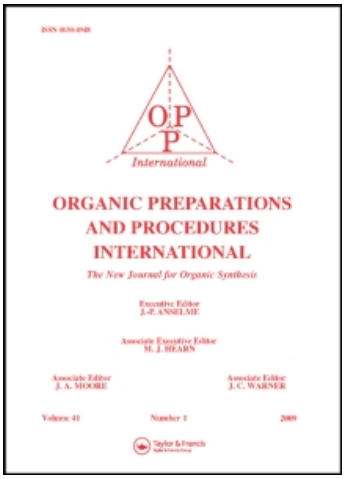

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AN IMPROVED SYNTHESIS OF (1*R*, 2*R*)-(-)-a-(1-ISOPROPYLAMINOETHYL)BENZYL ALCOHOL

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AN IMPROVED SYNTHESIS OF

(1R, 2R)-(-)-a-(1-ISOPROPYLAMINOETHYL)BENZYL ALCOHOL

Submitted by (03/01/88) Duy H. Hua*, Roch Chan-Yu-King, Robert A. Ostrander and Jeffrey A. McKie

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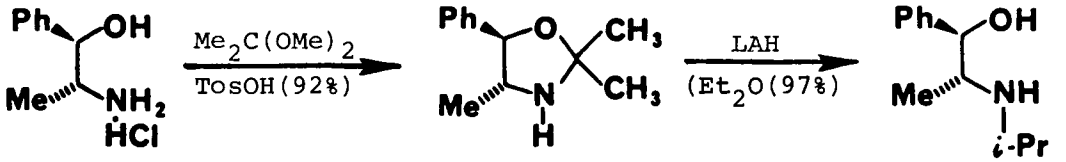
Directed asymmetric synthesis via 1,4-addition reactions of chiral allylphosphonyl anions with cyclic enones is a powerful new synthetic tool.[1] The chiral director (1R,2R)-(-)-a-(1-isopropyl-aminoethyl)benzyl alcohol (1) was originally prepared from the coupling reaction of (1R, 2R)-(-)-norpseudoephedrine hydrochloride (2) with acetone-sodium acetate-sodium borohydride in acetic acid-water at 0° followed by reduction of the resulting (4R, 5R)-(-)-5-phenyl-2,2,4-trimethyl-1,3-oxazolidine (3) with lithium aluminum hydride in ether at room temperature.[1,2] We later found that in the first step, the formation of the intermediate, oxazolidine 3 is very much dependent on the sodium borohydride used. The reaction proceeded to varying degree depending on the lot number of sodium borohydride employed. These undependable results prompted us to explore a different method for the formation of 3. Herein, we now report an improved and simple procedure for the preparation of 1 in excellent yield.



2 3 1

Treatment of amino alcohol 2 with 2,2-dimethoxypropane and anhydrous p-toluene

sulfonic acid (p-TsOH) in refluxing 1,2-dichloroethane provided oxazolidine 3 in 92% yield. Although, condesation of 2-aminoethanol with carbonyl compounds[3] has been reported to produce a mixture of the oxazolidine and the b-hydroxyl imine, oxazolidine 3 was the sole product in our case. 2,2-Dimethoxypropane was used instead of acetone, because it is higher boiling (83°), and the methanol which is formed instead of water, is more easily remove azeotropically from refluxing 1,2-dichloroethane (the latter is a better solvent for ammonium salt 2 than the more commonly used benzene). Reduction of oxazolidine 3 with lithium aluminum hydride in ether at room temperature for 30 min afforded 97% yield of amine 1. A possible intermediate, β-imino alkoxide, is produced via ring opening of the amide ion (deprotonation of 3 by lithium aluminum hydride) and the imino function undergoes reduction.

^{1}H- and ^{13}C-NMR spectra indicated 1 to be a single isomer and the relative stereochemistry was firmly established from single-crystal x-ray structure determination of (2S,4R, 5R)-2-[hydroxycyclohexyl)methyl]-3-isopropyl-4-methyl-5-phenyl-1,3,2-oxazaphos-1,3,2-oxazaphospholidine 2-oxide[4] derived from 1.

EXPERIMENTAL SECTION

All reagents were of commerical quality. (1R, 2R)-(-)-Norpseudo-ephedrine hydrochloride, sodium borohydride, 2,2-dimethoxypropane, p-toluenesulfonic acid monohydrate and analytical TLC plates were purchased from Aldrich Chemical Co. Lithium aluminum hydride was purchased from Alfa Products. Reagent quality solvents (acetic acid, acetone, methylene chloride, etc.) were used without further purification. Anhydrous ether was dried over sodium benzophenone ketyl and distilled under argon prior to use. Microanalyses were carried out by the MicAnal Organic Microanalysis, Tucson, AZ. Optical rotations at the Na-D line were obtained at 22° using a Perkin-Elmer 241 polarimeter. Mass specra were obtained using a Finnigan 4000 automated gas chromatography mass spectrometer with either DEI or FAB ionization. IR spectra were obtained using a Perkin-Elmer 1330 spectromenter. ^{1}H- and ^{13}C-NMR spectra were obtained using a Bruker WM 400 MHz spectrometer.

(4R,5R)-(-)-5-Phenyl-2,2,4-trimethyl-1,3-oxazolidine (3). Method A (with Acetone and Sodium Borohydride).- In a three-necked, round-bottomed flask equipped with an overhead stirrer, (1R, 2R)-(-)-norpseudoephedrine hydrochloride (2) (7.48 g, 0.04 mol), sodium acetate (13.12 g, 0.16 mol), acetic acid (68 mL, 1.13 mol) and acetone (40 mL, 0.55 mol) were dissolved in water (200 mL). This solution was stirred at room temperature for 30 min, then cooled to 0°. Sodium borohydride (16 g, 0.42 mol; lot No. 110687)[5] was added in small portions over 40 min. After the resulting mixture is stirred at 0° for 3 hrs, an aliquot (5 mL) was removed, diluted with 1N sodium hydroxide (20 mL), and extracted three times with methylene chloride (20 mL each). The combined extracts were washed with water (20 mL), then brine (20 mL), and dried with magnesium sulfate. The solvent was evaporated and the product was analyzed by ^{1}H-NMR. If starting alcohol 2 is not present, the reaction mixture is worked up (vide supra) to give 6.8 g (90%) of 3 as a colorless oil which was dried at 22°/0.1 mm, bp. 115°/6 mm (the undistilled material was used in the next step); $[\alpha]_D^{22}$: -76.7° (c = 0.93, CH_2Cl_2). IR(neat): 3300 (NH), 1600 (ArC = C), 1255 (C-O) cm^{-1}. ^{1}H-NMR ($CDCl_3$):

δ 7.35-7.26 (m, 5H, Ar-H); 4.19 (d, J = 8.6 Hz, 1H, CHO); 3.15 (m, 1H, CHN); 2.05 (bs, 1H, NH); 1.55 (s, 3H, CH_3); 1.54 (s, 3H, CH_3); 1.22 (d, J = 6.3 Hz, 3H, CH_3). ^{13}C-NMR ($CDCl_3$): δ 139.9 (s); 128.33 (d, 2C); 127.61 (d); 126.11 (d, 2C): 94.89 (s, NCO); 87.07 (d, CO); 61.86 (d, CN); 28.45 (q); 28.4 (q), 15.7 (q). MS (DEI): m/e = 192 (m+1).

Anal. Calcd. for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.17; H, 9.03; N, 7.24

Method B (improved; with 2,2-dimethoxypropane).- In a dried, argon-filled three necked, round-bottomed flask fitted with stirrer, a Dean-Stark apparatus and refluxing condenser, (1R, 2R)-(-)-norpseudoephedrine hydrochloride (2) (8.0 g, 0.043 mol), 2,2-dimethoypropane (26.3 mL, 0.214 mol) and anhydrous p-toluenesulfonic acid (0.15 g, 0.79 mmol) (p-toluenesulfonic acid monohydrate was dehydrated by flame-drying under high vacuum until it melts) were dissolved in 1,2-dichloroethane (400 mL). The reaction mixture was stirred under reflux for 12 hrs with occasional removal of the azetrope (50 mL each, three times), cooled to room temperature, and then diluted with 1N sodium hydroxide (50 mL) and water (200 mL). The organic phase was separated and the aqueous layer was extracted three times with methylene chloride (100 mL each). The combined organic layers were washed with brine (100 mL), and dried over magnesium sulfate. The solvent was evaporated to give 7.5 g (92%) of 3 as a colorless oil which was dried at 22°/0.1 mm.

(1R, 2R)-(-)-a-(1-Isopropylaminoethyl)benzyl Alcohol (1).- A round-bottomed flask fitted with stirrer, containing oxazolidine 3 (11 g, 0.0576 mol) was gently flame-dried under vacuum, then maintained under argon. Anhydrous ether (580 mL) was added, followed by lithium aluminum hydride (2.2 g, 0.0576 mol) added in small portions over 10 min. The mixture was stirred at 25° for 30 min, then carefully diluted with concentrated ammonium chloride (50 mL). Water (350 mL) and methylene chloride (100 mL) were then added and the mixture was filtered through Celite. The organic phase of the filtrate was separated, and the aqueous layer was extracted three times with methylene chloride (200 mL each). The combined organic phase and extracts were washed with brine (100 mL) and dried with magnesium sulfate. The solvent was evaporated to give 10.7 g (97%) of 1 as a colorless oil which was dried at 22°/0.1 mm; $[\alpha]_D^{22}$: -129° (c = 1.0, CH_2Cl_2). IR (neat): 3300 (b, NH, OH), 1600 (ArC = C), 1450, 1370, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 7.38-7.27 (m, 5H, Ar-H); 4.03 (d, J = 8.6 Hz, 1H, CHO); 2.93 (m, 1H, CHN); 2.67 (m, 1H, CHN); 1.10 (d, J = 6.3 Hz, 3H, CH_3); 1.07 (d, J = 6.2 Hz, 3H, CH_3); 0.93 ppm (d, J = 6.3 Hz, 3H CH_3). ^{13}C-NMR ($CDCl_3$): δ 142.31 (s); 127.99 (d, 2C); 127.35 (d); 126.
91 (d, 2C); 77.64 (d, CO); 57.27 (d, CN); 45.99 (d, CN); 24.29 (q); 22.71 (q); 17.12 ppm (q). MS (DEI): m/e = 194 (M+1).

Anal. Calcd. for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.39; H, 9.98; N, 7.11

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This paper is dedicated to Professor Cal Y. Meyers on the occasion of his 60th birthday.

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5. Sodium borohydride (purchased from Aldrich or Fisher Chemical Co.) bearing different lot numbers often led to incomplete reaction, which required more sodium borohydride (added in small portions). In some cases, but not all, an additional 16 g of sodium borohydride led to completion.

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A FACILE SYNTHESIS OF BENZYL ISOTHIOCYANATES BY USE OF 18-CROWN-6 ETHER

Submitted by (12/21/87)

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The reaction of alkyl halides with potassium thiocyanate invariably results in the formation of alkyl thiocyanates.[1,2] Benzyl halides (1) on treatment with KSCN have been reported to give benzyl isothiocyanates (2) in 90-96% yields; however, we obtained only benzyl thiocyanate in 80% yield from benzyl chloride under the conditions reported (30°, 4 hrs, DMF).[2] We now report here the information of benzyl isothiocyanate (2) in 50-66% yields, by the use of crown ether at sufficiently high temperature (180°) in o-dichlorobenzene (ODCB); at 100°, even in the presence of the crown ether, benzyl thiocyanate was obtained. The thiocyanates (3) were prepared in over 70% yields in acetone under reflux for 1 hr.

A 40:1 ratio of benzyl chloride to crown ether required 2.5 hrs reaction time whereas 80:1 ratio needed 6 hrs to effect the reaction. The isolated yield of benzyl isothiocyanate was generally 50%, based on 10 and 50 g scales. The thiocyanates showed a sharp peak at 2160 cm^{-1} whereas the isothiocyanates showed a broad peak around 2100 cm^{-1}. The methylene hydrogens of the isothiocyanates appeared at d 4.4 whereas thiocyanates exhibited singlets at δ