Alkylation of sterically hindered 1,3-diketones under phase-transfer conditions

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Sterically hindered 1,3-diketones react selectively with propargyl and allyl bromides under conditions of phase transfer catalysis to give *C*-alkylated products, whereas reactions with butyl and benzyl chlorides yield mixtures of *C*- and *O*-isomers. An increase in the size of the substituents present in the initial 1,3-diketone hampers introduction of the second propargyl group. The propargyl-substituted 1,3-diketones undergo cyclization under the alkylation conditions to give substituted furans.

Key words: 1,3-diketones; steric hindrance, alkylation; phase transfer catalysis.

Alkylation of 1,3-dicarbonyl compounds is of interest as an efficient method for formation of a C—C bond. 1,3-Diketones are known to yield both *C*- and *O*-substitution products in reactions with electrophilic reagents.[1,2]

C-Alkylated 1,3-diketones are valuable intermediates in the synthesis of liquid crystals[3] and various heterocyclic compounds.[4,5] However, methods for selective *C*-alkylation of 1,3-diketones are quite scarce, and, as a rule, they have been tested only for the simplest compounds of this class.[6—8] In the present work, we studied alkylation of sterically hindered 1,3-diketones as a method for introducing unsaturated hydrocarbon substituents into the methylene group. To introduce propargyl and allyl groups into 1,3-diketones, we used the method for selective *C*-alkylation of acetylacetone.[8]

A series of 1,3-diketones (**1**) incorporating identical substituents at one of the carbonyl groups and substituents with continuously increasing sizes at the other carbonyl group were used as the starting substrates (Scheme 1).

Scheme 1

$$\underset{\mathbf{1a{-}c}}{\mathrm{RCOCH_2COCMe_2OMe}} \xrightarrow[\mathrm{K_2CO_3,\ Bu^n_4NBr}]{\mathrm{R'X\ (2)}} \underset{\mathbf{3a{-}f}}{\mathrm{RCOCHR'COCMe_2OMe}} \xrightarrow[\mathrm{K_2CO_3,\ Bu^n_4NBr}]{\mathrm{R'X}} \underset{\mathbf{4a,b}}{\mathrm{RCOCR'_2COCMe_2OMe}}$$

1: R = Ph (**a**), $\mathrm{Pr^i}$ (**b**), $\mathrm{Bu^t}$ (**c**)
2: R′ = $\mathrm{CH_2C{\equiv}CH}$, X = Br (**a**);
R′ = $\mathrm{CH_2CH{=}CH_2}$, X = Br (**b**);
R′ = $\mathrm{Bu^n}$, X = Cl (**c**);
R′ = $\mathrm{PhCH_2}$, X = Cl (**d**)
3: R′ = $\mathrm{CH_2C{\equiv}CH}$, R = Ph (**a**); $\mathrm{Pr^i}$ (**b**); $\mathrm{Bu^t}$ (**c**);
R′ = $\mathrm{CH_2CH{=}CH_2}$, R = Ph (**d**); $\mathrm{Pr^i}$ (**e**); $\mathrm{Bu^t}$ (**f**)
4: R′ = $\mathrm{CH_2C{\equiv}CH}$, R = Ph (**a**); $\mathrm{Pr^i}$ (**b**)

The reaction was carried out in the presence of anhydrous K_2CO_3 and $\mathrm{Bu^n_4NBr}$ in toluene or benzene in an atmosphere of N_2. It was found that allylation of diketones **1a—c** yields only *C*-substitution products **3d—f**. Diketones **1b,c** react readily and selectively with propargyl bromide **2a** under the same conditions. The reactions are completed over a period of 2—3 h at 70—100 °C, and products **3b,c** are formed in 70—85% yields.

Phenyl-substituted diketone **1a** reacts with bromide **2a** much more slowly (7 h); the process is accompanied by formation of by-products, and the yield of compound **3a** does not exceed 46%. When a twofold excess of bromide **2a** is used, the reaction duration is shortened to 2 h and the yield of compound **3a** increases to 69%.

It was shown that cyclic isomer **5a** of monopropargylated diketone **3a** is formed as one of the by-products (Scheme 2). Compounds **3a** and **5a** have identical elemental compositions but differ in their chemical properties.

The structure of isomer **5a** as a substituted furan was confirmed by ^{1}H NMR and IR spectroscopy using the known data[9] for related compounds.

It can be assumed that in alkaline medium, the propargyl group is rearranged to an allenyl group; subsequent cyclization gives the furan derivative. This is probably facilitated by the tendency of diketone **3a** to enolize. The data on the structure of **5a** are insufficient

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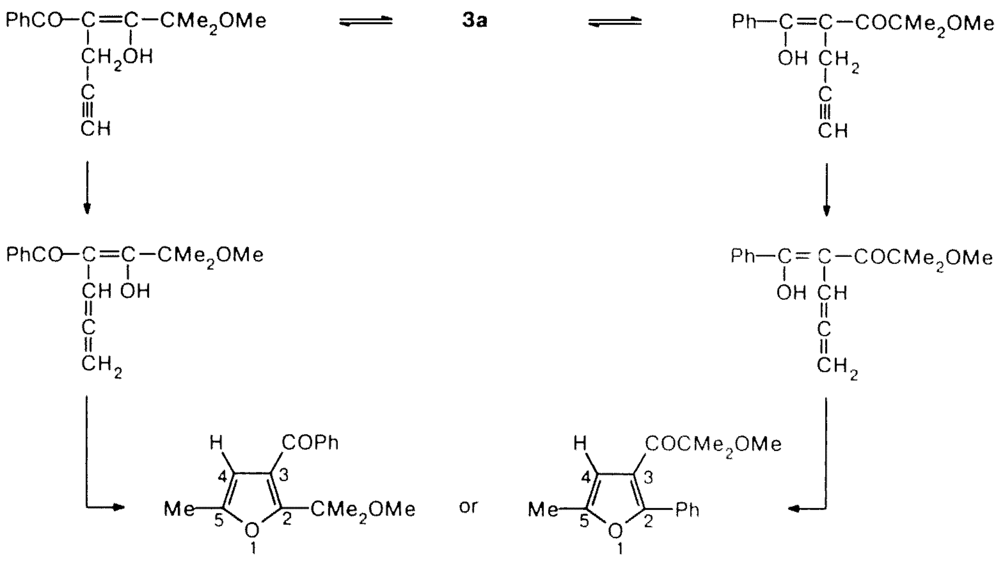
Scheme 2



5a

to choose between the two possible routes of cyclization to furan.

Dipropargylation of diketone **1a** under known conditions[8] occurs over a period of 8 h and is accompanied by substantial resinification, so the yield of compound **4a** is relatively low. The use of a fourfold excess of alkylating reagent **2a** makes it possible to obtain **4a** in a preparative yield (58%) and to shorten the reaction duration to 1 h.

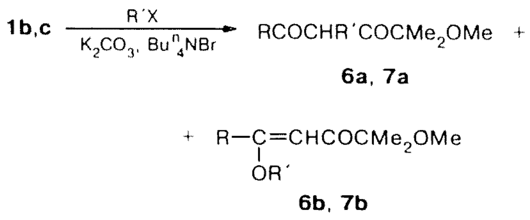
Introduction of the second propargyl group into monosubstituted diketone **3b** is even more difficult to accomplish. Although a substantial excess of bromide **2a** is taken, the reaction is completed only after 40 h at 100 °C, and the yield of compound **4b** is 71%. In this case, a considerable amount of a by-product (according to GLC) is also formed. It was shown in special experiments that monopropargyl diketone **3b** is converted into this by-product after prolonged heating with K_2CO_3 and $Bu^n{}_4NBr$ in the absence of bromide **2a**. According to the ^1H NMR spectrum, this product is apparently a mixture of isomers of a substituted furan similar to **5a**. The most sterically hindered monopropargyl diketone **3c** (R = Bu^t) does not react with bromide **2a**.

The steric factors also had an effect on the route of the reaction of compound **1b** with butyl chloride **2c**. Unlike acetylacetone,[8] diketone **1b** reacts with chloride **2c** to give a mixture of products (GLC analysis), from which two main individual compounds, namely, the *C*- and *O*-isomers were isolated in yields of 51 % and 36 %, respectively (Scheme 3). The purity and structure of isomers **6a,b** were confirmed by the data from GLC and elemental analysis as well as by IR and ^1H NMR spectroscopy.

It was assumed that the most sterically hindered diketone **1c** would be alkylated more selectively with an active electrophilic reagent such as benzyl chloride **2d**. However, in this case, too, the reaction gave a mixture of products, which corresponded in its elemental composition to monobenzyl diketone **7**, and, according to GLC analysis and ^1H NMR spectrum, it contained *C*-alkylated (**7a**) and *O*-alkylated (**7b**) isomers in a ratio of 1 : 1.

The ^1H NMR spectrum of the mixture of isomers **7a,b** exhibits signals corresponding either to two products of *O*-alkylation at different oxygen atoms or to two geometric isomers with respect to the C=C bond, present in a ratio of 1.5 : 1 (singlets at 6.22 and 6.28 ppm for HC= and singlets at 5.12 and 5.18 ppm for the OCH_2 group, as well as broadened signals at 7.30 and 7.44 ppm due to Ph groups). It should be noted that attempts to introduce two benzyl groups into diketone **1c** also were unsuccessful.

Scheme 3



$$\mathbf{1b,c} \xrightarrow[K_2CO_3,\ Bu^n{}_4NBr]{R'X} RCOCHR'COCMe_2OMe + R-\underset{OR'}{C}=CHCOCMe_2OMe$$

6a,b: R = Pr^i, R′ = Bu^n
7a,b: R = Bu^t, R′ = $PhCH_2$

Experimental

The IR spectra were recorded on a UR-20 spectrophotometer in $CHCl_3$. The ^{1}H NMR spectra were recorded on a JEOL FX 90 instrument (90 MHz) in $CDCl_3$. The course of the reactions was monitored and the purity of the products was checked by GLC using a Chrom-5 instrument (flame ionization detector), a 3.6×0.003 m glass column with 5% SE-30 on Inerton N-AW-DMCS (0.2—0.3 mm), and nitrogen as the carrier gas.

The initial 1,3-diketones **1a—c** were prepared by a known procedure.[10] The alkylating reagents **2a—d** were dried with K_2CO_3 and distilled prior to use. K_2CO_3 was dried *in vacuo* for 12 h at 150 °C. Bu^n_4NBr was stored in a desiccator over P_2O_5.

2-Methoxy-2,6-dimethyl-4-propargylheptane-3,5-dione (3b). A solution of diketone **1b** (9.3 g, 0.05 mol), anhydrous K_2CO_3 (28.5 g, 0.2 mol), and Bu^n_4NBr (0.8 g, 0.0025 mol) in 100 mL of toluene was stirred for 2 h at 100 °C in an atmosphere of N_2. Then the mixture was cooled to 40 °C, and compound **2a** (4.1 g, 0.034 mol) was added over a period of 30 min. The mixture was stirred for 2.5 h at 65 °C (GLC monitoring) and cooled, and potassium carbonate was filtered off and washed with toluene. The toluene solution was washed with water and dried with $MgSO_4$. Distillation gave 8.8 g (78%) of compound **3b**, b.p. 107 °C (1 Torr), n_D^{23} 1.4570. Found (%): C, 69.56; H, 8.92. $C_{13}H_{20}O_3$. Calculated (%): C, 69.61; H, 8.99. ^{1}H NMR, δ: 1.04 (d, 6 H, $\underline{Me}_2$CH, J = 7.1 Hz); 1.12 (s, 6 H, 2 Me); 1.87 (t, 1 H, HC≡, J = 2.7 Hz); 2.35 (m, 1 H, C$\underline{H}$Me$_2$, J = 7.1 Hz); 2.42 and 2.48 (both td, 2 H, CH$_2$C≡, J = 7.5 Hz, 7.5 Hz, and 2.7 Hz); 3.12 (s, 3 H, MeO); 4.48 (t, 1 H, HC, J = 7.5 Hz).

4-Methoxy-4-methyl-1-phenyl-2-propargylpentane-1,3-dione (3a) was prepared similarly to **3b** from diketone **1a** and a twofold excess of bromide **2a** (1 h, 80 °C), yield 69%, m.p. 45—46 °C (petroleum ether). Found (%): C, 74.51; H, 6.97. $C_{16}H_{18}O_3$. Calculated (%): C, 74.39; H, 7.02. ^{1}H NMR, δ: 1.20 (s, 6 H, 2 Me); 1.81 (t, 1 H, HC≡, J = 2.7 Hz); 2.62 and 2.70 (both td, 2 H, CH$_2$C≡, J = 7.1 Hz, 7.1 Hz, and 2.7 Hz); 2.85 (s, 3 H, MeO); 5.13 (t, 1 H, HC, J = 7.1 Hz); 7.35—7.60 (m, 3 H, Ph); 7.85—8.05 (m, 2 H, Ph).

Substituted furan (5a) was isolated as a by-product, m.p. 53—54 °C (ethanol). Found (%): C, 74.00; H, 6.80. $C_{16}H_{18}O_3$. Calculated (%): C, 74.39; H, 7.02. ^{1}H NMR, δ: 1.42 (s, 6 H, 2 Me); 2.35 (d, 3 H, Me); 3.22 (s, 3 H, MeO); 6.83 (d, 1 H, HC= in the ring); 7.21—7.48 (m, 3 H, Ph); 7.70—7.90 (m, 2 H, Ph). IR, ν/cm^{-1}: 1680, 1610, 1550.

2-Methoxy-2,6,6-trimethyl-4-propargylheptane-3,5-dione (3c) was prepared similarly to **3a** from compounds **1c** and **2a** (3 h, 95—100 °C), yield 82%, b.p. 112—113 °C (1 Torr), n_D^{21} 1.4590. Found (%): C, 70.55; H, 9.31. $C_{14}H_{22}O_3$. Calculated (%): C, 70.54; H, 9.35. ^{1}H NMR, δ: 1.15 (s, 9 H, 3 Me); 1.16 and 1.17 (both s, 6 H, 2 Me); 1.89 (t, 1 H, HC≡, J = 2.7 Hz); 2.35 and 2.68 (d, dd, 2 H, CH$_2$C≡, J = 1.16, 6 Hz, and 2.7 Hz and ddd, J = 1.6, 7.2, and 2.7 Hz); 3.17 (s, 3 H, MeO); 4.73 (dd, 1 H, HC, J = 7 and 2.6 Hz).

2-Allyl-4-methoxy-4-methyl-1-phenylpentane-1,3-dione (3d) was prepared from compounds **1a** and **2b** (1 h, 80 °C), yield 75%, m.p. 57—58 °C (ethanol). Found (%): C, 73.82; H, 7.74. $C_{16}H_{20}O_3$. Calculated (%): C, 73.72; H, 7.72. ^{1}H NMR, δ: 1.23 (s, 6 H, 2 Me); 2.20—2.85 (m, 2 H, C$\underline{H}_2$CH=); 2.95 (s, 3 H, MeO); 4.85—5.15 (m, 3 H, CH$_2$=, CH); 5.45—5.85 (m, 1 H, CH=); 7.40—7.60 (m, 3 H, Ph); 7.85—8.03 (m, 2 H, Ph).

4-Allyl-2-methoxy-2,6-dimethylheptane-3,5-dione (3e) was obtained from **1b** and **2b** (2.5 h, 70 °C), yield 85%, b.p. 98 °C (1 Torr), n_D^{23} 1.4505. Found (%): C, 69.00; H, 9.86. $C_{13}H_{22}O_3$. Calculated (%): C, 68.99; H, 9.80. ^{1}H NMR, δ: 1.11 and 1.13 (both d, 6 H, Me$_2$CH, J = 7 Hz); 1.20 (d, 6 H, 2 Me); 2.10—2.65 (m, 1 H, C$\underline{H}$Me$_3$, J = 7 Hz); 3.12 (s, 3 H, MeO); 4.40 (dd, 1 H, HC, J = 7.52 and 8.2 Hz); 4.85—5.15 (m, 2 H, CH$_2$=); 5.45—5.95 (m, 1 H, CH=).

4-Allyl-2-methoxy-2,6,6-trimethylheptane-3,5-dione (3f) was obtained from **1c** and **2b**, yield 85%, b.p. 106 °C (2 Torr), n_D^{20} 1.4540. Found (%): C, 70.10; H, 10.10. $C_{14}H_{24}O_3$. Calculated (%): C, 69.99; H, 10.07. ^{1}H NMR, δ: 1.09 (s, 9 H, 3 Me); 1.10 and 1.12 (both s, 6 H, 2 Me); 2.05—2.30 (m, 1 H, HC$\underline{H}$—CH=); 2.45—2.65 (m, 1 H, $\underline{H}$CH—CH=); 3.14 (s, 3 H, MeO); 4.57 (dd, 1 H, HC—CH$_2$, J = 4.6 and 8.2 Hz); 4.80—5.0 (m, 2 H, CH$_2$=); 5.45—5.70 (m, 1 H, CH=).

4-Butyl-2-methoxy-2,6-dimethylheptane-3,5-dione (6a) and 5-butoxy-2-methoxy-2,6-dimethylhept-4-en-3-one (6b) (a mixture of *C*- and *O*-isomers) were obtained from compounds **1b** and **2c** by the procedure described for the preparation of **3b** (3.5 h, 75 °C). Vacuum distillation gave compound **6a**, yield 51%, b.p. 93—94 °C (5 Torr). n_D^{18} 1.4450. Found (%): C, 69.34; H, 10.73. $C_{14}H_{26}O_3$. Calculated (%): C, 69.38; H, 10.81. ^{1}H NMR, δ: 0.85 (t, 3 H, Me in the chain); 1.0—1.3 (m, 12 H, 2 Me + 3 CH$_2$); 2.75 (m, 1 H, C$\underline{H}$Me$_2$); 3.18 (s, 3 H, MeO); 4.9 (dd, 1 H, C*$\underline{H}$—CH$_2$), IR, ν/cm^{-1}: 1740, 1710 (CO); and compound **6b**, yield 36%, b.p. 84—85 °C (5 Torr). n_D^{18} 1.4575. Found (%): C, 69.65; H, 10.67. $C_{14}H_{26}O_3$. Calculated (%): C, 69.38; H, 10.81. ^{1}H NMR, δ: 0.8—1.35 (m, 15 H, 5 Me, 4 H, 2 CH$_2$); 3.15 (s, 3 H, MeO); 3.75 (t, 2 H, OCH$_2$); 4.0 (t, 1 H, C$\underline{H}$Me$_2$); 5.81 (s, 1 H, CH=). IR, ν/cm^{-1}: 1680 (CO).

A mixture of products of alkylation of diketone **1c** with benzyl chloride **2d** [**4-benzyl-2,6,6-trimethyl-2-methoxyheptane-3,5-dione (7a) and 3(5)-benzyloxy-2,6,6-trimethyl-2-methoxyhept-3(4)-ene-5(3)-one (7b)**] was obtained by the procedure described for the preparation of **3b** (5 h, 85—90 °C), yield 90%, b.p. 148—149 °C (3 Torr), n_D^{21} 1.4992. Found (%): C, 74.46; H, 9.10. $C_{18}H_{26}O_3$. Calculated (%): C, 74.44; H, 9.03. ^{1}H NMR, δ: 1.12—1.48 (m, 15 H, 5 Me); 3.0 and 3.38 (dd, 2 H, C$\underline{H}_2$CH); 3.3 (s, 3 H, MeO); 5.02 (t, 1 H, C$\underline{H}$—CH$_2$); 5.12 and 5.18 (both s, 4 H, 2 OCH$_2$), 6.22 and 6.28 (both s, 2 H, 2 HC=); 7.3 and 7.44 (both s, 10 H, 2 Ph).

4-Methoxy-4-methyl-1-phenyl-2,2-dipropargylpentane-1,3-dione (4a). A mixture of diketone **1a** (2.2 g, 0.01 mol), K_2CO_3 (13.8 g, 0.1 mol), and Bu^n_4NBr (0.8 g, 0.0025 mol) in 50 mL of toluene was stirred for 2 h at 80 °C in an atmosphere of N_2 and cooled to 40 °C. Compound **2a** (4.76 g, 0.04 mol) was added dropwise. The mixture was stirred for 1 h at 80 °C and worked up as described above for **3b** to give 1.8 g of compound **4a**, yield 58%, m.p. 144 °C (petroleum ether). Found (%): C, 77.00; H, 6.80. $C_{19}H_{20}O_3$. Calculated (%): C, 76.70; H, 6.79. ^{1}H NMR, δ: 1.0 (s, 6 H, 2 Me); 1.83 (t, 2 H, 2 HC=, J = 2.7 Hz); 2.71 (s, 3 H, MeO); 3.03 (d, 4 H, 2 CH$_2$C≡, J = 2.4 Hz); 7.15—7.35 (m, 3 H, Ph); 7.45—7.60 (m, 2 H, Ph).

2-Methoxy-2,6-dimethyl-4,4-dipropargylheptane-3,5-dione (4b). A mixture of K_2CO_3 (13.8 g, 0.1 mol), Bu^n_4NBr (0.8 g, 0.0025 mol), and diketone **3b** (11.2 g, 0.05 mol) in 100 mL of toluene was stirred for 2 h at 100 °C in an atmosphere of N_2 and cooled to 40 °C. Compound **2c** (7.65 g, 0.064 mol) was added, and the mixture was stirred for 40 h at 100 °C, and a 30 % excess of **2a** was constantly maintained. When the reaction was completed (GLC monitoring), the reaction mixture was worked up as described for **3b**. Distillation gave 9.3 g of diketone **4b**, yield 70%, m.p. 55 °C (pentane). Found (%): C, 73.17; H, 8.46. $C_{16}H_{22}O_3$. Calculated (%): C, 73.25; H, 8.45. ^{1}H NMR, δ: 1.09 (d, 6 H, 2 $\underline{Me}$CH, J = 6.8 Hz); 1.30 (s, 6 H, 2 MeC); 2.0 (t, 2 H, 2 HC=); 2.55 (m, 1 H, C$\underline{H}$Me, J = 6.8 Hz); 2.95 and 3.05 (both d, 4 H, 2 CH$_2$C≡, J = 2.5 Hz); 3.20 (s, 3 H, MeO).

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