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PREPARATION OF ENOL LACTONES OF 3,5,7-TRIKETO AND 3,5,7,9-TETRAKETO ACIDS BY THE CONDENSATION OF 4,6-DIMETHOXY-2-PYRONE WITH ANIONS OF MONO- AND DIKETONES

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Condensations of the anions of acetone, acetophenone, acetylacetone and benzoylacetone with 4,6-dimethoxy-2-pyrone afforded good yields of the corresponding 6 substituted 4-methoxy-2-pyrones which were converted to the 4-hydroxy analogs by demethylation with iodotrimethylsilane

The enol lactones of 3,5-diketo acids have received extensive study because (1) many of them have been found in nature and (2) they are useful for synthesis of more complex species, undergoing a variety of different types of reactions[1-4] The corresponding lactones of 3,5,7-triketo acids and 3,5,7,9-tetraketo acids have received much less study because they are not as readily accessible by synthesis Two of them, the enol lactones of 3,5,7-trioxooctanoic acid[5] and 3,5,7,9-tetraoxodecanoic acid,[6] are elaborated by a microorganism and others are probably unrecognized natural products. Several reports of the use of enol lactones of 3,5-diketo acids or their O-methyl derivatives to acylate enolate anions[7] led us to investigate analogous reactions of 4,6-dimethoxy-2-pyrone These reactions provide an attractive new route to the enol lactones of tri- and tetraketo acids.

4,6-Dimethoxy-2-pyrone was prepared by a modification of the method of Willstatter and Pfannenstiel[8] Acetonedicarboxylic acid was treated with 2 9 equiv of Ac_2O at 0° for 15 min, then stored at -17° to bring about complete crystallization of the anhydride, which was collected by vacuum filtration and dried in vacuo The colorless solid (93%) was treated with an excess of alcohol-free, ethereal CH_2N_2 for 3 hr at 25° to give the pyrone (82%) as white needles, mp 105°, after recrystallization from CH_2Cl_2/hexane

The pyrone was used as an electrophile in condensations with the monoanions of acetone and acetophenone and the dianions of acetylacetone and benzoylacetone The reactions proceeded rapidly and cleanly to give the 6 substituted 4-methoxy-2-pyrones (See Scheme 1 and Table 1) Maximum yields were obtained in condensations employing a 2 3 1 mole ratio of nucleophile to pyrone with the reaction being carried out for 4 hr at ambient temperature A typical procedure follows

Scheme 1

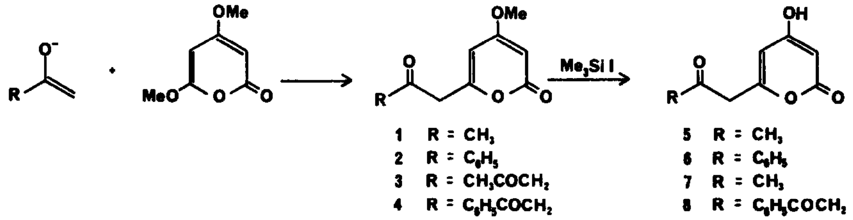
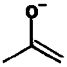
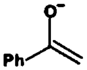
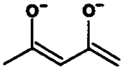
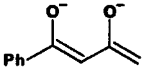


Table 1 Reactions of Nucleophiles with 4,6-Dimethoxy-2-pyrone followed by Demethylation

Condensation			Demethylation		
Nucleophile	Product	Yield	Conditions	Product	Yield
	<u>1</u>[a]	52%	72 hr, 25°	<u>5</u>[e]	54%
	<u>2</u>[b]	67%	40 hr, 50°	<u>6</u>[f]	52%
	<u>3</u>[c]	82%	48 hr, 25°	<u>7</u>[g]	65%
	<u>4</u>[d]	74%	26 hr, 25°	<u>8</u>[h]	56%

(a) Mp 83° (EtOH), lit [5] mp 80-81° NMR ($CDCl_3$) δ 2 26 (CH_3), 3 56 (CH_2), 3 87 (CH_3O), 5 47 (3-CH), 5 93 (5-CH)

(b) Mp 135° (EtOH), lit [10] mp 135 5-137 5° NMR ($CDCl_3$) δ 3 80 (CH_3O), 4 12 (CH_2), 5 43 (3-CH), 5 99 (5-CH), 7 20-8 10 (C_6H_5)

(c) Mp 90° (EtOH), lit [11] mp 92-93° NMR of enol form ($CDCl_3$) δ 2 10 (CH_3), 3 43 (CH_2), 3 83 (CH_3O), 5 50 (3-CH), 5 62 (chain CH), 5 99 (5-CH)

(d) Mp 162° (EtOH) NMR enol form ($CDCl_3$) δ 3 60 (CH_2), 3 85 (CH_3O), 5 50 (3-CH), 6 05 (5-CH), 6.29 (chain CH), 7 35-8 05 (C_6H_5) <u>Anal</u> Calcd for $C_{16}H_{14}O_5$ C, 67.13, H, 4 89 Found C, 66 94, H, 5 03

(e) Mp 118° (acetone/$CHCl_3$), lit [5] mp 118-119° NMR (acetone-d_6) δ 2 23 (CH_3), 3 72 (CH_2), 5 37 (3-CH), 6 09 (5-CH)

(f) Mp 185° (EtOH/H_2O), lit [12] mp 185° NMR (acetone-d_6) δ 4 40 (CH_2), 5 43 (3-CH), 6.25 (5-CH), 7 45-8 25 (C_6H_5)

(g) Mp 96° (acetone/$CHCl_3$), lit [6] mp 95-100° NMR of enol form (acetone-d_6) δ 2 10 (CH_3), 3 67 (CH_2), 5 52 (3-CH), 5 87 (chain CH), 6 25 (5-CH)

(h) Mp 157° (EtOH), lit [13] mp 150-154 5° NMR of enol form (acetone-d_6) δ 3 82 (CH_2), 5 50 (3-CH), 6 30 (5-CH), 6 70 (chain CH), 7 50-8 20 (C_6H_5)

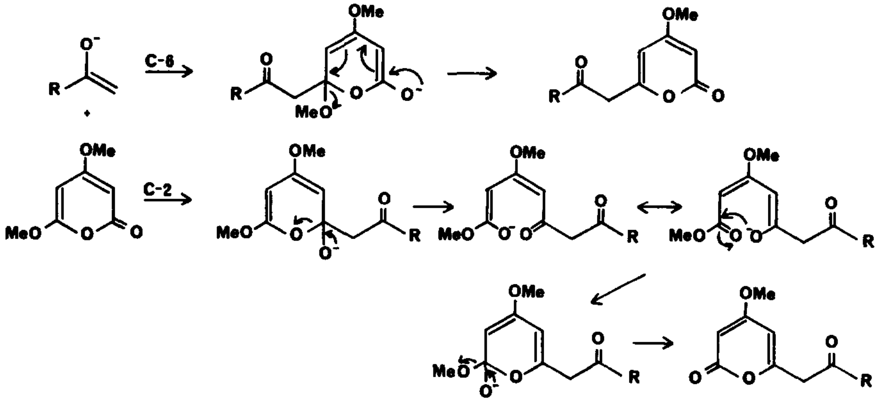
Hydroxylic signals are not reported A 4-bond coupling constant was observed between 3-CH and 5-CH on the pyrone rings

6-(2,4-Dioxo-4-phenylbutyl)-4-methoxy-2-pyrone (4) The dilithium salt of benzoylacetone was prepared by the addition of 1 20 g (7 4 mmol) of the diketone to a solution of 14.8 mmol of lithium diisopropylamide (prepared from n-butyllithium and diisopropylamine) in 60 mL of dry tetrahydrofuran at 0° under a N_2 atmosphere. After 10 min, a solution of 0 5 g (3 2 mmol) of the pyrone in tetrahydrofuran (15 mL) was added dropwise at 0° The mixture was stirred for 4 hr at room temperature The solvent was removed *in vacuo*, the residue was dissolved in cold, dilute HCl The organic layer was collected and the aqueous layer was re-extracted with EtOAc The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give an orange solid which was washed sparingly with Et_2O Recrystallization from EtOH gave 4 as white needles (0 68 g, 74%), mp 162°

The condensation products were demethylated to give the corresponding 4-hydroxy-2-pyrones by treatment with a large excess of Me_3SiI[9] in $CHCl_3$ The course of demethylation was monitored by TLC. In general the reactions proceeded slowly, requiring 24-72 hr to reach completion In order to obtain good reults, it was important for the Me_3SiI to be free of HI and I_2 Results of the demethylations are summarized in Table 1

The mechanism of the pyrone condensations is not known Previous examples of enolate anions reacting with pyrones have involved 6-alkyl-4-methoxy-2-pyrones which gave products consistent with attack on the 2-carbonyl group with subsequent ring opening,[7] whereas the present reactions would appear to involve displacement of the 6-methoxy group by the nucleophile We doubt, however that the reactions go by a straightforward addition-elimination process at C-6, an attractive alternative is that the enolate anions attack the carbonyl group in these cases also, causing ring opening to give the enolate anion of an unsaturated δ-keto ester which recyclizes by displacement of methoxide ion to give the observed products as shown in Scheme 2

Scheme 2



Investigations of the mechanism of reaction of nucleophiles with 4,6-dimethoxy-2-pyrone and synthetic applications involving other nucleophiles are presently being pursued

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