

# A Novel Oxidative Rearrangement of 6-Methoxypyran-2-ones

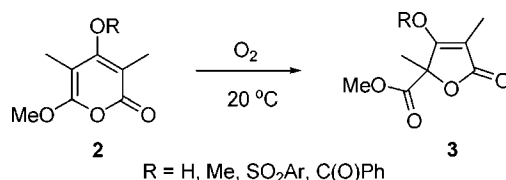
Serena J. Eade, Robert M. Adlington, Andrew R. Cowley, Magnus W. Walter,<sup>†</sup> and Jack E. Baldwin\*

Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford OX1 3TA, U.K., and Lilly Research Centre, Erl Wood Manor, Windlesham, Surrey GU20 6PH, U.K.

jack.baldwin@chem.ox.ac.uk

Received June 9, 2005

## ABSTRACT

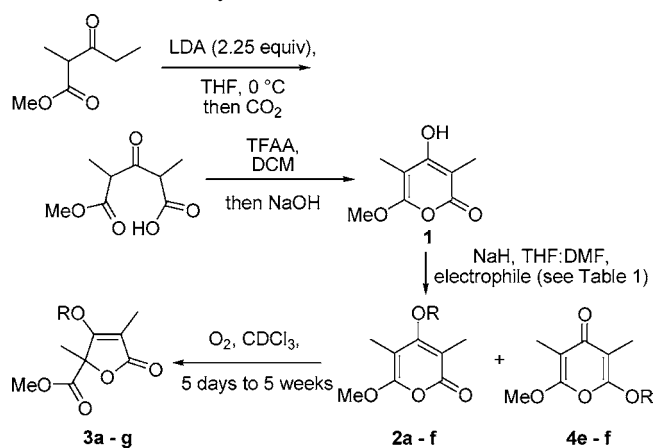


As part of our continuing studies of pyrone-containing natural products, a series 6-methoxypyran-2-ones were synthesized. These were found to react with molecular oxygen at 20 °C, and this novel reaction yielded a series of highly functionalized  $\alpha,\beta$ -butenolides.

In our studies of pyrones and the synthesis of pyrone–polyene natural products so far,<sup>1</sup> we have achieved the synthesis of cyercene A,<sup>2</sup> 9,10-deoxytridachione,<sup>3</sup> aureothin,<sup>4</sup> spectinabilin, and the SNF compounds.<sup>5</sup> In the course of this work, solid 4-hydroxy-6-methoxy-3,5-dimethyl-2H-pyran-2-one **1** was synthesized by carboxylation of the dianion of methyl 2-methyl-3-oxopentanoate<sup>6</sup> and subsequent TFAA activation and cyclization of the resulting tricarbonyl<sup>7</sup> to the pyrone **1** (Scheme 1).

Reaction of **1** with sodium hydride and 4-toluenesulfonyl chloride yielded the  $\alpha$ -pyrone **2a** as the sole product (Scheme 1). However, this compound was found to be unstable in CDCl<sub>3</sub> solution in the presence of molecular oxygen at rt

## Scheme 1. Pyrone Functionalization and Oxidation



<sup>†</sup> Lilly Research Centre.

(1) Moses, J. E.; Baldwin, J. E.; Brückner, S.; Eade, S. J.; Adlington, R. M. *Org. Biomol. Chem.* **2003**, *1*, 3670.

(2) Moses, J. E.; Baldwin, J. E.; Adlington, R. M. *Tetrahedron Lett.* **2004**, *45*, 6447.

(3) Moses, J. E.; Adlington, R. M.; Rodriguez, R.; Eade, S. J.; Baldwin, J. E. *Chem. Commun.* **2005**, 1687.

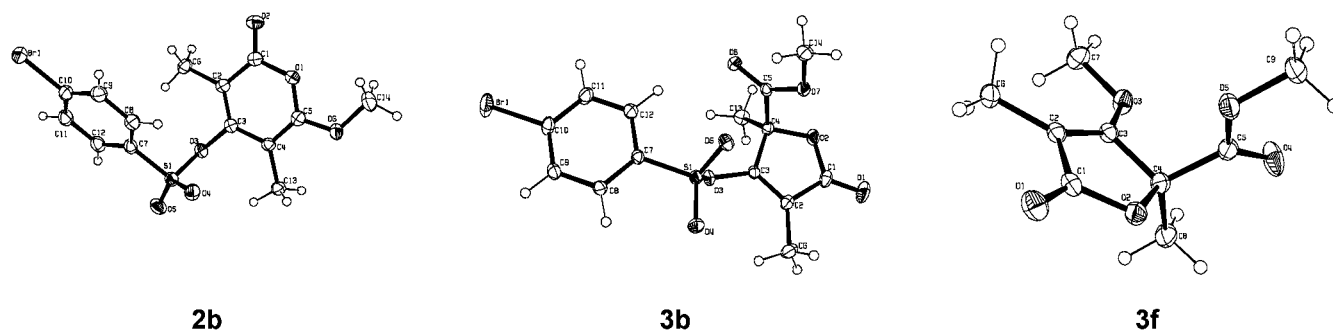
(4) Jacobsen, M. F.; Moses, J. E.; Adlington, R. M.; Baldwin, J. E. *Org. Lett.* **2005**, *7*, 641.

(5) Jacobsen, M. F.; Moses, J. E.; Adlington, R. M.; Baldwin, J. E. *Org. Lett.* **2005**, *7*, 2473.

(6) Sung, K.; Wu, S. *Synth. Commun.* **2001**, *31*, 3069.

(7) Cha, J. K.; Harris, T. M.; Ray, J. A.; Venkataraman, H. *Tetrahedron Lett.* **1989**, *30*, 3505. Venkataraman, H.; Cha, J. K. *Tetrahedron Lett.* **1989**, *30*, 3509.

and underwent conversion to a new product **3a** which, according to mass spectrometry, contained one more oxygen atom than the starting material. The analogous 4-bromobenzenesulfonyl compound **2b** was likewise synthesized and recrystallized in the absence of oxygen to confirm its identity (Figure 1, Scheme 1).<sup>8</sup>



**Figure 1.** X-ray crystal structures of  $\alpha$ -pyrone **2b** and  $\alpha,\beta$ -butenolides **3b** and **3f**.

Again, upon exposure to molecular oxygen in  $\text{CDCl}_3$  solution at rt, **2b** gave oxidized  $\alpha,\beta$ -butenolide **3b** whose structure was proven by X-ray crystallography (Figure 1, Scheme 1).<sup>8</sup> Further functionalizations of **1** were carried out using 4-nitrobenzenesulfonyl chloride and benzoyl chloride to afford **2c** and **2d**, respectively, which once again could be simply oxidized to **3c** and **3d** (Scheme 1).

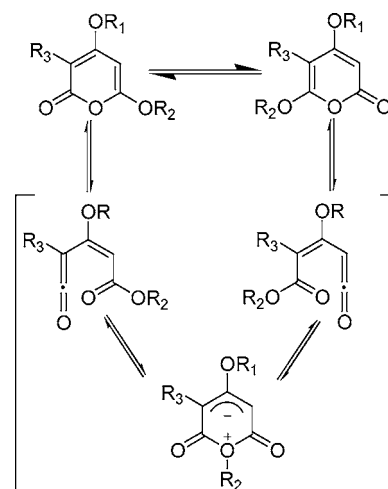
Reaction of pyrone **1** with 2,4,6-triisopropylbenzenesulfonyl chloride gave two products:  $\alpha$ -pyrone **2e**, which underwent oxidation to **3e**, and  $\gamma$ -pyrone **4e**, which was stable in the presence of oxygen (Scheme 1). Methylation of pyrone **1** with dimethyl sulfate similarly afforded  $\alpha$ -pyrone **2f** and  $\gamma$ -pyrone **4f**. Compound **2f** was oxidized to yield  $\alpha,\beta$ -butenolide **3f** (Figure 1, Scheme 1).<sup>8</sup> These results are summarized in Table 1. Some similar 3-methoxy  $\alpha,\beta$ -butenolides were synthesized by Pelter et al. in their studies of synthetic routes toward piperolides, fadyenolides, epoxypiperolides, and related compounds.<sup>9</sup>

The solid 4-hydroxypyrene starting material **1** was also observed to undergo slow oxidation in air (and in the presence of molecular oxygen) in the absence of solvent over 2 months, yielding **3g**. Reaction of **3g** with NaH and 4-bromobenzenesulfonyl chloride yielded previously synthesized **3b**.

Cha et al.<sup>7</sup> have previously reported scrambling of similar 6-methoxy-2*H*-pyran-2-ones pyrones via ring opening of  $\alpha$ -pyrones to form ketenes (Scheme 2). They also carried out corresponding isotope labeling experiments to confirm the intramolecular nature of the migration of the methoxy group, as well as carrying out ketene-trapping experiments.<sup>7</sup> In addition, the autoxidation of diphenylketene to form

polyesters via  $\alpha$ -lactones has been reported by Bartlett.<sup>10</sup> We therefore propose that the unusual oxidation mechanism

**Scheme 2.** Pyrone Scrambling Observed by Cha et al.<sup>7</sup>

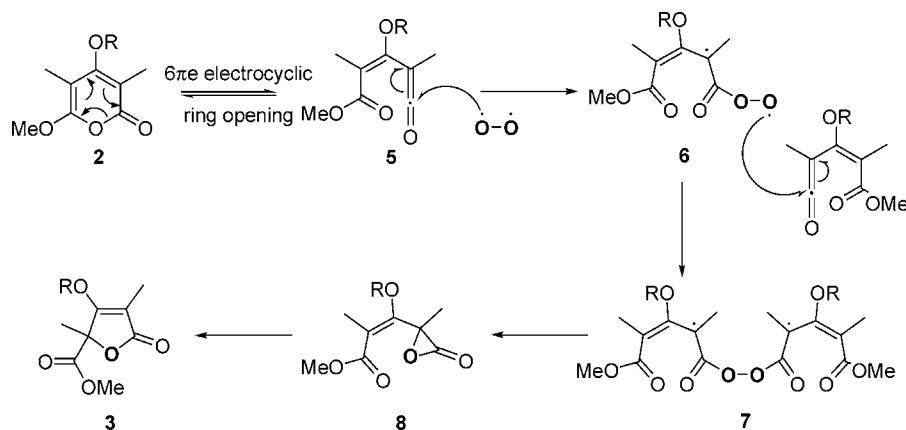


proceeds first via a  $6\pi$  thermal electrocyclic ring opening of **2** to ketene **5**, consistent with the observations of Cha et al.<sup>7</sup> (Scheme 3). This is followed by a radical reaction with molecular oxygen in its triplet ground state and subsequent reaction of **6** with a second molecule of the ketene to form a dimeric species **7** which then collapses to  $\alpha$ -lactone **8**, consistent with the results of Bartlett et al.<sup>10</sup> However, unlike in previous work,  $\alpha$ -lactone **8** contains an intramolecular trap

**Table 1.** Reagents, Substituents, and Products of Functionalization and Oxidation

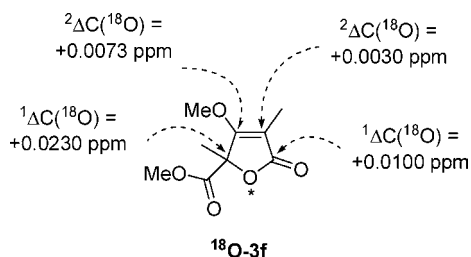
R	electrophile (Scheme 1)	$\alpha$ -pyrone <b>2</b>	yield (%)	$\alpha,\beta$ -butenolide <b>3</b>	yield (%)	$\gamma$ -pyrone <b>4</b>	yield (%)
4-MeC <sub>6</sub> H <sub>4</sub> SO <sub>2</sub> –	4-MeC <sub>6</sub> H <sub>4</sub> SO <sub>2</sub> Cl	<b>2a</b>	79	<b>3a</b>	53		
4-BrC <sub>6</sub> H <sub>4</sub> SO <sub>2</sub> –	4-BrC <sub>6</sub> H <sub>4</sub> SO <sub>2</sub> Cl	<b>2b</b>	63	<b>3b</b>	45		
4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> SO <sub>2</sub> –	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> SO <sub>2</sub> Cl	<b>2c</b>	58	<b>3c</b>	40		
C(O)Ph	Ph C(O)Cl	<b>2d</b>	44	<b>3d</b>	52		
2,4,6-( <i>i</i> -Pr) <sub>3</sub> C <sub>6</sub> H <sub>2</sub> SO <sub>2</sub> –	2,4,6-( <i>i</i> -Pr) <sub>3</sub> C <sub>6</sub> H <sub>2</sub> SO <sub>2</sub> Cl	<b>2e</b>	69	<b>3e</b>	61	<b>4e</b>	15
Me	Me <sub>2</sub> SO <sub>4</sub>	<b>2f</b>	39	<b>3f</b>	61	<b>4f</b>	37
H		<b>1</b>		<b>3g</b>	35		

**Scheme 3.** Proposed Mechanism for Conversion from  $\alpha$ -Pyrone **2** to  $\alpha,\beta$ -Butenolide **3**



and thus  $\alpha,\beta$ -butenolide **3** is formed in an analogous manner to the conversion of a vinylcyclopropane to a cyclopentene, via a [1,3] sigmatropic migration which could alternatively be considered as an internal  $[\pi 2 + \sigma 2]$  cycloaddition. An alternative mechanism in which conversion of the resonance form of **7** to **3** directly without an intermediate  $\alpha$ -lactone **8** is also possible. The stability of  $\gamma$ -pyrones **4e** and **4f** in the presence of oxygen supports the mechanism since ring opening of  $\gamma$ -pyrones to ketenes is not possible.

To confirm the position of the oxygen atom in the oxidized product originating from molecular oxygen, the oxidation of **2f** was carried out in the presence of  $^{18}\text{O}_2$ . This afforded  $^{18}\text{O}$ -**3f** whose observed isotope shifts in the  $^{13}\text{C}$  NMR spectrum (Figure 2) confirmed that the oxygen atom had been incorporated into the ring.<sup>11</sup>



**Figure 2.** Isotope shifts in the  $^{13}\text{C}$  NMR spectrum of  $^{18}\text{O}$ -**3f**.

In conclusion, we have found a novel oxidative reaction of  $\alpha$ -pyrones enabling facile synthesis of a variety of highly functionalized 3-substituted  $\alpha,\beta$ -butenolides.

**Acknowledgment.** We thank Tim Claridge and Barbara Odell for NMR assistance, the O'Hare group, Luke McNeill, and Hermann Wegner. S.J.E. thanks the EPSRC for funding and Eli Lilly Ltd. for CASE support.

**Supporting Information Available:** Experimental procedure for the preparation of **1**, general experimental procedures for the preparation of **2–4**, and associated spectroscopic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL0513490

(8) CCDC 274197 contains the supplementary crystallographic data for compound **2b**, CCDC 274198 for **3b**, and CCDC 274199 for **3f**, respectively. These data can be obtained free of charge via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif), or by emailing [data\\_request@ccdc.cam.ac.uk](mailto:data_request@ccdc.cam.ac.uk), or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

(9) (a) Pelter, A.; Al-Bayati, R.; Lewis, W. *Tetrahedron Lett.* **1982**, 23, 353. (b) Pelter, A.; Al-Bayati, R. *Tetrahedron Lett.* **1982**, 23, 5229. (c) Pelter, A.; Al-Bayati, R. I. H.; Ayoub, M. T.; Lewis, W.; Pardasani, P.; Hansel, R. *J. Chem. Soc., Perkin Trans. 1* **1987**, 717.

(10) Bartlett, P. D.; McCluney, R. E. *J. Org. Chem.* **1983**, 48, 4165.

(11) For analogous  $^{18}\text{O}$  shifts of  $^{13}\text{C}$  signals and theory, see: (a) Hansen, P. E. *Ann. Rep. NMR Spectrosc.* **1983**, 15, 106. (b) Batiz-Hernandez, H.; Bernheim, R. A. *Prog. NMR. Spectrosc.* **1967**, 3, 63. (c) Jameson, C. J. *Bull. Magn. Reson.* **1981**, 3, 3.