Synthesis of alkyl *N*-(α-amidomethyl)glycinates from glycine esters, aroylamides, and formaldehyde

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A one-step synthesis of alkyl *N*-(α-amidomethyl)glycinates from glycine esters or their salts, formaldehyde, and aroylamides was developed. The effect of the structure of the amide component and the reaction conditions on the yields of the products was investigated.

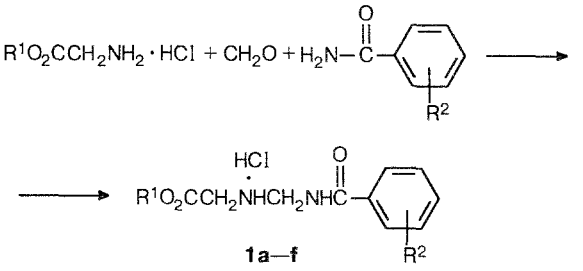
Key words: glycine, esters; formaldehyde; aroylamides; Mannich bases.

Compounds containing the N—C—N structural moiety, in which one or both nitrogen atoms are incorporated in a CO—NH peptide bond between α-amino acid residues, are convenient models for the study of the mechanism of the biological action of peptides.[1—5] Moreover, they seem to be promising carriers of therapeutically useful compounds into microbial cells.[6—8] It can be assumed that compounds that contain a N—C—N moiety incorporated in the amino group of functional derivatives of α-amino acids and in the terminal amino group of peptides should possess useful biological properties.

It has been reported previously[9] that α-amino acids react with formaldehyde and amides to give *N*-(α-amidomethyl) derivatives of α-amino acids, which have high antibacterial activity.[10] Neither α-amino acids modified at the carboxyl group nor peptides have been used in this reaction before.

It the present work we demonstrated for the first time that the reaction of glycine esters or salts with formaldehyde and amides of aromatic acids makes it possible to introduce an amidomethyl substituent at the amino group of an α-amino acid derivative containing a protected carboxyl group.

Hydrochlorides of methyl or ethyl glycinates were used as alkyl glycinates; benzamide as well as *p*- and *m*-substituted benzamides were used as amides. It was shown that the above compounds undergo a three-component reaction in an organic solvent at 20—100 °C to give the salts of (*N*-amidomethyl)glycinates (**1a—f**).



The yields of compounds **1** depend on the structure of the amide and on the reaction conditions (Table 1).

Table 1. Effect of reaction conditions on the yields of alkyl *N*-amidomethylglycynate hydrochlorides **1a—f**

Compound	R^1	R^2	Solvent	*T*/°C	Time	Method of synthesis	Yield (%)
1a	Me	H	*i*-PrOH	82	15 min	A	89
1a	Me	H	*i*-PrOH	20—25	24 h	B	61
1b	Et	H	*i*-PrOH	82	15 min	A	80
1c	Me	*p*-NO_2	*i*-PrOH	82	15 min	A	40
1c	Me	*p*-NO_2	*i*-PrOH	82	30 min	A	52* (83)
1d	Et	*p*-NO_2	*i*-PrOH	82	10—15 min	A	17
1d	Et	*p*-NO_2	*i*-PrOH	82	40—50 min	A	34*
1d	Et	*p*-NO_2	Dioxane	20—25	24 h	A	81
1e	Me	*m*-NO_2	*i*-PrOH	82	40—45 min	A	0*
1e	Me	*m*-NO_2	Dioxane	101	3—5 min	A	90
1e	Me	*m*-NO_2	*i*-PrOH	20—25	24 h	B	52
1f	Et	*m*-NO_2	Dioxane	101	3—5 min	A	85

* The reactions were carried out with continuous removal of water by azeotropic distillation.

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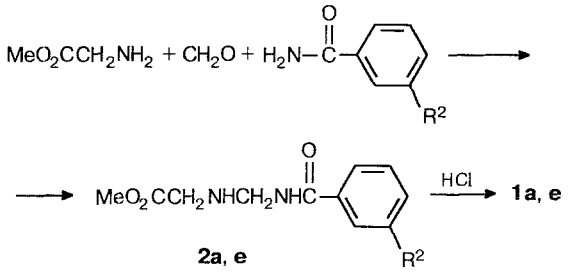
Hydrochlorides **1a—f** were obtained in preparative yields by heating all three reagents together in a suitable solvent at 80—100 °C. The reactions involving nitro-substituted benzamides take longer than similar reactions with benzamide. The yields of compounds **1a—f** can be increased significantly if the reaction is carried out either in a hydroxyl-containing solvent (such as *i*-PrOH) with simultaneous removal of water by azeotropic distillation, or in an aprotic solvent. For example, the use of dioxane permits one to obtain adducts **1e,f**, which practically do not form under other conditions studied, in nearly quantitative yield.

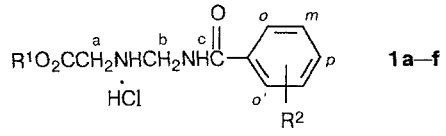
Not only hydrochlorides of alkyl glycinates but also free bases can undergo condensation with amides and formaldehyde.

The reactions involving the free alkyl glycinates occur under milder conditions than the condensation of the respective salts (Table 1). For example, methyl glycinate, obtained *in situ* from the respective hydrochloride by treatment with an equimolar amount of ethanolic NaOH, reacts with CH_2O and amides even at room temperature. The Mannich bases thus formed (**2a,e**) can be isolated (although in low yields) in the chemically pure state (*e.g.*, compound **2e**) or transformed, without isolation and purification, to the corresponding hydrochlorides (**1a,e**) by treatment with an ethanolic solution of HCl.



Compounds **1a—f** and **2e** are stable crystalline substances that can undergo further transformations involving the amino and alkoxycarbonyl groups. The structures of these compounds follow from their IR, ^1H NMR (Table 2), and ^{13}C NMR spectral data and are confirmed by the data of their elemental analyses.

Table 2. Melting points and IR and ^1H NMR spectroscopic data for alkyl *N*-(α-amidomethyl)glycinate hydrochlorides



Compound	R^1	R^2	M.p./°C	IR, ν/cm^{-1}	^1H NMR, δ, *J*/Hz
1a	Me	H	150—155	1752 (νC=O, ester) 1660 (νC=O, amide) 2640—3336 (νNH)	3.71 (s, 3 H, Me); 4.03 (s, 2 H, CCH_2N); 4.64 (d, 2 H, NCH_2N, *J* = 6.3); 7.50 (t, 2 H, *m*-H, *J* = 7.4); 7.59 (t, 1 H, *p*-H, *J* = 7.4); 7.99 (d, 2 H, *o*-H, *J* = 7.4); 9.81 (t, 1 H, C(O)NH, *J* = 6.3)
1b	Et	H	128—132	1744 (νC=O, ester) 1660 (νC=O, amide) 2631—3312 (νNH)	1.22 (t, 3 H, Me, *J* = 7.0); 4.01 (s, 2 H, CCH_2N); 4.16 (q, 2 H, CH_2Me, *J* = 7.8); 4.64 (d, 2 H, NCH_2N, *J* = 6.3); 7.51 (t, 2 H, *m*-H, *J* = 7.3); 7.60 (t, 1 H, *p*-H, *J* = 7.3); 8.00 (d, 2 H, *o*-H, *J* = 7.3); 9.80 (t, 1 H, C(O)NH, *J* = 6.3)
1c	Me	*p*-NO_2	201—204	1750 (νC=O, ester) 1670 (νC=O, amide) 1520 (νNO_2) 2590—3360 (νNH)	3.72 (s, 3 H, Me); 4.02 (s, 2 H, CCH_2N); 4.62 (br.s, 2 H, NCH_2N); 8.12 (d, 2 H, *o*-H, *J* = 10.5); 8.33 (d, 2 H, *m*-H, *J* = 10.5); 9.84 (t, 1 H, C(O)NH, *J* = 7.5)
1d	Et	*p*-NO_2	193—195	1750 (νC=O, ester) 1670 (νC=O, amide) 1520 (νNO_2) 2590—3370 (νNH)	1.20 (t, 3 H, Me, *J* = 8.5); 4.00 (s, 2 H, CCH_2N); 4.18 (q, 2 H, CH_2Me, *J* = 8.5); 4.62 (m, 2 H, NCH_2N); 8.12 (d, 2 H, *o*-H, *J* = 10.5); 8.33 (d, 2 H, *m*-H, *J* = 10.5); 9.66 (t, 1 H, C(O)NH, *J* = 7.5)
1e	Me	*m*-NO_2	180—185	1745 (νC=O, ester) 1660 (νC=O, amide) 1530 (νNO_2) 2590—3350 (νNH)	3.74 (s, 3 H, Me); 4.05 (s, 2 H, CCH_2N); 4.64 (d, 2 H, NCH_2N, *J* = 7.7); 7.83 (t, 1 H, *m*-H, *J* = 9.0); 8.39 (d, 1 H, *o*-H, *J* = 9.0); 8.43 (d, 2 H, *p*-H, *J* = 9.0); 8.73 (s, 1 H, *o'*-H); 10.04 (t, 1 H, C(O)NH, *J* = 7.7)
1f	Et	*m*-NO_2	178—184	1745 (νC=O, ester) 1660 (νC=O, amide) 1530 (νNO_2) 2600—3350 (νNH)	1.21 (t, 3 H, Me, *J* = 8.5); 4.03 (s, 2 H, CCH_2N); 4.17 (q, 2 H, CH_2Me, *J* = 8.5); 4.64 (d, 2 H, NCH_2N, *J* = 7.7); 7.81 (t, 1 H, *m*-H, *J* = 9.0); 8.35 (d, 1 H, *o*-H, *J* = 9.0); 8.44 (d, 1 H, *p*-H, *J* = 9.0); 8.73 (s, 1 H, *o'*-H); 9.95 (t, 1 H, C(O)NH, *J* = 7.7)

Experimental

The IR spectra of solid compounds were recorded in KBr pellets on a Specord-75 IR spectrometer. ^1H and ^{13}C NMR spectra were obtained in DMSO-d_6 on a Bruker AM-300 spectrometer at frequencies of 300.13 MHz (^1H) and 75.5 MHz (^{13}C). The chemical shifts of ^1H and ^{13}C signals were measured relative to DMSO-d_6 (δ 39.57).

Hydrochlorides of *N*-amidomethyl glycinates (1a—f). Method A. A 31 % solution of formaldehyde (0.09 mL, 0.93 mmol) was added to a boiling solution of a glycinate hydrochloride (0.93 mmol) and a benzamide (0.93 mmol) in an appropriate solvent. The reaction was performed under the conditions indicated in Table 1. The reaction mixture was kept for 24 h at ~20 °C. The precipitated hydrochloride was collected by filtration, washed with the same solvent (1—2 mL), and dried in a stream of air. Salts **1a,b** were purified by reprecipitation with ether from a methanolic solution. Compounds **1c—f** required no additional purification. The yields of compounds **1a—f** are presented in Table 1. The melting points along with the IR and ^1H NMR spectroscopic data are presented in Table 2. The results of the elemental analyses of compounds **1a—f** were satisfactory.

^{13}C NMR, δ, for compound **1a**: 44.8 (N—CH_2(C)); 51.6 (N—CH_2—N); 52.6 (OCH_3); 127.8, 128.6 (*o*-, *m*-C, Ar); 132.3 (*p*-C, Ar); 167.0, 167.5 (C=O); for **1b**: 13.9 (CH_3); 44.8 (N—CH_2(C)); 51.6 (N—CH_2—N). 61.6 (OCH_2). 127.7, 127.8 (*o*-, *m*-C, Ar); 132.2 (*p*-C, Ar); 166.5, 167.4 (C=O).

Method B. A solution of NaOH (0.037 g, 0.93 mmol) in *i*-PrOH (1—2 mL) and a 31 % solution of formaldehyde (0.09 mL, 0.93 mmol) were successively added at ~20 °C with stirring to a solution of methylglycine hydrochloride (0.12 g, 0.93 mmol) and a benzamide (0.93 mmol) in *i*-PrOH (5 mL). The reaction mixture was kept for 24 h at ~20 °C, then the precipitate of NaCl was filtered off. Concentrated HCl (0.08 mL, 0.95 mmol) was added to the filtrate (to pH ~3), and the solvent was removed *in vacuo*. The residue was crystallized by addition of ether (for compound **1a**) or acetone (for compound **1e**) to give hydrochlorides **1a,e**. The melting points and spectral data of the products coincided with those of the compounds obtained according to method A. The yields of compounds **1a,e** are given in Table 1.

Methyl *N*-(*m*-nitrobenzamidomethyl)glycinate (2e). The reaction was carried out by analogy with method B (for the synthesis of compounds **1**) starting from methyl glycinate hydrochloride, *m*-nitrobenzamide, NaOH in *i*-PrOH, and 31 % formaldehyde. The precipitate of NaCl was filtered off, and the solvent was removed from the filtrate by distillation. The residue was solidifed by treatment with acetone to give 0.07 g (27 %) of compound **2e**, m.p. 160—165 °C. IR, ν/cm^{-1}: 1760 (C=O), 1665 (C=O), 1530 (NO_2), 2850—3030 (NH). ^1H NMR, δ: 3.71 (s, 3 H, CH_3); 4.04 (s, 2 H, C—CH_2—N); 4.64 (d, 2 H, N—CH_2—N, J = 7.0 Hz); 7.81 (t, 1 H, NH, J = 7.0 Hz); 8.34—8.40 (m, 3 H, Ph); 8.73 (s, 1 H, Ph); 9.98 (br.s, 1 H, NH).

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