Synthesis of *N*-(2-chloroethyl)glycine and -DL-alanine esters

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Two methods for the synthesis of *N*-(2-chloroethyl)glycine and -DL-alanine esters are proposed: 1) reductive amination of the C=O group of glyoxilic or pyruvic acids upon treatment with 2-chloroethylamine and sodium cyanoborohydride in methanol and 2) alkylation of 2-chloroethylamine with α-haloalkanoic acid esters in K_2CO_3—MeCN two-phase system.

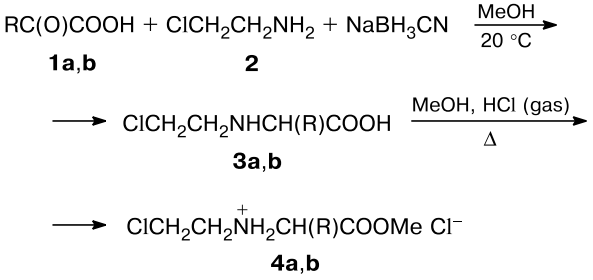
Key words: *N*-(2-chloroethyl)glycine, *N*-(2-chloroethyl)-DL-alanine, amino acids, reductive amination, alkylation, two-phase systems.

1,2-Azaphosphetidines belong to the poorly available and not well studied class of phosphorus-containing heterocyclic compounds.[1] At the same time, 2-oxo derivatives of 1,2-azaphosphetidines are structural analogs of β-lactams, many of which show biological activity. It could have been expected that 2-oxo-1,2-azaphosphetidines, containing amino acid fragment, would possess interesting biological properties. To obtain 1,2-azaphosphetidines with amino acid fragment, it is necessary to synthesize *N*-(2-haloethyl)-substituted α-amino acid esters as the starting compounds. Few such compounds are described in the literature,[2—6] and all of them were synthesized from *N*-(2-hydroxyethyl)-substituted amino acid esters. Thus, *N*-(2-chloroethyl)glycine ethyl ester[2] and *N*-(2-chloroethyl)-L-alanine methyl ester[3] were obtained by the three-step synthesis in 29 and 36% yield, respectively. A reductive amination of glyoxilic acid with 2-chloroethylamine and sodium cyanoborohydride was used[7] for the synthesis of *N*-(2-chloroethyl)glycine, which was obtained as the intermediate product and was not isolated and characterized.

We found that the known method[8] for the synthesis of *N*-alkylated derivatives of glycine and DL-alanine by the reaction of bromoacetic or α-bromopropionic acid esters with amines in the presence of organic bases is not good for 2-haloethylamines, since complicated mixtures of products are formed in this case.

In the present communication, two methods for the synthesis of *N*-(2-chloroethyl)glycine and -DL-alanine esters from available starting reagents are proposed. The first method consists in the reductive amination of the C=O group of glyoxilic or pyruvic acids **1a**,**b** upon treatment with 2-chloroethylamine **2** and sodium cyanoborohydride in methanol (Scheme 1).

Scheme 1



R = H (**a**), Me (**b**)

Compound **4b** was synthesized in 43%, while the yield of glycine derivative **4a** varied and did not exceed 20%. That is why we developed another method for the synthesis of *N*-(2-chloroethyl)glycine and -DL-alanine esters based on the alkylation of 2-chloroethylamine with α-halocarboxylates in a two-phase system (Scheme 2). The reaction of 2-chloroethylamine **2** with ethyl haloacetates **5a** and **5´a** and ethyl 2-halopropionates **5b** and **5´b** was carried out in MeCN in the presence of excess K_2CO_3 at 20 °C. The starting 2-chloroethylamine **2** was obtained from the hydrochloride in the same two-phase system.

Ethyl esters of *N*-(2-chloroethyl)glycine (**6a**) and -DL-alanine (**6b**) formed in this reaction were converted to hydrochlorides **4c**,**d** upon treatment with a solution of HCl in ether. It was found that hydrochloride **4c** is formed from ethyl bromoacetate in 52% yield; the substitution of ethyl bromoacetate for ethyl iodoacetate virtually has no effect on the yield of **4c**. At the same time, the use of ethyl 2-iodopropionate (**5´b**) instead of ethyl 2-bromopropionate (**5b**) allowed us to increase the yield of **4d** from 33 to 59%.

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Table 1. Yields, melting points, and elemental analysis data of *N*-(2-chloroethyl)glycine and -DL-alanine ester hydrochlorides **4a—d**

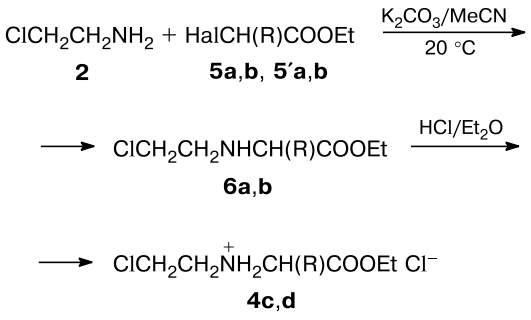
Compound	Yield (%)	M.p./°C (solvent)	Found / Calculated (%)				Molecular formula
			C	H	Cl	N	
4a	20	139—141 (MeOH—AcOEt)	31.96 / 31.92	5.96 / 5.89	37.39 / 37.70	7.46 / 7.44	$C_5H_{11}Cl_2NO_2$
4b	43	167—168 (MeOH—AcOEt)	35.44 / 35.65	6.45 / 6.48	35.07 / 35.15	6.91 / 6.93	$C_6H_{13}Cl_2NO_2$
4c	52 [a]	152—153 [b] (MeCN—AcOEt)	35.53 / 35.65	6.37 / 6.48	34.88 / 35.15	6.88 / 6.93	$C_6H_{13}Cl_2NO_2$
	48 [c]						
4d	33 [d]	119—121 (MeCN—AcOEt)	38.83 / 38.49	6.80 / 6.94	32.64 / 32.87	6.52 / 6.48	$C_7H_{15}Cl_2NO_2$
	59 [e]						

[a] From ethyl bromoacetate.
[b] *Cf.* Ref. 2: m.p. 152 °C (EtOH—AcOEt).
[c] From ethyl iodoacetate.
[d] From ethyl 2-bromopropionate.
[e] From ethyl 2-iodopropionate.

Table 2. ^1H and ^{13}C NMR spectra of hydrochlorides **4a—d**

Compound	Solvent	NMR spectra, δ (*J*/Hz)	
		^1H	^{13}C
4a	D_2O	3.42—3.47 (m, 2 H, CH_2Cl); 3.72 (s, 3 H, Me); 3.78—3.83 (m, 2 H, CH_2CH_2N); 3.98 (s, 2 H, CH_2CO)	39.10 (CH_2Cl); 47.14 (CH_2CH_2N); 48.86 (CH_2CO); 53.60 (MeO); 167.46 (C=O)
4b	CD_3OD	1.81 (d, 3 H, MeCH, $^3J_{H,H}$ = 7.2); 3.67—3.72 (m, 2 H, CH_2Cl); 4.05 (s, 3 H, MeO); 4.09—4.16 (m, 2 H, CH_2CH_2N); 4.44 (q, 1 H, CHMe, $^3J_{H,H}$ = 7.2)	14.17 (MeCH); 39.50 (CH_2Cl); 47.99 (CH_2CH_2N); 53.16 (MeO); 56.07 (CH); 169.97 (C=O)
4c	$CDCl_3$	1.30 (t, 3 H, Me, $^3J_{H,H}$ = 7.2); 3.48—3.57 (m, 2 H, CH_2Cl); 3.98 (s, 2 H, CH_2CO); 4.02—4.08 (m, 2 H, CH_2CH_2N); 4.28 (q, 2 H, CH_2O, $^3J_{H,H}$ = 7.2); 10.1 (br.s, 2 H, NH_2)	13.84 (Me); 38.28 (CH_2Cl); 47.46 (CH_2CH_2N); 48.76 (CH_2CO); 62.65 (CH_2O); 165.85 (C=O)
4d	$CDCl_3$	1.30 (t, 3 H, $MeCH_2$, $^3J_{H,H}$ = 7.2); 1.75 (d, 3 H, MeCH, $^3J_{H,H}$ = 7.2); 3.38—3.51 (m, 2 H, CH_2Cl); 4.02—4.17 (m, 3 H, CH_2CH_2N+CHMe); 4.28 (q, 2 H, CH_2O, $^3J_{H,H}$ = 7.2); 9.8, 10.4 (both br.s, 1 H each, NH)	13.89 ($MeCH_2$); 14.68 (MeCH); 38.28 (CH_2Cl); 46.78 (CH_2CH_2N); 55.39 (CH); 62.81 (CH_2O); 168.45 (C=O)

Scheme 2



R = H (**4c**, **5a**, **5′a**, **6a**), Me (**4d**, **5b**, **5′b**, **6b**);
Hal = Br (**5a**,**b**), I (**5′a**,**b**)

Hydrochlorides **4c**,**d** are crystalline compounds, the composition and structure of which were confirmed by elemental analysis data, IR spectroscopy, and ^1H and ^{13}C NMR spectroscopy (see Tables 1 and 2). In the IR spectra of hydrochlorides **4c**,**d**, along with strong absorption bands of the C=O group at 1747 cm^{-1} (**4c**) and 1746 cm^{-1} (**4d**), a wide and intensive absorption is observed in the region 3250—2250 cm^{-1}, related to the stretching vibrations of the NH_2^+ group with strong hydrogen bonds. In contrast to methyl ester hydrochlorides **4a**,**b**, ethyl ester hydrochlorides **4c**,**d** are well soluble in chloroform. This enabled us to register signals of the protons for the NH_2^+ group in the ^1H NMR spectra in $CDCl_3$, and it should be noted that in the spectrum of glycine hydrochloride **4c**, there is a broadened singlet of the protons for the NH_2^+

group with chemical shift of 10.1 ppm, whereas in the spectrum of alanine hydrochloride **4d**, protons for the NH_2^+ group are nonequivalent, which results in the two broadened singlets with chemical shifts of 9.8 and 10.4 ppm.

From the results obtained, we conclude that among the two proposed methods for the synthesis of *N*-(2-chloroethyl)glycine and -DL-alanine esters, the alkylation of 2-chloroethylamine with α-halocarboxylates in two-phase system K_2CO_3/MeCN has undoubted advantage. The developed method can be recommended for the synthesis of *N*-(2-chloroethyl)-substituted derivatives of other α-amino acids.

Experimental

Reactions were carried out in anhydrous solvents. ^1H and ^{13}C NMR spectra were recorded on a Bruker AVANCE-400 spectrometer (400.13 and 100.61 MHz, respectively) in D_2O, CD_3OD, and $CDCl_3$ with the use of signal of the residual protons in a deuterated solvent as the internal standard. IR spectra were recorded on a Nicolet Magna-IR 750 Fourier spectrometer (in KBr pellets). Commercial $ClCH_2CH_2NH_2 \cdot HCl$, $OCHCOOH \cdot H_2O$, MeCOCOOH, $BrCH_2COOEt$ (Acros), and BrCH(Me)COOEt (Aldrich) were used for the synthesis. The starting ICH_2COOEt and ICH(Me)COOEt were obtained according to the known procedure.[9] The yields, melting points, elemental analysis data, and parameters of ^1H and ^{13}C NMR spectra of the synthesized hydrochlorides **4a—d** are given in Tables 1 and 2.

***N*-(2-Chloroethyl)glycine methyl ester hydrochloride (4a).** 2-Chloroethylamine hydrochloride (2.32 g, 20 mmol) was dissolved in 0.75 *M* NaOH in methanol (26.7 mL, 20 mmol). After 1 h, the precipitate of NaCl was filtered off and washed with methanol. Solutions of $OCHCOOH \cdot H_2O$ (1.84 g, 20 mmol) in methanol (10 mL) and $NaBH_3CN$ (1.26 g, 20 mmol) in methanol (10 mL) were added to the filtrate. The reaction mixture was stirred at 20 °C for 22 h, then a flow of HCl was passed through it until complete saturation was achieved and this was refluxed for 2 h. After cooling, the precipitate formed was filtered off and washed with methanol, the filtrate was concentrated *in vacuo* with addition of benzene for the removal of water. The residue was recrystallized from MeOH—AcOEt to give hydrochloride **4a** (0.74 g).

***N*-(2-Chloroethyl)-DL-alanine methyl ester hydrochloride (4b)** was obtained similarly to **4a** from $ClCH_2CH_2NH_2 \cdot HCl$ (1.22 g, 10.5 mmol), 1.25 *M* NaOH in methanol (8.4 mL, 10.5 mmol), MeCOCOOH (2.92 g, 10.5 mmol) in methanol (5 mL), and $NaBH_3CN$ (0.66 g, 10.5 mmol) in methanol (3 mL). The reaction mixture was stirred at 20 °C for 10 h and treated as in the preceding experiment to furnish hydrochloride **4b** (0.90 g).

***N*-(2-Chloroethyl)glycine ethyl ester hydrochloride (4c). *A*. Synthesis from ethyl bromoacetate (5a).** A suspension of $ClCH_2CH_2NH_2 \cdot HCl$ (1.16 g, 10 mmol) and K_2CO_3 (6.90 g, 50 mmol) in MeCN (30 mL) was stirred at 20 °C for 2.5 h, then, another portion of K_2CO_3 (6.90 g, 50 mmol) in MeCN (20 mL) was added followed by the dropwise addition (for 1 h) of a solution of $BrCH_2COOEt$ (1.34 g, 8 mmol) in MeCN (10 mL) under vigorous stirring at 20 °C. The reaction mixture was stirred at 20 °C for 8 h, the precipitate of inorganic salts was filtered off, washed with MeCN, the solvent was evaporated *in vacuo*. Ether (50 mL) was added to the oil-like residue, the etheral solution was filtered, and 2 *M* HCl in ether (5 mL, 10 mmol) was added to the filtrate. The precipitate formed was filtered off, washed with hot benzene, ether, and dried *in vacuo* to furnish hydrochloride **4c** (0.84 g).

***B*. Synthesis from ethyl iodoacetate (5´a)** was carried out similarly to the procedure in method *A* from $ClCH_2CH_2NH_2 \cdot HCl$ (1.39 g, 12 mmol), ICH_2COOEt (2.14 g, 10 mmol), and K_2CO_3 (16.26 g, 120 mmol) in MeCN (60 mL). After the precipitate of inorganic salts and the solvent were removed, ether (50 mL) was added to the residue, the precipitate of KI was filtered off, washed with ether, the etheral solution was filtered, and 1.5 *M* HCl in ether (7 mL, 10.5 mmol) was added to it. The precipitate formed was filtered off, washed with hot benzene, ether, and dried *in vacuo* to give hydrochloride **4c** (0.96 g).

***N*-(2-Chloroethyl)-DL-alanine ethyl ester hydrochloride (4d). *A*. Synthesis from ethyl 2-bromopropionate (5b).** A suspension of $ClCH_2CH_2NH_2 \cdot HCl$ (4.64 g, 40 mmol) and K_2CO_3 (27.60 g, 200 mmol) in MeCN (50 mL) was stirred at 20 °C for 2.5 h, after that another portions of K_2CO_3 (27.60 g, 200 mmol) and MeCN (30 mL) were added followed by the dropwise addition (for 1 h) of BrCH(Me)COOEt (6.97 g, 38.5 mmol) in MeCN (40 mL) under vigorous stirring at 20 °C. The reaction mixture was stirred at 20 °C for 13 h. The precipitate of inorganic salts was filtered off, washed with MeCN, the solvent was evaporated *in vacuo*. Ether (100 mL) was added to the residue, the etheral solution was separated from the oil formed, filtered, and 1.5 *M* HCl in ether (26.6 mL, 40 mmol) was added to it; the oil formed solidified on trituration. The precipitate was filtered off, washed with hot benzene and ether, dried *in vacuo* to give hydrochloride **4d** (2.70 g).

***B*. Synthesis from ethyl 2-iodopropionate (5´b)** was carried out similarly to the procedure in method *A* from $ClCH_2CH_2NH_2 \cdot HCl$ (3.48 g, 30 mmol), ICH(Me)COOEt (6.84 g, 30 mmol), and K_2CO_3 (41.40 g, 300 mmol) in MeCN (100 mL). After the precipitate of inorganic salts and the solvent were removed, benzene (100 mL) was added to the residue, the precipitate of KI was filtered off, washed with benzene, and benzene was evaporated dry. Ether (100 mL) was added to the residue, the etheral solution was separated from the oil formed, filtered, and 1.5 *M* HCl in ether (20 mL, 30 mmol) was added to the filtrate. The oil formed solidified at once, the precipitate was filtered off, washed with hot benzene and ether, dried *in vacuo* to isolate hydrochloride **4d** (3.80 g).

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