Synthesis of *N*-(imidomethyl)glycine esters from alkyl glycinates, imides of dicarboxylic acids, and formaldehyde

S. G. Zlotin, I. V. Sharova, and O. A. Luk'yanov*

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., 117913 Moscow, Russian Federation. Fax: +7 (095) 135 5328

A method for preparing *N*-(imidomethyl)glycine esters by the reaction of alkyl glycinates with formaldehyde and imides has been developed.

Key words: alkyl glycinates, formaldehyde, imides, Mannich bases.

Previously we reported the synthesis of esters of *N*-(amidomethyl)glycine, which are possible carriers of therapeutically useful substances into the cells of living organisms, by the reaction of alkyl glycinates with formaldehyde and aroylamides.[1] In the present work we have demonstrated for the first time the possibility of introducing an imidomethyl substituent into the amino group of esters of α-amino acids using the reactions of glycine esters with formaldehyde and imides of dicarboxylic acids as examples.

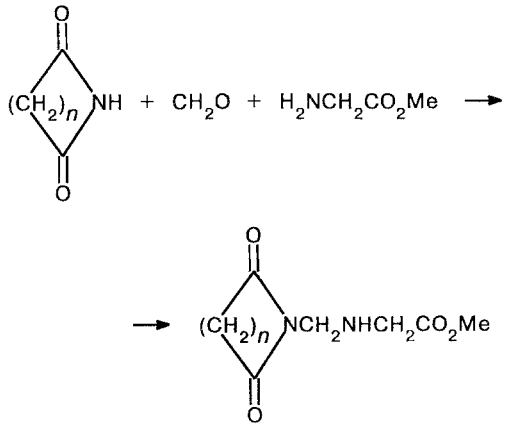
Imides of both aliphatic (succininc, glutaric) and aromatic (*o*-phthalic and *m*-nitro-*o*-phthalic) dicarboxylic acids were found to react with alkyl glycinates and formaldehyde when they are heated in Pr^{i}OH to give *N*-(imidomethyl)glycinates (**1—5**) in 53—77 % yields (Scheme 1).

The structure of the imide component exerts an effect on the process of condensation. In fact, succinimide reacts with formaldehyde and methyl glycinate to give adduct **1** even on short-term (~5 min) heating in Pr^{i}OH, whereas to achieve a preparative yield (53 %) of the Mannich base (**2**) derived from glutarimide, boiling of the reaction mixture for 1 h is required. The reaction of 4-nitrophthalimide with formaldehyde and methyl glycinate, irrespective of the temperature and duration of the condensation, affords a mixture of adduct **5** and the starting 4-nitrophthalimide that is difficult to separate. According to IR spectroscopy, the desired aminomethylimide **5** is the major component of this mixture.

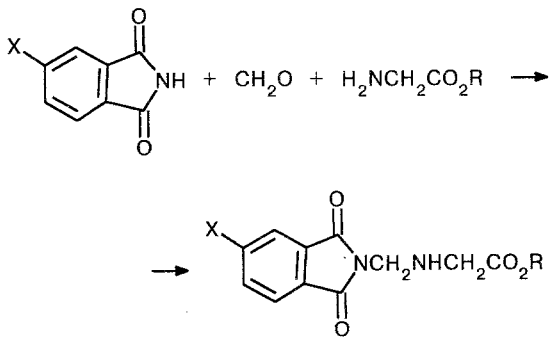
Unlike imides of dicarboxylic acids, diacetamide gives no crystalline adduct with formaldehyde and alkyl glycinates.

It should be noted that acetates or hydrochlorides of glycine esters, unlike the free bases, do not produce adducts **1—5** or their salts with formaldehyde and imides, and they are recovered from the reaction mixtures unchanged. We believe that this is due to the fact that the formation of **1—5** is an equilibrium process, and in acidic media this equilibrium shifts toward the starting compounds. In fact, when we heated adduct **1** in Pr^{i}OH

Scheme 1



1: $n = 2$
2: $n = 2$



3: X = H, R = Me
4: X = H, R = Et
5: X = NO_2, R = Me

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 7, pp. 1306—1307, July, 1995.

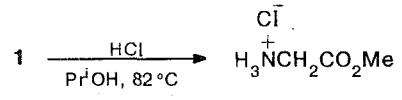
1066-5285/95/4407-1260$12.50

Table 1. Melting points, yields, and IR and ^{1}H NMR spectral data of adducts **1—5**

Compound	M.p. °C	Yield (%)	IR, ν/cm^{-1}		^{1}H NMR, δ							Found / Calculated (%)		
					R									
			C=O	NH	CH_2	CH_3	CH_2	Ar	NCH_2C	NCH_2N	NH	C	H	N
1	130—135	57	1700 1750	2980	—	3.56 s	2.6 s (4 H)	—	3.65 s	4.55 s	3.80 s	47.79 48.00	5.88 6.00	13.72 14.00
2	93—97	53	1680 1735 1750	2920 2960	—	3.62 s	1.93 t (2 H) 2.60 t (4 H)	— —	3.66 s	4.87 s	3.94 s	50.13 50.47	6.77 6.54	12.65 13.08
3	107—112	76	1710 1750 1770	2900 2950	—	3.50 s	—	7.83 s (4 H)	3.77 s	4.83 s	4.00 s	57.67 58.06	5.08 4.84	10.65 11.29
4	88—90	77	1710 1730 1770	2950 3000	3.97 q	1.13 t	—	7.89 s (4 H)	3.78 s	4.89 s	4.02 s	59.23 59.54	5.51 5.34	10.19 10.68
5*	166—171	54	1710 1745 1780	2980 3100	—	—	—	—	—	—	—	—	—	—

* The ^{1}H NMR spectrum of the adduct could not be recorded due to its poor solubility in organic solvents.

in the presence of hydrochloric acid, we isolated methyl glycinate hydrochloride in 33 % yield.



Compounds **1—5** synthesized are stable crystalline solids. The structures of adducts **1—4** were determined by the IR and ^{1}H NMR spectra (Table 1) and confirmed by the results of elemental analysis. The structure of adduct **5**, which we were not able to isolate in the analytically pure state, was proved by the synthesis of its functional derivatives at the amino group.[2]

Experimental

The IR spectra of solids were recorded on a Specord-IR-75 spectrometer in KBr. ^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer in acetone-d_6 or $CDCl_3$.

***N*-Imidomethylglycinates (1—5).** $MeCOONa \cdot 3H_2O$ (0.95 mmol) and 25% Formalin (0.88 mL, 0.95 mmol) were successively added with stirring to a solution of alkyl glycinate hydrochloride (0.95 mmol) and imide (0.95 mmol) in Pr^{i}OH heated to the boiling temperature. The reaction mixture was cooled, kept for 24 h at ~20 °C (in the case of adduct **2** or **5**, it was preliminarily refluxed for 1 h), and washed with acetone and chloroform. The solvent was removed, and products **1—5** were crystallized by treatment with dry ether (2—3 mL). The yields, melting points, and the IR and ^{1}H NMR spectral data of adducts **1—5** are listed in Table 1. For compounds **1—4**, satisfactory data of elemental analysis were obtained.

Reaction of methyl *N*-succinimidomethylglycinate (1) with hydrochloric acid. A solution of adduct **1** (0.1 g, 0.5 mmol) in Pr^{i}OH was acidified with hydrochloric acid to pH 2—3. The reaction mixture was boiled for 15 min and kept for 24 h at ~20 °C. The precipitate was filtered off and dried in an air flow to give 0.02 g (33 %) of methyl glycinate hydrochloride, m.p. 175—181 °C.

References

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Received December 16, 1994