Tetrahedron Vol. 35, pp. 2181 to 2185
Pergamon Press Ltd., 1979. Printed in Great Britain

REGIOSPECIFIC ALKYLATION OF TETRONIC ACIDS

FORMATION OF 4-ALKOXY-5H-FURAN-2-ONES AND 2-ALKOXY-5H-FURAN-4-ONES

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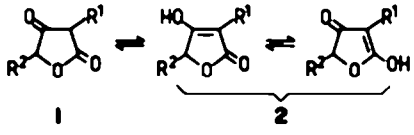
(*Received in UK 22 April 1979*)

Abstract—2-Alkoxy-5H-furan-4-ones (7, 8) and 4-alkoxy-5H-furan-2-ones (4, 5) were prepared regiospecifically and in high yields from tetronic acids (4-hydroxy-5H-furan-2-ones) (2) in the first case by acetylating the 4-OH group and then reacting with trialkyloxonium tetrafluoroborate, and in the second case by alkylating tetrabutylammonium tetronates with dialkyl sulfate, respectively. Direct alkylation of tetronic acids with trialkyloxonium tetrafluoroborate gave in four cases regiospecific 2-O-alkylation, in one case 4-O-alkylation and in two other cases mixtures of 2- and 4-alkoxy derivatives.

Several reports exist on the formation of 4-O-alkyltetronic acids (4-alkoxy-5H-furan-2-ones) from tetronic acids (4-hydroxy-5H-furan-2-ones) 2 and various alkylating agents.[1-6] In no case the possibility of other products being formed is mentioned, and the yields obtained are either not recorded or meager. Some investigators report on preparative problems or complete irreproducibility of the procedures.[3,4,7] 4-Alkoxy-5H-furan-2-ones have also been reported formed upon lactonization of γ-acetoxy-β-keto esters with hydrogen chloride in alcohol.[8]

Because of the tautomeric equilibrium which can exist between the diketo form 1 and its two enolic forms 2, isomeric alkylated products may be formed as demonstrated by the diazomethane methylation of 3-methyltetronic acid (2: R^1 = Me, R^2 = H)[9] behaving analogous



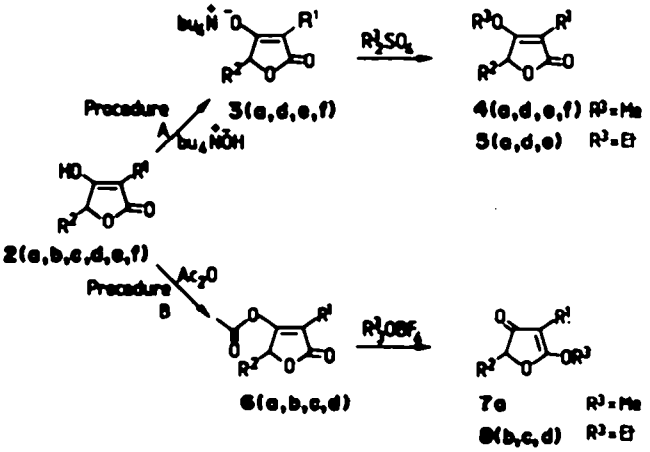
1 2

to the 2,4-pyrandiones.[10] As we are interested[11] in using 2-alkoxy- and 4-alkoxy-5H-furanones as synthons for the synthesis of naturally occurring compounds, we have investigated the alkylation of some tetronic acids (2) and we wish to report on regiospecific procedures leading to 4-alkoxy-5H-furan-2-ones (4, 5) and 2-alkoxy-5H-furan-4-ones (7, 8), respectively.

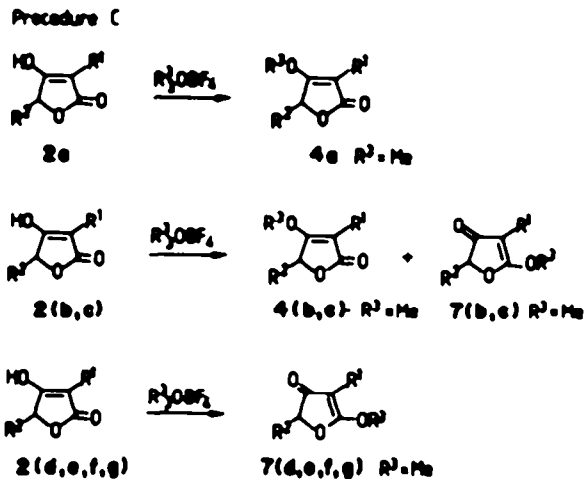
RESULTS AND DISCUSSION

Attempts to prepare the 4-alkoxy-5H-furanones (4, 5) by general methods as treatment of 2 with HCl in alcohol or treating silver or sodium salts of 2 with alkyl iodide or dialkyl sulfate are generally unsuccessful. Considerable high-boiling material, apparently of a di- and polymeric nature from aldol condensations, are obtained along with several other unidentified products. Only methylation with diazomethane affords separable mixtures of 4 and 7.

It has been demonstrated that in many cases the alkylation of a tetraalkylammonium salt of an ambident anion is superior to other methods of alkylation and in some cases it has been the only useful method.[12] Therefore, the tetraethylammonium salt of 2a was prepared and alkylated in dichloromethane with dimethyl sulfate. It resulted not only in a regiospecific introduction of a 4-alkoxy group to give exclusively 4a, but also without introducing a purification step in the direct preparation of 4a in acceptable yield. To test the applicability of the method, some other derivatives (2d, 2e, 2f) were alkyl-



Scheme 1.



	a	b	c	d	e	f	g
R^1	H	H	H	Me	Et	Bz	Me
R^2	H	Me	Et	H	H	H	Me

Scheme 2.

ated. Without purification they all gave exclusively 4-methoxy-(4d, 4e, 4f) and 4-ethoxy-5H-furan-2-ones (5a, 5d, 5e), respectively. These clear cut and preparatively useful results contrast the analogous alkylation procedure of methyl acetoacetate, in which C-alkylation dominates, but with three components in the reaction mixture to separate.[13]

As a result of our attempts to produce 2-alkylated derivatives of tetronic acids (2) we have found that it is possible to achieve a high yield of 2-methoxy (7a) and 2-ethoxy-5H-furan-4-ones (8b, 8c, 8d), respectively, by the following simple method: O-acylation of 2 with acetic anhydride and alkylation of this ester (6) with trialkyloxonium tetrafluoroborate to give after hydrolysis the desired 2-alkoxy derivatives (7, 8). The formation of 2-methoxy-6-methyl-4-pyrone from 4-hydroxy-6-methyl-2-pyrone has been reported with either trimethylsilyl[14] or acetyl blocking groups.[15]

The two regiospecific alkylation procedures described above offer excellent alternatives to previous procedures using diazomethane which involve a laborious separation of the two isomeric products. Nevertheless, it was of interest to explore the direct reaction of tetronic acids with tertiary oxonium salts, since an efficient alkylative conversion of monosubstituted amides to amidates have been achieved in recent years using particularly trialkyloxonium tetrafluoroborate and methyl fluorosulfonate.[16] Recently, Beak and Lee[17] have observed regiospecific alkylation of 4-hydroxy-6-methyl-2-pyrone to give 2-methoxy-6-methyl-4-pyrone and have interpreted their results in terms of kinetically controlled alkylation. Although the mobility of an active hydrogen generally precludes its function as a blocking or directing group in the traditional sense, the above alkylations suggest that in certain cases the proton of a prototropic ambident nucleophile can direct alkylation away from its bonding site in the major tautomer. Five other similar systems behave analogously, e.g. with methyl fluorosulfonate they are methylated at the heteroatom which does not bear the proton in the major tautomer,[17] whereas another report exists in which the alkylating agent does not exhibit the requisite selectivity.[18]

The tetronic acids can be considered as prototropic ambident nucleophiles and upon reaction with trimethyloxonium tetrafluoroborate we find that the unsubstituted tetronic acid (2a) is alkylated at the oxygen carrying the proton giving 4-O-methoxy-5H-furan-2-one (4a) in high yield. In contrast 3-substituted tetronic acids (2d, 2e, 2f, 2g) are all alkylated at the oxygen not carrying the proton to give high yields of 2-alkoxy-5H-furan-4-ones (7d, 7e, 7f, 7g). In a further test of the applicability of the reaction two 5-alkyltetronic acids (2b, 2c) were reacted with the same alkylating reagent to give a mixture of 2-alkylated and 4-alkylated products (4b + 7b and 4c + 7c). In the case of 3-substituted tetronic acids direct alkylation provides a useful alternative for the regiospecific alkylation of the 2-O-alkyl derivatives.

Recently γ-acetoxy-β-ketoesters have been cyclized in alcoholic solution to 4-alkoxy-5H-furan-2-ones.[8] The structure of these compounds was assigned according to spectral data. The IR spectra exhibited an α,β-butenolide stretching frequency at 1760–1770 cm^{-1}, and an allylic coupling constant $J_{3,5}$ = 1.5 c/s was indicated in the ^1H NMR spectrum.

Our results confirm the above assignment since all 4-alkoxy-5H-furan-2-ones (4, 5) exhibit in the IR spectra stretching frequencies at 1745–1780 cm^{-1} and the ^1H NMR spectrum of suitably substituted derivatives display allylic couplings with identical coupling constants. It has also to be mentioned that three of the compounds (4a, 4b, 5a) in the IR spectrum exhibit two bands in the carbonyl region due probably to a Fermi resonance effect.[19] These spectral results contrast the data for the 2-alkoxy-5H-furan-4-ones (7, 8). This is of interest because these latter compounds could not be excluded as cyclization products of γ-acetoxy-β-ketoesters.[8] The 2-alkoxy derivatives all show stretching frequencies at 1865–1700 cm^{-1} characteristic of α,β-un-

Table 1. Summary of experimental and physical data for 4-alkoxy-5H-furan-2-ones and 2-Alkoxy-5H-furan-4-ones

Comp.	R^1	R^2	R^3	Procedure	Yield[a] %			Reaction time/hrs.	Reaction temp/°C	m.p. °C	b.p./ torr °C	IR ν_{max} cm^{-1}			M^+ exp.	M^+ calc. for:
					A	B	C									
1a	H	H	Me	A,C	58		67	1[A,C]	22[A]; ref1[C]	60-65[8]		1780	1740	1625	114.0321	$C_5H_6O_3$: 114.0316
1a	H	H	Et	A	78			30	22		75/0.1[8]	1775	1740	1625	128.0470	$C_6H_8O_3$: 128.0473
1b	H	Me	Me	C			24	1	reflux		100/0.5[8]	1775	1745	1630	128.0476	$C_6H_8O_3$: 128.0473
1d	Me	H	Me	A	59			1	22	ca. 25	93-97/0.3[1]	1750	1675		128.0466	$C_6H_8O_3$: 128.0473
5d	Me	H	Et	A	65			30	22		78-80/0.05[8]	1750	1670		142.0629	$C_7H_{10}O_3$: 142.0629
1e	Et	H	Me	A	65			1	22		83-85/0.05	1750	1665		142.0620	$C_7H_{10}O_3$: 142.0629[b]
1e	Et	H	Et	A	88			72	22		90-93/0.5[23]	1750	1665		156.0770	$C_8H_{12}O_3$: 156.0786
1f	Bz	H	Me	A	58			1	22		154-156/0.1	1745	1665		204.0758	$C_{12}H_{12}O_3$: 204.0786[b]
2a	H	H	Me	B		30		48	22	71-72		1685	1580		114.0327	$C_5H_6O_3$: 114.0316[b]
8b	H	Me	Et	B		60		20	22		70/0.1	1695	1570		142.0641	$C_7H_{10}O_3$: 142.0629[b]
8c	H	Et	Et	B		87		72	22		84-86/0.5	1700	1575		156.0765	$C_8H_{12}O_3$: 156.0786[b]
2d	Me	H	Me	C			49	1	reflux	54-55		1700	1595		128.0463	$C_6H_8O_3$: 128.0473[b]
8d	Me	H	Et	B		93		20	22		65-68/0.1	1690	1605		142.0633	$C_7H_{10}O_3$: 142.0629[b]
2e	Et	H	Me	C			63	1	reflux	ca. 30	90-91/0.1	1690	1600		142.0628	$C_7H_{10}O_3$: 142.0629[b]
2f	Bz	H	Me	C			77	2	reflux		125-127/0.1	1695	1600		204.0764	$C_{12}H_{12}O_3$: 204.0786[b]
2g	Me	Me	Me	C			53	1	reflux		51-52/0.1	1700	1605		142.0617	$C_7H_{10}O_3$: 142.0629[b]

[a]Yields calculated for the alkylation step. [b]New compounds.

Table 2. ^{1}H NMR parameters of 4-alkoxy-5H-furan-2-ones and 2-alkoxy-5H-furan-4-ones[a]

Comp.	R^1	R^2	R^3	5-H (for $R^2 \neq H$)
4a	5.10(t,1H,$J_{5,3}$=1.5)	4.65(d,2H,$J_{3,5}$=1.5)	3.93(s,3H)	cp.R^2
5a	5.03(t,1H,$J_{5,3}$=1.5)	4.53(d,2H,$J_{3,5}$=1.5)	4.13(q,2H,$J_{7,6}$=7);1.10(t,3H,$J_{6,7}$=7)	cp.R^2
4b	5.10(d,1H,$J_{5,3}$=1.5)	1.46(d,3H,$J_{5,6}$=7)	3.93(s,3H)	4.86(dq,1H,$J_{6,5}$=7,$J_{3,5}$=1.5)
4d	1.83(t,3H,$J_{5,6}$=1.5)	4.78(q,2H,$J_{6,5}$=1.5)	4.04(s,3H)	cp.R^2
5d	1.70(t,3H,$J_{5,6}$=1.5)	4.62(q,2H,$J_{6,5}$=1.5)	1.40(t,3H,$J_{8,7}$=7);4.23(q,2H,$J_{7,8}$=7)	cp.R^2
4e	1.10(t,3H,$J_{6,7}$=7);2.26(q,2H,$J_{7,6}$=7)	4.73(s,2H)	4.03(s,3H)	cp.R^2
5e	1.06(t,3H,$J_{6,7}$=7);2.28(q,2H,$J_{7,6}$=7)	4.63(s,2H)	1.33(t,3H,$J_{8,9}$=7);4.20(q,2H,$J_{9,8}$=7)	cp.R^2
4f	3.63(s,2H);7.30(s,5H)	4.70(s,2H)	3.93(s,3H)	cp.R^2
7a	4.86(s,1H)	4.66(s,2H)	4.03(s,3H)	cp.R^2
8b	4.76(s,1H)	1.51(d,3H,$J_{5,6}$=7)	4.30(q,2H,$J_{7,8}$=7);1.46(t,3H,$J_{8,7}$=7)	4.66(q,1H,$J_{6,5}$=7)
8c	4.76(s,1H)	1.02(t,3H,$J_{7,6}$=7);1.93(dq,2H)	1.48(t,3H,$J_{9,8}$=7);4.30(q,2H,$J_{8,9}$=7)	4.63(t,1H,$J_{5,6}$=7)
7d	1.60(s,3H)	4.56(s,2H)	4.06(s,3H)	cp.R^2
8d	1.64(s,3H)	4.56(s,2H)	1.43(t,3H,$J_{8,7}$=7);4.45(q,2H,$J_{7,8}$=7)	cp.R^2
7e	1.03(t,3H,$J_{6,7}$=7);2.13(q,2H,$J_{7,6}$=7)	4.56(s,2H)	4.10(s,3H)	cp.R^2
7f	3.43(s,2H);7.23(s,5H)	4.50(s,2H)	4.00(s,3H)	cp.R^2
7g	1.60(s,3H)	1.50(d,3H,$J_{6,5}$=7)	4.06(s,3H)	4.63(q,1H,$J_{6,5}$=7)

[a]Spectra were run in $CDCl_3$, and Me_4Si was used as an internal standard. Values are recorded in ppm relative to Me_4Si. Observed multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants are in Hz.

saturated cyclic ketones and with C=C stretching vibrations at *ca.* 1590 cm^{-1} (the equivalent values for the 4-alkoxy derivatives are *ca.* 1675 cm^{-1}).

EXPERIMENTAL

M.ps and b.ps are uncorrected. ^1H NMR spectra were recorded on a Jeol C-60 LH spectrometer and IR spectra were obtained with a Perkin–Elmer infrared spectrophotometer 580. Mass spectra were obtained on a Varian 311 A mass spectrometer.

Thin layer and preparative layer chromatography were performed with silica gel 60 F 254 Merck. The regioselectivity of the different procedures could easily be estimated by tlc with ether or dichloromethane as eluents. Upon irradiation with UV light the 4-alkoxyfuranones, which generally have the higher R_f-values, show up by fluorescence and the 2-alkoxyfuranones by absorption.

Compounds **2a**,[20] **2b**,[20] **2c**,[20] **2d**,[20] **2e**,[20] **2f**,[21] and **2g**[20] were prepared by the published procedure.

Procedure A

Tetrabutylammonium tetronates (3). To a stirred soln (100 ml) of 0.427 M aqueous tetrabutylammonium hydroxide was added 0.0427 mol of the tetronic acid. When dissolved (*ca.* 15 min), the mixture was evaporated *in vacuo*. The precipitated crystals were then washed with refluxing EtOAc (15 ml) and filtered hot. *Tetrabutylammonium tetronate* (**3a**), yield: 93%; m.p. 149.5–151°. *Tetrabutylammonium 3-methyltetronate* (**3d**), yield: 92%; m.p. 182–188°. *Tetrabutylammonium 3-ethyltetronate* (**3e**), yield: 94%; m.p. 102–105°. *Tetrabutylammonium 3-benzyltetronate* (**3f**), yield: 88%; m.p. 92–95°.

4-Alkoxy-5H-furan-2-ones (4, 5). The tetrabutylammonium tetronate (16.5 mmol) dissolved in 70 ml CH_2Cl_2 and dimethyl or diethyl sulfate (17.3 mmol) was added. After stirring for the time required (Table 1) the mixture was evaporated *in vacuo*. Water (50 ml) was added and the residual CH_2Cl_2 was removed upon renewed concentration *in vacuo*. The aqueous phase was extracted continuously with ether for 2 × 3 hr. The combined ether extracts were extracted with a very small volume of sat. $NaHCO_3$ aq, dried and evaporated to give crystalline or oily material. All products formed were pure according to NMR and tlc. Scheme 1 gives the compounds synthesized and Tables 1 and 2 summarize the results.

Procedure B

4-Acetoxy-5H-furan-2-ones (6). The enol acetates were prepared by mixing the appropriate tetronic acid with a small excess of Ac_2O and adding a few drops of conc H_2SO_4.[22] After standing at room temp. for 2–3 hr the soln was diluted with $CHCl_3$ and washed with satd $NaHCO_3$ aq. The organic phase was dried, the solvent evaporated and the remaining oil was distilled *in vacuo*. The purity was checked by ^1H NMR. *4-Acetoxy-5H-furan-2-one*, yield: 43%: b.p./torr 100/0.2 mm; NMR ($CDCl_3$): 5.95 (t, 1H, J = 1.5), 4.86 (d, 2H, J = 1.5), 2.33 (s, 3H). *4-Acetoxy-5-methyl-5H-furan-2-one*, yield: 75%; b.p./torr 74–76/0.1 mm; NMR ($CDCl_3$): 6.03 (d, 1H, J = 1.5), 4.93 (dq, 1H, J = 1.5, J = 7), 1.50 (d, 3H, J = 7), 2.33 (s, 3H). *4-Acetoxy-5-ethyl-5H-furan-2-one*, yield: 87%; not distilled; NMR ($CDCl_3$): 6.10 (d, 1H, J = 1.5), 4.86 (m, 1H), 2.36 (s, 3H), 1.86 (m, 2H), 1.00 (t, 3H, J = 7). *4-Acetoxy-3-methyl-5H-furan-2-one*, yield: 90%; b.p./torr 78–80/0.1 mm; NMR ($CDCl_3$): 5.06 (q, 2H, J = 1.5), 2.36 (s, 3H), 1.80 (t, 3H, J = 1.5).

2-Alkoxy-5H-furan-4-ones (7, 8). The enol acetate **6** (10 mmol) in CH_2Cl_2 (10 ml) was treated with either triethyloxonium or trimethyloxonium tetrafluoroborate (10 mmol) under N_2. For time and temp. cp. Table 1. To the stirred soln was cautiously added an excess of satd $NaHCO_3$ aq. The organic phase was dried and the solvent removed *in vacuo*. Crystalline compounds were washed with ether and liquid compounds were purified by distillation.

Procedure C

4-Methoxy-5H-furan-2-one (**4a**). Tetronic acid (**2a**) was alkylated directly with trimethyloxonium tetrafluoroborate as described under procedure B. For details see Tables 1 and 2.

2-Alkoxy-5H-furan-4-ones (7, 8). Direct methylation of **2d**, **2e**, **2f** and **2g** without any blocking group (procedure B) gave the 2-methoxy derivatives **7d**, **7e**, **7f**, **7g** and 3-methyl-tetronic acid (**2d**) gave upon ethylation compound **8d**. Tables 1 and 2 summarize the results.

2-Methoxy-5H-furan-4-ones (**7b**, **7c**) and *4-methoxy-5H-furan-2-ones* (**4b**, **4c**). The two 5-alkylated tetronic acids **2b** and **2c** gave upon direct methylation with trimethyloxonium tetrafluoroborate following procedure B mixtures of as well the 2- as the 4-methylated furanones as easily recognized by tlc and ^1H NMR. Only **4b** was isolated upon preparative layer chromagraphy (see Tables 1 and 2).

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