Tetrahedron Letters,Vol.30,No.27,pp 3509-3512,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Maxwell Pergamon Macmillan plc

THE SCOPE AND MECHANISM OF REARRANGEMENT OF 4,6-DIALKOXY-2-PYRONES[1]

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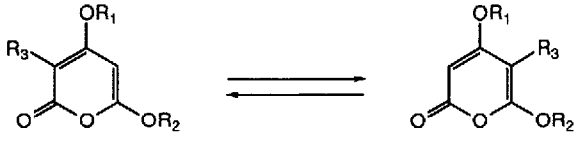
Abstract: The scope and mechanism of a remarkably facile interconversion between 4,6-dialkoxy-3-alkyl-2-pyrones and their corresponding 5-alkyl isomers is described. The preponderance of the latter over the former is rationalized by the stereoelectronic conformational preference of the C4-alkoxy group.

The preceding paper in this journal describes a rapid interconversion between 4,6-dimethoxy-3-methyl-2-pyrone **1a** and its corresponding 5-methyl isomer **2a**.[2] We have shown that 4-hydroxypyrones **1b** and **2b** also undergo an interconversion, wherein **1b** is more stable.[3] The rearrangement readily takes place at room temperature (or even below) in a variety of organic solvents. In addition, it was found that pure **2a** can be isolated due to selective crystallization from the equilibrium mixture.[4a] Pyrones **1a** and **1b**, as solids, do not appear to undergo the interconversion.



1 **2**

a: $R_1 = R_2 = CH_3$, $R_3 = CH_3$

b: $R_1 = H$, $R_2 = R_3 = CH_3$

c: $R_1 = R_2 = CH_3$, $R_3 = CH_2CH{=}CH_2$

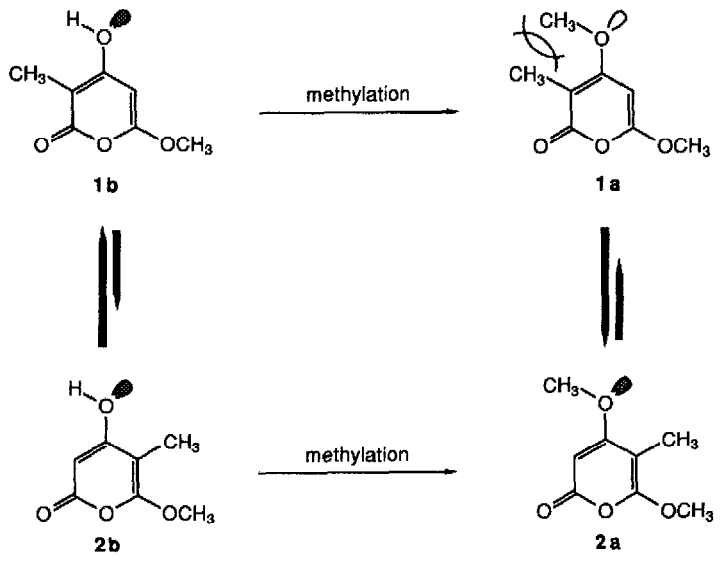
d: $R_1 = R_2 = CH_3$, $R_3 = CH_2CH_2CH_3$

e: $R_1 = R_2 = CH_3$, $R_3 = SMe$

f: $R_1 = R_3 = CH_3$, $R_2 = CH(CH_3)_2$

g: $R_1 = R_3 = -(CH_2)_3-$, $R_2 = CH_3$

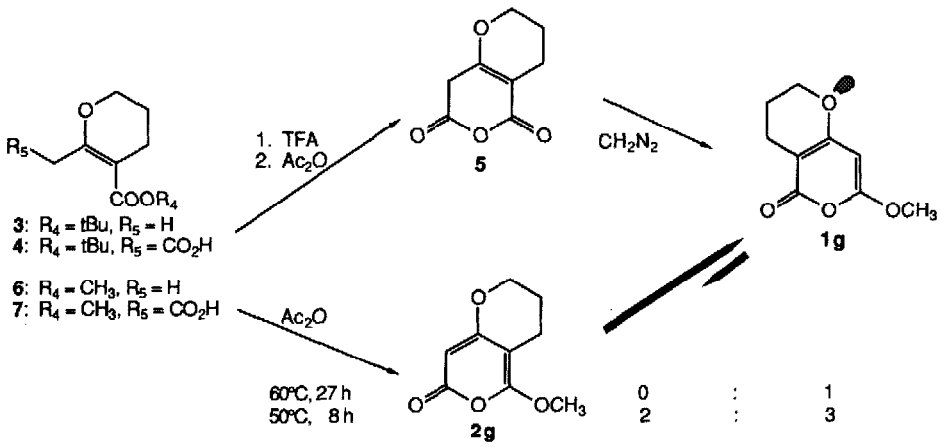
This apparent "migration" of substituents between the 3 and 5 positions appears to be a general phenomenon in the 4,6-dialkoxy-2-pyrones. For example, allyl, n-propyl and methylthio pyrones (**1&2c-e**) likewise equilibrate at 25°C. In marked contrast to 4,6-dimethoxypyrones, however, rearrangement of 4-methoxy-6-isopropoxy-2-pyrones (**1f** and **2f**) requires temperatures higher than 60°C. Apparently, the bulkier isopropyl group at the 6 position impedes the rearrangement (*vide infra*). Although the exact position of equilibrium is dependent upon substrates, solvents and temperatures,[4b] 5-alkyl-2-pyrones **2a,c-f** are more stable than their corresponding 3-alkyl pyrones.



1b 1a 2b 2a

The presence of two alkoxy groups was thought to be necessary for the rearrangement to take place at room temperature. Furthermore, we believe that the distinct conformational preference of the alkoxy group(s) in the pyrones, together with its steric consequences, determines the position of equilibrium. Methyl vinyl ethers[5a] and related systems[5b,c], as well as carboxylic esters[5d], are known to exhibit a strong preference for the *s-cis* conformation. This conformational preference has been attributed to the stabilization by n → σ* overlap, apart from the main p-conjugation. Also, 2-pyrone can be best considered as an enol lactone rather than as a pyrylium betaine. Consequently, the 4-MeO group of the pyrones is expected to prefer the conformation with the lone pair on oxygen antiperiplanar to the C-3 and C-4 bond of the higher bond order.[6] This extra stabilization has to be forfeited in **1a, c-f** due to severe steric strain.[7] On the other hand, the conformation of the 6-alkoxy group is assumed to be of less importance since the C_5- C_6 bond is cross-conjugated with two oxygen atoms.[8]

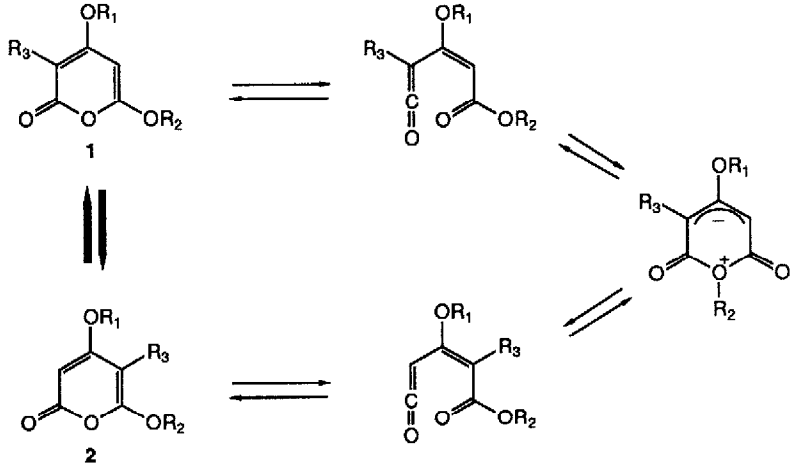
In order to test this hypothesis, we decided to prepare bicyclic pyrones, **1g** and **2g**.[9] Thus, the known ester **3** was carboxylated via its conjugate base to provide half-ester **4** in 50%



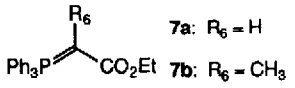
5 1g 2g

yield. Deprotection of the t-butyl ester group (TFA) and subsequent cyclization (Ac_2O) gave anhydride **5**. Treatment of **5** with diazomethane then provided a single 2-pyrone **1g**.[10] Similarly, half-ester **7** was prepared and cyclized by means of Ac_2O (60°C, 27 hr) to afford the same pyrone **1g**. Under milder conditions (50°C, ~8hr), however, a mixture of regioisomers, **1g** and **2g**, was obtained and then purified by SiO_2 chromatography. The structural determination of **1g** and **2g** was unequivocally made by difference NOE spectroscopy. As expected, the position of equilibrium in bicyclic pyrones strongly favors **1g** (≥20:1), where the n $\rightarrow \sigma^*$ interaction, as well as the coplanarity of the 6-OMe group, is maximized.

The intramolecular nature of the rearrangement was firmly established by the fact that none of crossover products between **2a** and d_7-**2a** were found that might arise if the rearrangement involves the intermolecular process.[2] The rearrangement can be rationalized in analogy to the mechanism proposed by Pirkle for a similar skeletal rearrangement of 2-pyrones during gas-phase pyrolysis.[11] Reversible electrocyclic ring-opening of 2-pyrones, **1** and **2**, would lead to ketenes,[12] which then suffer nucleophilic attack by the alkoxy substituent at the 6-position.[13] Furthermore, the higher temperature required for the rearrangement of the 6-isopropoxy derivatives might be due to the slow addition of a bulkier isopropoxy group.

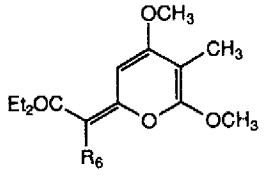


Additional evidence for the proposed mechanism was found in successful ketene trapping experiments. Thus, treatment of **2a** with phosphoranes **7a,b** (benzene, reflux) gave in an excellent yield single adducts **8a,b** contaminated with triphenylphosphine oxide.[14] Although all attempts at further purification of **8a,b** were unsucessful because of instability, the spectroscopic data were consistent with the assigned structures.[9] On the other hand, 5,6-dimethyl-4-methoxy-2-pyrone did not react with phosphoranes under similar reaction conditions.



7a: $R_6 = H$

7b: $R_6 = CH_3$



8a: $R_6 = H$

8b: $R_6 = CH_3$

Further studies are being carried out in order to further clarify the reaction mechanism and determine which factors influence ease of the rearrangement.[15]

References and Footnotes

1. Presented at the 194th National Meeting of the American Chemical Society, New Orleans, LA, August 30 - September 4, 1987: ORGN 191.
2. Cha, J. K.; Harris, T. M.; Ray, J. A.; Venkataraman, H. *Tetrahedron Lett.* preceding paper.
3. The structures of **1b** and **2b** were assigned by comparison of ^{1}H and ^{13}C chemical shifts with those of other 2-pyrones, the details of which will be published shortly in a full paper. The assignment is also consistent with the synthetic method of their preparation.
4. (a) On the other hand, **1a** could not be isolated in pure form because of its facile interconversion to **2a**: r_f for **1a** (in 2:1 EtOAc / hexane) 0.33; r_f for **2a** 0.46. (b) In chloroform and benzene at 25°C, for example, the equilibrium ratio of **1a** and **2a** is *ca* 1:4 and 1:5.6, respectively.
5. (a) Larson, J. R.; Epiotis, N. D.; Bernardi, F. *J. Am. Chem. Soc.* **1978**, *100*, 5713; Hine, J.; Linden, S. M. *J. Org. Chem.* **1981**, *46*, 1635. (b) Mersh, J. D.; Sanders, J. K. M. *Tetrahedron Lett.* **1981**, 4029. (c) Kruse, L. I.; Cha, J. K. *J. Chem. Soc., Chem. Commun.* **1982**, 1333 & 1329; Kruse, L. I.; DeBrosse, C. W.; Kruse, C. H. *J. Amer. Chem. Soc.* **1985**, *107*, 5435 and references cited therein. (d) Curl, R. F. *J. Chem. Phys.* **1959**, *30*, 1529; True, N. S.; Bohn, R. K. *J. Am. Chem. Soc.* **1976**, *98*, 1188.
6. For an excellent review, see Kirby, A. J. "The Anomeric Effect and Related Stereoelectronic Effects at Oxygen," Springer-Verlag, 1983.
7. Similar stereoelectronic considerations appear to be of importance in determining the regioselectivity in the reaction of enolate nucleophiles with 2-pyrones: Venkataraman, H.; Cha, J. K. *unpublished results.*
8. The hydroxyl group in both **1b** and **2b**, being smaller than the methyl, maintains its preferred *s-cis* conformation with the C-3 and C-4 bond. However, the unfavorable steric interaction of the 6-methoxy group with the 5-methyl in **2b** accounts for the preponderance of **1b** over **2b**.
9. Satisfactory spectroscopic data were obtained for all new compounds. Listed below are some selected spectroscopic data ($CDCl_3$):
(a) **1g**: ^{1}H nmr (300 MHz) δ 1.92 (m, 2H), 2.39 (t, J = 6.4 Hz, 2H), 3.81 (s, 3H), 4.17 (t, J = 5.1 Hz, 2H), 5.04 (s, 1H). (b) **2g**: ^{1}H nmr (300 MHz) δ 1.90 (m, 2H), 2.39 (t, J = 6.4 Hz, 2H), 4.02 (s, 3H), 4.17 (t, J = 5.1 Hz, 2H), 5.15 (s, 1H). (c) **8a**: ^{1}H nmr (300 MHz) δ 1.18 (t, J = 7.2 Hz, 3H), 1.63 (s, 3H), 3.73 (s, 3H), 3.77 (s, 3H), 4.04 (q, J = 7.2 Hz, 2H), 4.80 (s, 1H), 6.81 (s, 1H); ^{13}C nmr (100 MHz) δ 6.12, 14.57, 55.70, 55.98, 58.26, 81.09, 85.67, 87.17, 158.10, 166.99(two C's), 168.60; HRMS (M^+) 240.0997 calcd for $C_{12}H_{16}O_5$, found 240.0996. (d) **8b**: ^{1}H nmr (300 MHz) δ 1.28 (t, J = 7.2 Hz, 3H), 1.70 (s, 3H), 1.86 (s, 3H), 3.75 (s, 3H), 3.91 (s, 3H), 4.15 (q, J = 7.2 Hz, 2H), 7.08 (s, 1H); ^{13}C nmr (100 MHz) δ 6.17, 10.57, 14.61, 55.56, 55.74, 58.83, 86.23, 87.05, 89.41, 157.90, 162.75, 165.00, 169.01; HRMS (M^+) 254.1154 calcd for $C_{13}H_{18}O_5$, found 254.1152
10. The exclusive formation of **1g** in the O-methylation step can be attributed to the additive effect of steric and stereoelectronic consideration, as well as a facile equilibration of the initial products. cf. Jung, M. E.; Lowe III, J. A.; Lyster, M. A.; Node, M.; Pfluger, R. W.; Brown, R. W. *Tetrahedron* **1984**, *22*, 4751.
11. Pirkle, W. H.;Seto, H.;Turner, W. V. *J. Am. Chem. Soc.* **1970**, *92*, 6984; Pirkle, W. H.; Turner, W. V. *J. Org. Chem.* **1975**, *40*, 1617 and 1644.
12. (a) Eder, M.; Ziegler, E.; Prewedourakis, E. *Monatsch. Chem.* **1968**, *99*, 1395. (b) Bird,C. W.; Wong, C. W.; Wong, D. Y.; Koh, F. L. K. *Tetrahedron* **1976**, *32*, 269. (c) Roedig, A.; Märkl, G.; Schlosser, M. *Liebigs Ann. Chem.* **1979**, 446. (d) Kappe, T.; Schmidt, H. Chem. Ber. **1979**, *112*, 2756.
13. The alternate 1,5-sigmatropic shift of the alkoxy substituent at the 6-position would require a higher activation energy, and thus is less likely.
14. It is well-known that ketenes undergo a Wittig reaction with phosphoranes to provide allene esters: Bestmann, H.-J.; Hartung, H. *Chem. Ber.* **1966**, *99*, 1198; Lang, R. W.; Hansen, H. *Helv. Chim. Acta* **1980**, *63*, 438.

15. Financial support from the National Institutes of Health (GM 35956) is gratefully acknowledged. We thank Professor Thomas M. Harris for many helpful discussions, and Dr. Larry I. Kruse (Smith Kline & French) for critical comments of the manuscript. We are also indebted to Dr. Brian Sweetman (NIH RR 01688) for obtaining the mass spectral data.

(Received in USA 22 February 1989)