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Convenient Method for the Synthesis of Chiral α,α-Diphenyl-2-pyrrolidinemethanol

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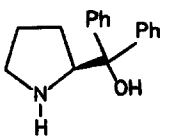
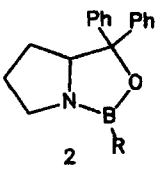
Abstract: A simplified, convenient synthesis of chiral α,α-diphenyl- 2-pyrrolidine-methanol involving one step N-and O-protection of S-proline using ethylchloroformate followed by Grignard addition-alkaline hydrolysis (KOH/CH_3OH) is described.

The chiral α, α-diphenyl -2-pyrrolidinemethanol S-1 has become one of the important molecules in view of it being a precursor for the synthesis of chiral oxazaborolidines, the CBS asymmetric reduction catalysts 2[1].



S-1



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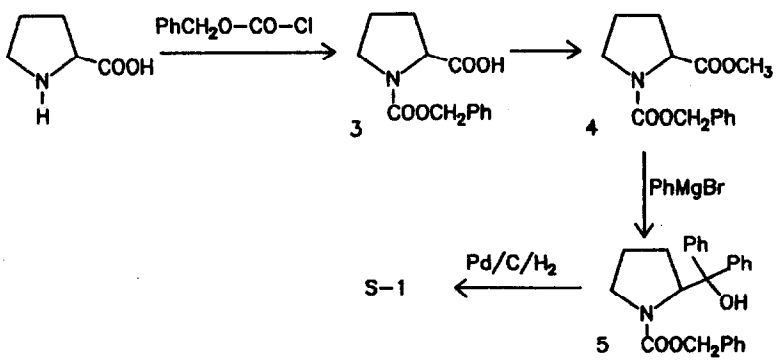
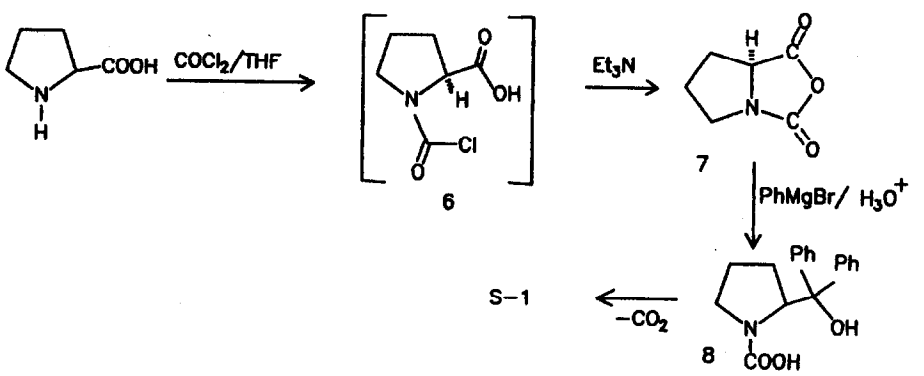
The α,α-diphenyl-2-pyrrolidinemethanol S-1, can be prepared from S-proline through the sequence of reactions shown in Scheme 1.

Scheme 1



Recently, Mathre and co-workers reported an alternative method which they found suitable for their needs(Scheme 2)[2].

Scheme 2

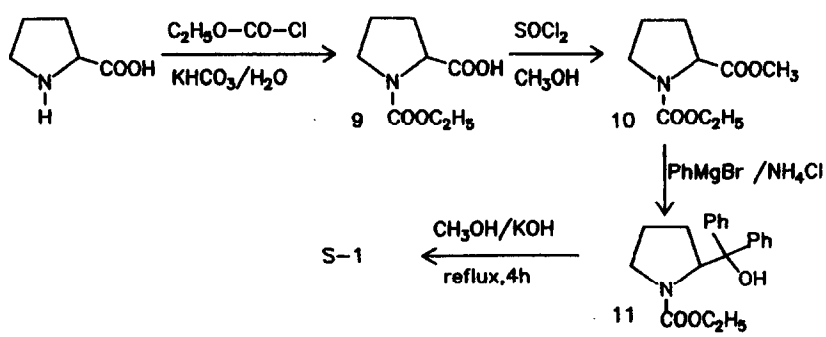


Unfortunately, this method (Scheme 2) requires utilisation of the highly toxic phosgene and the intermediate proline-N-carboxanhydride 7 is not stable. Even at 0°C, it polymerises rapidly on standing, releasing CO_2.

In the course of our investigations on the use of chiral amine borane complexes,[3] we were looking for a convenient method of synthesis of S-1. We wish to report such methods of syntheses of S-1, by simplification of the sequence outlined in Scheme 1.

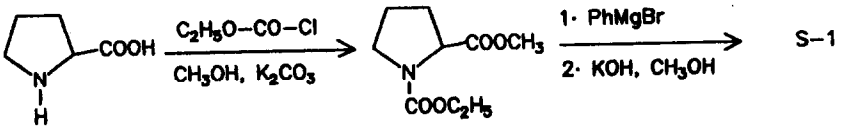
In the sequence outlined in Scheme 1, the N-protection was carried out using benzylchloroformate as it can be readily deprotected using $Pd/C/H_2$ in the final step. Recently, it has been reported that the N-benzylcarbamate 5 prepared from pyrrolidine-N-benzylcarbamate through asymmetric deprotonation using *sec*-BuLi/(-)Sparteine followed by the addition of benzophenone, can be readily deprotected by refluxing in $NaOH/C_2H_5OH$.[4] Since the alkaline hydrolysis of the carbamate would go through the corresponding tetrahedral intermediate, it should work equally well with the corresponding ethyl carbamate. Indeed, we have observed this in the case of 11, which can be readily prepared through the sequence of transformations shown in Scheme 3 involving relatively less expensive ethylchloroformate for N-protection. The use of alkaline hydrolysis in the final step instead of $Pd/C/H_2$, would make this method more attractive.

Scheme 3

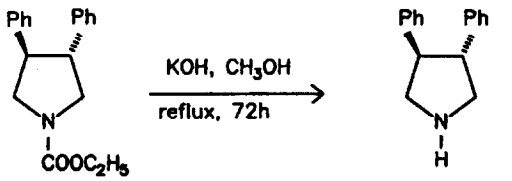


The procedure will be still simple if both N- and O- protection can be performed in a single pot operation. This objective has been attained(Scheme 4) and the transformation can be readily carried out through only two isolation procedures compared to four isolations required in the sequence outlined in Scheme 1.

Scheme 4



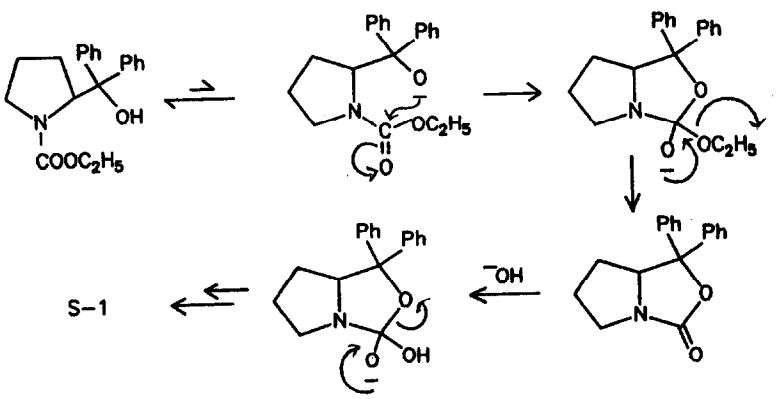
The ease of deprotection of the N-carbamate through alkaline hydrolysis may also have some interesting mechanistic implications. For example, we have found that attempted N-deprotection of the N-ethylcarbamate derivative of 3,4-diphenylpyrrolidine 12 even under relatively harsh conditions (i.e, 10 M KOH in CH_3OH, 72h reflux) gives only 30% of the secondary amine 13 besides unreacted carbamate.



12 13 (30%)

Presumably, presence of the 2-substituent facilitates the hydrolysis which may be tentatively explained as outlined in Scheme 5.

Scheme 5



In conclusion, the synthesis reported here should serve as a simple, convenient and economical method for the preparation of (S)-1, which has been proved to be an important and useful organic compound.[1]

EXPERIMENTAL SECTION

General: S- Proline (99%) supplied by SD fine chemicals (India) and ethyl chloroformate(98%) supplied by Spectrochem (India) were utilised. Tetrahydrofuran, THF freshly distilled over benzophenone-sodium was used. Infrared spectra were recorded on a Perkin-Elmer IR spectrometer 1310 with polystyrene as reference. NMR spectra were recorded on a JEOL-FX-100 and Bruker-AC-200 spectrometers in deuterated chloroform using tetramethyl silane as internal standard. The chemical shifts (δ) are expressed in (δ)ppm downfield from the signal for internal Me_4Si. Optical rotations were measured with an Autopol II-automatic polarimeter at 20°C. For TLC analysis, plates coated with silicagel were run in hexane/ethyl acetate mixture and spots were developed in an iodine chamber. For column chromatographic separations under gravity, column grade silica gel (100-200 mesh) was employed.

Synthesis of S(1) from S-Proline following the reaction sequence in Scheme 3.

Preparation of S-Proline-N-ethyl carbamate (2):

S-Proline was converted to N-ethyl carbamate by following a reported method[5]. To S-proline (1.15g, 10 mmol) in water (20 ml), $NaHCO_3$(0.84g, 10 mmol) was added followed by ethyl chloroformate (1.1g, 10 mmol) and the reaction mixture was stirred for 12h at 25°C. The reaction mixture was extracted with ethyl acetate (3x15 ml). The combined organic extract was washed with brine and dried over anhydrous $MgSo_4$. Evaporation of solvent afforded essentially pure proline-N-ethyl carbamate. Yield: 1.79g(96%). IR(cm^{-1}): 1670, 1720.

Preparation of S-Proline-N-ethyl carbamate methyl ester (3):

S-Proline-N-ethyl carbamate(1.87g, 10 mmol), prepared as above was placed in dry methanol (20 ml), thionyl chloride (1.77g, 15 mmol) was added slowly during 10 min at 0°C and stirred for 8h at 25°C. Evaporation of solvent under reduced pressure gave 3,(Scheme 3), which was used for the Grignard addition without further purification. Yield: 1.9g(95%). IR(cm^{-1}):1700,1740. ^1H NMR($CDCl_3$)δ: 1.2(t,3H) 2.0(m,4H), 3.5(m,2H) 3.7(s,3H), 4.1(m,3H).

Preparation of compound 4:

Magnesium turnings (1.94g, 80 mmol) were placed in a oven dried two-necked RB flask with a reflux condensor attached. The flask was cooled to room temperature by flushing nitrogen gas. Dry THF (30 ml) was added through a double ended needle under nitrogen atmosphere. Freshly distilled bromobenzene (6.28g, 40 mmol) in dry THF(15 ml) was added dropwise through a pressure-equaliser during 15 min. The contents were further stirred for 30 min. The N-carbamate ester 3 (2.01 g, 10 mmol)

was taken in dry THF (20 ml) in a two necked RB flask and phenyl magnesium bromide, prepared as above. was added through a cannula under nitrogen atmosphere at 0°C. The contents were further stirred at 0°C for 3h. The reaction was quenched with saturated ammonium chloride solution (20 ml). The supernatant liquid was decanted leaving behind the white precipitate. The precipitate was stirred with chloroform (2x10 ml) and the organic extract was collected. The combined organic extract was washed with brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded 4, (Scheme 3) which was further purified by column chromatography (n-hexane:ethyl acetate/ 90:10). Yield: 2.53g (78%). IR(cm^{-1}): 3375,1680. ^1H NMR ($CDCl_3$)δ: 1.2(t,3H), 1.6(s,1H), 2.0(m,2H), 3.0(m,2H), 3.4(m,2H), 4.1(m,2H), 5.0(m,1H) 7.2-7.6(m,10H). ^{13}C NMR(25 MHz)δ: 14.4, 22.7, 29.4, 47.6, 61.7, 65.8, 81.4, 127.1, 127.4, 127.6, 127.8, 128.0, 143.7, 146.3, 158.2. Analytical data, calculated: C;73.82, H;7.12, N;4.30; obtained: C;73.58, H;6.99, N;4.35.

N-Deprotection of 4:

Into a flask containing dry methanol(20 ml) the compound 4 (3.25 g, 10 mmol) and KOH(5.6 g) were added. The mixture was refluxed for 4h Methanol was distilled off and water(15 ml) was added. The contents were extracted with chloroform (3x20 ml). The combined organic extract was washed with brine and dried over anhydrous $MgSO_4$. Evaporation of solvent afforded S-1 as gummy liquid which upon standing crystallised. This can be further purified by recrystallisation from n-hexane. Yield: 2.3g (92%). MP = 74°C Lit[1a] 74-74.8°C. $[\alpha]^{20}_D$ = -68°(C3,CH_3OH), Lit[1a] $[\alpha]^{20}_D$ = -68.1° (C3.17, CH_3OH). IR(cm^{-1}): 3350, 1600. ^1H NMR($CDCl_3$): 1.25-1.7(m,5H), 2.9(m,2H), 4.2(t,1H), 4.8(s,1H), 7.1-7.6(m,10H). ^{13}C NMR(25 MHz): 25.4, 26.2, 46.7, 64.5, 77.1, 125.6, 126.0, 126.4, 126.5, 128.0, 128.7, 145.6, 148.3.

We have found that these transformations work equally well starting from 50 mmol of S-proline without significant changes in the yields in various steps.

Preparation of S-1 following the sequence in Scheme 4:

Preparation of N-and O-protected S-Proline:

S-Proline (1.15 g,10 mmol) in dry methanol (20 ml) was taken in a two-necked RB flask. Anhydrous K_2CO_3(1.32g, 10 mmol) was added followed by the addition of ethyl chloroformate (2.5.g, 22 mmol) during 5 min. at 25°C. The reaction mixture was further stirred for 12h at 0°C. Methanol was evaporated and distilled water (10 ml) was added. The contents were extracted with chloroform (3x15 ml). The combined organic extract was washed with brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent yielded the N,O-protected S-Proline 6 (Scheme 4) which was used for Grignard reaction without further purification. Yield: 1.90 g(95%). Comparison of

the spectral data showed 1:1 correspondence with the data for compound 3 obtained following the sequence in Scheme 3.

The compound 10 (2.01 g,10 mmol) in dry THF (20 ml) was taken in a dry two-necked RB flask. Phenyl magnesium bromide (40 mmol), prepared as outlined previously (Scheme 3) was added through a cannula under nitrogen atmosphere at 0°C. The reaction mixture was further stirred for 3h at 0°C. The reaction was quenched with saturated ammonium chloride solution(20 ml). The supernatant liquid was collected leaving behind a white precipitate which was stirred with chloroform (2x15 ml) and the organic extracts were collected. The combined organic extract was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure. The residue was taken in dry methanol(20 ml) and KOH(5.6 g) was added. The mixture was refluxed for 4h. Methanol was distilled off and water (10 ml) was added. The contents were extracted with chloroform(3x15 ml). The combined organic extract was washed with brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded S-1 as gummy liquid which crystallises upon standing. It was further recrystallised from hexane. Physical constant and spectroscopic data of the sample showed 1:1 correspondence with the compound prepared following the sequence in Scheme 3. We have also carried out this transformations (Scheme 4) starting from 50 mmol of S-proline and found no significant change in the yield of S-1.

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