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TETRONIC ACIDS AND DERIVATIVES—IV[1] SYNTHESIS AND LACTONIZATION OF γ-ACETOXY β-KETOESTERS

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Abstract—Through our investigation of synthetic routes to tetronic acids, elaboration and cyclization of γ-acetoxy-β-ketoesters were examined. Synthesis of these β-ketoesters **2** has been realized by selective monoacylation of the magnesioenolate of monoethyl malonate. Lactonization of **2** leading to tetronic acids or to 4-alkoxy-furan-2(5*H*)-ones is reported.

The published methods for the synthesis of tetronic acids **1** depend, in many cases, on the preparation of γ-hydroxy,[2] halogeno[3] β-ketoesters or of diethyl (α-acetoxyacyl),[4] (α-halogenoacyl)[5,6] malonates. We have recently reported the lactonization of ethyl γ-acetoxy-α-ethoxycarbonylacylacetates and subsequent acid-catalyzed decarboxylation.[7] The present paper is an extension of our research in order to find a more direct route to tetronic acids from ethyl γ-acetoxy-acylacetates **2** as precursors.

Hitherto, only compound **2a** was known and was synthetized, in moderate yield, from ethyl γ-bromoacetoacetate by Br/OCOCH$_3$ exchange with potassium acetate.[8][†] Our attempts on ethyl γ-bromopropionylacetate gave a mixture from which no identifiable compound could be obtained.

We now wish to report a new procedure leading to monoacylation of magnesium monoethyl malonate **3** by α-acetoxyacid chlorides, having at least one proton at the α position.[‡] It was known that the monoethyl magnesiomalonate underwent diacylation by acid chlorides.[10] Monoacylation was only reported with mixed anhydride or imidazoline derivatives of carboxylic acids.[11][§] The mixed α-acetoxypropionic ethylcarbonic anhydride showed, in our hands, the formation of ethyl-2-acetoxypropionate only. We then turned our attention towards α-acetoxyacid chlorides.

After a complete examination of the reaction parameters we founded critical conditions leading to the monoacylation: the monoethyl malonate was converted to the magnesium complex **3** with two equivalents of isopropyl magnesium bromide in methylene chloride-tetrahydrofuran 1–5 solution and then acylated by 0.4 equivalent of α-acetoxy acid chloride. Immediate aqueous acidic work-up and subsequent purification afforded directly the expected compounds **2a–e** in reproductible yields (56–88%).[¶] Furthermore, the potential broad applicability of this β-ketoester preparation was demonstrated by a facile elaboration of γ,δ-unsaturated-β-ketoesters from the corresponding α,β-unsaturated acid chlorides.[14]

The NMR spectra of the β-ketoesters **2** indicated that they exist, in solution, at least, mainly in the diketo form (9–10% of enolic form in carbon tetrachloride), according to published data of ethyl acetoacetate and higher homologues.[15]

The compounds **2a–e** on heating in a water-bath with 1% hydrogen chloride in absolute primary alcohols (methanol, ethanol, benzyl alcohol) afforded the 4-alkoxyfuran-2(5*H*)-one derivatives **4–6** respectively in good yields. However, in order to facilitate the final elimination of the benzyl alcohol, compounds **6** can be more conveniently prepared by azeotropic elimination of water from a benzenic solution of **2**, benzyl alcohol and *p*-toluenesulfonic acid.

The detection of tetronic acids along this reaction course (TLC and ink-blue sodium nitrite coloration[16]) led us to examine the reaction of tetronic acids **1** and primary alcohols in acidic conditions. As expected, we found that all C-3 unsubstituted compounds **1** yielded enol ethers **4–6**.[‖] With various 3-substituted tetronic acids, the starting materials were recovered, even after a lengthened reaction time.

The structure of these compounds as 4-alkoxy-furan-2(5H)-one derivatives rather than isomeric 2-alkoxy-furan-4(5H)-ones **8** was assigned according to spectral data. In all cases the IR spectrum of the crude reaction mixture exhibited only one lacton stretching frequency at 1780 cm^{-1} attributable only to a α,β-butenolide. The ^{1}H-NMR spectrum displayed an allylic coupling constant $J_{3,5} = 1.5$ cps.

Compounds **2a–e**, in acetonitrile solution were converted to tetronic acids **1a–e** by the action of two equivalents of 50% sulfuric acid at room temperature.

Previously known *O*-alkyl tetronates[17,18] **4,5** (from other routes) have surprising stability and they are only converted in hard acidic conditions to tetronic acids. Interestingly, the hydrogenolysis of the 4-benzyl enol

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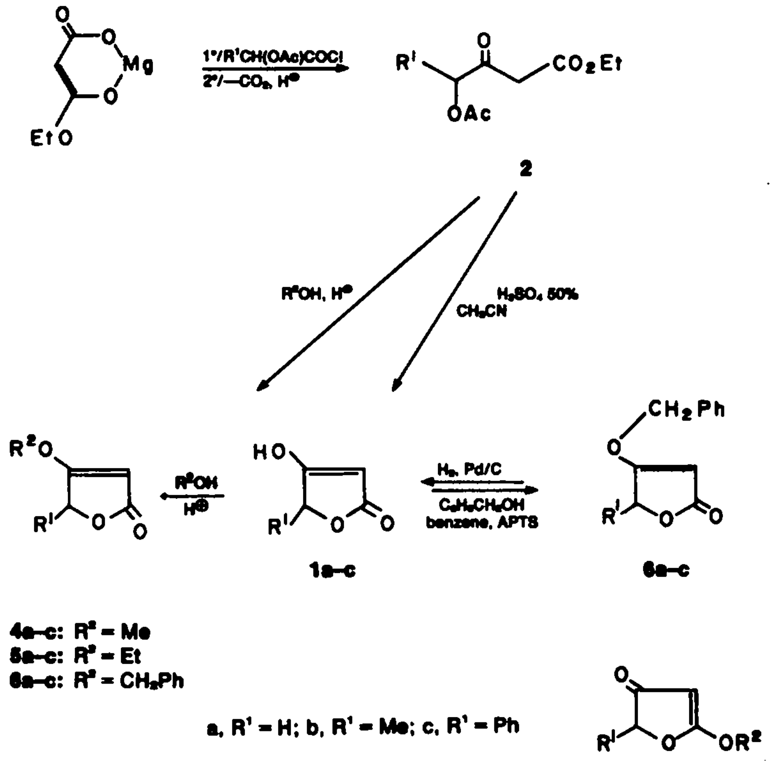
[†] **2a** was also obtained from ethyl 4-diazoacetoacetate.[9]

[‡] This method is unfortunately ineffective with α-acetoxy-α,α-disubstituted acid chlorides.

[§] Monoalkylation of the dianion of monoethyl malonate was recently reported.[12]

[¶] Isopropyl magnesiom bromide was founded superior to magnesium ethoxide or other Grignard reagents. The presence of methylene chloride is essential to the homogeneity of the reaction mixture. Upon prolonged reaction time dimerisation to 2,5-diethoxycarbonyl-1,4-dioxocyclohexane occured in the basic conditions.[13]

[‖] 4-Hydroxy-5,5-disubstituted-furan-2(5*H*)-ones were also converted to enol ethers in the same conditions.



Scheme 1.

ether derivatives 6 with the aid of Pd/C as catalyst, quantitatively afforded the corresponding tetronic acids 1. This behavior allows them to be considered as possible synthons to more sophisticated butenolides with a temporary protected keto group.

The overall procedures are outlined in the scheme

Further investigations on synthesis and reactivity of the tetronic ring systems are in progress.

EXPERIMENTAL

All m.ps were taken on a Kofler block. The IR spectra were obtained with a Beckman Model Acculab 2. The NMR spectra were measured using tetramethylsilane as the internal standard with a Varian A-60 spectrometer. Microanalyses were performed by Microanalytical Laboratory, Centre National de la Recherche Scientifique, Villeurbanne, France.

2-Acetoxyacetic,[19] propionic,[20] phenylacetic acid chlorides,[19] and monoethyl malonate[11,21] were prepared by the procedure employed previously.

Ethyl γ-acetoxyacylacetates 2

General procedure. To a stirred solution of monoethyl malonate (16.5 g, 125 mmol) in methylene chloride (50 mol), isopropyl magnesium bromide in tetrahydrofuran (1 M), was added dropwise until 5.6 l. of propane (250 mmol) were evolved. The green solution was cooled to −10° followed by the addition oyer a 10 min period, of redistilled acetoxy-acid chloride (50 mmol) in methylene chloride (20 ml). The mixture is then immediatly poured into a mixture of 10% iced hydrochloric acid (200 ml)-chloroform (200 ml). After removal of the aqueous solution, the organic layer was washed with saturated sodium bicarbonate solution to basicity, then twice with water, dried and concentrated *in vacuo*. Crude 2a–b, were distillated *in vacuo*; 3c was recrystallized. Washing fractions, upon acidification, ether extraction and careful distillation afforded unreacted monoethyl malonate (5.6–6.4 g, 57–67% of the theoretical recovery amount) which could be conveniently recycled.

Ethyl-4-acetoxy-3-oxobutanoate 2a: (5.64 g 60%), b.p. 91–2°/0.5 torr., lit. 86–87°/0.2 torr[8], m.p. 17–18°, NMR(CCl_4) δ: 1.32 (t, 3 H, J = 7 Hz); 2.13 (s, 3 H); 3.52 (s, 2 H, 90%, keto form); 4.25 (q, 2 H, J = 7 Hz); 4.78 (s, 2 H); 5.27 (s, 1 H, 10% enol form); 12 (s, 1 H, 10%).

Ethyl-4-acetoxy-3-oxopentanoate 2b: (8.1 g, 80%); b.p. 96–97°/0.5 torr., n_D^{23} 1.4325; NMR (CCl_4) δ: 1.26 (t, 3 H, J = 7 Hz); 1.4 (d, 3 H, J = 7 Hz); 2.1 (s, 3 H); 3.55 (s, 2 H, 90%, keto form); 4.23 (q, 2 H, J = 7 Hz); 5.25 (q, 1 H, J = 7 Hz); 5.27 (s, 1 H, 10% enol form); 12 (s, 1 H, 10%). (Found: C, 53.73; H, 7.15. Calc. for $C_9H_{14}O_5$: C, 53.46; H, 6.98%).

Ethyl-4-acetoxy-4-phenyl-3-oxobutanoate 2c: (11.5 g, 88%), m.p. 41° (ether-hexane 50–50). NMR (CCl_4) δ: 1.25 (t, 3 H, J = 7 Hz); 2.23 (s, 3 H); 3.53 (s, 2 H, 90% keto form): 4.2 (q, 2 H, J = 7 Hz); 5.43 (s, 1 H, 10% enol form); 6.3 (s, 1 H); 7.5 (s, 5 H); 12.3 (s, 1 H, 10% enol form). (Found: C, 63.35; H, 6.10. Calc. for $C_{14}H_{16}O_5$: C, 63.62; H, 6.10%).

4-Alkoxy-furan-2(5H)-ones

General procedure. Compounds 4–5. Compounds 2 (15 mmol) (procedure A) or tetronic acids (15 mmol) (procedure B) were added to an approximatively 1% solution of hydrogen chloride in methanol or ethanol (25 ml) the solution was heated at reflux for 4–10 h (Table 1). Evaporation of the volatiles *in vacuo* afforded oils which were dissolved in chloroform (20 ml), washed with aqueous sodium bicarbonate solution, then with water. Drying ($CaCl_2$) followed by removal of solvent and column chromatography (neutral alumina, ether-hexane (3–7 to 4–6) afforded the title compounds which could be further purified by vacuum distillation or recrystallization.

Compounds 6. A solution of 2 (15 mmol) (procedure A) or 1 (15 mmol) (procedure B), *p*-toluene sulfonic acid (200 mg) and benzyl alcohol (3.24 g, 30 mmol) in benzene (50 ml) was refluxed in a flask topped with a water separator for 80 h, and then worked up as precedently described. The results are summarized in Table 1.

Table 1.

Compd	R^1	R^3	Yield%		Reaction time/hrs	m.p. (Solvent) (c)	b.p./torr (c)	I.R. ν max cm^{-1}	^{1}H-NMR($CDCl_3$) δ ppm, JHz
			(a)	(b)					
4a	H	Me	74	75	4	63° [17]	105°/0.5	1760 1635	3.91 (s,3H); 4.62 (d,2H,$J_{3,5}$=1.5); 5.22 (t,1H,$J_{3,5}$=1.5).
4b	Me	Me	80	81	4	12-13°	110°/0.5 (d)	1760 1635	1.35 (d,3H,J=7); 3.92 (s,3H); 4.75 (dq,1H,J=7,$J_{3,5}$=1.5); 5.2 (d,1H,$J_{3,5}$=1.5).
4c	Ph	Me	74	79	10	97° [22]		1770 1650	3.91 (s,3H); 5.25 (d,1H,$J_{3,5}$=1.5); 5.78 (d,1H,$J_{3,5}$=1.5); 7.5 (s,5H).
5a	H	Et	91	93	4	12-13° [18]	100°/0.5	1760 1635	1.42 (t,3H,J=7); 4.19 (q,2H,J=7); 4.65 (d,2H,$J_{3,5}$=1.5); 5.12 (d,1H,$J_{3,5}$=1.5).
5b	Me	Et	81	87	10		105°/0.5 (e)	1760 1635	1.45 (t,3H,J=7); 1.48 (d,3H,J=7); 4.25 (q,2H,J=7); 4.95 (dq,1H,J=7,$J_{3,5}$=1.5); 5.17 (d,1H,$J_{3,5}$=1.5).
5c	Ph	Et	81	87	10	57-58° (f) (pet. ether)		1760 1635	1.38 (t,3H,J=7); 4.16 (q,2H,J=7); 5.2 (d,1H,$J_{3,5}$=1.5); 5.75 (d,1H,$J_{3,5}$=1.5); 7.5 (s,5H).
6a	H	CH_2Ph	61	59	80	103-104° (g) (benzene)		1760 1645	4.72 (d,2H,$J_{3,5}$=1); 5.17 (s,2H); 5.25 (d,1H,$J_{3,5}$=1); 7.5 (s,5H).
6b	Me	CH_2Ph	50	49	80	72° (h) (diisopropylether)		1760 1645	1.5 (d,3H,J=7);4.86 (dq,J=7,$J_{3,5}$=1); 5.1-5.2 (s,3H); 7.5 (s,5H).

(a) Procedure A. (b) Procedure B. (c) Physical data, UV, IR are in agreement with previously published values. (d) C, 56.16; H, 6.15. $C_7H_8O_3$ calcd for C, 56.24; H, 6.29%. (e) C, 59.10; H, 7.25. $C_7H_{10}O_3$ calcd for C, 59.14; H, 7.09%. (f) C, 70.25; H, 5.90. $C_{12}H_{12}O_3$ calcd for C, 70.57; H, 5.92%. (g) C, 69.67; H, 5.27. $C_{11}H_{10}O_3$ calcd for C, 69.46; H, 5.30%. (h) C, 69.89; H, 5.90. $C_{12}H_{12}O_3$ calcd for C, 70.57; H, 5.92%.

Table 2.

Compd	Starting material		Yield %		m.p.
	(a)	(b)	(a)	(b)	(c)
1a	2a	6a	71	91	140-141°
1b	2b	6b	77	86	118-119°
1c	2c		77		142°

(a) procedure A ; (b) procedure B ; (c) physical, spectroscopic data are in agreement with ref.[5-7]

4-Hydroxy-furan-2(5 H)-ones 1

Procedure A. To a stirred solution of compounds 2 (10 mmol) in acetonitrile (10 ml) 50% sulfuric acid (3 ml, 27 mmol) was added. After stirring for 4 h at room temp. the solution was poured into aqueous sodium bicarbonate solution, washed twice with ether, the aqueous layer was acidified (HCl) and continuously extracted with ether for 24 h. Concentration and drying by azeotropic elimination of benzene (50 ml) afforded pure tetronic acids.

Procedure B. A stirred mixture of benzyl ethers 6 (10 mmol), 5% Pd/C catalyst (250 mg) in ethyl acetate (100 ml) was hydrogenated at room temperature and atmosphere pressure until hydrogen uptake ceased (35–45 min for about 235–240 ml). Filtration of the catalyst and evaporation of the filtrate gave crystalline tetronic acids. The results are summarized in Table 2.

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