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Esterification of *N*-(Benzyloxycarbonyl)amino Acids and Amino Acids Using BF_3-Etherate as Catalyst

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Synopsis. Methyl and ethyl esters of *N*-(benzyloxycarbonyl)amino acids were prepared conveniently in good yields using BF_3–etherate as catalyst. Esterification of free amino acids was also examined.

Methyl or ethyl esters of *N*-(benzyloxycarbonyl)amino acids are useful intermediates not only for the peptide syntheses,[1] but also for the preparation of amino aldehydes[2,3] *etc.* While these compounds are usually prepared by benzyloxycarbonylation of amino acid esters, esterification of *N*-(benzyloxycarbonyl)amino acids is also useful and often affords better results than the former.[2] In the latter category, methylation with diazomethane is most widely used. The reagent is, however, highly toxic and known to react with phenol as well as carboxylic acid. Therefore, it is still unsuitable for the large scale preparation. Recently, Meienhofer and his co-workers[4] reported the facile syntheses of

TABLE 2. ETHYL ESTERIFICATION OF *N*-(BENZYLOXYCARBONYL)AMINO ACIDS

Amino acid	Yield (%)	$[\alpha]_D^{20}$ Obsd	Lit (*c*, solvent)
Gly	95[a]		
Ala	90[b]	−38.4	
Val	90[c]	−19.6	
Leu	91	−30.4	−27.5 (1.0 MeOH)[2]
Phe	99	−13.8	
		−11.2[d]	−10.1 (1.4 EtOH)[2]

a) Mp 35—35.5 °C; lit mp 35.5—36.5 °C.[15] b) Found C, 61.94; H, 6.96; N, 5.61%. c) Found C, 64.18; H, 7.66; N, 5.09%. d) *c* 1.4, EtOH.

TABLE 1. METHYL ESTERIFICATION OF *N*-(BENZYLOXYCARBONYL)AMINO ACIDS

Amino acid	Yield (%)	Mp (°C) Obsd	Mp (°C) Lit	$[\alpha]_D^t$ Obsd	$[\alpha]_D^t$ Lit (*c*, solvent, *t* °C)
Gly	88	oil[f]	24.5—25.5[7]		
Ala	89	46—47	45—46[8]	−36.5	−36.0 (1 MeOH 22)[8]
Val	97	55.5—56.5	54—55[9]	−21.9	−18.9 (1 MeOH 20)[9]
Leu	85	oil		−29.5	
Ile	94	oil		−15.5	−11.5 (1.1 MeOH 20)[2]
Phe	95	oil	oil[3]	−17.1	−15.6 (1.02 MeOH 19)[3]
Tyr	95	92—93	92—93[10]	− 9.7	
				−30.4[g]	−32.7 (2 DMF 23)[10]
Ser	93	oil	oil[11]	−14.2	−12.5 (1 MeOH 22)[11]
Thr	92	89—90	90—91[12]	−18.7	−17.3 (1 MeOH 21)[12]
Met	71	oil		−35.6	−34.1 (1.1 MeOH 20)[2]
Cys[a] | Cys	95	71—73	71—73[13]	−96.7	−105 (2 MeOH 22)[13]
Trp	95	oil		−11.8	−11.4 (1.1 MeOH 20)[2]
His[b]	57	75—77		−12.1	
Asp[c]	85	oil	oil[8]	−20.4	
				+27.5[h]	+29.4 (1 $CHCl_3$ 22)[8]
Asn	87	151—152	150[14]	−17.4	
				− 0.9[i]	− 2.0 (AcOH 20)[14]
Glu[c]	94	oil		−22.6	
Pro	94	oil		−64.0	−57.3 (1.0 MeOH 20)[2]
Lys[d]	85	oil		−13.3	−13.0 (1.1 MeOH 20)[2]
Arg[e]	59	oil		−16.0	

a) *N*,*N′*-Bis(benzyloxycarbonyl) derivative. b) Reaction time, 6 h. c) Dimethyl ester. d) *α*,*ε*-Bis(benzyloxycarbonyl) derivative. e) Reaction time, 6 h. Isolated as boron trifluoride monohydrate of the ester (Found: C, 44.28; H, 5.99; N, 13.16%). f) The structure was confirmed by comparing its IR and NMR spectra with those of the authentic sample prepared by methylating Z–Gly–OH with diazomethane. g) *c* 1, DMF, 20 °C. h) *c* 1, $CHCl_3$, 22 °C. i) *c* 1, AcOH, 20 °C.

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Table 3. Methyl esterification of amino acids (esters were isolated as *p*-toluenesulfonates)

Amino acid	Yield (%)	Mp (°C)		$[\alpha]^t_D$	
		Obsd	Lit[16]	Obsd	Lit (*c*, solvent, *t* °C)[16]
Gly	14	115—116	116—117		
Ala	44	105—106		+ 3.7	
Val	60	174—175	175—176	+12.7	+13.4 (10 MeOH 23)
Leu	71	173—174	175.5—176	+11.5	+11.6 (6.9 MeOH 19—23)
Phe	82	162—163	162—162.5	+10.2	+13.1 (7.5 MeOH 19—23)
Glu[a]	73	127—129	130—130.5	+14.5	+15.8 (8.0 MeOH 19—23)

a) Diester.

protected amino acid esters by alkylating their cesium salts.

In another attempt at finding a mild esterification method, we thus utilized the reaction of carboxylic acid with alcohol, using boron trifluoride-etherate as catalyst, which was reported by Kadaba and his co-workers.[5] This method has previously been applied to the preparation of ε-*N*-benzyloxycarbonyl-L-lysine ester by Coggins *et al.*[6] We could successfully extend this method to the esterification of a series of *N*-(benzyloxycarbonyl)amino acids. The results thus obtained are summarized in Tables 1 and 2. The method was very convenient and required neither special apparatus nor complicated manipulation: the alcoholic solution of *N*-(benzyloxycarbonyl)amino acid was refluxed for a short time in the presence of boron trifluoride-etherate. But the reactions of histidine and arginine were exceptionally slow (6 h-reflux was required) and the latter ester was isolated as boron trifluoride salt after the usual work-up.

Moreover, we tried to apply this method to free amino acids. The results are summarized in Table 3. While the results were not as good as in the cases of the *N*-protected amino acids, some lipophilic amino acids gave good results. It should be noted here that washing with water or a saturated aqueous sodium chloride solution, after neutralization of the reaction product, should be avoided, because any washing process markedly decreased the yield and the omission of this process had no influence upon the purity of the ester.

Experimental

The melting points are uncorrected. Optical rotations were measured on a Yanagimoto Polarimeter OR-10 for 1% solutions in methanol at 20 °C unless otherwise stated. The amino acids used in this experiment, except glycine, are all of L-configuration.

Esterification of N-*(Benzyloxycarbonyl)amino Acid.* A solution of *N*-(benzyloxycarbonyl)amino acid (4.76 mmol) in absolute methanol or ethanol (20 ml) was refluxed for 1 h in the presence of BF_3-etherate (10 mmol, 2.1 equivalent). After the solvent was evaporated, the residue was treated with ice-water (40 ml), and extracted with ethyl acetate. The extract was successively washed with water, 1M aqueous sodium hydrogencarbonate solution, and water, and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, almost analytically pure ester was obtained.

Esterification of Amino Acid. A mixture of a finely ground amino acid (2 mmol) and BF_3-etherate (10 mmol) in absolute methanol was refluxed for 24 h. After removal of the solvent, the residue was dissolved in ethyl acetate or ether, neutralized with a saturated aqueous solution of potassium carbonate, and dried over anhydrous sodium sulfate for 1 h. Into this solution was added *p*-toluenesulfonic acid (2 mmol) in ethyl acetate. After 1 h the separated crystals were collected.

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