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ALKYLATION OF β-DICARBONYL COMPOUNDS AS A METHOD FOR THE PRODUCTION OF FUNCTIONALLY SUBSTITUTED DIHYDROFURANS

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The alkylation of some representatives of β-dicarbonyl compounds by 1,4-dibromo-2-butene and ethyl 2,3-dibromopropionate was investigated.

Keywords: 1,4-dibromo-2-butene, β-dicarbonyl compounds, dihydrofurans, ethyl 2,3-dibromopropionate, isoxazole.

Furans represent one of the important classes of heteroaromatic compounds. Substituted furans are usually synthesized by the regioselective insertion of carbon substituents into furan or its acyclic precursors [1]. Universal and convenient synthons for the "construction" of furans and related heterocycles containing an acyl group at position 3 of the heterocycle are β-dicarbonyl compounds. In recent years [2-4] a series of reviews have been published on numerous methods for the synthesis of furans from 1,3-diketones, which are valuable intermediates in the synthesis of liquid crystals, various heterocycles, and physiologically active substances and particularly pheromones and prostaglandins [5-8].

We investigated the alkylation of some representatives of β-dicarbonyl compounds by various dihalides in order to obtain functionally substituted dihydrofurans.

While continuing study of the reactivity of β-dicarbonyl compounds [9, 10] we realized the reactions of dimedone, allyl acetoacetate, acetylacetone, and acetoacetic ester with ethyl 2,3-dibromopropionate (**1**) and 1,4-dibromo-2-butene (**2**) in the K_2CO_3–DMSO system. It was established that the alkylation of dimedone with compounds **1** (Scheme 1) and **2** (Scheme 2) takes place exclusively in the direction of C,O-cycloalkylation with the formation of 2-ethoxycarbonyl-6,6-dimethyl-2,3,4,5,6,7-hexahydrobenzo[*b*]furan-4-one (**3**) and 6,6-dimethyl-2-vinyl-2,3,4,5,6,7-hexahydrobenzo[*b*]furan-4-one (**9**) respectively.

In the reaction of allyl acetoacetate with the ester **1** we obtained 4-allyloxycarbonyl-2-ethoxycarbonyl-5-methyl-2,3-dihydrofuran (**4**).

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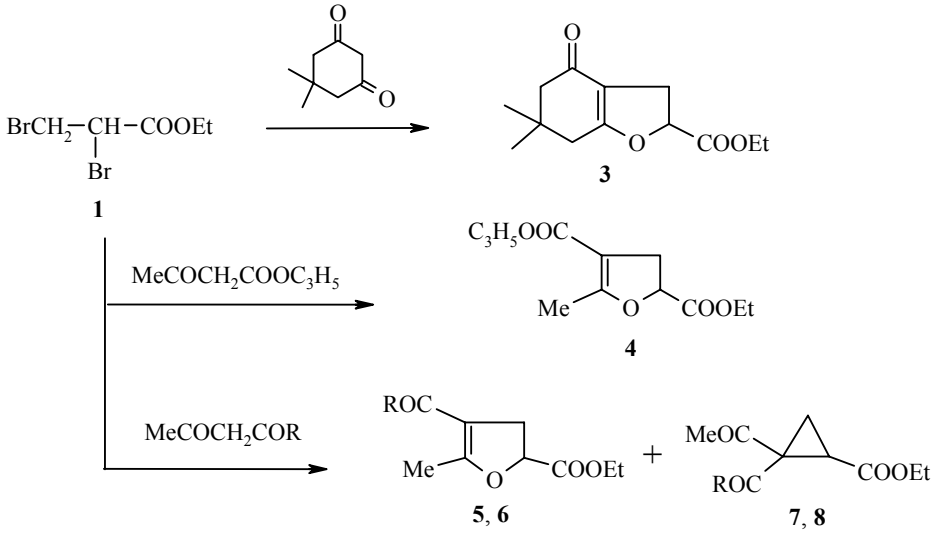
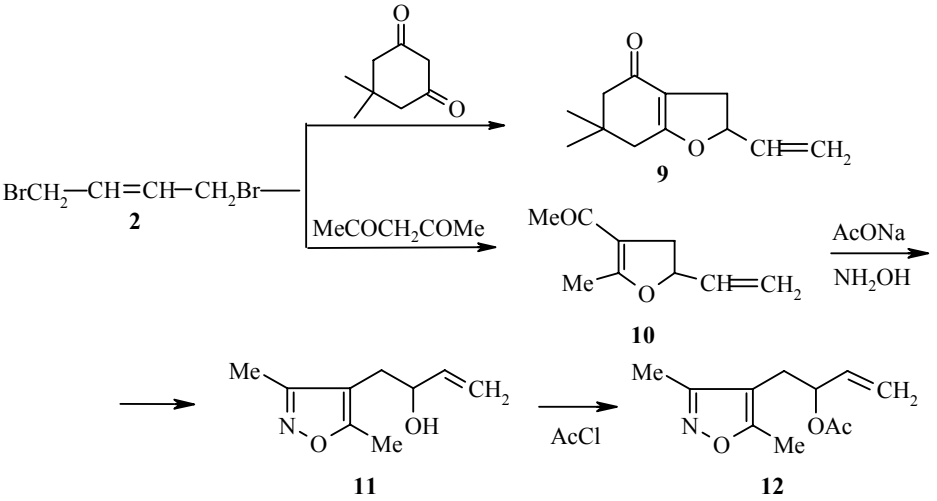
Scheme 1



In the case of acetylacetone and acetoacetic ester the reaction with compound **1** takes place in two directions: C,O- and C,C-cycloalkylation with the formation of 2,4-di(ethoxycarbonyl)-5-methyl-2,3-dihydrofuran (**5**), 4-acetyl-2-ethoxycarbonyl-5-methyl-2,3-dihydrofuran (**6**), 1-acetyl-1,2-di(ethoxycarbonyl)cyclopropane (**7**), and 1,1-diacetyl-2-ethoxycarbonylcyclopropane (**8**). However, only 4-acetyl-5-methyl-2-vinyl-2,3-dihydrofuran (**10**) is formed in the reaction of dimedone with dibromobutene **2**.

Scheme 2



Derivatives of isoxazole are widely used in the synthesis of medicinal products (oxacillin, cloxacillin, cycloserine) [11] and also natural compounds [12, 13].

The reaction of β-dicarbonyl compounds with hydroxylamine hydrochloride is used for the production of isoxazoles. By the condensation of compound **10** with hydroxylamine hydrochloride we obtained 3,5-di-methyl-4-(2-hydroxybut-3-enyl)isoxazole (**11**), further treatment of which with acetyl chloride led to 4-(2-acetoxybut-3-enyl)-3,5-dimethylisoxazole (**12**).

The obtained products are potential biologically active compounds, and investigations in this region will be continued.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300 spectrometer (300 and 75 MHz) in DMSO-d_6 (compounds **3**-**8**) and $CDCl_3$ (compounds **9**-**12**) with TMS as internal standard.

Alkylation of Dicarbonyl Compounds (General Method). A solution of the dicarbonyl compound (0.05 mol) and ester **1** or dibromobutene **2** (0.05 mol) was stirred in the K_2CO_3–DMSO system at 50°C for 20 h. The reaction mass was cooled, water was added to dissolve the potassium carbonate, and product was extracted with ether. The extracts were washed with water and dried over anhydrous $MgSO_4$, the ether was distilled off, and the residue was distilled under vacuum.

2-Ethoxycarbonyl-6,6-dimethyl-2,3,4,5,6,7-hexahydrobenzo[*b*]furan-4-one (3). From a mixture of dimedone (10 g, 0.05 mol), ethyl 2,3-dibromopropionate (13 g, 0.05 mol), and K_2CO_3 (22 g, 0.16 mol) in DMSO (70 ml) we obtained compound **3** (10.8 g), (yield 64.6%); bp 150-151°C (1 mm Hg), n_D^{20} 1.5001. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.38 (1H, dd, ^3J = 7.5, ^3J = 7.5, CHO); 4.17 (2H, q, ^3J = 6.8, CH_2O); 3.08 and 2.75 (each 1H, dd, ^2J = 13.5, ^3J = 7.5, CH_2 in heterocycle); 2.39 and 2.15 (each 2H, s, CH_2 in dimedone fragment); 1.22 (3H, t, ^3J = 6.8, CH_3); 1.05 (6H, s, $2CH_3$). ^{13}C NMR spectrum, δ, ppm: 194.6; 176.3; 170.1; 101.8; 80.1; 62.5; 41.3; 37.7; 34.8; 30.8; 27.2; 27.1; 14.9. Found, %: C 65.73; H 7.42. $C_{13}H_{18}O_4$. Calculated, %: C 65.53; H 7.61.

4-Allyloxycarbonyl-2-ethoxycarbonyl-5-methyl-2,3-dihydrofuran (4). From a mixture of allyl acetoacetate (7.1 g, 0.05 mol), ethyl 2,3-dibromopropionate (13 g, 0.05 mol), and of K_2CO_3 (22 g, 0.16 mol) in DMSO (25 ml) we obtained 9.5 g (75%) of compound **4**; bp 116-116.5°C (1 mm Hg), n_D^{20} 1.4768. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.92 (1H, m, CH=); 5.25 (2H, dd, $^3J_{cis}$ = 9.4, $^3J_{trans}$ = 17.4, CH_2=); 4.62 (1H, m, CHO); 4.6 (2H, d, ^3J = 7.9, CH_2O); 4.18 (2H, q, ^3J = 6.9, CH_2O); 3.2 and 2.9 (each 1H, dd, ^2J = 13.5, ^3J = 7.5, CH_2 in heterocycle); 2.2 (3H, s, CH_3); 1.2 (3H, t, ^3J = 6.9, CH_3). ^{13}C NMR spectrum, δ, ppm: 170.9; 168.3; 164.9; 114.3; 117.9; 102.7; 78.8; 62.2; 63.9; 24.3; 14.6; 14.4. Found, %: C 59.74; H 6.82. $C_{12}H_{16}O_5$. Calculated, %: C 59.99; H 6.71.

2,4-Di(ethoxycarbonyl)-5-methyl-2,3-dihydrofuran (5). From a mixture of allyl acetoacetate (6.5 g, 0.05 mol), ethyl 2,3-dibromopropionate (13 g. 0.05 mol), and K_2CO_3 (22 g, 0.16 mol) in DMSO (25 ml) we obtained 7.2 g (63%) of compound **5**; bp 114-115°C (1 mm Hg), n_D^{20} 1.4770. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.15 (1H, dd, ^3J = 7.5, ^3J = 7.5, CHO); 4.15 (2H, q, ^3J = 7.1, CH_2O); 4.05 (2H, q, ^3J = 6.81, CH_2O); 3.15 and 2.85 (each 1H, dd, ^2J = 13.5, ^3J = 7.5, CH_2 in heterocycle); 2.15 (3H, s, CH_3); 1.21 (3H, t, ^3J = 7.1, CH_3); 1.19 (3H, t, ^3J = 6.8, CH_3). ^{13}C NMR spectrum, δ, ppm: 171.2; 167.3; 164.8; 102.9; 78.7; 62.8; 59.9; 23.4; 14.2; 14.0; 13.8. Found, %: C 58.14; H 6.65. $C_{11}H_{16}O_5$. Calculated, %: C 57.89; H 7.07.

4-Acetyl-2-ethoxycarbonyl-5-methyl-2,3-dihydrofuran (6). From a mixture of acetylacetone (5 g, 0.05 mol), ethyl 2,3-dibromopropionate (13 g. 0.05 mol), and K_2CO_3 (22 g, 0.16 mol) in DMSO (25 ml) we obtained 7 g (70.7%) of compound **6**; bp 112-113.5°C (1 mm Hg), n_D^{20} 1.4655. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.17 (1H, dd, ^3J = 7.5, ^3J = 7.5, CHO); 4.15 (2H, q, ^3J = 6.9, CH_2O); 3.25 and 2.95 (each 1H, dd, ^2J = 13.5, ^3J = 7.5, CH_2 in heterocycle); 2.15 (3H, s, CH_3); 2.1 (3H, s, CH_3); 1.17 (3H, t, ^3J = 6.87, CH_3). ^{13}C NMR spectrum, δ, ppm: 194.8; 169.2; 167.3; 102.3; 78.6; 61.9; 34.9; 30.1; 27.3; 14.8. Found, %: C 60.90; H 6.64. $C_{10}H_{14}O_4$. Calculated, %: C 60.59; H 7.2.

1-Acetyl-1,2-di(ethoxycarbonyl)cyclopropane (7). From a mixture of acetoacetic ester (6.5 g, 0.05 mol), ethyl 2,3-dibromopropionate (13 g, 0.05 mol), and K_2CO_3 (22 g, 0.16 mol) in DMSO (25 ml) we obtained 6 g (52.6%) of compound **7**; bp 122-122.5°C (1 mm Hg), n_D^{20} 1.4600. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.16 (2H, q, ^3J = 6.8, CH_2O); 4.1 (2H, q, ^3J = 6.8, CH_2O); 2.57 (1H, dd, ^3J = 7.4, ^3J = 7.4, CH); 2.21 (3H,

s, CH_3); 1.78 and 1.65 (each 1H, m, CH_2 in ring); 1.22 (3H, t, ^3J = 6.8, CH_3); 1.18 (3H, t, ^3J = 6.8, CH_3). ^{13}C NMR spectrum, δ, ppm: 201.3; 168.1; 165.2; 62.4; 59.8; 42.7 (quaternary carbon); 28.3; 20.1; 18.7; 14.1; 13.9. Found, %: C 57.65; H 7.36. $C_{11}H_{16}O_5$. Calculated, %: C 57.89; H 7.07.

1,1-Diacetyl-2-ethoxycarbonylcyclopropane (8). This compound was obtained from a mixture of acetylacetone (5 g, 0.05 mol), ethyl 2,3-dibromopropionate (13 g, 0.05 mol), and K_2CO_3 (22 g, 0.16 mol) with a yield of 4.5 g (45.5%); bp 120-121°C (1 mm Hg), n_D^{20} 1.4635. ^1H NMR spectrum, δ, ppm (*J*, Hz): 4.05 (2H, q, ^3J = 6.8, CH_2O); 2.61 (1H, m, CH); 2.17 (3H, s, CH_3); 2.15 (3H, s, CH_3); 1.82 and 1.73 (each 1H, m, CH_2 in ring); 1.2 (3H, t, ^3J = 6.8, CH_3). ^{13}C NMR spectrum, δ, ppm: 203.5; 203.4; 170.1; 61.8; 49.9; 30.2; 30.1; 27.8; 19.2; 14.9. Found, %: C 60.27; H 7.33. $C_{10}H_{14}O_4$. Calculated, %: C 60.59; H 7.2.

6,6-Dimethyl-2-vinyl-2,3,4,5,6,7-hexahydrobenzo[*b*]furan-4-one (9). From a mixture of dimedone (14 g, 0.1 mol), 1,4-dibromo-2-butene (21.3 g, 0.1 mol), and K_2CO_3 (27.6 g, 0.2 mol) in DMSO (150 ml) we obtained 10 g (52%) of compound **9**; bp 115-115.5°C (1 mm Hg), n_D^{20} 1.5000. ^1H NMR spectrum, δ, ppm (*J*, Hz): 5.85 (1H, m, CH=); 5.26 and 5.15 (each 2H, d, $^3J_{cis}$ = 10.1, $^3J_{trans}$ = 16.9, CH_2=); 5.21 (1H, m, CHO); 2.93 and 2.50 (each 1H, dd, ^2J = 14.7, ^3J = 9.5, CH_2 in ring); 2.22 and 2.13 (each 2H, s, CH_2 in dimedone ring); 1.13 (6H, s, $2CH_3$). ^{13}C NMR spectrum, δ, ppm: 194.9; 177.1; 137.6; 117.8; 106.3; 86.3; 52.1; 43.3; 38.2; 32.7; 27.4. Found, %: C 74.73; H 8.39. $C_{12}H_{16}O_2$. Calculated, %: C 74.97; H 8.39.

4-Acetyl-5-methyl-2-vinyl-2,3-dihydrofuran (10). From a mixture of acetylacetone (10 g, 0.1 mol), 1,4-dibromo-2-butene (21.3 g, 0.1 mol), and K_2CO_3 (42 g, 0.3 mol) in DMSO (70 ml) we obtained 12 g (79%) of compound **10**; bp 80-80.5°C (1 mm Hg), n_D^{20} 1.4970. ^1H NMR spectrum, δ, ppm (*J*, Hz): 6.0 (1H, m, CH=); 5.39 and 5.29 (each 2H, d, $^3J_{cis}$ = 10.36, $^3J_{trans}$ = 16.82, CH_2=); 5.1 (1H, m, OCH); 3.20 and 2.79 (each 1H, dd, ^2J = 16.6, ^3J = 8.9, CH_2 in ring); 2.30 and 2.19 (each 3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 192.8; 166.8; 137.9; 117.5; 111.2; 83.1; 36.9; 28.4; 14.99. Found, %: C 70.83; H 8.16. $C_9H_{12}O_2$. Calculated, %: C 71.03; H 7.95.

4-(2-Hydroxybut-3-enyl)-3,5-dimethylisoxazole (11). To 40 ml of a 10% solution of sodium acetate we added of compound **10** (1.56 g, 0.010 mol) and hydroxylamine hydrochloride (0.69 g, 0.010 mol). The mixture was stirred at 50°C for 5 h, cooled, and extracted with ether. The extracts were washed with water and dried with anhydrous $MgSO_4$. The residue after distillation of the ether was distilled under vacuum. We obtained 0.86 g (52%) of compound **11**; bp 132-134°C (0.1 mm Hg), n_D^{20} 1.4940. ^1H NMR spectrum, δ, ppm (*J*, Hz): 5.82 (1H, m, CH=); 5.20 and 5.08 (2H, dd, $^3J_{cis}$ = 10.2, $^3J_{trans}$ = 16.9; CH_2=); 4.30 (1H, s, OH); 4.14 (1H, q, ^3J = 7.8, OCH); 2.48 (2H, d, ^3J = 9.5, CH_2); 2.33 and 2.15 (each 3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 166.3; 159.6; 140.7; 114.8; 110.1; 73.4; 31.4; 12.3; 11.2. Found, %: C 64.87; H 7.62; N 87.56. $C_9H_{13}NO_2$. Calculated, %: C 64.65; H 7.84; N 8.38.

4-(2-Acetoxybut-3-enyl)-3,5-dimethylisoxazole (12). To a solution of compound **11** (2 g, 0.012 mol) in CCl_4 (10 ml) we added acetyl chloride (1 g, 0.0127 mol). The mixture was shaken carefully on a water bath (80°C) and left until the morning. The residue after distillation of the CCl_4 was distilled under vacuum. We obtained 1.8 g (71.4%) of compound **12**; bp 165-166.5°C (1 mm Hg), n_D^{20} 1.4791. ^1H NMR spectrum, δ, ppm (*J*, Hz): 5.85 (1H, m, CH=); 5.2 (2H, dd, $^3J_{cis}$ = 10.3, $^3J_{trans}$ = 16.7, CH_2=); 5.13 (1H, m, CHO); 2.63 (2H, d, ^3J = 9.2, CH_2); 2.29 and 2.15 (each 3H, s, CH_3); 2.00 (3H, s, CH_3C=O). ^{13}C NMR spectrum, δ, ppm: 169.8; 167.6; 159.8; 138.4; 117.7; 109.8; 74.3; 26.9; 21.4; 10.2; 10.1. Found, %: C 63.48; H 7.04; N 6.46. $C_{11}H_{15}NO_3$. Calculated, %: C 60.3; H 6.84; N 6.39.

REFERENCES

1. V. Nair, J. Mathew, and J. Prabhakaran, *Chem. Soc. Rev.*, **26**, 127 (1997).
2. X. L. Hou, H. Y. Cheung Hon, T. Y. Kwan, T. H. Lo, S. Y. Tong, and H. N. Wong, *Tetrahedron*, **54**, 1955 (1998).
3. T. L. Gilchrist, *J. Chem. Soc.*, *Perkin Trans. 1*, 2849 (1999).

4. A. V. Kelin and M. Andrew, *Curr. Org. Chem*., **7**, 1855 (2003).
5. C. Cativiela, J. L. Serrano, and M. M. Zurlano, *J. Org. Chem*., **60**, 3074 (1995).
6. J. A. Giller, N. Martin, M. Quinteiro, C. Seoane, and J. Soto, *Org. Prep. Proc. Int.*, **18**, 227 (1986).
7. A. L. Baumstark, M. Dotrong, and P. C. Vasquez, *Tetrahedron Lett*., **28**, 1963 (1987).
8. T. Shono, S. Kashimura, M. Savamura, and T. Socjima, *J. Org. Chem*., **53**, 907 (1988).
9. N. D. Sadykhova, N. S. Sadykhov, and R. A. Gasymov, *Izv. Vuzov. Khimiya i Khim. Tekhnologiya*, **49**, 80 (2006).
10. A. M. Maharramov, N. D. Sadikhova, I. G. Mammadov, and M. A. Allahverdiyev, *Processy Neftekhim. Neftepererabotki*, **28**, 26 (2007).
11. V. L. Gein, N. V. Nosova, K. D. Potemkin, Z. G. Aliev, and A. P. Kriven'ko, *Zh. Org. Khim.*, **41**, 1039 (2005).
12. A. T. Soldatenkov, N. M. Kolyadina, and I. V. Shendrik, *Principles of Organic Chemistry of Pharmaceutical Substances* [in Russian], Mir, Moscow (2003).
13. V. V. Lipson, S. M. Desenko, S. V. Shishkina, M. G. Shirobokova, O. V. Shishkin, and V. D. Orlov, *Khim. Geterotsikl. Soedin.,* 1194 (2003). [*Chem. Heterocycl. Comp*., **39**, 1041 (2003)].