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Reaction of α-Carbanions of Lithium Acylates with 1,2-Dibromoethane

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Abstract—The reaction of 1,2-dibromoethane with α-carbanions of lithium acylates generated from acetic, butyric, isobutyric, and capronic acids with lithium diisopropylamide has been studied. Anion-radical and anionic pathways of the products formation have been discussed.

Keywords: 1,2-dibromoethane, dicarboxylic acid, enolate anion, carbanion, metalation, oxidative coupling

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Metalated CH-acids (esters, nitriles, acylates, diphenylmethane, etc) are known to react with alkyl halides and dihalides (the latter containing distant CH_2Hlg) groups via the nucleophilic substitution of the halogen with the carbanion [1]. The interaction involving vicinal alkyl dihalide follows a more complicated path yielding products of the halogen nucleophilic substitution as well as of oxidative dimerization of carbanions [1, 2]. The reaction direction depends on structure of the carbanion, the 1,2-dihaloalkane, and the halogen nature [1, 2].

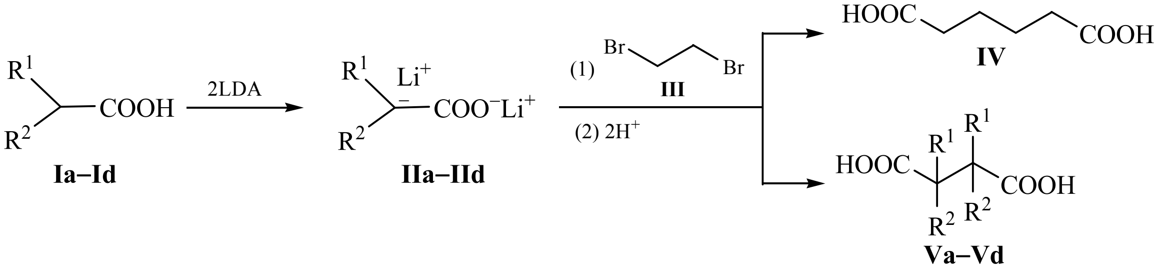
The interaction of carbanions with 1,2-dihaloalkanes occurring under mild conditions with the high product yield is of practical importance; however, its mechanism has not been investigated so far.

We studied the interaction of α-carbanions of lithium acylates with 1,2-dibromoethane in order to elucidate the effect of the reactants structure on the reaction direction, the yield of the target products, and the possible pathway of their formation.

We have earlier studied the reaction of carbanion of lithium acetate (generated from acetic acid **Ia** with lithium diisopropylamide LDA) with 1,2-dibromoethane **III** in THF medium at 20–25°C under argon atmosphere at the **Ia** : LDA : **III** molar ratio of 2 : 4 : 1 during 2 h [3]. The reaction yields a mixture of products of nucleophilic substitution of bromine with carbanion of lithium acetate (adipic acid **IV**) and oxidative coupling of the carbanions (succinic acid **Va**).

The interaction of 1,2-dibromoethane with α-carbanions of lithium acylates generated with lithium diisopropylamide from isobutyric **Ib**, butyric **Ic**, and capronic **Id** acids (under the same conditions) gave, respectively, 2,2,3,3-tetramethylsuccinic acid **Vb** (yield 37%), 2,3-diethylsuccinic acid **Vc** (64%), and 2,3-dibutylsuccinic acid **Vd** (76%). The ^1H and ^{13}C

Scheme 1.



$R^1 = R^2 = H$ (**a**); $R^1 = R^2 = CH_3$ (**b**); $R^1 = H$, $R^2 = C_2H_5$ (**c**), C_4H_9 (**d**).

NMR spectral parameters of the products satisfactorily coincided with the reference data [4] (Scheme 1).

The acids **Vc** and **Vd** were formed as ≈(8–10) : 1 mixtures of the *meso-* and *rac*-diastereomers, as followed from ^{1}H and ^{13}C NMR spectroscopy as well as chromato-mass spectrometry data.

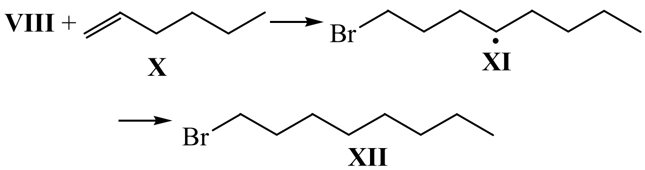
In order to elucidate the possible reaction mechanism we thoroughly investigated the products composition. Gas-liquid chromatography and mass spectrometry studies revealed that all reaction mixtures contained ethyl bromide **IX** along with the dicarboxylic acids **IV** and **Va**–**Vd**. Compound **IX** could be formed via the stage of electron transfer from the α-carbanion **IIa–IId** to 1,2-dibromoethane **III** accompanied by the formation of the lithium acylate radical **VIa**–**VId** and the anion-radical **VII**.

$$\textbf{IIa–IId} + \textbf{III} \longrightarrow \underset{\textbf{VIa–VId}}{R^1(R^2)\dot{C}COO^-Li^+} + \underset{\textbf{VII}}{[BrCH_2CH_2Br]^{\dot{-}}}$$

The elimination of bromide anion with anion-radical **VII** to form the 2-bromoethyl radical **VIII** and the stabilization of the latter via hydrogen abstraction from the solvent finally led to ethyl bromide **IX**.

$$\textbf{VII} \xrightarrow[-Br^-]{} \underset{\textbf{VIII}}{\dot{C}H_2CH_2Br} \xrightarrow{[H]} \underset{\textbf{IX}}{CH_3CH_2Br}$$

The formation of the 2-bromoethyl radical was confirmed using the spin trap method [5, 6] with hex-1-ene **X** as the trap. The interaction of α-carbanions of lithium acylates **IIa**–**IId** with 1,2-dibromoethane in the presence of hex-1-ene yielded the dicarboxylic acids **IV** and **Va**–**Vd** along with ethyl bromide **IX** and octyl bromide **XIII** (mass spectrometry data). Compound **XII** was formed via the stage of formation of the spin-adduct **XI** further stabilized via hydrogen abstraction from the solvent.



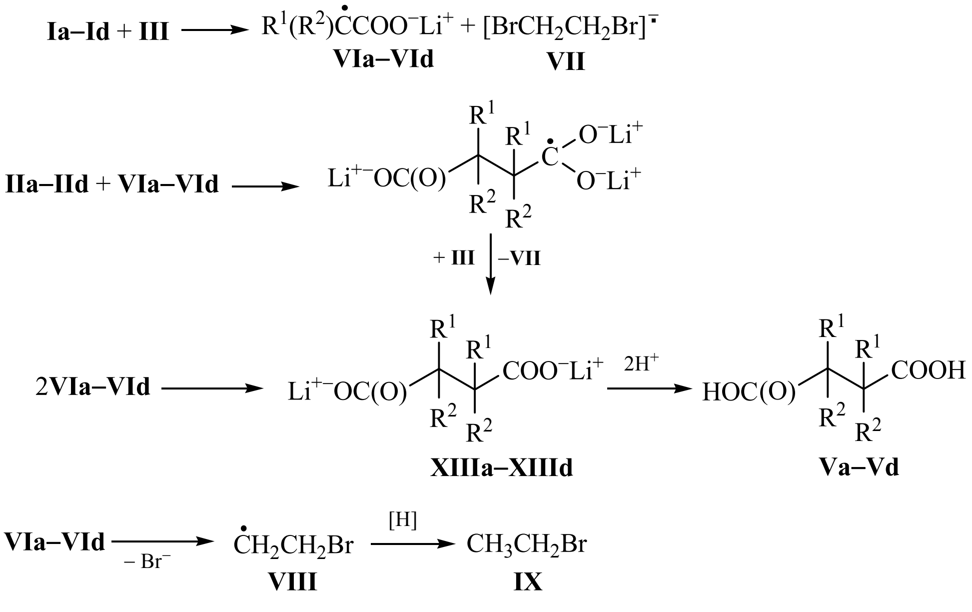
Taking into account the collected results, we suggested the following scheme of the formation of dicarboxylic acids **Va**–**Vd**, the formal products of oxidative coupling of α-carbanions of lithium acylates **IIa**–**IId** (Scheme 2).

Analysis of the gas phase of the reaction mixtures revealed the presence of ethylene that could be formed via bromine elimination from 2-bromoethyl radical **VIII** [7] or the carbanion **XIV** [8, 9].

$$\textbf{VIII} \xrightarrow[-Br^{\bullet}]{} CH_2{=}CH_2 \xleftarrow[-Br^-]{} \underset{\textbf{XIV}}{\bar{C}H_2CH_2Br}$$

Electrophilic transfer of bromine from 1,2-dibromoethane to α-carbanion of the lithium acylates **IIa**–**IId** could be suggested yielding lithium salts of α-bromocarboxylic acids; the latter were further involved

Scheme 2.



Yield of products of oxidative coupling and nucleophilic substitution in the reaction[a] of α-carbanions of lithium acylates **IIa**–**IId** with 1,2-dibromoethane **III**

Starting compound	Product of oxidative coupling	Yield, %	Product of nucleophilic substitution	Yield, %
Ia	**Va**	40	**IV**	38
Ib	**Vb**	37	–	–
Ic	**Vc**	64	–	–
Id	**Vd**	76	–	–

in formation of dicarboxylic acids **Va**–**Vd** via nucleophilic substitution of bromine assisted by the corresponding compound **IIa**–**IId**.

$$\mathrm{BrCH_2CH_2Br} + \mathbf{IIa\text{–}IId} \rightarrow \mathrm{\bar{C}H_2CH_2Br} + \mathrm{R^1(R^2)C(Br)COO^-},$$

$$\mathrm{R^1(R^2)C(Br)COO^-} + \mathbf{IIa\text{–}IId} \rightarrow \mathbf{XIIIa\text{–}XIIId} \xrightarrow{2\mathrm{H}^+} \mathbf{Va\text{–}Vd}.$$

The transfer of electrophilic bromine to anionic reactive site is a known trans-metalation reaction [10–17]. However, this process is exclusively possible when it is thermodynamically favorable, like in the case of the interaction of 1,2-dibromoethane with dicarbanions [15].

The possibility of electrophilic bromine transfer from 1,2-dibromoethane to the α-carbanion of lithium acylate **IIa**–**IId** seems unlikely, as follows from the comparison of pK_a values of alkanes and acylates (40–42 and 24 [18], respectively) reflecting their CH-acidity and the carbanions proton affinity correlated to the halogen affinity [19].

The appearance of the carbanion **XIV** in the reaction could be confirmed by the formation of octyl bromide from hex-1-ene involving that carbanion [11].

Aklyllithium compounds could be prepared via direct interaction of alkyl chlorides or alkyl bromides with lithium metal [11, 20–21]. In view of that, we investigated the possibility of formation of octyl bromide under the similar condition via generation of 2-bromoethyl carbanion **XIV** from 1,2-dibromoethane with lithium [20] in the presence of hex-1-ene. Noteworthily, the interaction of alkyl bromides with lithium could occur via a single-electron transfer giving the anion-radical **VII** and the radical **VIII** [11].

Mass spectrometry study revealed that under the described conditions only traces of octyl bromide were formed in the reaction mixture.

Hence, even though the anion-radical mechanism of the studied reaction was more plausible, the collected data did not allow for the unambiguous pathway elucidation.

Analysis of the yields of the dicarboxylic acids led to a conclusion that the interaction with 1,2-dibromoethane was the most efficient in the cases of the carbanions **IIc**–**IId** containing the anionic site at the secondary α-carbon atom. Yield of the dicarboxylic acids from the carbanions **IIa, IIb** was noticeably lower (see the table).

To summarize, the interaction of carbanions with 1,2-dibromoethane can be used for preparation of dicarboxylic acids under mild conditions with satisfactory yields.

EXPERIMENTAL

NMR spectra of the solutions in a $\mathrm{CDCl_3}$–$\mathrm{CF_3COOH}$ mixture were recorded using a Bruker AM-300 [300 (^{1}H) and 75.47 (^{13}C) MHz] with TMS reference. Chromato-mass spectral analysis was performed using a GCMS-QP2010S Shimadzu instrument (EI at 70 eV). An HP-1MS capillary column (30 m × 0.25 mm × 0.25 μm) was used, the vaporizer temperature was 280°C, the ionization chamber temperature was 200°C. The analysis was carried out at heating from 50 to 280°C at a rate 10 deg/min using helium (1.1 mL/min) as carrier gas. Elemental analysis was performed using an Hekatech Euro EA 3000 CHNS/O analyzer.

Reaction of carboxylic acids with 1,2-dibromoethane. A solution of 0.02 mol of lithium diisopropylamide in 30 mL of anhydrous THF was cooled to 0–5°C under argon, and a solution of 0.01 mol of carboxylic acid **Ia**–**Id** in 20 mL of anhydrous THF was added dropwise at stirring. The reaction mixture was heated to 35–40°C and stirred during 30–40 min. The mixture was then cooled to 20–25°C, a solution of 0.005 mol of 1,2-dibromoethane in 20 mL of anhydrous THF was added, and the resulting mixture was stirred during 2 h. A gas was evolved in the course of the reaction; it was passed through a solution of bromine in tetrachloromethane to test for the presence of ethylene. 30 mL of distilled water was then added to the reaction mixture. The aqueous layer was treated with 10 wt % HCl solution till pH 1; the reaction products were extracted with diethyl ether (3 × 30 mL). The combined extracts were dried over $\mathrm{MgSO_4}$. After the ether removal, crystalline dicarboxylic acids **IV** and **Va**–**Vd** were obtained. The bromine solution containing the absorbed gases was analyzed by gas-liquid chromatography and mass spectrometry.

The experiments in the presence of hex-1-ene were conducted similarly; equimolar amount of the alkene was added together with 1,2-dibromoalkane.

Reaction of lithium metal with 1,2-dibromoethane in the presence of lithium acetate and hex-1-ene. A solution of 0.005 mol of acetic acid in 20 mL of anhydrous THF was added dropwise under argon at stirring to a solution of 0.01 mol of lithium diisopropylamide in 30 mL of anhydrous THF cooled to 0–5°C, and the resulting mixture was stirred during 5-10 min. The reaction mixture was cooled to –(20–25°C), and 0.005 mol of cut lithium metal was added. Then a solution of 0.005 mol of 1,2-dibromoethane and 0.005 mol of hex-1-ene in 20 mL of anhydrous THF was added dropwise. The reaction mixture was stirred during 40 min, and 40 mL of water was added. The aqueous layer was separated, and the organic layer was analyzed by gas-liquid chromatography and mass spectrometry.

^{1}H and ^{13}C NMR spectral parameters of the products coincided with the reference data [4].

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