

REACTION OF O-TRIMETHYLSILYLATED CYANOHYDRINS WITH  $\alpha$ -BROMOESTERS:  
A NEW SYNTHESIS OF TETRONIC ACIDS

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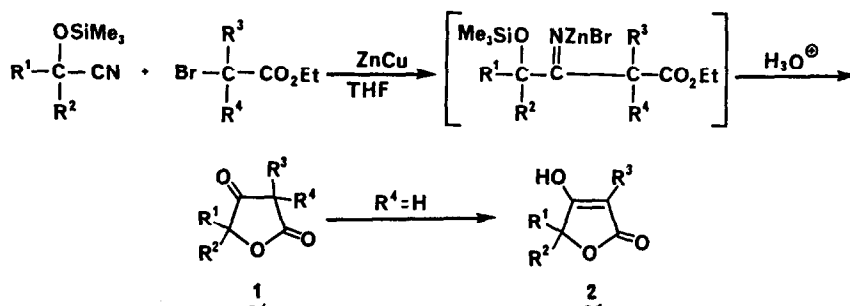
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**Abstract:** Tetronic acids and  $\beta$ -keto- $\gamma$ -butyrolactones are easily prepared by the zinc induced reaction of O-trimethylsilylated cyanohydrins and  $\alpha$ -bromoesters.

A variety of natural products have as a common structural feature an unsaturated  $\gamma$ -butyrolactone ring.<sup>1</sup> Among the  $\Delta^{\alpha,\beta}$ -butenolides, those hydroxylated at the  $\beta$  position (commonly known as tetronic acids) are a subclass of considerable importance.<sup>2</sup> In addition to the familiar ascorbic acid, tetronic acids are widely distributed in nature. These butenolides are characteristic of a large number of sponge, fungal, and lichen metabolites, and include important pigments as well as compounds with significant antibiotic, anticoagulant, insecticidal, and herbicidal activities.<sup>2,3</sup>

A number of synthetic routes to tetronic acids have been developed.<sup>4</sup> Few of these methods, however, are particularly general, simple, or proceed from readily available starting materials.

We have recently shown<sup>5</sup> that Grignard reagents react with O-trimethylsilylated cyanohydrins to produce acyloins. We have now examined the addition of Reformatsky<sup>6</sup> reagents (Blaise<sup>7</sup> reaction) to O-trimethylsilylated cyanohydrins and have found that this reaction constitutes an exceptionally facile synthesis of tetronic acids 2 (or  $\beta$ -keto- $\gamma$ -butyrolactones 1) as outlined below.



In practice, an excess of the  $\alpha$ -bromoester is added to a slurry of the O-trimethylsilylated cyanohydrin, activated zinc dust,<sup>8</sup> and a trace of iodine in tetrahydrofuran to cause a mildly exothermic reaction. Disappearance of organic starting materials can be monitored by gas chromatography. The reaction was also examined in ether and in mixed ether-benzene solvents. In these latter solvent systems, however, the reaction was sometimes difficult to initiate until an extra charge of zinc, iodine, or  $\alpha$ -bromoester was added.

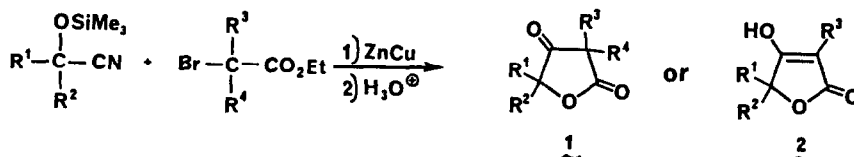
Acid hydrolysis of reaction intermediates causes spontaneous lactonization. An interesting feature of this reaction is that acid hydrolysis of imine (or possibly enamine) intermediates requires several hours at room temperature, so that aqueous acid extraction of the reaction mixture effects a separation of water soluble product intermediates from side products and any unreacted starting materials. In many cases, a major portion of the tetrionic acid 2 (or  $\beta$ -keto- $\gamma$ -butyrolactone 1) product later separates from this aqueous phase in a very pure form.

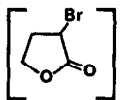
Some representative examples are presented in Table 1. The reaction seems to have considerable steric constraints, since *O*-trimethylsilylated cyanohydrins derived from ketones and pivaldehyde gave significantly lower yields (see Table 1, entries 10 and 11). Despite this shortcoming, we believe this reaction has several features to recommend it: 1) *O*-trimethylsilylated cyanohydrins are readily available<sup>9</sup> from a variety of aldehydes and ketones; 2) a number of  $\alpha$ -bromoesters are either commercially available or easily prepared<sup>10</sup>; 3) the reaction is operationally simple; and 4) in many cases, a major portion of the reaction product can be obtained in a very pure form by simple filtration and/or extraction of the aqueous phase from the reaction work-up (see experimental example). We believe these features should make the zinc induced reaction of  $\alpha$ -bromoesters with *O*-trimethylsilylated cyanohydrins a useful new method for the synthesis of  $\beta$ -keto- $\gamma$ -butyrolactones and tetrionic acids.

The following procedure, for the preparation of 2-methyl-4-phenyltetrionic acid (3-methyl-5-phenyl-2,4(3H,5H)-furandione, entry 5, Table 1) is representative. A solution of ethyl  $\alpha$ -bromopropionate (5.0 mL, 38.5 mmol) in dry tetrahydrofuran (25 mL) was added dropwise over a period of about 0.5 hr to a stirred slurry of the *O*-trimethylsilylated cyanohydrin of benzaldehyde (5.1 g, 25 mmol), activated zinc dust<sup>8</sup> (4.9g, 75 mmol) and a crystal of iodine in dry tetrahydrofuran (35 mL) under argon. When addition was complete, the mixture was refluxed for 2 hr, then stirred at room temperature overnight. The mixture was filtered and the unreacted zinc washed with ether (200 mL). The organic solution was poured onto a mixture of ice ( $\sim$ 200g) and sulfuric acid ( $\sim$ 25 mL). The layers were separated and the organic layer extracted with several portions of a 10% hydrochloric acid solution (75 mL). The aqueous extracts were combined and allowed to stand at room temperature overnight. The white crystals which separated from the aqueous solution were filtered off and dried to afford the nearly pure tetrionic acid (2.07g). Extraction of the aqueous solution with several portions of ethyl acetate afforded another portion of the desired tetrionic acid (1.42g). The organic layer from the reaction was dried over magnesium sulfate, filtered and evaporated to leave an oil (1.25g). Ethanol (50 mL) and a 10% hydrochloric acid solution (5 mL) were added and the solution refluxed for 1 hr and then allowed to stand overnight at room temperature. Solvent was evaporated, the residue taken up in ether (150 mL), and extracted with several portions of a 5% sodium hydroxide solution (25 mL). The combined basic extracts were acidified by the addition of hydrochloric acid and extracted with several portions of ethyl acetate. The ethyl acetate solution was dried over magnesium sulfate, filtered

and evaporated to leave another 0.16g of the desired product. The various portions of the tetrionic acid were combined and recrystallized from ethyl acetate-hexanes to afford 3.1g (65%) of 2-methyl-4-phenyltetrionic acid, mp 141-143°C [lit.<sup>4p</sup>, mp 145-146°C] IR (nujol)  $\nu_{\max}$  3400-2400, 1720, 1640, 1460, 1260, 1230, 1100, 1015, 770, and 705  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$  11.8 (bs, 1H), 7.4 (m, 5H), 5.74 (s, 1H), and 1.70 (s, 3H). Anal. Calcd. for  $\text{C}_{11}\text{H}_{10}\text{O}_3$ : C, 69.5; H, 5.3. Found: C, 69.2; H, 5.2.

Table 1  
Preparation of  $\beta$ -Keto- $\gamma$ -Butyrolactones(1) or Tetrionic Acids(2)  
from O-Trimethylsilylated Cyanohydrins and  $\alpha$ -Bromoesters



Entry	$\underline{R}^1$	$\underline{R}^2$	$\underline{R}^3$	$\underline{R}^4$	Product, Yield <sup>a</sup>	m.p.; °C
1	Ph	H	CH <sub>3</sub>	CH <sub>3</sub>	1, 72%	50-52
2	Ph	H	-(CH <sub>2</sub> ) <sub>3</sub> -		1, 54%	72-74
3	CH <sub>3</sub>	H	CH <sub>3</sub>	CH <sub>3</sub>	1, 42%	(bp 189-191°C)
4 <sup>b</sup>	Ph	H	H	H	2, 69%	132-132.5 <sup>c</sup>
5	Ph	H	CH <sub>3</sub>	H	2, 65%	141-143 <sup>d</sup>
6	Ph	H	Ph	H	2, 56%	202-204 <sup>e</sup>
7	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	H	C <sub>2</sub> H <sub>5</sub>	H	2, 67%	121.5-123
8	3,4-(CH <sub>3</sub> O) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	H	n-C <sub>4</sub> H <sub>9</sub>	H	2, 64%	139-142
9	CH <sub>3</sub>	H	Ph	H	2, 40%	166-168 <sup>f</sup>
10	t-Bu	H	CH <sub>3</sub>	H	2, 23%	179-181
11		-(CH <sub>2</sub> ) <sub>5</sub> -	CH <sub>3</sub>	H	2, 21%	221-224 <sup>g</sup>
12	Ph	H			2 <sup>h</sup> , 68%	134-136

a) Isolated yield. All products were fully characterized including satisfactory IR,  $^1\text{H-NMR}$ , combustion analysis, and/or accurate mass MS. b) Four equivalents of  $\alpha$ -bromoester were used in this example; 1.5 equivalents of  $\alpha$ -bromoester were used in all other cases. c) lit.<sup>4c</sup>, mp 128°C. d) lit.<sup>4p</sup>, mp 145-146°C. e) lit.<sup>11</sup>, mp 205-208°C. f) lit.<sup>11</sup>, mp 165°C, "solidifies and remelts 181-182°C". g) lit.<sup>12</sup>, mp 218°C. h) In this tetrionic acid  $\text{R}^3 = \text{CH}_2\text{CH}_2\text{OH}$ .

## REFERENCES AND NOTES

1. For a recent butenolide review, see Rao, Y.S. Chem. Rev. **1976**, 76, 625.
2. Reviews: a) Haynes; L.J.; Plimmer, J.R. Quart. Rev., **1960**, 14, 292. b) Pattenden, G. Fortschr. Chem. Org. Naturst. **1978**, 35, 133.
3. a) Ibi, A.; Taniguchi, E.; Maekawa, K. Agric. Biol. Chem. **1979**, 43, 1641. b) Rehse, K.; Wagenknecht, J.; Rietbrock, N. Arch. Pharm. **1978**, 311, 986.
4. Many methods are outlined in references 2. Also see a) Svendsen, A.; Boll, P.M. Tetrahedron **1973**, 29, 4251. b) Svendsen, A.; Boll, P.M. J. Org. Chem. **1975**, 40, 1927. c) Gelin, S.; Pollet, P. Bull. Soc. Chim. Fr. **1975**, 307. d) Damon, R.E.; Luo, T.; Schlessinger, R.H. Tetrahedron Lett. **1976**, 2749. e) Pollet, P.; Gelin, S., Tetrahedron, **1978**, 34, 1453. f) Weinstock, J.; Blank, J.E.; Oh, H.-J.; Sutton, B.M. J. Org. Chem. **1979**, 44, 673. g) Jerris, P.J.; Wovkulich, P.M.; Smith, III A.B. Tetrahedron Lett. **1979**, 4517. h) Knight, D.W.; Pattenden, G. J. Chem. Soc., Perkin Trans. 1 **1979**, 62, 70, 84. i) Begley, M.J.; Gedge, D.R.; Knight, D.W.; Pattenden, G. J. Chem. Soc., Perkin Trans. 1 **1979**, 77. j) Gedge, D.R.; Pattenden, G. J. Chem. Soc., Perkin Trans. 1 **1979**, 89. k) Fell, S.C.M.; Heaps, J.; Holker, J.S.E. J. Chem. Soc., Chem. Commun. **1979**, 81. l) Yamada, T.; Hagiwara, H.; Uda, H. J. Chem. Soc., Chem. Commun. **1980**, 838. m) Schmidt, D.G.; Zimmer, H. Synth. Commun. **1981**, 11, 385. n) Schmidt, R.R.; Betz, R. Synthesis **1982**, 748. o) Clemo, N.G.; Pattenden, G. Tetrahedron Lett. **1982**, 23, 581, 585, 589. p) Anderson, J.R.; Edwards, R.L.; Whalley, A.J.S. J. Chem. Soc., Perkin Trans. 1 **1982**, 215. q) Booth, P.M.; Fox, C.M.J.; Ley, S.V. Tetrahedron Lett. **1983**, 24, 5143. r) Wrobel, J.E.; Ganem, B. J. Org. Chem. **1983**, 48, 3761. s) Brandänge, S.; Flodman, L.; Norberg, A. J. Org. Chem. **1984**, 49, 927. t) Ramage, R.; Griffiths, G.J.; Shutt, F.E.; Sweeney, J.N.A. J. Chem. Soc., Perkin Trans. 1 **1984**, 1539.
5. Krepski, L.R.; Heilmann, S.M.; Rasmussen, J.K. Tetrahedron Lett. **1983**, 24, 4075.
6. For general reviews of the Reformatsky reaction, see a) Gaudemar, M. Organomet. Chem. Rev. A **1972**, 8, 183. b) Rathke, M.W. Org. React. **1975**, 22, 423.
7. a) Kagan, H.B.; Suen, Y. Bull. Soc. Chim. Fr. **1966**, 1819. b) Improved procedure: Hannick, S.M.; Kishi, Y. J. Org. Chem. **1983**, 48, 3833.
8. Zinc was activated with cupric acetate by LeGoff's procedure: LeGoff, E. J. Org. Chem. **1964**, 29, 2048. After washing the activated zinc with ether, it was dried overnight at room temperature in a vacuum oven (~0.5 mm). Argon was admitted when the vacuum was broken. The activated zinc can be stored in a closed bottle for at least several months without any apparent loss of activity.
9. See, for example a) Evans, D.A.; Carroll, G.L.; Truesdale, L.K. J. Org. Chem. **1974**, 39, 914. b) Rasmussen, J.K.; Heilmann, S.M. Synthesis **1978**, 219. c) Livinghouse, T. Org. Synth. **1981**, 60, 126. d) Duboudin, F.; Cazeau, P.; Moulines, F.; LaPorte, O. Synthesis **1982**, 212. e) Greenlee, W.J.; Hangauer, D.G. Tetrahedron Lett. **1983** 24, 4559. f) Rasmussen, J.K.; Heilmann, S.M. Org. Synth. **1984**, 62, 1196.
10. See, for example: a) Buu-Hoi, N.P.; Demerseman, P. J. Org. Chem. **1953**, 18, 649. b) Rathke, M.W.; Lindert, A. Tetrahedron Lett. **1971**, 3995. c) Arnold, R.T.; Kulenovic, S.T. J. Org. Chem. **1978**, 43, 3687.
11. Haynes, L.J.; Stanners, A.H. J. Chem. Soc. **1956**, 4103.
12. Payard, M.; Paris, J.; Tronche, P. J. Heterocycl. Chem. **1978**, 15, 1493.

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