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A FACILE SYNTHESIS OF SIMPLE TETRONIC ACIDS AND PULVINONES

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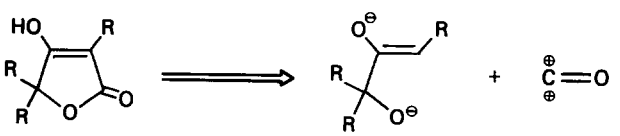
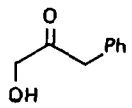
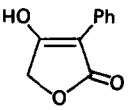
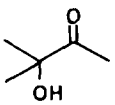
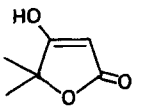
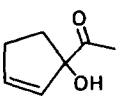
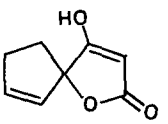
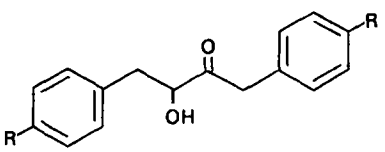
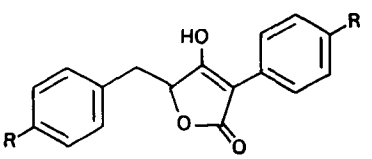
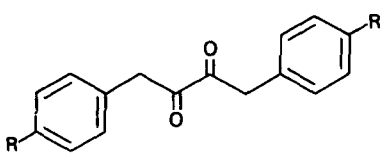
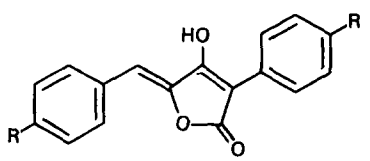
Summary: Condensation of the dianions derived from simple α-hydroxyketones and 1,2-diketones with 1,1'-carbonyldiimidazole provides a facile one step synthesis of tetronic acids and pulvinones.

Although a number of synthetic strategies to tetronic acids are on record,[2] most are multistep and at best proceed only in moderate yield. In connection with another investigation, we developed a general one step synthesis of simple tetronic acids and pulvinones (i.e. 2-phenyl-4-benzylidenetronic acids), respectively from readily available α-hydroxyketones and 1,2-diketones. From a retrosynthetic perspective, we reasoned that condensation of the dianion derived from a variety of α-hydroxyketones, through agency of an amide base, would yield the desired tetronic acid derivative upon addition of an appropriate carbonyl equivalent. An ideal candidate for the required carbonyl equivalent appeared to be 1,1'-carbonyldiimidazole. Similarly, by taking advantage of the dianion derived from suitable 1,2-diketones, condensation with carbonyldiimidazole was expected to yield pulvinone derivatives.



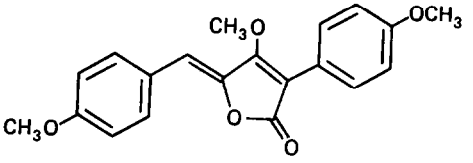
We are pleased to report that this is indeed the case; our results are illustrated in Table I. Several comments are in order. First, although the reported condensation proceeds only in modest yield (31-57%),[4] the approach is economical in

Table 1: Synthesis of Simple Tetronic Acids and Pulvinones

Substrate[3]	*Tetronic acid or pulvinone*[3]	*Yield (percent)*[4]
		57
(1)[5]	(8)[11]	
		48
(2)[6]	(9)[12]	
		33
(3)[7]	(10)[13]	
		
(4)[8] R = H (5)[9] R = OCH_3	(11)[13] R = H (12)[13] R = OCH_3	40 31
		
(6)[8] R = H (7)[10] R = OCH_3	(13)[14] R = H (14)[15] R = OCH_3	42 32

view of the versatile methods available for elaboration of α-hydroxyketones and 1,2-diones. For example, hydroxyketone (1) was prepared by addition of phenyl magnesium chloride to glyconitrile,[5] while (3) was readily available via addition of the lithium anion derived from 2-propyl-1,3-dithiane to 2-cyclopentenone,[16] followed by careful hydrolysis with methyl iodide in aqueous acetonitrile buffered with excess calcium carbonate.[17] On the other hand, hydroxyketones (4) and (5) and in turn, diones (6) and (7), were prepared by acyloin condensation[8,9] of ethyl phenylacetate and its p-methoxy derivative followed in the case of (6) and (7) by Jones oxidation.[18]

Combination of the dithiane approach to α-hydroxyketones with the reported synthesis of tetronic acids would provide, in principle at least, a strategy for the elaboration of unsymmetrically substituted pulvinones, assuming the availability of an effective tetronic acid to pulvinone oxidation protocol. To our knowledge only one other general approach to unsymmetrical pulvinones has been reported.[19] Towards this end, we have demonstrated that the methyl enol ether of 12 can be oxidized with DDQ in toluene to pulvinone 15,[15,19] a metabolite recently isolated from cultures of Aspergillus terreus. Pulvinone 15 is also available from 14 via methylation with dimethyl sulfate in aqueous potassium hydroxide.



(15)

A typical experimental procedure is illustrated by preparation of 4,4-dimethyl tetronic acid (9): To a solution consisting of 0.73 mL (5.2 mmol) of diisopropylamine and 10 ml THF (distilled from Na) was added 2.4 mL (5.3 mmol 2.2 M) of n-butyl lithium at 0° under nitrogen with stirring. After 20 min. the temperature was lowered to -78° and a solution of 208 mg (2.0 mmol) of 3-hydroxy-3-methyl-2-butanone in 5 mL of THF was added dropwise. After an additional 40 min. a solution of 819 mg (5.1 mmol) of 1,1'-carbonyldimidazole in 6 mL of THF was added over a period of 15 min; the resulting mixture was stirred at -78° for 1.5 hr. The cooling bath was then removed and the reaction mixture allowed to warm to room temperature. Work up consisted of addition to 6.0 mL of 3 M H_2SO_4; after 2 min the pH of reaction mixture was

adjusted to ca. 9, extracted with ether, the aqueous phase acidified (ca. pH ∿2)with 3 M H_2SO_4 and extracted several times with ether and the latter washed with water, brine and then dried over $MgSO_4$. Removal of the solvent in vacuo yielded 124 mg (48%) of (9) as a solid which upon recrystallization from benzene afforded white needles, mp 141.5-142.5° C (lit mp. 144-146° C).

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References and Footnotes

1. Camille and Henry Dreyfus Teacher Scholar, 1978-1983.

2. For an excellent review on the synthesis and chemistry of tetronic acids and pulvinones see: G. Pattenden, Fortschr. Chem. Org. Naturst., 133 (1977).

3. The structure assigned to each new compound was in accord with its infrared and 220 or 360 MHz NMR spectra. Analytical samples of all new compounds, obtained by recrystallization or chromatography (TLC or LC), gave satisfactory C and H combustion analysis within 0.4% and/or appropriate parent ion identification by high resolution mass spectrometry. Identity of known tetronic acids and pulvinones was established by comparison with literature melting points.

4. All yields recorded here are based on isolated material which was > 97% pure.

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7. (3): IR ($CHCl_3$): 3480(s,br),1710(s) 1620(w) cm^{-1}; NMR (60 MHz) δ1.04 (t, 3H), 1.6-2.8(m, 6H) 4.0(br s, 1H) 5.04-5.6 (m, 1H), 6.0-6.3 (m, 1H).

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12. E. Benary, Chem. Ber., 40, 1082 (1907).

13. (10): mp 197.5-198.5°C from 1:1 cyclohexane/ethyl acetate (v/v); IR ($CHCl_3$): 3400-2700 (s, br), 1720 (s) and 1660 (s) cm^{-1}; NMR (360 MHz, d_6-DMSO): δ1.90-2.00 (m, 2H), 2.22-2.32 (m, 2H), 2.51 (s, 3H), 5.50-5.56 (m, 1H), 6.24-6.28 (m, 1H). (11): mp 200-215° C(decomp) from 1:1 cyclohexane/ethyl acetate (v/v); IR (KBr): 3100-2800 (s, br), 1700 (s) and 1600 (s) cm^{-1}; NMR (360 MHz, d_6-DMSO): δ 2.93-2.99 (dd, J = 14.4 and 7.2 Hz, 1H), 3.36-3.43 (dd, J = 14.4 and 3.6 Hz, 1H), 5.12-5.20 (dd, J = 7.2 and 3.6 Hz, 1H), 7.14-7.38 (m, 8H), 7.76-7.80 (m, 2H). (12): mp 213-218° C (decomp) from benzene/ethyl acetate; IR (KBr): 3200-2800 (s, br), 1600 (s), 1500 (m), 1375 (s), 1260 (s), 1180 (m), 1130 (s), 825 (s) cm^{-1}; NMR (360 MHz, d_6-DMSO); δ 3.15 (dd, J = 7.4 and 14.8 Hz, 1H), 3.44 (dd, J = 4.3 and 14.8 Hz, 1H), 3.86 (s, 3H), 3.88 (s, 3H), 4.97 (dd, J = 4.3 and 7.4 Hz, 1H), 7.05 (d, J = 9 Hz, 2H), 7.36 (d, J = 9 Hz, 2H), 7.88 (d, J = 9 Hz, 2H).

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19. For a recent synthesis of (13) see: D. W. Knight and G. Pattenden J. C. S. Chem. Commun. 876 (1975); we are grateful to Professor G. Pattenden for an authentic sample of pulvinone (15).

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