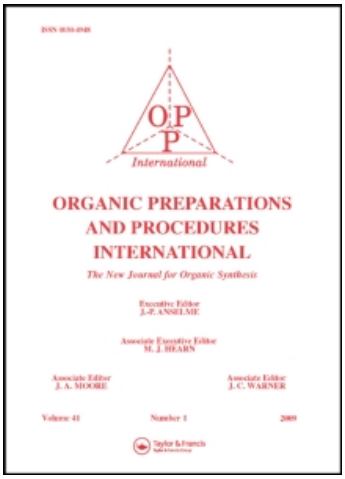

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A CONVENIENT SYNTHESIS OF t-BUTYL ESTERS OF AMINO ACIDS

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4. Water was added to the residue in the reaction vessel immediately after the completion of distillation in order to avoid problems in cleaning.

A CONVENIENT SYNTHESIS OF t-BUTYL ESTERS OF AMINO ACIDS

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(03/17/87)

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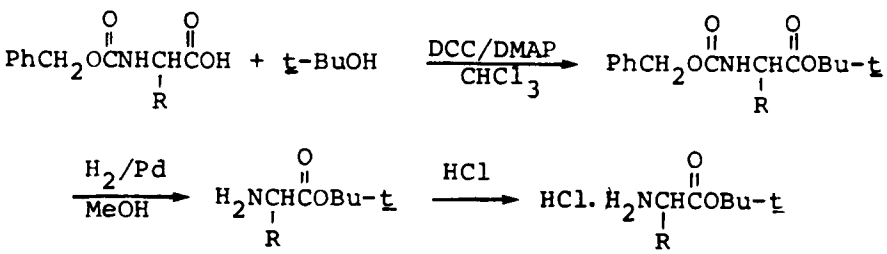
The t-butyl esters of amino acids are valuable precursors of peptide synthesis. The compounds can be prepared from the free amino acids with 2-methyl-1-propene[1] or with t-butyl acetate.[2] The main disadvantages of these methods are the rather low yields and large solvent requirement. Satisfactory yields were obtained, when N-protected amino acids were used as starting compounds, but the average reaction time was still 3-4

days.[3,4] A direct esterification is possible with phosphorus oxychloride,[5] but this procedure is not generally applicable and the work-up is usually difficult. Some other less important methods are also known for the synthesis of t-butyl ester of amino acids.[3,6] We now describe a facile and convenient method which is suitable for the introduction of the t-butyl ester group at any stage of peptide synthesis.

It has been known that carboxylic anhydrides are easily converted to the appropriate esters in the presence of 4-dimethylaminopyridine, even with tertiary alcohols.[7,8] 4-Dimethylaminopyridine was used as a catalyst for the synthesis of depsipeptides[9] and to facilitate coupling in solid phase peptide synthesis.[10] We have prepared the carboxylic anhydrides from the N-benzyloxycarbonyl amino acids with N,N-dicyclohexylcarbodiimide and allowed them to react with 2-methyl-2-propanol in the presence of 4-dimethylaminopyridine (DMAP). In order to avoid racemization, the reaction mixture was kept at 0° and DMAP was added to the reaction mixture last. After removal of the protective benzyloxycarbonyl group by hydrogenolysis in methanol in the presence of 10% Pd/C, the resulting amine was converted to its hydrochloride salt.



We used N-protected amino acids to determine the scope and limitations of this method. It was possible to obtain t-butyl esters from multifunctional amino acids (see the example with glutamic acid or the lysine derivative); an additional example with a dipeptide is also given. The advantages of this method are the mild and simple reaction conditions,

simple work-up, the formation of optically pure products and possible extension to large-scale preparation.

EXPERIMENTAL SECTION

General Procedure.- To a stirred solution of the N-benzyloxycarbonyl amino acid (30 mmol) in a mixture of chloroform (25 ml) and 2-methyl-2-propanol (4 ml) cooled in an ice-water bath, was added a solution of dicyclohexylcarbodiimide (33 mmol) in chloroform (25 ml). Then 4-dimethylaminopyridine (0.3 mmol) was added to the reaction mixture. Stirring was continued at 0° for 2 hrs, then the mixture was kept at 4° overnight. The precipitated dicyclohexylurea was removed by filtration and the solvent was evaporated in vacuo. The residue was dissolved in ethyl acetate (100 ml) and acetic acid (1 ml) was added. The solution was kept at 4° for 2 hrs. After filtration, the solution was washed with 5% sodium bicarbonate and water and dried over magnesium sulfate. The residue obtained after removal of the solvent in vacuo was dissolved in methanol (100 ml) and hydrogenolyzed over 10% Pd/C under hydrogen atmosphere for 1 hr. The reaction mixture was filtered and the solvent was removed in vacuo. The residue was dissolved in methanol (10 ml) and 2M hydrogen chloride (31 mmol) in methanol was added and the solution was diluted with diethyl ether. The solid product was collected, washed with ether and dried.

TABLE. Physical Data of t-Butylesters

Compound	Yield (%)	mp. [lit.][a]	$[\alpha]_D^{25}$ [lit.][a]	Analytical Data C (calculated)	H (calculated)	N (calculated)
HCl.HAlaO^{t}Bu	79	168(dec.)	+3.0(c=2 EtOH)	46.28	8.88	7.71
		[167][11]	[+1.7(c=2 EtOH)][11]	(45.92)	(8.57)	(7.63)
HCl.HGlnO^{t}Bu	75	149(dec.)	+21.7(c=1 MeOH)[b]	45.28	8.02	11.74
		-	[-15.6(c=1 MeOH)][13]	(45.19)	(8.00)	(12.05)
HCl.HGlu(O^{t}Bu)O^{t}Bu	76	115-116	+17.5(c=2 EtOH)	52.76	8.86	4.74
		[116-117][2]	[+18.7(c=2 EtOH)][2]	(52.64)	(8.61)	(4.83)
HCl.HGlyO^{t}Bu	81	140-141	-	42.99	8.42	8.36
		[135][4]	-	(43.22)	(8.57)	(8.18)
HCl.HLeuO^{t}Bu	75	164-165	+16.3(c=2 EtOH)	53.68	9.91	6.26
		[166-167][1]	[+12.4(c=2 EtOH)][1]	(53.33)	(9.94)	(6.17)
HCl.HLys(Boc)O^{t}Bu	56	146-147	+12.7(c=1 EtOH)	53.17	9.22	8.27
		[139-140][12]	[+12.1(c=1 EtOH)][12]	(53.19)	(9.24)	(8.21)
HCl.HPheO^{t}Bu	76	230(dec.)	+27.3(c=2 EtOH)	60.58	7.82	5.43
		-	[+44.2(c=2 EtOH)][1]	(59.88)	(7.44)	(5.50)
HCl.HProO^{t}Bu	71	109-111	-31.0(c=2 EtOH)	52.06	8.73	6.74
		[110-112][4]	[-30.5(c=2 EtOH)][4]	(52.23)	(8.57)	(6.77)
HCl.HTrpO^{t}Bu	68	214(dec.)	+3.4(c=1 MeOH)	60.70	7.13	9.44
		-	-	(60.61)	(7.18)	(9.27)
ZPheLeuO^{t}Bu	72	82-86	-27.3(c=1 MeOH)	68.86	7.14	5.88
		[94-95][14]	[-27.0(c=1 MeOH)][14]	(69.15)	(7.74)	(5.98)

a) See references. b) The opposite rotation is given in ref. 13.

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A CONVENIENT SYNTHESIS OF β-KETO DIESTERS

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In connection with our studies of the reaction of ethoxymethylenemalononitrile with active methylene compounds,[1,2] we had need for a convenient and general synthesis of ω-carbethoxy β-keto esters. In 1978, Yonemitsu and coworkers[3] described a general and versatile method for the preparation of β-keto esters. In this method, Meldrum's acid 1 is acylated in the presence of pyridine with an acyl chloride to give the C-acylated derivative, which usually exists largely in the enol form (see 3). When heated under reflux with an alcohol, the acyl derivative is rapidly converted into the β-keto ester. We report herein the preparation