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CYCLIZATIONS OF ACETOACETATES TO α-ACYLTETRONIC ACIDS

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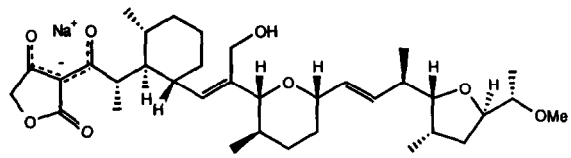
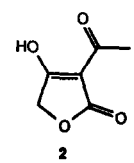
Summary: Cyclizations of β-ketoesters derived from α-hydroxyacetates have proven problematic; adjustment of reaction conditions allows for good yields of the γ-unsubstituted-α-acyltetronic acid.

As part of our studies towards the synthesis of the ionophoric antibiotic M139603 (1)[1], we required a method for the preparation of the γ-unsubstituted-α-acyltetronic acid (2). This problem has also been encountered by others.[2] This paper describes a simple, direct approach for the synthesis of the tetronic acid (2) which constitutes the first high yielding preparation of this γ-unsubstituted compound.



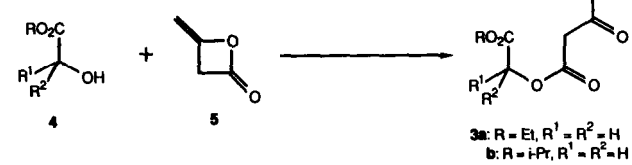
1



2

Our first approach followed the published method for the cyclization of α-substituted derivatives of ethyl glycolate (3; R^1 or $R^2 \neq H$).[3] This ester (3a) was, in turn, prepared from the a-hydroxyester (4) and diketene (5) in excellent yield (>95%) (Scheme 1).[4]

Treatment of the β-ketoester with diisopropylaminomagnesium iodide



4 5 3a: R = Et, $R^1 = R^2 = H$
b: R = i-Pr, $R^1 = R^2 = H$

Scheme 1.

resulted only in the recovery of 3a;[4,5] no cyclized product (2) was detected. These initial findings surprised us although the literature does suggest that the cyclization is sensitive to the substitution in the

α-alkoxyacetate moiety. For example, with sodium in toluene, the disubstituted tetronic acid was formed from 3 (R = Et, R^1 = R^2 = Me) in 67% yield, while the monosubstituted analogue from 3 (R = Et, R^1 = Me, R^2 = H) was obtained in 50% yield. Certainly, the reaction is known to be sensitive to the metal counterion.[4,6,7]

A variety of bases and solvents were employed to effect the cyclization and the results are summarized in the Table. With lithium as the counterion, the starting material (3a or 3b) was recovered unchanged. Deprotonation was occurring as trapping with methyl iodide resulted in a 75% yield of the O-methyl enol ether (6). The analogous reaction with

$EtO_2CCH_2OCOCH{=}C(OR)Me$

6: R = Me
7: R = $SiMe_3$

chlorotrimethylsilane resulted in almost complete conversion to 7.[8] Thus, the absence of a substituent at the carbon atom juxtaposed to the ethyl carboxylate group does not promote significant deprotonation at this position. As cyclization was only observed with a lithium counterion in the presence of HMPA, it was concluded that an oxygen metal bond with considerable ionic characteristics must be present for cyclization to occur. Although sodium hydride in THF at ambient temperature did not effect the required transformation, limited success was achieved under more vigorous conditions. Use of t-butanol as solvent, however, gave good yields of the tetronic acid (2). Comparable, although slightly lower yields were obtained with a potassium counterion.

The use of tetrabutylammonium fluoride has been advocated for the cyclization of γ-substituted-α-acyltetronic acids.[2,7] This reagent brought about the required transformation, but in significantly higher yield with the isopropyl ester (3b) as substrate.[9]

Overall, a counterion which provides an enolate with significant ionic character is required for the cyclization of 3 to 2. The transformation is aided by use of a polar solvent. These two effects are not surprising.

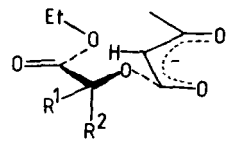


Figure.

However, the reluctance of the unsubstituted esters (3a and 3b) to cyclize compared with the substituted analogues is not so obvious and the role of the alkyl groups in promoting cyclization is more subtle. The absence of

TABLE

Cyclizations of β-ketoesters to α-tetronic acid (2).

Ester	Reagent	Solvent	Conditions	Yields (%)[a] 3	2	Other
3a	$i\text{-Pr}_2\text{NMgI}$	Et_2O	Δ/24h	73	–[b]	–
		dioxan	"	75	–	–
	$i\text{-Pr}_2\text{NLi}$	Et_2O	$-78^o \rightarrow$rt[c]/24h[d]	80	–	–
		THF	Δ/24h	81	–	–
		THF/TMEDA[e]	$-78^o \rightarrow$rt/24h	80	–	–
		THF/HMPA[e]	"	–	70	–
	$BF_3.OEt_2$	Et_2O	0^o/1h	85	–	–
	NaH	THF	rt/24h	82	–	–
			Δ/24h	40	43	–
		neat[f]	150^o/24h	–	60	15
3b	NaH	THF	Δ/24h	<5	79	–
	NaOBu-t	t-BuOH	"	44[g]	33[g]	–
3a	NaOBu-t	THF	Δ/24h	<1	75	–
		t-BuOH	"	<1	80	–
	KOBu-t	THF	"	<5	75	–
		t-BuOH	"	<1	73	–
3b	KOBu-t	t-BuOH	Δ/24h	–	75	5
	Morpholine,TsOH[h]	C_6H_6	"	80	–	–
3a	NBu_4F[i]	THF	rt/12h	<10	56	–
3b	NBu_4F	THF	rt/12h	<4	78	–

[a] Yields are by nmr and glc which gave results within ±2%.
[b] Denotes not detected.
[c] Denotes room temperature.
[d] The reaction mixture was allowed to warm slowly to rt after the addition of the ester.
[e] The additive was present at a concentration of 5%.
[f] The reaction was performed in the hydrocarbon present from the commercial hydride suspension.
[g] For reasons not readily apparent, this reaction gave various ratios of 3:2 - the best result is quoted.
[h] The enamine is formed in this reaction. In a separate experiment methyl iodide was introduced after the heating period before aqueous work up and the C-methylated analogue of 3b was formed.
[i] The best results were obtained with the fluoride obtained as a solution in THF.

substituents in the α-alkoxyester moiety could promote kinetic deprotonation at this position but the much lower pK_a of the β-ketoester portion in

conjunction with the trapping experiments described above greatly detract from this explanation. Molecular model studies show that the transition state is very crowded, but the presence of a γ-substituent has little effect on the overall energy profile (see figure).[10,11] The preferred conformation of the enolate prior to cyclization would seem to be an open chain form. Introduction of a substituent in the α-alkoxyester part increases the steric interactions between this substituent and the enolate or ester moieties (ca 2-3 kCal/mol). This small difference can be related to steric interactions between the γ-substituents and the ester and enolate moieties. In the unsubstituted cases (**3a** and **3b**) these interactions are at a minimum. When γ-substituents are present, particularly in the disubstituted series, the steric interactions between the substituent and the functional groups could move the preferred conformation towards that required for cyclization to occur. The more forcing conditions required for cyclization of the unsubstituted cases are consistent with this argument. The higher yields associated with the isopropyl ester (**3b**) may be the result of isopropanol being a better leaving group provided there is a late transition state.

The reasons for the slight advantage of sodium over potassium or tetraalkylammonium are not clear. However, a high yielding route to **2** has been found.

References and Notes:

1. D. H. Davies, E. W. Snape, P. J. Suter, T. J. King, and C. P. Falshaw, J. Chem. Soc., Chem. Commun., 1981, 1073.
2. S. V. Ley, P. M. Booth, and C. M. Fox, J. Chem. Soc., Perkin Transactions I, 1987, 121.
3. L. J. Haynes and A. H. Stanners, J. Chem. Soc., 1956, 4103.
4. R. N. Lacey, J. Chem. Soc., 1954, 832.
5. F. C. Frostick and C. R. Hauser, J. Am. Chem. Soc., 1949, 71, 1350.
6. J. L. Bloomer and F. E. Kappler, J. Chem. Soc., Perkin Transactions I, 1976, 1485.
7. S. V. Ley, P. M. Booth, and C. M. Fox, Tetrahedron Lett., 1983, 24, 5143.
8. Reaction of **7** with a Lewis acid did not result in formation of the cyclic compound **2**.
9. Attempts were made to perform this reaction with the t-butyl ester but all efforts to prepare the precursor failed.
10. The cyclization, as it is derived from a β-ketoester, may be viewed as either a 5-(enolendo)-exo-trig or a 5-(enolexo)-exo-trig process by Baldwin's nomenclature (see ref. 12). The 5-(enolendo)-exo-trig process is not favored compared to the 5-(enolexo) analogue (a Dieckmann type cyclization), but the limitations imposed by the planarity of the conjugated β-ketoester enolate system certainly places severe restrictions upon the transition state for the cyclization. The trapping experiments described in the text suggest that the preferred tautomer of the enolate is that which gives rise to the favored cyclization process.
11. The molecular modelling studies were performed with MacroModel.
12. J. E. Baldwin and M. J. Lusch, Tetrahedron, 1982, 39, 2939.

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