Selective Acylations of Anions of 3-Isobutoxy-2-cycloalken-1-ones

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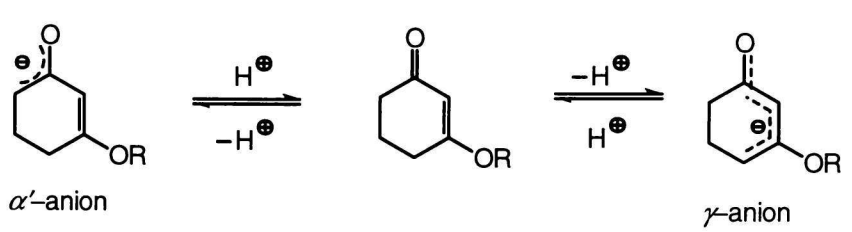
Dedicated to Professor RNDr. Š. Toma, DrSc., in honour of his 60th birthday

A new method for synthesis of 5-acyl-3-isobutoxy-2-cyclopenten-1-ones and 6-acyl-3-isobutoxy-2-cyclohexen-1-ones from corresponding 3-isobutoxy-2-cyclopenten-1-one and 3-isobutoxy-2-cyclohexen-1-one was developed. The key step involved a selective deprotonation at the α'-position of the starting 3-alkoxy enones accomplished by two equivalents of lithium diisopropylamide at low temperature. Acylation of the obtained enolates with ethyl chloroformate, 5-ethoxycarbonylpentanoyl chloride, and benzoyl chloride led to the desired products in high yields and selectivity.

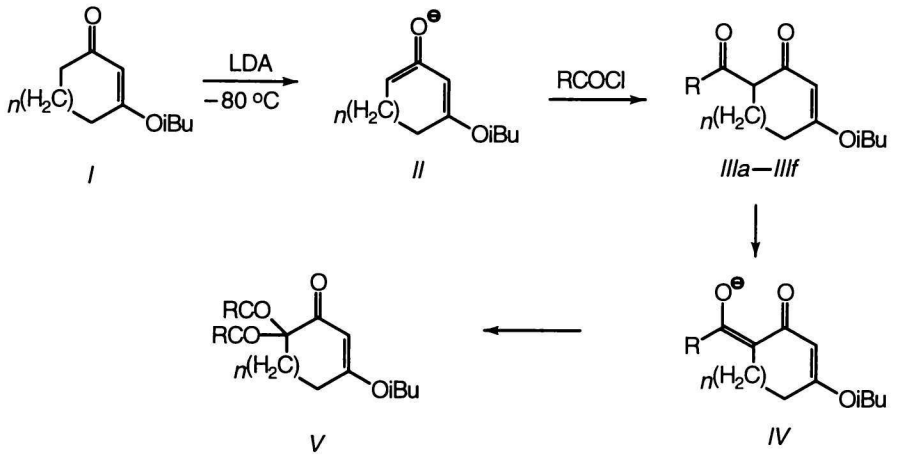
Alkylation and acylation of cyclopentane- and cyclohexane-1,3-dione and their derivatives have drawn considerable attention [1—8]. The key step in these transformations is enolate formation, which governs regioselectivity of the reactions. Enolization under kinetic conditions, accomplished by excess of lithium diisopropylamide (LDA) at low temperature, directs substitution at the α-carbon. Under conditions that permit equilibration of the α'-enolate through proton exchange a thermodynamic γ-anion is formed (Scheme 1). Selective alkylations of the γ-enolates are rather complicated and only a few methodologies were designed for this purpose. For example, β-enamino ketones have been found to be suitable substrates for the selective γ-substitution when weaker bases are used for their deprotonation [8].

Although alkylations of 1,3-diketones are known, acylations of enolates derived from 3-alkoxy-2-cycloalken-1-ones have not been previously described. In this context, we were interested to introduce an acyl substituent selectively to the α'-position of enolates derived from 3-alkoxy-2-cycloalken-1-ones (*I*). In contrast to the analogous alkylation, the acylation of these compounds at the α'-carbon results in a new β-dicarbonyl structure with strongly activated hydrogen available for proton exchange. This promotes equilibration of the α'-enolate either to the starting compound or to its thermodynamically more stable γ-isomer. Moreover, the newly formed anion *IV* (Scheme 2) can undergo further acylation.

The primary purpose of this work was to develop optimal conditions for syntheses of 5-acyl-3-isobutoxy-2-cyclopenten-1-ones and 6-acyl-3-isobutoxy-2-cyclohexen-1-ones (*IIIa—IIIf*) by selective acylations of 3-alkoxy-2-cycloalken-1-one (*I*). First attempts to carry out the acylations, when the enolates were generated with only a slight excess of LDA (1.1 equivalent) at −78 °C, resulted in a mixture of the starting compound and products *IIIa—IIIf* and *V* (Scheme 2). These results supported our expectation that proton exchange between the monoacylated product *IIIa—IIIf* and the enolate *II* takes place giving rise to anion *IV* and the



Scheme 1



	R	n
a	EtO	1
b	EtO	0
c	Ph	1
d	Ph	0
e	$EtOCO(CH_2)_4$	1
f	$EtOCO(CH_2)_4$	0

Scheme 2

starting compound *I*. Consequently, only a very low yield of the desired α'-monoacylated product was isolated under these conditions. However, the use of 2 equivalents of LDA entirely prevented formation of the product *Va* [9] and resulted in a very selective monoacylation at the α'-carbon affording high yields of products *IIIa—IIIf*. These results indicate that in the case of the competing reaction of the acyl chlorides with anions *II* and *IV* higher nucleophilicity of the anion *II* is the determining factor. Interestingly, neither change in temperature nor modifications of the amount of LDA used have resulted in isolation of the γ-acylated products.

EXPERIMENTAL

The starting isobutyl ethers (*I*) were prepared from the corresponding cycloalkane-1,3-diones and isobutyl alcohol according to a literature procedure [10]. The solvents used were dried and purified by standard procedures. The butyllithium was purchased from Fluka and its exact concentration was determined by titration of the solution of diphenylacetic acid. The ^{1}H NMR spectra were taken with Tesla BS 487 (80 MHz) instrument with tetramethylsilane as an internal standard. The IR spectra were recorded on the Perkin—Elmer 567 spectrophotometer. Melting points were obtained by Kofler hot-plate apparatus. All reactions were carried out under nitrogen atmosphere.

Acylation of 3-Isobutoxy-2-cycloalken-1-ones

To a solution of butyllithium (27.5 mmol) in hexane (17.2 cm^3) at −30 °C solution of diisopropylamine (2.79 g; 27.5 mmol) in THF (5 cm^3) was added over a period of 15 min and the mixture was stirred at the same temperature for 4 h. The resulting solution was then cooled down to −78 °C and 3-isobutoxy-2-cycloalken-1-one (12.5 mmol) was added as a THF solution (15 cm^3) over a period of 45 min. This was followed by the addition of acyl chloride (15 mmol) dissolved in 5 cm^3 of THF. The resulting mixture was allowed to warm up to 10 °C, then it was mixed with diluted HCl (3 cm^3 of concentrated HCl in 100 cm^3 of H_2O) and extracted with diethyl ether (6 × 100 cm^3). The combined ethereal solutions were washed with saturated NaCl solution (3 × 15 cm^3), dried ($MgSO_4$), and concentrated *in vacuo* to afford a crude product which was recrystallized from petroleum ether (b.p. = 30—50 °C).

6-Ethoxycarbonyl-3-isobutoxy-2-cyclohexen-1-one (*IIIa*)

Yield 91 %, m.p. = 48—49 °C. For $C_{13}H_{20}O_4$ (M_r = 240.29) w_i(calc.): 64.98 % C, 8.39 % H; w_i(found): 65.14 % C, 8.43 % H. IR spectrum (CCl_4), $\tilde{\nu}$/cm^{-1}: 1135, 1158, 1640, 1730, 2950. ^{1}H NMR spectrum ($CDCl_3$), δ: 0.96 (d, J = 7 Hz, 6H), 1.28 (t, J = 7 Hz, 3H), 1.75—2.65 (m, 5H), 3.30 (m, 1H), 3.60 (d, J

= 7 Hz, 2H), 4.21 (q, J = 7 Hz, 2H), 5.38 (s, 1H).

5-Ethoxycarbonyl-3-isobutoxy-2-cyclopenten-1-one (*IIIb*)

Yield 80 %, m.p. = 36—38 °C. For $C_{12}H_{18}O_4$ (M_r = 226.21) w_i(calc.): 63.70 % C, 8.15 % H; w_i(found): 63.82 % C, 8.17 % H. IR spectrum (CCl_4), $\tilde{\nu}$/cm^{-1}: 1135, 1598, 1640, 1730, 2950. ^{1}H NMR spectrum ($CDCl_3$), δ: 1.00 (d, J = 7 Hz, 6H), 1.28 (t, J = 7 Hz, 3H), 1.83—2.25 (m, 1H), 2.73—3.09 (m, 2H), 3.34—3.59 (m, 1H), 3.78 (d, 2H), 4.21 (q, J = 7 Hz, 2H), 5.23 (s, 1H).

6-Benzoyl-3-isobutoxy-2-cyclohexen-1-one (*IIIc*)

Yield 75 %, m.p. = 71—73 °C. For $C_{17}H_{20}O_3$ (M_r = 272.33) w_i(calc.): 74.97 % C, 7.35 % H; w_i(found): 75.04 % C, 7.18 % H. ^{1}H NMR spectrum ($CDCl_3$), δ: 0.96 (d, J = 7 Hz, 6H), 1.70—2.90 (m, 5H), 3.63 (d, 2H), 4.22—4.48 (m, 1H), 5.41 (s, 1H), 7.20—8.18 (m, 5H).

5-Benzoyl-3-isobutoxy-2-cyclopenten-1-one (*IIId*)

Yield 68 %, m.p. = 58—60 °C. For $C_{16}H_{18}O_3$ (M_r = 258.31) w_i(calc.): 74.42 % C, 6.98 % H; w_i(found): 74.58 % C, 6.73 % H. ^{1}H NMR spectrum ($CDCl_3$), δ: 1.00 (d, J = 7 Hz, 6H), 1.85—2.25 (m, 1H), 2.73—3.00 (m, 2H), 3.25—3.42 (m, 1H), 3.79 (d, J = 7 Hz, 2H), 5.17 (s, 1H), 7.10—8.25 (m, 5H).

6-(5-Ethoxycarbonylpentanoyl)-3-isobutoxy-2-cyclohexen-1-one (*IIIe*)

Yield 78 %, m.p. = 53—55 °C. For $C_{18}H_{28}O_5$ (M_r = 324.36) w_i(calc.): 66.64 % C, 8.70 % H; w_i(found): 66.90 % C, 8.91 % H. ^{1}H NMR spectrum ($CDCl_3$), δ: 0.98 (d, J = 7 Hz, 6H), 1.24 (t, J = 7 Hz, 3H), 1.45—2.80 (m, 13H), 3.25—3.42 (m, 1H), 3.60 (d, J = 7 Hz, 2H), 4.10 (q, J = 7 Hz, 2H), 5.24 (s, 1H).

5-(5-Ethoxycarbonylpentanoyl)-3-isobutoxy-2-cyclopenten-1-one (*IIIf*)

Yield 70 %, m.p. = 49—51 °C. For $C_{17}H_{26}O_5$ (M_r = 310.21) w_i(calc.): 65.78 % C, 8.71 % H; w_i(found): 65.93 % C, 8.49 % H. ^{1}H NMR spectrum ($CDCl_3$), δ: 0.99 (d, J = 7 Hz, 6H), 1.26 (t, J = 7 Hz, 3H), 1.45—2.98 (m, 11H), 3.20—3.36 (m, 1H), 3.70 (d, J = 7 Hz, 2H), 4.18 (q, J = 7 Hz, 2H), 5.24 (s, 1H).

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