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DIRECT CARBON ALKYLATION OF CYCLIC α-DIKETONES

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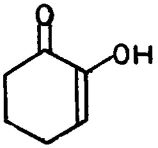
In connection with an alkaloid synthesis we required a method for C-alkylation of a cyclic α-diketone which would leave the dicarbonyl system intact (1 → 2). Under normal conditions however the direct alkylation of 1,2-cycloalkanediones, known to exist predominantly in the enol forms (1, 3),[1] leads in the presence of base only to O-alkylated products.[2,3] Carbon alkylation involving Grignard addition to a monoketal[4] or enamine[5] of a cyclic α-diketone has been achieved, but these routes destroy the original dicarbonyl function.[6]



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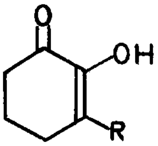

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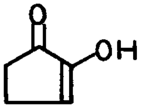

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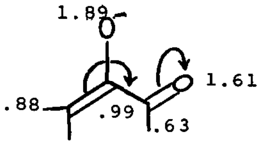
Failure to achieve C-alkylation with simple enolates derived from 1 or 3 is consistent with Hückel molecular orbital calculations for such mesomeric anions.[7] These reveal a partial positive charge on the carbon required to act as nucleophile in the alkylation step. Such an electron deficiency develops because normal enone resonance (4, arrows) overcomes electron release from enolate oxygen (cf. 5). Further calculations reveal that such an effect is totally absent for the corresponding dianions (6) in which an essentially typical enolate structure is maintained. These calculations suggest the likelihood that the dianions of 1 and 3 might undergo C-alkylation in the fashion of simple ketone monoenolates. This expectation has now been confirmed by experiment.



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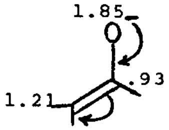

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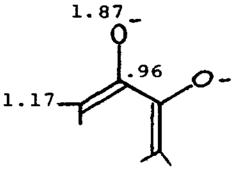

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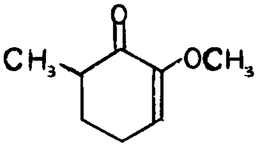
When 1 is treated with two equivalents of lithium diisopropylamide in tetrahydrofuran at -78°, followed by addition of excess methyl iodide and warming to room temperature overnight, three new compounds are formed in the ratio of ca 6:3:1. The major product was characterized as 3-methyl-2-hydroxy-2-cyclohexenone (2,R=CH_3), mp 59.5-61° (lit mp 60°),[3] ir 2.97, 5.98, 6.11μ, nmr δ5.95 (1H,S), 2.3-2.6 (6H,m), 1.86 (3H,s). The second product was 2-methoxy-6-methyl-2-cyclohexenone (7), ir 5.95μ, 6.11μ nmr δ5.65 (1H,t), 3.48 (3H,s), 2.2 (4H,m), 1.87 (1H,m), 1.15 (3H,d), whereas the minor component was identified as the isomeric 2-methoxy-3-methyl-2-cyclohexenone (8),[8] ir 5.95,6.08μ, nmr δ3.50 (1H,s), 2.2 (4H,m), 1.9 (2H,m), 1.87 (3H,s). With the simple modification of maintaining the reaction temperature at -78° until no starting material remained (glc), the product becomes almost exclusively that of simple C-alkylation. In a typical experiment, 40 ml of tetrahydrofuran was distilled from $LiAlH_4$ into a flask containing 2.12g (.021 mole) diisopropylamine. The flask, equipped with a septum cap and magnetic stirring bar, was flushed with N_2 and cooled to -78° in acetone-solid CO_2

Addition of 9.1 ml of a 2.3M solution of n-butyllithium in hexane, followed after 15 minutes by dione 1 (1.12g, .01 mole) in 5 ml tetrahydrofuran, generated the dianion. After an additional 15 mins, 5.7g (.04 mole) methyl iodide was added, followed by stirring at -78° for 2.5 hours. The reaction was quenched with 20 ml of 3N hydrochloric acid, the product extracted with 40 ml ether, the organic layer washed with 3x50 ml saturated salt solution, dried over magnesium sulfate, and evaporated in vacuo. The crude oil was short-path distilled at 50° and 0.5mm to yield 0.88g of 2(R=CH_3), mp 59-61° (70% yield).



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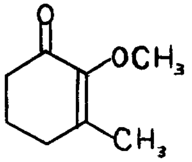

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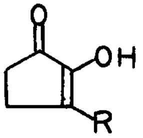

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The scope of this dianion alkylation is illustrated in Table I below. Under the reaction conditions noted there was essentially complete disappearance of starting material and no O-alkylation or dialkylation could be detected by nmr and glc.

TABLE I. YIELDS IN DIANION ALKYLATIONS OF 1,2-CYCLOALKANEDIONES

Starting Material	Halide	Product	Yield
1	CH_3I	2,R = CH_3	70%
	C_2H_5I	R = C_2H_5	62%
	CH_2=$CHCH_2Br$	R = CH_2CH=CH_2	67%
3	CH_3I	9,R = CH_3	60%
	C_2H_5I	R = C_2H_5	56%

Applications of this technique to alicyclic syntheses are under investigation.

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5. R. T. Dahill,Jr., J. Org. Chem., 31, 2694 (1966).
6. The low yield conjugate addition of phenyl Grignard reagent to 2-hydroxy-2-cyclohexenone has been reported (P. Tomboulian and C. A. A. Bloomquist, J. Org. Chem., 24, 1239, 1959).
7. The Hückel parameters $\alpha_O=\alpha_C+\beta$, $\beta_{CO}=0.8\beta_{CC}$ were utilized; the electron densities shown were not significantly altered by moderate variation of these parameters.
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