The Preparation of *N*-Protected Amino Alcohols and *N*-Protected Peptide Alcohol by Reduction of the Corresponding Esters with Sodium Borohydride. An Improved Procedure Involving a Slow Addition of a Small Amount of Methanol

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Synopsis. Esters of *N*-protected amino acids and an *N*-protected peptide were reduced selectively to the corresponding alcohols in high yields using lesser amounts of sodium borohydride than does the conventional method by the slow addition of methanol to the mixture of ester and $NaBH_4$ in *t*-butyl alcohol or tetrahydrofuran at 50 °C.

N-Protected amino alcohols (**1**) and *N*-protected peptide alcohols (**2**) have received considerable recent attention. **1** can be utilized as intermediates in the preparation of amino aldehydes,[1] which are inhibitors of proteolytic enzymes[2] and are important synthetic intermediates.[3] On the other hand, **2** are intermediates of peptide aldehydes of which biological activity is different from the corresponding peptides.[4] **2** can also be used for the determination of carboxy (*C*-) terminals of peptides.[5]

In connection with the synthesis of **1** and/or **2**, following three types of the methods have been reported: (1) Reduction of carboxylic acid by a borane–tetrahydrofuran (THF) complex.[6] In principle, this method is not applicable to the synthsis of **2**, because the borane complex is known to reduce amide groups (peptide bonds).[7] (2) Reduction of activated ester, azide, acid anhydride *etc.*[8] The procedure needs the conversion of carboxylic acids to the appropriate activated compounds, which are often sensitive toward hydroxy or mercapto groups.[9] In the synthesis from methyl or ethyl esters, an hydrolysis step from ester to acid should be additionally required. (3) Reduction of common esters such as methyl or ethyl esters. We would like to point out that carboxy (*C*-) terminal groups are often protected as methyl or ethyl esters in peptide synthesis. Direct reduction of these esters is preferable to the type (2) reaction because the hydrolysis step of the esters is not required. Reduction of these esters by lithium aluminium hydride is accompanied by the reduction of the peptide bonds.[7] Reduction by sodium borohydride ($NaBH_4$) in water[10] or in 50% aqueous ethanol[11] has been reported. However, these methods require the use of a large excess of $NaBH_4$ (4—25 mol equiv) and relatively long reaction time (3 h—2 d). Moreover, the possibility of alkaline hydrolysis of the esters is present because the solvents contain water.

During our continuing study on the stereoselectivity[12a] and chemoselectivity[12b–e] of metal borohydride reductions, we have noticed that the role of MeOH is important.

In this paper, we wish to describe a convenient method for the repid and selective reduction of esters of *N*-protected amino acid and *N*-protected peptide with $NaBH_4$. The essential part of the procedure is the addition of a small amount of MeOH to the mixture of esters and $NaBH_4$.

Table 1. Comparative study on the reduction of ethyl ester of *N*-(*t*-butoxycarbonyl)-L-phenylalanine (**3**) with sodium borohydride

Solvent	Molar ratio $NaBH_4$/**3**	Temp /°C	Time /min	Yield /% of **4**
50% aqueous EtOH[a]	2.0	50—55	30	61
Slow addition of MeOH to THF	2.0	50—55	30	88

a) See Ref. 11.

In the first place, we compared the effectiveness of the present procedure with the conventional method.[11] The results are shown in Table 1. Using the ethyl ester of *t*-butoxycarbonyl-L-phenylalanine [Boc-L-Phe(OEt), **3**] as a model compound, it was reduced with $NaBH_4$ (2 mol equiv) in THF by the addition of a small amount of MeOH at 50—55 °C for 30 min. The yield of Boc-L-phenylalaninol (**4**) was 88%. On the other hand, reduction of **3** in 50% aqueous EtOH[11] under the same reaction conditions (amount of $NaBH_4$, reaction temperature, time) afforded only 61% of **3** in our hands. Therefore the present procedure would seem to be superior to the conventional method.

This procedure using a slow addition of MeOH was applied to the reduction of esters of other *N*-protected amino acids and peptide. As shown in Table 2, even a hindered peptide (2*S*, 2′*S*)-(*N*-benzyloxycarbonylprolyl)-proline methyl ester was found to be reduced selectively in 84% yield. *t*-Butyl alcohol instead of THF was also effective for the conversion of esters to the corresponding alcohols.

Table 2. Synthesis of *N*-protected amino alcohol (**1**) and peptide alcohol (**2**)

Ester	Alcohol **1**,**2**	$NaBH_4$/ester	Solvent[a]	Yield /%[b]	Mp or Bp θ_m or θ_b °C	$[\alpha]_D^{20}$ (*c*, solvent)
Z-L-Phe-OEt		2.5	A	94	90—91 (90—92)[c]	−41.8°[c] (1.4, EtOH)
Boc-L-Phe-OEt (**3**)	 **4**	2.0	B	88	94.5	−24.6°[d] (1.1, $CHCl_3$)
Z-L-Pro-OMe		2.5	A	89	150—151/ 0.005 mmHg	−39.5°[e] (1.7, $CHCl_3$)
Z-L-Pro-L-Pro-OMe (**5**)	 **6**	2.4	A	84	114—114.5	−33 5° (1.0, $CHCl_3$)

a) A; *t*-BuOH:MeOH=5:1 (v/v). B; THF:MeOH=5:1 (v/v). b) Yields of the isolated products. c) Lit, $[\alpha]_D^{20}$ −41.5°(*c* 1.4, EtOH). A.Ito, *Chem. Pharm. Bull.*, **23**, 3081(1975). d) Lit, $[\alpha]_D^{23}$ −0.80° (*c* 1.1, $CHCl_3$). See Ref. 6. e) Lit, $[\alpha]_D$ −42.4°(*c* 1.0, $CHCl_3$). J.Cassel and A.Furst, *Helv. Chim. Acta*, **59**, 1917(1976).

As described above, esters of *N*-protected amino acids and peptides were reduced selectively to the corresponding alcohols in high yields with $NaBH_4$ in THF or *t*-BuOH by the addition of a small amount of MeOH. The present procedure requires a lesser amount of $NaBH_4$ and shorter reaction time than the conventional method.[11] Moreover it avoids the possibility of the hydrolysis of the esters during the reduction in an aqueous medium,[11] neither does it require alkaline earth metal salt additives.[13]

Experimental

All of the melting points were uncorrected. Tetrahydrofuran (THF) was distilled from lithium aluminium hydride prior to use. *t*-Butyl alcohol was purchased from Kanto Chemical Co., and was used without further purification. Reagent grade methanol was dried over molecular sieves (3 Å) and used without distillation.

General Procedure. MeOH (0.8 ml) was added dropwise over a period of 20 min to a mixture of ester of *N*-protected amino acid or peptide (1.0 mmol) and $NaBH_4$ (2.0—2.5 mmol) in *t*-BuOH or THF (4 ml) at 50—55 °C. The mixture was stirred for 10—25 min, then water (2.0 ml) was added to the reaction mixture. Most of the organic solvent was evaporated under reduced pressure. Brine (3 ml) was added, and the mixture was extracted with ether (5×8 ml). The extract was washed with brine (2×3 ml), dried over anhydrous sodium sulfate, then evaporated. The residue was purified by distillation or on silica gel TLC (ethyl acetate: MeOH=15:1 as developing solvent). The physical properties of the products are summarized in Table 2. Yields of the alcohols were 84—94%. Structures of known compounds were confirmed by NMR and IR spectra.

(2S, 2'S)-(N-Benzyloxycabonylprolyl)prolinol (6). Z-L-Pro-L-Pro-OMe (**5**)[14] was reduced according to the general procedure. **6** was obtained in 84% yield. Mp 114—114.5 °C. $[\alpha]_D^{20}$ −33.5° (*c* 1.0, chloroform). ^{1}H-NMR ($CDCl_3$): δ=1.2—2.4 (m, 8H), 3.0—4.7 (m, 9H), 5.1 (s, 2H), 7.25 (s, 5H); IR: 3520, 2960, 1700, 1650, 1440, 1365, 1180 cm^{-1}; MS: *m/z* 332 (M^+). Found: C, 65.09; H, 7.30; N, 8.45%. Calcd for $C_{18}H_{24}N_2O_4$: C, 65.04; H, 7.28; N, 8.43%.

References

1) a) C. F. Stanfield, J. E. Parker, and P. Kanellis, *J. Org. Chem.*, **46**, 4797 (1981); b) Y. Hamada and T. Shioiri, *Chem. Pharm. Bull.*, **30**, 1921 (1982); c) R. P. Sharma, M. G. Gore, and M. Akhtar, *J. Chem. Soc., Chem. Commun.*, **1979**, 875.

2) H. Umezawa, "Enzyme Inhibitors of Microbial Origin," Univ. of Tokyo Press, Tokyo, (1972).

3) E. Nakamura, *Tetrahdron Lett.*, **1981**, 663; M. Narita, M. Otsuka, S. Kobayashi, M. Ohno, Y. Umezawa, H. Morishima, S. Saito, T. Takita, and H. Umezawa, *ibid.*, **1982**, 525; H. Newmann, *J. Am. Chem. Soc.*, **95**, 4098 (1973).

4) For instance, [D-Ala^2, Leu^5-ol] enkephalin is known to be a long-lasting analog of enkephalin which is an opioid hormone. J. S. Morley, *Ann. Rev. Pharmacol. Toxicol.*, **20**, 81 (1980).

5) J. P. Greenstein and M. Winitz, "Chemistry of Amino Acids," John Wiley & Sons, New York, (1960).

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

7) For a review, see A. Hajós, "Complex Hydrides," Akademiai Kiado, Budapest, (1979).

8) J. Nikawa and T. Shiba, *Chem. Lett.*, **1979**, 981, and references cited therein.

9) N. Izumiya, M. Oono, T. Kato, and H. Aoyagi, "Peptide Gosei," Maruzen, Tokyo (1975), Chap. 5.

10) T. Hamada, M. Suzuki, and O. Yonemitsu, *Chem. Pharm. Bull.*, **20**, 994 (1972).

11) H. Seki, K. Koga, and S. Yamada, *Chem. Pharm. Bull.*, **15**, 1948 (1967).

12) a) K. Soai, K. Komiya, Y. Shigematsu, H. Hasegawa, and A. Ookawa, *J. Chem. Soc., Chem. Commun.*, **1982**, 1282; b) K. Soai, A. Ookawa, and H. Hayashi, *ibid.*, **1983**, 668; c) K. Soai, H. Oyamada, and A. Ookawa, *Synth. Commun.*, **12**, 463 (1982); d) K. Soai, A. Ookawa, H. Oyamada, and M. Takase, *Heterocycles*, **19**, 1371 (1982); e) K. Soai, H. Oyamada, M. Takase, and A. Ookawa, *Bull. Chem. Soc. Jpn.*, **57**, 1948 (1984).

13) In the presence of alkali earth metal salt, $NaBH_4$ is known to become $LiBH_4$ which is capable of reducing esters. H. C. Brown and B. C. S. Rao, *J. Am. Chem. Soc.*, **78**, 2582 (1956). See also Ref. 1b.

14) T. Mukaiyama, K. Soai, T. Sato, H. Shimizu, and K. Suzuki, *J. Am. Chem. Soc.*, **101**, 1455 (1979)