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

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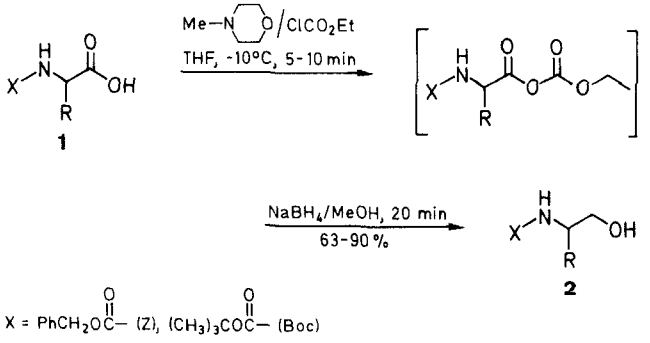
N-Protected amino acids and peptides are converted to alcohols by chemoselective reduction of their corresponding mixed anhydrides with sodium borohydride in tetrahydrofuran with dropwise addition of methanol.

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 acids[6] 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).



1 **2**

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 uneffected 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*-butyloxycarbonyl (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 monoisobutyl or monobenzyl carbonates. The difference between the determined values of specific rotations (Table, products **2e** and **2h**) and those reported for the borane/tetrahydrofuran method[7] 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 ^{1}H-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 CaH_2 and stored over molecular sieves. *N*-Methylmorpholine was distilled from ninhydrin. Isobutyl chloroformate was distilled and stored over $CaCO_3$. 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

Product	(L)	Yield (%)	mp (°C) (solvent)[a]	Molecular Formula[b] or Lit. mp (°C)	$[\alpha]_D$ (*c*, solvent) found	$[\alpha]_D$ (*c*, solvent) reported	IR (KBr) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, *J*(Hz)
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, *J* = 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, *J* = 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, *J* = 6), 3.70 (t, 2H, *J* = 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, *J* = 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, *J* = 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, *J* = 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, *J* = 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)	$C_{19}H_{28}N_2O_6$ (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, *J* = 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)	$C_{14}H_{20}N_2O_4$ (280.3)	−29.4° (1, $CHCl_3$)	–	3520 (OH), 3280 (NH), 1680 (Boc C=O), 1645 (peptide C=O)	1.15 (d, 3H, *J* = 7), 1.38 (d, 3H, *J* = 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 = Et_2O/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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(1) Cassal, J.-M.; Fürst, A.; Meier, W. *Helv. Chim. Acta* **1976**, *59*, 1917.
Miyoshi, M.; Nunami, K.; Sugano, H.; Fujh, T. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1433.
Thaisrivongs, S.; Pals, D. T.; Kati, W. M.; Turner, S. R.; Thomosco, L. M.; Watt, W. *J. Med. Chem.* **1986**, *29*, 2080.
Schlessinger, R. H.; Iwanowicz, E. J. *Tetrahedron Lett.* **1987**, *28*, 2083.

(2) Thompson, R. *Methods Enzymol.* **1977**, *46*, 220.
Sharma, R. P., Gore, M. G.; Akhtar, M. *J. Chem. Soc., Chem Commun.* **1979**, 875.
Stanfield, C. F.; Parker, J. E.; Kanellis, P. *J. Org. Chem.* **1981**, *46*, 4797.
Nishikata, M.; Yokosawa, H.; Ishii, S.-I. *Chem. Pharm. Bull.* **1986**, *34*, 2931.

(3) Pless, J.; Bauer, W.; Cardinaux, F.; Closse, A.; Hauser, D.; Huguenia, R.; Roemer, D.; Buescher, H.-H.; Hill, R. C. *Helv. Chim. Acta* **1979**, *62*, 398.

(4) Soai, K.; Oyamada, H.; Takase, M. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2327.

(5) Hamada, Y.; Shibata, M.; Sugiura, T.; Kato, S.; Shioiri, T. *J. Org. Chem.* **1987**, *52*, 1252.

(6) Nikawa, J.; Shiba, T. *Chem. Lett.* **1979**, *981*.

(7) Stanfield, C. F.; Parker, J. E.; Kanellis, P. *J. Org. Chem.* **1981**, *46*, 4799.

(8) Meienhofer, J., in: *The Peptides*, Vol. 1, Gross, E.; Meienhofer, J. (eds.), Academic Press, New York, 1979, p. 263.

(9) Soai, K.; Yokoyama, S.; Mochida, K. *Synthesis* **1987**, 647.

(10) Soai, K.; Oyamada, H.; Takase, M.; Ookawa, A. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1948.

(11) Sandrin, E.; Boissonnas, R. A. *Helv. Chim. Acta* **1966**, *49*, 76.

(12) Rose, W. G. *J. Am. Chem. Soc.* **1947**, *69*, 1384.

(13) Liskamp, R. M. J.; Zeegers, H. J. M.; Ottenheijm, H. C. J. *J. Org. Chem.* **1981**, *46*, 5408.