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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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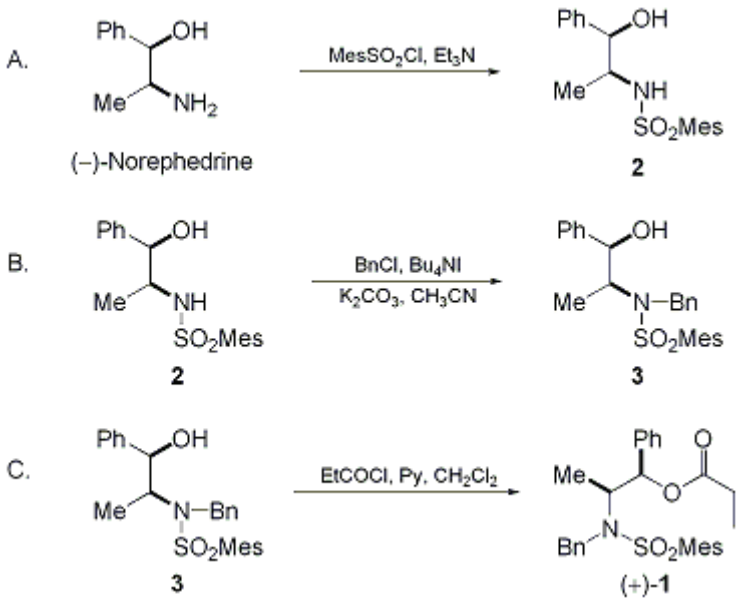
2-(N-BENZYL-N-MESITYLENESULFONYL)AMINO-1-PHENYL-1-PROPYL PROPIONATE

[[Benzenesulfonamide, 2,4,6-trimethyl-N-[1-methyl-2-(1-oxopropoxy)-2-phenylethyl]-N-(phenylmethyl)-, [R-(R*,S*)]-]



Submitted by Atsushi Abiko[1]
Checked by Lloyd J. Simons and William R. Roush.

1. Procedure

A. 2-(N-Mesitylenesulfonyl)amino-1-phenyl-1-propanol , ***2*** . To a stirred solution of (−)-norephedrine (30.2 g, 0.200 mol) (Note 1) and triethylamine (33.4 mL, 0.24 mol) in dichloromethane (400 mL) is added mesitylenesulfonyl chloride (43.8 g, 0.20 mol) (Note 1) at 0°C. The reaction mixture is stirred at 0°C for 2 hr and diluted with diethyl ether (600 mL). The mixture is washed successively with 100 mL each of water, 1 M hydrochloric acid(HCl), water, saturated sodium hydrogen carbonate solution and brine, and dried over anhydrous sodium sulfate . The organic solution is filtered, and the filtrate is concentrated to give an oily residue, which is dissolved in dichloromethane (50 mL). Hexane (100 mL) is added in portions with swirling to the dichloromethane solution to cause crystallization. Additional hexane (300 mL) is added and the crystalline (1R, 2S)- **2** (60.8 g, 91%) is isolated by filtration (Notes 2, 3).

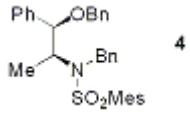
B. 2-(N-Benzyl-N-mesitylenesulfonyl)amino-1-phenyl-1-propanol , ***3*** . A mixture of **2** (16.7 g, 50 mmol), benzyl chloride (6.90 mL, 60 mmol) (Note 1), tetrabutylammonium iodide (200 mg) (Note 1) and potassium carbonate (8.4 g, 60 mmol) in acetonitrile (100 mL) is heated under reflux for 17 hr (Note 4). The cooled mixture is filtered and the salt is washed with diethyl ether (100 mL). The combined organic layers are concentrated and the residue is crystallized from dichloromethane (25 mL) and hexane (100 mL) to give **3** (17.0 g, 80%) (Notes 5, 6).

C. 2-(N-Benzyl-N-mesitylenesulfonyl)amino-1-phenyl-1-propyl propionate , ***1*** . To a solution of **3** (15.0 g, 35.4 mmol) and pyridine (3.7 mL, 46 mmol) in dichloromethane (200 mL), propionyl chloride (3.8 mL, 44 mmol) (Note 1) is added dropwise at 0°C. The reaction mixture is stirred at room temperature for 13 hr and diluted with diethyl ether (300 mL). The mixture is washed successively with 100 mL each of water, 1 M HCl, water, saturated sodium hydrogen carbonate solution, and brine, and dried with anhydrous sodium sulfate . The filtered organic solution is concentrated to give a crystalline

residue, which is triturated with hexane to give **1** (16.8 g, =99%) (Note 7).

2. Notes

1. (−)- and (+)-Norephedrine, benzyl chloride, tetrabutylammonium iodide, and propionyl chloride were purchased from Wako Pure Chemical Ltd. Japan or Aldrich Chemical Company, Inc. , and used as received. mesitylenesulfonyl chloride was obtained from Tokyo Kasei Kogyo Ltd. Japan or Aldrich Chemical Company, Inc. and used as received. Dichloromethane and acetonitrile were distilled from calcium hydride (CaH_2) under an inert atmosphere prior to use. Merck 60 silica gel, 0.040-0.063 mm, or Whatman 60 Å 230-400 mesh silica gel was used for column chromatography.
2. The submitter reports that a second crop of pure **2** (6.0 g) could be obtained by concentration and recrystallization of the mother liquors. However, the second crops obtaine by the checkers were highly colored and were not sufficiently pure for use in the next step.
3. Sulfonamide **2** exhibited the following physical and spectroscopic properties: mp 121-122°C, TLC (silica gel) R_f = 0.28 in 3:1 hexanes : ethyl acetate; (1R, 2S)-**2**: $[\alpha]_D^{23}$ −12.4 (c 2.12, $CHCl_3$). (*1S, 2R*)-**2**: $[\alpha]_D^{23}$ +12.8 (c 2.12, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) (concentration dependent; 20 mg/mL) δ: 0.87 (d, 3 H, J = 6.8), 2.30 (s, 3 H), 2.52 (1 H, -OH), 2.66 (s, 6 H), 3.53 (m, 1 H), 4.76 (br,1 H, -NH), 4.82 (d,1 H, J = 8.8), 6.96 (s, 2 H), 7.20-7.36 (m, 5 H) ; (200 mg/mL) δ: 0.88 (d, 3 H, J = 6.8), 2.32 (s, 3 H), 2.68 (s, 6 H), 3.08 (1 H, -OH), 3.51 (ddq, 1 H, J = 3.1, 6.8, 9.0), 4.81 (br, 1 H, -NH), 5.23 (br, 1 H), 6.98 (s, 2 H), 7.20-7.36 (m, 5 H) . ^{13}C NMR (125 MHz, $CDCl_3$, c = 20 mg/mL) δ: 14.3, 20.9, 22.9, 54.6, 75.6, 125.9, 127.5, 128.3, 132.0, 134.2, 138.9, 140.5, 142.2 . IR (thin film from CH_2Cl_2) cm^{-1}: 3504, 3302, 2981, 1064, 1452, 1320, 1156, 1058, 972, 895, 702, 657 . HRMS-FAB: Calcd for $C_{18}H_{24}NO_3S$ [M+H]+, 334.1477 *m/z* ; Found, 334.1478 *m/z* . Anal. Calcd for $C_{18}H_{23}NO_3S$: C, 64.84; H, 6.95; N, 4.20. Found: C, 64.94; H, 6.98; N, 4.17.
4. The checkers observed that the reaction is not complete according to TLC analysis after the prescribed 17-hr reaction period. However, if the reaction is allowed to proceed for longer reaction times, the dibenzylated product **4** is obtained with correspondingly diminished yields of **3**. When the reaction was terminated after 17 hr, the checkers obtained an 86% yield of recrystallized **3**.



4

5. The submitter reports that an additional 3.2 g (15%) of **3** was isolated by chromatography (Note 1) of the mother liquor on silica gel (100 g) with 10% ethyl acetate in hexane . The checkers observed that the concentrated mother liquors were not soluble in the chromatography solvent, so they dissolved the viscous oil in dichloromethane (<7 mL) and applied this solution to the column. Once this material was adsorbed, the column was flushed with hexanes (400 mL) to remove the CH_2Cl_2. Elution of the column with 10% ethyl acetate-hexanes then provided additional product **2**. The combined yield of **2** obtained by the checkers via the crystallization and chromatography sequence was 90-93%.
6. N-Benzylsulfonamide **3** exhibited the following physical and spectroscopic properties: mp 123-124° C; TLC (silica gel) R_f = 0.48 in 3:1 hexanes : ethyl acetate ; R_f = 0.15 in 9:1 hexanes : ethyl acetate; (*1R, 2S*)-**3**: $[\alpha]_D^{23}$ −6.3° (c 2.06, $CHCl_3$); (*1S, 2R*)-**3**: $[\alpha]_D^{23}$ +6.4° (c 2.05, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) (concentration dependent; 18 mg/mL) δ: 1.03 (d, 3 H, J = 7.0), 2.14 (1 H, -OH), 2.29 (s, 3 H), 2.65 (s, 6 H), 3.82 (dq, 1 H, J = 1.9, 7.0), 4.54 (1 H, A of ABq, J_{AB} = 16.1), 4.77 (1 H, B of ABq, J_{AB} = 16.1), 5.00 (br s, 1 H), 6.93 (s, 2 H), 7.04-7.08 (m, 2 H), 7.10-7.36 (m, 8 H) ; (218 mg/mL) δ: 1.02 (d, 3 H, J = 7.0), 2.27 (s, 3 H), 2.34 (1 H, -OH), 2.62 (s, 6 H), 3.82 (dq, 1 H, J = 1.9, 7.0), 4.56 (1 H, A of ABq, J_{AB} = 16.1), 4.75 (1 H, B of ABq, J_{AB} = 16.1 Hz), 4.96 (br s, 1 H), 6.91 (s, 2 H), 7.04-7.08 (m, 2 H), 7.10-7.36 (m, 8 H) ; ^{13}C NMR (125 MHz, $CDCl_3$, 18 mg/mL) δ: 9.8, 20.9, 23.0, 49.1, 59.7, 76.6, 125.5, 127.2, 127.4, 127.7, 128.2, 128.6, 132.2, 133.4, 138.6, 140.2, 142.1, 142.6 ; IR (film from CH_2Cl_2) cm^{-1}: 3502, 2981, 1604, 1454, 1314, 1150, 1022, 924, 855, 699, 658 ; HRMS-FAB: Calcd for $C_{25}H_{30}NO_3S$ $[M+H]^+$, 424.1946 *m/z* ; Found, 424.1947 *m/z*; Anal. Calcd for $C_{25}H_{29}NO_3S$: C, 70.89; H, 6.90; N, 3.31; Found: C, 70.91; H, 6.95; N, 3.32.
7. The checkers obtained **1** in 96% yield after recrystallization of the crude product (see Note 8).
8. (*1R, 2S*)- and (*1S, 2R*)-**1** exist as polymorphic forms. Recrystallization from hot ethyl acetate (4 mL/g of **1**) and hexane (ethyl acetate : hexane = 1 : 2) afforded higher melting crystals: mp 124°C, 147-148° C, TLC (silica gel) R_f = 0.52 in 3:1 hexanes : ethyl acetate; R_f = 0.22 in 9:1 hexanes : ethyl acetate; (*1R,*

2S)-**1** $[\alpha]_D^{23}$ +11.1° (c 2.24, $CHCl_3$); (*1S, 2R*)-**1**: $[\alpha]_D^{23}$ −11.2° (c 2.38, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ: 1.01 (t, 3 H, J = 7.4), 1.12 (d, 3 H, J = 7.0), 2.14 (m, 2 H), 2.27 (s, 3 H), 2.51 (s, 6 H), 4.04 (dq, 1 H, J = 4.0, 7.0), 4.60 (1 H, A of ABq, J_{AB} = 16.6), 4.72 (1 H, B of ABq, J_{AB} = 16.6), 5.84 (d, 1 H, J = 3.9), 6.87 (s, 2 H), 6.88-6.96 (m, 2 H), 7.13≈7.35 (m, 8 H) . ^{13}C NMR (125 MHz $CDCl_3$) δ: 8.5, 12.3, 20.6, 22.7, 27.1, 47.9, 56.5, 77.7, 125.6, 126.8, 127.1, 127.5, 128.1 (2C), 131.9, 133.2, 138.4, 138.5, 139.9, 142.3, 172.2 ; IR (film from CH_2Cl_2) $cm^{-}1$: 2982, 1747, 1604, 1454, 1381, 1324, 1205, 1153, 1080, 1056, 1020, 859, 764, 730, 699, 659 ; HRMS-FAB Calcd for $C_{28}H_{34}NO_4S$ [M+H]+, 480.2209 *m/z* ; Found, 480.2186 *m/z* ; Anal. Calcd for $C_{28}H_{33}NO_4S$: C, 70.12; H, 6.93; N, 2.92. Found: C, 70.40; H, 6.97; N, 2.90.

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

The present procedure is a modification of that originally reported by the submitter and co-workers.[2] This procedure is applicable to a large scale preparation of the title compound in high overall yield (≈ 80%) without purification of the intermediates by chromatography. The title compound is reported to be a useful reagent for *anti*-selective aldol reactions with dicyclohexylboron triflate and triethylamine as enolization reagents.[3]

References and Notes

1. Venture Laboratory, Kyoto Institute of Technology, Matsugasaki, Kyoto, 606-8585, Japan.
2. Abiko, A.; Liu, J.-F.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586.
3. See the procedure describing the anti-selective asymmetric aldol reaction of carboxylic esters, p. 116.

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

2-(N-Benzyl-N-mesitylenesulfonyl)amino-1-phenyl-1-propyl propionate:
Benzenesulfonamide, 2,4,6-trimethyl-N-[1-methyl-2-(1-oxopropoxy)-2-phenylethyl]-N-(phenylmethyl)- (14); [R-(R*,S*)]-, (187324-66-9), [S-(R*,S*)]-, (187324-67-0)

2-(N-Mesitylenesulfonyl)amino-1-phenyl-1-propanol:
Benzenesulfonamide, N-(2-hydroxy-1-methyl-2-phenylethyl)-2,4,6-trimethyl-, [S-(R*,S*)]- (14); (187324-62-5)

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

Triethylamine (8);
Ethanamine, N,N-diethyl- (8,9); (121-44-8)

Mesitylenesulfonyl chloride:
2-Mesitylenesulfonyl chloride (8);

Benzenesulfonyl chloride, 2,4,6-trimethyl- (9); (773-64-8)

2-(N-Benzyl-N-mesitylenesulfonyl)amino-1-phenyl-1-propanol:
Benzenesulfonamide, N-(2-hydroxy-1-methyl-2-phenylethyl)-2,4,6-trimethyl-N-(phenylmethyl)- (14);
[R-(R*,S*)]-, (187324-63-6), [S-(R*,S*)]-, (187324-64-7)

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