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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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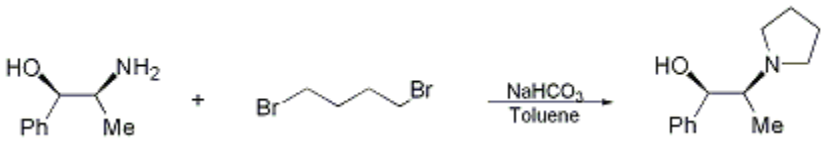
PREPARATION OF [R-(R,S)]-β-METHYL-α-PHENYL-1-PYRROLIDINEETHANOL

[1-Pyrrolidineethanol, β-methyl-α-phenyl-, [R-(R,S)]-]



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Checked by Jonathan W. Burton and Andrew B. Holmes.

1. Procedure

A 500-mL, three-necked, round-bottomed flask, equipped with a mechanical stirrer, condenser with Dean-Stark trap, nitrogen bubbler and a thermometer (Note 1), is charged with toluene (200 mL), (1R,2S)-(−)-norephedrine (37.8 g, 0.25 mol), 1,4-dibromobutane (59.38 g, 0.275 mol) and sodium bicarbonate (46.2 g, 0.55 mol) (Note 2). The stirred heterogeneous reaction mixture is heated to reflux (105-118°C, (Note 3)) under a nitrogen atmosphere until completion of the reaction (Note 4). At the end of the reaction approximately 9 mL of water has collected in the Dean-Stark trap (Note 5).

The reaction mixture is cooled to ambient temperature, filtered through a sintered glass funnel to remove inorganic salts, and the cake is washed with toluene (75 mL). The combined filtrate and wash are washed with water (150 mL). The organic layer is separated, and placed in a 500-mL, three-necked flask equipped with a mechanical stirrer. The toluene solution is concentrated by reduced pressure distillation with mechanical stirring (45-50°C, 25-30 mm) to a volume of approximately 120 mL, and the final volume is adjusted to approximately 250 mL with toluene (Note 6).

The toluene solution is cooled to 10-15°C and hydrochloric acid (HCl) in 2-propanol (0.275 mol) (Note 7) is added slowly over 1 hr via a pressure-equalizing dropping funnel, keeping the internal temperature below 25°C (Note 8). During the acid addition the product precipitates as its hydrochloride salt. The mixture is stirred at room temperature under nitrogen for 2 hr, and is reduced in volume by distillation under reduced pressure (45-50°C, 25-30 mm) with mechanical stirring to produce a distillate of approximately 120 mL and a residual volume of about 100 mL. Toluene (50 mL) is added and the slurry is reconcentrated under reduced pressure (45-50°C, 25-30 mm) until a residual volume of 100 mL is obtained. This process is repeated once more (Note 9). Toluene is added to adjust the total volume to about 250 mL. The mixture is then cooled to 10-15°C and stirred under nitrogen at this temperature for 2 hr. The HCl salt is isolated by filtration and the wet cake is washed with toluene (2 × 50 mL).

The wet cake (Note 10) is transferred to a mixture of 100 mL of heptane and 138 mL of 2 M sodium hydroxide (NaOH) with stirring (Note 11). The two layers are separated. The aqueous layer (pH > 12) is extracted with heptane (75 mL). The combined organic layers are washed with water (50 mL), filtered through a cotton wool plug and concentrated under reduced pressure (rotary evaporator, ca. 30 mm). The residue is transferred to a three-necked flask equipped with a mechanical stirrer and thermometer, and the volume is adjusted to 120 mL. The mechanically stirred solution is cooled to −25°C to form a slurry. The slurry is stirred under nitrogen at −25°C for 1 hr and then filtered through a precooled (−18° C, freezer) sintered glass funnel. The solid is rapidly washed with 25 mL of heptane that is precooled (freezer) and then dried by suction to give [R-(R,S)]-β-methyl-α-phenyl-1-pyrrolidineethanol as an off-white crystalline solid (45.9 g, 90% yield, (Note 12) and (Note 13)).

2. Notes

1. The submitters used a thermocouple to monitor the temperature.

2. The submitters purchased (1R,2S)-(−)-norephedrine from Alps Pharmaceutical Co. and 1,4-dibromobutane from Leeds Chemical Co. For small scale reactions (50 g or less) both compounds can be purchased from the Aldrich Chemical Company, Inc.
3. Efficient mechanical stirring and gentle heating are essential to avoid bumping during the early stages of the reaction when gas evolution is at a maximum. The reaction temperature gradually increases from 105°C to 118°C as the reaction progresses.
4. The reaction typically takes 18-22 hr to complete and completion of the reaction is easily monitored by TLC (silica gel; diethyl ether saturated with aqueous ammonia ; R_f of norephedrine 0.05; R_f of product 0.2). An alternative HPLC assay can also be used. HPLC sample preparation: A 50-µL filtered clear reaction solution (Whatman syringe filter 0.45 µM PTFE) is dissolved in acetonitrile (MeCN) to 50 mL. The ratio of the product to starting material (1R,2S)-(−)-norephedrine HPLC area percentage should be 99:1 or higher at the end of the reaction. HPLC Column (used by checkers): Rainin Dynamax® 5-mm × 25-cm C_{18} (the submitters used 4.6-mm × 25-cm Inertsil phenyl). Eluent: MeCN / pH 6.0 phosphate buffer, 15 mM (8.28 g $NaH_2PO_4 \cdot H_2O$ and 0.8 mL of triethylamine (Et_3N) in 4 L of HPLC grade water) (45/55 v/v) (the submitters used these solvents in a gradient elution: 15% MeCN kept for 5 min then changed to 45% MeCN over 11 min and kept at this ratio for another 6 min). Injection: 20 µL; flow rate: 0.75 mL/min (submitters used 1.5 mL/min). Detection: 210 nm; temperature: 23°C. Retention times: norephedrine: 3.9 min; product: 6.7 min. (The submitters observed sodium bromide : 1.8 min; norephedrine: 5.0 min; product: 12.0 min; toluene: 22.5 min).
5. Water is generated soon after the reaction mixture begins to reflux and is mostly removed by the toluene-water azeotropic distillation. The presence of a small amount of water appears to be essential to the reaction. However, too much water remaining in the reaction mixture mixes with the inorganic salts and forms a sticky, wet solid lump at the bottom of the flask that could be a potential problem for the stirring and subsequent filtration.
6. Removal of most of the water in the toluene solution increases the recovery of the [R-(R,S)]-β-methyl-α-phenyl-1-pyrrolidineethanol HCl salt. The temperature must be kept below 50°C to avoid bumping. This step can be carried out on a rotary evaporator.
7. The HCl in 2-propanol solution (5-6 M) was purchased from Acros Organics . Titration against NaOH solution revealed a concentration of 4.8 M. The titer varies according to batches. The actual volume of HCl in 2-propanol solution was selected to deliver 1.1 mol equiv of HCl .
8. Purification by formation of the [R-(R,S)]-β-methyl-α-phenyl-1-pyrrolidineethanol HCl salt is necessary to remove non-amine organic components such as 1,4-dibromobutane that are known to decrease the enantioselectivity of the subsequent chiral addition reaction (Scheme 1).
9. 2-Propanol and residual amounts of water are removed by distillation to minimize the loss of the [R-(R,S)]-β-methyl-α-phenyl-1-pyrrolidineethanol HCl salt that is soluble in 2-propanol. The submitters monitored product concentration in the supernatant liquid using HPLC (Note 4) relative to a standard concentration of analytically pure product to ensure that the concentration was less than 3 mg/mL. While the checkers did monitor the concentration of the product in the supernatant liquid, reproducibly high yields of product were realized without carrying out the monitoring procedure.
10. The wet cake was partially dried for 12 hr in a 500-mL, round-bottomed flask at 25°C under vacuum (5 mm). The submitters partially dried the wet cake under nitrogen/vacuum for 2-3 hr and used it directly in the next salt-breaking step. They prepared a fully dried sample for storage by drying in a vacuum oven (≈50 mm, 40°C for 1-2 days).
11. Alternatively, [R-(R,S)]-β-methyl-α-phenyl-1-pyrrolidineethanol free base may be prepared as a toluene solution. The solution could be used directly in the chiral addition reaction (Scheme 1).
12. The submitters ran the procedure on different scales (10 g to 30 kg) with yields ranging from 90-94%.
13. The product is fully characterized: mp 44-45°C. The checkers obtained $[\alpha]_D^{20}$ +15.7 ($CHCl_3$, *c* 2.05). The submitters reported $[\alpha]_D^{20}$ +15.2 ($CHCl_3$, *c* 2.00). The specific rotation of the enantiomer (1S,2R)-N-pyrrolidinylnorephedrine has been reported:[3] $[\alpha]_D^{20}$ −7.3 (*c* 2, $CHCl_3$); IR ($CDCl_3$) cm^{-1}: 3440 (OH), 2970, 2805, 1450, 1380, 1200, and 975 ; ^1H NMR (250 MHz, $CDCl_3$) δ: 0.80 (d, 3 H, J = 6.5), 1.79-1.84 (m, 4 H), 2.47 (qd, 1 H, J = 6.5, 3), 2.6-2.7 (m, 2 H), 2.7-2.9 (m, 2 H), 3.69 (s, 1 H), 5.00 (d, 1 H, J = 3), 7.23-7.35 (m, 5 H) ; ^{13}C NMR (62.5 CDCl, MHz_3) δ: 12.0, 23.5, 51.8, 65.3, 72.7, 125.8, 126.7, 128.0, 141.7 . MS (ES^+) m/z (rel intensity) 206 [100, $(M + H)^+$] . Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.1; H, 9.3; N, 6.8. Found: C, 76.3, H. 9.3; N, 6.9.

Waste Disposal Information

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

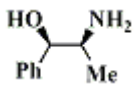
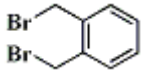
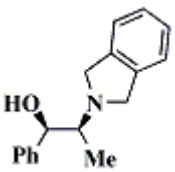
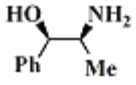
3. Discussion

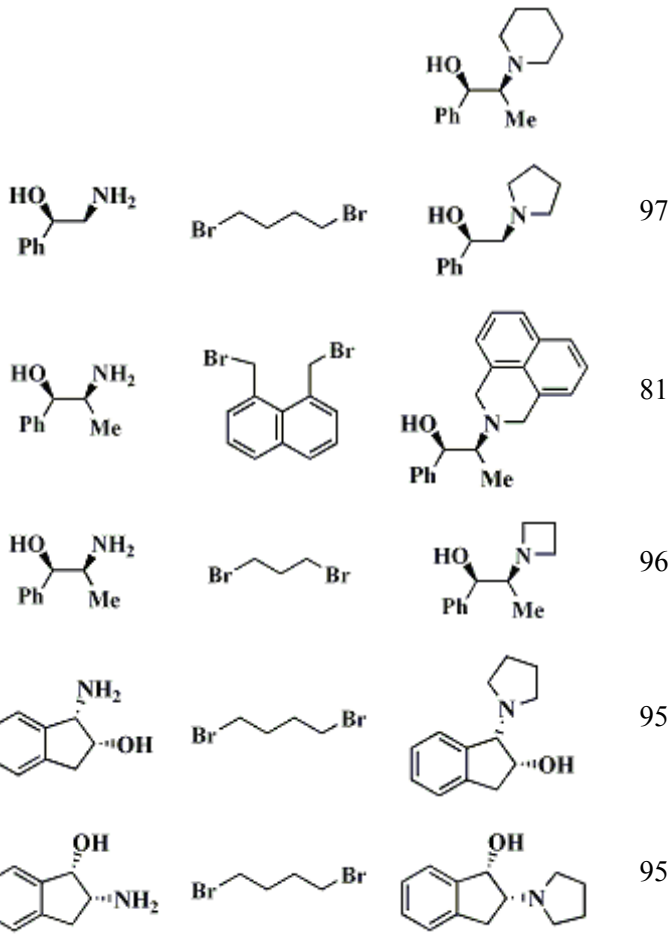
[R-(R,S)]-β-Methyl-α-phenyl-1-pyrrolidineethanol is an important chiral mediator for the enantioselective addition of an acetylide to a prochiral ketone.[3,4] This reaction has been successfully applied to the synthesis of the reverse transcriptase inhibitor efavirenz (DMP-266) (Scheme 1).[4,5] Preparation of the enantiomer, (1S,2R)-N-pyrrolidinylnorephedrine, has been reported.[3] The method used potassium carbonate (K_2CO_3) as base, but the yield of the product was only 33%. The submitters have extensively studied the formation of the pyrrolidinyl ring under various conditions as summarized in Table I. Eventually they found that the reaction was extremely efficient when it was run in toluene using sodium bicarbonate ($NaHCO_3$) as base (entry 8, Table I),[6] which gave [R-(R,S)]-β-methyl-α-phenyl-1-pyrrolidineethanol quantitatively. Enantioselective (up to 99% ee) addition of cyclopropylacetylene to the ketoaniline **1** is achieved when the solution of [R-(R,S)]-β-methyl-α-phenyl-1-pyrrolidineethanol is used as a chiral additive.[4] In addition, this method is also applicable to the preparation of a variety of alkylated norephedrines and other amino alcohols in excellent yields as illustrated in Table II. These amino alcohols are potentially useful in asymmetric syntheses.

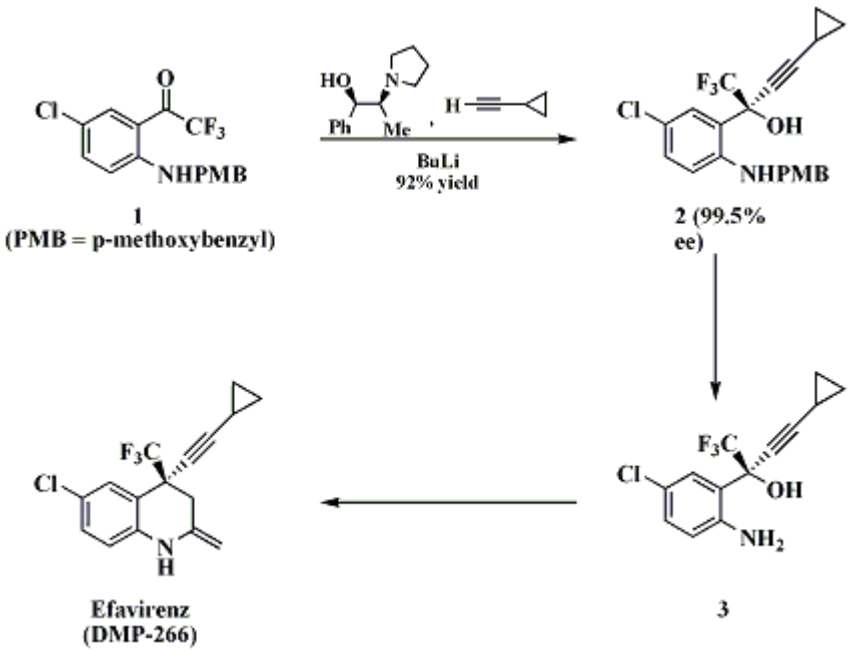
TABLE I
PREPARATION OF [R-(R,S)]-β-METHYL-α-PHENYL-1-PYRROLIDINEETHANOL WITH DIFFERENT BASES AND SOLVENT

Entry	Base	Solvent	Temperature (°C)	Yield (%)
1	Aq. K_2CO_3 (1:1 water: K_2CO_3)	n-BuOH	95	75
2	5 N NaOH	Toluene	93	87
3	5 N NaOH	THF	65	91
4	5 N NaOH	Heptane	88	82
5	$NaHCO_3$	THF	67	90
6	$NaHCO_3$	Heptane	95	76
7	Na_2CO_3/$NaHCO_3$/NaI (1.0:1.0:0.5)	Toluene	110	80
8	$NaHCO_3$	Toluene	115	94

TABLE II
PREPARATION OF N-ALKYLATED NOREPHEDRINE ANALOGS

Ephedine	Alkyl Halide	Product	Yield (%)
			93
			98





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6. Synthesis of pyrrolidyl alkanols using $NaHCO_3$ as a base was reported to give pyrrolidyl derivatives in moderate yields. Moffett, R. B. *J. Org. Chem.* **1949**, *14*, 862.

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

[R-(R,S)]-β-Methyl-α-phenyl-1-pyrrolidineethanol:
1-Pyrrolideneethanol, β-methyl-α-phenyl-, [R-(R,S)]- (12); (127641-25-2)

(1R, 2S)-(−)-Norephedrine:
Norephedrine (8);
Benzeneethanol, α-(1-aminoethyl)-, [R-(R, S)]- (9); (492-41-4)

1,4-Dibromobutane:
Butane, 1,4-dibromo- (8,9); (110-52-1)

Hydrochloric acid in
2-propanol:
Hydrochloric acid (8,9); (7647-01-0)

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