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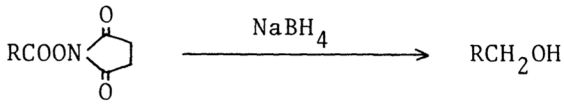
REDUCTION OF CARBOXYLIC ACIDS TO ALCOHOLS THROUGH 1-SUCCINIMIDYL ESTERS WITH $NaBH_4$

Jun-ichi NIKAWA and Tetsuo SHIBA*
Department of Chemistry, Faculty of Science, Osaka University, Toyonaka, Osaka 560

1-Succinimidyl esters of various aliphatic acids and amino acids were reduced with sodium borohydride in tetrahydrofuran to the corresponding alcohols under mild conditions in fairly good yields. The facile reaction offers a convenient method for the preparation of alcohols from carboxylic acids, and can be effectively applied to a selective conversion of an appropriate carboxyl group to a hydroxymethyl group in the presence of other functional groups.

It is generally accepted that sodium borohydride, one of the most useful reducing agents for aldehydes and ketones, does not affect carboxylic acids or esters under the usual reaction conditions. For the reduction of carboxylic acid alkyl esters with sodium borohydride, rather drastic conditions are required such as high temperature, co-existence of alkaline-earth metal cations, addition of Lewis acids, etc.[1] We wish to report here a novel and simple method for the conversion of carboxylic acids to alcohols with sodium borohydride under mild reaction conditions.



Carboxylic acid 1-succinimidyl esters, which are well known intermediates as the activated esters in the peptide synthesis,[2] were found to be readily reduced to the corresponding alcohols with a 2.5-fold excess of sodium borohydride in tetrahydrofuran (THF) at room temperature or even at 0°C. Various kinds of carboxylic acid could be converted in this manner to the corresponding alcohols in fairly good yields, where neither a high temperature nor an anhydrous condition was required. Owing to such simplicity and mildness, this novel method is of advantage particularly for a selective reduction of an appropriate carboxyl group in the presence of other functional groups like an amide or other alkyl ester in the same molecule. Furthermore, according to the present procedure, one can handle easily the succinimidyl ester as a stable synthetic intermediate in contrast to the cases in the acid azide[3,4] or the mixed anhydride[4,5] method.

A typical example is given below to illustrate the reduction procedure. To a solution of N-benzyloxycarbonyl-L-phenylalanine 1-succinimidyl ester (200 mg, 0.50 mmol) in THF (5 ml) was added sodium borohydride (48 mg, 1.3 mmol) at room temperature. After the reaction mixture had been stirred at the same temperature for 1 h, it was poured into 10 % aqueous citric acid and extracted with ethyl acetate. Organic layer was washed with water, saturated aqueous $NaHCO_3$ and water

Table 1. Reduction of carboxylic acid 1-succinimidyl esters with $NaBH_4$ in THF

Ester	Temp	Time(h)	Product[a] Yield(%)	Mp(°C)[b]	$[\alpha]_D^{17}$ (EtOH)
Z-L-Phe-ONSu	r.t.	1	83	94-94.5	-41.7° (*c* 1.00)
Z-L-Leu-ONSu	r.t.	3.5	79	36-37	-28.5° (*c* 1.09)
Z-L-Lys(Boc)-ONSu	r.t.	2	98	50-51	-14.8° (*c* 1.01)
Boc-L-Ile-ONSu	r.t.	25	93	oil	-25.2° (*c* 1.19)
Boc-D-Asp(ONSu)-OBzl	0°C	6.5	50	57-58	+39.6° (*c* 1.08)
Boc-D-Asp(ONSu)-L-Ala-OBzl	0°C	2	47	129-130	- 4.3° (*c* 1.17)
$CH_3(CH_2)_{14}COONSu$	r.t.	5	74	49-50	-
$CH_3OOC(CH_2)_{14}COONSu$	r.t.	1.5	75	57-58	-
$CH_3OOC(CH_2)_{16}COONSu$	r.t.	1.5	70	65-65.5	-

Abbreviations: Z; benzyloxycarbonyl, Boc; *t*-butoxycarbonyl, NSu; 1-succinimidyl.
a) Structures of all reduction products were confirmed by elemental analyses and spectral data.
b) All melting points are uncorrected.

successively, and dried over $MgSO_4$. The residual solid obtained by evaporation of the solvent *in vacuo* was crystallized from ethyl acetate-hexane to yield 120 mg (83 %) of pure N-benzyloxycarbonyl-L-phenylalaninol, mp 94-94.5°C. This reaction proceeded smoothly even at 0°C and no racemization was observed in the product.[6]

The results of the reduction for various carboxylic acid 1-succinimidyl esters are summarized in Table 1. The reduction of usual succinimidyl esters finished within a few hours except in the case of the isoleucine ester. Caution had to be taken for the reduction of β-active ester group in D-aspartic acid derivative to carry out the reaction at 0°C in order to minimize the formation of N-*t*-butoxycarbonyl-D-homoserine lactone as a by-product. This reduction provided us D-homoserine derivative very easily which would be a useful intermediate for the synthesis of a new antibiotic nocardicin. Methyl 1-succinimidyl esters of long chain dicarboxylic acid gave us ω-hydroxy fatty acid methyl esters. Actually, this procedure could be applied successfully to a preparation of isotopically labeled ω-hydroxy fatty acids, which are useful tools for the biochemical study of the fatty acid, by means of sodium boro[^{3}H]hydride.[7]

For the reason mentioned above, this novel procedure may provide a versatile and convenient synthetic method for the reduction of carboxylic acids to alcohols.

References and Notes

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6) The reduction product was hydrogenolyzed in the presence of palladium charcoal to give phenylalaninol which showed an optical rotation value of $[\alpha]_D^{20}$ -23.9° (*c* 1.07, EtOH). In order to check an optical purity of phenylalaninol obtained here, it was coupled with benzyloxycarbonyl-L-phenylalanine and the product was analyzed with HPLC. A peak due to L-D diastereomer was not detected at all.
7) Preparation of [^{3}H]-labeled fatty acid derivatives will be described elsewhere.

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