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NUCLEOPHILIC ATTACK ON 4,6-DIMETHOXY-2-PYRONES; DISCOVERY OF A REMARKABLY FACILE REARRANGEMENT OF THE PYRONES

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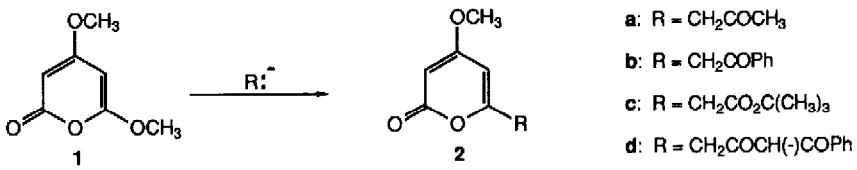
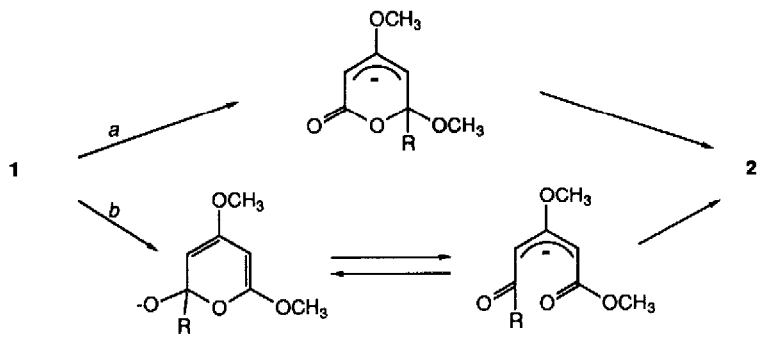
Abstract: During the course of mechanistic investigations of nucleophilic attack on 4,6-dimethoxy-2-pyrones, a rapid scrambling reaction has been found between 4,6-dimethoxy-3-methyl-2-pyrone and the corresponding 5-methyl isomer.

In 1982 two of us reported the condensation of strongly nucleophilic enolate anions with 4,6-dimethoxy-2-pyrone; the reaction led to good yields of the corresponding 6-substituted-4-methoxy-2-pyrones.[1] Two possible mechanisms were proposed for the reaction. One (route *a*) was a simple addition-elimination reaction at the 6-methoxy group; the other (route *b*) an attack on the carbonyl group leading to ring opening and then reclosure to give a new pyrone. By the latter route C-2 in the starting pyrone becomes C-6 in the product and C-3 becomes C-5.

Scheme I



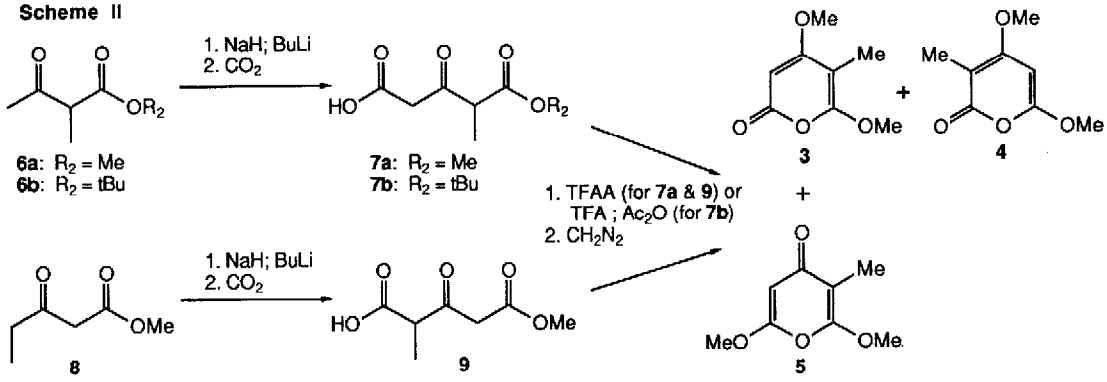


Syntheses of methyl-substituted 4,6-dimethoxy-2-pyrones (**3** and **4**) were undertaken to provide probes for distinguishing between the two mechanisms. Following the previously developed synthetic protocol,[2] the dianion (1.0 equiv. NaH - 1.0 equiv. nBuLi, THF, -10°C, 10 min) of **6a** was carboxylated (CO_2, -78°C to RT) to afford keto ester acid **7a** in 65% overall yield (Scheme II). Cyclization of the latter (TFAA, RT, 1 h) was followed by methylation (CH_2N_2-acetone or Me_2SO_4, K_2CO_3, acetone, reflux, 2 h). Purification by column chromatography and subsequent recrystallization from hot methanol yielded the desired pyrone **3**[3a] in 70% overall

yield, along with a small amount (9%) of 2,6-dimethoxy-3-methyl-4-pyrone **5**.[3b] Similarly, methyl 3-oxopentanoate **8**, which was readily available by methylation *via* the dianion, was subjected to the same reaction sequence. Upon recrystallization from methanol, a single pyrone was obtained, which unexpectedly turned out to be **3**! An alternate synthesis of **3** was also carried out starting from *tert*-butyl α-methylacetoacetate **6b**; 2-methyl-3-oxoglutaric acid was converted to the anhydride and then treated with CH_2N_2 to give 2-pyrone **3** along with 4-pyrone **5**.

At this point the structure of pyrone **3** was established by an NMR study with $Eu(thd)_3$ (Resolve-Al). The carbonyl group is the primary site of coordination with a europium shift reagent;[4] the shift study showed that the methyl signal is less sensitive to the europium reagent than the vinyl hydrogen signal.

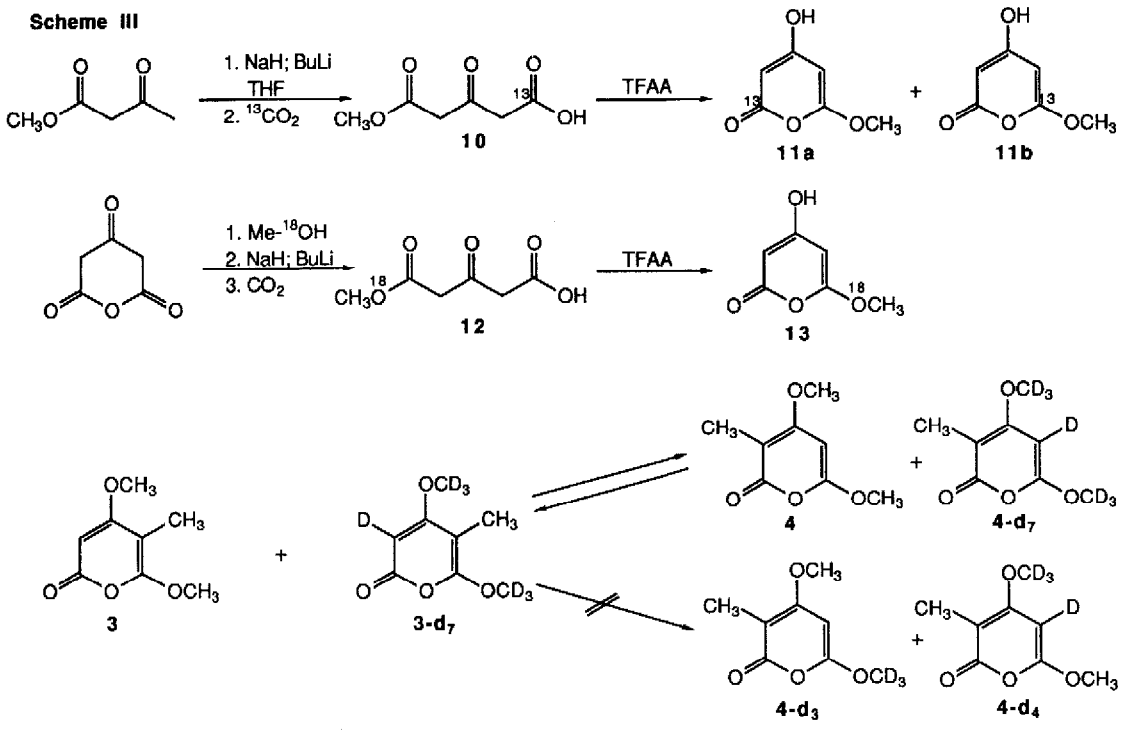
Scheme II



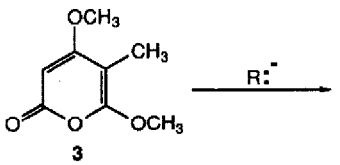
The mechanism of the **4** ⇌ **3** isomerization was further probed using isotopic tracers (Scheme III). First, a ^{13}C labeled 4,6-dimethoxy-2-pyrone was prepared. Carboxylation of the dianion of methyl acetoacetate with $^{13}CO_2$ gave the keto half-ester **10** with the ^{13}C label in the free carboxyl position (δ 171.26 ppm). Treatment with TFAA yielded 4-hydroxy-6-methoxy-2-pyrone **11a,b**,[5] the ^{13}C NMR spectrum of which showed that the ^{13}C label was equally distributed between positions 2 and 6.[6] The result is consistent with mechanisms involving either methyl or methoxy migration; the former was ruled out by an ^{18}O experiment. Pyrone **13** was prepared by cyclization (TFAA) of half-ester **12**, which was readily available by methanolysis (with $CH_3{}^{18}OH$) of acetonedicarboxylic anhydride.[7] Mass spectral analysis (based on the M-OCH_3 fragment)[8] revealed that the ^{18}O label lay exclusively in the methoxy group; *i.e.*, rearrangement involves methoxyl migration. The intramolecular nature of the isomerization process was demonstrated by a third isotope experiment, wherein d_7-2-pyrone **3**-d_7[9] was incubated with the undeuterated pyrone **3**.[10]

Careful scrutiny of the reaction mixture in each of the three pyrone syntheses (*vide supra*) revealed that 2-pyrone **4**[11] was indeed present along with 2-pyrone **3** and 4-pyrone **5**. Subsequently, it was established that the unexpected isolation of **3** from methyl 3-oxopentanoate **8** is a consequence of selective crystallization from an equilibrium mixture.

Scheme III



At this juncture the shortcoming of methyl-substituted 2-pyrones **3** and **4** as a probe of the condensation in Scheme I became apparent --- the facile interchange of substituents between the 3 and 5 positions of 4,6-dimethoxy-2-pyrones renders these pyrones unsuitable for use in mechanistic investigations.[12] Nonetheless, pyrone **3** was treated with three nucleophiles: the monolithium salt of acetophenone, the dilithium salt of acetylacetone and the dilithium salt of benzoylacetone. In all cases 6-substituted 3-methyl pyrones **14** were obtained as the major products.[13-15]



14: $R_1 = CH_3$; $R_2 = H$ (*major*)
15: $R_1 = H$; $R_2 = CH_3$ (*minor*)

a: R = CH_2COPh
b: R = $CH_2COCH(-)COCH_3$
c: R = $CH_2COCH(-)COPh$

We hypothesize that this scrambling reaction involves cleavage of the pyrone ring to a ketene ester, transfer of the methoxy group from C-6 to C-2 *via* an oxonium ion and reclosure. The accompanying paper describes further details of the mechanism, and accounts for the preponderance of 4,6-dimethoxy-5-methyl-2-pyrone **3** over the corresponding 3-methyl isomer **4**.[16]

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References and Footnotes

1. Ray, J. A.; Harris, T. M. *Tetrahedron Lett.* **1982**, *23*, 1971.

2. Huckin, S. N.; Weiler, L. *Tetrahedron Lett.* **1972**, 2405; see also Harris, T. M.; Harris, C. M.; Hindley, K. B. *Fortschr. Chem. organ. Naturstoffe* **1974**, *31*, 217.

3. (a) **3**: mp 140°C (MeOH); IR (KBr) 1700, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.76 (s, 3H), 3.83 (s, 3H), 3.97 (s, 3H), 5.22 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 5.89, 55.43, 56.08, 80.87, 86.83, 159.67, 161.45, 174.37; MS 170 (M^+, 20), 142 (23), 127 (46), 126 (62), 110 (30), 98 (73), 85 (43), 69 (100); Anal. calcd. for $C_8H_{10}O_4$: C, 56.47; H, 5.88. Found: C, 56.60; H, 6.00. (b) **5**: mp 109°C (MeOH); IR (KBr) 1680, 1620, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.80 (s, 3H), 3.85 (s, 3H), 3.96 (s, 3H), 5.41 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 6.46, 56.19, 87.40, 98.99, 159.61, 164.05, 182.53; MS 170 (M^+, 91), 155 (32), 113 (100), 83 (25), 69 (34).

4. Shift reagent studies were carried out with 4,6-dimethoxy-2-pyrone and 6-(carbomethoxymethyl)-4-methoxy-2-pyrone as models. The latter was chosen as the second model because unequivocal assignment of the vinyl protons was possible due to the presence of long-range couplings. In both cases the europium reagent was shown to coordinate at the pyrone carbonyl.

5. (a) Litynski, J.; Malachowski, R. *Roczniki Chem.* **1927**, *7*, 579. (b) mp 148~150°C [lit. mp 146~147.5°C]; ^1H NMR ($CDCl_3$) δ 3.73 (br s, 1H), 4.00 (s, 3H), 5.52 (d, J = 2.2 Hz, 1H), 5.89 (d, J = 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 57.09, 78.06, 94.58, 160.19, 165.77, 166.64; MS 142 (M^+, 22), 114 (35), 111(8), 101 (12), 69 (100), 59 (14).

6. The signals at δ 160.19 and 166.64 ppm in $CDCl_3$ (or 160.74 and 165.50 ppm in DMSO-d_6) were enhanced.

7. Willstatter, R.; Pfannenstiel, A. *Liebigs Ann. Chem.* **1920**, *422*, 1.

8. MS 144 (M^+, 17), 116 (29), 111(8), 69 (100), 61 (19). The fragment ion at m/e 111 is assigned as M^+-$^{18}OCH_3$, indicating that the ^{18}O label was in the methoxyl group.

9. Prepared from the anhydride derived from **7b** in two steps: 1. acetone-D_2O; 2. CD_2N_2 (generated from the Aldrich deutero-Diazald prep set).

10. (a) **3**: HRMS (M^+, 53%) 170.0579 calcd for $C_8H_{10}O_4$, found 170.0573. (b) **3**-d_7: HRMS (M^+, 53%) 177.1018 calcd for $C_8H_3D_7O_4$, found 177.1017.

11. ^1H NMR ($CDCl_3$) δ 1.84 (s, 3H), 3.84 (s, 3H), 3.91 (s, 3H), 5.32 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 8.11, 55.66, 56.14, 72.82, 93.43, 162.53, 163.55, 170.16.

12. Furthermore, for steric and electronic reasons the presence of the methyl group might play an important role in determining the site of nucleophilic attack.

13. The product ratio appears to be dependent on solvents and reaction conditions.

14. (a) **14a**:[15] mp 150°C (EtOH); IR (KBr) 1700, 1560 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.91 (s, 3H), 3.87 (s, 3H), 4.16 (s, 2H), 6.25 (s, 1H), 7.47~8.02 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 8.44, 43.25, 56.25, 97.42, 102.21, 128.41, 128.87, 133.88, 135.91, 156.55, 165.16, 165.27, 193.39; MS 258 (M^+, 12), 154 (17), 105 (100), 77 (28); Anal. calcd. for $C_{15}H_{14}O_4$: C, 69.77; H, 5.43. Found: C, 69.44; H, 5.33. (b) **14b**: mp 97°C (EtOH); IR (KBr) 1700 cm^{-1}; ^1H NMR ($CDCl_3$, enol form) δ 1.91 (s, 3H), 2.05 (s, 3H), 3.51 (s, 2H), 3.83 (s, 3H), 5.50 (s, 1H), 5.54 (s, 1H), 15.03 (br s, 1H); ^{13}C NMR ($CDCl_3$, enol form) δ 8.41, 24.12, 43.57, 56.25, 88.59, 96.43, 100.18, 156.74, 165.25, 170.50, 188.54, 190.06; MS 238 (M^+, 13), 154 (100), 84 (25); Anal. calcd. for $C_{12}H_{14}O_5$: C, 60.50; H, 5.88. Found: C, 60.75; H, 6.01. (c) **14c**: mp 127°C (EtOAc-hexane); IR (KBr) 1720, 1600 cm^{-1}; ^1H NMR ($CDCl_3$, enol form) δ 1.96 (s, 3H), 3.66 (s, 2H), 3.84 (s, 3H), 5.52 (s, 1H), 6.21 (s, 1H), 7.40~7.90 (m, 5H), 15.67 (br s, 1H); ^{13}C NMR ($CDCl_3$, enol form) δ 9.55, 42.16, 56.19, 88.75, 96.06, 109.99, 127.11, 129.68, 132.58, 133.99, 153.81, 163.84, 170.55, 182.04, 191.52; MS 300 (M^+, 19), 154 (100); Anal. calcd. for $C_{17}H_{16}O_5$: C, 68.00; H, 5.33. Found: C, 68.27; H, 5.36.

15. The structure of **14a** was unequivocally assigned by a shift reagent study and by an independent synthesis of **15a** from 5,6-dimethyl-4-methoxy-2-pyrone [1. LDA; 2. PhCOCl].

16. Venkataraman, H.; Cha, J. K. *Tetrahedron Lett.* accompanying paper.

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