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STUDY OF THE INFLUENCE OF THE NATURE OF HALOGEN AND TEMPERATURE ON THE DIRECTION OF THE ALKYLATION REACTION OF β -DICARBONYL COMPOUNDS BY MONO- AND POLYHALOGENALKANES

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ARTICLE INFO	ABSTRACT
<p><i>Article history:</i></p> <p>Received:2024-09-20</p> <p>Received in revised form:2024-09-26</p> <p>Accepted:2024-10-24</p> <p>Available online</p>	<p>The data on the influence of the halogen nature and temperature on the direction of the alkylation reaction of β-dicarbonyl compounds with halogenated alkanes are presented. It is shown that the main products of the reaction of acetylacetone with 1,2-dichloroethane at 80°C are the product of O,O-intermolecular alkylation, and a small amount of the product of C,O-dialkylation, a furan derivative, is formed. The alkylation of dimedone with dichloroethane proceeds according to a similar scheme, yielding an O,O-dialkylation product. Alkylation of dimedone with 1,2,3-trichloropropane yields only the product of O-alkylation, enol ether. It has been established that dimedone with 1,3-dichloroethane, under identical conditions, gives a bicyclic compound. Acylation of dimedone with chloroacetic acid chloride in the presence of pyridine forms O-acylation products. The reaction of alkylation of ethyl cyanoacetate with dichloroethane leads to the formation of three compounds – intramolecular C, C-alkylation with the formation of heme-ethoxycarbonylnitrile cyclopropane, a product of intermolecular dialkylation of bis(1,4-ethoxycarbonyl-cyano)cyclohexane and a polymer compound.</p>
<p>Key words:</p> <p>alkylation, acetylacetone, dichloroethane, trichloropropane, furan</p>	

INTRODUCTION

Systematic studies of alkylation of β -dicarbonyl compounds with halogenated alkanes have shown that depending on the nature of the substrate and alkylating reagent, C- and O-alkylation products were obtained. The effect of solvent and temperature on the direction of the alkylation reaction was shown [1-4].

It was found [5-7] that during alkylation of β -dicarbonyl compounds (acetylacetone, acetoacetic ester, indanedione, etc.) with dibromoethane in DMSO in the presence of potash, C,C-cyclopropylalkylation products were obtained. The study of the indicated condensations

with 1,2-dichloroethane under identical conditions gave distinctive results, which served as the basis for a complete study of the indicated reactions depending on the nature of the halogen, solvent and temperature.

Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker AV 300 [300 (^1H) and [300 (1H) and 75 (13C) MHz, respectively] spektrometer, internal standard – TMS. Melting point was determined on an SMP 30 Stuart. 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, eluent – acetone-hexane (1:1).

General procedure for alkylation of compounds with an active methylene group. 0.12 mol of the reagent was added dropwise to a mixture of 0.12 mol of the compound with an active methylene group and 0.25 mol of K_2CO_3 in 50 ml of DMSO with stirring. The mixture was stirred for 12 h at 80°C . Cooled, treated with water and extracted with ethyl ether. The extract was dried with MgSO_4 , the solvent was distilled off, and the residue was distilled under vacuum.

4-[2-(4-oxopent-2-en-2-yl)oxy]ethoxy]pent-3-en-2-one (1). Yield 28 g (70%), b.p. 145°C (2 mm Hg). Found, %: C 63.23; H 8.17 $\text{C}_{12}\text{H}_{18}\text{O}_4$ Calculated, %: C 63.71; H 7.96. ^1H NMR spectrum (CDCl_3), δ ppm: 2.15 s (6H, 2CH_3), 2.3 s (6H, 2OCH_3), 4.15 s (4H, 2CHO), 5.45 s (2H, $2\text{CH}=\text{}$). ^{13}C NMR spectrum (CDCl_3), δ ppm: 19.31, 62.5, 100, 171, 198.

1-(2-methyl-4,5-dihydrofuran-3-yl)ethan-1-one (2). Yield 3.2 g (8%), b.p. $68\text{--}70^\circ\text{C}$ (2 mm Hg). Found, %: C 65.98; H 8.32 $\text{C}_7\text{H}_{10}\text{O}_2$ Calculated, %: C 66.66; H 7.93. ^1H NMR spectrum (CDCl_3), δ ppm: 1.75 s (3H, $\text{CH}_3\text{-C}=\text{C}$), 1.95 s (3H, $\text{CH}_3\text{-C}=\text{O}$), 2.72 t (2H, $\text{CH}_2\text{-C}=\text{}$), 4.20 s (2H, CH_2O). ^{13}C NMR spectrum (CDCl_3), δ ppm: 13, 21, 2, 23, 29, 30, 31, 41, 61, 62, 69.5, 108, 112, 168, 204.

3,3-(ethane-1,2-diyl)bis(oxy)bis(5,5-dimethylcyclohex-2-ene-1-one) (3). Yield 15 g (65%), m.p. $143\text{--}145^\circ\text{C}$. Found, %: C 70.12; H 18.97 $\text{C}_{18}\text{H}_{26}\text{O}_4$ Calculated, %: C 70.58; H 18.49. ^1H NMR spectrum (DMSO-d_6), δ ppm: 1.02 s (12H, 4CH_3), 2.15 s (4H, 2CH_2), 2.25 s (4H, 2CH_2), 4.15 s (4H, 2CH_2), 5.4 s (2H, $2\text{CH}=\text{}$). ^{13}C NMR spectrum (DMSO-d_6), δ ppm: 19, 22, 41, 51, 63, 101, 176, 198.

3,3,12,12-tetramethyldispiro[5,2,5,9,2,6]hexadecane-1,5,10,14-tetraone (4). Yield 7 g (23%), m.p. 300°C . Found, %: C 72.76; H 8.68 $\text{C}_{20}\text{H}_{28}\text{O}_4$ Calculated, %: C 72.28; H 8.43. ^1H NMR spectrum (DMSO-d_6), δ ppm: 1.02 s (12H, 4CH_3), 1.8 m (8H, 4CH_2), 2.30 s (8H, 4CH_2). ^{13}C NMR spectrum (DMSO-d_6), δ ppm: 22.1 ($\text{CH}_2\text{-CH}_2$), 27.3 (CH_3), 32.4 ($(\text{CH})_3\text{C}$), 50.4 (C-CO), 68.7 ($\text{C}(\text{CH})_2$), 220 (CO).

3-[(2-chloroallyl)oxy]-5,5-dimethylcyclohex-2-en-1-on (5). 10 g (0.07 mol) of the reagent was added dropwise to a mixture of 0.12 mol of the compound with an active methylene group and 0.25 mol of K_2CO_3 in 50 ml of DMSO with stirring. The mixture was stirred for 12 h at 80°C . Cooled, treated with water and extracted with ethyl ether. The extract was dried with MgSO_4 , the solvent was distilled off, and the residue was distilled under vac

Found, %: C 51.27; H 5.69; Cl 13.87. $\text{C}_{11}\text{H}_{15}\text{O}_2\text{Cl}$ Calculated, %: C 51.86; H 5.9; Cl 13.94. ^1H NMR spectrum (DMSO-d_6), δ ppm: 0.98 s (6H, 2CH_3), 2.1 s (2H, CH_2), 2.25 s (2H, CH_2), 4.35 s (2H, OCH_2), 5.24 s (1H, $\text{CH}=\text{}$), 5.45 d (2H, $=\text{CH}_2$, $^2J_{\text{HH}} 4 \text{ Гц}$). ^{13}C NMR spectrum (DMSO-d_6), δC ppm.: 28, 33, 41.5, 50.5, 70, 101, 113, 133, 175, 198.

7,7-dimethyl-4,6,7,8-tetrahydro-2H-chromene-3,5-dione (6). 10 g (0.09 mol) dichloroacetone were added dropwise to a mixture of 10 g (0.07 mol) and 10 g K_2CO_3 in 30 ml DMSO at room temperature. Partial heating of the mixture (25 °C) was observed, cooled to room temperature and stirred for 6 h. The color of the mixture changed to orange. The mixture was treated with water, extracted with ether, the extract was dried with $MgSO_4$, and the solvent was distilled off. Yield of precipitated crystals **6** was 9.8 g (54%), m.p. 137-139 °C. Found, %: C 67.56 H 7.67. $C_{11}H_{14}O_3$ Calculated, %: C 68.0; H 7.21. 1H NMR spectrum (DMSO- d_6), δ ppm.: 1.05 s (6H, 2 CH_3), 1.82 s (2H, $CH_2CH=$), 1.99 s ($CH_2C=O$), 3.12 s (2H, $=C-CH_2$), 5.12 s (2H, O- CH_2). ^{13}C spectrum (DMSO- d_6), δC ppm: 27.2, 27.8, 33.3, 37.9, 78.9, 105.8, 172.6, 205.8.

5,5-Dimethyl-3-oxocyclohex-1-en-1-yl-2-chloroacetate (7). To a mixture of 3.1 g (0.02 mol) dimedone, 1.8 g (0.02 mol) pyridine in 20 ml of ether, 3 g (0.025 mol) of chloroacetic acid chloride was added drop by drop. The mixture was stirred for 4 hours at room temperature. The ether layer was separated, crystals fell out, recrystallized in benzene. White crystals fell out **7**. Yield 4.2 g (67%), t.pl. 138-140 °C. Found, %: C 56.3; H 4.86; Cl 20.98 $C_{10}H_{12}O_3Cl$ Calculated, %: C 55.6; H 5.5; Cl 21.5. 1H NMR spectrum (DMSO- d_6), δ ppm.: 0.96 s (6H, 2 CH_3), 2.07 s (2H, $CH_2C=$), 2.35 c (2H, $CH_2C=O$), 4.39 s (2H, CH_2Cl), 5.40 d (1H, $CH=$). ^{13}C spectrum (DMSO- d_6), δC ppm: 27.2, 32.6, 41.5, 44.6, 47.8, 118.8, 171.7, 189.2.

Method of alkylation of ethyl cyanoacetate with dichloroethane. Drops of

10 g (0.065 mol) of dichloroethane were added to a mixture of 10 g (0.07 mol) of ethyl cyanoacetate and 10 g of K_2CO_3 in 40 ml of DMSO. The mixture was stirred at room temperature for 6 hours. After that, the mixture was treated with water, extracted with ether, $MgSO_4$ dried, and the solvent was distilled.

Ethyl 1-cyanocyclopropane-1-carboxylate (8). Yield 14.8 g (62%), b.p. 145°C (2 mm Hg). Found, %: C 63.23; H 6.17; N 11.16. $C_7H_9O_2N$ Calculated, %: C 60.43; H 6.47; N 10.07. 1H NMR spectrum ($CDCl_3$), δ ppm: 1.32 t (3H, CH_3), 1.82-1.87 m (4H, 2 CH_2), 4.6 k (2H, CH_2). ^{13}C NMR spectrum ($CDCl_3$), δ ppm: 9.1, 13.6, 15.2, 61.1, 114.9, 172.4.

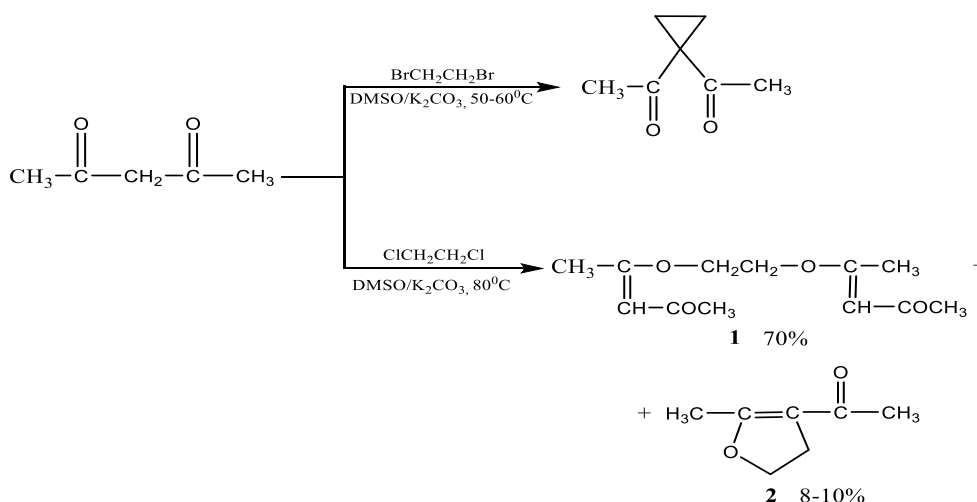
Diethyl(1s,4s)-1-carboxyl-4-cyanocyclohexane-1,4-dicarboxylate (9).

Crystals fell out of the remaining liquid after 4 days. Yield 5 g (25%), m.p. 173-175°C. Found, %: C 56.12; H 8.97; N 10.15. $C_{14}H_{20}O_5N_2$ Calculated, %: C 56.75; H 6.75; N 9.46. 1H NMR spectrum (DMSO- d_6), δ ppm: 1.1 t (6H, 2 CH_3), 2.15 m (4H, 2 CH_2), 2.25 m (4H, 2 CH_2), 4.25 k (4H, 2 CH_2), 7.4 s (2H, NH_2). ^{13}C NMR spectrum (DMSO- d_6), δ ppm: 16, 22.7, 26.4, 34, 51.8, 63, 124, 172, 178.8, 188.

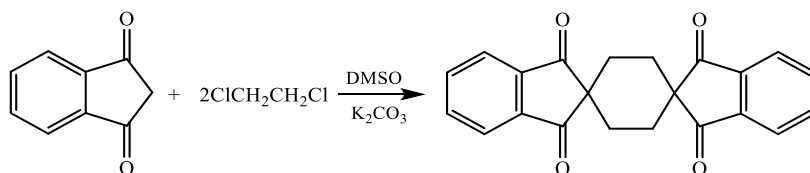
Triethyl 3-cyano-3,4-diiminopentane-1,3,5-tricarboxylate (10). A mixture consisting of 10 g of ethyl cyanoacetate and 3 g of triethyl phosphite was heated for 5 hours in a flask with a reverse cooler at 120 °C. Cooled, white crystals fell out, and recrystallized with benzene. The yield of product **10** was 7.8 g (67 %), m.p. 156 °C. Found, %: C 54.12; H 6.97; N 10.15. $C_{15}H_{21}O_6N_3$ Calculated, %: C 53.09; H 6.20; N 12.40. 1H NMR spectrum (DMSO- d_6), δ ppm: 1.1 t (9H, 3 CH_3), 4.23 m (6H, 3 O- CH_2), 2.25 m (4H, 2 CH_2), 9.4 s (2H, 2NH). ^{13}C NMR spectrum (DMSO- d_6), δ ppm: 16, 44.3, 61.8, 114, 164.6, 168.1, 172.

Result and Discussion

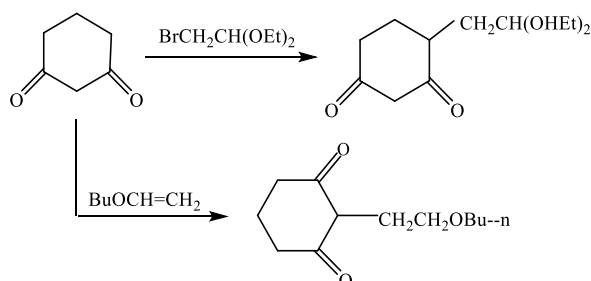
As noted above [5], acetylacetone is alkylated with 1,2-dibromoethane in DMSO in the presence of potash to form gem-diacetylcyclopropane (C,C-dialkylation). This reaction under the specified conditions with 1,2-dichloroethane at a temperature of 80 °C yields as the main product – O,O-intermolecular dialkylation (1), where two moles of acetylacetone and one mole of dichloroethane participate in the reaction and a small amount of the C,O-dialkylation product is formed – a furan derivative (2).



Similar to acetylacetone, indanedione is also alkylated with 1,2-dibromoethane to form a cyclopropane derivative [9], while this reaction with 1,2-dichloroethane has been shown to proceed in a 2:2 ratio to give a product with a dispiro structure.

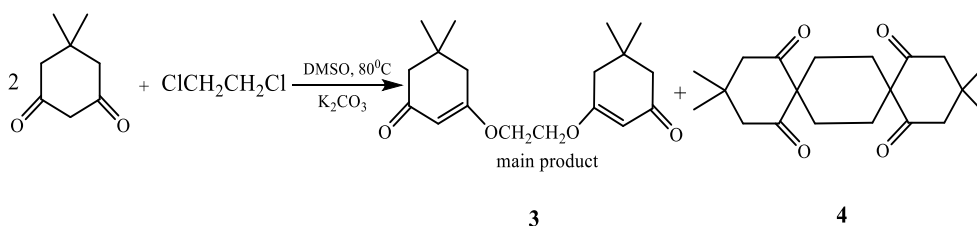


In [10] it was shown that alkylation of cyclohexadione-1,3 with diethyl acetal of bromoacetic aldehyde, contrary to expectations, occurs at position 4, while the active methylene group remains unaffected, whereas alkylation of the said diketone with enol ethers occurs at the active methylene group [11].

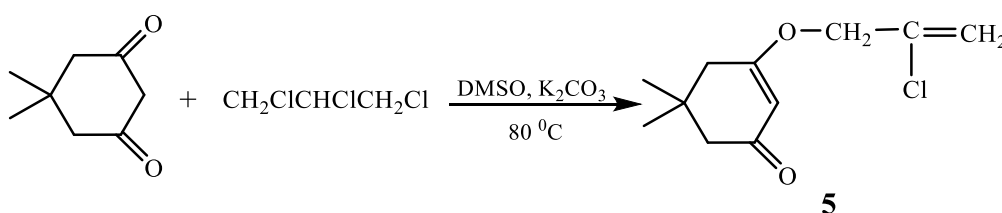


In subsequent studies on the alkylation of dimethylcyclohexadione (dimedone) with acetaldehyde bromoacetal, it was shown that, depending on the nature of the solvent, the reaction proceeds to form O-alkylation products (in DMSO), while in dimethylformamide (DMF) the reaction proceeds via the active methylene group to form a C-alkylation product [12].

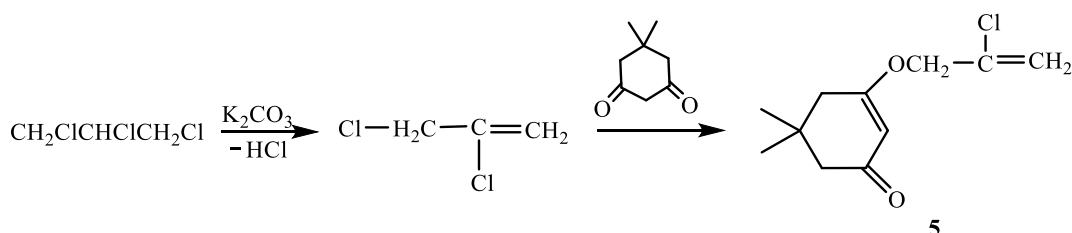
However, the condensation of dimedone with 1,2-dichloroethane in DMSO at a temperature of 80°C proceeds via the oxygen atom to form the O,O-intermolecular dialkylation product 3.



The condensation product of dimedone with 1,2,3-trichloropropane in the presence of potash in DMSO also forms an O-alkylation product. Dehydrochlorination occurs simultaneously, resulting in the formation of the enol ether of dimedone 5.



Unlike dichloroethane, only one chlorine atom participates in this condensation, which is apparently due to the fact that in the first stage, 1,2,3-trichloropropane, under the action of potash, undergoes dehydrohalogenation with the formation of 2,3-dichloropropene, in which allyl chlorine, being active, enters into condensation with the formation of enol ether 7.



This judgment has been confirmed experimentally. Chlorine in the resulting enol ether is passive and does not enter into a substitution reaction under normal conditions.

It should be noted that along with the enol ether 3, an insignificant amount of a crystalline mass is formed, which does not dissolve in common organic solvents, melts at a temperature above 300 °C and, according to the ¹H NMR spectrum, is a product of C,C-intermolecular alkylation having a bispiro structure 4, as in the case of indanedione.

In the literature [13], it is noted that the condensation of dimedone with 1,3-dichloroacetone in the presence of potassium hydroxide in methanol gives a product of C,C-intermolecular alkylation, which is subsequently converted into 1,1-bis(2,6-dioxy-4,4-dimethylcyclohexyl)-2-propanone.

We noted that this reaction in DMSO in the presence of potash as a result of intramolecular C,O-cycloalkylation gives a bicyclic compound 6.

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