PREPARATION OF N-PROTECTED α-AMINO ALCOHOLS BY ACETOXYBOROHYDRIDE REDUCTION OF N-PROTECTED α-AMINO ACID ESTERS

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N-Protected α-amino alcohols were prepared by reduction of N-protected α-amino acid esters by sodium acetoxyborohydride in dioxane at elevated temperature. The reductions proceed with excellent yields and without racemisation. Reduction of the carbamate protecting groups was not observed.

Optically active N-protected α-amino alcohols, derived from natural α-amino acids are frequently used as precursors for preparation of N-protected α-amino aldehydes in stereocontrolled organic synthesis[1]. Several procedures for reduction of N-protected α-amino acids and esters have been reported[2-7]. Lithium aluminium hydride[2] and diisobutyl aluminium hydride[3], reagents of general use for carboxyl reductions, were found unsuitable for reduction of N-protected α-amino esters because of their detrimental effect on protecting groups[4]. Reduction of Boc-amino acids by a borane--tetrahydrofuran complex is reported[4] as smooth, but our inspection of published data on optical rotations of Boc-amino alcohols obtained revealed that the enantiomeric homogeneity was lost. Several reductions of N-protected α-amino acid esters by metal borohydrides were described[5-7]. However, these methods often require large excess of borohydride and long reaction times. Recently, in attempts to prepare peptides with reduced amide bond[8], we have treated dipeptide Z-Leu-Gly--OEt with sodium acetoxyborohydride in dioxane, a reagent used once[9] for this purpose. Surprisingly, spectral properties of single reaction product formed in very high yield (98%) were in disagreement with formula expected according to literature[9]. From IR spectrum followed that the amide bond as well as the carbamate bond were conserved. The suggestion that the product was N-protected peptide alcohol was corroborated by ^{1}H NMR spectrum where resonances for CH_2OH group protons were identified.

The stereoselectivity of this reduction and high yield of peptide alcohol led us to investigate this reaction more closely, with large-scale preparation of N-protected α-amino alcohols as the aim of our effort. We have found that the best yields could

be obtained by heating of N-protected α-amino acid esters with 2–5 molar excess of sodium acetoxyborohydride in dioxane at temperatures between 50–80°C. In some experiments the yields of N-protected α-amino alcohols were unsatisfactory (40–60%). We have discovered that low efficiency of the reduction was caused by some impurities formed from sodium borohydride in the course of long storage (sodium borohydride content lower than 94%). The choice of solvent is not critical: the same results were obtained in tetrahydrofuran or N,N-dimethylformamide. Acetoxyborohydride reagent could be prepared in situ by slow addition of acetic acid to a mixture of N-protected α-amino acid ester and sodium borohydride in a solvent or a suitable solvent mixture. In small-scale experiments it was found advantageous to prepare the reagent separately[10].

Reaction time is only slightly dependent on the nature of the ester bond (methyl, ethyl and benzyl esters were tested). Generally, the reduction is finished in one to three hours. Free carboxyl groups are reduced as well, but at considerably slower rate. We have never observed reduction of carbamate amide bond in common N-protecting groups.

The merit of the acetoxyborohydride reagent is in the racemisation-free ester bond reduction. This conclusion based on the data taken from Table I was corroborated as follows: Boc-phenylalanine was esterified by diazomethane and the methyl ester was reduced to Boc-phenylalaninol. Oxidation of this alcohol by potassium permanganate[11] afforded Boc-phenylalanine with optical rotation identical with starting material.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. ^{1}H NMR spectra were recorded on Varian XL-200 spectrometer (FT mode) at 200·01 MHz in deuterochloroform with tetramethylsilane as internal standard. Optical rotations at 589 nm were measured with Perkin–Elmer 141 MC polarimeter at 20°C with a cell of 1·00 dm path-lenght. Thin-layer chromatography were carried out on Merck GF_{254} 60 silica gel plates (thickness 0·25 mm), in solvent system hexane–ethyl acetate–methanol–acetic acid 40 : 15 : 4 : 1 (S1) or hexane–tert-butyl methyl ether 2 : 1 (S2). Visualization was done with UV light and/or ninhydrin, or chlorine and starch-iodine reagent, or by spraying with 5% solution of cerium(VI) sulphate in 2M-H_2SO_4 and pyrolysis. Peroxide free dioxane and tetrahydrofuran were stored over a A4 molecular sieves in argon atmosphere.

Reduction of N-Protected α-Amino Acid Methyl Esters

A) Solution of acetic acid (11·4 ml, 0·20 ml) in dioxane (60 ml) was added dropwise over a period of 20–30 min to a suspension of sodium borohydide (7·56 g, 0·20 mol) and N-protected α-amino acid ester (0·05 mol) in dioxane (120 ml) at 10–15°C (hydrogen is evolved). The resulting mixture was then warmed to 80°C and kept at this temperature until the amino ester disappeared (TLC, S2). The solution was cooled to ambient temperature and with stirring and cooling (ice-water) methanol (100 ml) was added. The solvents were evaporated and the residue

was distributed between 1M sodium bicarbonate and tert-butyl methyl ether (or ethyl acetate). Organic layer was washed with brine, dried over magnesium sulfate and evaporated to drynes. The residue was crystallized from tert-butyl methyl ether–hexane. Properties and yields of prepared N-protected α-amino alcohols are given in Tables I and II.

B) A solution of sodium acetoxyborohydride[10] (2·0 mmol) in tetrahydrofuran was added dropwise to a stirred solution of Z-Leu-Gly-OEt (175 mg, 0·5 mmol) in tetrahydrofuran at reflux temperature. After 65 min (no ester detected by TLC, S2) the reaction mixture was worked up as above.

Oxidation of Boc-phenylalaninol to Boc-phenylalanine

Boc-L-Phenylalanine ($[\alpha]_D^{20}$ +24·5° (*c* 1·0, C_2H_5OH), m.p. 84–85°C) was converted to its methyl ester by diazomethane in diethyl ether–methanol solution. This ester was reduced to

TABLE I

Analytical data and yields of prepared N-protected α-amino alcohols

Alcohol Method	Yield, % M.p., °C	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)	Formula (M.w.)	Calculated/Found		
				% C	% N	% H
Boc-L-Phe-ol	90	−23·5 (1·0)[a]	$C_{14}H_{21}NO_3$	66·91	5·57	8·42
A	93–94[b]		(251·3)	66·84	5·67	8·30
Z-L-Phe-ol	82	−28·6 (1·0)[c]	$C_{17}H_{19}NO_3$	71·56	4·91	6·71
A	91–92[d]		(285·3)	71·44	5·14	6·61
Fmoc-L-Phe-ol	98	−25·0 (1·0)	$C_{24}H_{23}NO_3$	77·19	3·75	6·21
A	165·5–166·5		(373·5)	77·13	3·85	6·20
Boc-L-Pro-ol	84	−47·5 (1·0)	$C_{10}H_{19}NO_3$	59·68	6·96	9·52
A	57–58[e]		(201·3)	59·89	7·03	9·40
Boc-L-Ile-ol	86[f]	−18·3 (0·2)	$C_{11}H_{23}NO_3$	60·80	6·45	10·67
A	53–54		(217·3)	60·45	6·60	10·77
Boc-L-Ala-ol	91	−11·6 (0·6)[g]	$C_8H_{17}NO_3$	54·84	7·99	9·78
B	53–54·5		(175·2)	54·62	8·20	9·64
Boc-L-Arg(Tos)-ol	88	−8·6 (0·3)	$C_{18}H_{30}N_4O_5S$	52·16	13·52	7·29
A	—[h]		(414·5)	52·50	13·33	7·37
Boc-L-Cys(PMB)-ol[i]	98	−6·7 (0·8)	$C_{16}H_{25}NO_3S$	61·71	4·50	8·09
B	71–72		(311·4)	61·70	4·73	8·00
Z-L-Leu-Gly-ol	98	−12·0 (0·3)	$C_{16}H_{24}N_2O_4$	62·32	9·08	7·84
B	124–126		(308·4)	62·13	9·08	7·60

[a] Ref.[7] −24·6° (*c* 1·1, $CHCl_3$); [b] ref.[7] m.p. 94·5°C; [c] −37·5° (*c* 1, C_2H_5OH), ref.[7] −41·8° (*c* 1·4, C_2H_5OH); [d] ref.[3] m.p. 90–92°C; [e] ref.[12] m.p. 57–58°C; [f] without crystallization; [g] ref.[4] −1·0° (*c* 1·3, $CHCl_3$); [h] amorphous solid; [i] PMB — *p*-methylbenzyl.

TABLE II

^{1}H NMR (δ in ppm, (J in Hz)) of α-aminoalcohols

Alcohol	CH_2OH		α	β	γ	δ	Boc	NH
Boc-L-Phe-ol[a]	3·55 dd (5·2, 10·9)	3·67 dd (3·8, 10·9)	3·88 m (3·8, 5·2, 3 × 7·2)	2·84 d (7·2)	—	—	1·41 s	4·79 bs
Z-L-Phe-ol[b]	3·56 dd (5·0, 11·2)	3·67 dd (3·8, 11·2)	3·94 m (3·8, 5·0, 3 × 7·1)	2·85 d (7·1)	—	—	—	5·03 bs
Fmoc-L-Phe-ol[c]	3·63 m (2 H)		3·92 m	2·86 d (6·4)	—	—	—	4·93 bs
Boc-L-Pro-ol	3·57 dd (6·8, 11·0)	3·63 dd (4·4, 11·0)	1·70—2·10 m			3·31 dt (2 × 6·7, 11·0) 3·45 dt (2 × 6·8, 11·0)	1·47 s —	—
Boc-L-Ile-ol	3·60 dd (6·4, 10·8)	3·72 dd (3·6, 10·8)	3·50 m (3·6, 2 × 6·4, 7·3)	2·56 m	1·50 m 0·92 d (6·9)	0·91 t (2 × 7·3)	1·45 s	4·69 bs
Boc-L-Ala-ol	3·50 dd (7·3, 10·8)	3·64 dd (3·6, 10·8)	3·78 m (3·6, 3 × 6·8, 7·3)	1·15 d (6·8)	—	—	1·45 s	4·65 bs
Boc-L-Arg(Tos)-ol[d]	3·48 m (2 H)		3·53 m	1·28—1·60 m		3·15 m	1·34 s	5·05 bs
Boc-L-Cys(PMB)-ol[e]	3·62 dd (6·4, 10·6)	3·72 dd (3·4, 10·6)	3·70 m	2·60 d (6·0)	—	—	1·45 s	4·92 bs
Z-L-Leu-Gly-ol[f]								
Gly	3·67 m (2 H)		3·40 m (2 H)	—	—	—	—	6·53 bs
Leu	—	—	4·15 dt (5·3, 2 × 8·4)	1·46—1·69 m		0·93 d (6·4) 0·94 d (6·4)	—	5·22 bd (8·4)

Other signals: [a] 7·17—7·36 m, 5 H (arom-H); [b] 7·13—7·40 m, 5 H (arom-H), 5·06 s, 2 H (CH_2Ph); [c] 7·02—7·58 m, 13 H (arom-H), 4·31 m, 2 H (CH_2-fluorenyl); [d] 7·15 m, 2 H (arom-H), 7·66 m, 2 H (arom-H), 2·32 bs, 3 H (CH_3); [e] 7·11 m, 2 H (arom-H), 7·21 m, 2 H (arom-H), 3·70 s, 2 H (SCH_2), 2·33 bs, 3 H (CH_3); [f] 7·27—7·36 m, 5 H (arom-H), 5·09 s, 2 H (CH_2Ph).

Boc-phenylalaninol by the procedure described ad *A*. Crude Boc-phenylalaninol (125 mg, 0·5 mmol) suspended in 0·2M-NaOH (3·25 ml) was treated with finely ground $KMnO_4$ (103 mg, 0·65 mmol) at 20°C with vigorous stirring. Progress of the reaction was followed by TLC. Dark heterogeneous mixture was decolorized by addition of aqueous 37% $NaHSO_3$. Homogeneous clear solution was acidified to pH 3 by 20% citric acid and extracted with tert-butyl methyl ether. Organic phase was washed with brine, dried over magnesium sulfate and the solvent was evaporated. The product (110 mg, 83%) was identified by TLC (S1, single spot, R_F 0·20) as Boc-phenylalanine, m.p. 83–85°C, $[\alpha]_D^{20}$ +24·3° (*c* 1·0, C_2H_5OH).

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