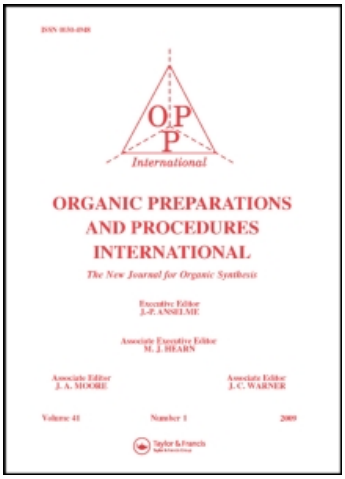

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A TRIPHOSGENE-BASED SYNTHESIS OF (S)-α,α-DIPHENYL-2-PYRROLIDINEMETHANOL

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A TRIPHOSGENE-BASED SYNTHESIS OF (*S*)-α,α-DIPHENYL-2-PYRROLIDINEMETHANOL

Submitted by (10/17/95)

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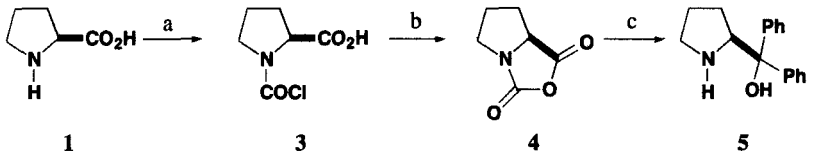
Chiral oxazaborolidines became a useful tool for synthetic chemists in the enantioselective reduction of prochiral ketones, imines and oximes,[1] due to their enzyme-like catalytic activity; therefore, the synthesis of the aminoalcohol precursors in enantiomerically pure form is of current interest. The set of oxazaborolidines developed by Corey,[2] based on (*S*)-α,α-diphenyl-2-pyrrolidinemethanol (**5**), has renewed the interest in the preparation of this compound,[3] originally synthesized by Kapfhammer.[4] Many of the available procedures[3a-d] start from proline (**1**) and use phosgene or liquid phosgene derivatives for the protection of the amino group; however, handling of these toxic and volatile reagents is hazardous.



1 **3** **4** **5**

a) Triphosgene (**2**), THF 15-20°, 1 hr, 30-40°, 1 hr, 64%, and recovered 36% of unreacted **1**
b) TEA, 0°, 0.5 hr, then filtrate c) PhMgBr, -15°, 3 hrs, 0°, 1 hr, 75% yield (from **3**).

Triphosgene [*bis*(trichloromethyl)carbonate, **2**],[5] a commercially available solid material safer to store, transport and use than phosgene, has been employed with increasing frequency as phosgene precursor or substitute. Since **2** has been used to prepare *N*-carboxyanhydrides (NCA) of α-aminoacids,[6] the synthesis of the NCA of proline (**4**)[7] as key intermediate in the preparation of **5**,[3a] using triphosgene, was explored (Scheme).

Treatment of anhydrous **1** with triphosgene in dry tetrahydrofuran (THF) provided the *N*-chlorocarbonyl derivative **3**. However, this reaction was incomplete even by the addition of excess **2** and/or by extending the reaction time (3.5 hrs). This problem has been ascribed to the protonation of **1** by the hydrogen chloride generated[6a] and the by-product had to be removed prior to the cyclization of **3** to NCA **4** with triethylamine. This step could *not* be replaced by adding twice as much triethylamine, since rapid polymerization of the unstable NCA[3a] led to dramatically lowered yields of product. Reaction of a THF solution of the crude **4** with phenylmagnesium bromide in THF gave **5**, isolated and purified as its sulfate salt. The corresponding free base was quantitatively obtained by treatment of the sulfate with excess of aqueous sodium hydroxide solution followed by extraction with

hexane and removal of the solvent. Spectral data of **3**, **4** and **5** as well as the optical rotation of **5** were in agreement with previously reported data.

EXPERIMENTAL SECTION

Reactions were carried out in a dry nitrogen atmosphere. Melting points (uncorrected) were measured on an Ernst Leitz hot-stage microscope apparatus. IR spectra were taken on a Bruker IFS 25 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-200E instrument at 200.13 and 50.33 MHz respectively, with TMS as the internal standard. J and $w_{1/2}$ values are given in Hz. Superscripts $^{\#}$, *, † and ¶ indicate that signal assignment may be interchanged.

(*S*)-α,α-Diphenyl-2-pyrrolidinemethanol (5).- A solution of triphosgene (**2**, 4.52 g, 15.22 mmol) in anhydrous THF (25 mL) was added dropwise during 1 hr to a well stirred suspension of **1** (5.0 g, 43.48 mmol) in dry THF (50 mL), while mantaining the internal temperature between 15 and 20° (water bath). Stirring continued for 60 min at 30-40°,[8] then the suspension was filtered to remove unreacted proline (as its hydrochloride), the HCl evolved during the reaction was removed by concentration of the reaction *in vacuo* to a volume of 10 mL, and the remaining viscous oil was diluted with dry THF (50 mL) and cooled to 0°. Anhydrous triethylamine was added dropwise during 15 min with constant stirring to the resulting solution and triethylamine hydrochloride precipitated. Stirring was continued for another 30 min, then the suspension was filtered and the residue was washed with dry THF (3 x 10 mL). Analysis of a 0.5 mL sample (from which volatiles were completely removed under reduced pressure) indicated that NCA **4** was obtained.

^{1}H NMR ($CDCl_3$): δ 1.80-2.40 (m, 4 H, H-C_3 and H-C_4), 3.31 (ddd, 1 H, J = 5.1, 7.8 and 11.4, H-C_5), 3.79 (dt, 1 H, J = 7.3 and 11.4, H-C_5); ^{13}C NMR ($CDCl_3$): δ 26.79 (C_5), 27.54 (C_4), 46.43 (C_6), 62.93 (C_{3a}), 154.45 (C_1) and 168.58 (C_3).

The combined filtrates were added dropwise over 1 hr to a well stirred solution of phenylmagnesium bromide in anhydrous THF (146 mL, 131 mmol), cooled to -15°. The reaction mixture was stirred for 3 hrs at -15° and 1 hr at 0°, then it was slowly poured on 2M cold aqueous H_2SO_4 (100 mL, 200 mmol) and left overnight at 0°. The $MgSO_4$ formed was separated by filtration and washed with EtOAc (3 x 20 mL), and the combined filtrates were concentrated under reduced pressure until the organic solvents were removed. The resulting precipitate, containing the sulfate of **5**, was filtered and successively washed with water (3 x 10 mL) and EtOAc (3 x 10 mL). After drying, the pure sulfate resulted in a white solid (6.34 g, 48%; 75% based on unreacted **1**), mp. 277-288° (dec.), lit.[3a] 275-290° (dec.).

IR (KBr): 3400, 3300, 2960, 1630, 1560, 1450, 1385, 1290, 1175, 1068, 970, 880, 750 and 690 cm^{-1}.

The salt (907 mg, 1.5 mmol) was added portionwise to a well stirred mixture of THF (3 mL) and 2N aqueous NaOH (3 mL). After the complete dissolution of the sulfate, the free base was extracted with hexane (2 x 5 mL) and the organic extracts were washed with water (2 x 3 mL), dried (Na_2SO_4), and concentrated *in vacuo*, affording **5** (754 mg, 99% from the sulfate) as a solid, mp.

79-79.5° (hexane), lit.[3a] mp. 79-79.5° (hexane); $[\alpha]_D^{20}$ = -58.47 (c = 3.01, MeOH), lit.[4] $[\alpha]_D^{20}$ = -58.8 (c = 3, MeOH).

IR (KBr): 3600-3300, 3160, 3140, 2980, 2790, 1490, 1450, 1390, 1190, 1030, 1020, 750 and 700 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.50-1.88 (m, 5 H, NH, H-C_3 and H-C_4), 2.88-3.13 (m, 2 H, H-C_5), 4.25 (t, 1 H, J = 7.4, H-C_2), 7.10-7.40 (m, 6 H, ArH) and 7.45-7.61 (m, 4 H, ArH); ^{13}C NMR ($CDCl_3$): δ 25.29 (C_4), 26.05 (C_3), 46.54 (C_5), 64.29 (C_2), 77.03 (C_α), 125.33 ($C_{2'}$),* 125.67 ($C_{2''}$),* 126.16 ($C_{6'}$),* 126.28 ($C_{6''}$),* 126.74 ($C_{4'}$),# 127.33 ($C_{4''}$),# 127.77 ($C_{3'}$),† 128.04 ($C_{3''}$, $C_{5'}$),† 128.30 ($C_{5''}$),† 145.18 ($C_{1'}$)¶ and 147.85 ($C_{1''}$).¶

Anal. Calcd. for $C_{17}H_{19}NO$: C, 80.60; H, 7.50; N, 5.53. Found: C, 80.80; H, 7.60; N, 5.50

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8. At this time, a small sample (3 mL) of the reaction mixture was withdrawn and the solvent was removed *in vacuo*, leaving a residue (230.3 mg), to which $CHCl_3$ (3 mL) was added; the resulting

suspension was centrifuged and the residue, washed with $CHCl_3$ (2 x 1 mL), proved to be unreacted **1** (as its hydrochloride, 84 mg, 36%). ^1H NMR (D_2O): δ 1.87-2.38 (m, 4 H, H-C_3 and H-C_4), 3.20-3.32 (m, 2 H, H-C_5) and 4.27 (t, 1 H, J = 6.7, H-C_2). The combined chloroform supernatants were concentrated *in vacuo* and analyzed, indicating **3** as the sole product. ^1H NMR ($CDCl_3$): δ 1.80-2.46 (m, 4 H, H-C_3 and H-C_4), 3.50 -3.88 (m, 2 H, H-C_5), 4.50 (dd, 0.6 H, J = 3.7 and 8.5, H-C_2 rotamer), 4.62 (dd, 0.4 H, J = 2.8 and 8.5, H-C_2 rotamer) and 9.28 (br s, 1 H, $w_{1/2}$ = 25, CO_2H).

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SYNTHESIS OF PENTACOORDINATE PHOSPHORUS COMPOUNDS BY THE ATHERTON-TODD REACTION

Submitted by (11/13/95)

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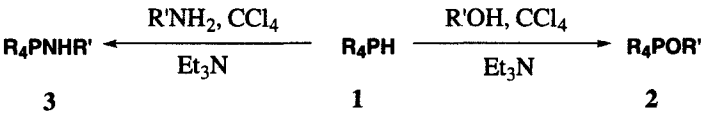
The Atherton-Todd reaction is a synthetically valuable method for the preparation of tetracoordinate phosphorus compounds.[1] The reaction has recently been extended to some hydridophosphoranes by Houalla[2] and by us.[3] It is the purpose of this work to further explore the scope of the reaction using a variety of hydridophosphoranes. The principal advantages of this reaction are that the starting materials are readily obtained, the operation is simple (one-pot reaction) and the reaction proceeds smoothly under mild conditions.

Scheme



3 **1** **2**

a) R' = n-C_3H_7, R_4P = A
b) R' = i-C_3H_7, R_4P = A

a) R' = CH_3, R_4P = B
b) R' = C_2H_5, R_4P = B
a) R' = n-C_3H_7, R_4P = C
b) R' = n-C_4H_9, R_4P = C