Substitution and Michael Reactions of Bicyclic Tetronic, Tetramic and Thiotetronic Esters

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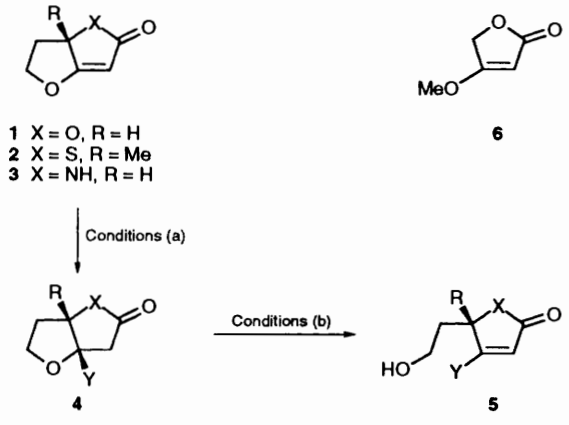
The 1,4-addition of several heteroatom and carbon nucleophiles to the bicyclic structures **1**, **2**, **3** and **13** are reported along with the conversion of the resultant adducts to substituted tetronic, tetramic, thiotetronic acids and butenolides; a novel reaction mechanism has been observed for the iodotrimethylsilane (TMSI) or acetic anhydride/magnesium bromide-mediated furan ring-opening reactions of the bicyclic tetronate **1**.

As part of an ongoing programme aimed towards development of the chemistry and applications in synthesis of tetronic, thiotetronic and tetramic acids, we have prepared a range of bicyclic derivatives[1] and are at present investigating their potential as synthetic intermediates.[2] Our original studies concentrated on the bicyclic derivatives **1**, **2** and **3** and are concerned with their conversion into the corresponding free acids such as **5** (X = NH, O, S; Y = OH; R = H, Me). During our investigation we found that we were able to effect this and other transformations under relatively mild conditions and, somewhat surprisingly, we found that it was also possible in some cases to intercept the intermediate compounds **4** which occur in these processes. For comparison, a series of control reactions were performed using a model system, namely, methyl tetronate **6** (Scheme 1).



Scheme 1 For (a) and (b) see Table 1: X = O, S, NH; R = H, Me; Y = OBn, STol, NHTol, OH, OMe, CF_3CO_2

We were originally interested in developing a range of ring-opening reactions and firstly looked at transesterification; it was found that reactions with methanol were easily effected and led to mixtures of both **4** and **5** (Scheme 1; Table 1, entries 1–5). The reaction of **1** with methanolic camphorsulfonic acid (CSA, catalytic) led to the formation of the substitution product **5** in 81% yield together with the Michael adduct **4** in 13% yield (entry 2). Surprisingly, when the reaction was repeated in the absence of CSA (entry 1) we obtained a high yield (by ^{1}H NMR) of the assumed intermediate from the previous reaction **4**; this result illustrates the reactivity of the system. This intermediate could then be converted into the methyl tetronate **5** by further treatment with methanolic CSA. Similar treatment of the thiotetronate **2** with methanolic CSA gave the methyl thiotetronate **5** in 64% yield together with the intermediate adduct **4** in 34% yield (entry 3). Treatment of the tetramate **3** (X = NH) under acidic conditions (entry 4) again led to a mixture of the two products, but this time favouring the Michael adduct (52% yield) over the product of substitution (36% yield). Interestingly, when the reaction was repeated at reflux (entry 5) the product composition changed fully in favour of the bicyclic product **4** indicating that under these conditions an equilibrium exists between **4** and **5** which strongly favours the bicyclic product **4** over the methyl tetramate **5**. Treatment of **1** or **2** with methanolic CSA at reflux had little effect on the observed ratios, however the existence of the equilibrium was confirmed by experiment, as isolated samples of **5** (X = NH, O or S) are all rapidly converted into the previously observed mixtures when treated in refluxing methanolic CSA. This difference in reactivity and preference for the cyclised product in the reaction of **3** may be due to diminished resonance interactions between the amide and enol ether function present in the disfavoured methyl tetramate product.†

Heterocycles **1**–**3** were treated with further oxygen, sulfur and nitrogen nucleophiles again yielding either **4** or **5**. The tetronate **1** reacted smoothly with benzyl alcohol (entry 6) under acid catalysis to yield the Michael product **4** which was characterisable by ^{1}H NMR but underwent rearrangement to the ring-opened product **5** on chromatography. The reaction of **1** with *p*-thiocresol (entry 7) was rapid, required no catalysis and gave the Michael adduct **4** in 95% yield; attempted rearrangement of the adduct to the ring-opened product under acid catalysis led only to decomposition. The thiotetronate **2** required base catalysis to effect the same transformation, however it did so in 95% yield (entry 8). In the reaction of **1** with *p*-toluidine (entry 9) we were unable to observe (^{1}H NMR) the Michael product and obtained instead an 88% yield of the ring-opened substitution product **5**. The reaction of the thiotetronate **2** with *p*-toluidine was slow and required reflux in chloroform to effect the formation of a low yield of the substitution product **5**; the reaction was accompanied by considerable decomposition, probably due to thio ester cleavage (entry 10).

The reaction of heterocycles **1** or **3** with trifluoroacetic acid (entries 11 and 13) was surprising in that the Michael adducts **4** were obtained in near quantitative yield, indicating the ease with which the system will react with even poor nucleophiles; on further reaction of these adducts with aqueous trifluoroacetic acid the free tetronic and tetramic acids were obtained in good yield. In contrast, the reaction of the thiotetronate **2** with

† To support this, it is also known that tetramic acid has an unenolised and thus an unconjugated structure in neutral solution, whereas the tetronic or thiotetronic acids exist in enolised form.[3]

Table 1 Reactions of compound **1**

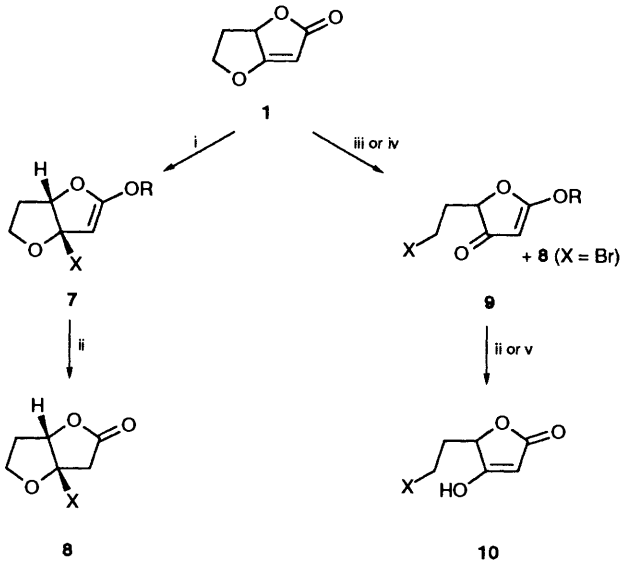
Entry	X	R	Conditions (a)[a]	Y	Yield (%) 4	5	Conditions (b)[a]	Y	Yield 5
1	O	H	MeOH/48 h	OMe	72[b]	—			
2	O	H	MeOH/CSA/48 h	OMe	13	81			
3	S	Me	MeOH/CSA/48 h	OMe	34	64			
4	NH	H	MeOH/CSA/48 h	OMe	52	36			
5	NH	H	MeOH/CSA/heat/48 h	OMe	95	—[c]			
6	O	H	BnOH/CSA/48 h	BnO	95[b]	—	Silica gel	BnO	52
7	O	H	TolSH/2 h	TolS	95	—			
8	S	Me	TolSH/DBU(cat)/24 h	TolS	95	—			
9	O	H	$TolNH_2$/8 h	TolNH	—[c]	88			
10	S	Me	$TolNH_2$/heat/$CHCl_3$/72 h	TolNH	—[c]	32[d]			
11	O	H	TFAH/neat/30 min	TFA[e]	95	—	H_2O	OH	50[f]
12	S	Me	TFAH/$CHCl_3$/168 h	TFA[e]	9	91	H_2O	OH	65[f]
13	NH	H	TFAH/neat/2 h	TFA[e]	95	—	H_2O	OH	77[f]

[a] All reactions in dichloromethane at room temp. unless otherwise stated. [b] >95% by NMR, ring opens on silica. [c] Not observed by NMR. [d] Accompanied by extensive decomposition. [e] TFA = trifluoroacetoxy. [f] In equilibrium with **4** (Y = OH).

trifluoroacetic acid (entry 12) was sluggish and over the 7-day reaction period it was possible to observe (^{1}H NMR) the slow formation of the intermediate adduct **4** and its subsequent rearrangement to the major substitution product **5**. The slow reaction of **2** and relative instability of the adduct **4** can be rationalised by considering the steric hindrance created by the methyl group present in **2**. The mixture obtained was easily converted into the free thiotetronic acid on aqueous hydrolysis. In contrast to these results a series of control experiments were performed on methyl tetronate **6**, which proved to be totally inert to all of the reaction conditions described even with prolonged reaction times. To the best of our knowledge mild transesterification/substitution reactions of this type have not been reported for tetronates or tetramates.*

We were also interested in the reaction of iodotrimethylsilane (TMSI) with these systems since it is a reagent that has previously been reported to effect the de-esterification of methyl[5] or benzyl tetronates[6] and the ring-opening of tetrahydrofurans.[7] Indeed, in our hands treatment of methyl tetronate **6** with a two-fold excess of TMSI in chloroform led to the slow formation of an intermediate silyl enol ether; the reaction proceeded to 75% completion (^{1}H NMR) after 2 weeks at room temperature and on hydrolysis this intermediate gave free tetronic acid. By contrast, on treatment of **1** with a slight excess of freshly prepared TMSI we observed the rapid (30 min) formation of the silyl enolate **7** (X = I, R = TMS) (by ^{1}H NMR) which on careful hydrolysis led to the iodonated lactone **8** (X = I) in good overall yield (Scheme 2). The intermediate **7** has arisen from 1,4-addition of TMSI to tetronate **1** and its rapid formation presents a stark contrast to the previous result involving methyl tetronate. By careful observation (^{1}H NMR) it was shown that no stable intermediates of this type were present in the reaction of TMSI with methyl tetronate **6**. Further reaction of **1** with an excess of TMSI for 14 h led to the formation of the ring-opened product **9** (X = I, R = TMS) (^{1}H NMR), the furan ring being cleaved in analogy with previous reports.[7] Hydrolysis of **9** gave the free tetronic acid **10** (X = I) in 59% overall yield.

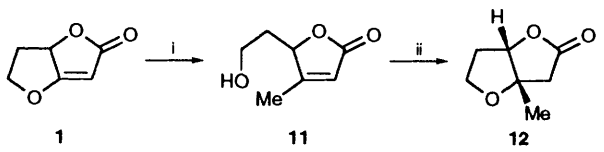
A similar reaction is observed on treatment of **1** with acetic anhydride and magnesium bromide in acetonitrile, conditions previously used for the ring-opening of tetrahydrofurans.[8] Under these conditions a ring-opened enol acetate **9** (X = Br, R = Ac) was formed in 84% yield. The reaction is thought to proceed *via* the intermediate **7** (X = Br, R = Ac), in a parallel mechanism to that for TMSI; evidence for this is that a small quantity (*ca.* 5%) of the bicyclic product **8** (X = Br), which has arisen from hydrolysis of **7**, is isolated. The initial step in the reaction is thus assumed to be the conjugate addition of a bromide ion to **1** under Lewis acidic conditions followed by trapping of the enolate as an acetate and subsequent ring-opening by a further bromide ion. Acidic hydrolysis of **9** gave the free tetronic acid **10** (X = Br) in 70% yield.



Scheme 2 *Reagents and conditions:* i, 1.1 equiv. TMSCl, NaI, MeCN, 30 min (X = I, R = TMS); ii, NH_4Cl(aq.) (X = I); iii, 1.5 equiv. TMSI, MeCN, 14 h (X = I, R = TMS); iv, Ac_2O, $MgBr_2$, MeCN, 24 h (X = Br, R = Ac); v, CF_3CO_2H(aq.) (X = Br).

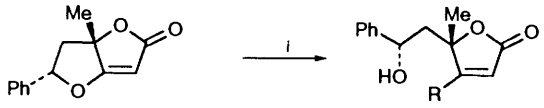
Following these findings we were interested in the reaction of the bicyclic tetronate esters **1** with carbon nucleophiles, particularly dialkylcuprates because of their known preference to undergo 1,4-additions. Our initial attempts using simple and higher order cuprates were unsuccessful, probably due to competitive deprotonation of the tetronate starting material and some instability of the intermediate enolates. However, it was found that on addition of an excess of trimethylsilyl chloride to act as a trap for these intermediates it was possible to obtain a substitution product **11** in 50% yield together with some addition product **12** in 3% yield. The latter is easily prepared by treatment of **11** with a catalytic quantity of DBU[9] (Scheme 3).

* There has, however, been one report of a transesterification of methyl tetramate under forcing conditions (BnOH, methanesulfonic acid, 24 h, 80 °C, 20 mbar).[4]



Scheme 3 *Reagents and conditions:* i, Me_2CuLi_2I (1.5 equiv.), TMSCl (10 equiv.), THF, Et_2O, −20 °C, 5 min; ii, DBU (0.2 equiv.), $CHCl_3$ (80%)

Competitive deprotonation was shown to be the main cause of decomposition, since similar reactions involving **13** in which the acidic position (C-8) is blocked by a methyl group were cleaner and higher yielding. Reaction of **13** with either dimethyl- or dibutyl-cuprate resulted in the formation of the vinylic substitution products **14** in 75 and 70% yield respectively. Several other minor by-products were also isolated which have arisen from single and double addition of the cuprate (Scheme 4).



Scheme 4 *Reagents and conditions:* i, 6.0 equiv. R_2CuLi_2I, HMPA, THF, hexane, −20 °C, 1 h (R = Me, Bu)

These results represent, to the best of our knowledge, the first report of a conjugate addition of a carbanion to a tetronate, indeed our own model studies of dialkylcuprate additions to methyl tetronate **6** showed its inertness to all the reaction conditions employed above.

This reactivity of substrates **1**, **2**, **3** and **13** towards addition and substitution can be rationalised by consideration of the strain imposed on the bicyclic structures by the double bond present at the 5,5-ring junction. Relief of this strain is obviously a thermodynamically favourable process which consequently aids the addition of the incoming nucleophile. The development and further application of these reactions will be reported in due course.

Experimental

Typical Experimental Procedure: 3a-*Methoxytetrahydrofuro*[3,2-b]*furan-2-one* **4** (X = O, R = H, Y = OMe) *and* 5-(2-*Hydroxyethyl*)-4-*methoxyfuran*-2(5H)-*one* **5** (X = O, R = H, Y = OMe) (*Entry 2, Table 1*).—6,6a-Dihydrofuro[3,2-*b*]furan-2(5*H*)-one **1** (144.9 mg, 1.15 mmol) and camphorsulfonic acid (20 mg), were dissolved in dry methanol (2 cm^3) and the reaction mixture stirred at room temperature for 48 h. Removal of solvent followed by chromatography of the residue gave **4** (X = O, R = H, Y = OMe) (23.6 mg, 0.149 mmol, 13%) as an oil (chromatography solvent 50% diethyl ether in light petroleum, R_f 0.28); δ_H 2.22 (1 H, m, CH), 2.36 (1 H, m, CH), 2.78 (1 H, d, *J* 17.4, CH), 2.93 (1 H, d, *J* 17.4, CH), 3.33 (3 H, s, OMe) 4.03 (1 H, m, CH), 4.13 (1 H, m, CH) and 4.78 (1 H, dd, *J* 1.9, 6.2, CH); δ_C 30.70 (CH_2), 38.24 (CH_2), 51.30 (CH_3), 67.85 (CH_2), 86.03 (CH), 111.37 (C) and 172.72 (C); ν_{max}/cm^{-1} 2942, 2838 (CH) and 1790 (C=O); *m*/*z* (EI) 158 (25%, M^+) and 127 (5%, M^+ − MeO). Further elution gave **5** (X = O, R = H, Y = OMe) (147.0 mg, 0.930 mmol, 81%) as a white solid (chromatography solvent 20% ethyl acetate in diethyl ether, R_f 0.20); m.p. 68–69 °C; δ_H 1.71 (1 H, m, CH), 2.10 (1 H, br s, OH), 2.16 (1 H, m, CH), 3.73 (2 H, dd, *J* 5.2, 6.9, CH_2), 3.84 (3 H, s, OMe), 4.90 (1 H, dd, *J* 3.5, 9.0, CH) and 5.01 (1 H, s, CH); δ_C 34.75 (CH_2), 58.00 (CH_2), 59.48 (CH_3), 76.23 (CH), 88.20 (CH), 172.79 (C) and 183.03 (C); ν_{max}/cm^{-1} 3470 (OH), 1722 (C=O), 1626 (C=C); *m*/*z* (EI) 158 (45%, M^+); λ_{max}/nm 220 (ε 11 000) (Found: C, 53.4; H, 6.8. $C_7H_{10}O_8$ requires C, 53.16; H, 6.37%).

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