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SYNTHESIS OF (*S*)-PROLINE DERIVATIVES WITH AN ALKYLATED N-BENZYL SUBSTITUENT. BENZYLATION OF (*S*)-INDOLINE-2-CARBOXYLIC ACID

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The synthesis is reported of (S)-proline derivatives which contain a 2,4,6-trimethyl-, 4-tert-butyl-, or pentamethylbenzyl substituent on the nitrogen atom. Under similar conditions the benzylation of indoline-2-carboxylic acid was unsuccessful. Treatment of indoline-2-carboxylic acid with benzyl chloride in the presence of KOH in dimethylacetamide gave the benzyl ester of N-benzylindoline-2-carboxylic acid which is unstable on light.

Keywords: N-benzylproline, proline, chiral synthon, asymmetric synthesis.

Tightening up of environmental standards has stimulated the development of highly selective catalysts for fine organic synthetic manufacture. In particular, they are of great interest for the synthesis of enantiomerically pure medicines with the aim of eliminating the side effects of the racemic form [1].

N-Benzylproline derivatives are used as chiral catalysts and chiral inductors in various reaction [2-9]. On the basis of a study of the conformation of several chiral synthons which contained an N-benzyl residue, a higher degree of asymmetric induction was anticipated for similar compounds containing substituents in the *ortho* positions of the benzyl group [10]. In this connection it was of interest to study N-benzylprolines substituted in the benzene ring as potential chiral inductors.

N-Benzylprolines, having alkyl substituents in the benzene ring have not been reported before. In this work we describe the synthesis of novel (*S*)-prolines which contain a 2,4,6-trimethyl-, 4-tert-butyl-, or pentamethylbenzyl substituent on the nitrogen atom (**1-3** respectively) and also the methyl esters of the first two amino acids (**4, 5** respectively). For the preparation of compounds **1-3** there was used a method previously reported for the example of the reaction of proline with benzyl chloride [11]. In this way, products **1-3** were synthesized in 32-60% yields (Scheme 1). The reaction conditions were not optimized. Methylation of the acids **1** and **3** with excess of diazomethane solution gave the corresponding esters **4** and **5** in quantitative yield. Compound **1** was used for the preparation of the recoverable chiral reagent (*S*)-2-[N-(2,4,6-trimethylbenzyl)prolyl]-aminobenzophenone, thus permitting the synthesis of (*S*)-[^{11}C]alanine with a 97% enantiomeric excess (e. e.) [12]. From the unsubstituted (*S*)-2-(N-benzylprolyl)aminobenzophenone the (*S*)-[^{11}C]alanine was obtained with 80% e. e.

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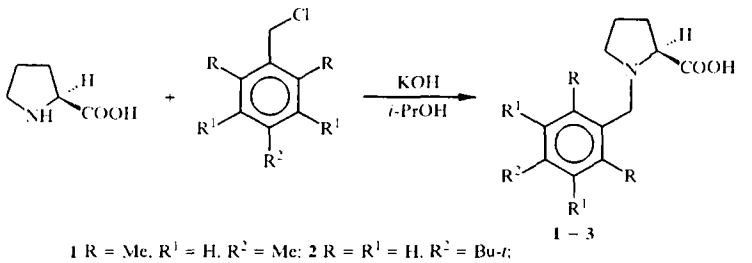
Scheme 1

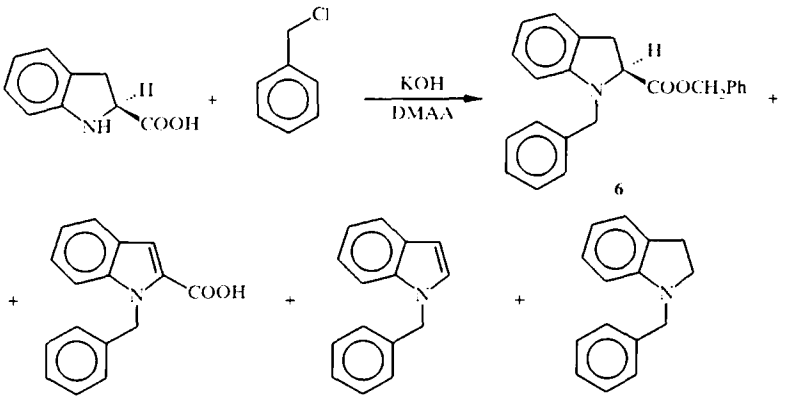


1 R = Me, R^1 = H, R^2 = Me; 2 R = R^1 = H, R^2 = Bu-*t*;
3 R = R^1 = R^2 = Me

We also studied the possible benzylation of a proline analog, indoline-2-carboxylic acid. The racemic ethyl ester of N-benzylindoline-2-carboxylic acid has previously been used for design of the skeleton of α_2-adrenoblockers [14]. However, the material obtained by reduction of the corresponding indole-2-carboxylic acid was used without separation in a reaction with the trimethylaluminium ethylenediamine complex. Hence no kinds of parameters were presented for the compound.

The reaction of indoline-2-carboxylic acid with benzyl chloride in the conditions reported in [11] did not lead to N-benzylindoline-2-carboxylic acid. Using a similar reaction in dimethylacetamide (DMAA) we obtained the benzyl ester of N-benzylindoline-2-carboxylic acid (**6**) in 23% yield (according to chromato-mass spectrometry) based on the identified compounds with an indoline / indole skeleton (see Scheme 2). The content of product **6** in neutral chloroform solution in the reaction mixture decreased to 11% over 16 h at + 4°C. The ester is light sensitive and can be used with difficulty on a preparative purposes as an intermediate compound. This is in agreement with published data concerning the light sensitivity of N-benzylindoline [15]. Attempts to lower it by addition of base or acid or removal of solvent proved unsuccessful. A chloroform solution of compound **6** or an amorphous powder prepared by addition of dry ether to this solution became intensely purple or violet in color.

Scheme 2



EXPERIMENTAL

Analytical samples of the synthesized compounds were prepared using preparative TLC on silica gel (methylchloroform–acetone gradient from 10 : 1 to 2 : 1). ^{1}H NMR spectra were recorded on a Varian Gemini 200 spectrometer using $CDCl_3$ solvent and TMS internal standard. Optical rotations were measured on a Schmidt-Haenich Polatronic NH 8 polarimeter using a 5 cm cuvette. Chromato-mass spectra were obtained on a Kratos MS25RFA instrument (70 eV) combined with a Hewlett-Packard 5890 capillary gas chromatograph using an

Ultra-2 column (25 m × 0.22 mm, 5% loading, phenylmethyl silicone, layer thickness 0.11 mm). The sample was introduced into the column. Ionization current 100 μA. Low resolution ($R_{10\%}$) = 600, calibration 28-480 daltons. The temperature of the ion source, the column inlet into the ion source and the injector were 220°C and the temperature program 2 min at 80°C followed by 10°C / min to 280°C.

High resolution mass spectra were obtained on a VG analytical ZAB-SEQ instrument.

(*S*)-Proline derivatives (1-3) were synthesized by a known method [11]. The substituted benzyl chloride (100 mmol) was added to a solution of (*S*)-proline (11.6 g, 100 mmol) and KOH (14 g, 250 mmol) in isopropanol (250 ml) over 30 min with vigorous stirring at 60°C. The reaction mixture was then stirred for 30 min and evaporated in vacuo. Water (50 ml) was added to the residue which was filtered, 10% HCl added with stirring to the filtrate to pH 6-7, and the precipitate formed was washed on the filter with water (200 ml) and dried in vacuo. The dry precipitate was dissolved in a minimum amount of MeOH at 40-50°C, filtered, and added dropwise to diethyl ether (500 ml) with vigorous stirring. The precipitated product **1-3** was then washed on the filter with diethyl ether (200 ml) and dried in vacuo.

(*S*)-N-(2,4,6-Trimethylbenzyl)proline (1). Yield 41%; mp 150-152°C. $[\alpha]_{576}^{25}$ = -44°, $[\alpha]_{546}^{25}$ = -40° (*c*. 0.005, $CHCl_3$). ^1H NMR spectrum: 1.90-3.70 (6H, m, H_{pro}); 2.23 (3H, s, 4-CH_3); 2.41 (6H, s, 2- and 6-CH_3); 4.00-4.20 (1H, m, α -H_{pro}); 4.36 and 4.52 (2H, AB, *J* = 13.6 Hz, $\underline{CH_2}$-Ar); 6.89 ppm (2H, s, H_{Ar}). Found: $[M+H]^+$: 248.1613 (FAB-MS). $C_{15}H_{21}NO_2$. Calculated 248.1651.

(*S*)-N-(4-tert-Butylbenzyl)proline (2). Yield 32%; mp 171-173°C. $[\alpha]_{576}^{25}$ = -24°, $[\alpha]_{546}^{25}$ = -32° (*c*. 0.005, $CHCl_3$). ^1H NMR spectrum: (9H, s, $-C(CH_3)_3$); 1.90-3.70 (6H, m, H_{pro}); 3.95-4.10 (1H, m, α-H_{pro}); 4.33 and 4.45 (2H, AB, J = 12.8 Hz, $\underline{CH_2}$-Ar); 7.41 ppm (4H, s, H_{Ar}). Found $[M+H]^+$: 262.1776 (FAB-MS). $C_{16}H_{23}NO_2$. Calculated 262.1807.

(*S*)-N-(Pentamethylbenzyl)proline (3). Yield 60%; mp 142-146°C. $[\alpha]_{576}^{25}$ = -39°, $[\alpha]_{546}^{25}$ = -47° (*c*. 0.005, $CHCl_3$). ^1H NMR spectrum: 1.95-3.6 (6H, m, H_{pro}); 2.22 (6H, s, 3- and 5-CH_3); 2.24 (3H, s, 4-CH_3); 2.42 (6H, s, 2- and 6-CH_3); 3.40-3.60 (1H, m, α-H_{pro}); 4.30 and 4.35 ppm (2H, AB, *J* = 7.0 Hz, $\underline{CH_2}$-Ar). Found $[M+H]^+$: 276.1888 (FAB-MS). $C_{17}H_{25}NO_2$. Calculated 276.1963.

The methyl ethers of the substituted (*S*)-prolines **4** and **5** were prepared by a known method [16] by treatment of compounds **1** and **2** with an excess of diazomethane solution in diethyl ether.

Methyl Ester of (*S*)-N-(2,4,6-Trimethylbenzyl)proline (4). Yield ~ 100%; oil. ^1H NMR spectrum: 1.70-3.80 (7H, m, H_{pro}); 2.24 (3H, s, 4-CH_3); 2.36 (6H, s, 2- and 6-CH_3); 3.59 (3H, s, OCH_3); 3.63 and 3.82 (2H, AB, *J* = 12.5 Hz, $\underline{CH_2}$-Ar); 6.81 ppm (2H, s, H_{Ar}). Found M^+: 261.1642 (EI-MS). $C_{16}H_{23}NO_2$. Calculated: 261.1729.

Methyl Ester of (*S*)-N-(4-Tert-butylbenzyl)proline (5). Yield ~ 100%. Oil. ^1H NMR spectrum: 1.30 (9H, s, 3-CH_3); 1.70-3.70 (7H, m, H_{pro}); 3.62 (3H, s, OCH_3); 3.62 and 3.88 (2H, AB, *J* = 13.4 Hz, $\underline{CH_2}$–Ar); 7.10-7.50 ppm (4H, m, AA'BB', H_{Ar}). Found M^+: 275.1865 (EI-MS). $C_{17}H_{25}NO_2$. Calculated: 275.1885.

Benzyl Ester of N-Benzylindoline-2-carboxylic Acid (6). Benzyl chloride (2 ml, 17.4 mmol) was added dropwise with vigorous stirring over 30 min at 60°C to a solution of N-benzylindoline-2-carboxylic acid (1 g, 6.13 mmol) and KOH (2 g, 35.7 mmol) in DMAA (15 ml) which had been placed in a flask covered by black paper with the whole under an argon atmosphere. The reaction mixture was stirred for 30 min, an aqueous solution of citric acid (20%, 70 ml) added, and the product extracted with chloroform (3 × 10 ml). The combined extract was immediately analyzed by chromato-mass spectrometry. The mass spectrum identified product **6** (13.3%) in the mixture with *m/z*: 344 ($M^{+\cdot}$), 10.208 ($M\text{-}COOCH_2C_6H_5^{+\cdot}$), 63.91 ($CH_2C_6H_5^+$) 100. The remaining components of the mixture were, %: N-benzylindoline 3.6, N-benzylindole 22.1, N-benzylindole-2-carboxylic acid 1.1, benzyl chloride 19.7, and benzyl alcohol 33.3.

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