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SYNTHESIS OF α-PYRONES FROM α-OXO KETENE DITHIOACETALS

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Abstract: α-Oxo ketene dithioacetals can be converted into α-pyrones in a three step process involving 1,2-nucleophilic addition of ester or ketone enolate anions, acid promoted rearrangement, and subsequent enol lactonization. Utilization of ester enolates affords 6-alkylthio α-pyrones while ketone enolates give 3-alkyl substituted α-pyrones.

We recently described a synthesis of α-pyrones[1] from vinylogous thiol esters[2] which in turn were readily prepared[3] from α-oxo ketene dithioacetals.[4] The synthetic route from α-oxo ketene dithioacetals involved chemoselective organocopper substitution reactions followed by 1,2-nucleophilic addition of ester enolates to the vinylogous thiol esters, acid promoted rearrangement of intermediate α-hydroxy ketene dithioacetals, and a "one pot" ester hydrolysis and enol lactonization process. Although the substitution pattern at all four of the olefinic carbon atoms of the pyrone ring could be readily altered in this versatile synthetic route, the method required four steps. In addition, the synthesis of 3-alkyl substituted pyrones required the addition of secondary carbanions derived from substituted acetates. In an effort to shorten the synthetic sequence and to provide a general route to 6-alkylthio and 3-alkyl substituted α-pyrones we have examined procedures involving direct addition of ester and ketone enolates to α-oxo ketene dithioacetals (eqs. 1-2).

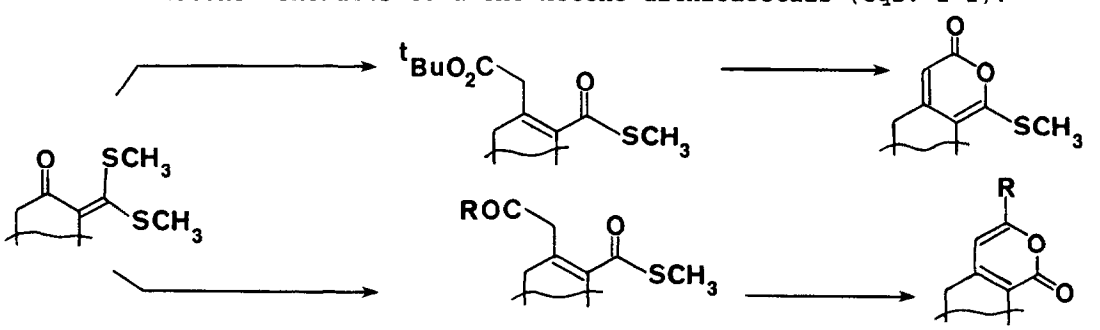
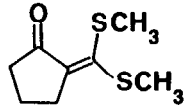
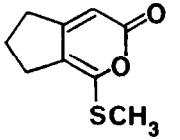
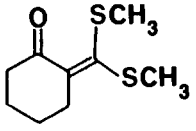
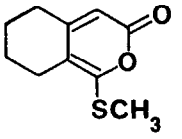
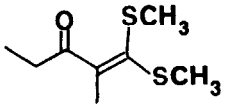
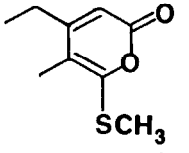
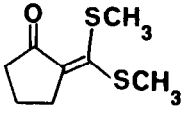
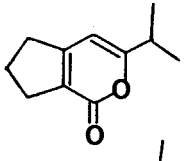
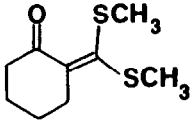
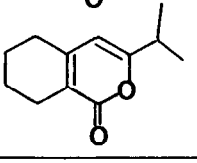


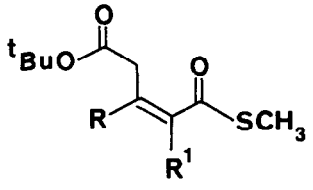
Table 1. Synthesis of α-Pyrones from α-Oxo Ketene Dithioacetals.

Entry	Substrate	Enolate[a]	Hydrol cond[c] (time)	Hydrol Products 1[d], 2a[e], 2b[f], 3[g] % Yield[b]	Enol Lactonization cond[h] (time)	α-Pyrone	% Yield[b]
1		A	1 (7 h)	87[d]	X (21 h)		93
2		A	1 (6 h)	76[d]	X (16 h)		85
3		A	1 (24 h)	21[d] +	X (16 h)		74 88(92)
4		B	1 (2 h)	46[e]	Y (20 h)		96
5			2 (18 h)	63[f]	X (10 h)		62
6		B	3 (5 min)	93[g,i]	1 (20 h)		52

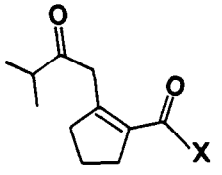
[a] A = $LiCH_2CO_2{}^tBu$. B = $LiCH_2COCHMe_2$. [b] Yields are based upon isolated products purified by chromatography (gravity or medium pressure) unless otherwise noted. [c] 1 = 1.5 M HBF_4, THF, H_2O (2:1:1 v/v). 2 = HgO (1.75 eq), HBF_4, THF, H_2O (2:1:1). 3 = 1 M HCl. [d,e,f,g] See text for structures. [h] X = $(CF_3CO)_2O$ (2-3 mL/0.5 mmol substrate), CF_3COOH (5-10 eq). Y = $Hg(OAc)_2$ (1.2 eq), $(CF_3CO)_2O$, CF_3COOH. [i] Determined from NMR on the isolated crude material.

Utilization of ketone enolates could in principle provide a general route to 3-alkyl substituted pyrones and afford a different regiochemistry than ester enolates in the annulation of the pyrone ring onto cycloalkanones.

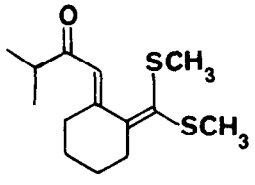
Although treatment of α-oxo ketene dithioacetals with tert-butyl lithioacetate[5] (i. LDA, THF, -78°C. ii. $CH_3CO_2{}^tBu$) resulted in complete consumption of starting material, quenching the reaction with HBF_4 afforded eleven spots on a TLC chromatogram. Increasing the reaction time or utilization of HBF_4/HgO afforded mixtures of unsaturated acid, unsaturated thiol ester, α-hydroxy ketene dithioacetal, or α-pyrone depending upon the substrate structure. Under these hydrolysis conditions, the cyclohexanone derivative never afforded the annulated pyrone in yields greater than 40%. Subsequently, it was discovered that quenching of the Rathke[5] ester enolate addition reaction with 2 M HCl afforded the α-hydroxy ketene dithioacetals in nearly quantitative yield. These crude allylic alcohols could be rearranged [1.5 M HBF_4, THF, H_2O (2:1:1)] to the corresponding δ-carboalkoxy-α,β-unsaturated thiol esters **1a-c** (Table 1, entries 1-3). The cyclic substrates afforded thiol esters **1a-b** in excellent to good yields while the acyclic analog gave a low yield of thiol ester **1c** along with the desired pyrone in good yield. The unsaturated thiol esters were converted uneventfully into 6-alkylthio pyrones by treatment with CF_3COOH in $(CF_3CO)_2O$ in excellent yields with enol lactonization occuring exclusively onto the carboalkoxy ester (Table 1, entries 1-3). No cyclization onto the thiol ester was observed.



1 **a** R = R^1 = -$(CH)_3$-
b R = R^1 = -$(CH_2)_4$-
c R = Et; R^1 = Me



2 **a** X = SCH_3
b X = OH



3

The intermolecular aldol reaction between ketones is often problematic, although conditions have been devised to drive the equilibrium of the initial 1,2-nucleophilic addition step to the right.[6] Utilization of the lithium enolate of isopropyl methyl ketone in Et_2O between -35 and -30° C for 20 min [6b] afforded the aldol adducts in excellent yields for the cyclopentanone (91%) and cyclohexanone (93%) derivatives, respectively. However, only very low yields could be obtained with acyclic substrates and these yields could not be increased by utilization of zinc[6b] or cerium[7] enolates. These aldol addition

products were very sensitive to hydrolysis conditions. The cyclopentanone derivative could be hydrolyzed to either the unsaturated thiol ester **2a** (entry 4) or acid **2b** (entry 5) while the cyclohexanone afforded the aldol condensation product **3** in high yield (entry 6) upon quenching with 2 M HCl. Quenching of the latter reaction with HBF_4 and stirring for 18 h afforded the pyrone in 32% yield in one pot. This yield could not be increased by variation of reaction time or addition of HgO and the multi-pot process gave the higher overall yield of 52%. Dienone **3** could be cyclized to the pyrone with HBF_4 while the thiol ester **2a** was treated with trifluoroacetic acid/trifluoroacetic anhydride in the presence of HgO to facilitate expulsion of the methylthio leaving group.

In summary, the direct addition of ester or ketone enolate anions to α-oxo ketene dithioacetals can be utilized in a short synthesis of 6-alkylthio and 3-alkyl substituted α-pyrones. The three step transformation can be accomplished in good overall yield without the isolation and purification of intermediates. The 6-alkylthio derivatives provide a functional group control element that can be exploited in subsquent reactions of the α-pyrones. The 6-alkoxy α-pyrones have been elegantly exploited in syntheses of anthracyclines.[8]

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