ISSN 1070-3632, Russian Journal of General Chemistry, 2016, Vol. 86, No. 11, pp. 2469–2472. © Pleiades Publishing, Ltd., 2016.
Original Russian Text © A.V. Zorin, A.T. Zainashev, V.V. Zorin, 2016, published in Zhurnal Obshchei Khimii, 2016, Vol. 86, No. 11, pp. 1826–1829.

Reactions of α-Carbanions of Lithium Acylates with *N*,*N*-Diethyl-*N*-chloro- and *N*,*N*-Diethyl-*N*-bromoamines

A. V. Zorin*, A. T. Zainashev, and V. V. Zorin

Ufa State Petroleum Technological University, ul. Kosmonavtov 1, Ufa, 450062 Russia
**e-mail: chemist.518@mail.ru*

Received June 9, 2016

Abstract—The interaction of α-carbanions of lithium acylates (prepared via metalation of acetic, butyric, or isobutyric acid with lithium diisopropylamide in tetrahydrofuran under argon atmosphere) with *N,N*-diethyl-*N*-chloro- or *N,N*-diethyl-*N*-bromoamine has resulted in the formation of succinic acid or its 2,3-diethyl- and 2,2,3,3-tetramethyl-substituted derivatives in yields of 47–66% and the corresponding α-halocarboxylic acids (12–34%). Anion–radical scheme of the reaction products formation has been suggested.

Keywords: α-halocarboxylic acid, dicarboxylic acid, *N*,*N*-diethyl-α-haloamine, α-carbanions of lithium acylates, nucleophilic substitution, oxidative coupling

DOI: 10.1134/S1070363216110116

The interaction of α-carbanions of alkyl acylates (generated by metalation of diethyl malonate and its derivatives) with monochloroamine is known to afford diethyl esters of aminomalonic acids in 72–90% yield [1]. In order to investigate the synthetic potential of this reaction, we attempted to apply this approach to synthesis of amino acids via the interaction of α-carbanions of lithium acylates containing the anionic site at the primary, secondary, or tertiary α-carbon atom with *N*,*N*-diethyl-*N*-chloro- and *N*,*N*-diethyl-*N*-bromoamine and studied the effect of the α-carbanion structure on the target product yield.

We found that the interaction of α-carbanions of lithium acylates **2a**–**2c** (prepared via metalation of acetic **1a**, butyric **1b**, or isobutyric **1c** acid with lithium diisopropylamide LDA in tetrahydrofuran under argon atmosphere) with *N*,*N*-diethyl-*N*-chloro- **3a** or *N*,*N*-diethyl-*N*-bromoamine **3b** at 20–25°C during 2 h at the reactants molar ratio **1** : LDA : **3** = 1 : 2 : 1 resulted in the formation of succinic acid **8a** or its 2,3-diethyl-, and 2,2,3,3-tetramethyl- homologs **8** and the corresponding α-halocarboxylic acids **9** (Scheme 1) instead of the anticipated products of nucleophilic substitution of the halogen with the α-carboxyalkyl group. ^{1}H and ^{13}C NMR parameters of the prepared compounds were in satisfactory agreement with the reference data [2, 3].

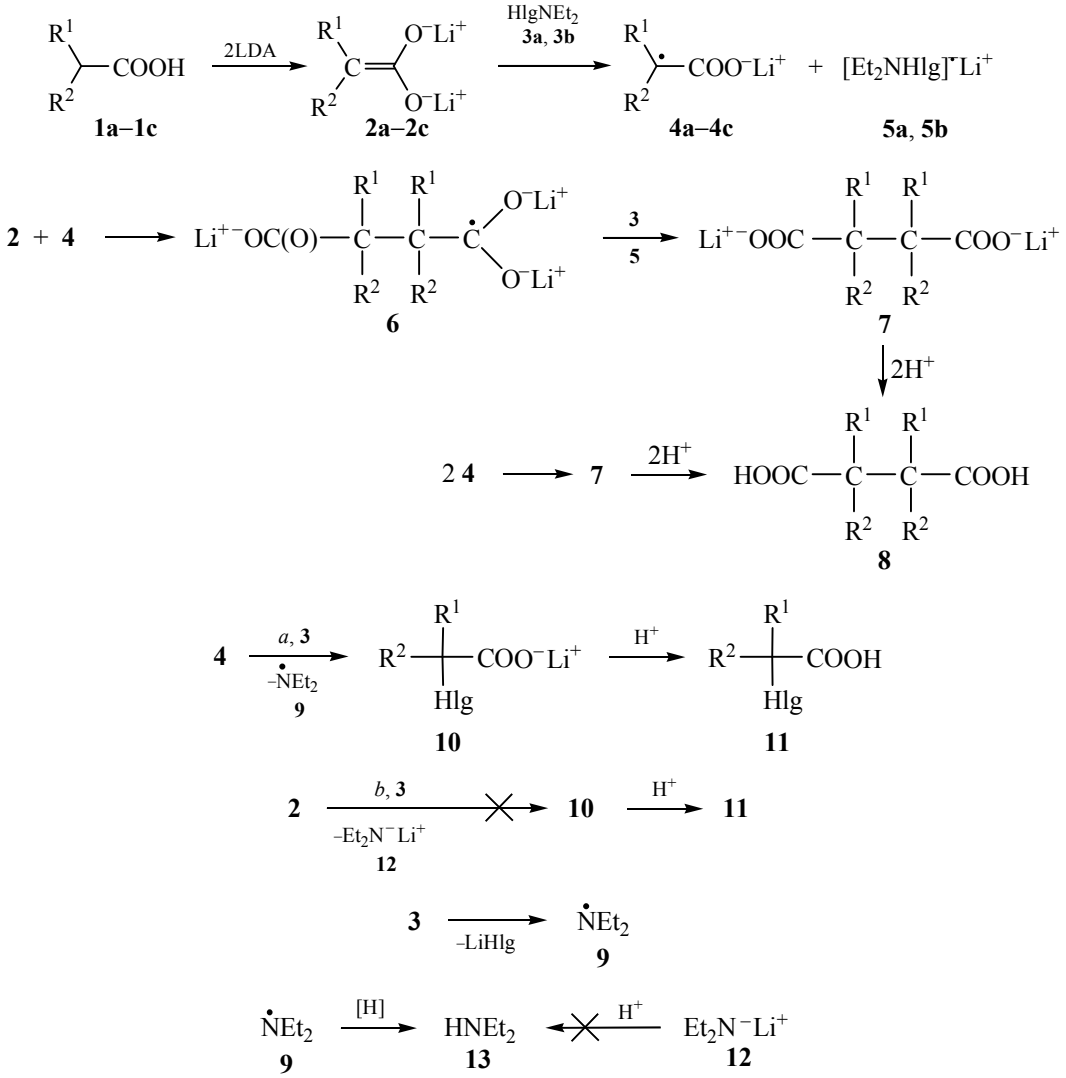
Products **8**, **11**, and **13** can be formed via the anion-radical as well as ionic route (Scheme 1). The structure of the reaction products pointed at their possible formation through the stage of electron transfer from an α-carbanion of lithium acylate **2** to *N*,*N*-diethyl-*N*-haloamine **3** yielding α-carboxyalkyl (**4**) and *N*,*N*-diethyl-*N*-haloaminyl (**5**) anion-radicals that were further transformed into compounds **8**, **11**, and **13**. Diethylamine **13** was formed via the elimination of hydrogen atom from the solvent by *N*,*N*-diethylaminyl radical **9**.

The alternative pathway of the dicarboxylic acids **8a**–**8c** formation could include nucleophilic substitution of the halogen in the formed α-halocarboxylic acids **11a**–**11f** with α-carboxyalkyl fragment under the action of α-carbanions of lithium acylates **2a**–**2c** (Scheme 2).

It is important to determine the most probable pathway of formation of halocarboxylic acids: via homolytic halogenation of anion-radicals **4a**–**4c** under the action of *N*,*N*-diethyl-*N*-haloamine **3** (route *a*) or via heterolytic halogenation of α-carbanions **2a**–**2c** with the same reactant (route *b*, Scheme 1).

The application of spin traps [4, 5], as has been described earlier [6], was not informative in the considered case: it is known that the reactions of addition at the olefinic double bond are not typical of aminyl radicals [7–9]. In view of that, the reaction via

Scheme 1.



1, **2**, **4**, **6**, **8**, **10**, **11**, R^1 = H, R^2 = H (**a**), R^2 = C_2H_5 (**b**), R^1 = R^2 = CH_3 (**c**); **3**, **5**, Hlg = Cl (**a**), Br (**b**); **10**, **11**, Hlg = Cl (**a**–**c**), Br (**d**–**f**).

path *b* (for example, in the case of acetic acid) could be confirmed by the formation of *N*,*N*-diethylaminoacetic acid **14** in the reaction of α-carbanion of lithium acetate **2a** with *N*,*N*-diethyl-*N*-haloamine **3**. The formation of acid **14** could be anticipated in the interaction of haloacetic acid **11a**, **11d** with lithium diethylamide **12** formed in the case of route *b*. However, this acid was not detected in the reaction mixture, even though acid **14** was formed in the case of the interaction of lithium salts of haloacetic acids **10a**, **10d** with lithium diethylamide **12** under the same conditions (Scheme 3).

Hence, the observed result evidenced the formation of α-halocarboxylic acids via the homolytic halogenation of anion-radicals **4** formed via the electron transfer from α-carbanion of lithium acylate **2** on *N*,*N*-diethyl-*N*-haloamine **3**.

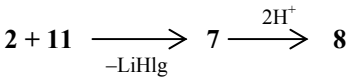
To confirm the formation of anion-radicals **4a**–**4c** we applied the spin trap method [4–6]; hex-1-ene **15** was used as the spin trap. Chromato-mass spectrometry analysis of the reaction mixture during the interaction of α-carbanions of lithium acetate **2a** with *N*,*N*-diethyl-*N*-chloroamine **3a** in the presence of twofold excess of hex-1-ene revealed the formation of octanoic acid **18** on top of compounds **8a**, **11a**, and **13**, other conditions being the same. Mass spectrometry parameters of acid **18** coincided with the reference data [10].

Yields (%) of products of the reaction[a] between α-carbanions of lithium acylates **2a–2c** with *N*,*N*-diethyl-*N*-chloro- and *N*,*N*-diethyl-*N*-bromoamines

Acid	*N*,*N*-Diethyl-*N*-chloroamine				*N*,*N*-Diethyl-*N*-bromoamine			
	dicarboxylic acid	%	α-chlorocarboxylic acid	%	dicarboxylic acid	%	α-bromocarboxylic acid	%
1a	**5a**	47	**11a**	12	**5a**	52	**11d**	13
1b	**5b**	62	**11b**	23	**5b**	47	**11e**	34
1c	**5c**	59	**11c**	10	**5c**	66	**11f**	15

[a] Reaction conditions: 20–25°C, THF as solvent, inert (Ar) atmosphere, **1** : LDA : **3** molar ratio 1 : 2 : 1, reaction duration 2 h

Scheme 2.



The formation of octanoic acid could be explained by the formation of spin adduct **16**, stabilization of the latter via hydrogen elimination from the solvent affording lithium salt of octanoic acid **17** (Scheme 4).

The obtained result evidenced the anion-radical pathway of formation of compounds **8a–8c**, **11a–11f**, and **13**.

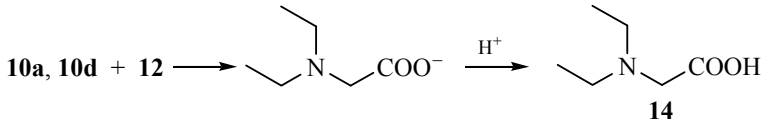
The structure of α-carbanion of lithium acylate **2a–2c** and the nature of halogen in haloamines **3a**, **3b** marginally influenced the yield of dicarboxylic acids **8a–8c** (see the Table). The highest yield was achieved in the case of α-carbanion of lithium butyrate **2b**, the yield of α-bromobutyric acid **11e** being somewhat higher than that of α-chlorobutyric acid **11b**.

EXPERIMENTAL

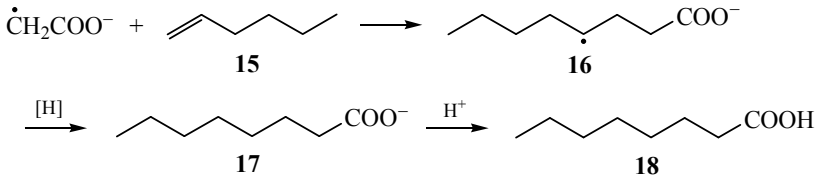
^{1}H and ^{13}C NMR spectra of the solutions in $CDCl_3$ or D_2O were recorded using a Bruker AM-300 instrument (300 and 75.47 MHz, respectively). Chromatomass spectrometry analysis was performed using a QP 2010S Shimadzu apparatus equipped with an HP-1MS capillary column (length 30 m); evaporator temperature 250°C, ionization chamber temperature 250°C, ramp from 50 to 250°C at a rate10 deg/min, helium as the carrier gas (1.1 mL/min). Chromatography analysis was performed using a Kristall 5000.2 Khtomatek apparatus equipped with a Solgel-Wax capillary column (length 60 m); evaporator temperature 290°C, detector temperature 290°C, ramp from 100 to 250°C at a rate 10 deg/min, helium as carrier gas (1.1 mL/min).

Interaction of carboxylic acids with *N*,*N*-diethyl-*N*-haloamines. A solution of 0.005 mol of carboxylic acid **1** in 20 mL of anhydrous THF was added at stirring to a solution of 0.01 mol of LDA in 30 mL of anhydrous THF cooled to 0–5°C under argon atmosphere. The reaction mixture was warmed to 35–40°C and stirred during 30–40 min. Then the mixture was cooled to 20–25°C, and a solution of 0.005 mol of *N*,*N*-diethyl-*N*-haloamine **3** in 20 mL of anhydrous THF was added. The obtained mixture was stirred during 2 h, and then 30 mL of distilled water was

Scheme 3.



Scheme 4.



added. The aqueous layer was treated with 10% solution of HCl till pH 1, and the reaction products were extracted with diethyl ether (3×30 mL). Combined extracts were dried over Na_2SO_4 and concentrated. After ether elimination, mixtures of dicarboxylic **8a–8c** and α-halocarboxylic **9a–9f** acids were obtained. Spectral parameters (^{1}H and ^{13}C NMR) of the products coincided with the reference data [2, 3].

The runs in the presence of hex-1-ene were performed in the same way; the hydrocarbon was added to the flask in a double excess, and then the solution of *N*,*N*-diethyl-*N*-chloroamine was added.

Interaction of lithium salts of haloacetic acids 10a and 10d with lithium diethylamide 12 was performed under the same conditions during 2 h, and then 30 mL of distilled water was added to the reaction mixture. After elimination of water from the aqueous layer the precipitate was dissolved in D_2O and analyzed by ^{1}H NMR.

***N*,*N*-Diethylaminoacetic acid (14)**. ^{1}H NMR spectrum, δ, ppm: 1.25 t (6H, CH_3, J = 7.2 Hz), 2.81 q (4H, CH_2, J = 6.9 Hz), 3.34 s (2H, CH_2).

Octanoic acid (17). Mass spectrum, m/z (I_{rel}, %): 101 (23), 87 (14), 85 (18), 84 (18), 73 (66), 61 (14), 60 (100), 55 (34), 45 (19), 44 (17), 43 (58), 42 (17), 41 (44), 39 (15), 32 (38).

ACKNOWLEDGMENTS

This work was financially supported by the Ministry of Education and Science of Russian Federation in the scope of the basic part of governmental contract (project no. 49).

REFERENCES

1. Horiike, M., Oda, J., Inouye, Y., and Ohno, M., *Agric. Biol. Chem*., 1969, vol. 33, p. 292. doi 10.1080/00021369.1969.10859316
2. Watson, H.B., *Chem. Rev*., 1930, vol. 7, p. 173. doi 10.1021/cr60026a001
3. Chanysheva, A.R., Zorin, A.V., and Zorin, V.V., *Bash. Khim. Zh*., 2014, vol. 21, no. 2, p. 99.
4. Zubarev, V.E., *Metod spinovykh lovushek. Primenenie v khimii, biologii i meditsine* (Spin Trapping Method. Applications in Chemistry, Biology and Medicine), Moscow: Mosk. Gos. Univ., 1984.
5. Zorin, V.V., Nayanov, V.P., Zlotskii, S.S., and Rakhmankulov D.L., *Zh. Prikl. Khim*., 1977, vol. 50, no. 5, p. 1131.
6. Zorin, A.V., Zaynashev, A.T., Chanysheva, A.R., and Zorin, V.V., *Russ. J. Gen. Chem*., 2015, vol. 85, no. 6, p. 1382. doi 10.1134/S1070363215060043
7. Cowley, B.R. and Waters, W.A., *J. Chem. Soc.,* 1961, p. 1228. doi 10.1039/JR9610001228
8. Mackay, D. and Waters, W.A., *J. Chem. Soc. (C)*, 1966, p. 813. doi 10.1039/J3966000081.
9. Michejda, C.J. and Hoss, W.P., *J. Am. Chem. Soc*., 1970, vol. 92, p. 6298. doi 10.1021/ja00724a032
10. Kafkas, E., Cabaroglu, T., Sell, S., Bozdogan, A., Kurkcuoglu, M., Paydas, S., and Baser, K.H.C., *Flavour Fragr. J.,* 2006, vol. 21, p. 68. doi 10.1002/ffj.1503