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Mendeleev Commun., 2013, **23**, 292–293
Mendeleev Communications

A straightforward synthesis of 2(3),6,6-trimethyl-6,7-dihydrobenzofuran-4(5*H*)-ones

Niftali N. Yusifov,[a] Valeh M. Ismayilov,[a] Nurlana D. Sadigova,[a] Maximilian N. Kopylovich*[b] and Kamran T. Mahmudov[a,b]

[a] *Department of Chemistry, Baku State University, Az 1148 Baku, Azerbaijan*
[b] *Centro de Química Estrutural, Complexo I, Instituto Superior Técnico, Technical University of Lisbon, 1049–001 Lisbon, Portugal. Fax: +1 21 846 4455; e-mail: kopylovich@yahoo.com*

DOI: 10.1016/j.mencom.2013.09.019

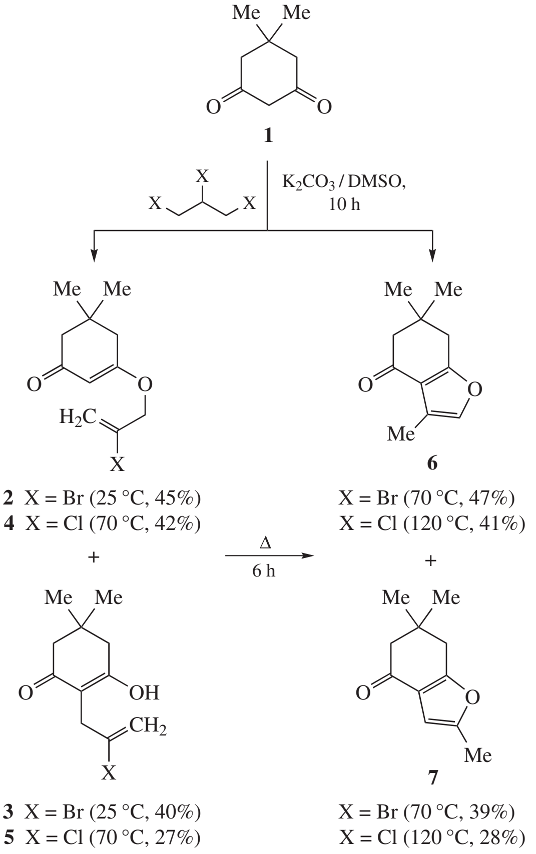
Alkylation of dimedone with 1,2,3-trichloro- or 1,2,3-tribromopropanes in the presence of K_2CO_3 in DMSO follows both O- and C-alkylation pathways giving 3-(2-haloprop-2-enyloxy)-5,5-dimethylcyclohex-2-enone and 2-(2-haloprop-2-enyl)-3-hydroxy-5,5-dimethylcyclohex-2-enone. These compounds on heating afford 3,6,6-trimethyl- and 2,6,6-trimethyl-6,7-dihydrobenzofuran-4(5*H*)-ones, respectively.

1,3-Dicarbonyl compounds, including dimedone, are known to yield both C- and O-alkylation products in reactions with electrophilic reagents.[1,2] For example, the alkylation of 1,3-dicarbonyl compounds can be an efficient method for C–C bond formation.[3–6] Alkylation of cyclohexane-1,3-diones with 2,3-dibromopropene is also reported.[7–9] The C-alkylated 1,3-diketones are valuable intermediates in the synthesis of liquid crystals[10] or heterocyclic compounds such as furan, pyrazole, *etc*.[2,11,12]

From another perspective, much of the recent activity in organic synthesis has been focused on the development of regiospecific reactions. In spite of great success in development of many regioselective reactions, the methods for selective C-alkylation of 1,3-diketones are quite scarce, and, as a rule, involve only their simplest representatives.[13] Alkylations of 1,3-dicarbonyl compounds with α,ω-dibromoalkanes, 1,2,3-trihalopropane and 1,2-dibromocyclohexane[14–18] in the K_2CO_3/DMSO system has been studied fairly comprehensively, however, the alkylation of dimedone with 1,2,3-trihalopropanes has not yet been reported. Hence, the development of such functionalization would be of interest.

First, we studied the reaction of dimedone **1** with 1,2,3-trihalopropanes in the presence of anhydrous K_2CO_3 in DMSO for 10 h. The alkylation of **1** with 1,2,3-tribromopropane at room temperature yields O- and C-substitution products **2** and **3** (Scheme 1) in 45 and 40% yields, respectively, which can be easily separated by distillation. The ^{1}H NMR spectrum of **3** in $CDCl_3$ shows a signal at δ 13.10 ppm which can be assigned to the OH group of the enol form.[19–21] In the case of **2**, the olefin proton is observed at δ 5.18 ppm, the signal of enol proton is absent. To confirm the structures of compounds **2** and **3**, they were prepared independently. Indeed, the alkylation of **1** with 2,3-dibromoprop-1-ene (see Online Supplementary Materials) afforded the same compounds **2** and **3**.

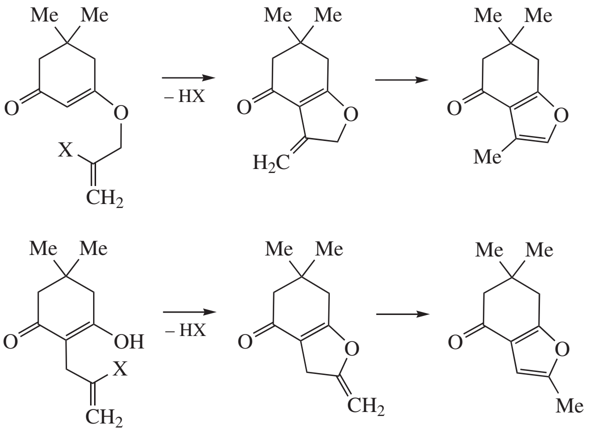
The reaction of **1** with 1,2,3-trichloropropane proceeds at higher temperature (70 °C) giving compounds **4** and **5** (see Scheme 1), however, with lower yields (42 and 27%, respectively). In the ^{1}H NMR spectra of **4** and **5** the olefin and enol protons were observed at δ 5.02 and 13.00 ppm, respectively. Other analytical data also confirm the structures of compounds **4** and **5**.



Scheme 1

Upon alkylation of **1**, further increase in temperature to 70 °C (if 1,2,3-tribromopropane is used as an alkylating agent), or to 120 °C (in the case of 1,2,3-trichloropropane) affords known[22–24] 3,6,6-trimethyl-6,7-dihydrobenzofuran-4(5*H*)-one **6** and 2,6,6-trimethyl-6,7-dihydrobenzofuran-4(5*H*)-one **7** (Scheme 1). The ^{1}H NMR spectra of products **6** and **7** contain signals at 7.06 and 6.63 ppm, characteristic of the α- and β-protons of the furan ring.[22–25] Note that furan **6** was previously obtained by oxidation of 3,6,6-trimethyl-2-(phenylthio)-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one with $NaIO_4$.[22] The described synthesis of furan derivatives is of particular significance due to its relative simplicity, availability of the starting materials and possible applications of the products, *e.g*., in medicinal chemistry.[26–35]

As known, vicinal dihaloalkanes easily loose hydrogen halide to give haloalkenes. Apparently, 1,2,3-trihalopropanes similarly



Scheme 2

transform to 2,3-dihalopropenes which are the true alkylating agents.[7–9] We can postulate the transformations shown in Scheme 2 taking into consideration that treatment of the mixture of **2** + **3** or **4** + **5** for 6 h at 70 or 120 °C, respectively, leads to the β- or α-substituted furans (Scheme 1).

In summary, alkylation of dimedone with 1,2,3-trihalopropanes gives mixtures of O- and C-alkylation products, whose heating leads to 3,6,6-trimethyl- and 2,6,6-trimethyl-6,7-dihydrobenzofuran-4(5*H*)-ones.

This work was partially supported by the Baku State University, Azerbaijan.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2013.09.019.

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Received: 24th April 2013; Com. 13/4112