Synthesis of functionalized heterocycles by alkylation of β-dicarbonyl compounds with 2,3-dibromopropan-1-ol

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Alkylation of β-dicarbonyl compounds with 2,3-dibromopropan-1-ol in the K_2CO_3—dibenzo-18-crown-6 system in toluene leads to products of C,O- or C,C-cycloalkylation.

Key words: β-dicarbonyl compounds, alkylation with 2,3-dibromopropan-1-ol; 3-acyl-5-hydroxymethyl-2-methyl-4,5-dihydrofurans; diethyl 2-hydroxymethylcyclopropane-1,1-dicarboxylate; derivatives of spirocyclopropane-5-barbituric and -thiobarbituric acids.

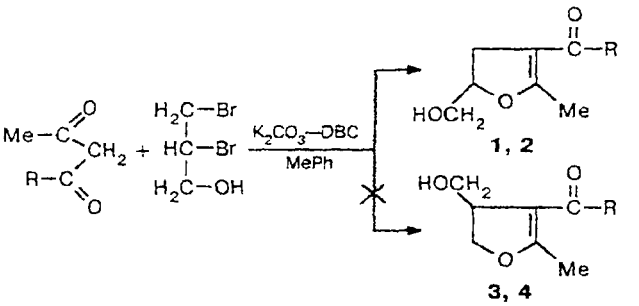
Previously, we obtained acyclic products of C-mono- and C,C-dialkylation or the furan derivatives resulting from intramolecular C,O-alkylation, depending on reaction conditions, by alkylating β-dicarbonyl compounds with 1,2,3-tribromopropane in the K_2CO_3—DMSO system.[1] The products of C-monoalkylation were used in the synthesis of 1,2-azoles[2,3] and barbituric acids.[4,5]

In the present work, the alkylation of β-dicarbonyl compounds was performed with 2,3-dibromopropan-1-ol in the K_2CO_3—dibenzo-18-crown-6 (DBC) system in toluene. The replacement of the K_2CO_3—DMSO system used earlier by the K_2CO_3—DBC system in toluene was due to the fact that 2,3-dibromopropan-1-ol loses a hydrogen bromide molecule under the reaction conditions in the former system to give 2-bromoprop-2-en-1-ol, in which the bromine atom is located at the double bond and is therefore unable to participate in alkylation.

The alkylation of acetylacetone and ethyl acetoacetate with 2,3-dibromopropan-1-ol in the K_2CO_3—DBC system in toluene was carried out at 90—100 °C (alkylation does not proceed in the temperature range of 20—70 °C) for 20 h. These reactions led to the products of C,O-cycloalkylation, 3-acetyl-5-hydroxymethyl-2-methyl-4,5-dihydrofuran (**1**) and ethyl 5-hydroxymethyl-2-methyl-4,5-dihydrofuran-3-carboxylate (**2**) in 54.6 and 52.1% yields, respectively (Scheme 1), although one would also expect 3-acetyl-4-hydroxymethyl-2-methyl-4,5-dihydrofuran (**3**) and ethyl 4-hydroxymethyl-2-methyl-4,5-dihydrofuran-3-carboxylate (**4**) to be reaction products.

The exclusive formation of dihydrofurans **1** and **2** can be explained by the fact that the carbanion generated from a carbonyl compound attacks the primary C atom of 2,3-dibromopropan-1-ol because of steric hindrances caused by the CH_2Br and CH_2OH groups of the latter and the substituents of the carbonyl reagent. As a result, intermediate linear products of C-alkylation are

Scheme 1

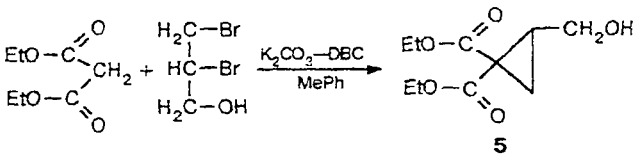


R = Me (**1**, **3**), OEt (**2**, **4**)

formed, which undergo further intramolecular C,O-alkylation owing to the hydrogen atom of the hydroxyl group and the bromine atom at the secondary C atom.

Unlike acetylacetone and ethyl acetoacetate, diethyl malonate reacts with 2,3-dibromopropan-1-ol according to the classic scheme of Perkin's reaction (C,C-cycloalkylation) to give diethyl 2-hydroxymethylcyclopropane-1,1-dicarboxylate (**5**) in a 56.5% yield (Scheme 2).

Scheme 2



Hence, the direction of the alkylation of β-dicarbonyl compounds with 2,3-dibromopropan-1-ol in the K_2CO_3—DBC system in toluene depends on the nature of the starting β-dicarbonyl derivative.

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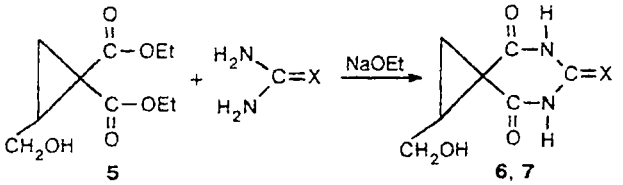
The interaction of diethyl malonate with urea and thiourea is a classic method for the synthesis of barbituric and thiobarbituric acids.[6] With the goal of obtaining new spiroderivatives of barbituric (**6**) and thiobarbituric (**7**) acids, we carried out the condensation of diethyl dicarboxylate **5** with urea and thiourea in the presence of NaOEt in anhydrous EtOH (Scheme 3).

Scheme 3



X = O (**6**), S (**7**)

Thus, the reaction described is a simple and convenient method for the laboratory synthesis of spiroderivatives of barbituric and thiobarbituric acids.

Experimental

The ^{1}H NMR spectra were recorded on a C-60HL spectrometer (60 MHz) with HMDS as the internal standard. The IR spectra were recorded on a UR-20 instrument in the 3600—400 cm^{-1} range.

All reagents, except 2,3-dibromopropan-1-ol, were used as received. 2,3-Dibromopropan-1-ol was obtained by brominating allyl alcohol according to the known procedure.[7] Before use, potassium carbonate was calcined for 1 h.

3-Acetyl-5-hydroxymethyl-2-methyl-4,5-dihydrofuran (1). A mixture of acetylacetone (20 g, 0.2 mol), 2,3-dibromopropan-1-ol (43 g, 0.2 mol), K_2CO_3 (70 g, 0.5 mol), and DBC (1.5 g, 4%, if converted to the alkyl halide involved) was stirred in 200 mL of anhydrous toluene at 90—100 °C for 20 h. Then, the reaction mixture was cooled, washed with water until the potassium carbonate dissolved, and extracted with toluene. The toluene extracts were washed with water and dried with anhydrous Na_2SO_4. After the toluene was removed, the residue was distilled *in vacuo*. Product **1** (16.8 g, 54.6%) was obtained, m.p. 117—119 °C (5 Torr), n_D^{20} 1.4882, d_4^{20} 1.2189. Found (%): C, 61.60; H, 7.59. $C_8H_{12}O_3$. Calculated (%): C, 61.54; H, 7.67. ^{1}H NMR (CCl_4), δ: 2.06 (s, 3 H, Me); 2.10 (s, 3 H, MeC=O); 2.70 (d, 2 H, CH_2); 3.42 (s, 1 H, OH); 3.50 (d, 2 H, CH_2O); 4.54 (m, 1 H, CH). IR, ν/cm^{-1}: 1620 (C=C); 1700 (C=O).

Ethyl 5-hydroxymethyl-2-methyl-4,5-dihydrofuran-3-carboxylate (2). Compound **2** (19.1 g, 52.1%) was obtained analogously from a mixture of ethyl acetoacetate (26 g, 0.2 mol), 2,3-dibromopropan-1-ol (43 g, 0.2 mol), K_2CO_3 (70 g, 0.5 mol), and DBC (1.5 g), m.p. 109 °C (1 Torr), n_D^{20} 1.4910, d_4^{20} 1.1515. Found (%): C, 57.97; H, 7.45. $C_9H_{14}O_4$. Calculated (%): C, 58.06; H, 7.53. ^{1}H NMR (CCl_4), δ: 1.16 (t, 3 H, Me); 2.05 (s, 3 H, MeC=); 2.68 (d, 2 H, CH_2); 3.44 (s, 1 H, OH); 3.50 (d, 2 H, $C\underline{H}_2OH$); 4.03 (q, 2 H, CH_2O); 4.56 (m, 1 H, CH). IR, ν/cm^{-1}: 1625 (C=C); 1710 (C=O).

Diethyl 2-hydroxymethylcyclopropane-1,1-dicarboxylate (5). Compound **5** was obtained from diethyl malonate (32 g, 0.2 mol), 2,3-dibromopropan-1-ol (43 g, 0.2 mol), K_2CO_3 (70 g, 0.5 mol), and DBC (1.5 g) similarly to the synthesis of compound **1**. Yield 24.0 g (56.5%), m.p. 86—87 °C (2 Torr), n_D^{20} 1.4414, d_4^{20} 1.1303. Found (%): C, 55.48; H, 7.35. $C_{10}H_{16}O_5$. Calculated (%): C, 55.56; H, 7.41. ^{1}H NMR (CCl_4), δ: 1.14 (t, 6 H, 2 Me); 1.24 (d, 2 H, CH_2); 1.50 (t, 1 H, CH); 3.42 (s, 1 H, OH); 3.56 (d, 2 H, $C\underline{H}_2OH$); 4.04 (q, 4 H, 2 $C\underline{H}_2Me$).

2-Hydroxymethylspiro(cyclopropane-1,5′-barbituric acid) (6). A mixture of diethyl dicarboxylate **5** (10 g, 0.05 mol), finely cut sodium metal (1.15 g, 0.05 g-at.), and urea (3.6 g, 0.06 mol) in 50 mL of anhydrous EtOH was refluxed at 110 °C for 7 h. The sodium salt that formed was filtered off and washed with anhydrous EtOH, and then dissolved in water and acidified with HCl until a weakly acidic pH value. The precipitate that formed was isolated by filtration and recrystallized from water. Acid **6** was obtained (8.1 g, 93.1%), m.p. 166—167 °C (from H_2O). Found (%): C, 44.59; H, 6.30; N, 14.81. $C_7H_{12}O_4N_2$. Calculated (%): C, 45.65; H, 6.38; N, 14.89. ^{1}H NMR (DMSO-d_6), δ: 1.22 (d, 2 H, CH_2); 1.54 (m, 1 H, CH); 3.40 (br.s, 1 H, OH); 3.64 (d, 2 H, $C\underline{H}_2OH$); 12.95 (br.s, 2 H, 2 NH).

2-Hydroxymethylspiro(cyclopropane-1,5′-thiobarbituric acid) (7). Analogously, acid **7** was isolated from a mixture of diethyl dicarboxylate **5** (10 g), sodium metal (1.15 g), and thiourea (4.5 g) in 50 mL of anhydrous EtOH. Yield 8.4 g (89.4%), m.p. 191—193 °C (from H_2O). Found (%): C, 41.31; H, 5.80; N, 14.68; S, 16.58. $C_7H_{12}O_3N_2S$. Calculated (%): C, 41.18; H, 5.88; N, 14.73; S, 15.69. ^{1}H NMR (DMSO-d_6), δ: 1.24 (d, 2 H, CH_2); 1.52 (m, 1 H, CH); 3.52 (br.s, 1 H, OH); 3.71 (d, 2 H, $C\underline{H}_2OH$); 10.34 (br.s, 2 H, 2 NH).

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