

A Convenient One-Pot Conversion of *N*-Protected Amino Acids and Peptides into Alcohols

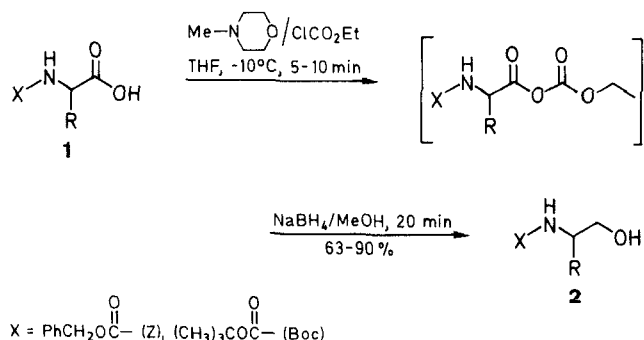
George Kokotos

Department of Chemistry, University of Athens, 13A Navarinou Str., Athens 10680, Greece

N-Protected amino acids and peptides are converted to alcohols by chemoselective reduction of their corresponding mixed anhydrides with sodium borohydride in tetrahydrofuran with dropwise addition of methanol.

N-Protected amino alcohols and peptide alcohols are important synthetic intermediates,¹ especially useful in the synthesis of peptide aldehydes which are potent inhibitors of proteases.² Some biologically active peptides, e.g. enkephalins, exhibit better biological activity when their terminal carboxyl group is reduced to a hydroxymethyl group.³ *N*-protected amino and peptide alcohols can be prepared by reduction of alkyl esters of amino acids^{4,5} and peptides,⁴ and active esters of amino acids⁶ with sodium borohydride. Borane tetrahydrofuran complex has also been used for the direct reduction of *N*-protected amino acids,⁷ but this method is limited only to the reduction of amino acids.

We report here a convenient one-pot conversion of *N*-protected amino acids and peptides to alcohols by chemoselective reduction of their corresponding mixed anhydrides. The mixed anhydrides of *N*-protected amino acids and peptides with monoethyl carbonates were prepared *in situ* in tetrahydrofuran by conventional methods.⁸ As previously demonstrated,⁹ the reducing power of sodium borohydride increases in tetrahydrofuran when methanol is added dropwise during the reaction. Following this procedure, the mixed anhydrides of *N*-protected amino acids and peptides **1** were reduced rapidly at 0°C in good to high yields with retention of optical activity (Table).



The advantages of this method are that the disulfide bridge of cystine, and also the methyl or benzyl ester groups used for the protection of ω -carboxyl of glutamic and aspartic acid, remain unaffected under the described conditions; esters are reduced by sodium borohydride at elevated temperature.^{4,10} By this reducing procedure the peptide bond and the *N*-terminal urethane bond of benzyloxycarbonyl (Z) or *tert*-butoxycarbonyl (Boc) protective groups are not reduced.

We also studied the influence of the nature of monoalkyl carbonate mixed anhydride on the reaction yield. As shown in the Table (product **2a**) the mixed anhydride of *N*-benzyloxycarbonyl-L-phenylalanine with monoethyl carbonate was more effective than those with mono-isobutyl or monobenzyl carbonates. The difference between the determined values of specific rotations (Table, products **2e** and **2h**) and those reported for the borane/tetrahydrofuran method⁷ show that our method gives products of higher chemical and optical purity.

In conclusion, the present reducing procedure is a rapid and convenient method, which can be applied to both *N*-protected amino acids and peptides and permits a selective conversion of their carboxyl group to a hydroxymethyl group in the presence of other functional groups under mild conditions.

Melting points were measured with a Büchi apparatus and are uncorrected. $[\alpha]_D$ were measured at 25°C on a Perkin-Elmer 141 polarimeter. IR spectra were recorded on a Perkin-Elmer 283 B IR spectrophotometer, and ¹H-NMR spectra at 60 MHz on a Varian EM 360 spectrometer.

All amino acids (L configuration) were purchased from Fluka Chemical Co. THF was passed through a column of aluminum oxide, distilled over CaH₂ and stored over molecular sieves. *N*-Methylmorpholine was distilled from ninhydrin. Isobutyl chloroformate was distilled and stored over CaCO₃. All other solvents and chemicals were of reagent grade and used without further purification.

N-Protected Amino and Peptide Alcohols **2**; General Procedure:

To a stirred solution of *N*-protected amino acid or peptide **1** (1 mmol) in THF (5 mL) at -10°C, *N*-methylmorpholine (0.101 g, 1 mmol) is added, followed by ethyl chloroformate (ethyl car-

Table. *N*-Protected Amino and Peptides Alcohols 2 Prepared

Prod- uct	(L)	Yield (%)	mp (°C) (solvent) ^a	Molecular Formula ^b or Lit. mp (°C)	[α] _D (c, solvent)		IR (KBr) ν (cm ⁻¹)	¹ H-NMR (CDCl ₃ /TMS) δ, J (Hz)
					found	reported		
2a	Z-Phe-ol	84 ^c	87–88 (A)	90–91 ⁴ 90 ¹¹	–41.1° (2, MeOH)	–42.0° ¹¹ (2, MeOH)	3350 (OH, NH), 1690 (C=O)	2.90 (d, 2H, <i>J</i> = 7), 3.45–4.10 (m, 3H), 5.05 (s, 2H), 7.30 (s, 5H), 7.35 (s, 5H)
2b	Z-Ala-ol	71	55–56 (A)	58 ¹¹	–6.5° (1, CHCl ₃)	–	3320 (OH, NH), 1690 (C=O)	1.15 (d, 3H, <i>J</i> = 7), 3.40–4.15 (m, 3H), 5.05 (s, 2H), 7.35 (s, 5H)
2c	Z-Gly-ol	64	58–59 (A)	62.0–62.5 ¹²	–	–	3325 (OH, NH), 1690 (C=O)	3.35 (t, 2H, <i>J</i> = 6), 3.70 (t, 2H, <i>J</i> = 6), 5.05 (s, 2H), 7.35 (s, 5H)
2d	Z-Glu(OMe)-ol	78	64–66 (A)	C ₁₄ H ₁₉ NO ₅ (281.3)	–18.2° (1, CHCl ₃)	–	3310 (OH, NH), 1730 (ester C=O), 1685 (amide C=O)	1.95 (m, 2H), 2.45 (t, 2H, <i>J</i> = 7), 3.40–4.10 (m, 3H), 3.70 (s, 3H), 5.05 (s, 2H), 7.30 (s, 5H)
2e	Boc-Phe-ol	90	90–91 (B)	94.5 ⁴	–21.6° (1, CHCl ₃)	–24.6° ⁴ , –0.80° ⁷ (1.1, CHCl ₃)	3360 (OH, NH), 1690 (C=O)	1.45 (s, 9H), 2.90 (d, 2H, <i>J</i> = 7), 3.50–4.10 (m, 3H), 7.35 (s, 5H)
2f	Boc-Met-ol	80	39–40 (B)	40 ¹¹	–12.9° (1, CHCl ₃)	–	3360 (OH, NH), 1690 (C=O)	1.50 (s, 9H), 1.90 (m, 2H), 2.18 (s, 3H), 2.65 (t, 2H, <i>J</i> = 8), 3.65–4.05 (m, 3H)
2g	Boc-Cys-ol Boc-Cys-ol	75	121–122 (A)	124–125 ¹³	+28.1° (1, CHCl ₃)	–	3360 (OH, NH), 1685 (C=O)	1.50 (s, 18H), 2.98 (d, 4H, <i>J</i> = 7), 3.70–4.10 (m, 6H)
2h	Boc-Ser(Bzl)-ol	81	56–58 (B)	–	+12.1° (1, CHCl ₃)	+0.25° ⁷ (1, CHCl ₃)	3360 (OH, NH), 1680 (C=O)	1.40 (s, 9H), 3.50–3.95 (m, 5H), 4.48 (s, 2H), 7.35 (s, 5H)
2i	Boc-Asp(OBzl)-Ala-ol	63	78–80 (A)	C ₁₉ H ₂₈ N ₂ O ₆ (380.4)	–11.6° (1, CHCl ₃)	–	3340 (OH, NH), 1740 (ester C=O), 1690 (Boc C=O), 1660 (peptide C=O)	1.15 (d, 3H, <i>J</i> = 7), 1.45 (s, 9H), 2.85 (m, 2H), 3.40–4.10 (m, 3H), 4.30–4.80 (m, 1H), 5.13 (s, 2H), 7.35 (s, 5H)
2j	Z-Ala-Ala-ol	70	143–144 (A)	C ₁₄ H ₂₀ N ₂ O ₄ (280.3)	–29.4° (1, CHCl ₃)	–	3520 (OH), 3280 (NH), 1680 (Boc C=O), 1645 (peptide C=O)	1.15 (d, 3H, <i>J</i> = 7), 1.38 (d, 3H, <i>J</i> = 7), 3.35–4.45 (m, 4H), 5.08 (s, 2H), 7.35 (s, 5H) ^d

^a A = EtOAc/petroleum ether (bp 40–60°C, 1 : 4); B = Et₂O/petroleum ether (bp 40–60°C, 1 : 7).
^b Satisfactory microanalyses obtained: C ± 0.40, H ± 0.07, N ± 0.17.

^c Yields of **2a** using isobutyl and benzyl chloroformates are 79% and 70%, respectively.
^d Measured in acetone-*d*₆.

bonochloridate) (0.108 g, 1 mmol). After 5–10 min, NaBH_4 (113 mg, 3 mmol) is added in one portion. MeOH (10 mL) is then added dropwise to the mixture over a period of 10 min at 0°C . The solution is stirred for additional 10 min, and then neutralized with 1 N HCl or 1 N H_2SO_4 (2 mL). The organic solvents are evaporated under reduced pressure and the product is extracted with EtOAc (3×7 mL). The organic phase is washed consecutively with 1 N HCl or 1 N H_2SO_4 (4 mL), H_2O (10 mL), 5% aq NaHCO_3 (5 mL), H_2O (2×10 mL), dried (Na_2SO_4), and the solvent is evaporated under reduced pressure. The residue is purified by recrystallization (Table).

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