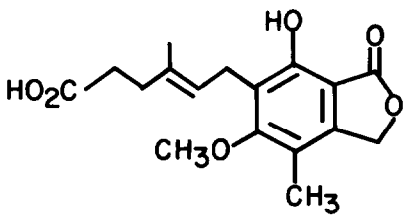
Tetrahedron Letters No. 44, pp 4241 - 4244.

0040-4039/78/1029-4241$02.00/0

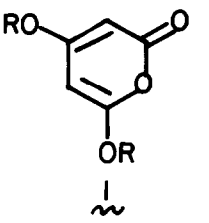
REACTIVITY OF 4,6-DIOXY-2-PYRONES IN THE DIELS-ALDER PROCESS

Alan P. Kozikowski* and Richard Schmiesing
Department of Chemistry, University of Pittsburgh
Pittsburgh, Pennsylvania 15260

Mycophenolic acid, an antibiotic isolated from a culture of Penicillium glaucum, has been shown to possess mild tumor inhibitory activity.[1] In designing routes to this molecule



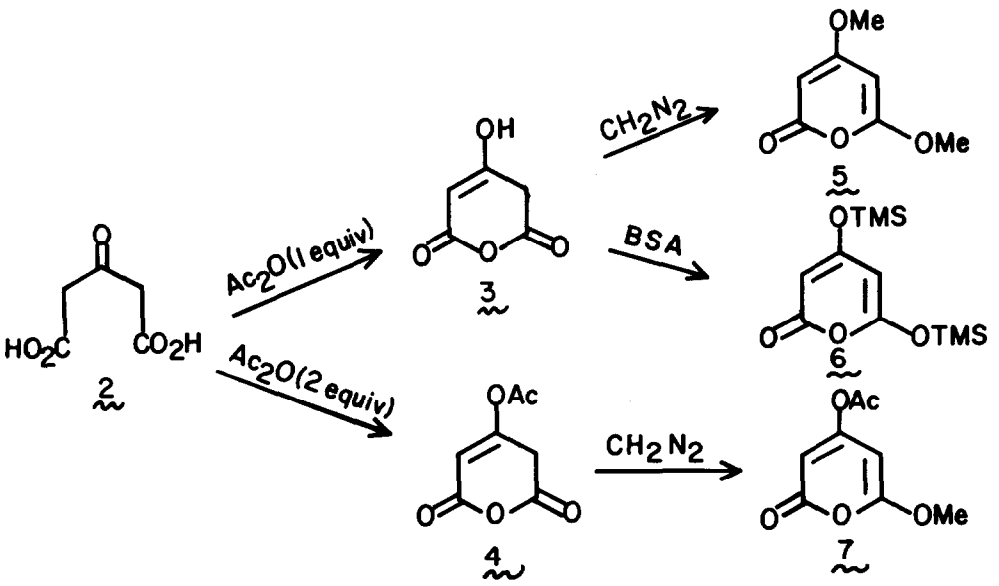
mycophenolic acid



and related compounds, it became of interest to investigate the reactivity of 4,6-dioxy-2-pyrones 1 as dienes for the Diels-Alder process. The ability to perform cycloaddition reactions with these compounds could establish a general method for preparing the dioxygenated aromatic ring systems present in such natural products.[2]

1,3-Acetone dicarboxylic acid 2, a commercially available starting material, is readily converted to the glutaconic anhydride 3 through a modification of the procedure described by Willstatter and Pfannenstiel.[3] Compound 2 is thus treated with one equivalent of acetic anhydride at 45°C for 1 hr. The off-white solid that forms is simply filtered and dried to furnish 3 in 80% yield (the crude product, m.p. 130°, was used in subsequent reactions without further purification). If the above reaction conditions are followed using two equivalents of acetic anhydride, the lower melting acetoxyglutaconic anhydride 4 is formed. The glutaconic anhydrides 3 and 4 are in turn readily transformed to the difunctional pyrones 5-7. Accordingly, treatment of 3 with ethereal diazomethane affords the previously reported 4,6-dimethoxy-2-pyrone 5 (70%).[4] Reaction of 3 with bis(trimethylsilyl)acetamide in benzene at 30°C for 1 hr affords the moisture sensitive disilyloxypyrone 6 (94%).[5] Reaction of 4 with diazomethane yields 4-acetoxy-6-methoxy-2-pyrone (7, 80%).[6]

The Diels-Alder behavior of these pyrones was examined with a variety of olefinic and acetylenic dienophiles. In general, unsymmetrical dienophiles of moderate reactivity (ethyl acrylate, methyl methacrylate, etc.) failed to give isolable products with these pyrones.



Synthesis of 4,6-Dioxy-2-pyrones

Although it has been shown that the presence of a functional group substituent in the 6-position of a pyrone can inhibit cycloaddition reactions for steric reasons, this factor, is significant only for reactions with dienophiles bearing bulky groups (e.g., trimethystannyl).[7]

With more reactive, symmetrical olefinic partners,[8] such as maleic anhydride and N-phenylmaleimide, cycloadducts resulting from addition of a second equivalent of the dienophile to the cyclohexadienes generated by extrusion of carbon dioxide from the primary cycloadducts were obtained (Table, 8 and 9).[9]

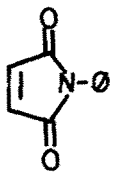
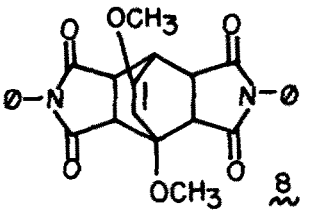
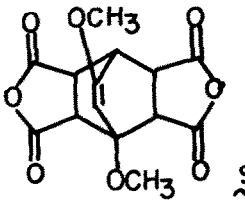
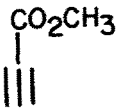
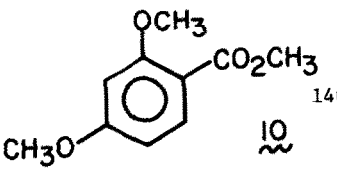
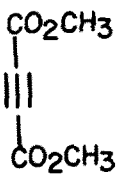
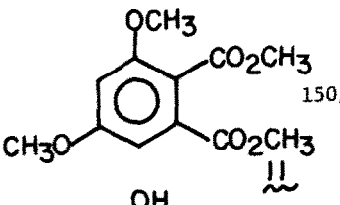
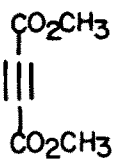
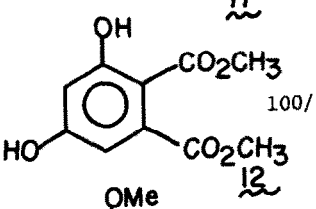
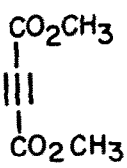
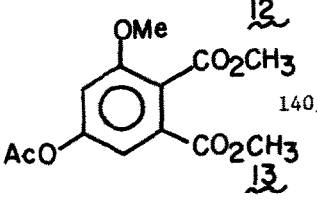
With acetylenic dienophiles, formation of the dioxyarenes (10-13) proceeded in satisfactory yield, thus fulfilling the primary objective of this research.[10] The use of pyrone 7 which bears differentiated oxy-groups, affords an arene which is amenable to further regioselective transformations. An exemplary procedure follows:

Dimethyl 3,5-Dimethoxyphthalate (11). A toluene solution (2 mL) of 4,6-dimethoxy-2-pyrone (0.11 g, 0.72 mmol) and dimethyl acetylenedicarboxylate (0.61 g, 4.35 mmol) was heated at 150°C for 15 hr in a Kimax screw cap culture tube. The toluene was removed by rotary evaporation and the residue chromatographed on 12 g of silica gel (activity III) with a gradient solvent system of ethyl acetate-hexane (0-25%) to afford 128 mg (70%) of 11: ir ($CHCl_3$) 3025, 1735 cm^{-1}; nmr ($CDCl_3$) δ 7.05 (d, 1H, J=2Hz), 6.63 (d, 1H, J=2Hz), 3.93-3.80 (4s, 12H); mass spectrum (70 eV) m/e 254 (M^+), 225.

Since other derivatives of acetone dicarboxylic acid are known, their conversion to 4,6-dioxy-2-pyrones through intermediate glutaconic anhydrides should serve as a general entry into highly functionalized aromatics for synthesis design.

Acknowledgements. We are indebted to the American Cancer Society (Grant IN-58P) for support of these investigations.

Table. Diels-Alder Reactions of 4,6-Dioxy-2-pyrones

Pyrone	Dienophile	Cycloadduct[a]	Reaction Conditions[b] (°C/solvent/hr)	Yield (%)
5		 8	140/ϕCH_3/28	34
5		 9	140/ϕCH_3/30	63
5		 10	140/none/56	70
5		 11	150/ϕCH_3/15	70
6		 12	100/ϕCH_3/17	48[c]
7		 13	140/ϕCH_3/14	73

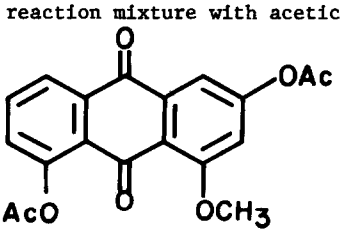
a. Satisfactory spectral and physical data were obtained for all new compounds.

b. All reactions were carried out in Kimax screw cap culture tubes.

c. Desilylation occurred during chromatography of the phthalate.

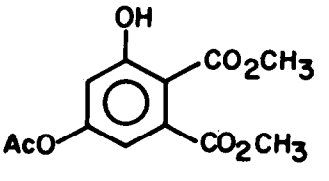
References and Notes

1. J. H. Birkinshaw, H. Raistrick and D. S. Ross, Biochem. J., 50, 630 (1952); M. J. Sweeny, K. Gerzon, P. N. Harris, R. E. Holmes, G. A. Poore, and R. H. Williams, Cancer Res. 32, 1795 (1972).
2. (a) For other applications of glutaconic anhydrides to pyrone construction, see M. E. Jung and J. A. Lowe, Chem. Commun., 95 (1978), and references cited therein. (b) For butadiene based strategies to aromatics, see S. Danishefsky, R. K. Singh and R. B. Gammill, J. Org. Chem., 43, 379 (1978) and references cited therein.
3. R. Willstatter and A. Pfannenstiel, Ann. Chem., 422, 1 (1921).
4. L. Litynski and R. Malachowski, Roczniki Chem., 7, 597 (1927).
5. J. F. Klebe, H. Finkbeiner and D. M. White, J. Amer. Chem. Soc., 88, 3390 (1966).
6. After treating 3 with excess diazomethane and stirring the reaction mixture for 1 hr at room temperature, the isolated crude pyrone 5 was purified by rapid chromatography through florisil with $CHCl_3$ as eluent: nmr ($CDCl_3$) δ 5.20 (d, 1H, J = 2Hz), 5.10 (d, 1H, J = 2Hz), 3.88 (s, 3H), 3.82 (s, 3H).
   Pyrone 6 was purified by bulb-to-bulb distillation (95°C oven temperature, 0.65 mm): nmr (CCl_4) δ 4.92 (d, 1H, J = 2Hz), 4.88 (d, 1H, J = 2Hz), 0.35 (s, 9H), 0.28 (s, 9H).
   Pyrone 7 was purified by bulb-to-bulb distillation (107-115°C oven temperature, 0.15 mm) followed by recrystallization from $CHCl_3$-hexane: mp 65-66° (lit.[4] mp 66-67°); nmr (CCl_4) δ 5.73 (d, 1H, J = 2Hz), 5.33 (d, 1H, J = 2Hz), 3.92 (s, 3H), 2.30 (s, 3H).
7. A. B. Evnin and D. Seyferth, J. Amer. Chem. Soc., 89, 952 (1967).
8. With juglone as dienophile, the tricyclic product i was obtained in low yield from pyrone 7 after treatment of the crude reaction mixture with acetic anhydride and pyridine.



i

9. J. D. Bu'Lock and H. G. Smith, J. Chem. Soc., 502 (1960).
10. With glutaconic anhydride 4, Diels-Alder reaction with dimethyl acetylenedicarboxylate does take place through the pyrone tautomer to afford phthalate ii. Since the yield for this cycloaddition reaction is only 20%, prior conversion of anhydride to the fixed pyrone derivative is preferable.



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(Received in USA 5 May 1978)