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CHEMOSELECTIVE REDUCTION OF CARBOXYLIC ACIDS INTO ALCOHOLS USING N,N-DIMETHYLCHLOROMETHYLENIMINIUM CHLORIDE AND SODIUM BOROHYDRIDE

Tamotsu FUJISAWA,* Toshiki MORI, and Toshio SATO
Chemistry Department of Resources, Mie University, Tsu, Mie 514

A new method for the direct conversion of carboxylic acids to alcohols using *N*,*N*-dimethylchloromethyleniminium chloride and sodium borohydride was established. This method fulfills the chemoselective reduction of carboxylic acids with a functional moiety such as halide, ester, nitrile, and olefin.

Reduction of carboxylic acids to alcohols is widely used in the syntheses of natural products. However, the reducing reagents which can directly reduce carboxylic acids to alcohols are limited to only powerful ones such as lithium aluminum hydride, boran, aluminum hydride, sodium borohydride-aluminum chloride, and so on, because of the poor reactivity of carboxyl group.1) Since these powerful reducing reagents can also reduce many functional groups, chemoselective reduction of carboxyl group is very difficult. For the chemoselective reduction, carboxylic acids are generally converted into reactive derivatives and then reduced by a weak reducing reagent such as sodium borohydride. Several examples of such reductions using sodium borohydride are as follows; mixed carboxylic diphenylphosphoric anhydrides,2) enol ester derivatives prepared from *N*-ethyl-5-phenylisoxazolium 3'-sulfonate,3) 3-acylthiazolidine-2-thiones,4) and 1-succinimidyl esters.5) However, these reductions are somewhat troublesome because of the two step procedure. Perron *et al.*6) reported the one-step reduction of benzylpenicillinic acid *via* the mixed anhydride to the corresponding alcohol using ethyl chloroformate and sodium borohydride. Yamada *et al.*7) reported the improved method in which the deposited triethylammonium chloride formed by the reaction of carboxylic acids with ethyl chloroformate in the presence of triethylamine was filtered off, and then the mixed anhydrides were reduced with the aqueous solution of sodium borohydride. In the Yamada's method, however, the removel of triethylammonium chloride is practically troublesome. We now wish to report a direct and chemoselective reduction of carboxylic acids to alcohols using sodium borohydride and *N*,*N*-dimethylchloromethyleniminium chloride which is derived from easily available *N*,*N*-dimethylformamide and oxalyl chloride.

Iminium salt is known to react with carboxylic acid to produce carboxymethyleniminium salt which reacts with various nucleophiles such as alcohol, amine, and azide to give ester, amide and acylazide, respectively.8) Thus, the reaction of carboxymethyleniminium salt with hydride as a nucleophile was studied for the chemoselective reduction of carboxylic acids. Carboxylic acids reacted with *N*,*N*-dimethylchloromethyleniminium chloride at -30 °C for 1 h in a co-solvent of acetonitrile and THF to form carboxymethyleniminium chloride *in situ*, and two molar equivalents of sodium borohydride in *N*,*N*-dimethylformamide solution was added at -78 °C, and the temperature was raised to -20 °C for 2 h. The results of the reduction of various kinds of carboxylic acids were summarized in Table I. The use of one and a half equivalents of sodium borohydride for carboxymethyleniminium salt decreased the yield of alcohol, therefore, more than two molar equivalents of sodium borohydride were needed. In the reduction of aliphatic carboxylic acids, primary, secondary and tertiary ones were easily reduced to the corresponding alcohols in high yields. Although the reduction of benzoic acid under the same conditions gave benzyl alcohol in 43% yield, the reaction of benzoic acid with *N*,*N*-dimethylchloromethyleniminium chloride at 0 °C for 1 h increased the yield of benzyl alcohol up to 97%. Under the conditions, various benzoic acids with methoxy, nitro and chloro groups, or 2-furoic acid could be reduced to the corresponding alcohols in high yields. Thus, both aliphatic and aromatic alcohols were obtained

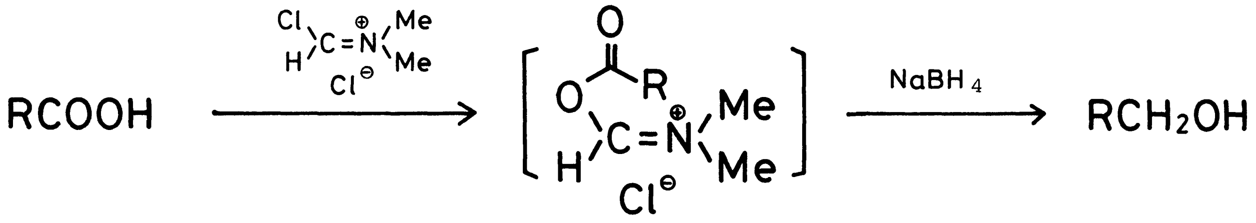
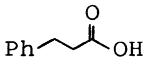
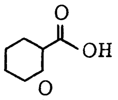
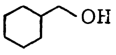
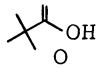
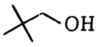
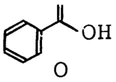
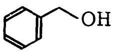
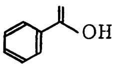
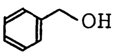
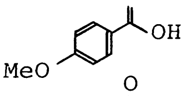
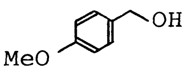
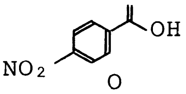
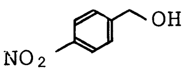
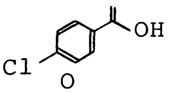
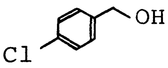
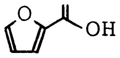
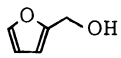


Table I. Yields of Alcohols by the Reduction of Various Carboxylic Acids[a]

Run	Acid	Alcohol[b]	Temp (°C)[d]	Yield(%)
1			-30	92
2			-30	90
3			-30	88[c]
4			-30	43
5			0	97
6			0	97
7			0	90
8			0	90
9			0	88

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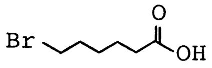
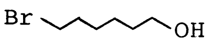
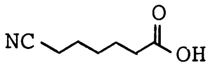
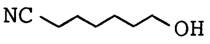
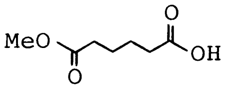
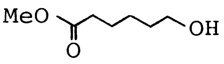
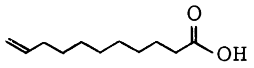
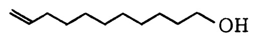
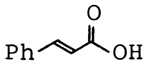
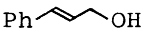
[a] All reactions were performed on 2 mmol scales. [b] The products were isolated by silica gel TLC and identified by IR and NMR spectra. [c] Determined by GLC. [d] The temperature in the reaction of carboxylic acids with *N*,*N*-dimethylchloromethyleniminium chloride.

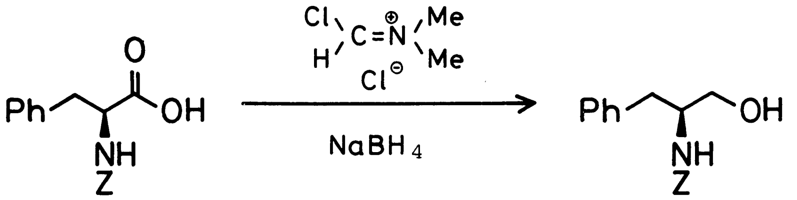
Table II. Yields of Alcohols by the Reduction of Carboxylic Acids with Various Functional Groups

Run	Acid	Alcohol	Yield(%)[a]
10			93
11			89
12			89
13			91
14			95[b]

[a] All reductions were performed on 2 mmol scales and the products were isolated by silica gel TLC and identified by IR and NMR spectra. [b] Two and a half molar equivalents of sodium borohydride was used.

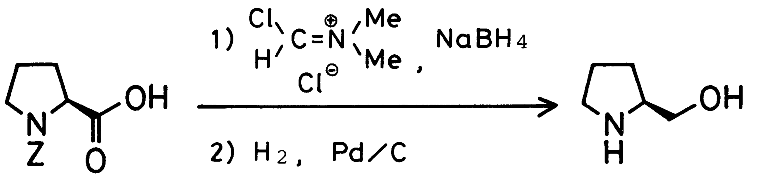
in high yields from carboxylic acids in one-pot operation.

The mild reaction conditions of the present method using *N*,*N*-dimethylchloromethyleniminium chloride and sodium borohydride make possible a chemoselective reduction of carboxylic acids. The results of chemoselective reduction of carboxylic acids with various functional groups were summarized in Table II. Thus, functional groups such as bromo, cyano and ester, which are reduced by powerful reductant such as lithium aluminum hydride, were not reduced, and carboxylic acid moiety could be only reduced to the corresponding alcohol. Olefin which is reduced by borane was tolerant by the present method. In the reduction of α,β-unsaturated carboxylic acid, the use of two and a half molar equivalents of sodium borohydride gave a better result than the use of two molar eqivalents of the reductant. Although sodium borohydride can not reduce chemoselectively the carbonyl groups of α,β-unsaturated carbonyl compounds,⁹⁾ this method could reduce chemoselectively the carboxylic acid moiety of α,β-unsaturated carboxylic acid to give the corresponding unsaturated alcohol. Furthermore, this procedure can be applied to the reduction of *N*-protected amino acids. For example, *N*-benzyloxycarbonyl-(*S*)-phenylalanine was reduced to the corresponding protected amino alcohol



y = 81%

$[\alpha]_D^{23}$ -41.7° (C 1.01, EtOH)¹⁰⁾



y = 81%

$[\alpha]_D^{23}$ +30.9° (C 1.10, C_6H_6)¹¹⁾

without racemization in a high yield. (*S*)-Prolinol was also obtained in a high yield by the reduction of *N*-benzyloxycarbonyl-(*S*)-proline.

In this manner, carboxylic acids with various functional groups could be reduced chemoselectively. This is reasonably explained by the concept that the positive charge on carboxymethyleniminium chloride activates the carbonyl group on it to accelerate attack of the hydride to the carbonyl group.

The representative procedure for the reduction of 3-phenylpropionic acid is as follows. Oxalyl chloride (0.5 ml) was added to a solution of *N*,*N*-dimethylformamide (2 mmol) in dichloromethane (3 ml) at 0 °C. After the solution was stirred for 1 h, the solvent was removed under a reduced pressure. To the residual white powder in acetonitrile (3 ml) and THF (5 ml) was added a solution of 3-phenylpropionic acid (2 mmol) in THF (3 ml) at -30 °C, and the reaction mixture was stirred for 1 h at the same temperature. Then, to the reaction mixture was added a solution of sodium borohydride (2 ml of 2.00 M solution in *N*,*N*-dimethylformamide, 4 mmol) at -78 °C, and the temperature of the mixture was slowly raised to -20 °C for 2 h. The reaction was quenched by the addition of 2N HCl aq solution. The organic layer was extracted with ether, washed with $NaHCO_3$ aq solution and dried over $MgSO_4$. After removal of the solvent, 3-phenyl-1-propanol was obtained by silica gel TLC (hexane: ether = 3:2) in 92% yield.

As mentioned above, the reduction of various carboxylic acids using *N*,*N*-dimethylchloromethyleniminium chloride and sodium borohydride gave directly the corresponding alcohols in high yields with high chemoselectively. This method, therefore, is useful for the reduction of complex molecules in natural product synthesis.[12)]

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9) M. S. Brown and H. Rapoport, *J. Org. Chem.*, 28, 3261 (1963).
10) Lit. $[\alpha]_D^{17}$ -41.7° (C 1.00, C_2H_5OH), see references 5 .
11) Lit. $[\alpha]_D^{20}$ +31.6° (C 1.00, C_6H_6), D. Enders and H. Eichenauer, *Chem. Ber.*, 112, 2933 (1979).
12) Partial financial supports of this research by the Asahi Glass Foundation and a Grant-in-Aid from the Ministry of Education, Science and Culture are greatly acknowledged.

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