ISSN 1070-3632, Russian Journal of General Chemistry, 2017, Vol. 87, No. 5, pp. 1097–1100. © Pleiades Publishing, Ltd., 2017.
Original Russian Text © G.Z. Raskil'dina, Yu.G. Borisova, L.V. Spirikhin, S.S. Zlotsky, 2017, published in Zhurnal Obshchei Khimii, 2017, Vol. 87, No. 5, pp. 872–875.

LETTERS TO THE EDITOR

Alkylation of CH Acids with Haloidalkyl-1,3-dioxolanes

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Received February 2, 2017

Abstract—Alkylation of diethyl malonate and Meldrum acid with haloalkyl-1,3-dioxolanes has afforded the substituted malonates; their decarboxylation has led to the formation of esters containing a cycloacetal fragment. Reactions of the substituted malonates with urea have yielded the corresponding substituted barbiturates. Monodecarboxylation of the obtained malonates has led to the formation of 1,3-dioxolane-carboxylates.

Keywords: diethyl malonate, urea, haloalkyl-1,3-dioxolane, Meldrum acid, *cis*-1,4-dichlorobutene

DOI: 10.1134/S1070363217050358

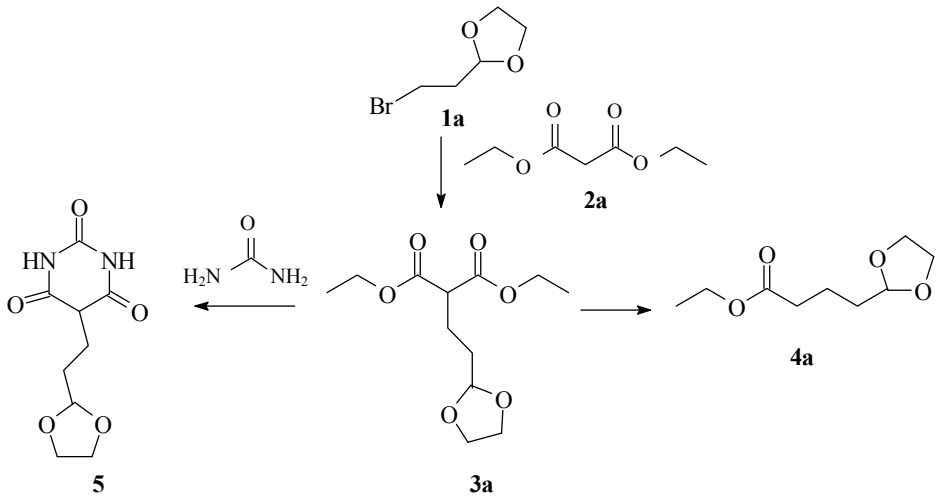
We have earlier synthesized several polyfunctional cyclic acetals via *O*- and *N*-alkylation of alcohols and amines with haloalkyl-1,3-dioxolanes [1–3]. These available halide derivatives are of interest for the alkylation of CH acids.

2-β-Bromoethyl-1,3-dioxolane **1a** reacted with diethyl malonate **2a** under phase transfer catalysis conditions to form the corresponding adduct **3a** in 70% yield (Scheme 1). Monodecarboxylation of compound **3a** led to the formation of γ-1,3-dioxolanyl-2-butyric acid ethyl ester **4a**.

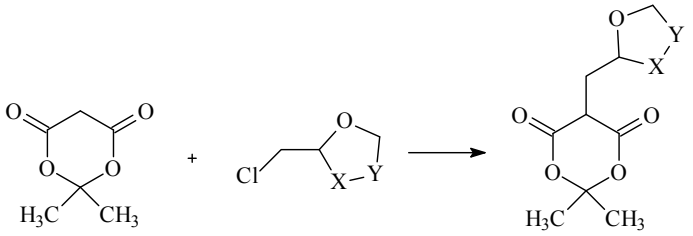
It is known that barbituric acids possess high biological activity [4, 5], therefore their derivatives containing dioxolane fragment can be of interest. Hence, we performed condensation of compound **3a** with urea to obtain the corresponding 1,3-dioxolane barbiturate **5** in 60% yield (Scheme 1).

Note that transformations of diethyl [2-(1,3-dioxolan-2-yl)-ethyl]malonate **3a** into compounds **4a** and **5** proceeded with preservation of the 1,3-dioxolane ring. For example, ^{1}H NMR spectra of compounds **4a** and **5** contained the triplet signal of the proton at the C^2 atom of the dioxolane ring at 4.85 and 4.90 ppm (^3J = 4.6 and 4.9 Hz, respectively). The signals of the protons at C^4 and C^5 atoms were manifested in the range of 3.82–3.94 ppm as doublets of doublets with spin-spin

Scheme 1.



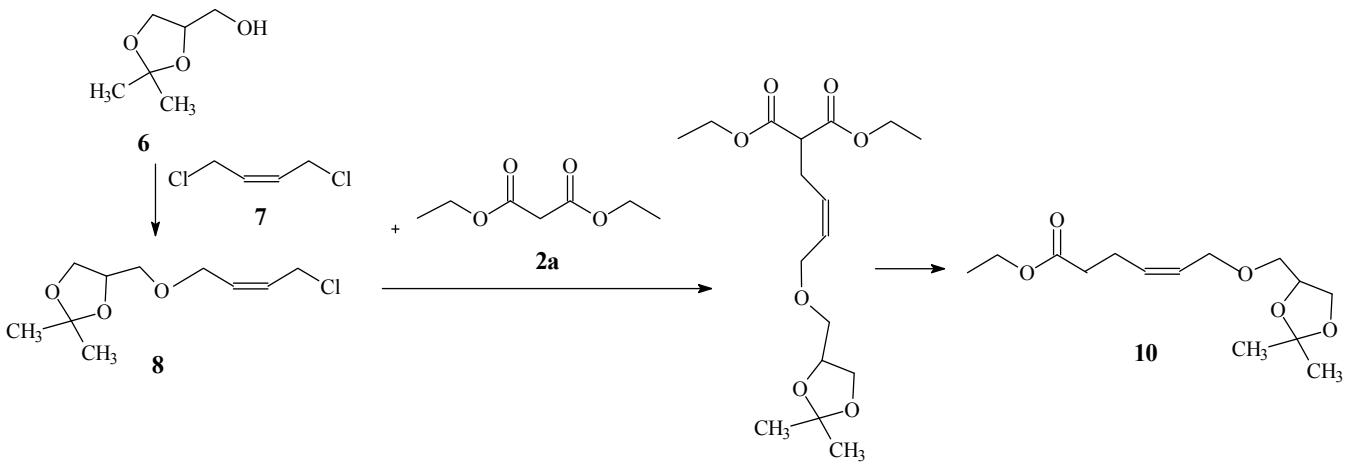
Scheme 2.



2b **1b**, **1c** **3b**, **3c**

X = O, Y = CH_2 (**1b**, **3b**); X = CH_2, Y = O (**1c**, **3c**).

Scheme 3.



6 **7** **2a** **8** **9** **10**

coupling constants ^2J = 10.5 and ^3J = 3.4 Hz (**4a**), ^2J = 10.9 and ^3J = 7.2 Hz (**5**), further confirming the presence of the dioxolane fragment. ^{13}C NMR spectra of compounds **4a** and **5** contained the signals of dioxolane CH_2 groups in the range of 64.50–64.81 ppm and of methine group at 104.06–104.46 ppm.

The ^{1}H NMR spectrum of ethyl 4-(1,3-dioxolan-2-yl)butanoate **4a** contained the signal of CH_3 group at 1.24 ppm (^3J = 7.2 Hz). The signal of carboxyl group was observed at 173.16 ppm in the ^{13}C NMR spectrum.

In the ^{13}C NMR spectrum of compound **5**, two symmetric C=O groups resonated at 162.21 pm; the signal of C=O group located between two NH moieties was observed at 172.48 ppm, typical of barbiturates **5** [6].

2-(4)-Chloromethyl-1,3-dioxolanes **1b** reacted with diethyl malonate **2a** to give the target products with extremely low yields (<3%). However, alkylation of Meldrum acid **2b** afforded the corresponding cycloacetals **3b** and **3c** with yields of 25–30%.

^{1}H NMR spectrum of compound **3b** contained two doublets at 3.65 and 3.67 ppm with spin-spin coupling constants ^2J = 10.4 and ^3J = 3.0 Hz, corresponding to the protons of methyl groups at C^4 and C^5 atoms, respectively. The proton of methine group at C^2 atom was registered as a multiplet at 5.03 ppm, indicating the presence of the 2-alkyl-1,3-dioxolane fragment. In the case of compound **3c**, the protons of the methylene group at C^2 atom resonated at 4.80 and 4.90 ppm, and there was also a triplet of doublets at 4.09 ppm (^3J = 6.3 and 5.3 Hz) assigned to the proton of methine group at C^4 atom, indicating the presence of the 2-alkyl-1,3-dioxolane fragment.

In the ^{13}C NMR spectra, the signals of C^4 (62.11 ppm) and C^2 atoms (92.50 ppm) were characteristic of compounds **3b** and **3c**, respectively.

Condensation of glycerol ketal **6** with *cis*-1,4-dichlorobutene **7** via the known procedure [7] led to the formation of compound **8** with allyl CH_2Cl group (Scheme 3). Alkylation of diethyl malonate **2a** with

chloromethyl derivative **8** proceeded with the quantitative formation of diester **9**, decarboxylation of which resulted in the desired 1,3-dioxolane carboxylic acid derivative **10**.

The ^{1}H NMR spectrum of compound **10** contained a doublet of triplets at 5.62 ppm with a ^3J = 10.9 Hz belonging to *cis*-oriented double bond. The presence of dioxolane ring with two methyl groups was also confirmed by the signals of diastereotopic protons at C^5 (4.03 and 3.70 ppm, ^2J = 10.9 and ^3J = 6.0 Hz) and C^4 atoms (4.20–4.28 ppm), as well as singlets of two CH_3 groups (1.42 ppm). In the ^{13}C NMR spectrum the signals of double bond fragment were observed at 128.99 and 129.13 ppm, characteristic of *cis*-isomers, whereas in *trans*-isomers the signal is shifted downfield [8, 9]. Note that the studied transformations of *cis*-1,4-dichlorobutene derivatives **8** and **9** into dioxolane carboxylic acid **10** proceeded with preservation of the *cis*-configuration. A similar result has been obtained earlier during alkylation of diethyl malonate with *cis*-1,4-dichlorobut-2-ene [10].

In summary, the studied reactions open the ways to the synthesis of acid esters containing cycloacetal fragments.

Synthesis of compounds 3a–3c, 9. A mixture of 0.01 mol of CH acid **2**, 0.015 mol of haloalkyl-1,3-dioxolane **1** or **8**, 0.01 mol of K_2CO_3 (or 0.01 mol of triethylamine in the case of compound **2b**), 50 mL of acetonitrile, and 10% Catamine AB was stirred at 50°C for 6–8 h. In the case of dioxolane **8**, the reaction mixture was microwave-irradiated for 1 h. After the reaction was complete (GLC control), the mixture was cooled, washed with water (in the case of compound **2b**, the mixture was washed successively with a 30% sodium bicarbonate solution and with water), extracted with chloroform, dried with potassium carbonate, and evaporated. The residue was distilled in vacuum (**3a**) or purified by chromatography (**3b**, **3c**, **9**) using benzene–ethyl acetate (9 : 1) as the eluent.

Diethyl [2-(1,3-dioxolan-2-yl)ethyl]malonate (3a). Yield 1.8 g (70%), bp 161–162°C (3 mmHg). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.24 t (6H, CH_3, ^3J = 7.1), 1.70 t.d (2H, C^6H_2, ^3J = 7.1, 4.5), 2.01 q (2H, C^7H_2, ^3J = 7.6), 3.38 t (1H, C^8H, ^3J = 7.6), 3.85 d.d (2H, C^4H_A, C^5H_A, ^2J = 10.5, ^3J = 3.5), 3.95 d.d (2H, C^4H_B, C^5H_B, ^2J = 10.5, ^3J = 3.5), 4.16 q (4H, $C^{11}H_2$, $C^{12}H_2$, ^3J = 7.1), 4.86 t (1H, C^2H, ^3J = 4.5). ^{13}C NMR spectrum, δ_C, ppm: 14.01 (CH_3), 22.97 (C^7), 31.16 (C^6), 51.56 (8), 61.28 (C^{11}, C^{12}), 64.95 (C^4, C^5), 103.73 (C^2), 169.22 (C=O). Mass spectrum, *m*/*e*, (I_{rel}, %): 215 (2), 171 (5), 99 (15), 73 (100), 45 (15).

5-(1,3-Dioxolan-2-ylmethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (3b). Yield 0.7 g (30%). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.84 s (6H, CH_3), 2.20 d.d (2H, C^6H_2, ^2J = 5.6, ^3J = 4.3), 3.55 d (1H, C^7H, ^3J = 5.6), 3.65 d.d (2H, C^4H_A, C^5H_A, ^2J = 10.4, ^3J = 5.6), 3.68 d.d (2H, C^4H_B, C^5H_B, ^2J = 10.4, ^3J = 3.0), 5.03 t (1H, C^2H, ^3J = 4.3). ^{13}C NMR spectrum, δ_C, ppm: 26.43 (CH_3), 29.43 (C^6), 45.77 (C^7), 62.11 (C^4, C^5), 102.55 (C^2), 104.32 (C^{10}), 166.23 (C=O).

5-(1,3-Dioxolan-4-ylmethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (3c). Yield 0.5 g (20%). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.25 s (6H, CH_3), 1.60 d.d (2H, C^6H_2, ^3J = 6.3, 5.1), 3.45 d (1H, C^7H, ^3J = 5.1), 3.80 d.d (2H, C^4H_A, C^5H_A, ^2J = 9.0, ^3J = 5.3), 3.90 d.d (2H, C^4H_B, C^5H_B, ^2J = 10.4, ^3J = 5.1), 4.09 m (1H, C^5H), 4.80 d (1H, C^2H, ^3J = 1.0), 4.90 d (1H, C^2H, ^3J = 1.0). ^{13}C NMR spectrum, δ_C, ppm: 26.19 (CH_3), 29.40 (C^6), 49.55 (C^7), 67.91 (C^5), 77.15 (C^4), 92.50 (C^2), 105.44 (C^{10}), 165.95 (C=O).

Diethyl (2*Z*)-4-[(2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy]but-2-en-1-yl)malonate (9). Yield 2.6 g (80%). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.23 t (6H, CH_3, ^3J = 7.0), 1.30 s (6H, CH_3), 2.63–2.65 m (2H, $C^{13}H_2$), 3.40 d.d (1H, C^8H_A, ^2J = 9.8, ^3J = 6.3), 3.49 d.d (1H, C^8H_B, ^2J = 9.8, ^3J = 5.9), 3.68 d.d (1H, $C^{14}H$, ^2J = 8.2, ^3J = 6.5), 4.02 d. t (1H, $C^{10}H_A$, ^2J = 8.2, ^3J = 6.3), 4.06–4.30 m (8H, C^4H_2, C^5H, $C^{10}H_B$, $C^{17}H_2$, $C^{18}H_2$), 5.47 d. t (1H, $C^{11}H$, ^2J = 10.9, ^3J = 7.5), 5.63 d.t (1H, $C^{12}H$, ^2J = 10.9, ^2J = 6.3). ^{13}C NMR spectrum, δ_C, ppm: 13.98 (CH_3), 26.30 (CH_3), 51.60 (C^{14}), 61.43 (C^{17}, C^{18}), 66.82 (C^{10}), 71.19 (C^8), 74.61 (C^5), 109.35 (C^2), 128.22 (C^{12}), 129.13 (C^{11}), 168.76 (2C=O). Mass spectrum, *m*/*e* (I_{rel}, %): 241(15), 213 (10), 184 (25), 126 (30), 101 (100), 95 (32), 73 (25), 67 (35), 43 (75), 41 (20).

Decarboxylation of compounds 3a and 9. A mixture of 0.01 mol of ester **3a** or **9**, 0.03 mol of lithium chloride, 0.02 mol of water, and 10 mL of DMSO was stirred at 140°C for 8 h until complete conversion of the substrate. The mixture was cooled to ambient, washed with water, extracted with chloroform, dried with freshly calcined sodium sulfate, and evaporated. The residue was distilled in vacuum.

Ethyl 4-(1,3-dioxolan-2-yl)butanoate (4a). Yield 1.4 g (58%), bp 100–101°C (5 mmHg). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.24 t (3H, CH_3, ^3J = 7.2),

1.68 d.t (2H, C^6H_2, ^2J = 4.6, ^3J = 7.2), 1.74 m (2H, C^7H_2, ^3J = 7.1), 2.30 t (2H, CH_2, ^3J = 7.1), 3.82 d.d (2H, C^4H_A, C^5H_A, ^2J = 10.5, ^3J = 3.4), 3.94 d.d (2H, C^4H_B, C^5H_B, ^2J = 10.5, ^3J = 3.4), 4.10 q (2H, $C^{10}H_2$, ^3J = 7.2), 4.85 t (1H, C^2H, ^3J = 4.6). ^{13}C NMR spectrum, δ_C, ppm: 14.18 (CH_3), 19.36 (C^7), 33.02 (C^8), 33.92 (C^6), 60.18 (C^{10}), 64.81 (C^4, C^5), 104.46 (C^2), 173.16 (C=O). Mass spectrum, *m/e* (I_{rel}, %): 143 (2), 99 (20), 73 (100), 45 (20).

Ethyl (4*Z*)-4-[(2,2-dimethyl-1,3-dioxolan-4-yl) methoxy]hex-4-enoate (10). Yield 1.4 g (58%), bp 160–162°C (2 mmHg). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.10 t (3H, CH_3, ^3J = 7.0), 1.42 s (6H, $2CH_3$), 2.40–2.45 m (4H, $C^{13}H_2$, $C^{14}H_2$), 3.40–3.45 m (4H, C^8H_2,), 3.70 d.d (1H, C^5H_A, ^2J = 8.0, ^3J = 6.0), 4.03 d.d (1H, C^5H_B, ^2J = 8.0, ^3J = 6.0), 4.04 q (2H, $C^{18}H_2$, ^3J = 7.2), 4.10–4.15 m (2H, $C^{10}H_2$), 4.20–4.28 m (1H, C^4H), 5.61 d. t (1H, $C^{12}H$, ^2J = 10.9, ^3J = 7.6). 5.63 d. t (1H, $C^{11}H$, ^2J = 10.9, ^2J = 6.4). ^{13}C NMR spectrum, δ_C, ppm: 14.16 (C^6, C^7), 15.20 (CH_3), 23.06 (C^{13}), 33.66 (C^{14}), 60.46 (C^{18}), 65.80 (C^5), 66.76 (C^8), 70.50 (C^4), 71.49 (C^{10}), 109.55 (C^2), 128.99 (C^{11}), 129.13 (C^{12}), 168.84 (C=O). Mass spectrum, *m/e* (I_{rel}, %): 141 (45), 113 (75), 99 (42), 95 (20), 71 (98), 67 (100), 41 (45), 30 (22).

5-[2-(1,3-Dioxolan-2-yl)ethyl]pyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (5). 0.4 mol of urea and 0.08 mol of compound **3a** were added at stirring to a solution of sodium ethoxide prepared by dissolving 0.024 mol of sodium in 110 mL of anhydrous ethanol. The mixture was refluxed for 4 h to form a precipitate, and then cooled to ambient. The precipitate was filtered off. The filtrate was evaporated, and the residue was washed on a Büchner funnel with hexane. The resulting powder was dried in air. Yield 1.4 g (60%), mp 101–102°C. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.58 t.d (2H, C^6H_2, ^2J = 7.5, ^3J = 4.9), 1.72 t.d (1H, C^7H_2, ^2J = 7.5, ^3J = 7.7), 2.98 t (1H, $C^{5'}H$, ^3J = 7.7), 3.82 d.d (2H, C^4H_A, C^5H_A, ^2J = 10.9, ^3J = 7.2), 3.95 d.d (2H, C^4H_B, C^5H_B, ^2J = 10.5, ^3J = 7.2), 4.60 br. s (NH, H_2O), 4.90 t (1H, C^2H, ^3J = 4.9). ^{13}C NMR spectrum, δ_C, ppm: 24.72 (C^7), 31.42 (C^6), 58.23 ($C^{5'}$), 64.50 (C^4, C^5), 104.06 (C^2), 162.21 (2C=O), 172.48 (C=O).

Chromatography analysis was carried out using an HRGC 5300 Mega Series Carlo Erba chromatograph equipped with a flame ionization detector (carrier gas helium, flow rate 30 mL/min, column length 25 m, analysis temperature 50–280°C, heating rate 8 deg/min, detector temperature 250°C, evaporator temperature 300°C). Chromato–mass spectra were recorded using a Fisons instrument (capillary quartz column DB 560, 50 m) and Focus Finingan DSQ II mass spectrometer (ion source temperature 200°C, direct input temperature 50–270°C, heating rate 10 deg/min, ThermoTR-5MS column, $50 \times 2.5 \times 10^{-4}$ m, the flow rate of helium 0.7 mL/min); electron impact ionization method was used. NMR spectra were recorded with a Bruker AVANCE-400 spectrometer in $CDCl_3$.

ACKNOWLEDGMENTS

This work was financially supported by the Russian Science Foundation (project no. 15-13-10034) and the President of the Russian Federation (Scholarship for Young Scientists and Post-Graduates no. SP-1960.2015.4).

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