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of Reliable Methods
for the Preparation
of Organic Compounds

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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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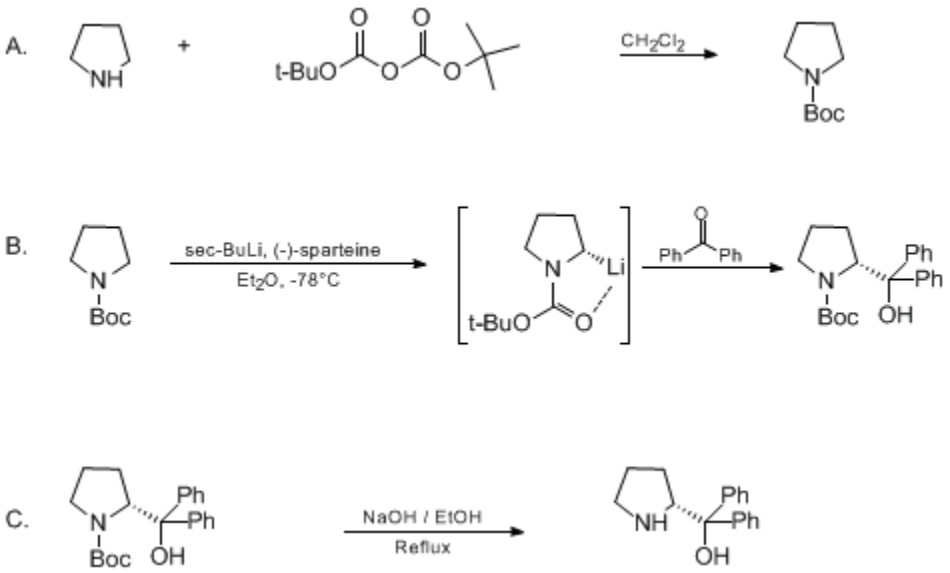
(R)-(+)-2-(DIPHENYLHYDROXYMETHYL)PYRROLIDINE

[2-Pyrrolidinemethanol, α,α-diphenyl-, (R)-]



Submitted by Nikola A. Nikolic and Peter Beak[1].
Checked by Michael R. Reeder and Robert K. Boeckman, Jr..

1. Procedure

A. *N-(tert-Butoxycarbonyl)pyrrolidine*. A 500-mL round-bottomed flask, equipped with magnetic stirring bar, is charged with dichloromethane (CH_2Cl_2) (120 mL) and pyrrolidine (11.3 mL, 133 mmol) (Note 1). The flask is fitted with a 60-mL, pressure-equalizing addition funnel vented through a mineral oil bubbler and charged with a solution of di-tert-butyl dicarbonate (24.6 g, 112 mmol) in CH_2Cl_2 (35 mL) . After the pyrrolidine solution is cooled to 0°C in ice, the colorless dicarbonate solution is added dropwise over a period of 30 min, and the resulting solution is stirred at room temperature for 3 hr (Note 2). The solvents are then removed under reduced pressure, and two consecutive Kugelrohr distillations of the residual oil (oven temperature 80°C at 0.2 mm) afford 16.6 g (87%) of N-Boc-pyrrolidine as a colorless oil (Note 3).

B. *(R)-(+)-2-(Diphenylhydroxymethyl)-N-(tert-butoxycarbonyl)pyrrolidine*. An oven-dried, 2-L, three-necked flask, equipped with a magnetic stirring bar and a thermocouple (Note 4), is charged with (−)-sparteine (30.2 mL, 131 mmol) (Note 5), N-Boc-pyrrolidine (15.0 g, 87.6 mmol), and anhydrous ether (900 mL) (Note 6). The solution is cooled to ∼−70°C (dry ice/acetone bath) (Note 4). To this solution is added sec-butyllithium (96 mL, 1.16 M in cyclohexane, 111 mmol) (Note 7) and (Note 8) dropwise over a period of 35 min (Note 9). The reaction is then stirred at ∼−70°C for 5.5 hr (Note 10).

After this interval, a solution of benzophenone (25.5 g, 140 mmol) (Note 11) in anhydrous ether (200 mL) is added dropwise over a period of 1.25 hr (Note 9). The dark green to greenish-yellow suspension is maintained at −70°C for 2.0 hr, and the reaction is then quenched by dropwise addition of glacial acetic acid (8.5 mL, 150 mmol) over a period of 15 min. The resulting lemon-yellow suspension is allowed to warm slowly to room temperature over a period of 12 hr, during which time the mixture becomes cream colored.

After the solution is warmed to 25°C, 5% phosphoric acid (H_3PO_4) (150 mL) is added to the reaction mixture, and the resulting biphasic mixture is stirred for 20 min. The layers are partitioned and the organic phase is washed with additional 5% H_3PO_4 (3 × 150 mL). Combined aqueous phases are extracted with ether (3 × 200 mL). The original organic phase and the ethereal extracts are combined,

washed with brine (200 mL), dried over magnesium sulfate ($MgSO_4$), filtered, and the solvents are removed under reduced pressure to afford crude product as an off-white solid. The crude (R)-(+)-2-(diphenylhydroxymethyl)-N-(tert-butoxycarbonyl)pyrrolidine is purified by recrystallization from a mixture of hexanes-ethyl acetate (~675 mL, 20 : 1, v/v) affording in two crops 20.9–22.0 g (73–74%) of analytically pure product as a white solid (Note 12) having greater than 99.5% ee (Note 13).

Sparteine is recovered by making the aqueous phases basic with aqueous 20% sodium hydroxide (NaOH) (160 mL) (Note 14). The aqueous phase is extracted with Et_2O (4 × 150 mL), and the combined organic phases are dried over potassium carbonate (K_2CO_3), filtered, and the solvents removed under reduced pressure to afford 30.3 g (98%) of crude, recovered sparteine as a pale yellow oil (Note 15). Fractional distillation of the residual oil from calcium hydride (CaH_2) (Note 5) affords 27.0 g of sparteine (88%) suitable for reuse.

C. *(R)-(+)-2-(Diphenylhydroxymethyl)pyrrolidine*. A 1-L, round-bottomed flask, equipped with a magnetic stirring bar, is charged with 325 mL of absolute ethanol and NaOH (27.0 g, 675 mmol). The NaOH is dissolved with vigorous stirring, and (R)-(+)-2-(diphenylhydroxymethyl)-N-(tert-butoxycarbonyl)pyrrolidine (22.0 g, 62.3 mmol) is added (Note 16). The flask is fitted with a reflux condenser, and the resulting milky white suspension is heated to reflux for 2.5 hr. The suspension is cooled to room temperature, and the solvents are removed under reduced pressure. To the residual off-white solids are added ether (800 mL) and deionized water (400 mL). The suspension is stirred until the solids are dissolved, and the resulting biphasic mixture is transferred to a 2-L separatory funnel. The layers are partitioned, and the aqueous phase is extracted with ether (4 × 200 mL). The organic phases are combined, dried over K_2CO_3 (ca. 100 g), filtered, and the solvents are removed under reduced pressure (Note 17) to afford 14.5–15.8 g (92–100%) of the pure title compound as a white solid (Note 18).

2. Notes

1. Dichloromethane was obtained from Mallinckrodt Inc., and was used without further purification. Pyrrolidine and di-tert-butyl dicarbonate were obtained from Aldrich Chemical Company, Inc., and used as received.
2. Toward the end of the addition, gas evolution (CO_2) occurs. Care should be taken to provide adequate venting to avoid pressure buildup.
3. The product, N-Boc-pyrrolidine, has the following spectral characteristics: ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.43 (s, 9 H), 1.81 [s (br), 4 H], 3.27 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.78, 25.54, 28.32, 45.38, 45.71, 78.57, 154.41; IR (film) cm^{-1}: 2974, 2875, 1698, 1403, 1168, 877, 772.
4. The internal temperature was monitored throughout the reaction with an Omega D730 or equivalent thermocouple.
5. Sparteine is liberated from the commercially available sulfate salt (Aldrich Chemical Company, Inc.) as follows: Sparteine sulfate pentahydrate (100 g, 240 mmol) is dissolved in deionized water (125 mL), and to this solution is slowly added aqueous 20% NaOH (100 mL). The resulting milky-white, oily mixture is then extracted with ether (4 × 150 mL). The combined ethereal extracts are dried over anhydrous K_2CO_3, filtered, and the solvent is removed under reduced pressure. Vacuum distillation of the residual oil from CaH_2 affords 52 g (92%) of sparteine as a clear, colorless to slightly yellow, viscous oil (bp 115–120°C/0.3 mm). The sparteine free base readily absorbs atmospheric carbon dioxide (CO_2) and should be stored under argon at −20°C in a freezer.
6. Anhydrous ethyl ether was obtained by distillation under nitrogen from sodium benzophenone ketyl.
7. sec-Butyllithium (1.3 M in cyclohexane) was titrated in toluene immediately before use using a standard solution (1 M) of sec-butyl alcohol in o-xylene with 0.2% 2,2'-biquinoline in toluene as the indicator according to Watson and Eastham.[2]
8. The checkers found that the yields obtained in this procedure are critically dependent on the quality of the sec-butyllithium employed. Best results are obtained with fresh (< 3 months shelf life) commercial samples (FMC Lithium Division, and Aldrich Chemical Company, Inc.) that are colorless to deep yellow, largely free of precipitated salts, and that have been kept refrigerated and have not been exposed to traces of moisture or oxygen by extensive previous sampling. Samples of sec-butyllithium that contain alkoxide or hydroxide undergo alkoxide/hydroxide-catalyzed decomposition to butene and lithium hydride (LiH), particularly when stored at room temperature; the latter cannot be readily

removed. In the hands of the checkers, such aged sec-butyllithium samples provide the N-Boc amino alcohol of comparable enantiomeric purity in ~5–15% lower yield.
9. During the addition, the internal temperature of the reaction did not exceed −68°C.
10. The reaction mixture became milky white during this interval.
11. Commercially available benzophenone (Aldrich Chemical Company, Inc., 99+ %) was used without further purification.
12. The product has the following characteristics: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.65–0.80 (m, 1 H), 1.40–1.60 (s, 11 H), 1.82–1.95 (m, 1 H), 1.98–2.14 (m, 1 H), 2.75–2.90 (m, 1 H), 3.20–3.45 (m, 1 H), 4.86 (dd, 1 H, J_1 = 8.9, J_2 = 3.8), 7.20–7.45 (m, 10 H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.84, 28.29, 29.67, 47.77, 65.50, 80.54, 81.62, 126.96, 127.00, 127.27, 127.61, 127.77, 128.14, 143.72, 146.41, 159.00; IR (film) cm^{-1}: 3370, 2979, 1659, 1415, 1164, 763, 70. Anal. Calcd for $C_{22}H_{27}NO_3$: C, 74.76; H, 7.70; N, 3.96. Found: C, 74.62; H, 7.72; N, 4.13. $[\alpha]_D^{25}$ +150° ($CHCl_3$, *c* 3.62); mp 150.5–152°C. The checkers found $[\alpha]_D^{25}$ +144° ($CHCl_3$, *c* 3.89).
13. The enantiomeric excess was determined by alkaline ethanolysis of the Boc group followed by conversion of the amine to the 3,5-dinitrobenzamide. HPLC analysis of a saturated solution of the benzamide in 5% 2-propanol in hexane using a Pirkle Covalent S-N1N-Naphthylleucine Column (Regis Chemical Company) with 5% 2-propanol in hexane as the eluent, and a flow rate of 1.5 mL/min indicates a single peak with retention time of 35 min. HPLC analysis of the corresponding racemic benzamide affords two peaks at 27 and 32 min corresponding to the (S)- and (R)-enantiomers respectively. The differences in retention times arise from the size of sample that was injected; the ^{1}H NMR of the racemic and enantio-enriched benzamides were identical.
14. The aqueous solution was brought to ca. pH 11 as tested by Hydrion Paper (Micro Essential Laboratories, Brooklyn, NY).
15. The ^{1}H NMR of the recovered (−)-sparteine was identical to that of pure (−)-sparteine.
16. The concentration of the reactants is ~0.2 M. If more dilute solutions of base are employed (0.01 M), the checkers found that the reaction required at least 24 hr to completion and that impure product was obtained. At higher dilution, formation of significant amounts of the cyclic urethane was observed, and this by-product required removal by chromatography.
17. The residual, colorless, viscous oil solidified slowly upon exposure to high vacuum.
18. The title compound has the following characteristics: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40–1.95 (m, 5 H), 2.89–3.05 (m, 2 H), 4.23 (t, 1 H, J = 7.4), 4.55 [(s (br), 1 H], 7.10–7.35 (m, 4 H), 7.45–7.60 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.47, 26.23, 46.71, 64.42, 76.65, 125.47, 125.80, 126.29, 126.40, 127.91, 128.17, 145.36, 148.13; IR (film) cm^{-1}: 3352, 2968, 1598, 1492, 1448, 1173, 748, 701. Anal. Calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.56; H, 7.60; N, 5.68. $[\alpha]_D^{25}$ +73.8° ($CHCl_3$, *c* 3.37); mp 76–77°C; R_f = 0.13 (CH_2Cl_2 : MeOH, 95 : 5). The checkers found $[\alpha]_D^{25}$ +67.9° ($CHCl_3$, *c* 3.37)

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

α,α-Diaryl-2-pyrrolidinemethanols represent an important class of ligands for asymmetric synthesis.[3] For example, reaction of these amino alcohols with boranes affords oxazaborolidinones that are effective enantioselective reagents for asymmetric reduction of ketones.[3,4 5 6,7 8 9 10 11 12] The chiral non-racemic amino alcohols have been prepared through addition of organometallic agents to enantio-enriched proline,[3,7,8,9,10,11,12,13] or by resolution of racemic pyrrolidinemethanols.[11] The procedure reported here describes a new approach to the synthesis of the title compound based on an asymmetric lithiation/substitution sequence.[14 15]

Treatment of Boc-pyrrolidine with sec-butyllithium in the presence of (−)-sparteine affords the putative enantio-enriched organolithium reagent. This organolithium reagent can be quenched with electrophiles to afford 2-substituted-Boc-pyrrolidines.[14,15] This approach offers several advantages over existing methodologies. First, the use of the (−)-sparteine ligand affords 2-substituted pyrrolidines with high enantioselectivity. Second, the ligand can be recovered and purified in high yields; [in this

example, (−)-sparteine was recovered and purified in 88% yield]. Third, this approach obviates the preparation of enolizable proline derivatives that have been shown to racemize.[3] Finally, this two-step approach affords the (R)-α,α-diphenylpyrrolidine enantiomer that has previously been obtained from relatively expensive "unnatural" D-proline.

The approach reported here should facilitate the preparation of α,α-disubstituted-pyrrolidinemethanol analogs. By using this methodology, a single enantio-enriched organolithium intermediate can be treated with a variety of electrophiles (e.g., diaryl ketones) to afford aryl-substituted analogs of the title compound. Previously reported syntheses involve a variety of nucleophilic organometallic reagents that must be prepared and treated with proline derivatives.

An interesting feature of this study is the enantiomeric purity analysis of the products. By converting the amine functionality of the pyrrolidine to a 3,5-dinitrobenzamide, the substrate can be analyzed by chiral HPLC. To date, the 3,5-dinitrobenzamide of 2-substituted pyrrolidines that the submitters have prepared have been baseline-resolved by the Pirkle S-N1N-Naphthylleucine column. This approach obviates the need for MPTA-derivativization which has been previously employed in enantiomeric purity determinations.[3,7,8,9,10,11,12]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 676

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

hexanes

brine

sodium benzophenone ketyl

Sparteine

Sparteine sulfate pentahydrate

ethanol (64-17-5)

potassium carbonate (584-08-7)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

ether,
ethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

oxygen (7782-44-7)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

cyclohexane (110-82-7)

benzamide (55-21-0)

toluene (108-88-3)

Benzophenone (119-61-9)

2-propanol (67-63-0)

phosphoric acid (7664-38-2)

butene (106-98-9)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

urethane (51-79-6)

pyrrolidine (123-75-1)

hexane (110-54-3)

argon (7440-37-1)

calcium hydride (7789-78-8)

sec-butyl alcohol (78-92-2)

lithium hydride (7580-67-8)

2-Pyrrolidinemethanol

sec-butyllithium (598-30-1)

BOC

2,2'-biquinoline (119-91-5)

Di-tert-butyl dicarbonate (24424-99-5)

o-Xylene (95-47-6)

oxazaborolidine

(R)-(+)-2-(Diphenylhydroxymethyl)pyrrolidine (22348-32-9)

N-(tert-Butoxycarbonyl)pyrrolidine,
N-Boc-pyrrolidine,
Boc-pyrrolidine (86953-79-9)

(R)-(+)-2-(Diphenylhydroxymethyl)-N-(tert-butoxycarbonyl)pyrrolidine (137496-68-5)

N-Boc amino alcohol (36016-38-3)

3,5-dinitrobenzamide (121-81-3)

D-proline (344-25-2)

(R)-α,α-diphenylpyrrolidine

(−)-sparteine (90-39-1)