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.[22]

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Ketene Dithioacetals as Synthetic Intermediates. Synthesis of Unsaturated 1,5-Diketones[1]

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

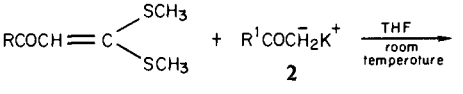
We now report a new and versatile synthesis of unsaturated 1,5-diketones from α-ketoketene dithioacetals. 1,5-Enediones are important intermediates in the synthesis of pyrylium and thiopyrylium salts[13] as well as pyridines[13,14] and have been prepared from β-chlorovinyl ketones and β-diketones or β-keto esters,[15] by HIO_4 oxidation of cyclopentane-1,2-diols,[16] or from pyridines and pyrylium salts.[17] None of these reaction sequences provides a general synthesis of this class of compound.

Table I. 1,5-Enediones[a] 3 Derived from α-Ketoketene Dithioacetals 1[21]

R	R^1	mp, °C	yield, %	M^+	ν_{CO} (KBr), cm^{-1}
C_6H_5	C_6H_5	106-108	76	267	1680, 1630
$4\text{-}CH_3OC_6H_4$	$4\text{-}CH_3OC_6H_4$	159-161	100	356	1655
C_6H_5	$2\text{-}C_4H_3S$	116-118	61	302	1700, 1680, 1645, 1625
C_6H_5	$2\text{-}C_5H_4N$	124-125	58	248	1680, 1640
$2\text{-}C_4H_3O$[b]	$2\text{-}C_4H_3S$	140-142	47	292	1690, 1670, 1640, 1620
$2\text{-}C_4H_3S$	$2\text{-}C_4H_3S$	161-162	74	308	1620
$2\text{-}C_4H_3S$	$5\text{-Cl-}2\text{-}C_4H_2S$	134-135	55	342	1623
$4\text{-}CH_3OC_6H_4$	CH_3	106-107	42	264	1710, 1640

[a] All colorless or cream needles. [b] Acetic acid workup.

Our new route involves the conjugate addition of a methyl ketone carbanion to the α-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[18] (**1**; R = C_6H_5) (2.0 g, 8.9 mmol) to a solution of acetophenone (**2**; R^1 = C_6H_5) (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^1 = C_6H_5). This salt was



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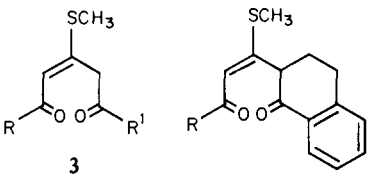

3 4

collected and added to an ice-cold aqueous 4% HCl solution[19] and, on standing, the resultant oily material crystallized. 1,5-Diphenyl-3-(methylthio)-2-pentene-1,5-dione (**3**; R = R^1 = C_6H_5) crystallized from petroleum ether (bp 80-100 °C) as pale yellow prisms, mp 106-108 °C. Similarly **4** (R = $4\text{-}CH_3OC_6H_4$) obtained from **1** (R = $4\text{-}CH_3OC_6H_4$) and α-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[20] consistently the best results; e.g., sodium ethoxide in ethanol resulted in β-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 (± 0.4%) for CHN where appropriate.

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as well as condensation to a more complex α-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 α-ketoketene dithioacetals employed reaction of the methyl ketone (0.5 mol) with NaH (1.0 mol) in Me_2SO 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 α-ketoketene dithioacetal component. In addition to the question of availability of the ketone, we found that the α-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[22] 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.

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Ketene Dithioacetals as Synthetic Intermediates. A Versatile Synthesis of Pyridines, Polypyridinyls, and Pyrylium Salts[1]

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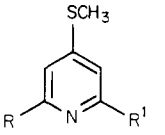
Noteworthy among the numerous syntheses of substituted pyridines described[2] in the literature is the use of organolithium compounds for the preparation of arylpyridines,[3] 2,2′-bipyridinyls,[4] and 2,2′,2″-terpyridinyls[5] and the application of pyridinium phenacylides or their salts in the synthesis of a wide variety of 2,4,6-trisubstituted pyridines.[6] 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,[7] and the 4′-(4-methoxyphenyl)terpyridinyl[8] and its sulfonated[9] derivative have been introduced in clinical chemistry for the estimation of Fe^{2+}. 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 a versatile, direct synthesis of a variety of substituted pyridines and oligopyridines with favorable solubility characteristics.

Table I. Substituted Pyridines Derived from α-Ketoketene Dithioacetals **2**[11]



R	R^1	mp, °C	yield, %	$M^{+\cdot}$[a]
C_6H_5	C_6H_5	105–107	81	277
4-$CH_3OC_6H_4$	CH_3	69–70	70	245[b]
4-BrC_6H_4	4-BrC_6H_4	115–116	85	435
4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	90.5–91	48	337
C_6H_5	2-C_5H_4N	80–81	89	278
2-C_5H_4N	2-C_5H_4N	133–133.5	79	279
2-C_5H_4N	2-C_4H_3S	133–134	80	284
6-Br-2-C_5H_3N	6-Br-2-C_5H_3N	184–185	31	437
2-C_4H_3S	2-C_4H_3S	115–116	99	289
2-C_4H_3S	5-Cl-2-C_4H_2S	115–116	72	323
2-C_4H_3O	2-C_4H_3O	96–97	64	257
2-C_4H_3O	2-C_4H_3S	95–97	74	273

[a] Relative intensities, 100%. [b] 93%.

Our "one-pot", two-component procedure involves the in situ generation of unsaturated 1,5-diketones derived[10] by reaction of α-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**, $R = R^1 = 2\text{-}C_5H_4N$; $R^2 = H$; X = N) illustrates the general procedure used.

2-Acetylpyridine (**1**, R = 2-C_5H_4N) was converted into 3,3-bis(methylthio)-1-(2-pyridinyl)-2-propen-1-one[11] (**2**; R = 2-C_5H_4N) by using NaH/Me_2SO, CS_2 and CH_3I and was obtained[10] as yellow needles (71%) from ethanol, mp 108–109 °C, ν_{CO} 1605 cm^{-1}, $M^{+\cdot}$ 225. This α-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**, $R = R^1 = 2\text{-}C_5H_4N$; $R^2 = SCH_3$; X = N) which crystallized from ethanol–water as colorless needles, 2.0 g (79%), mp 120–121 °C, $M^{+\cdot}$ 279. Refluxing this product with an excess of Raney nickel (6 h) in ethanol gave 2,2′,2″-terpyridine (**4**, $R = R^1 = 2\text{-}C_5H_4N$; $R^2 = H$; X = N) as cream prisms (60%), mp 84–85 °C (lit.[12] mp 84–85 °C), $M^{+\cdot}$ 233.2735 (100%).

This reaction sequence is also useful for pyridine ring annulation to a variety of cycloalkyl ketones. Reaction of **2** (R = 4-$CH_3OC_6H_4$) with cyclohexanone under the above conditions gave **5** (X = N) as colorless needles (10%), mp 105–106 °C, $M^{+\cdot}$ 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, $M^{+\cdot}$ 479.6271 (100%).

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

† Corning Glass Works Foundation Fellow, 1978.
(1) Supported in part by NSF Grant CHE 79-01704.
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