Easy Generation of the Dianions of 3-Isobutoxycyclopent-2-en-1-ones and their Reactions

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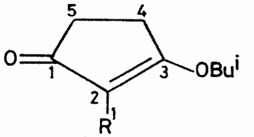
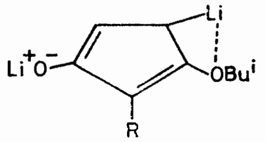
Summary The dianions of 3-isobutoxycyclopent-2-en-1-ones were readily generated with 2·2 mol. equiv. of lithium di-isopropylamide or lithium bis(trimethylsilyl)amide and their reactions with various electrophiles provided corresponding dialkyl derivatives including the *cis*-bicyclo[3.3.0]octenone system in good yields.

Notwithstanding their plausible stabilization due to aromaticity and their potential as valuable synthetic intermediates, the generation of the dianions of cyclopent-2-en-1-ones, as well as their reactions with electrophiles, have not been well documented. Trost and Latimer[1] recently reported the first successful example using 6-methoxyindan-1-one. In conjunction with the total synthesis of cyclopentanoid antibiotics, we have studied the generation of the dianions of 3-isobutoxycyclopent-2-en-1-ones and their alkylation reactions. We here report that: (i) the dianions of these compounds are readily produced under mild conditions, and (ii) their dialkylation, including a one-step synthesis of bicyclic systems or regio-selective mono-alkylation from dianions favouring the C-5-alkylation, can be realized.



(1) R^1 = H
(2) R^1 = Me
(3) R^1 = Et



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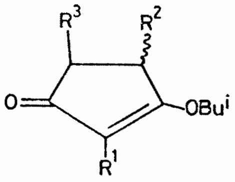

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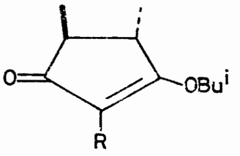
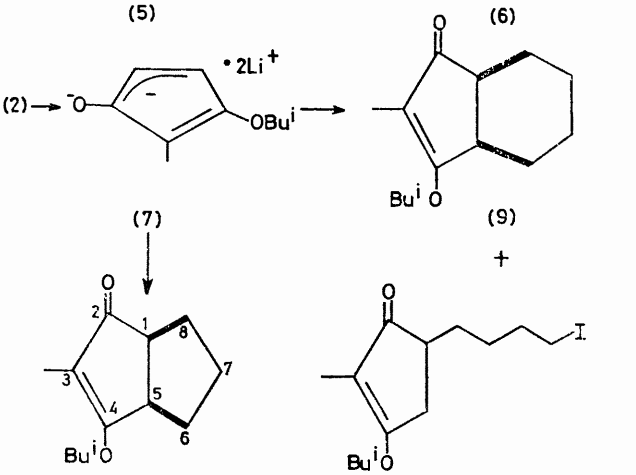
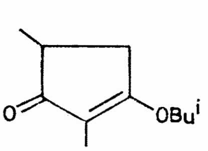


(6)



(8) (10)



(11)

Table. Dialkylation of 3-isobutoxycyclopent-2-en-1-ones[a]

$$\text{enol ether} \xrightarrow[0\,^{\circ}\text{C}]{\text{LDA (2·2 mol equiv.)}} \text{dianion} \xrightarrow{\text{electrophile}} \text{products}$$

Enol ether	Electrophile	Products	% Yield[b]
(1)	MeI	(5; R^1 = H, R^2 = R^3 = Me)	85[c]
(2)	MeI	(6)	70
(2)	HCHO	(5; R^1 = Me, R^2 = R^3 = CH$_2$OH)	55
(3)	HCHO	(5; R^1 = Et R^2 = R^3 = CH$_2$OH)	58

[a] In a typical procedure, the enol ether (1·0 mmol) in 1·0 ml of anhydrous THF was added to a solution of LDA (2·2 mmol) in THF (10 ml) at −78 °C. After 30 min at −78 °C, the mixture was warmed to 0 °C and kept at this temperature for 30 min. Excess of methyl iodide was then added and the mixture was stirred at 0 °C for 30 min. Work-up afforded 70—85% of the 4,5-dimethylated derivative. [b] Isolated yield. [c] A minor product (11) arising from C-2 and C-5 methylation of the dianion was also isolated in 7% yield.

Treatment of the 3-isobutoxycyclopent-2-en-1-ones (1)—(3)† with lithium di-isopropylamide (LDA) (2·2 mol. equiv.)‡ at 0 °C in tetrahydrofuran (THF) for 30 min or lithium bis(trimethylsilyl)amide at −78 °C in THF for 1 h smoothly generated their corresponding dianions [*e.g.*, (4) or equivalent structures] which afforded their 4,5-dideuterio derivatives (confirmed by ^{1}H and ^{13}C-n.m.r. spectroscopy) upon quenching with D$_2$O in >95% yield. Easy generation of these relatively stable dianions is

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† Prepared from their corresponding 1,3-diones according to: M. F. Ansell, J. E. Emmett, and B. E. Grimwood, *J. Chem. Soc.* (*C*), 1969, 141. (1) (85%): b.p. 116—118 °C at 8·5 mmHg; (2) (90%): b.p. 118—119 °C at 3 mmHg; and (3) (80%): b.p. 123—124 °C at 3 mmHg.

‡ The dianion formation with LDA requires a temperature near 0 °C. The use of 1 mol. equiv. of LDA at −78 °C produced mono-anions at C-5 of (1)—(3). However, interestingly, the C-4 mono-anions were obtained in high yields from (1)—(3) when 1 mol. equiv. of lithium bis(trimethylsilyl)amide was used at −78 °C (to be published). For the kinetic deprotonation of cyclic 1,3-dione enol ethers with LDA see: G. Stork and R. L. Danheiser, *J. Org. Chem.*, 1973, **38**, 1775; M. L. Quesada, R. H. Schlessinger, and W. H. Parsons, *ibid.*, 1978, **43**, 3968.

presumably ascribable to the possible chelation of the lithium of the C(4)–Li bond on to the 3-oxygen atom [see (**4**)]. These dianions produced 4,5-dimethyl- (exclusively *trans*-) and 4,5-bis(hydroxymethyl)-derivatives in acceptable yields, upon treatment with MeI and formaldehyde, respectively (Table). The *trans*-stereochemistry of the 4,5-dimethyl products was validated by base-catalysed equilibrium experiments and by analysis of the ^{13}C n.m.r. spectra. For example, treatment of (**6**)§ with LDA (1·1 mol. equiv.) followed by H_2O quenching afforded a 2 : 1 mixture of the starting enol ether (**6**) (*trans*) and the less stable one (*cis*). This assignment was further corroborated by the ^{13}C n.m.r. chemical shifts in $CDCl_3$ of the 4,5-methyl carbons of these *cis* and *trans* isomers with the former exhibiting high field shifts[2] over the latter: *i.e.*, δ 11·0 and 14·4 *versus* 16·1 and 18·1 p.p.m. from Me_4Si. Similar treatment of these dianions with a 1,ω-dihalogenoalkane has provided an efficient means of constructing *cis*-bicyclic unsaturated ketonic systems. Thus, the dianion (**7**) upon treatment with 1,3-di-iodopropane afforded the *cis*-bicyclo-[3.3.0]octene (**8**)¶ in $>60\%$ yield (stereochemistry unchanged after base treatment). The yield of the bicyclic compound (**9**), however, decreased sharply to *ca.* 20% when 1,4-di-iodobutane was used, providing a significant amount of the 5-mono-alkylated derivative (**10**) (15%).

We have further examined the possible regioselective alkylation of these dianions. Thus, the dianion (**7**) was treated with n-butyl iodide (1·0 mol equiv.) at 0 °C followed by D_2O quenching which provided, in 65% yield, a mixture of 5-n-butyl (**5**, R^1 = Me, R^2 = D, R^3 = Bu^n), 4-n-butyl (**5**, R^1 = Me, R^2 = Bu^n, R^3 = D), and 4,5-di-n-butyl (**5**, R^1 = Me, R^2 = R^3 = Bu^n) in a ratio of 70 : 23 : 7.

The results described above lead to various dialkylated cyclopentanones possessing a 1,3-dione enol ether group amenable for further syntheses. In addition, the convenient synthesis of the *cis*-bicyclo[3.3.0]octenone system would be useful for the synthesis of various natural products.

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§ Compound (**6**): i.r. (neat): 1695 (νC=O) and 1625 cm^{-1} (νC=C); ^{1}H n.m.r. (Me_4Si; $CDCl_3$): δ 1·02 (6H, d, *J* 7 Hz, *Me*$_2$CH), 1·18 and 1·24 (both 3H, d, *J* 6·5 Hz, 4- and 5-Me), 1·80 (3H, br. s, 2-Me), *ca.* 2·0 (1H, m, Me$_2$*CH*–), 2·04 (1H, m, $W_{\frac{1}{2}}$ 22 Hz, 5-H), 2·38 (1H, m, $W_{\frac{1}{2}}$ 24 Hz, 4-H), 4·07 and 4·11 [2H, d of AB quartet, *J* 6·5 and 9·5 (J_{AB}) Hz]; ^{13}C n.m.r.| δ (Me_4Si; $CDCl_3$): 7·53 (2-Me), 16·1 and 18·0 (4- and 5-Me), 18·8 (*Me*$_2$CH), 29·0 (Me$_2$*C*H), 42·3 (4-C), 48·2 (5-C), 76·5 (–CH_2–O–), 112·0 (2-C), 184·8 (3-C), and 208·3 (1-C) p.p.m.

¶ Compound (**8**): ^{1}H-n.m.r. (Me_4Si; $CDCl_3$): δ 2·82 (1H, m, $W_{\frac{1}{2}}$ 19 Hz, 1-H) and 3·20 (1H, m, $W_{\frac{1}{2}}$ 18 Hz, 5-H).

[1] B. M. Trost and L. H. Latimer, *J. Org. Chem.*, 1977, **42**, 3212.
[2] D. K. Dalling and D. M. Grant, *J. Amer. Chem. Soc.*, 1972, **94**, 5318; A. I. Scott, C. A. Townsend, K. Okada, M. Kajiwara, R. J. Kushley, and P. J. Whitman, *ibid.*, 1974, **96**, 8069.