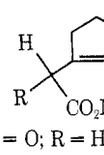
A Route to Furanoid Systems by Intramolecular Homoconjugate Addition

Summary: Intramolecular O-alkylation of β-keto ester enolates by activated cyclopropanes provides a pathway to dihydrofurans and tetrahydrofurylidene derivatives.

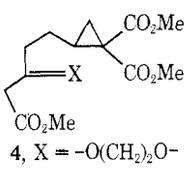
Sir: Recently we reported a new route to the synthesis of carbocyclic[1a] and nitrogen heterocyclic[1b] systems *via* intramolecular homoconjugate addition to activated cyclopropanes. In the cases thus far described,[1] the site of nucleophilic activity was predictable. Reliable rules concerning the sense (spiro *vs.* fused modes[1a]) of opening of the cyclopropanes were developed. It was thus of interest to study the intramolecular opening of such activated systems by enolates of β-keto esters, where ambient nucleophilicity (C- *vs.* O-alkylation) has often been encountered.[2] Below we describe expeditious entries to furanoid derivatives[3] by means of preferential intramolecular O-alkylation of such enolates. We also report an unusually high degree of specificity in the geometry of these enolates as a function of solvent.

Terminal allylation of methyl acetoacetate by the excellent method of Weiler[4] afforded **1.** Attempted cyclopropanation of 1 with dimethyl diazomalonate under the influence of copper bronze gave, as the major product (51%), enone triester **2,** mp 46–48°.[5a,6] While the generality of this potentially useful reaction[7,8] remains to be explored, for our immediate purposes it posed a problem. Accordingly, 1 was converted (91%) to its dioxolane derivative, **3,** and the latter was subjected to cyclopropanation (a solution of 1 equiv of olefin and 1 equiv of diazo compound was added to a mixture of 1 equiv of olefin and 400 mg of copper bronze/0.1 mol of diazo ester, heated at 140°). The ketal triester **4**[5a] so obtained in 70% yield was transformed (1:1 MeOH–concentrated HCl, room temperature) into the desired **5**[5] in 77% yield.

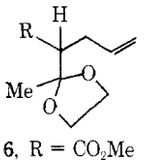
Similarly, cyclopropanation of unsaturated ketal **6**[5a] gave **7** (38%) which afforded **8**[5a] (75%) after deketalization. Finally, cyclopropanation of the dioxolane of allylacetone (**9**)[9] followed by deketalization afforded **10**[5] (49% overall), mp 50–52°.



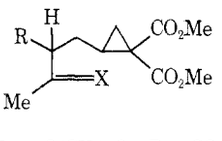
1, X = O; R = H
2, X = O; R = $CH(CO_2Me)_2$
3, X = $-O(CH_2)_2O-$; R = H



4, X = $-O(CH_2)_2O-$
5, X = O



6, R = CO_2Me
9, R = H



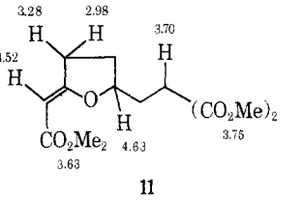
7, X = $-O(CH_2)_2O-$; R = CO_2Me
8, X = O; R = CO_2Me
10, X = O; R = H

Treatment of **5** with 1.6 equiv of sodium hydride in benzene at room temperature for 21 hr gave the tetrahydrofurylidene triester **11**[5] in 71% yield, after chromatography. Starting **5** was recovered (21%). While the possibility of trace amounts of products derived from C-alkylation cannot be excluded, O-alkylation is clearly to dominant pathway.

Reaction of **5** with dimsylsodium[10] (1.1 equiv of triester and 1 equiv of base, room temperature, 3 hr) in DMSO, gave a 49% yield of an isomeric substance, similar to but different from the sodium hydride product. On the basis of data summarized below, this isomer is formulated as **12.**[5] Starting material **5** was recovered to the extent of 5% and there was some indication (tlc) of the formation of **11.** Since the total recovery of neutral fraction was only 78%, O-alkylation is again the predominant pathway.

That the closely related **11**[11] [$\lambda_{max}^{CMCl_3}$ 1725, 1698, 1650 cm^{-1}; λ_{max}^{MeOH} 242 nm (ε 10,300)] and **12** [$\lambda_{max}^{CHCl_3}$ 1745, 1725, 1700, 1640 cm^{-1}; λ_{max}^{MeOH} 242 nm (ε 15,000)] are cis and trans isomers was verified chemically. Each compound, after ozonolysis [(1) O_3–CH_2Cl_2, −78°; (2) Zn–AcOH] gave the lactone diester **13**[5a] (nmr data appear in Chart I[12]). The assignment of configurations to **11** and **12** follows from their nmr spectra (Chart I[12]) in conjunction with known data in 3-alkoxycrotonate systems.[13] Thus, for the trans isomer **12** the resonance for the vinylic proton occurs at higher field than the corresponding resonance for the cis isomer **11.** The reverse order is seen in the allylic resonances.

Chart I[12]



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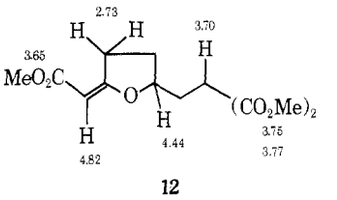

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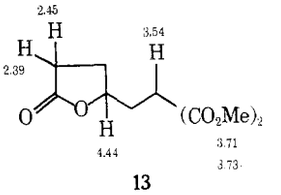

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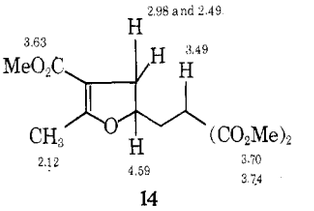

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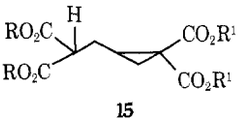

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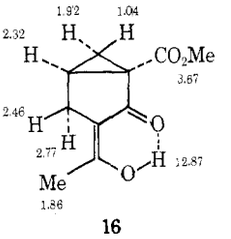

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Since the counterion for both reactions of **5** is sodium, and since both solvents (benzene and DMSO) are aprotic, the enormous difference in the two cases is likely to be a consequence of solvation. For the case of benzene, the U conformation[2,13] involving chelation of the cation by the β-dicarbonyl enolate ligand might be expected to predominate. This leads to cis product. For a solvent with high cation solvating capabilities, such as DMSO, the W or S conformations[2,13] of the enolates might predominate on dipole

repulsion grounds. Either of these would lead to trans product.[13,14]

Treatment of 8 with sodium hydride–benzene (1 equiv of 8 and 1.6 equiv of base) at room temperature for 96 hr gave a 74% yield of dihydrofuran derivative **14** [$\lambda_{max}^{CHCl_3}$ 1755, 1730, 1690, 1644 cm^{-1}; λ_{max}^{MeOH} 255 nm (ϵ 12,200); *m/e* 286 (P); nmr (Chart I[12]). While we do not rule out the possibility of small amounts of products derived from C-alkylation, O-alkylation is again the predominant pathway. It should be noted that in the case of closely related compound **15**, which differs from 8 only by carboalkoxyl *vs.* acetyl deprotonation induces rapid scrambling of the esters,[1c] undoubtedly *via* homoconjugate attack. Whether such an equilibrium is concurrent with the O-alkylation reaction is not known.

In an attempt to study the consequences of generating a monostabilized enolate in an intramolecular relationship to a cyclopropane ring, compound **10** was treated with sodium hydride–benzene and a trace of methanol. There was thus obtained, in 65% crude yield, the difficultly crystalline Dieckmann product **16**,[5,15] mp 35°. The predominant tautomeric form is tentatively assigned as shown, on the basis of the chemical shifts (Chart I[12]) which seem most compatible with the presence of an allylic type methyl. After Dieckmann cyclization had been undergone, possibility of ring mutation is blunted since an endocyclic type of SN2 displacement would now be required.[16]

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Supplementary Material Available. The experimental procedures for the reactions described in this investigation will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-2658.

References and Notes

(1) (a) S. Danishefsky, J. Dynak, E. Hatch, and M. Yamamoto, *J. Amer. Chem. Soc.*, **95**, 1256 (1974); (b) S. Danishefsky and J. Dynak, *J. Org. Chem.*, **39**, 1979 (1974); (c) S. Danishefsky, J. Dynak, and M. Yamamoto, *J. Chem. Soc., Chem. Commun.*, 81 (1973).
(2) For an excellent review, see H. O. House "Modern Synthetic Reactions," Second ed, W. A. Benjamin, Menlo Park, Calif., 1972, pp 520–530.
(3) For a recent synthetic approach to tetrahydrofuryledenes, see T. A. Bryson, *J. Org. Chem.* **38**, 3428 (1973).
(4) S. N. Huckin and L. S. Weiler, *J. Amer. Chem. Soc.*, **96**, 1082 (1974).
(5) (a) The structure of this compound is consistent with its ir, nmr, and low resolution mass spectra; (b) C and H combustion analysis within 0.4% of theory was obtained for this compound.
(6) This experiment was conducted by Dr. M. Yamamoto.
(7) A formal interpretation of this process would involve insertion of the copper carbenoid into the enolic double bond followed by ring opening of the resultant cyclopropanol.
(8) For a novel alkylation scheme based on openings of cyclopropanols, see E. Wenkert, R. A. Mueller, E. J. Reardon, S. S. Sathe, D. J. Scharf, and G. Tosi, *J. Amer. Chem. Soc.*, **92**, 7428 (1970).
(9) Cl. Feugas, *Bull. Soc. Chim. Fr.*, 2579 (1963).
(10) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1353 (1965).
(11) The compounds are easily differentiated by tlc on silica gel plates (Brinkmann Analytical). Thus the R_f values using a 2:1 benzene–ethyl acetate system are 0.26 (**11**) and 0.42 (**12**).
(12) The nmr spectra were measured at 250 MHz. Chemical shifts are reported in δ units from tetramethylsilane as an internal standard. When necessary, decoupling was employed for shift assignments. The spectra of **11** and **12** were measured in deuteriochloroform. Those of **13**, **14**, and **16** were measured in carbon tetrachloride.
(13) A. L. Kurts, M. Macias, I. P. Boletskaya, and O. A. Reutov, *Tetrahedron Lett.*, 3037 (1971).
(14) S. J. Rhoads and R. W. Holder, *Tetrahedron*, **25**, 5443 (1969).
(15) Attempted purification on silica gel was attended by substantial losses of material on the column reducing the yield to 50%.
(16) L. Tenud, S. Farooq, J. Seibl, and A. Eschenmoser, *Helv. Chem. Acta*, **53**, 2050 (1970).

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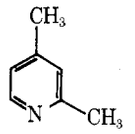
Selective Metalations of Methylated Heterocycles. III. Thermodynamic *vs.* Kinetic Control

Summary: Ethereal solutions of 2-lithiomethyl-4-methylquinoline (**4a**) can be isomerized to 4-lithiomethyl-2-methylquinoline (**4b**) and vice versa as a function of solvent and time.

Sir: Recently, selective metalations of one or the other of two methyl groups substituted 2 or 4 to the ring nitrogen atoms of 2,4-lutidine (**1**), 2,4,6-collidine (**2**), and 2,4-dimethylquinoline (**3**) as a function of the metalating agent were described.[1] In essence, exclusive metalations of the 2- or 4-methyl groups of such compounds were realized with *n*-butyllithium in ether–hexane and sodium amide in liquid ammonia, respectively.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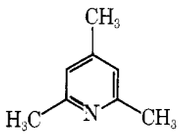
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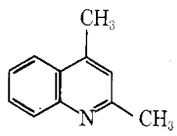
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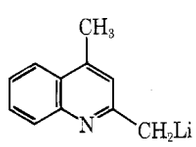
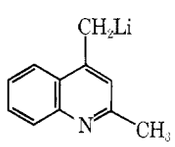
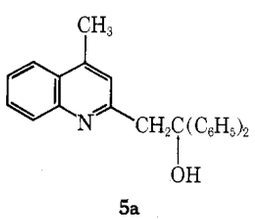
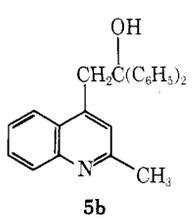
We now wish to report that, though selective metalations of polymethylated pyridines and quinolines continue to be realized, different organolithium derivatives can be cleanly obtained as a function of the ethereal solvent and the reaction periods employed. Thus, metalation of **3** by *n*-butyllithium in THF–hexane gives only **4a** after 1 hr, mixtures of **4a** and **4b** after 24 hr, and only **4b** after 144 hr. That **4a**


4a


4b

and/or **4b** were indeed present was demonstrated by condensation with benzophenone to afford **5a**[1] or **5b**,[1] respec-


5a


5b

tively. Interestingly, the rate of isomerization of **4a** to **4b** is dramatically increased in the presence of an extra equivalent of **3** since only **4b** is present at the end of 1 hr.