

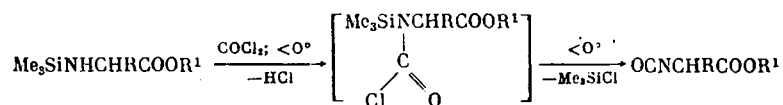
CONVENIENT METHOD FOR PREPARATION OF ESTERS OF N-CARBONYL- α -AMINO ACIDS

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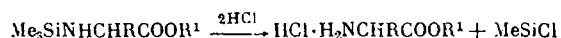
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The esters of N-carbonyl- α -amino acids have interest as reactive intermediates for the synthesis of peptides and the modification of biologically active compounds by amino acids [1, 2]. They are most frequently obtained by reacting the ester hydrochlorides of the corresponding amino acids with COCl_2 in a high-boiling aromatic hydrocarbon (toluene or xylene) as the medium at 120-160°C [3]. The reaction is slow and requires a large consumption of COCl_2 . In addition, the drastic conditions of the process create the danger of racemizing the optically active derivatives and favor the progress of side reactions.

Previously [4] it was reported that the esters of N-carbonyl- α -amino acids can be obtained by reacting the N-trimethylsilyl derivatives of the corresponding esters with COCl_2 below 0°. In the case of neutral amino acids the reaction proceeds with a quite high yield of the ester (60-70%) and is completed in several minutes when either an equimolar amount or a slight excess of COCl_2 is used. There is reason to assume [5] that the reaction proceeds via the step of forming the intermediate N-trimethylsilylcarbamoyl chlorides, for which the tendency to undergo β -decomposition is characteristic, and this is responsible for the thermal instability of these derivatives:



At the same time, the HCl that is formed in the first step and remains in the reaction mixture at low temperature, can cause the undesirable cleavage of the trimethylsilyl group and the formation of the corresponding ester hydrochlorides of the amino acids:



Actually, the formation of a substantial amount of the ester hydrochlorides of the corresponding amino acids and a decrease in the yield of the desired isocyanates were observed in a number of cases when the esters of the N-trimethylsilyl- α -amino acids are reacted with COCl_2 . In view of this it was expedient to investigate the effect of adding a tertiary amine as an HCl acceptor on the yield of the desired products. The reaction was run at -30 to 0° in an organic solvent (ether, THF, hexane). It proved that the addition of at least an equimolar amount of a tertiary amine made it possible to substantially increase the yield of the alkyl esters of the N-carbonyl- α -amino acids and bring it up to 80-95%, and at the same time exclude the formation of the above mentioned by-products.

In the series of studied tertiary amines (triethylamine, pyridine, N-methylmorpholine, dimethylaniline) the best results were obtained when an equimolar amount of triethylamine was used, which can be explained by its higher basicity when compared with the other tertiary amines.

The starting alkyl esters of the N-trimethylsilyl- α -amino acids are obtained in high yield by reacting the ester hydrochlorides of the α -amino acids with a suitable silylating agent [6, 7], for example trimethyldiethylamine. The constants of all of the synthesized compounds are given in Table 1.

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TABLE 1
 $\text{OCNCHCOOC}_2\text{H}_5$
 $\begin{array}{c} | \\ \text{R} \end{array}$

R	Amino acid	Yield, %	bp, °C (mm)	n_D^{20}	$[\alpha]_D^{20}$ (Cl, dioxane)	Found, %			Empirical formula	Calculated, %		
						C	H	N		C	H	N
H	Gly	85	80(20)	1,4251	—	46,48	5,43	10,80	$\text{C}_3\text{H}_7\text{NO}_3$	46,51	5,46	10,84
C_6H_5	L-Leu	94	103(15)	1,4258	-22,1	58,17	8,12	7,49	$\text{C}_{10}\text{H}_{13}\text{NO}_3$	58,25	8,05	7,55
C_6H_5	L- β -Leu	92	113(20)	1,4342	—	58,34	8,10	7,64	$\text{C}_9\text{H}_{12}\text{NO}_3$	58,25	8,05	7,55
C_6H_7	D,L-Val	90	73(8)	1,4249	—	55,81	7,58	8,10	$\text{C}_8\text{H}_{11}\text{NO}_3$	55,89	7,62	8,15
CH_3	L-Ala	92	70(15)	1,4249	—	50,28	6,30	9,80	$\text{C}_6\text{H}_9\text{NO}_3$	50,34	6,34	9,78
$(\text{CH}_3)_3\text{SCH}_3$	D,L-Meth	87	106(1,0)	1,4249	—	47,08	6,43	6,87	$\text{C}_8\text{H}_{13}\text{NSO}_3$	47,30	6,44	6,88
$(\text{CH}_3)_4\text{NCO}$	L-Lys	80	126-128(1,0)	1,4572	-34,8	53,16	6,23	12,20	$\text{C}_{10}\text{H}_{14}\text{N}_2\text{O}_4$	53,09	6,23	12,33
$(\text{CH}_3)_3\text{NCO}$	L-Orn	94	114-117(1,0)	1,4568	-20,4	50,78	5,63	12,93	$\text{C}_8\text{H}_{12}\text{N}_2\text{O}_4$	50,93	5,65	13,25

EXPERIMENTAL

The optical activity of the obtained compounds was measured on a Gouan polarimeter.

Typical Method for Preparation of Esters of N-Carbonyl- α -amino Acids. In a flask equipped with a stirrer, thermometer, and a deeply cooled reflux condenser were placed 1 mole of the N-trimethylsilyl- α -amino acid ester and 1 mole of triethylamine in bas. ether and to the stirred mixture was added at -30° a solution of 1.1 moles of COCl_2 in abs. ether. The temperature of the stirred mixture was brought up to $\sim 20^{\circ}$ and the obtained precipitate of $\text{Et}_3\text{N} \cdot \text{HCl}$ was filtered. The filtrate was evaporated and the residue was fractionally distilled in vacuo.

CONCLUSIONS

A convenient method was proposed for obtaining the esters of N-carbonyl- α -amino acids, which is based on the reaction of the esters of N-trimethylsilyl- α -amino acids with phosgene in the presence of a tertiary amine.

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