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ALKYLATION OF β-DICARBONYL COMPOUNDS BY 1,2,3-TRIHALOPROPANES AS A METHOD FOR THE PREPARATION OF β-SUBSTITUTED FURANS

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Alkylation of β-dicarbonyl compounds by 1,2,3-trihalides leads to a readily separable mixture of mono- and dialkylation products, and under more rigorous conditions, to 3-substituted 2,4-dimethylfurans. A similar reaction with propargyl bromide leads to furans with a "normal" structure, namely, 2,5-dimethylfurans.

The synthesis of β-substituted furans is of considerable interest, since derivatives of this type are natural compounds [1, 2]. For the synthesis of β-substituted furans, β-dicarbonyl compounds are widely used, the alkylation or condensation of which leads to structural units required for cyclization, such as 1,4-diketones, 1,4-unsaturated ketones, and their derivatives [3, 4]. Hence, a requirement for successful synthesis of β-substituted furans are convenient preparative processes for a synthesis of intermediate compounds. We have already made a detailed study of the synthetic aspects of the alkylation of compounds having an active methylene group (including β-dicarbonyl compounds) by α,ω-dihalides, and found that the use of potassium carbonate in DMSO as a condensing agent ensures high yields of the desired end products, and can be regarded as a convenient preparative method of cycloalkylation [5].

In the present work, we studied the alkylation of certain β-dicarbonyl compounds by 1,2,3-trihalopropanes. It was found that under previously proposed conditions (K_2CO_3 in DMSO) [5, 6], the reaction proceeds, depending on temperature, by two routes, and by selecting the proper conditions, it is possible to ensure a fair selectivity of its occurrence by each of these routes. Thus, alkylation of acetylacetone (I) by 1,2,3-tribromopropane (II) at 25°C gives 2-bromo-4-acetyl-1-hexen-5-one (III) as the main product. According to PMR data (see Experimental), this diketone is in equilibrium with an enol form, with the latter predominating. A small amount of a dialkylation product was obtained as a by-product, to which the structure of 2,6-dibromo-4,4-diacetyl-1,6-heptadiene (IV) can be ascribed. Compounds III and IV are readily separated by distillation. To confirm the structure of III, this compound was prepared by alkylation of acetylacetone by 2,3-dibromo-1-propene under the same conditions. The identity of the alkylation products obtained by different routes was confirmed by complete coincidence of physical constants and PMR spectral data.

In the study of the behavior of 1,2,3-tribromopropane under alkylation conditions, it was found that after 12 h of treatment of tribromopropane of K_2CO_3 in DMSO at 20°C, it converts to the extent of 43% into 2,3-dibromo-1-propene. Thus, the formation of the alkylation product of the β-dicarbonyl compound can occur by two parallel routes, including the alkylation and dehydrobromination stages, proceeding in different sequence.

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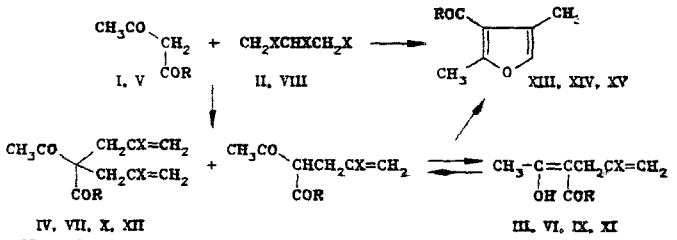
The alkylation of acetoacetic ester V by tribromide II requires somewhat more rigorous conditions, but proceeds fairly smoothly at 70°C, giving the keto ester VI as the main produc and a small amount of diene VII. According to the PMR data, compound VI exists preferentiall in the ketonic form. Alkylation by 1,2,3-trichloropropane (VIII) proceeded in a similar way. The alkylation of both acetylacetone and acetoacetic ester gives a readily separable mixture of mono- and dialkylation products.

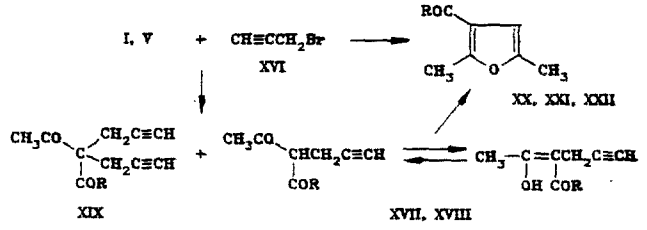
A different result was obtained when alkylation reactions were carried out under more rigorous conditions. The reaction of acetylacetone with tribromide II in DMSO in the presenc of potassium carbonate at 80°C gives 2,4-dimethyl-3-acetylfuran (XIII) as the main product. It can be assumed that the formation of furan XIII is due to the subsequent transformation of diketone III. In fact, treatment of diketone III under these conditions also leads to furan XIII.



I, III, IV, IX, X, XIII R=CH_3; V—VII, XI, XII, XIV R=OC_2H_5; XV R=OH;
II—IV, VI, VII X=Br; VIII—XII X=Cl

Similarly to the alkylation of acetoacetic ester by tribromide II (at 110°C) or trichlo ride VIII (130-140°C), the treatment of compounds VI and XI by potassium carbonate in DMSO at the corresponding temperature leads to the ethyl ester of 2,4-dimethyl-3-furancarboxylic acid (XIV). An alkaline hydrolysis of ester XIV gives acid XV.

This formation of 2,4-dimethyl derivatives of furan is difficult to explain. We therefore carried out a comparison with compounds of the acetylene series. For this purpose, we attempted to alkylate acetylacetone and acetoacetic ester by propargyl bromide (XVI) under conditions we used in our investigations (K_2CO_3, DMSO), and obtained the products of mono- (XVII, XVIII) and dialkylation (XIX) in good yields. More rigorous conditions of alkylation of compounds I and V using propargyl bromide, and also cyclization of compounds XVII and XVIII under these conditions led to the synthesis of β-substituted 2,5-dimethylfuran XX and XXI. Acid XXII was obtained by alkaline hydrolysis of compound XXI.



XVII, XX R=CH_3; XVIII, XIX, XXI R=OC_2H_5; XXII R=OH

The structure of all the β-substituted furans obtained was confirmed by comparison of their physical constants with the literature data, also with the data of the PMR spectrum (see Experimental).

The formation of furan derivatives with a function at the 3-position should include the stage of alkylation of the β-dicarbonyl compound by 1,2,3-trihalopropane with the formation of an alkylation product, intramolecular O-alkylation of the enolate-anion by the halovinyl group, and a prototropic rearrangement. This sequence of reactions should have led to a synthesis of β-derivatives of 2,5-dimethylfuran. In fact, there is no doubt that derivatives of 2,4-dimethylfuran are formed in the alkylation reaction by tribromopropanes. This result is quite unexpected, and in the absence of experimental dat aon the reaction mechanism we can give only a tentative hypothesis for their formation. The synthesis of β-derivatives of 2,4-dimethylfuran can be represented as starting from O-alkylated reaction products. However, we did not establish the existence of the latter, although the possibility of a thermal isomerization of the C-alkylated product into the O-alkylated one, followed by cycli-

zation into the furan derivatives is not excluded. An alternative explanation involves the assumption of formation in the course of the reaction of substituted acetylcyclopropanes, which isomerize at elevated temperatures into furans via the stage of formation of dihydrofurans [5, 7, 8].

However, despite these as yet uncertain aspects of the mechanism, the sequence of reactions including the monoalkylation of the β-dicarbonyl compound by trihalopropane, the intramolecular O-alkylation of the newly generated intermediate enolate anion with a displacement of the double bond, carried out in one preparative stage, can be regarded as a convenient method for the synthesis of furans containing a functional group at the β-position. This method uses available compounds and its preparative conception is simple.

EXPERIMENTAL

The PMR spectra were runon Varian T-60 and XL-100 spectrometers in CCl_4, using TMS as internal standard.

Alkylation of β-Dicarbonyl Compounds. An alkyl halide is added with vigorous stirring and cooling by cold water to a mixture of a β-dicarbonyl compound and calcined potassium carbonate in DMSO. The ratio of anlkyl halide—potassium carbonate—β-dicarbonyl compound is 1:2:4. The reaction mixture is stirred at the corresponding temperature to the completion of the reaction, cooled, diluted with water to dissolution of potassium carbonate, and extracted by ether. The ether extracts are washed with water, and dried over anhydrous magnesium sulfate. After distillation of ether, the residue is distilled in vacuum to yield the required compounds.

Compound III. From 25 g (0.25 mole) of I, 17 g (0.06 mole) of II, 17 g (0.125 mole) of K_2CO_3 in 30 ml of DMSO at 20°C (12 h), yield 10 g (73%), bp 103-104°C (9 mm), n_D^{20} 1.5190. PMR spectrum: 2.17 and 2.26 (6H, s, CH_3), 2.93 (2H, d, J = 7 Hz, CH_2 of the keto form), 3.40 (2H, s, CH_2 of the enol form), 4.10 (2H, t, J = 7 Hz, CH of the keto form), 5.42-5.80 ppm (2H, m, CH_2=). Found, %: C 43.9, H 5.1. $C_8H_{11}BrO_2$. Calculated, %: C 43.8, H 5.1.

Compound IV. Yield 2.8 g (7%), bp 120-140°C (10 mm), mp 63-63.5°C (from aqueous alcohol). PMR spectrum: 2.20 (6H, s, CH_3), 3.30 (4H, s, CH_2), 5.62 ppm (4H, s, CH_2). Found, %: C 39.0, H 4.3. $C_{11}H_{14}Br_2O_2$. Calculated, %: C 39.1, H 4.2.

Compound III. From 35 g (0.35 mole) of I, 17 g (0.085 mole) of 2,3-dibromo-1-propene* and 24 g (0.175 mole) of K_2CO_3 in 35 ml of DMSO at 20°C (12 h), yield 10.7 g (57.5%).

Compound IX. From 50 g (0.5 mole) of I, 25 g (0.17 mole) of VIII, 42 g (0.3 mole) of K_2CO_3 and 50 ml of DMSO at 70°C (12 h), yield 22 g (74%), bp 63-64°C (1 mm), n_D^{20} 1.4954. PMR spectrum: 1.90 and 2.05 (6H, s, CH_3): 2.60 (2H, d, J = 7 Hz, CH_2 of the keto form); 3.03 (2H, s, CH_2 of the enol form); 3.83 (1H, t, J = 7 Hz, CH of the keto form); 4.81-5.10 ppm (2H, m, CH=). Found, %: C 55.2, H 6.6. $C_8H_{11}ClO_2$. Calculated, %: C 55.0, H 6.4.

Compound X. Yield 3.5 g (8%), bp 102-103°C (1 mm), mp 54°C (from hexane). PMR spectrum: 2.00 (6H, s, CH_3), 2.81 (4H, s, CH_2), 4.92 ppm (4H, s, CH_2=). Found, %: C 53.2, H 5.3. $C_{11}H_{14}Cl_2O_2$. Calculated, %: C 53.1, H 5.7.

Compound XVII. From 40 g (0.4 mole) of I, 12 g (0.1 mole) of XVI and 27.5 g (0.2 mole) of K_2CO_3 in 40 ml of DMSO at 80°C (9 h), yield 8.2 g (60%), bp 95-98°C (13 mm), n_D^{20} 1.4730 [according to the data in [10], bp 78-80°C (11 mm), n_D^{20} 1.4734], PMR spectrum: 2.13 (1H, m, CH≡), 2.18 (6H, s, CH_3), 2.70 (2H, d.d, CH_2 of the keto form), 3.12 (2H, d, J = 7 Hz, CH_2 of the enol form), 3.93 ppm (1H, t, J = 7 Hz, CH of the keto form).

Compound VI. From 65 g (0.5 mole) of V, 35 g (0.125 mole) of II, and 34.5 g (0.25 mole of K_2CO_3 in 50 ml of DMSO at 80°C (12 h), yield 16.5 g (54%), bp 134-135°C (16 mm), n_D^{20} 1.4780. PMR spectrum: 1.25 (3H, t, J = 7 Hz, CH_3), 2.27 (3H, s, CH_3), 2.95 (2H, d, J = 7 Hz, CH_2 of the keto form), 3.32 (2H, s, CH_2 of the enol form), 3.90 (1H, t, J = 7 Hz, CH of the keto form), 4.22 (2H, q, J = 7 Hz, OCH_2), 5.46 and 5.70 ppm (2H, s, CH_2=). Found, %: C 43.8, H 5.7. $C_9H_{13}BrO_3$. Calculated, %: C 43.4, H 5.3.

*A mixture of 28 g (0.1 mole) of II and 27.6 g (0.2 mole) of K_2CO_3 in 40 ml of DMSO is stirred at 20°C for 12 g. After the above-described treatment, 8.6 g (43%) of 2,3-dibromo-1-propene, bp 72-74°C (70 mm) [according to the data in [9], bp 75-76°C (75 mm)], n_D^{20} 1.5460 and 15 g (53.5%) of unreacted II are obtained.

Compound VII. Yield 4.5 g (10%), bp 147-148°C (1 mm), n_D^{20} 1.5410. PMR spectrum: 1.30 (3H, t, J = 7 Hz, CH_3), 2.20 (3H, s, CH_3), 3.23 (4H, s, CH_2), 4.21 (2H, q, J = 7 Hz, CH_2), 5.60 ppm (4H, m, CH_2=). Found, %: C 39.2, H 4.4. $C_{12}H_{16}Br_2O_3$. Calculated, %: C 39.2, H 4.4.

Compound XI. From 100 g (0.75 mole) of V and 36.5 g (0.25 mole) of VIII, 69 g (0.5 mole) of K_2CO_3 in 70 ml of DMSO at 110-120°C (6 h), yield 36 g (66%), bp 72-74°C (1 mm), n_D^{20} 1.4594. PMR spectrum: 1.22 (3H, t, J = 7 Hz, CH_3), 2.3 (3H, s, CH_3), 2.92 (2H, d, CH_2 of the keto form), 3.3 (2H, s, CH_2 of the enol form), 3.92 (1H, t, J = 7 Hz, CH of the keto form), 4.22 (2H, q, J = 7 Hz, CH_2O), 5.25 ppm (2H, s, CH_2=). Found, %: C 52.9, H 6.6. $C_9H_{13}ClO_3$. Calculated, %: C 52.8, H 6.4.

Compound XII. Yield 10 g (24.5%), bp 108-109°C (1 mm), n_D^{20} 1.4866. PMR spectrum: 1.25 (3H, t, J = 7 Hz, CH_3), 2.25 (3H, s, CH_3), 3.12 (4H, s, CH_2), 4.21 (2H, q, J = 7 Hz, CH_2O), 5.25 ppm (4H, s, CH_2=). Found, %: C 51.1, H 5.7. $C_{12}H_{16}Cl_2O_3$. Calculated, %: C 51.6, H 5.8.

Compound XVII. From 40 g (0.4 mole) of I, 12 g (0.1 mole) of XVI and 27.5 g (0.2 mole) of K_2CO_3 in 50 ml of DMSO at 80°C (12 h), yield 6.8 g (40.5%), bp 103-104°C (14 mm), n_D^{20} 1.4510 [according to data in [3], bp 115°C (20 mm), n_D^{20} 1.4515]. PMR spectrum: 1.25 (3H, t, J = 7 Hz, CH_3), 2.18 (1H, t, CH≡), 2.25 (3H, s, CH_3), 2.53 (2H, m, CH_2 of the keto form), 2.70 (2H, d, CH_2 of the enol form), 3.70 (1H, t, CH of the keto form), 4.2 ppm (2H, q, J = 7 Hz, CH_2O).

Compound XIX. Yield 1 g (5%), bp 125-130°C (15 mm), n_D^{20} 1.4675 [according to data in [3], bp 102°C (11 mm), n_D^{20} 1.4625]. PMR spectrum: 1.20 (3H, t, J = 7 Hz, CH_3), 2.07 (3H, s, CH_3), 1.9-2.2 (2H, m, CH≡), 2.84 (4H, d, CH_2), 4.18 ppm (2H, q, CH_2).

2,4-Dimethyl-3-acetylfuran (XIII). A. From 25 g (0.25 mole) of I, 17 g (0.06 mole) of II, and 17 g (0.125 mole) of K_2CO_3 in 30 ml of DMSO at 70-80°C (12 h), yield 5.8 g (67%), bp 74-76°C (10 mm), n_D^{20} 1.4965 [according to the data in [11], bp 83°C (11 mm), n_D^{20} 1.4935]. PMR spectrum: 2.10, 2.27, and 2.45 (9H, s, CH_3), 7.23 ppm (1H, s, 5-H).

B. From 10.9 (0.05 mole) of III and 8 g (0.06 mole) of K_2CO_3 in 20 ml of DMSO at 80°C (6 h), yield 4 g (59%), bp 78-79°C (11 mm), n_D^{20} 1.4961.

Ethyl Ester of 2,4-Dimethyl-3-furancarboxylic Acid (XIV). A. From 52 g (0.4 mole) of V, 28 g (0.1 mole) of II, and 27.5 g (0.25 mole) of K_2CO_3 in 50 ml of DMSO at 110-120°C (12 h), yield 8 g (48%), bp 85-86°C (14 mm), n_D^{20} 1.4670 [according to the data in [11], bp 85°C (15 mm), n_D^{16} 1.4704]. PMR spectrum: 1.33 (3H, t, J = 7 Hz, CH_3), 2.10 and 2.47 (6H, s, CH_3), 4.23 (2H, q, J = 7 Hz, CH_2O), 7.03 ppm (1H, s, 5-H).

B. From 8.3 g (0.08 mole) of VI, 5.7 g (0.066 mole) of K_2CO_3 in 30 ml of DMSO at 120°C (6 h), yield 3.8 g (68%), bp 85-86°C (14 mm), n_D^{20} 1.4675.

2,4-Dimethyl-3-furancarboxylic acid (XV) was obtained by alkaline hydrolysis of ester XIV, mp 118-119°C (from aqueous alcohol) (according to the data in [12], mp 117°C). PMR spectrum ($CDCl_3$): 2.17 and 2.57 (6H, s, CH_3), 7.13 (1H, s, 5-H), 12.9 ppm (1H, s, COOH).

2,5-Dimethyl-3-acetylfuran (XX). From 7 g (0.05 mole) of XVII, 14 g (0.1 mole) of K_2CO_3 in 30 ml of DMSO at 160°C (2 h), yield 3.5 g (50%), bp 83-84°C (12 mm), n_D^{20} 1.4862 (according to the data in [13], bp 90°C (19 mm), n_D^{20} 1.4882). PMR spectrum: 2.21, 2.28, and 2.47 (9H, s, CH_3), 6.3 ppm (1H, s, 4-H).

Ethyl Ester of 2,5-Dimethyl-3-furancarboxylic Acid (XXI). From 52 g (0.4 mole) of V, 12 g (0.1 mole) of XVI and 27.5 g (0.25 mole) of K_2CO_3 in 50 ml of DMSO at 115°C (2 h), yield 8 g (47.5%), bp 90-91°C (14 mm), n_D^{20} 1.4681 (according to the data in [3], bp 78°C (5 mm), n_D^{20} 1.4670). PMR spectrum: 1.3 (3H, t, J = 7 Hz, CH_3), 2.20 and 2.47 (6H, s, CH_3), 4.30 (2H, q, J = 7 Hz, CH_2O), 6.27 ppm (1H, s, 4-H).

2,5-Dimethyl-3-furancarboxylic acid (XXII) was obtained by alkaline hydrolysis of ester XXI: mp 137-138°C (from aqueous alcohol). According to the data in [14], mp 138-139°C. PMR spectrum ($CDCl_3$): 2.20 and 2.55 (6H, s, CH_3), 6.20 (1H, s, 4-H), 11.8 ppm (1H, s, COOH).

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PYRYLOCYANINES.

23.* 2-PYRYLOCARBOCYANINES WITH SUBSTITUENTS IN HETERO RESIDUES

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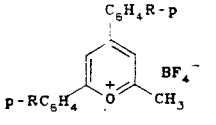
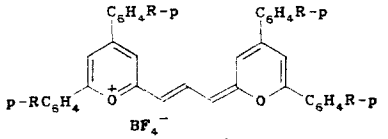
Symmetric 2-pyrylo- and asymmetric (indo)(2-pyrylo)trimethinecyanines with substituents of different electronic nature in the pyran residue were synthesized. The influence of the conjugation effect and inductive effect on the characteristics of absorption bands of the synthesized dyes was analyzed by a quantum chemical calculation according to a common MO Hückel method.

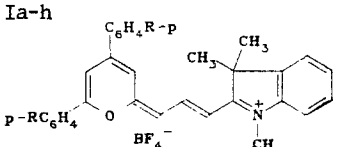
In [2, 3] we studied the influence of an electron-donor methoxy group on the position and form of absorption bands of symmetric and asymmetric 2-pyrylocarbocyanines. However, similar studies for other substituents in this class of dyes are not available. These investigations are required to establish the general relationship between the electronic effect of the substituents and the spectral properties of pyrylocyanines. To solve this problem, we synthesized symmetric (IIa-h) and asymmetric (IIIa-h) α-pyrylocarbocyanines.



Ia-h



IIa-h



IIIa-h

I—III a R=H, b R=OCH_3, c R=OC_2H_5, d R=CH_3, e R=F, f R=Cl, g R=Br, h R=NO_2

*For Communication 22, see [1].

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