Short Communication:

New Benzyl-Protected Derivatives of Glycine, Alanine, and Serine: Easily Accessible Building-Blocks for Synthesis

Neue Benzyl-geschützte Derivate des Glycins, Alanins und Serins: Leicht zugängliche Synthesebausteine

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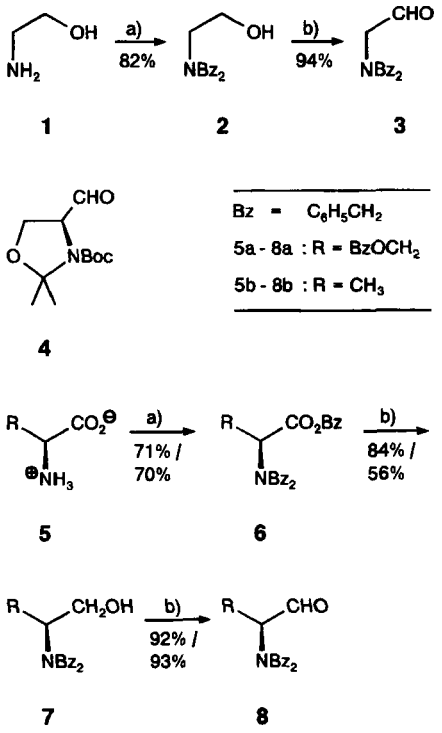
Amino acids and peptides are among the most important classes of compounds in pharmacy and agrochemistry. They are not only active agents and end products in their own right, but also play an increasingly important role in the chemical synthesis of various other products[1)2)]. Their synthetic versatility is due to the combination of functional groups comprised in a small molecule, in most cases including a stereocenter. To be useful as readily accessible "chiral pool" starting materials, the stereoconservative introduction of convenient protective groups is mandatory. We wish to disclose the facile preparation of *N,N*-dibenzyl protected derivatives of glycine, alanine, and serine, since at present there is a widespread need for amino acid synthons that are accessible in large quantities by straightforward procedures.



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N,N-Dibenzyl amino acids[3)4)] have rarely been used in spite of several advantages this protective group offers: convenient preparation (see below); ready purification of protected derivatives due to lipophilicity and TLC detectability (see below); smooth removal by hydrogenation[5)].

We benzylated 2-aminoethanol **1** with benzyl bromide in an aqueous solution of K_2CO_3, getting an 82% yield of colourless crystals of **2** with no concomitant *O*-benzylation. *Swern* oxidation[6)] gave the corresponding aldehyde **3** in high yield (94%). **2** and **3** are new derivatives of glycine.

The synthesis of a related *N,N,O*-triprotected aldehydic derivative of serine would appear to be highly desirable, as exemplified by the various methods published recently for getting the *Garner*-aldehyde **4**, a very useful intermediate and serine synthon[7)-10)]. Serine, because of its versatile functionality, has been especially focussed on as starting material for unusual amino acids[11)]. Notwithstanding the way it is prepared, **4** remains to be neither cheap nor easily accessible. We have set out to synthesize an alternative to **4** and devised the following synthetic route for the tribenzyl aldehyde **8a**: Commercial *O*-benzyl-L-serine (**5a**) was benzylated as described for **1** to give the ester **6a** (71%) which was smoothly reduced by $LiAlH_4$. The resulting alcohol **7** underwent *Swern* oxidation in high yield: the desired aldehyde **8a** was isolated after column chromatography. The optical purity of **8a** was checked by again reducing it to **7a** with $LiAlH_4$. Esterification of **7a** with *Mosher*-acid[12)] revealed 91% ee by analysis of the ^{19}F-NMR spectrum, as compared with 93-95% ee reported for the *Garner*-aldehyde[7)]. We recommend the protected aldehyde **8a** as a non-racemic C_3 building block in serine-related strategies.

We obtained the corresponding L-alanine derivatives via an analogous route. L-Alanine (**5b**) was converted to the *N,N*-dibenzyl-benzyl ester **6b** which, in turn, was reduced to the alcohol **7b**. *Swern* oxidation afforded the crystalline aldehyde **8b** in 93% yield. This protocol again furnishes a useful amino aldehyde synthon in very good yield, the final product and the intermediates being characterized by convenient large-scale purification procedures.

In summary, we have succeeded in procuring a number of new amino acid derivatives that should prove to be valuable building blocks in the amino acid field.

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Experimental Part

Solvents were dried according to standard procedures.- All substances were of reagent grade.- Chromatography: Merck silica gel (40-63 µm).- Melting points: uncorrected.- Mass spectra: Vacuum Generators 7070 spectrometer.- IR spectra: Perkin-Elmer 398 spectrometer.- ^{1}H- and ^{13}C-NMR spectra: Varian T-60 and Jeol JNM-GX-400 spectrometers, chem. shifts in δ (ppm).

N,N-Dibenzyl-2-aminoethanol (**2**)

A mixture of 2-aminoethanol (**1**, 1.5 g, 25 mmol), benzyl bromide (8.6 g, 50 mmol), K_2CO_3 (13.8 g, 100 mmol), and water (22 ml) was refluxed for 3 h. The org. phase was dissolved in diethyl ether and separated from the aqueous layer. It was washed two times with water (2 x 15 ml), dried (Na_2SO_4), filtered, and evaporated to give 5.6 g of crude product as a pale yellow oil. n-Pentane (30 ml) was added, and the mixture was kept at 5°C for 12 h: 4.9 g (82%) of white crystals were obtained; mp. 38°C.- IR (KBr): $\tilde{\nu}$ = 3390br; 3060; 3030; 2880br; 1600w; 1492; 1451; 1030; 740; 700 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ = 2.65 (t, J = 5.4 Hz, 2H, C$\underline{H}_2$CH$_2$OH), 3.57 (t, J = 5.7 Hz, 2H, C$\underline{H}_2$OH), 3.60 (s, 4H, CH$_2$Ph), 7.31-7.32 (m, 10 H, Ar-H).- ^{13}C-NMR ($CDCl_3$): δ = 54.7 (CH_2N), 58.4 ($C_6H_5CH_2$N), 58.5 (CH_2OH), 127.2, 128.4, 129.0, 138.7 (aromatic C-atoms).- MS (70 eV) m/z (%) = 241 (0.7), 91 (100).- $C_{16}H_{19}NO$ (241.4) Calcd. C 79.61 H 7.95 N 5.80 Found C 79.50 H 7.78 N 5.69.

N,N-Dibenzyl-2-aminoethanal (**3**)

Dry DMSO (3.2 g, 41 mmol) in CH_2Cl_2 (5 ml) was added dropwise to a stirred solution of oxalyl chloride (3.0 g, 24 mmol) in CH_2Cl_2 (15 ml) at -78°C, followed by the addition of **2** (5.0 g, 21 mmol) in CH_2Cl_2 (20 ml). After stirring for 30 min, the mixture was treated dropwise with triethylamine (6.3 g, 63 mmol) and allowed to warm up to room temp. The solution was washed two times with water (2 x 10 ml), dried (Na_2SO_4), and evaporated. The crude orange oil (5.0 g) was purified by cc on silica gel (n-pentane/ethyl acetate 7 + 3): 4.7 g (94%) of pure product were obtained as a yellow oil.- IR (film): $\tilde{\nu}$ = 3080; 3060; 3030; 2850b; 2720w; 1725s; 1600w; 1495; 1455; 750; 705 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ = 3.20 (d, J = 2 Hz, 2H, C$\underline{H}_2$CHO), 3.68 (s, 4H, CH$_2$N), 7.30 (mc, 10 H, Ar-H), 9.43 (t, J = 2 Hz, 1H, CHO).- MS (70 eV) m/z (%) = 106 (100), 91 (99).- $C_{16}H_{17}NO$ (239.3) Calcd. C 80.29 H 7.17 N 5.85 Found C 80.12 H 7.09 N 6.02.

(S)-O-Benzyl-N,N-dibenzylserine benzylester (**6a**)

6a was prepared from *O*-Benzyl-L-serine (2.5 g, 13 mmol) as described for **2**, yielding 8.5 g (71%) as a pale yellow oil after cc on silica gel (n-hexane/Et_2O 8+2); $[\alpha]^{20}_D$ (c = 1, ethyl acetate): -48.5. IR (film): $\tilde{\nu}$ = 3080; 3060; 3030; 2900b; 1725s; 1600w; 1493; 1451; 745; 700 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ = 3.66 (d, J = 14 Hz, 2H, NCH$_2$), 3.7-3.8 (m, 3H, CHCH$_2$), 3.90 (d, J = 11 Hz, 2H, NCH$_2$), 4.40 (d, J = 12 Hz, 1H, PhCH$_2$O), 4.45 (d, J = 12 Hz, 1H, PhCH$_2$O), 5.19 (d, J = 12 Hz, 1H, COOCH$_2$), 5.25 (d, J = 12 Hz, 1H, COOCH$_2$), 7.2-7.4 (m, 20 H, Ar-H).- ^{13}C-NMR ($CDCl_3$): δ = 55.4 (CH_2N), 60.9 (CHN), 66.1 (CHCH$_2$), 69.5 (OCH$_2$-aryl), 73.2 (CH_2OOC), 126.7-129.8, 136.0, 138.0, 139.6 (arom. C-atoms), 171.3 (C=O).- MS (70 eV) m/z (%): 465 (0.3, M$^{+\cdot}$), 91 (100), 44 (5.5).- $C_{31}H_{31}NO_3$ (465.6) Calcd. C 79.96 H 6.72 N 3.01 Found C 80.15 H 6.72 N 3.15.

(2)-O-Benzyl-N,N-dibenzyl-2-amino-1,3-propanediol (**7a**)

A suspension of $LiAlH_4$ (0.6 g, 13.5 mmol) in dry diethyl ether (10 ml) was cooled to 0°C. A solution of (**6a**) (8.0 g, 17.1 mmol) in diethyl ether (5 ml) was added dropwise. The mixture was stirred for 1 h at 0°C and for 12 h at room temp. Water (0.6 ml), 3 M NaOH (0.6 ml) and water (0.6 ml) were added at 0°C. After refluxing for 1 h, the precipitate was filtered off. The filtrate was shaken with 2 M HCl (15 ml), resulting in the formation of three phases; the two lower (aqueous) ones containing the hydrochloride of (**7a**). After basification of the aqueous phases to pH 9 with 3 M NaOH, they were extracted two times with diethyl ether (20 ml). The extracts were dried (Na_2SO_4) and evaporated, leaving a yellow oil (8.0 g). It was used without further purification. For analytical purposes, 1.00 g was purified by cc on silica gel (ethyl acetate/hexane 3 + 2): 0.84 g (84%) of colourless oil, $[\alpha]^{20}_D$ (c = 1, ethyl acetate): +65.4.- IR (film): $\tilde{\nu}$ = 3340b; 3080; 3060; 3030; 2900b; 1600s; 1491; 1451; 750; 700 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ = 3.12-3.15 (m, 1H, CH), 3.53-3.73 (m, 4H, OCH$_2$, C$\underline{H}_2$OH), 3.59 (d, J = 13 Hz, 2H, NCH$_2$), 3.80 (d, J = 13 Hz, 2H, NCH$_2$), 4.49 (d, J = 12 Hz, 1H, PhCH$_2$O), 4.52 (d, J = 12 Hz, 1H, PhCH$_2$O), 7.2-7.4 (m, 15 H, Ar-H).- ^{13}C-NMR ($CDCl_3$): δ = 54.1 (CH_2N), 58.3 (CHN), 59.7 (CH$\underline{C}$H$_2$O), 68.0 (CH_2OH), 73.4 (OCH$_2$C$_6$H$_5$), 127.1, 127.5, 127.7, 128.4, 128.4, 129.0, 138.1, 139.5 (arom. C-atoms).- MS (70 eV) m/z (%): 361 (0.22, M$^{+\cdot}$), 330 (10), 91 (100).- $C_{24}H_{27}NO_2$ (361.5) Calcd. C 79.73 H 7.54 N 3.88 Found C 79.66 H 7.46 N 3.79.

(2S)-O-Benzyl-N,N-dibenzyl-propanal (**8a**)

8a was prepared from **7a** (7.0 g, 19 mmol) as described for **3**, yielding 6.2 g (92%) of a pale yellow oil after cc on silica gel (n-hexane/ethyl acetate 3 + 7). **8a** quickly decomposes on storage at room temp. when exposed to air. The optical purity was confirmed by reduction of **8a** with $LiAlH_4$ and conversion into the *Mosher* ester. The ^{19}F NMR spectrum showed an ee of 91%; $[\alpha]^{20}_D$ (c = 1, ethyl acetate): +5.6.- IR (film): $\tilde{\nu}$ = 3410(b); 3080; 3060; 3030; 2850(b); 1730(s); 1600; 1491; 1451; 750; 700 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ = 3.90 (mc, 3H, CH$_2$CH), 3.82 (s, 4H, NCH$_2$), 4.50 (s, 2H, PhCH$_2$O), 7.33 (mc, 15 H, Ar-H), 9.65 (s, 1H, CHO).- MS (70 eV) m/z (%): 359 (0.03, M$^{+\cdot}$), 91 (100).- $C_{24}H_{25}NO_2$ (359.5) Calcd. C 80.18 H 7.02 N 3.90 Found C 79.48 H 6.83 N 3.88. Because of the instability of this aldehyde, a better analysis could not be obtained.

(2)-N,N-Dibenzylalanine benzylester (**6b**)

6b was prepared from L-alanine (5.0 g, 56 mmol) according to **2**, yielding 15.1 g (70%) of a pale yellow oil after cc on silica gel (n-pentane/Et_2O); $[\alpha]^{20}_D$ (c = 1, ethyl acetate): -91.8°.- IR (film): $\tilde{\nu}$ = 3090; 3065; 3030; 2900b; 1730s; 1600w; 1495; 1455; 745; 705 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ = 1.33 (d, J = 7 Hz, 3H, CH$_3$), 3.50 (q, J = 7 Hz, 1H, CH), 3.60 (d, J = 14 Hz, 2H, NCH$_2$), 3.81 (d, J = 14 Hz, 2H, NCH$_2$), 5.15 (d, J = 12 Hz, 1H, OCH$_2$), 5.22 (d, J = 12 Hz, 1H, OCH$_2$), 7.2-7.4 (m, 15 H, Ar-H).- ^{13}C-NMR ($CDCl_3$): δ = 14.9 (CH$_3$), 54.3 (CH_2N), 56.1 (CHN), 72.0 (CH_2OOC), 126.9-129.0, 139.7 (arom. C-atoms), 173.5 (C=O).- MS (70 eV) m/z (%): 230 (0.1), 91 (100).- $C_{24}H_{25}NO_2$ (359.5) Calcd. C 80.18 H 7.02 N 3.90 Found C 80.10 H 6.82 N 4.02.

(S)-N,N-Dibenzyl-2-amino-1-propanol (**7b**)

A solution of crude **6b** (18.0 g, 71 mmol) in diethyl ether (20 ml) was added dropwise to a suspension of $LiAlH_4$ (2.2 g, 56 mmol) in diethyl ether (40 ml) at 0°C. The mixture was stirred for 1 h at 0°C and for 12 h at room temp. Water (2 ml), 3 M NaOH (2 ml) and water (2 ml) were added at 0°C. After refluxing for 1 h, the precipitate was filtered off. The filtrate was acidified by shaking with 2 M HCl. After basification of the aqueous phase to pH 9 with 3 M NaOH, it was extracted two times with diethyl ether (50 ml). Drying (Na_2SO_4) and evaporation left a yellow oil (9.2 g). It

was frozen in liquid N_2 and treated with ice-cold pentane to afford 5.6 g (56%) of white crystals, mp. 41°C, $[\alpha]^{20}_D$ (c = 1, ethyl acetate): +53.6.- IR (KBr): $\tilde{\nu}$ = 3450b; 3080; 3060; 3025; 2900b; 1600w, 1491; 1451; 752; 749; 730 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ = 0.95 (d, J = 6.6 Hz, 3H, CH_3), 2.97 (m, 1H, CH), 3.30 (d, J = 13 Hz, 2H, NCH_2), 3.29-3.46 (m, 2H, CH_2OH), 3.80 (d, J = 13 Hz, 2H, NCH_2), 7.30 (mc, 10 H, Ar-H).- ^{13}C-NMR ($CDCl_3$): δ = 8.6 (CH_3), 52.9 (CH_2N), 54.1 (CHN), 62.7 (CH_2OH), 127.2, 128.5, 129.0, 139.3 (arom. C-atoms).- MS (70 eV) m/z (%): 255 (0.3, $M^{+\cdot}$), 91 (100).- $C_{17}H_{21}NO$ (255.4) Calcd. C 79.93 H 8.31 N 5.49 Found C 79.85 H 8.27 N 5.68.

(S)-N,N-Dibenzyl-2-aminopropanal (**8b**)

8b was prepared from **7b** (5.0 g, 20 mmol) (cf. **3**), yielding 5.0 g of a yellow oil (5.0 g). After six days at 0°C, it became a solid which was washed with cold n-pentane and dried *in vacuo*. **8b** quickly decomposes on storage at room temp. when exposed to air. Yield 4.7 g (93%), mp. 55.5°C, $[\alpha]^{20}_D$ (c = 1, ethyl acetate): -35.1.- IR (film): $\tilde{\nu}$ = 3090; 3060; 3030; 2900b; 2705w; 1725s; 1605w; 1495; 1455; 750; 705 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ = 1.15 (d, J = 7 Hz, 3H, CH_3), 3.27 (q, J = 7 Hz, 1H, CH), 3.57 (br s, 2H, NCH_2), 3.63 (br s, 2H, NCH_2), 7.40 (mc, 10 H, Ar-H), 9.67 (s, 1H, CHO).- MS (70 eV) m/z (%): 224 (68), 91 (100).- $C_{17}H_{19}NO$ (253.4) Calcd. C 80.58 H 7.57 N 5.53 Found C 81.18 H 7.46 N 5.79. Because of the instability of the aldehyde, a better analysis could not be obtained.

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