One-Pot Synthesis of Tetronic Acids from Esters

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Dedicated to the memory of the late Dr. Charles Mioskowski

Abstract: Tetronic acids substituted by various groups were synthesized in one pot from the corresponding aryl- or heteroarylacetic acid esters and hydroxyacetic acid esters, by a tandem process involving a transesterification and a subsequent Dieckmann cyclization.

Key words: cyclizations, esters, heterocycles, lactones, ring closure

Many natural products having biological properties contain in their structure a tetronic acid, or 4-hydroxybutenolide, moiety (Figure 1).[1] Examples of these natural products include ascorbic acid, or vitamin C, and pulvinic acid, a member of a large family of mushroom pigments.[2]

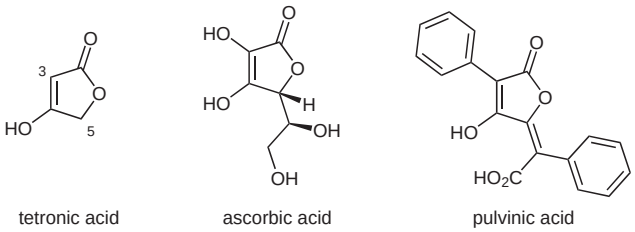
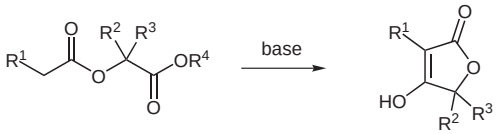


Figure 1 Structures of tetronic acid (parent compound), ascorbic acid, and pulvinic acid

Several synthetic methods to generate tetronic acids have been developed.[1] Among these methods, the Dieckmann cyclization has been widely employed and is still of much use.[3,4] It relies on the treatment of a glycolic ester with a base (Scheme 1).



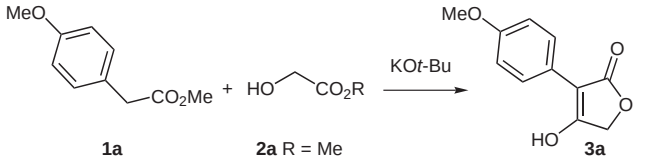
Scheme 1 Usual preparation of tetronic acids via Dieckmann condensation

We recently became interested in the synthesis of 3-aryltetronic acids. Such compounds have been reported as insecticides,[5] anti-oxidant, and anti-inflammatory compounds,[6] and could also be of use as building blocks in the synthesis of pulvinic acids.[7] We envisaged to prepare these compounds from substituted alkyl arylacetates, which are readily available from the corresponding aryl halides or aryl triflates, owing to recently reported cross-coupling methods.[8]

We reasoned that under certain conditions, it would be possible to effect the direct preparation of tetronic acids from an alkyl arylacetate and an alkyl hydroxyacetate. This implies that a transesterification process would occur at first, the diester formed being then suitable for the Dieckmann condensation. In this Letter, we report our first results concerning this study.

Various bases have been employed to realize the Dieckmann condensation. We chose to use potassium *tert*-butoxide (2.2 equiv), available in anhydrous form as a solution in THF. The conditions tested using methyl 4-methoxyphenylacetate **1a** and methyl glycolate **2a** as the two components of the process, either in THF or in DMF, are summarized in Table 1.

Table 1 Optimization of the Preparation of Tetronic Acid **3a**



1a (1 equiv) **2a** R = Me **2b** R = Et (1.1 equiv) **3a**

Entry	R	KO*t*-Bu (equiv)	Solvent	Temp	Time (h)	Yield (%)
1	Me	2.2	THF	r.t.	16	67
2	Me	2.2	THF	reflux	2	79
3	Me	2.2	THF	reflux	16	85
4	Me	2.2	DMF	r.t.	2	90
5	Me	2.2	DMF	r.t.	16	90
6	Et	2.2	DMF	r.t.	3	66
7	Me	1.1	DMF	r.t.	16	34

In THF, the reaction proceeded readily at room temperature, leading to the expected 4-hydroxy-3-(4-methoxyphenyl)-2-(5*H*)furanone (**3a**)[9] in 67% yield after 16 hours (entry 1). At reflux, the reaction occurred more rapidly (entry 2), although the best result was obtained after 16

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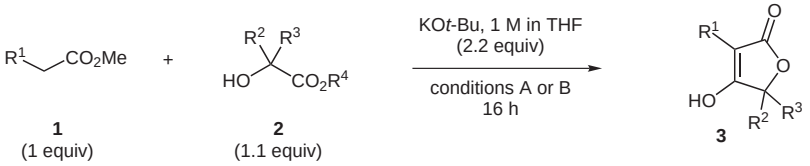
Table 2 One-Pot Preparation of Tetronic Acids **3**



1 (1 equiv) **2** (1.1 equiv) **3**

Entry	Ester **1**	Hydroxyester **2**	Product **3**	R^1	R^2	R^3	R	Conditions[a]	Yield (%)
1	**1b**	**2a**	**3b**	Ph	H	H	Me	A	97
2	**1c**	**2a**	**3c**	4-BrC_6H_4	H	H	Me	A	61
3	**1c**	**2a**	**3c**	4-BrC_6H_4	H	H	Me	B	59
4	**1d**	**2a**	**3d**	thien-2-yl	H	H	Me	B	70
5	**1a**	**2c**	**3e**	4-MeOC_6H_4	H	Me	Me	A	97
6	**1a**	**2c**	**3e**	4-MeOC_6H_4	H	Me	Me	B	96
7	**1a**	**2d**	**3f**	4-MeOC_6H_4	Me	Me	Me	A	72
8	**1a**	**2d**	**3f**	4-MeOC_6H_4	Me	Me	Me	B	64
9	**1a**	**2e**	**3g**	4-MeOC_6H_4	H	Bu	Et	B	60
10	**1a**	**2f**	**3h**	4-MeOC_6H_4	H	Ph	Me	B	39

[a] Conditions A: THF, reflux; conditions B: DMF, r.t.

hours (85% yield, entry 3).[10] In DMF, the reactions were all carried out at room temperature. After two hours, a very good yield was obtained, which was not improved after 16 hours (entries 4 and 5).[10] The reaction also proceeded well using ethyl glycolate **2b** (entry 6). A reaction performed using only 1.1 equivalents of KO*t*-Bu led to a much lower yield of adduct (entry 7).

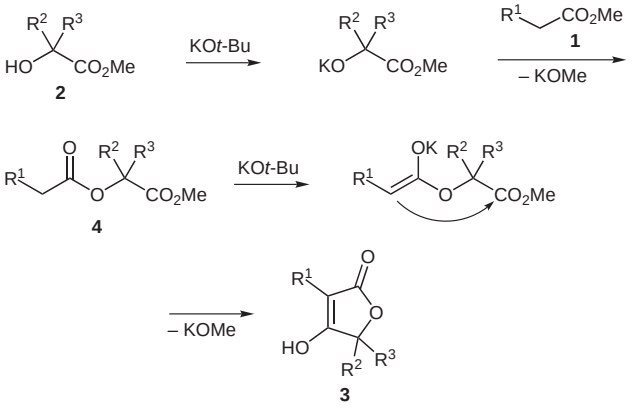
It is worthy of note that the preparation of compound **3a**, carried out on a larger scale, by the usual Dieckmann condensation was reported to proceed in 67% yield,[9] while our one-pot process afforded **3a** up to 90% yield.

The preparation of other tetronic acids was then realized, as summarized in Table 2. On the basis of our preliminary study, two conditions were applied: either in THF at reflux (conditions A) or in DMF at room temperature (conditions B). All the reactions were ran overnight (16 h), because shorter reaction times led to incomplete reactions in some cases.

At first, several tetronic acids were prepared from methyl glycolate **2a** and methyl acetates **1b**–**d** substituted by phenyl, 4-bromophenyl, and thien-2-yl groups, respectively (entries 1–4). They were obtained in 59–97% yield. Using either conditions A or B, tetronic acid **3c** was obtained in almost the same yield (entries 2 and 3).

Then, tetronic acids substituted at C_5 were prepared from methyl 4-methoxyphenylacetate (**1a**) and hydroxyesters **2c**–**f** (entries 5–10). Conditions A and B were found to be equally efficient in producing tetronic acid **3e**, substituted at C_5 by a methyl group (97% and 96% yield, entries 5 and 6). They also allowed the preparation of C_5-disubstituted tetronic acid **3f** (72% and 64% yield, entries 7 and 8). The reaction of **1b** with ethyl 2-hydroxyhexanoate **2e** yielded the corresponding adduct **3g** in 60% yield (entry 9). The reaction with methyl mandelate **2f** was found to be more sluggish, leading to the expected C_5-phenyl-substituted tetronic acid **3h** in only 39% yield (entry 10).

The overall pathway leading to the formation of the tetronic acids is depicted in Scheme 2. A transesterification of the methyl ester **1** by the alkoxide generated by deprotonation of hydroxyester **2** would yield ester **4**, which can then be converted to the corresponding tetronic acid by the usual Dieckmann condensation.



Scheme 2 Tandem transesterification–Dieckmann cyclization pathway

In conclusion, we report a direct synthesis of tetronic acids from a hydroxyester and an aryl- or heteroarylacetate by a one-pot method, which should be of value particular-

ly in the context of a total synthesis. This is a tandem process involving a transesterification and a subsequent Dieckmann condensation. Tetronic acids that are either unsubstituted, monosubstituted, or disubstituted at C_5 can be obtained from the corresponding hydroxyacetates. Further developments based on this tandem process are currently under way.

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(10) **Typical Experimental Procedures for Compound 3a**
In DMF: To a solution of methyl 4-methoxyphenylacetate (0.318 mL, 2.0 mmol) and methyl glycolate (0.170 g, 2.2 mmol) in DMF (10 mL) was added a 1 M solution of KO*t*-Bu in THF (4.4 mL, 4.4 mmol). The solution was stirred under argon at r.t. for 2 h. The reaction mixture was then poured into cooled 1 N HCl (15 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL), the combined organic layers were washed several times with brine, dried over Na_2SO_4. After filtration and concentration in vacuo, the residue was purified by column chromatography [silica gel, 200:1, then CH_2Cl_2–MeOH (95:5) containing 0.2% AcOH], to give compound **3a** as a white solid (0.370 g, 90%).
In THF: To a solution of methyl 4-methoxyphenylacetate (0.318 mL, 2.0 mmol) and methyl glycolate (0.170 g, 2.2 mmol) in anhyd, degassed THF (10 mL) was added a 1 M solution of KO*t*-Bu in THF (4.4 mL, 4.4 mmol). The suspension obtained was refluxed under argon for 16 h. After cooling to r.t., the reaction mixture was poured into 1 N HCl (15 mL). Treatment and purification as above afforded compound **3a** as a white solid (0.350 g, 85%).
Compound **3a**: mp 228 °C (lit. 9: 228–229 °C). IR (neat): 2955, 1695, 1641, 1610, 1514, 1426, 1398, 1351, 1297, 1256, 1169, 1053, 1030, 1022, 960, 836, 736 cm^{-1}. ^1H NMR (400 MHz, acetone-d_6): δ = 3.81 (s, 3 H, OCH_3), 4.76 (s, 2 H, CH_2), 6.95 (d, *J* = 9.0 Hz, 2 H, CH), 7.94 (d, *J* = 9.0 Hz, 2 H, CH), 10.94 (br s, 1 H, OH). ^{13}C NMR (100 MHz, acetone-d_6): δ = 55.5 (OCH_3), 66.6 (C_5), 100.3 (C_3), 114.3 ($C_{3'}$), 123.8 ($C_{1'}$), 129.2 ($C_{2'}$), 159.4 ($C_{4'}$), 172.1, 173.5 (C_2, C_4). MS (ESI-TOF): *m/z* = 207 $[M + H]^+$.