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Convenient Procedure for the Preparation of α-Amino Alcohols[1)]

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Various N^{α}-protected amino acid active esters used in peptide chemistry were found to be excellent source materials for the preparation of the corresponding amino alcohols by reduction with sodium borohydride. The validity of this procedure for the convenient preparation of aliphatic alcohols was demonstrated by taking stearyl alcohol as an example.

Keywords——sodium borohydride reduction; N^{α}-protected L-amino alcohols; N^{α}-protected amino acid active esters; stearyl alcohol; stearic acid

Sodium borohydride is one of the most useful reducing agents for aldehydes and ketones, but not generally for carboxylic acid esters. Yamada *et al.*[2-4)] reported that the facile reduction of optically active α-amino acid esters and their hydrochlorides with sodium borohydride took place to give the corresponding optically active α-amino alcohols in fairly good yields, and in better yields when the carboxylic acids were converted to the corresponding mixed anhydrides with ethyl chloroformate. Chaikin *et al.*[5)] reported that acid chlorides were effectively reduced to alcohols by sodium borohydride.

Information now available indicates that carboxylic acids in activated forms with increased electrophilicity are more susceptible to sodium borohydride reduction. We found that a number of N^{α}-protected L-amino acid active esters, more stable activated derivatives than mixed anhydrides and acid chlorides, could be smoothly converted, under cooling with ice, to the corresponding N^{α}-protected amino alcohols with retention of the configuration.

In order to determine optimum reaction conditions, reduction of four active esters of Z(OMe)–Met–OH; Z(OMe)–Met–OPCP, Z(OMe)–Met–OTCP,[6)] Z(OMe)–Met–OSu and Z(OMe)–Met–ONB, with sodium borohydride was performed in comparison with that of Z(OMe)–Met–OMe.

TABLE I. Preparation of Z(OMe)–Met-ol from the Various Active Esters

R Z(OMe)–Met–OR	$NaBH_4$ (eq.)	Temp. (°C)	Time (min)	Yield (%)	$[\alpha]_D^{24}$ (MeOH)
TCP	10	10	15	87	−24.2
TCP	5	10	15	85	−24.2
PCP	5	10	15	88	−23.8
Su	5	10	15	93	−23.9
NB	5	10	15	75	−24.1
Me	5	25	120	92	−24.1

As shown in Table I, five moles of sodium borohydride was sufficient to bring the reduction of active esters to Z(OMe)–Met-ol to completion at below 10° within 15 min, while reduction of Z(OMe)–Met–OMe required 120 min at 25°. The progress of reactions was monitored by thin layer chromatography, but the reduction of all active esters tested was so fast that we were not able to select the most efficient active ester at this stage. The retention of configuration during the reduction was confirmed by deprotection of the product followed by characterization of H–Met-ol as the oxalate.[2)]

Table II. Reduction of Various Z(OMe)-Amino Acid Active Esters with $NaBH_4$

Ester	Product					
	Yield (%)	mp	$[\alpha]_D^{24}$ in MeOH	*Anal.* Calcd / Found		
				C	H	N
Z(OMe)–Leu–OPCP	86	65—68°	−25.5° (c=0.4)	64.03	8.24	4.98
				63.88	8.20	5.00
Z(OMe)–Ile–ONB	88	61—63°	−17.7° (c=0.8)	64.03	8.24	4.98
				64.03	8.17	5.12
Z(OMe)-Arg(Mts)-OSu	88	43—48°	−7.2° (c=0.4)	56.90	6.76	11.06
				57.06	6.76	11.02
Z(OMe)–Phe–ONP	78	96—98°	−41.9° (c=0.6)	68.55	6.71	4.44
				68.39	6.76	4.90

As shown in Table II, we next confirmed that similar conditions could be applied for the reduction of other amino acid active ester by taking Z(OMe)–Leu–OPCP, Z(OMe)–Ile–ONB, Z(OMe)–Arg(Mts)–OSu and Z(OMe)–Phe–ONP[5)] as examples. From the practical viewpoint, we judged that Su or NB ester, bearing water-soluble partner components is preferable for our purpose, because they made the purification of products easier than with the other esters so far tested.

We also found that sodium borohydride could quantitatively reduce stearic acid N-hydroxy-5-norbornene-2,3-dicarboximide ester to stearyl alcohol, though somewhat prolonged treatment was required. The result implies that the N-hydroxy type active ester procedure we describe herein can be applied, like other phenyl esters,[7)] for the easy preparation of other aliphatic alcohols, and probably also more complex alcohols.

Experimental

Thin-layer chromatography was performed on silica gel (Kieselgel G, Merck). *Rf* values refer to the following solution systems: Rf_1 $CHCl_3$–MeOH–H_2O (8:3:1), Rf_2 $CHCl_3$–MeOH–AcOH (95:5:3), Rf_3 *n*-BuOH–AcOH–H_2O–AcOEt (1:1:1:1).

Z(OMe)-Amino Acid Active Esters——The active esters of Z(OMe)-amino acids: TCP, PCP, NP, Su and NB esters, were prepared according to the procedure for the preparation of the corresponding Z-derivatives. Among the compounds prepared, Z(OMe)–Met–OTCP and Z(OMe)–Phe–ONP are known compounds.

Z(OMe)–Met–OPCP (Recrystallized from AcOEt and *n*-Hexane): mp 113—115°. $[\alpha]_D^{24}$ −13.4° (c=0.4, THF). *Anal.* Calcd for $C_{20}H_{18}Cl_5NO_5S$: C, 42.76; H, 3.23; N, 2.49. Found: C, 42.20; H, 3.21; N, 2.52.

Z(OMe)–Met–OSu (Recrystallized from Isopropyl Alcohol): mp 85—87°, $[\alpha]_D^{24}$ −13.6° (c=0.9, THF). *Anal.* Calcd for $C_{18}H_{22}NO_7S$: C, 52.67; H, 5.40; N, 6.83. Found: C, 52.66; H, 5.38; N, 6.91.

Z(OMe)–Leu–OPCP (Recrystallized from AcOEt and *n*-Hexane): mp 108—110°. $[\alpha]_D^{24}$ −18.3° (c=0.9, THF). *Anal.* Calcd for $C_{21}H_{20}Cl_5NO_5$: C, 46.39; H, 3.71; N, 2.58. Found: C, 46.07; H, 3.73; N, 2.60.

Z(OMe)–Ile–ONB (Recrystallized from AcOEt and *n*-Hexane): mp 115—118°. $[\alpha]_D^{24}$ −12.5° (c=0.4, THF). *Anal.* Calcd for $C_{24}H_{28}N_2O_7$: C, 63.14; H, 6.18; N, 6.14. Found: C, 63.27; H, 6.34; N, 6.09.

Attempts to solidify Z(OMe)–Met–ONB and Z(OMe)–Arg(Mts)–OSu have been unsuccessful. Z(OMe)–Met–ONB: Rf_1 0.93. Z(OMe)–Arg(Mts)–OSu: Rf_1 0.83.

Z(OMe)-Met-OMe——An ethereal solution of diazomethane was added to an ice-chilled solution of Z(OMe)–Met–OH (1.25 g, 4 mmol) in MeOH (10 ml); the yellow color persisted for 15 min. After addition of a few drops of AcOH, the solvent was evaporated off. The residue was triturated with *n*-hexane and

recrystallized from AcOEt and *n*-hexane; yield 1.06 g (81%), mp 40—43°. $[\alpha]_D^{24}$ −30.8° (c=0.7, MeOH), Rf_2 0.78. *Anal.* Calcd for $C_{15}H_{21}NO_5S$: C, 55.03; H, 6.47; N, 4.28. Found: C, 54.90; H, 6.43; N, 4.33.

Reduction of Z(OMe)-Met-Active Esters with $NaBH_4$——$NaBH_4$ (1.9 g, 50 mmol or 0.95 g, 25 mmol) was dissolved in 80% MeOH (30 ml or 15 ml). To this ice-chilled solution, a solution of Z(OMe)–Met–active ester (5 mmol) in THF–MeOH (8 ml–8 ml) was added dropwise for 15 min. After the addition, stirring was continued in an ice-bath for 15 min, then the solution was neutralized with 1 N HCl. Thin-layer chromatography showed that the starting material had disappeared, and a new spot (Rf_2 0.51) was seen. The solvent was evaporated off and the residue was dissolved in AcOEt. The organic solution was washed with 1 N HCl, 5% $NaHCO_3$ and H_2O–NaCl, dried over Na_2SO_4 and then concentrated. The residue was triturated with *n*-hexane and the resulting powder was recrystallized from AcOEt and *n*-hexane. The results are listed in Table I. The product derived from the PCP ester was characterized by elemental analysis and the others were identified by comparison of the IR spectrum with that of the corresponding authentic sample. mp 62—64°, $[\alpha]_D^{24}$ −24.2° (c=1.4, MeOH), Rf_1 0.70, Rf_2 0.51. *Anal.* Calcd for $C_{14}H_{21}NO_4S$: C, 56.16; H, 7.07; N, 4.68. Found: C, 55.81; H, 6.97; N, 4.75.

L-Methioninol Oxalate——Z(OMe)–Met–ol (2.23 g, 7.5 mmol) derived from the PCP ester was treated with TFA-anisole (6 ml–4 ml) in an ice-bath for 60 min, then *n*-hexane was added. The resulting oily precipitate was dried over KOH pellets *in vacuo* for 3 hr and then dissolved in 5% $NaHCO_3$. The solution was extracted with $CHCl_3$. The organic layer was washed with H_2O–NaCl, dried over Na_2SO_4 and then concentrated. The oily residue was dissolved in EtOH (10 ml) and oxalic acid (0.94 g, 7.5 mmol) in EtOH (10 ml) was added. The resulting solid was recrystallized from EtOH; yield 1.23 g (73%), mp 165—168°, $[\alpha]_D^{24}$ +7.2° (c=0.3, H_2O) (lit.[2] mp 161—161.5°, $[\alpha]_D^{24}$ +6.4° in H_2O), Rf_3 0.68. *Anal.* Calcd for $C_7H_{15}NO_5S$: C, 37.32; H, 6.71; N, 6.22. Found: C, 37.33; H, 6.70; N, 6.23.

Reduction of Various Z(OMe)-Amino Acid Active Esters with $NaBH_4$——To an ice-chilled and stirred solution of $NaBH_4$ (0.95 g, 25 mmol) in 80% MeOH (15 ml), a solution of Z(OMe)-amino acid active ester (5 mmol) in THF–MeOH (8 ml–8 ml) was similarly added and the product was isolated in essentially the manner described above. The results are listed in Table II.

$CH_3(CH_2)_{16}COONB$——In the usual manner, DCC (2.06 g, 10 mmol) was added to a solution of stearic acid (2.84 g, 10 mmol) and HONB (1.79 g, 10 mmol) in THF (20 ml) and the solution was stirred at room temperature for 18 hr. After filtration, the filtrate was concentrated and the residue was triturated with *n*-hexane; yield 4.01 g (90%), mp 66—68°, Rf_2 0.80. *Anal.* Calcd for $C_{27}H_{43}NO_4$: C, 72.77; H, 9.73; N, 3.14. Found: C, 72.75; H, 9.45; N, 3.23.

$CH_3(CH_2)_{16}CH_2OH$ (Stearyl Alcohol)——To an ice-chilled solution of $NaBH_4$ (0.95 g, 25 mmol) in 80% MeOH (20 ml), a solution of $CH_3(CH_2)_{16}COONB$ (2.23 g, 5 mmol) in THF (30 ml) was added dropwise. The mixture was stirred at room temperature for 60 min, then neutralized with 1 N HCl. The solvent was evaporated off, and the residue was dissolved in AcOEt. The organic layer was washed with 1N HCl, 5% $NaHCO_3$ and H_2O–NaCl, dried over Na_2SO_4, and then evaporated to dryness. The resulting powder was recrystallized from EtOH and H_2O; yield 1.08 g (90%). The product was identified as stearyl alcohol by comparison with an authentic sample (Tokyo Kasei Kogyo Co., Ltd., lot. AFO 1). When the reaction was carried out in an ice-bath, the reaction did not reach completion within 60 min. The corresponding methyl ester was treated with $NaBH_4$ at room temperature, but the reaction was incomplete even after 180 min.

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References and Notes

1) The following abbreviations are used: Z(OMe)=*p*-methoxybenzyloxycarbonyl, OPCP=pentachlorophenyl ester, OTCP=2,4,5-trichlorophenyl ester, OSu=N-hydroxysuccinimide ester, ONP=*p*-nitrophenyl ester, ONB=N-hydroxy-5-norbornene-2,3-dicarboximide ester, Met-ol=methioninol, Mts=mesitylene-2-sulfonyl, CHA=cyclohexylamine, DCC=dicyclohexylcarbodiimide, THF=tetrahydrofuran.
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