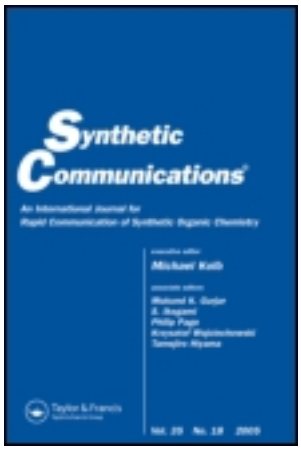

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One-Pot Synthesis of *N*-Protected β-Chiral Amino Alcohols

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ABSTRACT

N-tert-butyloxycarbonyl-*S*-benzyl-cysteine, *N*-fluorenylmethyloxy-carbonyl-alanine-, *S*-trityl-cysteine-, *O-tert*-butyl-serine- and *O-tert*-butyl-tyrosine were converted to the corresponding alcohols via sodium borohydride reduction of their in situ formed methyl esters. Enantiopurity of the products was checked by chiral HPLC method.

Key Words: Amino alcohols; Reduction; Enantiopurity.

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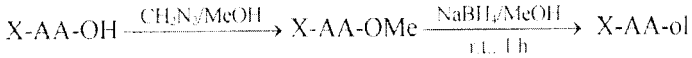
We report a convenient practical synthetic method for conversion of *N*-protected amino acids to the corresponding *N*-protected amino alcohols by sodium borohydride reduction at room temperature via in situ formation of their methyl esters. Fmoc-Ala-OMe, Fmoc-Cys(Trt)-OMe, Boc-Cys(Bzl)-OMe, Fmoc-Ser(^{t}Bu)-OMe and Fmoc-Tyr(^{t}Bu)-OMe can be obtained by direct esterification of the corresponding amino acids with etheric solution of diazomethane (instead of trimethylsilyldiazomethane in 20% methanol-benzene[1,2] or by methyl iodide and $KHCO_3$ in DMF[3]). Starting materials were dissolved in methyl alcohol at room temperature and their methyl esters were formed immediately after dropping the reagent solution prepared from *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine as usual.[4] Sodium borohydride was added in small portions and we found, that this reduction step can be completed in one hour, checked by TLC. Cooling of the reaction mixtures was unnecessary. Simple extraction with ethyl acetate was used to isolate Fmoc-Ala-ol (**1**), Fmoc-Cys(Trt)-ol (**2**, new compound), Boc-Cys(Bzl)-ol (**3**), Fmoc-Ser(^{t}Bu)-ol (**4**, new compound) and Fmoc-Tyr(^{t}Bu)-ol (**5**) from the reaction mixtures in 85–95% yield and no silica gel column chromatography was needed for final purification of the products. Physical data of the products are listed in Tables 1 and 2.

Enantiopurity of the synthesized *N*-protected amino alcohols (hence the degree of racemization of the hydride reductions) was measured by chiral HPLC method. The stereoisomer *N*-protected amino alcohols were separated on Chirobiotic T column. Table 3 depicts the chromatographic data (capacity factors of the enantiomers, separation factors and D-amino acid content) and also the degree of racemization in the hydride reduction process which practically showed less than 1% in all cases.

In conclusion, we offer here a straightforward hydride reduction method for the synthesis of enantiopure *N*-protected amino alcohols from the corresponding *N*-protected amino acids via their methyl esters.



X = Boc. Fmoc
AA = amino acid

1 X = Fmoc, AA = Ala
2 X = Fmoc, AA = Cys(Trt)
3 X = Boc, AA = Cys(Bzl)
4 X = Fmoc, AA = Ser(^{t}Bu)
5 X = Fmoc, AA = Tyr(^{t}Bu)

Reaction Scheme

Table 1. Compounds **1–5** prepared.

Product	Yield (%)	M.p. (°C)	TLC[a] (R_f)	HPLC t_R (min)	$[\alpha]_{546}$ ($c=1$)
1	93	157–158	0.23	8.16	−1.0
2	89	152–153	0.37	12.87	+37.0
3	95	56–58	0.44	9.19	−20.0
4	85	95–97	0.29	10.93	+20.5
5	91	152–153	0.32	15.68	−52.0

[a]EtOAc:*n*-hexane (1:1) solvent mixture.

Table 2. ^{1}H NMR data of *N*-protected amino alcohols **1–5**.

Product	^{1}H NMR ($CDCl_3$/TMS), δ(ppm), *J*(Hz)
1	1.18 (s, 3H, CH_3), 2.35 (b, 1H, OH), 3.55 (b, 2H, CH_2OH), 3.80 (b, 1H, NH), 4.25 (b, 1H, CH_α), 4.45 (d, 2H, $J=1.90$, CH_2), 4.93 (b, 1H, CH), 7.31–7.78 (8H, $CH_{aromatic}$)
2	2.03 (b, 1H, OH), 2.44 (s, 2H, CH_2S), 3.45 (b, 2H, CH_2OH), 3.51(b, 1H, NH), 4.36 (d, 2H, $J=6.69$, CH_2), 4.20 (b, 1H, CH_α), 4.88 (d, 1H, $J=1.55$, CH), 7.18–7.35 (15H, $CH_{aromatic}$), 7.31–7.72 (8H, $CH_{aromatic}$)
3	1.42 (s, 9H, ^{t}Bu), 2.30 (b, 1H, OH), 2.58 (s, 2H, CH_2S), 3.12 (b, 2H, CH_2OH), 3.63 (b, 1H, NH), 3.75 (s, 2H, CH_2), 4.11 (b, 1H, CH_α), 7.10–7.33 (5H, $CH_{aromatic}$)
4	1.18 (s, 9H, ^{t}Bu), 2.99 (b, 1H, OH), 3.58 (s, 2H, CH_2O^tBu), 3.81 (b, 2H, CH_2OH), 3.85 (b, 1H, NH), 4.22 (b, 1H, CH_α), 4.38 (d, 2H, $J=1.13$, CH_2), 5.53 (b, 1H, CH), 7.30–7.74 (8H, $CH_{aromatic}$)
5	(CH_2), 5.00 (b, 1H, CH), 6.59–7.05 (4H, $CH_{aromatic}$), 7.30–7.74 (8H, $CH_{aromatic}$)

The attractive features of this method (which can be applied principally for the conversion of each naturally occuring α-amino acid into β-functionalized amino alcohols) are mild reaction conditions, short reaction time, easy work-up, excellent yields and negligible racemization. Methyl ester formation of *N*-protected amino acids using diazomethane takes place in a few moments in contrast to other methods and isolation of the esters was unnecessary. *N*-protected amino alcohols might have important application for synthesis of biologically active peptide analogues containing C-terminal hydroxymethyl functional group.

Table 3. Chromatographic and racemization data of *N*-protected amino alcohols **1–5**.

	k'			Racemization data	
Product	L	D	α	D (%)	Racemization (%)
1	0.96	2.33	2.42	0.43	0.86
2	1.01	2.33	2.31	0.14	0.28
3	0.84	2.19	2.61	0.02	0.04
4	0.92	2.33	2.53	0.15	0.30
5	0.91	2.32	2.55	0.04	0.08

k' Retention factor.
α Separation factor.

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EXPERIMENTAL

All reagents and solvents were of reagent grade and purchased from commercial sources. Melting points were determined using a PAMK VEB apparatus and are uncorrected. TLC was performed on 60 F_{254} silica gel precoated glass plates. Spots on TLC plates were visualized with TMD reagent (*N*,*N*,*N*′*N*′-tetramethyl-4,4′-diaminodiphenylmethane) after chlorination. The chemical purities of the products **6–10** (97–99.5%) were checked by HPLC (column: LiChrosorb-100 10 RP 18, 250 × 4 mm, eluents: A: 0.1% TFA/H_2O, B: 80% MeCN in A, gradient: 80 → 100% B for 20 min, flow rate: 1.2 mL/min, detection: UV at 220 nm). The HPLC system applied for chiral analyses consisted of an M-600 low-pressure gradient pump, an M-996 photodiode-array detector (205 nm) and a Millenium[1] chromatography Manager data system (Water Chromatography, Milford, MA, USA). The chromatographic system was equipped with a Rheodyne Model 7125 injector (Cotati, CA, USA) with 20 μL loop. The column (250 × 4.6 mm, 5 μm particle size) used for analytical separation was Chirobiotic T, bonded with macrocyclic glycopeptide antibiotic teicoplanin as chiral detector (Astec, Whippany, NJ, USA). The chromatograph was operated isocratically with a flow rate of 1 mL/min and with MeOH/H_2O, 10:90 (v/v) eluent system at 20°C.

^{1}H NMR were recorded at 500 MHz with a Bruker DRX instrument. Optical rotations were measured in MeOH with a Polamat-A polarimeter (Carl Zeiss, Jena) at 22°C, $\lambda = 546$ nm. Microanalysis were made on a CHN Analyser (Prague).

General Procedure for the Synthesis of *N*-Protected Amino Alcohols 1–5

For generation of diazomethane, a mixture of diethyl ether (20 mL) and 40% aqueous KOH solution (5 mL) was cooled to 0°C and crystalline *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine (1.5 g) was added in portions with shaking. The yellow diazomethane solution was separated, dried on solid KOH, then dropped to the *N*-protected starting materials (10 mmol of each) dissolved in MeOH (40–50 mL) under stirring for 10–15 min. After checking by TLC, $NaBH_4$ (10 equiv.) was added in portions at room temperature in 1 h. The mixture was evaporated in vacuo, the residue was acidified with 10% $NaHSO_4$ solution and extracted with EtOAc (50 mL). The organic layer was washed successively with water, 10% $NaHCO_3$ solution and water, dried with Na_2SO_4, filtered and evaporated. The crude products were recrystallized from EtOAc/*n*-hexane solvent mixture to give the *N*-protected amino alcohols **1**, **2**, **3**, **4**, and **5**.

Fmoc-Ala-ol (1): $C_{18}H_{19}NO_3$ (297.39), calcd. C (72.69%), H (6.44%), N (4.71%), found C (72.43%), H (6.21%), N (4.60%).

Fmoc-Cys(Trt)-ol (2): $C_{37}H_{33}NO_3S$ (571.74), calcd. C (77.72%), H (5.82%), N (2.45%), found C (77.58%), H (5.60%), N (2.31%).

Boc-Cys(Bzl)-ol (3): $C_{15}H_{23}NO_3S$ (297.42), calcd. C (60.57%), H (7.80%), N (4.71%), found C (60.23%), H (7.58%), N (4.59%).

Fmoc-Ser(^{t}Bu)-ol (4): $C_{22}H_{27}NO_4$ (369.47), calcd. C (71.51%), H (7.37%), N (3.79%), found C (71.37%), H (7.25%), N (3.73%).

Fmoc-Tyr(^{t}Bu)-ol (5): $C_{28}H_{31}NO_4$ (445.56), calcd. C (75.47%), H (7.01%), N (3.14%), found C (75.21%), H (6.88%), N (3.03%).

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