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THE ACID CATALYZED CYCLIZATION OF DIAZOKETONES: PREPARATION OF 2,4(3H,5H) FURANDIONES

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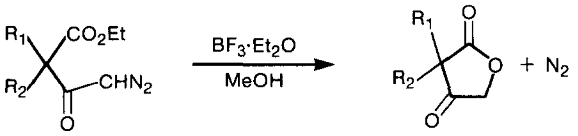
Summary: Diazoketones derived from substituted ethyl hydrogen malonates produced by the selective hydrolysis of the corresponding malonate esters cyclize in the presence of catalytic amounts of boron trifluoride etherate in methanol to yield 2,4(3H,5H) furandiones. The cyclic keto orthoesters appear to be intermediates in the reaction.

Derivatives of 2,4(3H,5H) furandione are valuable synthetic intermediates and are constituents of many natural products.[1] Those compounds which are not disubstituted at carbon-3 tend to be fully enolized and are highly acidic. Materials of this type are often referred to as tetronic acids and have most commonly been prepared by the cyclization of a variety of γ-substituted β-ketoesters.[1,2]

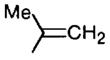
The observation that diazoketone derivatives are often prone to acid catalyzed cyclization in the presence of geometrically proximate nucleophilic functionality[3] suggested that the diazoketones derived from substituted hydrogen malonates might provide suitable precursors for the preparation of substituted tetronic acid derivatives. Starting materials of this type are readily available by the selective hydrolysis of substituted malonate esters.[4] In the acid catalyzed decomposition of the diazoketones, it was anticipated that the ester functionality would serve as an internal nucleophile for cyclization. We now report the realization of this synthetic goal.

The desired diazoketones, generated in good yield (75-85%) from the corresponding acid chlorides, were easily purified by flash column chromatography on silica gel.[5] Treatment of these materials with boron trifluoride etherate in dry methanol led to the rapid evolution of nitrogen and the formation of the substituted 2,4(3H,5H) furandiones shown in Table 1. The reaction was rapid, clean and catalytic in boron trifluoride etherate. Both mono and disubstituted 2,4(3H,5H) furandiones were produced with equal facility and, as expected, the former were extensively enolized. For this reason, the chemical and spectroscopic properties of 2e-g were quite different from the disubstituted materials 2a-d[6,7]. In the case of 1b where potentially competetive sites for cyclization exist, the reaction occurs exclusively at the ester site. When the diazoketones 1a-g were treated with boron trifluoride etherate in wet chloroform, the corresponding open chain hydroxymethyl ketones were produced. These materials could be converted to the cyclic furandiones by treatment with p-toluenesulfonic acid in benzene.

Table 1

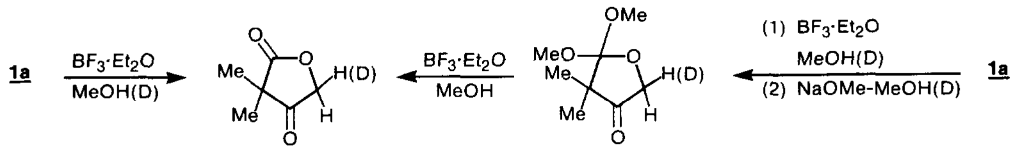


1 2

	R_1	R_2	Reaction[a] Conditions	Yield (%)[b]
a	Me	Me	0°, 15m 25°, 15h	90
b	Me		25°, 15h	72
c	$-(CH_2)_3-$		25°, 20h	86
d	$-(CH_2)_4-$		0°, 10m 25°, 10h	90
e	Bu	H	0°, 1h 25°, 10h	77
f	$PhCH_2$	H	0°, 45m 25°, 15h	82
g	Ph	H	0°, 2h	85

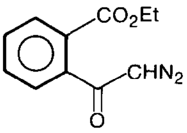
a. methanol solvent; diazoketone/$BF_3 \cdot Et_2O$ 10:1; b. isolated product yields

It seemed likely that the cyclized products produced in methanol resulted from the intramolecular displacement of nitrogen from a boron trifluoride complex of the diazoketone. The use of methanol-d$_1$ as the solvent in the cyclization of 1a leads to the specific incorporation of a single deuterium at position 5 of 2a. If the reaction is quenched with a solution of NaOMe-MeOH to destroy the acid catalyst prior to removing the solvent, the cyclic keto orthoester 3 could be isolated in 53% yield.[8] This material was extremely acid labile and was rapidly converted to 2a under normal workup conditions which suggests that the corresponding orthoesters may be precursors to the isolated furandiones in the decomposition of the diazoketones.



2a 3

Attempts to produce the corresponding six membered rings from the homologous diazoketones were only partially successful. Materials such as 4 , where the reactive functionality is held rigidly cis coplaner, cyclized rapidly (40%) to yield a mixture of 5 and 6 (1:1.6).[9,10] On the other hand, the saturated cyclic derivative 7 produced only the transesterified alcohol 8 under the reaction conditions. Acyclic derivatives required equivalent quantities of boron trifluoride etherate for complete reaction and yielded only the corresponding open chain α-hydroxy and/or α-methoxy methyl ketones resulting from substitution of nitrogen.



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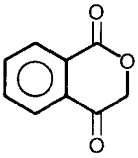

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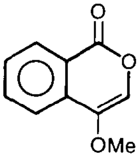

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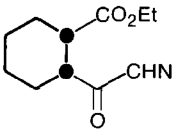

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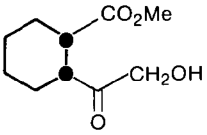

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2. Pollet, P.;Gelin, S.; *Tetrahedron*, **1978**, 34, 1453.
3. Smith, III, A. B.; Dieter, R. K., *Tetrahedron* **1981**, 37, 2407 and references cited therein.
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5. Still, W. C.; Kahn, M.; Mitra, A., *J. Org. Chem.* **1978**, 43, 2923.
6. Satisfactory elemental analyses were received for all new compounds.
7. Spectral data consistent with the proposed structures were obtained for all new compounds: 2a:[11] ^{1}H NMR δ ($CDCl_3$) 1.34 (s, 6H) 4.65 (s, 2H); IR(neat) 1800 and 1760 cm^{-1}; 2b: mp 52°C; ^{1}H NMR δ ($CDCl_3$) 1.43 (s, 3H), 1.78 (d, 1.5 Hz, 3H), 4.62 (ABq, J=16.5 Hz, 2H), 4.92 (s, 1H), 5.1 (m, 1H); IR(neat) 1790, 1760 and 1635 cm^{-1}; 2c: ^{1}H NMR δ ($CDCl_3$) 2.0-2.68 (m, 6H), 4.53 (s, 2H); IR (neat) 1790 and 1750 cm^{-1}; 2d: ^{1}H NMR δ ($CDCl_3$) 1.97 (m, 8H), 4.63 (s, 2H); IR (neat) 1795 and 1750 cm^{-1}; 2e: mp 121°C; ^{1}H NMR δ ($CDCl_3$) 0.75-1.05 (m, 3H), 1.05-1.68 (m, 4H), 2.0-2.33 (m, 2H), 4.62 (s, 2H), 7.5 - 9.9 (brs, 1H); IR ($CDCl_3$) 1725 and 1640 cm^{-1}; 2f: mp 167°C; ^{1}H NMR δ ($CDCl_3$) 3.0-3.4 (brs, 1H), 3.47 (s, 2H), 4.6 (s, 2H), 7.2 (m, 5H); IR (KBr) 1710 and 1600 cm^{-1}; 2g: mp 190°C (dec); ^{1}H NMR δ (acetone-d_6) 3.3-3.8 (brs, 1H), 4.72 (s, 2H), 7.15-8.05 (m, 5H); IR (KBr) 1690 and 1600 cm^{-1}.
8. Spectral data for 3: ^{1}H NMR δ ($CDCl_3$) 1.20 (s,6H,-CH_3), 3.37 (s,6H,-OCH_3), 4.07 (s,2H,-CH_2-); IR (neat) 2980(m), 2950(m), 1770(s), 1740(m), 1470(m), 1390(m), 1290(m), 1255(s), 1200(m), 1120(s), 1050(s), 1020(s), 1000(m); mass spectroscopic molecular weight, m/e 179.2. Addition of boron trifluoride etherate to a methanolic solution of 3 and removal of the solvent produced 2a in quantitative yield.
9. A similar cyclization employing HI has been reported: Bhati, A., *J. Org. Chem.* **1962**, 27, 1183.

10. 6: mp 73°C; ^{1}H NMR δ ($CDCl_3$) 3.83 (s,3H), 6.94 (s,1H), 7.3-8.4 (m,4H); IR ($CDCl_3$) 3130 (w), 3020 (w), 2960 (w) 2900 (w), 2850 (w), 1730 (s), 1710 (s), 1645 (s), 1610 (m), 1390 (m), 1310 (m), 1275 (m), 1256 (m), 1240 (m), 1210 (s), 1165 (s), 1120 (m) 1105 (m) 1055 (m), 1020 (m), 865 (m), 780 (m) and 695 (m) cm^{-1}, mass spectroscopic molecular weight 176.05.
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