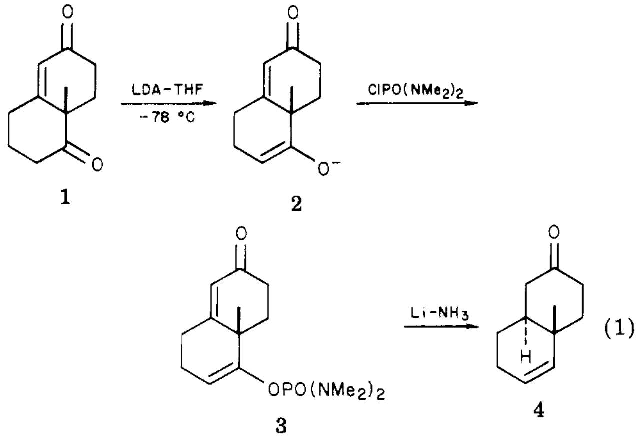
Kinetic Enolates of Enedione Systems Related to the Wieland-Miescher Ketone

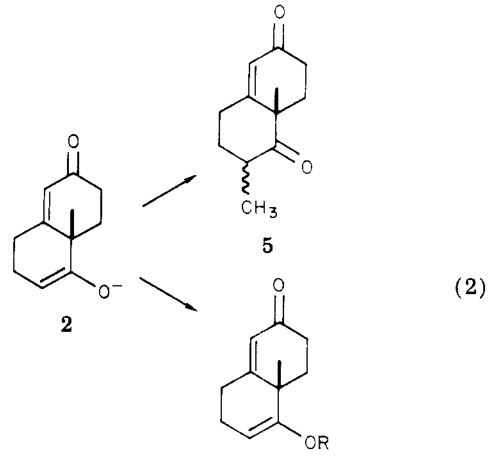
Summary: Kinetically controlled deprotonation of the Wieland-Miescher ketone and enedione **7** occurs at C(8), whereas in the case of enedione **11**, kinetic enolate formation takes place at C(4).

Sir: The ability to generate kinetic enolates directly from ketones using hindered amide bases (e.g., lithium diisopropylamide)[1] or indirectly via reduction of α,β-unsaturated ketones by alkali metal in liquid ammonia[2] has had considerable impact on the chemistry of carbonyl compounds. Recently the kinetic enolates of α,β-unsaturated ketones (e.g., pulegone, cholest-4-en-3-one) have been studied and shown to give rise to specific α' alkylation.[3] Essentially no attention has been focused on elucidating the nature of kinetic enolates derived from systems possessing a saturated ketone in the presence of an α,β-unsaturated ketone [e.g., Wieland-Miescher ketone (**1**)].[4] We wish to report our results which demonstrate (1) that kinetic enolates of enediones can be cleanly and regiospecifically generated and (2) that such species are reasonably stable and capable of being alkylated or trapped with a variety of reagents.

In conjunction with an ongoing program we required a short efficient route to octalone **4**. It was this specific need which prompted us to examine the kinetic enolate derived from enedione **1**. A priori, it was not obvious which enolate ($\Delta^{2,3}$ or $\Delta^{8,9}$), if any, would predominate under nonequilibrating conditions using a hindered amide base. However, it had occurred to us that successful generation of enolate **2** followed by trapping with bis(dimethylamino)phosphorochloridate and subsequent Birch reduction would provide directly octalone 4 (eq 1).



In a series of preliminary experiments, a tetrahydrofuran solution of commercially available diketone 1 was added at −78 °C to 1.1 equiv of lithium diisopropylamide (LDA) in THF. After enolate formation was complete (ca. 20 min), the reaction mixture was warmed to 0 °C and treated with methyl iodide. Usual workup and purification of the product on silica gel afforded a 78% yield of the C(8) methylated diketone **5**[5,7b] along with the 5% recovered starting enedione. No products derived from the $\Delta^{2,3}$-enolate or the γ-dienolate were detected. Trapping of enolate **2** with diethyl phosphorochloridate (DEPCl), trimethylchlorosilane (TMSCl), and acetyl chloride gave diethyl enol phosphate **6a**, silyl enol ether **6b**, and enol acetate **6c**, respectively, in yields of 85, 68, and 77% along with 5–10% of recovered starting material (eq 2).



6a, R = $(EtO)_2PO$
b, R = Me_3Si
c, R = CH_3CO

The preparation of octalone 4 proceeded in a straightforward manner. Quenching of enolate **2** at −10 °C in tetrahydrofuran containing 1 equiv of HMPA with bis(dimethylamino)phosphorochloridate provided a 74% yield of compound **3**. Simultaneous reductive cleavage of the C–O bond of the tetramethylphosphorodiamidate and reduction of the α,β-unsaturated enone moiety was accomplished in 72% yield by the addition of a solution of **3** and 2.0 equiv of *tert*-butyl alcohol in THF to a solution of 10 equiv of lithium in liquid ammonia.[6]

As illustrated in eq 3, diketone **7**[7] upon treatment with

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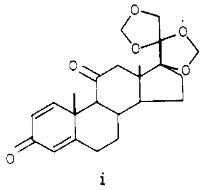
[1] House, H. O., "Modern Synthetic Reactions", 2nd Ed.; W. A. Benjamin: New York, 1972. For the successful aldol condensation of kinetic lithium enolates of methyl ketones see: Stork, G.; Kraus, G. A.; Garcia, G. A. *J. Org. Chem.* **1974**, *39*, 3459. Park, O. S.; Grillasca, Y.; Garcia, G. A.; Maldonado, L. A. *Synth. Commun.* **1977**, *7*, 345.

[2] Stork, G. *Pure Appl. Chem.* **1975**, *43*, 553.

[3] (a) Lee, R. A.; McAndrews, C.; Patel, K. M.; Reusch, W. *Tetrahedron Lett.* **1973**, 965. (b) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775. Also see (c) Lee, R. A.; Reusch, W. *Tetrahedron Lett.* **1973**, 969.

[4] We are aware of only two reports in the literature [Barton, D. H. R.; Hesse, R. H.; Tarzia, G.; Pechet, M. M. *Chem. Commun.* **1969**, 1947. Tanabe, M.; Crowe, D. F. *ibid.* **1969**, 1498] which have studied enolate formation in systems possessing two carbonyl functions. Both reports were concerned with the nature of the enolates derived from 17,20:20,21-bismethylenedioxypregna-1,4-diene-3,11-dione (i) employing sodium



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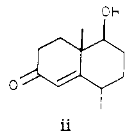
bis(trimethylsilyl)amide and lithium bis(trimethylsilyl)amide. Somewhat surprising was the finding that kinetically-controlled deprotonation of i takes place at C(6), whereas deprotonation under equilibrating conditions gives rise to the $\Delta^{9(11)}$-enolate.

[5] This product, a mixture of α and β isomers at the site of alkylation, was equilibrated to the more stable product with DBU in benzene at room temperature and identified by comparison with a sample prepared by an unambiguous route.

[6] (a) Ireland, R. E.; Muchmore, D. C.; Hengartner, U. *J. Am. Chem. Soc.* **1972**, *94*, 5098. Fetizon, M.; Jurion, M.; Anh, N. T. *Chem. Commun.*, **1969**, 122. Ireland, R. E.; Pfister, G. *Tetrahedron Lett.* **1969**, 2145. (b) For an alternate route to 4 see: Heathcock, C. H.; Ratcliffe, R.; Van, J. *J. Org. Chem.* **1972**, *37*, 1976.

[7] (a) Prepared by oxidation of the known alcohol ii [Grieco, P. A.:



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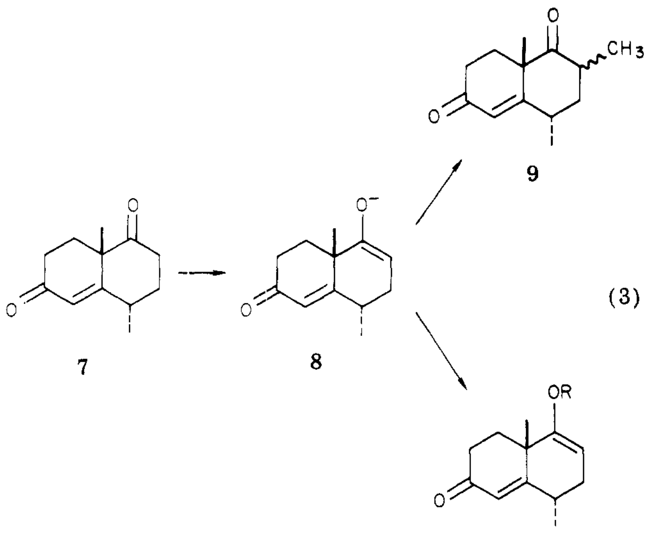
Oguri, T.; Gilman, S.; DeTitta, G. T., *J. Am. Chem. Soc.*, **1978**, 100, 1616]. (b) Telschow, J.; Reusch, W. *J. Org. Chem.* **1975**, *40*, 862.

0022-3263/79/1944-2593$01.00/0

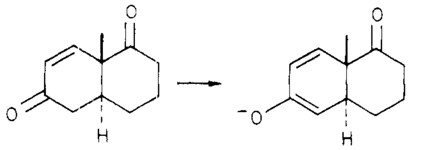


7 8 9 (3)

10a, R = $(EtO)_2PO$
b, R = Me_3Si
c, R = CH_3CO

LDA in THF gave rise to exclusive formation of enolate **8** which, in addition to being alkylated with methyl iodide (**8** → **9**[5], 76%), was trapped with DEPCl (**8** → **10a**, 75%), TMSCl (**8** → **10b**, 74%), and CH_3COCl (**8** → **10c**, 72%).

The above data clearly establishes the ability to generate kinetic enolates of diketones such as **1** and **7** without complications due to intermolecular and intramolecular processes. However, in sharp contrast to the results reported in eq 1–3, diketone **11**,[8] which possesses acidic hydrogens at C(4) and C(8) and is not capable of undergoing γ-dienolate formation due to the presence of the C(10) methyl group, undergoes exclusive deprotonation at C(4) under kinetically controlled conditions (eq 4) employing the procedure described above. Alkylation of cross-conjugated enolate **12** with methyl iodide gave rise to exclusive formation of pure diketone **13**[5] in 72% isolated yield. Trapping of **12** with DEPCl, TMSCl, and CH_3COCl produced dienes **14a–c** in the yields specified.



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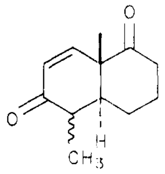

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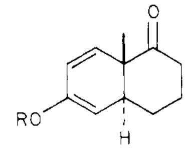

14a, R = $(EtO)_2PO$ [73%]
b, R = Me_3Si [65%]
c, R = CH_3CO [71%]

While it is not clear what factors are responsible for the differences observed during the kinetically controlled deprotonation of substrates **1**, **7**, and **11**, the ability to generate a specific enolate and carry out useful chemistry in the presence of an additional carbonyl unit, without prior protection, can be extremely useful during elaboration of complex molecules.

Acknowledgments. This investigation was supported by Public Health Service Research Grant CA 13689-07 from the National Cancer Institute and, in part, by a grant from G. D. Searle and Co.

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Received January 22, 1979

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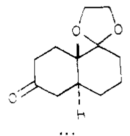
(8) Diketone **11** was prepared from the known keto ketal **iii**[9] via the



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following sequence of reactions: (a) $C_6H_5SeCl/EtOAc$; (b) $H_2O_2/CH_2Cl_2/Pyr$; (c) H_3O^+/THF.

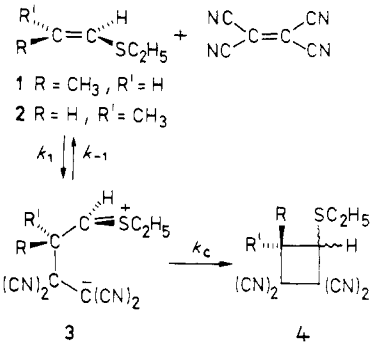
(9) Bauduin, G.; Pietrasanta, Y. *Tetrahedron* **1973**, *29*, 4225.

Rates and Mechanism of (2 + 2) Cycloaddition Reactions of Tetracyanoethylene to Thioenol Ethers

Summary: The high influence of solvent polarity on rate indicates the mechanistic analogy between tetracyanoethylene cycloadditions to thioenol ethers and those to enol ethers for which a pathway with zwitterionic intermediate was established previously, whereas the structure–rate relation reveals a higher sensitivity of thioenol ethers to steric effects.

Sir: The recent report of Okuyama, Nakada, Toyoshima, and Fueno[1] on the rates of tetracyanoethylene (TCNE) additions to thioenol ethers prompts us to publish our evidence for the zwitterionic pathway which is based on additional mechanistic criteria. After establishing zwitterionic intermediates in TCNE cycloadditions to enol ethers,[2] we applied the same mechanistic probes to the sulfur analogues.

We studied spectrophotometrically the kinetics of (2 + 2) cycloadditions of TCNE to *cis*- and *trans*-propenyl ethyl sulfides (**1** and **2**)[3] in ten solvents of widely varying polarity as judged by their E_T values, an empirical measure of solvent polarity.[4] The extinction of the violet or deep blue charge-transfer complexes (λ_{max} 500–600 nm) is proportional to the TCNE concentration when 10–30 equiv of thioenol ether are used. A low and constant concentration



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[1] T. Okuyama, M. Nakada, K. Toyoshima, and T. Fueno, *J. Org. Chem.*, **43**, 4546 (1978).

[2] Review: R. Huisgen, *Acc. Chem. Res.*, **10**, 117 (1977).

[3] Satisfactory C, H, N, and S analyses were obtained for all new cycloadducts.

[4] C. Reichardt, "Lösungsmitteleffekte in der organischen Chemie", Verlag Chemie, Weinheim, W. Germany, 1969, pp 141–149, 162.