ISSN 1070-4272, Russian Journal of Applied Chemistry, 2007, Vol. 80, No. 12, pp. 2165–2168. © Pleiades Publishing, Ltd., 2007.
Original Russian Text © S.A. Malin, B.M. Laskin, A.S. Malin, 2007, published in Khimicheskaya Promyshlennost', 2007, Vol. 84, No. 7, pp. 335–339.

TECHNOLOGY OF ORGANIC AND INORGANIC SUBSTANCES

Reaction of α-Bromocarboxylic Acids with Hydrazine and Dimethylhydrazine

S. A. Malin, B. M. Laskin and A. S. Malin

Russian Scientific center "Applied Chemistry," St. Petersburg, Russia

Received March 13, 2007

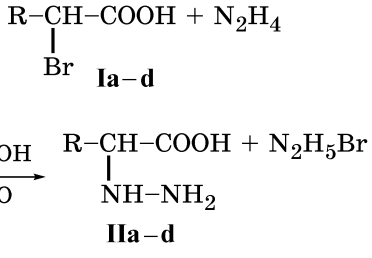
Abstract—Nucleofilic reaction of a series of α-bromocarboxylic acids with hydrazine and dimethylhydrazine is studied. High reactivity of α-bromocarboxylic acids is revealed and a series of α-hydrazinoarboxylic acids and *N*-(1-carboxyalkyl)-*N*,*N*-dimethylhydrazinium bromides are synthesized.

DOI: 10.1134/S1070427207120348

α-Bromocarboxylic acids are known as parent compounds for the synthesis of potentially biologically active compounds, α-hydrazino- and α-dimethylhydrazinocarboxylic acids, the analogs of aminoacids. These latter compounds show antiviral and antitumor activity and can serve as a basis for producing antibiotics, peptidomimetics and related substances [1–3].

Methods for the synthesis of α-hydrazinocarboxylic acids have not been sufficiently studied and the known data are mutually very contradicting in respect both conditions of carrying out the process and product yields [4–6]. Therefore we performed search of appropriate methods for the synthesis of α-hydrazinocarboxylic acids and study of main regularities of the process.

As the model targeted compounds we choose the following α-bromocarboxylic acids: α-bromopropanoic (**Ia**), α-bromobutyric (**Ib**), α-bromo-isovaleric (**Ic**) and α-bromophenylacetic (**Id**). These α-bromoacids were involved to the reaction of nucleophilic substitution with hydrazine and dimethylhydrazine according to the scheme:



where R is Me (**a**), Et (**b**), *i*-Pr (**c**) and Ph (**d**).

We studied influence of the reagents ratio, parameters of duration and temperature and solvent (medium) nature on the reaction proceeding and results. We found that reaction of compounds **Ia–d** with hydrazine proceeds smoothly enough at carrying out the process in the medium of aqueous ethanol at the molar ratio I : hydrazine = 1: 4–6, temperature 70–80°C and reaction dura-tion 6–8 h with high yield (50–70%) of compounds **IIa–d**. Reaction conditions of **IIa–d** are listed in Table 1.

The most smooth process occurs with 40–60% hydrazine hydrate which provides necessary solvation of removing anion in the process of nucleophilic substitution.

Isolation of α-hydrazinocarboxylic acids was carried out by concentrating the reaction solution (by 40 –50%) under vacuum followed by diluting with water and filtrating the product. The crystals formed were filtered off and recrystallized from 40% ethanol (α-hydrazinopropanoic acid or hydrazoalanine), from isopropyl alcohol (α-hydrazinobutyric acid), water (α-hydrazinoisovaleric acid) or ethyl acetate (α-hydrazinophenylacetic acid or hydrazinophenylalanine). The α-hydrazinocarboxylic acids obtained were characterized by means of elemental analysus, IR and ^{1}H NMR spectroscopy.

IR and NMR spectroscopy data (Table 2) and elemental analyses (Table 3) confirmed structure and composition of the obtained compounds.

The high reactivity of the bromine atom in α-bromocarboxylic acids in the reactions of nucleophilic sub-

Table 1. Reaction conditions for the synthesis of compoinds **IIa–d**

No.	α-Bromocarboxylic acids	Mole ratio I : hydrazine	Reaction duration, h	Temperature, °C	Yield, %	mp, °C
1	**I a**	1 : 4	6	80	62	188–189
2	**I b**	1 : 5	7	77	67	201–203
3	**I c**	1 : 6	8	75	71	239–241
4	**I d**	1 : 3	12	70	58	195–200

Table 2. Spectral characteristics of compounds **IIa–d**

No.	Compound	IR spectrum, cm^{-1}	^1H NMR spectrum, δ, ppm (DMSO-d_6)
1	**IIa**	3120 (NH_3^+); 1680 (C= O)	1.45 d (3H, CH_3); 3.5 q (1H, CH); 6.22 s (4H, NH, NH_2,OH)
2	**IIb**	3115 (NH_3^+); 1690 (C=O)	1.1 t (3H, CH_3); 1.7 m (2H, CH_2); 3.28 q (1H, CH); 5.98 s (4H, NH, NH_2,OH)
3	**IIc**	3130 NH_3^+); 1685 (C=O)	1.01 d (3H, CH_3); 1.9 d (3H, CH_3); 2.28 m (1H, CH); 3.1 d (1H); 6.1 C(4H, NH, NH_2, OH)
4	**IId**	3110 (NH_3^+); 1700 (C=O)	4.48 s (1H, CH); 6.6 s (4H, NH, NH_2,OH); 7.33–7.6 ($5H_{arom}$)

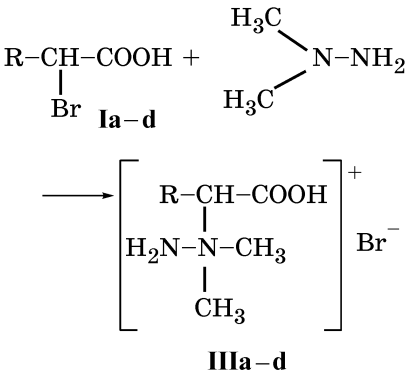
Table 3. Elemental analysis data for compounds **IIa–d**

No.	Compound	Formula	Elemental analysis data					
			found, %			calculated, %		
			C	H	N	C	H	N
1	**IIa**	$C_3H_8N_2O_2$	34.45	**7.8**	**27**	34.61	7.75	26.91
2	**IIb**	$C_4H_{10}N_2O_2$	41.0	8.7	22.8	40.67	8.53	23.71
3	**IIc**	$C_5H_{12}N_2O_2$	44.98	9.22	21.7	45.44	9.15	21.2
4	**IId**	$C_8H_{10}N_2O_2$	58.0	6.11	16.4	57.82	6.07	16.86

Table 4. Reaction conditions for the synthesis of *N*-(1-carboxyalkyl)-*N*,*N*-hydrazinium bromides **IIIa–c**

No.	Compound	Reaction duration, h	Temperature, °C	Yield, %	mp, °C
1	**IIIa**	8	60	62	244
2	**IIIb**	8.5	65	65	239
3	**IIIc**	9	70	68	232
4	**IIId**	12–15	65	73	203

stitution with hydrazine hydrate allowed us to expect that dimethylhydrazine can also be involved in this process. The latter compound is known possessing highr enucleophilicity and basicity as compared with the unsubstituted hydrazine, and this should promote bromine substitution in the α-bromocarboxylic acids and should lead to practically unstudied α-dimethylhydrazinocarboxylic acids. We studied reaction of dimethylhydrazine with compounds **Ia–d**. As might be expected, dimethylhydrazine reacts with compounds **Ia–d** in absolute alcohol or acetonitrile medium smoothly. Small excess of dimethylhydrazine (1.05 to 1.1 mol per 1 mol of α-bromocarboxylic acid) was used and reaction was carried out at 40–60°C during 5–10 h leading to formation of *N*-(1-carboxyalkyl)-*N*,*N*-hydrazinium bromides **IIIa–c** in 60–70% yield according to equation:



Ia–d **IIIa–d**

where R is Me (**a**), Et (**b**), *i*-Pr (**c**) and Ph (**d**).

The data on the synthesis conditions of hydrazonium salts **IIIa–d** are comprised in Table 4.

Isolation of the reaction products included concentrating the reaction solutions under vacuum, cooling from –5 to –10°C, filtrating the crystals formed and recrystallizing them from 2:1 isopropyl alcohol–dioxane mixture. It is noteworthy that the compounds obtained are hygroscopic ones and require use of absolute solvents both in the steps of synthesis and recrystallization.

Nature of the obtained compounds is confirmed by the data of IR and ^{1}H NMR spectroscopy (Table 5) and the data of elemental analysis (Table 6). Presence in the IR spectra of characteristic absorption bands in the region of 3220–3240 cm^{-1}characteristic adsorption attests presence of protonated NH_3^+ group and points probably to zwitter-ionic structure of α-dimethylhydrazinocarboxylic acids. This also is confirmed by ^{1}H NMR spectra where occur signals (multiplet) in the range 3.1–3.5 ppm depending on substituent R (500 MHz, DMSO-d_6) of α-methine fragment; presence of clearly defined signal at 5.6 ppm (4H) and absence of signals of OH and NH_2 groups points probably to zwitter-ionic structure of the compounds.

Like with hydrazinocarboxylic acids, the dimethylhydrazinium salts are characterized by signal of methine group at 3.05–4.3 ppm (multiplet), by signal of methyl groups at 3.5–3.6 ppm (singlet), while the signal at 5.35–5.67 ppm (singlet) is probably in correspondence with the existence of compounds **IIIa–d** as internal salts.

EXPERIMENTAL

^{1}H NMR spectra are registered on a Bruker AM 500 spectrometer (internal reference TMS) in DMSO-d_6. IR spectra are obtained on a IKS-29 spectrmeter from the pastes with Vaseline oil.

General procedure for preparation of α-hydrazinocarboxylic acids IIa–Id. To a three-necks flask equipped with mechanical stirrer, reflux condenser and

Table 5. Spectral characteristics of compounds **IIIa–d**

No.	Compound	IR spectrum, cm^{-1}	^{1}H NMR spectrum, δ, ppm (DMSO-d_6)
1	**IIIa**	3220 (NH_3^+); 1610 (C= O)	1.55 d (3H, CH_3); 3.15 q (1H, CH); 3.52 s (6H, $2CH_3$), 5.36 s (3H, NH_2, OH)
2	**IIIb**	3250 (NH_3^+); 1590 (C=O)	0.94 t (3H, CH_3); 2.2 m (2H, CH_2); 3.05 q (1H, CH); 3.52 d (6H, $2CH_3$), 5.4 s (3H, NH_2, OH)
3	**IIIc**	3300 NH_3^+); 1595 (C=O)	0.91 d (3H, CH_3); 0.94 d (3H, CH_3); 2.98 m (1H, CH); 3.6 d (6H, $2CH_3$), 4.28 m (1H, CH); 5.66 s (3H, NH_2, OH)
4	**IIId**	3320 (NH_3^+); 1620 (C=O)	3.58 d (6H, $2CH_3$), 4.12 C (1H, CH); 5.67 s (3H, NH2,OH); 7.64–8.03 ($5H_{arom}$)

Table 6. Elemental analysis data for compounds **IIa–d**

No.	Compound	Formula	Elemental analysis data							
			found, %				calculated, %			
			C	H	N	Br*	C	H	N	Br
1	**IIIa**	$C_5H_{13}N_2O_2$ Br	26.2	6.2	13.18	38.0	26.18	6.15	13.15	37.5
2	**IIIb**	$C_6H_{15}N_2O_2$ Br	31.6	6.7	12.4	35.22	31.73	6.66	12.34	35.18
3	**IIIc**	$C_7H_{17}N_2O_2$ Br	34.9	7.13	11.59	33.07	34.87	7.11	11.62	33.14
4	**IIId**	$C_{10}H_{15}N_2O_2$ Br	43.8	5.7	10.21	29.1	43.65	5.5	10.18	29.04

Note: Content of bromine ion in compounds **IIIa–d** was analysed by the mercurymetric method.

thermometer was placed 20–30% solution of α-bromocarboxylic acid in 60–80% aqueous ethanol and precalculated amount of 80% hydrzine hydrate (bromocarboxylic acid to hydrazine hydrate mole ratio is 1 : 4–5) was added dropwise. The reasction mixture was heated to slow boiling, kept at this temperature for 4–8 h and then left for 12 h at 0–5°C. The crystals formed were filtered off and recrystallized from water or alcohol, and dried. Yield of α-hydrazinocarboxylic acids 60–70%.

Procedure for preparation of *N*-(1-carboxyalkyl)-*N*,*N*-hydrazinium bromides IIIa–c. To a three-necks flask equipped with mechanical stirrer, reflux condenser and thermometer was placed 20–30% solution of α-bromocarboxylic acid in anhydrous acetonitrile. The solution was cooled to 10–15°C and to it was slowly dozed precalculated amount of 40–50% solution of dimethylhydrazine in acetonitrile (bromocarboxylic acid to dimethylhydrazine mole ratio is 1 : 2–2.5) at the temperature not below 20°C. The reaction mixture was then slowly heated to 40–50°C, kept at this temperature for 3–5 h monitoring continuously formation of mineral bromine (mercurymetry). After completing the process, the reaction mixture was cooled to 0–5°C, the crystals dropped were filtered off, washed with isopropyl alcohol and dried in a vacuum dessicator. Yield of hydrazonium salts **IIIa–d** is 60–75%.

CONCLUSION

The α-hydrazino- and α-dimethylhydrazino-derivatives of a series of carboxylic acids are synthesized, the process of synthesis regularities are revealed, some of physico-chemical properties of the compounds obtained are measured and nature and assumed salt structure of these compounds are established.

REFERENCES

1. Carmi, A., Pollak, G., et al., *J. Org. Chem.*, 1960, vol. 25, no. 1, pp. 44–46.
2. de Luca, L., Falorni, M., et al., *Tetrahedron Lett.*, 1999, vol. 40, pp. 8701–8704.
3. Oguz, U., McLaughlin, M., et al., *Tetrahedron Lett.*, 2002, vol. 43, pp. 2873–2875.
4. Carmi, A., Pollak, G., et al., *J. Org. Chem.*, 1964, vol. 7, pp. 220–224.
5. Gustafsson, H., *Acta Chem. Scand*., 1975B, vol. 29, no. 1, pp. 93–98.
6. Darapsky, A., *J. Prakt. Chem.*, 1936, vol. 146, pp. 268–288.