Organic Chemistry

Substitution of halogen atom in α-halonitro compounds of the aliphatic series

6.* Preparation and reduction of alkyl α-halo- and α-sulfosubstituted α-nitrocarboxylates

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Ethyl α-halo-α-nitropropionate and -butyrate were prepared by alkylating ammonium salts of ethyl bromo- and chloronitroacetates. The addition of alkyl acrylates to alkyl chloronitroacetates or their salts gives dialkyl α-chloro-α-nitroglutarates. Sodium salts of ethyl α-nitro-α-sulfo-β-hydroxypropionate and -butyrate were obtained by the sulfodehalogenation of ethyl α-chloro-α-nitro-β-hydroxypropionate and -butyrate with sodium dithionite. Esters of α-amino acid hydrochlorides were prepared by the reduction of alkyl α-chloro-α-nitrocarboxylates. The hydrogenation of alkyl nitrosulfoacetates leads to the corresponding disodium salts of alkyl aminodisulfoacetates and piperazine-2,5-dione.

Key words: halonitrocarboxylates, alkylation, Michael reaction, sulfodehalogenation, catalytic hydrogenation; amino acids; alkyl aminodisulfoacetates.

Halonitroacetates can undergo halogenation,[1] α-hydroxyalkylation (the Henry reaction),[2–4] deuteroexchange,[5,6] *etc.*[7] as strong CH-acids. The halogen atom in these compounds is replaced by a sulfo group and hydrogen.[8–11]

In the present work, the alkylation of halonitroacetates with alkyl iodides and alkyl acrylates (the Michael reaction) was studied for the first time. For α-substituted halonitroacetates, sulfodehalogenation and reduction were studied with the aim of preparing natural and abiogenic amino acids.

* For communication 5 see *Ivz. Akad. Nauk SSSR, Ser. Khim.*, 1990, 2012 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1990, **39**, 1826].

Results and Discussion

Alkylation of halonitroacetates. The ammonium salts of alkyl chloro- and bromonitroacetates (**1a,b**) are successfully alkylated when treated with RI (R = Me, Et) (Table 1).

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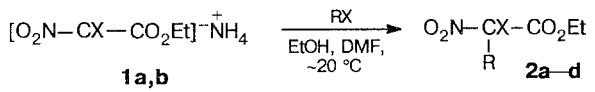
Table 1. Alkylation of alkyl halonitroacetates

Starting compound	Product (yield (%))	B.p./°C (*p*/Torr)	n_D^{20}	Molecular formula	Found / Calculated (%) C	H	Cl	N	IR, ν/cm^{-1} C—H	C=O	NO_2	C—Hal	^{1}H NMR ($CDCl_3$), δ[a]
1a	**2a** (60)	50—52 (1)[b]	1.4338[b]	$C_5H_8NClO_4$	32.91 / 33.07	4.21 / 4.44	19.76 / 19.53	7.83 / 7.71	2890	1750	1565	740	4.3 (q, CH_2); 2.3 (s, CH_3); 1.33 (t,CH_3)
1a	**2b** (11)	77—79 (6)[b]	1.4338[b]	—	—	—	—	—	2890	1750	1560	730	4.2 (m, CH_2); 1.28 (m, CH_3)[d]
1b	**2c** (28)	79—80 (12)[b]	1.4551[b]	—	—	—	—	—	2900	1745	1560	740	4.35 (q, CH_2); 2.35 (s, CH_3); 1.41 (t, CH_3)
1b	**2d** (7)	66—68 (2)[b]	1.4961[b]	$C_6H_{10}NBrO_4$	29.73 / 30.02	4.03 / 4.20	32.86[c] / 33.29	6.03 / 5.84	2900	1750	1560	735	4.25 (m, CH_2); 1.32 (m, CH_3)[d]
3a	**4a** (36)	131—3 (1.5)	1.4496	$C_8H_{12}NClO_6$	38.21 / 37.88	5.14 / 4.77	12.97 / 13.98	6.29 / 5.52	2890	1720	1580	800	4.19 (q, CH_2); 3.9 (s, CH_3); 2.9—2.4 (m, CH_2—CH_2)
3b	**4b** (31)	136—140 (2)	1.4493	$C_9H_{14}NClO_6$	40.96 / 40.39	5.31 / 5.27	12.87 / 13.24	5.68 / 5.23	2890	1710	1545	800	4.36 (q, CH_2); 4.16 (q, CH_2); 2.9—2.4 (m, CH_2—CH_2); 1.3 (t, CH_3)
1a	**4b** (77)	137—140 (2)	—	—	—	—	—	—	—	—	—	—	—
1c	**4c** (95)	114—115 (1)	1.4504	$C_8H_{12}NClO_6$	38.21 / 37.88	4.78 / 4.77	13.80 / 13.98	5.26 / 5.52	2890	1750	1580	800	3.9 (q, CH_2); 3.24 (s, CH_3); 2.6—2.1 (m, CH_2—CH_2); 1.1 (t, CH_3)
3b	**4c** (69)	113 (1)	—	—	—	—	—	—	—	—	—	—	—

[a] The spectrum was recorded relative to TMS. [b] *Cf.* Ref. 19. [c] For Br. [d] Averaged values.



1a,b **2a—d**

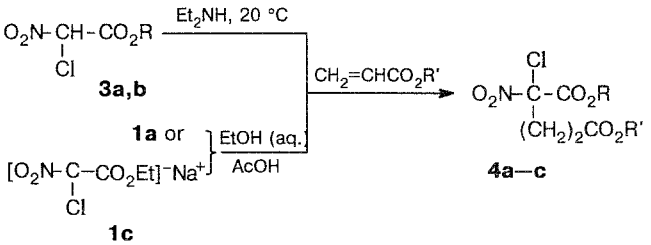
1: X = Cl (**a**), Br (**b**)
2: X = Cl, R = Me (**a**), Et (**b**);
X = Br, R = Me (**c**), Et (**d**)

In pure DMF, decomposition of the starting salts occurs. For this reason, the ratio of reagents and solvents had to be selected in each case. The optimum EtOH—DMF ratio ensures the formation of a transparent solution, high reactivity, and stability of the starting salt. Attempts at alkylating **1a,b** under similar conditions with chloro- and bromoalkanes or higher iodoalkanes failed.

The alkylation of alkyl chloronitroacetates with alkyl acrylates was performed in two ways, *i.e.*, in the presence of Et_2NH[12] or AcOH (Scheme 1). The second method provided better results (see Table 1).

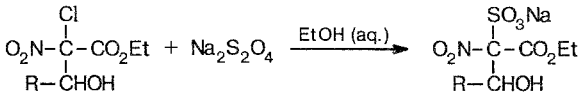
Synthesis of derivatives of α-sulfosubstituted nitroacetates, the precursors of amino acids. The reactions of ethyl α-chloro-α-nitro-β-hydroxypropionic[2] (**5a**), -butyric[13] (**5b**), and α-chloro-α-nitropropionic[14] (**5c**)

Scheme 1



3: R = Me (**a**), Et (**b**)
4: R = Me, R' = Et (**a**); R = R' = Et (**b**);
R = Et, R' = Me (**c**)

acids with sodium dithionite have been studied under the conditions described previously[10] (Table 2).



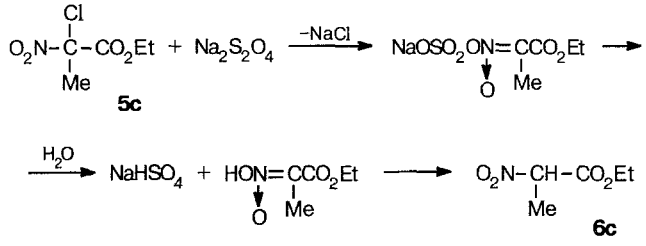
5a,b **6a,b**

5, 6: R = H (**a**); Me (**b**)

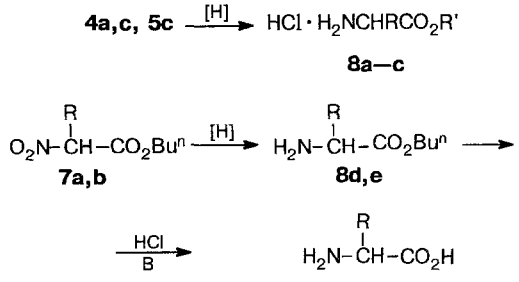
Table 2. Sulfodehalogenation of β-hydroxy derivatives of chloronitrocarboxylic acids

Starting compound	Product	Yield (%)	Molecular formula	Found / Calculated (%)				IR, ν/cm^{-1}
				C	H	N	S	
5a	**6a**	93	$C_5H_8NNaO_8S$	22.88 22.65	3.03 3.04	5.29 5.28	12.21 12.09	3500 (OH); 2890 (CH); 1700 (C=O); 1560 (NO_2); 1070 (SO_3)
5b	**6b**	78	$C_6H_{10}NNaO_8S$	25.73 25.82	3.73 3.60	4.71 5.02	11.22 11.48	3500 (OH); 2900 (CH); 1710 (C=O); 1550 (NO_2); 1065 (SO_3)

As a result, β-hydroxy derivatives **5a,b**, like unsubstituted halonitroacetates,[10] undergo sulfodehalogenation to give Na-salts of alkyl α-nitro-α-sulfo-β-hydroxycarboxylates. With chloronitropropionate **5c**, reduction occurs giving α-nitropropionate **6c** as the only product. This can be explained by the formation of an intermediate Na-salt of a mixed anhydride of sulfuric and nitronic acids,[15] which decomposes in aqueous-ethanolic media to give α-nitro ester **6c**.



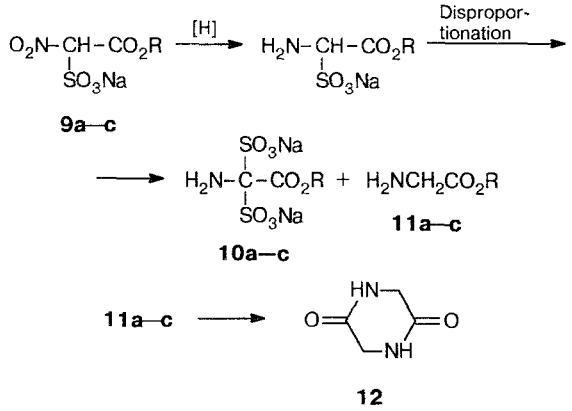
Preparation of amino acids. In order to study the possibility of obtaining amino acids from readily available α-halo-α-nitrocarboxylic acids, we hydrogenated nitro esters **4a**, **4c**, **5c**, and **7a,b** over 5 % Pd/C in an ethanolic or aqueous-ethanolic medium according to the procedure used previously for reducing chloronitroacetates to hydrochlorides of glycine esters.[8] The reduction proceeds smoothly to give sufficiently pure alkyl α-aminocarboxylate hydrochlorides **8a—c** in good yields (Table 3).



7: R = Me (**a**), Pr^i (**b**)
8: R = $(CH_2)_2CO_2Me$, R' = Me (**a**);
R = $(CH_2)_2CO_2Et$, R' = Me (**b**);
R = $(CH_2)_2CO_2Et$, R' = Et (**c**);
R = Me (**d**); R = Pr^i (**e**) (B is a base)

Additionally, the reduction of the previously obtained *n*-butyl α-nitrocarboxylates[16] (**7a,b**) was studied. Esters of amino acids **8d,e** were hydrolyzed for 35 h into DL-Ala and DL-Val without isolation (see Table 3).

The hydrogenation of alkyl nitrosulfoacetates[10,11] (**9a—c**) unexpectedly gave disodium salts of the respective alkyl aminodisulfoacetates **10a—c** and piperazine-2,5-dione (**12**). Probably, compounds **10a—c** result from the disproportionation of the primary reduction products, namely, aminosulfoacetates. Other disproportionation products, glycine esters **11a—c**, readily undergo cyclization into piperazine-2,5-dione.



9, 10, 11: R = Pr^n (**a**), Bu^n (**b**), $C_5H_{11}{}^n$ (**c**)

The structure of ester **10b** was unambiguously confirmed by the X-ray diffraction method; these results will be published in a separate communication.

Table 3. Catalytic hydrogenation of alkyl α-nitrocarboxylates

Starting compound	Product	Yield (%)	M.p./°C
4a	**8a**	59	148—149[20]
4c	**8b**	81	126—128*
	DL-Glu	88	184—186[18]
5c	**8c**	83	86—87[20]
7a	DL-Ala	59	296—297[18]
7b	DL-Val	72	295—296[18]

* Elemental analysis data for **8b**, found (%): C, 42.65; H, 6.91; Cl, 16.02; N, 6.07. $C_8H_{16}NClO_4$. Calculated (%): C, 42.58; H, 7.15; Cl, 15.71; N, 6.21.

Table 4. Catalytic hydrogenation of sodium salts of alkyl α-nitro-α-sulfoacetates

Starting nitro compound	Product (yield (%))	Molecular formula	Found / Calculated (%) C	H	N	S	IR, ν/cm^{-1} H_2O	NH	CH	C=O	SO_3Na	^{1}H NMR (DMSO-d_6), δ*
9a	**10a** (60)	$C_5H_9NNa_2O_8S_2 \cdot 3H_2O$	16.24 16.00	4.41 4.02	— 3.73	— 17.08	3500	3240	2890	1710	1085	4.01 (q, 1-CH_2); 1.6 (q, 2-CH_2); 0.9 (t, CH_3)
9b	**10b** (72)	$C_6H_{11}NNa_2O_8S_2 \cdot H_2O$	20.08 20.40	3.73 3.71	4.07 3.96	17.59 18.15	3500	3250	2890	1700	1080	4.14 (q, 1-CH_2); 3.38 (s, H_2N); 1.58 (q, 2-CH_2); 1.38 (q, 3-CH_2); 0.89 (t, CH_3)
9c	**10c** (36)	$C_7H_{13}NNa_2O_8S_2 \cdot H_2O$	22.74 22.89	4.37 4.12	3.87 3.81	17.06 17.46	3500	3255	2890	1710	1065	4.12 (q, 1-CH_2); 3.39 (s, H_2N); 1.57 (q, 2-CH_2); 1.31 (m, 4-CH_2, 3-CH_2); 0.88 (t, CH_3)

* The spectrum was recorded relative to TMS.

Salts **10a—c** are high-melting compounds (m.p. > 400 °C) easily soluble in water. Hydrogenation of the above nitrocarboxylates on Raney nickel gives the products in a much lower yield (10—20 %).

Experimental

IR spectra of solid (as suspensions in vaseline oil) and liquid samples (as thin films) were obtained on a Specord-IR-75 spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker CXP-200 spectrometer. Melting points were measured on a Boetius PHMK 05 hot stage. Chloro- and bromonitroacetates were obtained according to the known procedures.[2,19] Alkyl α-chloro-α-nitro-β-hydroxycarboxylates were obtained as described previously.[13] $Na_2S_2O_4$ from Fluka and 96 % ethanol were used.

Reaction of the ammonium salt of ethyl chloronitroacetate with MeI. A suspension of compound **1a** (7 g, 40 mmol) in EtOH was treated with MeI (5.68 g, 40 mmol), and DMF (70 mL) was added with stirring to the mixture obtained. After 0.5 h the mixture turned red, and after 2.5—3 h the crystals dissolved. The mixture was kept for 24 h at ~20 °C, diluted with water to 200 mL, and extracted with Et_2O (3×70 mL). The extract was washed with water (2×20 mL), dried with $CaCl_2$, and concentrated. The residue was distilled to give 4.35 g (60 %) of compound **2a** (see Table 1). The reaction with EtI was carried out using the same procedure.

Reaction of methyl chloronitroacetate with ethyl acrylate. Diethylamine (2.8 g, 20 mmol) was added at 20 °C over 3 h with stirring to a mixture of chloronitroacetate **3a** (3.6 g, 50 mmol) and ethyl acrylate (5 g, 50 mmol) in such a way that the temperature of the reaction mixture did not increase by more than 10 °C. The mixture was diluted with ether (50 mL), washed with water (3×10 mL), and dried with $CaCl_2$. The solvent was distilled off, and the residue was distilled *in vacuo* to give 4.6 g (36 %) of compound **4a** (see Table 1).

Reaction of the sodium salt of ethyl chloronitroacetate with methyl acrylate. The sodium salt of ethyl chloronitroacetate (**1c**) (1.9 g, 10 mmol) was dissolved in water, then methyl acrylate (1.88 g, 20 mmol) was added, and finally glacial acetic acid (0.6 g, 10 mmol) was added dropwise over 0.5 h. When ethanol was added, the solution gradually turned red. After 24 h the mixture was concentrated, the residue was dissolved in ether (50 mL), washed with water, and dried with Na_2SO_4. The solvent was distilled off, and the residue was distilled to give 2.12 g (95 %) of compound **4c** (see Table 1).

Catalytic reduction of the sodium salt of butyl nitrosulfoacetate. *n*-Butyl nitrosulfoacetate **9b** (1.4 g, 5 mmol) in 70 % EtOH (50 mL) and Pd/C (0.5 g) were placed in a round-bottom flask with a magnetic stirrer and a thermometer and a siphon with a three-way valve connected to a gas inlet and a burette. The system was filled three times with Ar and then with H_2. Stirring for 24 h resulted in the absorption of 336 mL of H_2. Then the catalyst was filtered off, the solution was concentrated to dryness, and the residue was recrystallized from aqueous ethanol to give 0.6 g (72 %) of compound **10b** (Table 4). The mother liquor was concentrated to dryness. The residue completely crystallized in 48 h. The crystals were treated with an ethanol—ether mixture (1 : 1), filtered off, washed with ether, and dried to give 80 mg (60 %) of large colorless crystals, subl.p. 255—265 °C. The IR spectrum of the product is identical with the spectrum of the authentic piperazine-2,5-dione. ^{1}H NMR (D_2O), δ: 5.63 (s, 1 H, NH); 4.11 (s, 2 H, CH_2); *cf.* Ref. 17. The yield of piperazine-2,5-dione from the reduction of compounds **9a** and **9b** was 45 % and 40 %, respectively.

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