-1,2-ethylenediamine (Note 11). A 1-L, round-bottomed flask equipped with a mechanical stirrer is charged with 42.5 g (0.200 mol) of the racemic diamine and 230 mL of **ethanol** (Note 9). The solids are dissolved by heating the mixture to 70°C whereupon a hot (70°C), homogeneous solution, of 30.0 g (0.200 mol) of **L-(+)-tartaric acid** (Note 12) in 230 mL of **ethanol** is added (Note 13). The tartrate salts precipitate immediately, and after the mixture is cooled to ambient temperature, the crystals are collected by filtration, washed twice with 60 mL of **ethanol**, and dried under reduced pressure. The solids are dissolved in 230 mL of boiling water, 230 mL of **ethanol** is added and the homogeneous solution is allowed to cool slowly to room temperature. The crystals are collected by filtration, washed with 40 mL of **ethanol** and dried under reduced pressure. The recrystallization procedure is then repeated twice using the same volumes of solvents (230 mL of water and 230 mL of **ethanol**) to give 23–25 g (63–69%) of the tartrate salt as colorless crystals,  $[\alpha]_D^{23} -10.8 \pm 0.2^\circ$  (H<sub>2</sub>O, *c* 1.3), lit.<sup>5</sup>  $[\alpha]_D^{23} -11^\circ$  (H<sub>2</sub>O).

The salt is transferred to a 1-L, one-necked, round-bottomed flask equipped with a magnetic stirring bar and suspended in 300 mL of water. After the mixture is vigorously stirred and then cooled to 0–5°C, 23 mL of 50% aqueous **sodium hydroxide** is added dropwise followed by 150 mL of **dichloromethane**, and stirring is continued for 30 min. The phases are separated, the aqueous phase is washed twice with 50 mL of **dichloromethane** and the combined organic extracts are washed with brine, dried over anhydrous **sodium sulfate** and filtered. Removal of the volatile material under reduced pressure gives a colorless solid that is recrystallized from **hexane** to yield 12–14 g (57–66%) of (*S,S*)-(-)-diamine as colorless crystals,  $[\alpha]_D^{23} -106 \pm 1^\circ$  (MeOH, *c* 1.1) lit.<sup>6</sup>  $[\alpha]_D^{23} -106.5^\circ$  (MeOH, *c* 1.09) (Note 14).

The filtrates from all crystallizations are combined and the solvent is evaporated on a rotary evaporator under vacuum (water aspirator). The residual solid is transferred to a 1-L, one-necked, round-bottomed flask equipped with a magnetic stirring bar, and suspended in 250 mL of water. To this vigorously stirred mixture is slowly added 25 mL of aqueous 50% **sodium hydroxide** followed by 200 mL of **dichloromethane** and the stirring is continued for 30 min. The phases are separated, the aqueous phase is washed twice with 50 mL of **dichloromethane** and the combined organic extracts are washed with brine, dried over anhydrous **sodium sulfate** and filtered. Removal of volatile material under reduced pressure gives 24–27 g of the enriched (*R,R*)-diamine as pale yellow crystals. This material is treated with **D-(-)-tartaric acid** (Note 12) and the resulting salt is recrystallized in exactly the same manner as described for the other enantiomer to give 29–31 g (80–85%) of colorless crystals,  $[\alpha]_D^{23} +4 \pm 0.5^\circ$  (H<sub>2</sub>O, *c* 1.3). (The checkers found that the salt from (-)-tartaric acid was optically impure even after five recrystallizations. However, this did not affect the optical purity of the (*R,R*)-(+)-diamine.) Treatment with **sodium hydroxide**, as described above, followed by crystallization from **hexane** gives 11.5–13 g (54–61%) of (*R,R*)-(+)-diamine as colorless crystals,  $[\alpha]_D^{23} +106 \pm 1^\circ$  (MeOH, *c* 1.1) (Note 14).

## 2. Notes

1. Step A is a modified literature procedure.<sup>3</sup>
2. Glacial **acetic acid** (99.8%), **benzil** (99%), anhydrous **ammonium acetate** (A.C.S.) and **cyclohexanone** (99.8%) were obtained from the Aldrich Chemical Company, Inc., and used as received.
3. As the reaction progresses there is a change of color from light yellow to dark green.
4. This material is pure enough for use in the next step. If necessary, it can be recrystallized from **hexane** or **methanol**-water. The properties of 2,2-spirocyclohexane-4,5-diphenyl-2H-imidazole are as

- follows:  $R_f = 0.48$  (hexane-ether 1:1, v/v;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.65–1.92 (m, 6 H), 1.95–2.00 (m, 4 H), 7.33–7.53 (m, 10 H);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 24.1, 25.7, 34.7, 104.1, 128.3, 128.9, 129.9, 133.1, 164.0.
5. Reagent grade [tetrahydrofuran](#) purchased from J. T. Baker Chemical Co., was freshly distilled from [sodium](#) metal and [benzophenone](#).
  6. Anhydrous [ammonia](#) (99.98%) was obtained from Matheson Gas Products, Inc., and used as received.
  7. The mixture stays homogeneous when cooled to  $-78^\circ\text{C}$ .
  8. [Lithium](#) wire (99% with 1% of [sodium](#)) was purchased from the Aldrich Chemical Company, Inc. The mineral oil is wiped off with a paper towel before use.
  9. Absolute [ethanol](#) (200 proof) was obtained from Aaper Alcohol and Chemical Co. and used as received.
  10. The racemic diamine contains 5–10% of an impurity (by  $^{13}\text{C NMR}$  analysis) that does not interfere with the subsequent resolution. The product has the following spectral properties:  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.59 (bs, 4 H), 4.10 (s, 2 H), 7.2–7.3 (m, 10 H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 61.9, 126.8, 126.9, 128.2, 143.4.
  11. This resolution procedure is essentially the same as described in the literature.<sup>5</sup>
  12. L-(+)- and D-(-)-Tartaric acids (99+ and 99%, respectively) were obtained from the Aldrich Chemical Company, Inc., and used as received.
  13. The [tartaric acid](#) solution should be added slowly to avoid spontaneous boiling of [ethanol](#).
  14. The spectral properties of this product are the same as that of the racemate (see (Note 10)). The optical purity is higher than 98% as confirmed by  $^1\text{H NMR}$  of its salt with [L-mandelic acid](#).<sup>7</sup>

### Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

### 3. Discussion

Enantiomerically pure (+)- and (-)-diphenylethylenediamines have recently been used for highly stereoselective Diels-Alder,<sup>8</sup> aldol,<sup>8</sup> allylation,<sup>9</sup> osmylation,<sup>10</sup> and epoxidation<sup>11</sup> reactions. Other synthetic applications involve enantioselective Michael addition<sup>12</sup> and asymmetric hydrogenation.<sup>13</sup>

The present two-step procedure for preparation of the racemic [diphenylethylenediamine](#) is significantly shorter and more suitable for scale-up than that described in the literature.<sup>4</sup> The resolution of the racemate has also been reported using the commercially available enantiomers of [mandelic acid](#).<sup>6</sup>

This preparation is referenced from:

- [Org. Syn. Coll. Vol. 9, 67](#)

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### References and Notes

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**Appendix**  
**Chemical Abstracts Nomenclature (Collective Index Number);**  
**(Registry Number)**

brine

2,2-Spirocyclohexane-4,5-diphenyl-2H-imidazole

(1R,2R)-(+)- AND (1S,2S)-(-)- 1,2-DIPHENYL-1,2-ETHYLENEDIAMINE

1,2-Ethanediamine, 1,2-diphenyl-, [R-(R,R)]- and [S-(R,R)]-

(1S,2S)-(-)- and (1R,2R)-(+)-1,2-Diphenyl-1,2-ethylenediamine

(S,S)-(-)-diamine

(R,R)-diamine

D-(-)-tartaric acid

(-)-tartaric acid

(R,R)-(+)-diamine

L-(+)- and D-(-)-Tartaric acids

(+)- and (-)-diphenylethylenediamines

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

methanol (67-56-1)

ether (60-29-7)

ammonium acetate (631-61-8)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

Mandelic acid,  
L-mandelic acid (90-64-2)

Cyclohexanone (108-94-1)

sodium sulfate (7757-82-6)

Benzil (134-81-6)

Benzophenone (119-61-9)

sodium (13966-32-0)

tartaric acid,  
L-(+)-tartaric acid (87-69-4)

methylene chloride,  
dichloromethane (75-09-2)

lithium (7439-93-2)

Tetrahydrofuran (109-99-9)

Imidazole (288-32-4)

hexane (110-54-3)

argon (7440-37-1)

(±)-1,2-Diphenyl-1,2-ethylenediamine

diphenylethylenediamine