

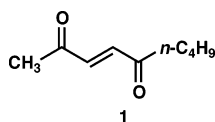
## A Mild, Catalytic, and Highly Selective Method for the Oxidation of $\alpha,\beta$ -Enones to 1,4-Enediones

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The position-selective replacement of hydrogen by oxygen results in an increase of molecular complexity, specifically, a gain in reactive functionality that is very useful in multistep synthesis. We describe herein a new, practical, and very mild method for the conversion of an enone subunit,  $-(CO)-CH=CH-CH_2-$ , to the corresponding 1,4-enedione,  $-(CO)-CH=CH(CO)-$ . To the best of our knowledge, there is no other general method for effecting this conversion. The 1,4-enedione system is found in a variety of bioactive natural products including marine natural products,<sup>1</sup> sesquiterpenes,<sup>2</sup> steroids,<sup>3</sup> antitumor agents,<sup>4</sup> antifungal agents,<sup>5</sup> and insect toxins, for example, (*E*)-non-3-ene-2,5-dione (**1**), an important toxic component of the fire bee *Trigona taira*.<sup>6</sup> In addition, by virtue of their electrophilicity and electron affinity, 1,4-enediones serve as excellent substrates for further synthetic elaboration. They have been used, for example, as highly reactive dienophiles for the construction of complex fused ring systems by Diels–Alder 2 + 4 cycloaddition<sup>7</sup> and as Michael acceptors.<sup>8</sup>



The oxidation reagent which we have developed for the synthesis of 1,4-enediones consists of a mixture of 5 equiv of *tert*-butylhydroperoxide (stoichiometric oxidant), 5 mol % of 20% Pd(OH)<sub>2</sub> on carbon (Pearlman's catalyst; Aldrich Co.),<sup>9</sup> and 0.25 equiv of K<sub>2</sub>CO<sub>3</sub> in methylene chloride at 4 °C or room temperature (24 °C), depending on the substrate. Although Pd(OH)<sub>2</sub>-on-carbon is normally used as a hydrogenation catalyst rather than as a catalyst for oxidation, in this case, it serves to initiate reaction by a remarkable activation of *t*-BuOOH. Under these conditions, a variety of  $\alpha,\beta$ -enones are smoothly oxidized in good yield to the corresponding 1,4-enediones, as documented in Table 1. Also shown in Table 1 are two cases (entries 3 and 4) in which a ketal of an  $\alpha,\beta$ -enone is oxidized to a monoketal of a 1,4-enedione. These examples are especially interesting not only because the method of synthesis outlined in Table 1 is both simple and advantageous, but also because the corresponding enediones are sensitive and not easily made.<sup>10</sup> As shown in entry 7 of Table 1, the new 1,4-enedione synthesis provides a simple route to the fire bee toxin **1**<sup>6</sup> and its homologues.

The experimental procedures for the oxidations shown in Table 1 are extremely simple. After the reactants were stirred in CH<sub>2</sub>Cl<sub>2</sub> until thin layer chromatographic analysis shows complete consumption of the starting  $\alpha,\beta$ -enone or monoketal,<sup>11</sup> the palladium on carbon catalyst is removed by filtration, the solvent is evaporated under reduced pressure, and the product is isolated either by flash

**Table 1.** Synthesis of 1,4-Enediones

entry	substrate	product	time (h), °C	yield, %
(1)			48, 24	81
(2)			36, 4	86
(3)			72, 24	80
(4)			64, 4	79
(5) <sup>a</sup>			60, 24	82
(6)			36, 4	90
(7)			72, 24	81

<sup>a</sup> Pd(OH)<sub>2</sub>-C pretreated with *t*-BuOOH; otherwise 10 equiv of *t*-BuOOH is required to achieve 82% yield.

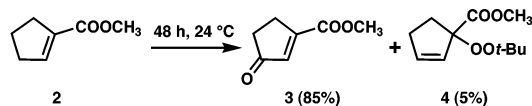
chromatography on silica gel (using hexanes–ether for elution) or by distillation in vacuo.<sup>12</sup> An alternative procedure, which may in some cases be advantageous, involves the pretreatment of Pd(OH)<sub>2</sub>-on-carbon with *t*-BuOOH in CH<sub>2</sub>Cl<sub>2</sub> at 24 °C with stirring for 1 h. Under these conditions, the initial rate of the oxidation reaction is faster, and, for example, for entry 5 in Table 1, a shorter reaction and a smaller excess of *t*-BuOOH can be used.<sup>13</sup> We believe that this method constitutes an advantageous route to 1,4-enediones from  $\alpha,\beta$ -enones in comparison to the use of other reagents which have been reported for such oxidations in a handful of cases (specifically pyridinium dichromate in DMF<sup>14a</sup> or CrO<sub>3</sub> in HOAc<sup>14b</sup> and tetrazolium salts<sup>15</sup>). It is also simpler than a variety of multistep routes which have been reported previously for accessing 1,4-enedione systems.<sup>16</sup>

$\alpha,\beta$ -Unsaturated esters are also transformed into  $\gamma$ -oxo derivatives using the conditions of Table 1 as shown for the conversion of **2** → **3**. Accompanying **3** in this case is a small amount of the

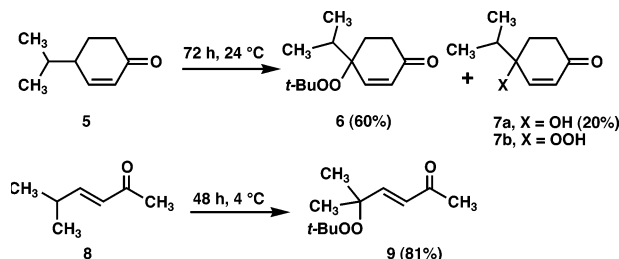
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product of oxidative attack at C( $\alpha$ ) (4). Significantly,  $\gamma$ -*tert*-butylperoxy ethers are formed as major products in the oxidation

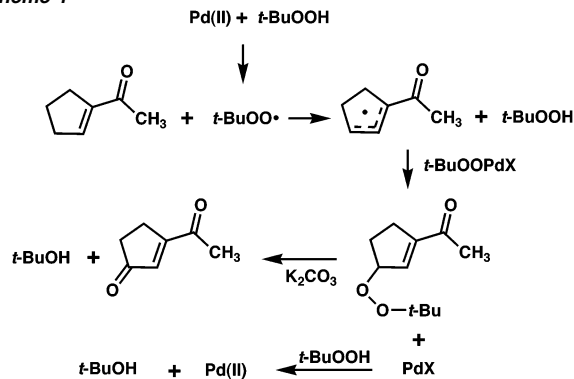


of  $\alpha,\beta$ -enones possessing only a single  $\gamma$ -hydrogen, as shown for the examples  $5 \rightarrow 6$  and  $8 \rightarrow 9$ . In the oxidation of **5**, the  $\gamma$ -hydroxy- $\alpha,\beta$ -enone **7a** is also formed (ca. 20%) along with a small amount of the corresponding hydroperoxide **7b** (ca. 4%) (isolated and characterized). Under the conditions for the oxidation of **5**, **7b** undergoes conversion to **7a** and clearly is a transient intermediate.



We have made a number of observations that are relevant to the mechanism of the Pd-promoted synthesis of 1,4-enediones which is disclosed herein. As reported earlier, various Pd(II) compounds and  $K_2CO_3$  are capable of generating the *tert*-butylperoxy radical (*t*-BuOO $\cdot$ ) from *tert*-butylhydroperoxide.<sup>17</sup> One indication of this is the generation of  $O_2$  from mixtures of Pd(II) compounds,  $K_2CO_3$ , and *t*-BuOOH, which can be accounted for by dimerization of *t*-BuOO $\cdot$  to di-*tert*-butyltetroxide.<sup>18,19</sup> Evolution of  $O_2$  is also observed with Pd(OH) $_2$ -on-C,  $K_2CO_3$ , and *t*-BuOOH under conditions of the oxidations described herein. The most likely mode of formation of *t*-BuOO $\cdot$  would seem to be electron transfer from *t*-BuOO $^-$  to Pd(II). A plausible mechanism for the *tert*-butylperoxy radical initiated conversion of  $\alpha,\beta$ -enones to 1,4-enediones is shown in Scheme 1. Although the exact nature of the lower valent PdX

Scheme 1



species is unclear, the postulate shown in Scheme 1 requires its reoxidation to Pd(II) by *t*-BuOOH. The final step of the process outlined in Scheme 1 is the carbonyl-forming elimination of a peroxy ether catalyzed either by base or by the *tert*-butylperoxy radical.<sup>20</sup> The conversions  $5 \rightarrow 6$  and  $8 \rightarrow 9$  support the intermediacy of a  $\gamma$ -*tert*-butylperoxy- $\alpha,\beta$ -enone as shown in Scheme 1. In the case of the oxidation of **5**, some radical trapping by  $O_2$  must occur leading to the sequential formation of **7b** and **7a**. Finally, the formation of *t*-BuOH as a coproduct of these oxidations was demonstrated by gas chromatographic analysis of the reaction mixtures.

In our judgment, the selectivity, simplicity, and practicality of the new oxidation methodology described herein will encourage and facilitate the wider use of highly reactive 1,4-enediones as intermediates for the construction of more complex molecules.

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**Supporting Information Available:** Experimental procedures and physical data for the reactions summarized in Table 1 (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- In the event that an oxidation reaction does not progress to completion, more Pd(OH) $_2$ -on-C should be added.
- The following procedure used for the monoethylene ketal of 2-cyclopenten-1,4-dione (Table 1, entry 3). A 25 mL round-bottom flask equipped with a stir bar was charged with 20% Pd(OH) $_2$ - (17 mg, 0.032 mmol Pd),  $K_2CO_3$  (11 mg, 0.08 mmol), 1 mL of  $CH_2Cl_2$ , and 2-cyclopenten-1-one ethylene ketal (76  $\mu$ L, 0.64 mmol). The mixture was cooled to 4 °C with an ice bath, and TBHP (160  $\mu$ L, 1.6 mmol) was added with vigorous stirring. The flask was sealed (without removal of air) with a rubber septum and allowed to warm to 24 °C, and the contents were stirred for 24 h at which time an additional 8.5 mg of 20% Pd(OH) $_2$ -C (0.016 mmol), 5.5 mg of  $K_2CO_3$  (0.04 mmol), and 80  $\mu$ L of *t*-BuOOH (0.8 mmol) were added. The reaction mixture was stirred at 24 °C for another 24 h, and a third batch of 8.5 mg of 20% Pd(OH) $_2$ -C (0.016 mmol), 5.5 mg of  $K_2CO_3$  (0.04 mmol), and 80  $\mu$ L of *t*-BuOOH (0.8 mmol) was added. After an additional 24 h at 24 °C, thin layer chromatographic analysis indicated that the reaction was complete. Filtration, removal of solvent from the filtrate, and flash chromatography on a column of silica gel (1.5:1 hexanes-ether for elution) afforded 72 mg (80%) of 2-cyclopenten-1,4-dione monoethylene ketal as a colorless liquid.  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  7.21 (d,  $J$  = 6.2 Hz, 1H), 6.20 (d,  $J$  = 6.2 Hz, 1H), 4.06 (m, 4H), 2.61 (s, 2H).  $^{13}C$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  203.9, 156.2, 135.3, 111.6, 65.1, 45.2. IR (film): 1723  $cm^{-1}$ . HRMS (EI)  $m/z$ , calcd 140.0473, found 140.0469. No precautions were taken to remove air. During the reaction, a slight positive pressure develops due to the coproduction of  $O_2$  gas; on a larger scale, this should be vented from the reactor.
- This observation indicate that Pd(OH) $_2$ -on-carbon is probably converted to a species such as Pd(OH)(OO*t*-Bu)-on-carbon, which is an active initiator of the oxidation of the  $\alpha,\beta$ -enone. If Pd(OH) $_2$ -on-carbon is prereduced to Pd(0)-on-carbon by stirring with hydrogen, it does not serve as an effective reaction catalyst, although it is gradually oxidized by *t*-BuOOH to a form that shows some catalytic activity.
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