

Two interesting perspectives of the biochemistry of superoxide are provided by the chemistry reported here. First, the facilitation of 1-electron reductions by NADH via hydroperoxyl radical may be one deleterious reaction of superoxide. Secondly, the inhibition of a reaction by catalase and superoxide dismutase does not necessarily imply the generation of hydroxyl radicals by the Haber-Weiss reaction. Both enzymes will also block reactions of hydroperoxyl radicals generated from hydroxyl radicals and hydrogen peroxide.<sup>22</sup>

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### Ketene Dithioacetals as Synthetic Intermediates. Synthesis of Unsaturated 1,5-Diketones<sup>1</sup>

Kevin T. Potts,\* Michael J. Cipullo, Philip Ralli, and George Theodoridis†

Department of Chemistry, Rensselaer Polytechnic Institute  
Troy, New York 12181

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Dithioacetals, in addition to their well established use as protecting groups<sup>2</sup> in organic synthesis, have found many applications as acyl anion equivalents,<sup>3</sup> most recently in the synthesis of ketenes and  $\alpha$ -phenylthio ketones.<sup>3</sup> They have also been utilized in the preparation of a variety of other organic functional groups including  $\alpha,\beta$ -unsaturated ketones,<sup>4</sup> carboxylic acids,<sup>5</sup>  $\alpha$ -chloro carboxylic acids,<sup>6</sup> *S*-methylthio carboxylates,<sup>7</sup> aldehydes,<sup>8a</sup> and  $\beta$ -keto esters.<sup>8b</sup> The corresponding monosulfoxide provides an attractive route to 1,4-dicarbonyl compounds with one carbonyl group being an aldehyde function.<sup>9</sup> Additional unsaturation as in vinyl ketene dithioacetals results in a dienic system that undergoes cycloaddition with reactive dienophiles.<sup>10</sup> A carbonyl-containing function or some other reactive, unsaturated group  $\beta$  to the dithioacetal carbon atom greatly extends the synthetic usefulness of these versatile intermediates,<sup>11</sup> especially in the synthesis of heterocycles.<sup>12</sup>

We now report a new and versatile synthesis of unsaturated 1,5-diketones from  $\alpha$ -ketoketene dithioacetals. 1,5-Enediones are important intermediates in the synthesis of pyrylium and thio-pyrylium salts<sup>13</sup> as well as pyridines<sup>13,14</sup> and have been prepared

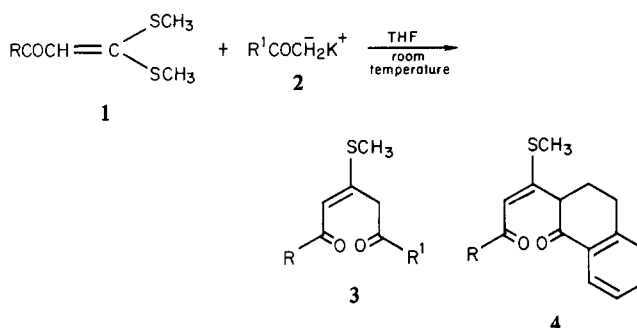
Table I. 1,5-Enediones<sup>a</sup> 3 Derived from  $\alpha$ -Ketoketene Dithioacetals 1<sup>21</sup>

R	R <sup>1</sup>	mp, °C	yield, %	M <sup>+</sup>	$\nu_{\text{CO}}$ (KBr), cm <sup>-1</sup>
C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	106-108	76	267	1680, 1630
4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	159-161	100	356	1655
C <sub>6</sub> H <sub>5</sub>	2-C <sub>6</sub> H <sub>5</sub> S	116-118	61	302	1700, 1680, 1645, 1625
C <sub>6</sub> H <sub>5</sub>	2-C <sub>6</sub> H <sub>5</sub> N	124-125	58	248	1680, 1640
2-C <sub>6</sub> H <sub>5</sub> O <sup>b</sup>	2-C <sub>6</sub> H <sub>5</sub> S	140-142	47	292	1690, 1670, 1640, 1620
2-C <sub>6</sub> H <sub>5</sub> S	2-C <sub>6</sub> H <sub>5</sub> S	161-162	74	308	1620
2-C <sub>6</sub> H <sub>5</sub> S	5-Cl-2-C <sub>6</sub> H <sub>4</sub> S	134-135	55	342	1623
4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	106-107	42	264	1710, 1640

<sup>a</sup> All colorless or cream needles. <sup>b</sup> Acetic acid workup.

from  $\beta$ -chlorovinyl ketones and  $\beta$ -diketones or  $\beta$ -keto esters,<sup>15</sup> by HIO<sub>4</sub> oxidation of cyclopentane-1,2-diols,<sup>16</sup> or from pyridines and pyrylium salts.<sup>17</sup> None of these reaction sequences provides a general synthesis of this class of compound.

Our new route involves the conjugate addition of a methyl ketone carbanion to the  $\alpha$ -ketoketene dithioacetal, and as the latter are readily available from a wide variety of methyl ketones and alicyclic ketones, this procedure is characterized by the variety of substituents that may be introduced into the 1,5-positions. Addition of 3,3-bis(methylthio)-1-phenyl-2-propen-1-one<sup>18</sup> (1; R = C<sub>6</sub>H<sub>5</sub>) (2.0 g, 8.9 mmol) to a solution of acetophenone (2; R<sup>1</sup> = C<sub>6</sub>H<sub>5</sub>) (1.07 g, 8.9 mmol) and potassium *tert*-butoxide (2.0 g, 17.8 mmol) in anhydrous THF, followed by stirring at room temperature for approximately 12 h, gave a red-brown precipitate of the potassium salt of 3 (R = R<sup>1</sup> = C<sub>6</sub>H<sub>5</sub>). This salt was



collected and added to an ice-cold aqueous 4% HCl solution<sup>19</sup> and, on standing, the resultant oily material crystallized. 1,5-Diphenyl-3-(methylthio)-2-penten-1,5-dione (3; R = R<sup>1</sup> = C<sub>6</sub>H<sub>5</sub>) crystallized from petroleum ether (bp 80-100 °C) as pale yellow prisms, mp 106-108 °C. Similarly 4 (R = 4-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>) obtained from 1 (R = 4-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>) and  $\alpha$ -tetralone in 54% yield, separated from ethanol as colorless needles, mp 151-152 °C. The variety of substituents that can be incorporated into the 1,5-enediones by this reaction sequence is illustrated by the representative sample shown in Table I.

These reaction conditions yield<sup>20</sup> consistently the best results; e.g., sodium ethoxide in ethanol resulted in  $\beta$ -keto ester formation

† Corning Glass Works Foundation Fellow, 1978.

(1) Supported in part by NSF Grant CHE 79-01704.

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(19) Acetic acid was used to neutralize the potassium salt when the substituents were unstable in the presence of HCl.

(20) Use of elevated reaction temperatures or only 1 equiv of base resulted in reduced yields of 3, the products usually being highly colored and requiring laborious workup procedures to effect satisfactory purification.

(21) All products gave satisfactory analytical data ( $\pm 0.4\%$ ) for CHN where appropriate.

as well as condensation to a more complex  $\alpha$ -pyranone. NMR data indicate that the enediones **3** are obtained as isomeric mixtures, and details of this aspect of these products will be described in a full publication.

The most consistently successful reaction conditions for the preparation of the  $\alpha$ -ketoketene dithioacetals employed reaction of the methyl ketone (0.5 mol) with NaH (1.0 mol) in Me<sub>2</sub>SO or benzene/dimethylacetamide, followed by the slow addition of carbon disulfide (0.5 mol) and then methyl iodide (1.0 mol), occasional cooling being used during this last addition. After 14 h at room temperature, the product was isolated from the reaction mixture by quenching with ice water and subsequent filtration or chloroform extraction.

In the preparation of the enediones **3** where  $R \neq R^1$ , a choice exists as to which ketone should be utilized as the  $\alpha$ -ketoketene dithioacetal component. In addition to the question of availability of the ketone, we found that the  $\alpha$ -ketoketene dithioacetal **1** in which R had some electron-withdrawing characteristic was usually the more reactive substrate and resulted in better yields of **3**.

This new synthesis of unsaturated 1,5-diketones now makes readily available a variety of pyrylium salts<sup>22</sup> and pyridine derivatives. Extensions of this reaction are currently under investigation in our laboratory, and full details of these and related transformations will be described in the complete publication.

(22) Potts, K. T.; Cipullo, M.; Ralli, P.; Theodoridis, G. *J. Am. Chem. Soc.*, following paper in this issue.

### Ketene Dithioacetals as Synthetic Intermediates. A Versatile Synthesis of Pyridines, Polypyridinyls, and Pyrylium Salts<sup>1</sup>

Kevin T. Potts,\* Michael J. Cipullo, Philip Ralli, and George Theodoridis<sup>†</sup>

Department of Chemistry, Rensselaer Polytechnic Institute  
Troy, New York 12181

Received February 20, 1981

Noteworthy among the numerous syntheses of substituted pyridines described<sup>2</sup> in the literature is the use of organolithium compounds for the preparation of arylpyridines,<sup>3</sup> 2,2'-bipyridinyls,<sup>4</sup> and 2,2',2''-terpyridinyls<sup>5</sup> and the application of pyridinium phenacylides or their salts in the synthesis of a wide variety of 2,4,6-trisubstituted pyridines.<sup>6</sup> This latter procedure has been applied to the synthesis of numerous substituted bi-, ter-, quater-, quinque-, sexi- and septipyridinyls, all of which are of interest as ligands for metal chelation. 2,2'-Bi- and 2,2',2''-terpyridinyl have attracted the most attention in this respect,<sup>7</sup> and the 4'-(4-methoxyphenyl)terpyridinyl<sup>8</sup> and its sulfonated<sup>9</sup> derivative have been introduced in clinical chemistry for the estimation of Fe<sup>2+</sup>. In general these oligopyridines are high melting products and are not easily soluble in the usual organic solvents, factors which have restricted somewhat their further development. We now describe

<sup>†</sup> Corning Glass Works Foundation Fellow, 1978.

(1) Supported in part by NSF Grant CHE 79-01704.

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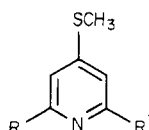
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Table I. Substituted Pyridines Derived from  $\alpha$ -Ketoketene Dithioacetals <sup>21</sup>



R	R <sup>1</sup>	mp, °C	yield, %	M <sup>+</sup> <sup>a</sup>
C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	105-107	81	277
4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	69-70	70	245 <sup>b</sup>
4-BrC <sub>6</sub> H <sub>4</sub>	4-BrC <sub>6</sub> H <sub>4</sub>	115-116	85	435
4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	90.5-91	48	337
C <sub>6</sub> H <sub>5</sub>	2-C <sub>5</sub> H <sub>4</sub> N	80-81	89	278
2-C <sub>5</sub> H <sub>4</sub> N	2-C <sub>5</sub> H <sub>4</sub> N	133-133.5	79	279
2-C <sub>5</sub> H <sub>4</sub> N	2-C <sub>4</sub> H <sub>3</sub> S	133-134	80	284
6-Br-2-C <sub>5</sub> H <sub>3</sub> N	6-Br-2-C <sub>5</sub> H <sub>3</sub> N	184-185	31	437
2-C <sub>4</sub> H <sub>3</sub> S	2-C <sub>4</sub> H <sub>3</sub> S	115-116	99	289
2-C <sub>4</sub> H <sub>3</sub> S	5-Cl-2-C <sub>4</sub> H <sub>2</sub> S	115-116	72	323
2-C <sub>4</sub> H <sub>3</sub> O	2-C <sub>4</sub> H <sub>3</sub> O	96-97	64	257
2-C <sub>4</sub> H <sub>3</sub> O	2-C <sub>4</sub> H <sub>3</sub> S	95-97	74	273

<sup>a</sup> Relative intensities, 100%. <sup>b</sup> 93%.

a versatile, direct synthesis of a variety of substituted pyridines and oligopyridines with favorable solubility characteristics.

Our "one-pot", two-component procedure involves the in situ generation of unsaturated 1,5-diketones derived<sup>10</sup> by reaction of  $\alpha$ -ketoketene dithioacetals and methyl ketone carbanions. Reaction of these enediones with ammonium acetate in hot acetic acid gives the 2,6-disubstituted-4-(methylthio)pyridines, a representative selection of which is shown in Table I. Alternatively, the 1,5-enedione may be isolated before conversion into the pyridine although, in general, this offers no advantages over the more direct procedure. The synthesis of 2,2',2''-terpyridine (**4**, R = R<sup>1</sup> = 2-C<sub>5</sub>H<sub>4</sub>N; R<sup>2</sup> = H; X = N) illustrates the general procedure used.

2-Acetylpyridine (**1**, R = 2-C<sub>5</sub>H<sub>4</sub>N) was converted into 3,3-bis(methylthio)-1-(2-pyridinyl)-2-propen-1-one<sup>11</sup> (**2**; R = 2-C<sub>5</sub>H<sub>4</sub>N) by using NaH/Me<sub>2</sub>SO, CS<sub>2</sub> and CH<sub>3</sub>I and was obtained<sup>10</sup> as yellow needles (71%) from ethanol, mp 108-109 °C,  $\nu_{\text{CO}}$  1605 cm<sup>-1</sup>, M<sup>+</sup> 225. This  $\alpha$ -ketoketene dithioacetal (3.0 g, 0.013 mol) was added to a solution of 2-acetylpyridine (1.6 g, 0.013 mol) and potassium *tert*-butoxide (3.0 g, 0.027 mol) in dry THF (80 mL). After stirring for 3 h at room temperature, ammonium acetate (10.0 g, 0.13 mol) and glacial acetic acid (80 mL) were added to the above solution which was then heated for 2 h with continuous removal of THF. After cooling, addition of ice water resulted in the separation of 2,6-di(2-pyridinyl)-4-(methylthio)pyridine (**4**, R = R<sup>1</sup> = 2-C<sub>5</sub>H<sub>4</sub>N; R<sup>2</sup> = SCH<sub>3</sub>; X = N) which crystallized from ethanol-water as colorless needles, 2.0 g (79%), mp 120-121 °C, M<sup>+</sup> 279. Refluxing this product with an excess of Raney nickel (6 h) in ethanol gave 2,2',2''-terpyridine (**4**, R = R<sup>1</sup> = 2-C<sub>5</sub>H<sub>4</sub>N; R<sup>2</sup> = H; X = N) as cream prisms (60%), mp 84-85 °C (lit.<sup>12</sup> mp 84-85 °C), M<sup>+</sup> 233.2735 (100%).

This reaction sequence is also useful for pyridine ring annulation to a variety of cycloalkyl ketones. Reaction of **2** (R = 4-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>) with cyclohexanone under the above conditions gave **5** (X = N) as colorless needles (10%), mp 105-106 °C, M<sup>+</sup> 285 (100%). In addition quinquepyridines may also be obtained by this route. Reaction of **6** (3.0 g, 0.013 mol) with 2-acetylpyridine (1.09 g, 0.0066 mol) and potassium *tert*-butoxide (3.0 g, 0.027 mol) in dry THF as above gave 2,6-bis[2'-(4'-methylthio)-6'-(2''-pyridinyl)pyridinyl]pyridine (**7**) as colorless flakes from DMF: 1.5 g (53%), mp 265-266 °C, M<sup>+</sup> 479.6271 (100%).

These 1,5-enediones also provide a ready entry into a variety of substituted pyrylium salts. This new procedure overcomes the

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