Selective One-Pot Conversion of Carboxylic Acids into Alcohols

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Carboxylic acids are converted into alcohols by chemoselective reduction of their corresponding fluorides with sodium borohydride and dropwise addition of methanol. The method is general and mild and displays a high level of functional group compatibility. *N*-Protected amino and peptide alcohols, bearing varieties of protecting groups, are prepared in the same way from their corresponding amino acids and peptides without racemization.

Introduction

Reduction of carboxylic acids into alcohols is a useful and important transformation in synthetic organic chemistry. Methods for the conversion of carboxylic acids and derivatives into primary alcohols have been summarized by Larock.[1] More recent methods for the reduction of carboxylic acids utilize aluminum hydride and triethylamine,[2] $Zn(BH_4)_2$ and trifluoroacetic anhydride,[3] electrolysis in the presence of $NaBH_4$,[4] and $NaBH_4$ with I_2[5] or catechol−TFA.[6] Primary alcohols may also be obtained by (a) reduction of esters with $ZnBH_4$ under sonication,[7] reduction of esters with $Ti(OPr\text{-}i)_4$ and $(EtO)_3SiH$,[8] electroreduction of esters,[9] and (b) reduction of acyl chlorides with $Zn(BH_4)_2$ and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.[10] However, many of these methods have limited use if the substrate contains sensitive functional groups. Thus, efforts are still directed toward the development of selective and more convenient methods. One such method, the conversion of carboxylic acids to alcohols by chemoselective reduction of their corresponding fluorides with sodium borohydride, is reported here.

Results and Discussion

Acyl fluorides have been rarely used in organic synthesis. They have greater stability than the corresponding chlorides toward neutral oxygen nucleophiles such as water and methanol, yet appear to be of equal reactivity toward anionic nucleophiles and amines.[11] Recently, α-Fmoc,[12] Boc, or Z amino acid fluorides[13] have been found to be stable rapid-acting acylating reagents for peptide bond formation. Cyanuric fluoride is a mild reagent that is suitable for the preparation of acyl fluorides even when unsaturated double bonds, hydroxyl groups, or aromatic rings are found in the molecule.[14]

Scheme 1

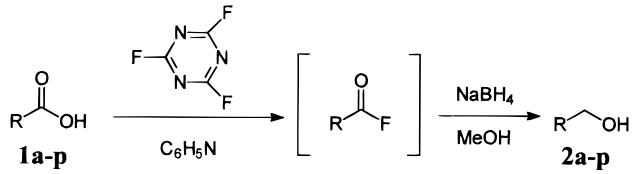
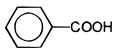
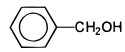
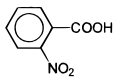
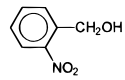
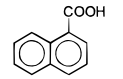
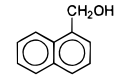
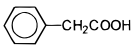
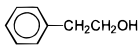
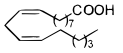
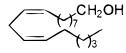
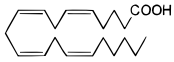
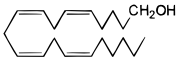
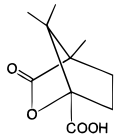
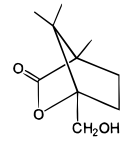


Table 1. Reduction of Carboxylic Acids to Alcohols

	starting compound		product[a]	yield (%)[b]
1a	$CH_3(CH_2)_8COOH$	**2a**	$CH_3(CH_2)_8CH_2OH$	92
1b	$CH_3(CH_2)_{14}COOH$	**2b**	$CH_3(CH_2)_{14}CH_2OH$	95
1c		**2c**		95
1d		**2d**		93
1e		**2e**		95
1f		**2f**		94
1g		**2g**		68
1h		**2h**		67
1i		**2i**		63

[a]The products **2a-h** were identified by the physical constants data , IR, ^{1}H NMR data and comparison with data reported in the literature. [b]Yields are of isolated and purified products.

Carboxylic acids were converted into the corresponding fluorides by treatment with cyanuric fluoride in the presence of pyridine (Scheme 1). Acyl fluorides were reduced *in situ* to primary alcohols by sodium borohydride with dropwise addition of methanol at room temperature. A variety of acids, namely decanoic, palmitic, benzoic, 1-naphthoic, o-nitrobenzoic, and phenylacetic, were converted into alcohols in very high yield (Table 1).

[⊗] Abstract published in *Advance ACS Abstracts*, September 1, 1996.

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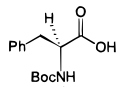
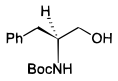
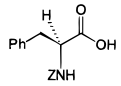
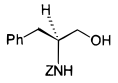
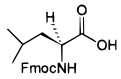
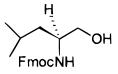
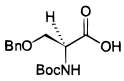
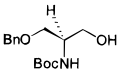
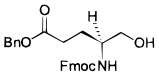
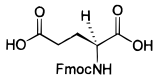
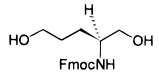
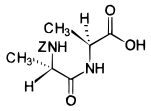
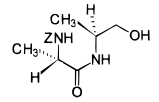
Table 2. Reduction of N-Protected Amino Acids to Amino Alcohols

	starting compound		product[a]	yield, (%)[b]	mp °C (lit.)	$[\alpha]^{25}_D$ (lit)
1j		**2j**		86	94-94.5 (94.5[19])	-23.5 (-24.6[19]) (*c* 1, $CHCl_3$)
1k		**2k**		81	91-92 (90-91[19])	-41.6 (-41.1[17a]) (*c* 2, MeOH)
1l		**2l**		90	130-130.5 (130[18])	-20.8 (-17.0[18]) (*c* 1, MeOH)
1m		**2m**		83	63.5-65 (56-58[17a])	+12.2 (+12.1[17a]) (*c* 1, $CHCl_3$)
1n		**2n**		89	90-92	-8.6 (*c* 1, $CHCl_3$)
1o		**2o**		80	151-152	-9.6 (*c* 0.5, MeOH)
1p		**2p**		54	145-147 (143-144[17a])	-27.3 (-29.4[17a]) (*c* 1, $CHCl_3$)

[a] IR and ^{1}H NMR spectra of compounds **2j-m** and **2p** were in accordance to their structure. [b] Yields are of isolated and purified products.

The polyunsaturated acids arachidonic and linoleic were reduced in good yields, as was camphanic acid. Under the conditions described, the double bonds, the nitro group, and the lactone group remained unaffected.

N-Protected amino alcohols are important synthetic intermediates, particularly useful in the synthesis of peptide aldehydes that are potent inhibitors of proteases.[15] They can also be incorporated at the C-terminal of biologically active peptides, e.g., enkephalins, to modify the biological activity.[16] The conversion of *N*-protected amino acids and peptides into alcohols by chemoselective reduction of their corresponding mixed anhydrides[17] and *N*-carboxyanhydrides[18] with sodium borohydride has also been reported. In the present work, a variety of *N*-protected amino acids were converted rapidly into alcohols by *in situ* reduction of their corresponding fluorides with sodium borohydride in high yields (Table 2). However the yield of the reduction for the dipeptide **1p** was moderate. The peptide bond and the *N*-terminal urethane bonds of benzyloxycarbonyl (Z), *tert*-butoxycarbonyl (Boc), and 9-fluorenylmethoxycarbonyl (Fmoc) protective groups are not reduced. Moreover, the benzyl ether and benzyl ester groups used for the protection of the side chain of serine and glutamic acid remained inert.

The present method proceeds with retention of optical purity as indicated by comparison of the specific rotation values with those reported in the literature (Table 2). To verify this point the enantiomeric purities of **2j**, **2m**, and **2p** were checked by NMR analysis of their esters with (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (Mosher esters).[20] The ^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of the Mosher ester of **2j** was compared with the spectra of the Mosher esters of (*R*)-Boc-phenylalaninol and (*RS*)-Boc-phenylalaninol. Enantiomeric excess >95% was indicated for **2j** by the absence of any diastereomeric proton signal in the spectrum of its Mosher ester since the NH proton, the methoxy protons, and the methylene protons of the hydroxymethyl group are well resolved in the spectrum of the Mosher ester of (*RS*)-Boc-phenylalaninol. Furthermore, no absorptions caused by the presence of the other enantiomer could be observed for the Mosher esters of **2m** and **2p**.

The method described herein has the advantage of chemoselectivity in comparison with the I_2-NaBH_4 method,[21] which cannot be applied to *N*-protected peptides and to substates containing *N*-acyl-type protecting groups or ester protective groups. The borane−tetrahydrofuran method[22] is only applied to *N*-protected amino acids giving products of lower chemical and optical purity, as is concluded by comparison of the determined values of specific rotations (Table 2) with those reported for the borane−tetrahydrofuran method [**2j**, $[\alpha]_D = -0.80$ (1.1, $CHCl_3$); **2m**, $[\alpha]_D = +0.25$ (1, $CHCl_3$)].[22]

In conclusion, the cyanuric fluoride−$NaBH_4$−MeOH procedure provides a general, rapid, and convenient method for the reduction of carboxylic acids into alcohols. Its compatibility with a variety of normally reducible

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functional groups makes it more useful for selective carboxylic acid reduction in polyfunctional molecules.

Experimental Section

General Procedures. Melting points are uncorrected. Optical rotations were measured at 25 °C. All asymmetric amino acid derivatives were of the L-configuration and were purchased from Fluka Chemical Co. Cyanuric fluoride was purchased from Lancaster. All solvents and chemicals were of reagent grade and used without further purification. Silica gel 60 (70−230 mesh, Merck) was used for column chromatography.

General Procedure for the Preparation of Alcohols. Pyridine (80 μL,1 mmol) and subsequently cyanuric fluoride (180 μL, 2 mmol) were added to a stirred solution of the acid or *N*-protected amino acid or dipeptide (1 mmol) in CH_2Cl_2 (2.5 mL), kept under a N_2 atmosphere, at −20 to −10 °C. Precipitation of cyanuric acid occurred and increased gradually as the reaction proceeded. After the mixture was stirred at −20 to −10 °C for 1 h, ice-cold water was added along with 15 mL of additional CH_2Cl_2. The organic layer was separated, and the aqueous layer was extracted once with CH_2Cl_2 (5 mL). The combined organic layers were washed with ice-cold water (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure to a small volume (2 mL). $NaBH_4$ (76 mg, 2 mmol) was added in one portion, and MeOH (2 mL) was then added dropwise over a period of 10−15 min at rt. The reaction mixture was neutralized with 1 N H_2SO_4, and the organic solvents were evaporated under reduced pressure. The residue was treated with EtOAc (10 mL) and H_2O (5 mL); the organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 8 mL). The combined organic layers were washed consecutively with 1 N H_2SO_4 (5 mL) and H_2O (2 × 10 mL) and dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The residue was purified by distillation or column chromatography using EtOAc/petroleum ether (bp 40-60 °C) (1:1) as eluent.

(1*S*)-1-Hydroxymethyl-4,7,7-trimethyl-2-oxabicyclo-[2.2.1]heptan-3-one (2i): mp 178−181 °C; $[\alpha]^{25}_D = +1.6$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.00 (dd, $J = 6$ Hz, $J_{gem} = 18$ Hz, 1H), 3.83 (dd, $J = 8.5$ Hz, $J_{gem} = 18$ Hz, 1H), 2.00 (m, 1H), 1.88−1.78 (m, 2H), 1.71 (m, 1H), 1.12, 0.98 and 0.95 (s, s, s, 9H); MS (FAB) *m*/*e* 207 (M + Na, 100). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.23; 8.90.

Benzyl (*S*)-4-[N-(9*H*-fluorenylmethoxycarbonyl)amino]-5-hydroxypentanoate (2n): ^{1}H NMR ($CDCl_3$) δ 7.75 (d, $J =$ 7 Hz, 2H), 7.55 (d, $J = 7$ Hz, 2H), 7.42−7.25 (m, 9H), 5.12−5.05 (m, 3H), 4.42−4.15 (m, 3H), 3.78−3.52 (m, 3H), 2.44 (m, 2H), 2.23 (m, 1H), 1.88 (m, 2H); MS (FAB) *m*/*e* 468 (M + Na, 100). Anal. Calcd for $C_{27}H_{27}NO_5$: C, 72.79; H, 6.11; N, 3.14. Found: C, 72.49; H, 6.21; N, 3.26.

(*S*)-2-[*N*-(9*H*-fluorenylmethoxycarbonyl)amino]pentane-1,5-diol (2o) was purified by column chromatography using $CHCl_3$/MeOH (95:5) as eluent: ^{1}H NMR (CD_3OD) δ 7.80 (d, $J = 7$ Hz, 2H), 7.68 (d, $J = 7$ Hz, 2H), 7.45−7.28 (m, 4H), 4.42−4.20 (m, 3H), 3.62−3.48 (m, 5H), 1.65−1.15 (m, 4H); MS (FAB) *m*/*e* 364 (M + Na, 100). Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.12; H, 6.93; N, 4.11.

General Procedure for the Preparation of Mosher Esters of N-Protected Amino Alcohols. To a stirred solution of *N*-protected amino alcohol (0.20 mmol) in dichloromethane (3 mL) were added 4-(dimethylamino)pyridine (5 mg, 0.04 mmol), (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (82 mg, 0.35 mmol), and dicyclohexylcarbodiimide (78 mg, 0.38 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and at room temperature overnight. After removal of the solvents the mixture was separated by column chromatography using $CHCl_3$ as eluent. The product was used for ^{1}H NMR ($CDCl_3$, 500 MHz) analysis.

Characteristic ^{1}H NMR Chemical Shifts (in ppm). (*S*)-(*tert*-Butoxycarbonyl)phenylalaninol Mosher ester: 4.53 (d, $J = 6.5$ Hz, 1H), 4.30 (dd, $J = 3.5$ Hz, $J_{gem} = 11$ Hz, 1H), 4.21 (dd, $J = 3.9$ Hz, $J_{gem} = 11$ Hz, 1H), 3.55 (s, 3H).

(*R*)-(*tert*-Butoxycarbonyl)phenylalaninol Mosher ester: 4.47 (d, $J = 6.5$ Hz, 1H), 4.36 (dd, $J = 3.8$ Hz, $J_{gem} =$ 10.6 Hz, 1H), 4.16 (dd, $J = 4.4$ Hz, $J_{gem} = 10.6$ Hz, 1H), 3.56 (s, 3H).

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Supporting Information Available: ^{1}H NMR spectra of Mosher esters of **2j**, (*S*)-Boc-Phe-ol, (*RS*)-Boc-Phe-ol, **2m**, and **2p** (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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