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Note

Ultrasound accelerated synthesis of proteinogenic and α,α-dialkylamino acid ester salts

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A simple and efficient sonochemical esterification of proteinogenic as well as cyclic α,α-dialkyl amino acid methyl and ethyl ester hydrochloride salts employing thionyl chloride and alcohol has been reported. All the amino acid esters made have been obtained in good yield (94-98%) as pure compounds.

Keywords: Amino acid methyl ester hydrochloride, *α,α*-dialkyl amino acid methyl ester hydrochloride, ultrasound accelerated

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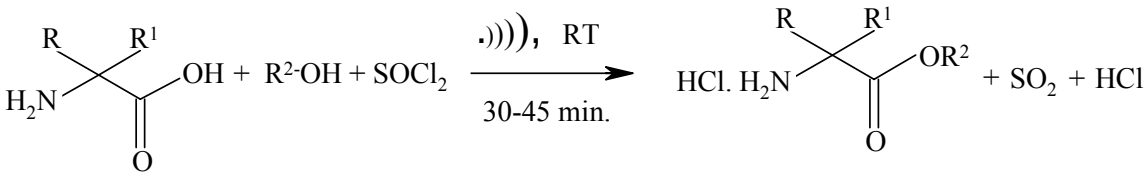
Methyl esters are excellent permanent protecting groups which additionally allow conversion of amino acid or peptide derivatives into amides or hydrazides by simple ammonolysis or hydrazinolysis respectively. The classical method of ester preparation involves the treatment of a suspension of amino acid hydrochloride in methanol in presence of gaseous HCl as a catalyst[1-3]. Hydrolytic and alcholytic cleavage of the side chain amide groups of glutamine and asparagine along with peptide bond cleavage prevents the use of this method for the esterification of peptide fragments. Alternatively, the synthesis of amino acid methyl esters has also been carried out by reaction of unprotected amino acid with 2,2-dimethoxypropane in presence of HCl[4]. The methyl esters of amino acids can be prepared under mild conditions by reaction with lithium hydroxide monohydrate/dimethylsulfate in THF[5]. The efficient and racemization free synthesis of amino acid methyl esters has been generally carried out using thionyl chloride and methanol as a solvent[6,7]. The by-products HCl and SO_2 can be easily removed from the equilibrium during this process[8].

Ultrasound has been employed to enhance the reaction rate in a large number of classical organic reactions[9,10]. Several articles have been published over the past few years describing the various applications of ultrasound in chemical synthesis[11-13]. A few examples such as the synthesis of Fmoc-β-amino acids[14], isocyanates derived from N^{α}-Fmoc-amino acids[15], N^{α}-Fmoc-amino acid chlorides[16], anchoring zinc salts of Boc-amino acids to Merrifield resin[17] and cleavage of protected peptides from polystyrene supports using aqueous sodium hydroxide[18], have been developed utilizing ultrasound. Herein is presented a simple and efficient method for the esterification of the carboxylic group of amino acids using alcohol (methanol or ethanol) in the presence of $SOCl_2$ and assisted by ultrasonic waves.

Results and Discussion

The standard procedure for the synthesis of amino acid esters involves the refluxing of a reaction mixture of an amino acid and methanol/ethanol for about 2-4 h or stirring of a mixture for over 24 h at RT (25-30ºC). In the present protocol, the esterification reactions have been carried out in an ultrasonic bath at ambient temperature. It has been demonstrated that the esterification can be significantly accelerated by the use of ultrasound (**Scheme I**). In a typical reaction, to cooled dry methanol, freshly distilled $SOCl_2$ was added. And, amino acid was slowly added and subjected to ultrasonication at ambient temperature using an ultrasonic bath. The reaction at ambient temperature, as monitored by TLC and IR, has been found to be complete in about 25-45 min.

The synthesis of methyl esters of Aib (α-amino-isobutyric acid) and several cyclic α,α-dialkyl amino acids[19] such as Ac_5c (1-aminocyclopentane-1-carboxylic acid), Ac_6c (1-aminocyclohexane-1-carboxylic acid), Ac_7c (1-aminocycloheptane-1-carboxylic acid) (**Table I**) has also been carried out. In their synthesis, the duration of the reaction was extended upto 1 h. After the completion of the reaction, the concentration of the resulting mixture under reduced pressure followed by purification by recrystallization using methanol and dry ether (1:2) resulted in the isolation of the amino acid ester salts. All the esters synthesized have been isolated as pure compounds and fully characterized by IR and ^{1}H NMR.



$R^2 = CH_3, C_2H_5$

R = side chain of amino acids, R^1 = H; R, R^1 = CH_3, -$(CH_2)_4$-, -$(CH_2)_5$-, -$(CH_2)_6$-,

Scheme I

Table I—Physical characterization data of amino acid ester salts

Amino acid derivatives	Time (min)	Yield (%)	m.p. (°C) Obs.	m.p. (°C) Lit.[4,20,21]	TLC R_fA	TLC R_fB	$[\alpha]_D^{25}$ Obs.	$[\alpha]_D^{25}$ Lit.[4,20,21]
H-Ala-OMe. HCl	30	98	108-10	111	0.38	0.68	+5.4 (c 2.9, MeOH)	+5.8
H-Gly-OMe. HCl	30	99	168-70	174-75	0.40	0.70	—	
H-Leu-OMe. HCl	35	96	150-52	146-48	0.38	0.68	-15.6 (c 1, MeOH)	
H-Phe-OMe. HCl	35	98	156-58	156-58	0.40	0.50	+35.2 (c 1, MeOH)	
H-Val-OMe. HCl	30	98	172-74	175	0.42	0.52	+15.0 (c 2, MeOH)	+15.5
H-Phg-OMe. HCl	35	96	165-67	165-67	0.44	0.50	-36.6 (c 1, MeOH)	
H-D-Phg-OMe. HCl	35	95	164-66	164-66	0.44	0.51	+36.3 (c 1, MeOH)	
H-Pro-OMe. HCl	35	96	68-70	71	0.48	0.58	-35.2 (c 1.1, DMF)	-35.5
H-Ser(OBn)-OMe.HCl	40	97	165	168	0.42	0.54	-8.4 (c1, MeOH)	-9.0
H-Tyr-OMe. HCl	40	95	183-85	184-85	0.40	0.52	+72.0(c 3, pyridine)	+72.4
H-Met-OMe. HCl	40	96	144-46	145-46	0.42	0.56	+26.5 (c 2, H_2O)	+26.8
H-His-OMe. 2HCl	40	94	203-05	199-02	0.34	0.48	+10.4 (c 2, H_2O)	+10.2
H-Trp-OMe. HCl	40	96	212-14	216	0.36	0.50	+4.6 (c 2, MeOH)	+4.0
H-Arg-OMe. 2HCl	40	95	192-94	196	0.34	0.56	+21.5 (c 2.5, MeOH)	+21.7
H-Thr-OMe. HCl	35	96	68-70	70-2	0.36	0.58	-12.0 (c 1, EtOH)	-11.4
H-Cys(OBn)-OMe.HCl	35	94	160-62	165	0.38	0.56	- 9.2 (c 1, MeOH)	-9.0
H-Gly-OEt. HCl	35	98	143-45	145-47	0.40	0.62	—	
H-Ala-OEt. HCl	35	96	75-7	77-8	0.40	0.60	-4.6 (c 1, MeOH)	-4.0
H-Phe-OEt. HCl	35	98	157-59	154-55	0.42	0.48	-7.4 (c 1, MeOH)	-7.0
H-Aib-OMe. HCl	50	95	188-90	192-93	0.34	0.56	—	
H-Ac_5c-OMe. HCl	55	96	207-10	210-05	0.32	0.54	—	
H-Ac_6c-OMe. HCl	60	94	210-12	208-10	0.32	0.54	—	
H-Ac_7c-OMe. HCl	60	95	212-14	214-16	0.30	0.56	—	

Experimental Section

All the solvents were freshly distilled prior to use. Melting points were determined by the capillary method and are uncorrected. TLC analysis was carried out on precoated silica gel plates using either of two solvent systems *viz*. A) *n*-butanol:acetic acid : water (40:1:1, v/v/v) and B) *n*-butanol:acetic acid:water (40:1:5, v/v/v) and the R_f values are designated as R_fA and R_fB respectively. IR spectra were recorded on a Nicolet Impact 400D FT-IR spectrometer (KBr pellets, 3 cm^{-1} resolution). Optical rotations were determined using automatic AA-10 polarimeter (Optical Activity, U.K.). The ultrasonication was carried out using a sonic bath (35 kHz, Elma, T 310/H, Germany) at ambient temperature.

General procedure for the preparation of amino acid ester salts: Freshly distilled $SOCl_2$ (1.3 mL, 11 mmoles) was added to absolute methanol or ethanol (10 mL) cooled to -10°C. Amino acid (10 mmoles) was suspended in the reaction mixture and

subjected to ultrasonication at RT until completion of the reaction. The progress of the reaction was monitored by TLC and IR. On completion of the reaction, the solvent was removed under reduced pressure and the residue was purified by recrystallization from methanol: diethyl ether. Yields of the isolated products are shown in **Table I**.

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