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ALKYLATION REACTIONS OF β-DICARBONYL COMPOUNDS ACCOMPANIED WITH REARRANGEMENTS

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The results of alkylation of dicarbonyl compounds with 1,2,3-trihalopropane are presented, which is accompanied by rearrangement of the carbon skeleton and leads to the formation of β-substituted furans. Alkylation of β-dicarbonyl compounds with 1,2-dibromoethane at room temperature gives a C,C-cycloalkylation product, which isomerizes at a temperature above 180°C into a C,O-dialkylation product, a dihydrofuran derivative. Alkylation of dimetylacetonedicarboxylate with methyl iodide occurs similarly, the primary O-alkylation product undergoes rearrangement into a C-alkylation product at 180°C. It is also shown that such rearrangements occur with small radicals. The product of O-alkylation of dimethylacetone dicarboxylate with dimethyl acetal of bromoacetic aldehyde is stable at a temperature of 200°C, whereas the product of its hydrolysis isomerizes into a product of C-alkylation with further conversion into furan derivatives.

Keywords: rearrangement, alkylation, dicarbonyl compounds, furan

INTRODUCTION

The multi-profile synthetic potential of di- and polycarbonyl compounds allows them to be used as objects for research, as well as in the synthesis of new polyfunctional compounds that have practical application in medicine, materials science, optoelectronics and other fields [1-4].

The literature [5-9] provides information on the alkylation of mono- and polycarbonyl compounds, and shows the dependence of the reaction direction on the conditions of their implementation. The results presented indicate the formation of C,O-alkylation products at low temperatures. With increasing temperature, the primary O-alkylation product undergoes an intramolecular rearrangement at 180 ^{0}C into a C-alkylation product.

The work [7] presents data on the synthesis of dimethyl -2-methylpentanedioate during the hydrolysis of enol ester dimethyl-3-methoxypent-2-enedioate obtained by S-alkylation of methyl iodide in the NaH/DMFA system, as well as the direction of the reaction depending on the nature of the alkylated agent. Similar results were obtained during the alkylation of tri- and tetracarbonyl compounds using the sodium hydride method [8].

This paper presents the results of the alkylation of dicarbonyl compounds with mono- and polyhaloalkanes and their derivatives, which are accompanied by rearrangement.

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EXPERIMENTAL

NMR spectra 1H and 13C were recorded on a Bruker "AV-300" spectrometer [working frequencies 300 (1H) and 75 (13C) MHz] internal standard – TMS. Elemental analysis was performed on a Carlo Erba 1106 instrument. The purity of the obtained compounds was monitored by TLC on Silufol UV-254 plates.

General method for the alkylation of dicarbonyl compounds with halogenated compounds. A halogenated compound (20 mmol) was added dropwise with vigorous stirring to a mixture of 20 mmol of dicarbonyl compounds and 20 mmol of K2CO3 in 50 ml of DMSO. The mixture was stirred for 2 h at room temperature and for the same amount of time at 60-70 0C for the bromine-containing compound and 100-110 0C for chlorine. The reaction mixture was cooled with ice water (5-10 0C), treated with water and extracted with ether. The extract was dried with Na2SO4, the ether portion was distilled off, and the residue was distilled under vacuum.

Dimethyl-3-methoxypent-2-enedioate (2). From 3.2 g of compound 1 and 2.4 g of methyl iodide, 2 was synthesized with a yield of 3.9 g. (64%), b.p. 103-105^{0}C (2 mm Hg.). Found %: C 49.45; H 6.26. C_8 $H_{12}O_5$ Calculated, %: C 51.06; H 6.26. ^{1}H NMR spectrum (DMSO-d_6), δ ppm: 3.5 s (6H, 2OCH_3), 3.8 s (3H, OCH_3), 3.4 s (2H, CH_2), 6.7 s (1H, CH-).

Dimethyl -2-methylpentanedioate (3). When compound 2 is heated at 180 0C for 3-4 hours, it isomerizes into the C-alkylation product 3, b.p. 108-109 ^{0}C (2 mm Hg). ^{1}H NMR spectrum (DMSO-d_6), δ ppm: 0.9 d (3H, CH_3-C), 3.3 q (1H, CH-C), 3.6-3.7 s (6H, 2OCH_3), 3.2 s (2H, CH_2-C=O).

Dimethyl 3-(2,2-diethoxyethyl)pent-2-enedioate (4). From 2.5 g of 1 and 3 g of diethyl acetal bromoacetaldehyde in a medium of 8.6 g of potash and 50 ml of DMSO carried out at 50-60 0C for 5-6 hours, product 4 was obtained. Yield 3.2 g (54 %), b.p. 97-98 ^{0}C (2 mm Hg). Found, %: C 52.72; H 7.81. $C_{13}H_{22}O_7$ Calculated, %: C 53.79; H 7.58. ^{1}H NMR spectrum (DMSO-d_6), δ ppm: 1.1 t (6H, 2CH_3), 3.3-3.8 m (10H, 2CH_3O, 2 CH_2O), 4.1 d (2H, 0$C\underline{H_2}$-CH), 4.8 t (1H, CH), 6.7 s (1H, CH=). ^{13}C NMR spectrum (DMSO-d_6), δ ppm: 167, 168 (2COO).

Methyl 2-(2-methoxy-2-oxoethyl)furan-3-carboxylate (6). To 2 g of ester 4 in 10 ml of methanol were added 2 ml of 7% HCl and left for 2 hours at room temperature. Dimethyl 3-(2-oxoethoxy)pent-2-enedioate (5) was obtained, [yield 1.4 g (76%). ^{1}H NMR spectrum (acetone-d_6) δ ppm: 9.2 t (1H, CH=O)] heating at ≥ 170 0C for 3 hours leads to the formation of 6**.** Yield 1.2 g (78 %), b.p. 108-109 ^{0}C (2 mm Hg). Found, %: C 54.12; H 5.89. $C_9H_{10}O_5$ Calculated, %: C 54.54; H 5.05. ^{1}H NMR spectrum (acetone-d_6), δ ppm: 2.7 s (2H, CH_2), 3.65 s (3H, CH_3O), 3.75 s (3H, CH_3O), 6.70 d (1H, CH=), 7.2 s (1H, =CHO).

Dimethyl 2-(cyanomethyl)-3-oxopentanedioate (7). Under the above conditions, 1.3 g of chloroacetonitrile was added to 3 g of 1 in a medium of 8 g of K2CO3 in 50 ml of DMSO, 7 was obtained, yield 2.2 g. (60%), b.p. 103-105 ^{0}C (1 mm Hg). Found, %: C 51.23; H 5.78; N 6.13. $C_9H_{11}O_5N$ Calculated, %: C 50.70; H 5.16; N 6.57. ^{1}H NMR spectrum (toluene-d_8), δ ppm: 2.9 m (2H, CH_2), 3.2 t (1H, CH), 3.4-3.8 m (8H, OCH_3, CH_2)

Methyl 5-amino-2-(2-methoxy-2-oxoethyl)furan-3-carboxylate (8). The alkylation product 7 (2 g) in an acidic medium (HCl) isomerizes into 8. Yield 1.8 g (64%), b.p.124-126 ^{0}C (3 mm Hg). Found, %: C 49.97; H 5.07; N 6.15. $C_9H_{11}O_5N$ Calculated, %: C 50.70; H 5.16; N 6.57. ^{1}H NMR spectrum (toluene-d_8), δ ppm.: 3.4-3.8 m (8H, 2OCH_3, CH_2), 5.06 d (2H, NH_2), 6.54 s (2H, NH_2). ^{13}C NMR spectrum (toluene-d_6), δ ppm: 166, 168 (2COO)

Methyl 1-(3-methoxy-3-oxopropanoyl)cyclopropane-1-carboxylate (9). The above conditions yielded 9 from 3.4 g of 1 and 2.0 g of dibromoethane. Yield 2.9 g (56%), b.p. 124-126 ^{0}C (3 mm Hg) Found, %: C 55.2; H 5.4. $C_9H_{12}O_5$ Calculated,%: C 54; H 6. ^{1}H NMR spectrum (DMSO-d_6), δ ppm: 1.72 t (4H, CH_2 – CH_2), 3.41 s (2H, CH_2), 3.66 s (6H, 2OCH_3).

Methyl 2-(2-methoxy-2-oxoethyl)-4,5-dihydrofuran-3-carboxylate (10). At a temperature of 180 0C, compound 9 isomerizes into 10**,** yield 1.8 g (38%), b.p. 135-136 ^{0}C (3 mm Hg) ^{1}H NMR spectrum (DMSO-d_6), δ ppm: 2.92 s (2H, CH_2), 3.63 t (2H, CH_2-C=), 3.71 s (6H, 2OCH_3), 4.48 t (2H, CH_2O).

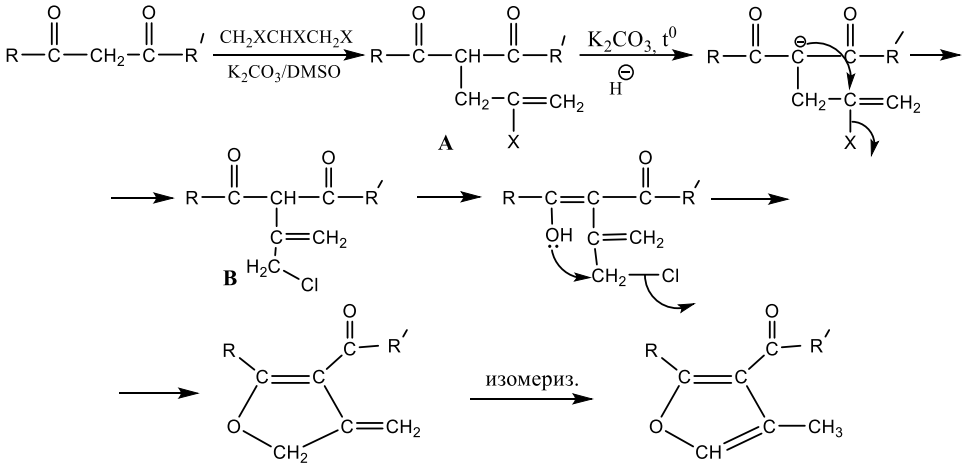
5,5-dimethyl-3-oxocyclohex-1-ene-1-yl-2-chloroacetate (11). A mixture of 3.4 g (0.22 mol), 1.8 g pyridine in 50 ml ether was cooled to 10-15 0C and 2.5 g (0.22 mol) chloroacetic acid chloride was added with stirring. The mixture was stirred for 5-6 hours in the cold. The resulting crystals 11 were washed with benzene and dried. Yield 2,6 g (67%), m.p. 138-139 ^{0}C. Found,%: C 56.18; H 6.12; Cl 17.11. $C_{10}H_{13}O_3Cl$. Calculated, %: C 55.42; H 6.00; Cl 16.39. ^{1}H NMR spectrum (DMSO-d_6), δ ppm: 1.00 s (6H, $2CH_3$), 1.82 s (2H, CH_2), 2.25 s (2H, -CH_2-CO), 4.32 s (2H, -CH_2-Cl), 5.61 s (1H, =CH).

2-(2-chloroacetyl)-5,5-dimethylcyclohexane-1,3-dione (12). At a temperature of 180 0C, compound 11 isomerizes into 12, yield 1.8 g (78%), bp 140-142 0C. ^{1}H NMR spectrum (DMSO-d_6), δ ppm: 1.00 s (6H, $2CH_3$), 2.31 s (4H, $2C\underline{H}_2CHO$), 4.08 s (1H, CH), 4.54 s (2H, CH_2Cl). ^{13}C NMR spectrum (DMSO-d_6), δ ppm: 26.6 ($2CH_3$), 30.1($(CH_3)_2\underline{C}$), 45.1 (CH_2Cl), 58.8 (CH_2), 196.3 (C=O), 199.2 ($\underline{C}$-CH_2Cl).

RESULTS AND DISCUSSION

It was previously shown [6] that during the alkylation of β-dicarbonyl compounds with 1,2,3-trihaloalkanes, β-substituted furan was obtained instead of the expected α,α-disubstituted furan. In all likelihood, the compound 2-halopropen-2-yl-1(A) is formed in the initial stage of the reaction, and then, under the action of potash, undergoes an intramolecular rearrangement with the formation of the product 3-halopropen-2-yl-1(B). The latter, under reaction conditions, as a result of intramolecular O-alkylation and prototropic isomerization yields β-substituted furan according to scheme 1.

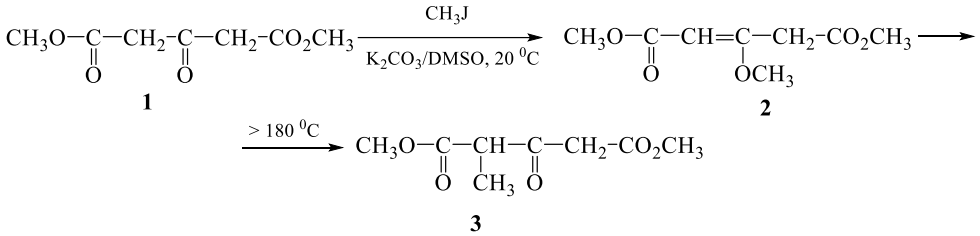
Scheme 1



X = Cl, Br

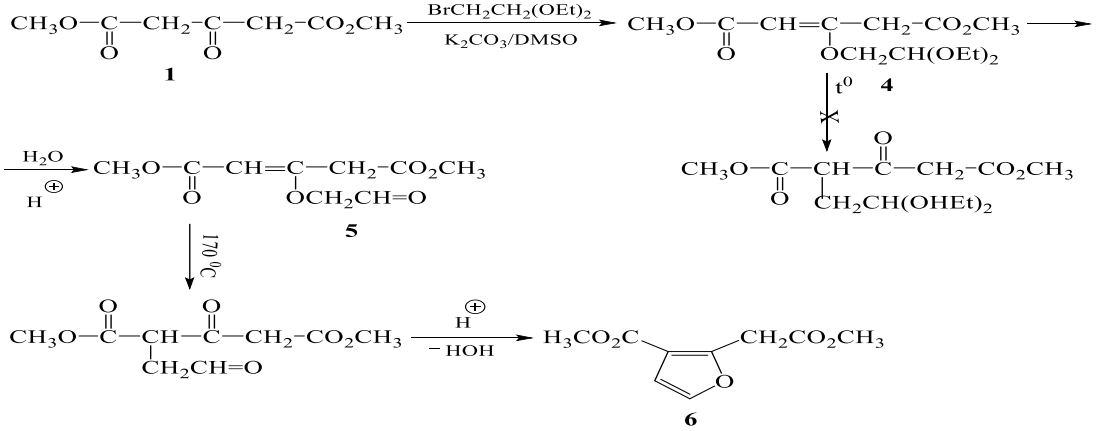
In subsequent works on the alkylation of dimethylacetone dicarboxylate with 1,2,3-trihalopropane, identical results were given [7]. Under similar conditions, the alkylation of dimethylacetone dicarboxylate (1) with methyl iodide was studied; only the O-alkylation product (2) was obtained. The latter, at a temperature of 180 0C and above, undergoes a rearrangement into the C-alkylation product (3), which is apparently associated with the thermodynamic stability of the latter.

Scheme 2



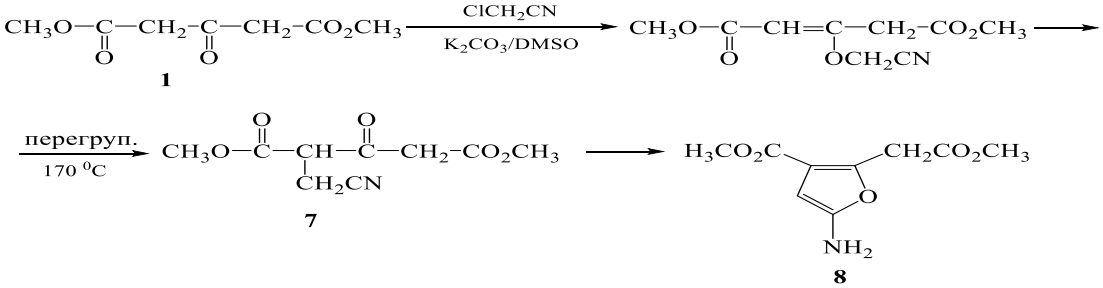
Alkylation of compound 1 with diethyl acetal of bromoacetic aldehyde also yielded an O-alkylation product. Unlike methyl ether, compound 4 is stable to temperature and does not undergo rearrangement into a C-alkylation product, although the hydrolysis product of the resulting acetal into the corresponding aldehyde undergoes rearrangement with subsequent conversion of the rearrangement product into a furan derivative according to scheme 3. It is possible that the acidic environment also contributes to the rearrangement in this case.

Scheme 3



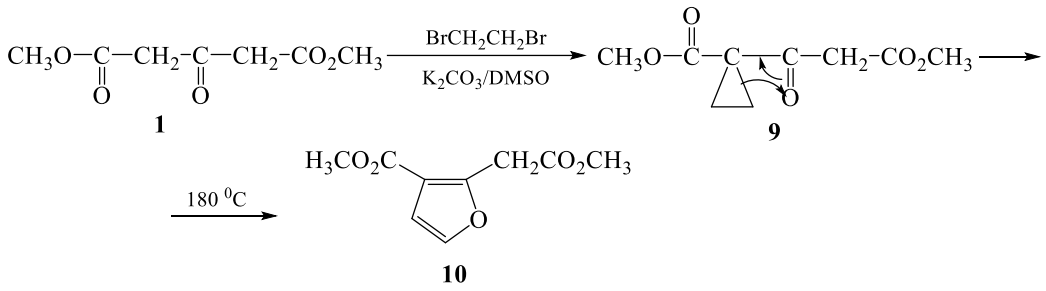
Alkylation of compound 1 with chloromethyl cyanide at 70 0C yields an O-alkylation product, which at elevated temperatures (~170°C) also undergoes rearrangement into a C-alkylation product. The latter, as a result of prototropic isomerization and intramolecular transformation, yields substituted furan 8 (Scheme 4).

Scheme 4



The cyclopropane derivative 9 obtained by alkylation of compound 1 with 1,2-dibromoethane at room temperature undergoes a ring-opening rearrangement at 180°C to form the furan derivative 10 (Scheme 5)

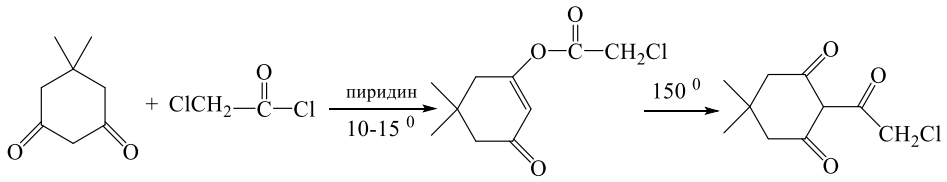
Scheme 5



1 **9** **10**

Acylation of dimedone with chloroacetic acid chloride in the presence of pyridine yielded the O-acylation product 11, which also undergoes a rearrangement under the influence of temperature into the C-acylation product 12 (Scheme 6)

Scheme 6



11 **12**

CONCLUSION

It has been shown that C or O-alkylation products are formed during the alkylation of carbonyl compounds with halogenated alkanes and their derivatives. However, O-alkylation products undergo a rearrangement under the influence of temperature into a C-alkylation product and the reverse C,C-dialkylation product is observed (cyclopropane derivative) is converted into a C,O-dialkylation product, which is explained by the stability of the final products

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