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# A facile method for the synthesis of substituted 2-ylidene-1,3-oxathioles from acetophenones

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We dedicate this Letter to our beloved teacher and research guide Dr. C. V. Asokan who passed away on February 3, 2007

**Abstract**—Compounds incorporating 1,3-oxathiole moieties in their frameworks are biologically active. Active methylene ketones can be easily converted to the corresponding dithiocarboxylates by treatment with trithiocarbonate in the presence of sodium hydride. The reactions of aroyl dithiocarboxylates with α-haloketones such as phenacyl bromide or bromoacetone afford substituted 2-ylidene-1,3-oxathioles in good yields.


As a part of our ongoing research on β-oxodithiocarboxylates and their derivatives[1–11] we reacted aroyl dithiocarboxylates with α-haloketones in the presence of sodium hydride, in an effort to overcome the difficulties involved in the selective sequential alkylation of dimetalloketene dithioacetals for the synthesis of thiophenes.[12–19] Contrary to our expectations, these reactions afforded substituted 1,3-oxathioles in good yields and the results are reported in this Letter. In the literature, there are only a few reports on the synthesis of 1,3-oxathioles.[20,21] 1,3-Dithiafulvenes,[22–27] being electronically equivalent to 1,3-oxathioles, have found wide applications as organic semiconductors, photosensitive materials and light emitting devices; 1,3-oxathioles are not common and their properties remain unexplored. Recent studies have shown that compounds incorporating this heterocyclic moiety in their skeleton are biologically active including anti-HIV activity.[21,28]

β-Oxodithiocarboxylates **2** have been prepared by refluxing active methylene ketones **1** with dimethyl trithiocarbonate[29–32] in the presence of a base or by the demethylation[7] or sulfhydrolysis[1,2] of α-oxoketene dithioacetals. However, in our laboratory we prepared them using a modified procedure.[33] In this method the acetophenones were treated with dimethyl trithiocarbonate in DMF/hexane solvent mixture (1:10) at room temperature in the presence of sodium hydride. The reaction was complete within an hour yielding the corresponding β-oxodithiocarboxylates **2** in excellent yields. These were then reacted with α-haloketones including phenacyl bromide and bromoacetone in the presence of sodium hydride in toluene.[34] The reactions were monitored by TLC and were complete within 48 h affording substituted 1,3-oxathioles **3a**–**e** in good yields (Scheme 1, Table 1).

The formation of β-oxodithiocarboxylates **2** from acetophenones had been described earlier.[29–32] However, the enhancement in the reaction rate in DMF can be explained by the stabilizing effect of the polar solvent on the intermediate thiolate ion. The formation of 2-ylidene-1,3-oxathioles **3** occurs via a two-step reaction. Firstly, reaction of the α-haloketone with aroyl dithiocarboxylate **2** in the presence of sodium hydride gives an intermediate ketene dithioacetal **4**. We expected that **4** would undergo an intramolecular aldol type condensation reaction in the presence of sodium hydride to yield functionalized thiophene **6**. In contrast to our expectations **4** underwent base induced intramolecular heteronucleophilic addition of the enolate anion to the ketene dithioacetal moiety resulting in the formation of substituted 1,3-oxathioles **3a**–**f** (Scheme 2).

*Keywords*: 1,3-Oxathioles; α-Oxoketene dithioacetals; Active methylene ketones; Dithiocarboxylates.
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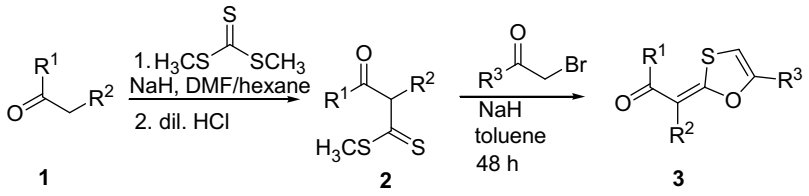
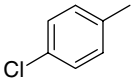
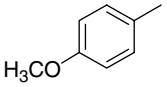
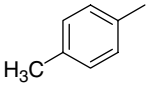
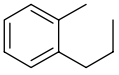
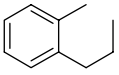



**Scheme 1.**

**Table 1.** Synthesis of 1-aryl-2-(5-aryl/alkyl-1,3-oxathiol-2-yliden)-1-ethanones **3**

| 3 | $R^1$ | $R^2$ | $R^3$ | Yield (%) |
|---|---|---|---|---|
| **a** |  | H | Ph | 55 |
| **b** |  | H | Ph | 60 |
| **c** |  | H | Ph | 65 |
| **d** |  | H | Ph | 52 |
| **e** |  | | Ph | 50 |
| **f** |  | | $CH_3$ | 60 |

The IR spectrum of **3a** showed absorptions at 1690, 1480, 1300 and 1120 $cm^{-1}$. In the $^1H$ NMR spectrum (300 MHz, $CDCl_3$), **3a** demonstrated resonances at $\delta$ 6.66 and 7.20 in addition to signals at $\delta$ 7.41–7.49, 7.66 and 7.98 due to the phenyl protons. The absence of a methylsulfanyl group and the presence of vinylic protons in the spectrum indicated that the product formed in this reaction was the 1,3-oxathiole derivative. In the $^{13}C$ NMR spectrum, C-4 and C-5 of 1,3-oxathiole occurred as resonances at $\delta$ 99.62 and 124.90, respectively. The signals at $\delta$ 175.92, 186.43 and 150.48 correspond to C-2 of the oxathiole ring, the carbonyl carbon atom and the α-carbon atom, respectively, and are in accordance with the proposed structure. The EIMS spectrum ($M^+ = 280$, 99%) and CHN ($C_{17}H_{12}O_2S$ requires C, 72.83; H, 4.31. Found: C, 72.68; H, 4.33.) also confirmed the structure of **3a** as 1-phenyl-2-(5-phenyl-1,3-oxathiol-2-yliden)-1-ethanone. Similarly, 1-(4-methoxyphenyl)-2-(5-phenyl-1,3-oxathiol-2-yliden)-1-ethanone **3c** showed absorptions at 1595, 1548, 1440, 1305 and 1140 $cm^{-1}$ in the IR spectrum; resonances at $\delta$ 3.87 due to $OCH_3$, $\delta$ 6.65 due to the vinylic proton and at $\delta$ 7.18 due to H-4 in the $^1H$ NMR spectrum. Signals at $\delta$ 55.40 due to $OCH_3$, $\delta$ 99.50 due to C-4, $\delta$ 124.90 due to C-5, $\delta$ 150.19 due to the α-carbon atom, $\delta$ 175.25 due to C-2 and at $\delta$ 185.49 due to the carbonyl carbon atom in the $^{13}C$ NMR spectrum also confirmed the structure of **3c**. The EIMS spectral value ($M^+ = 310$, 61%) and CHN ($C_{18}H_{14}O_3S$ requires C, 69.66; H, 4.55. Found: C, 69.93; H, 4.52.) further confirmed the structure. All compounds **3a**–**f** showed characteristic spectral properties of 1,3-oxathiole-2-ylidene derivatives.

In conclusion we have reported the simple alkylation reactions of aroyl dithiocarboxylates for the synthesis of potentially biologically important 1,3-oxathioles.

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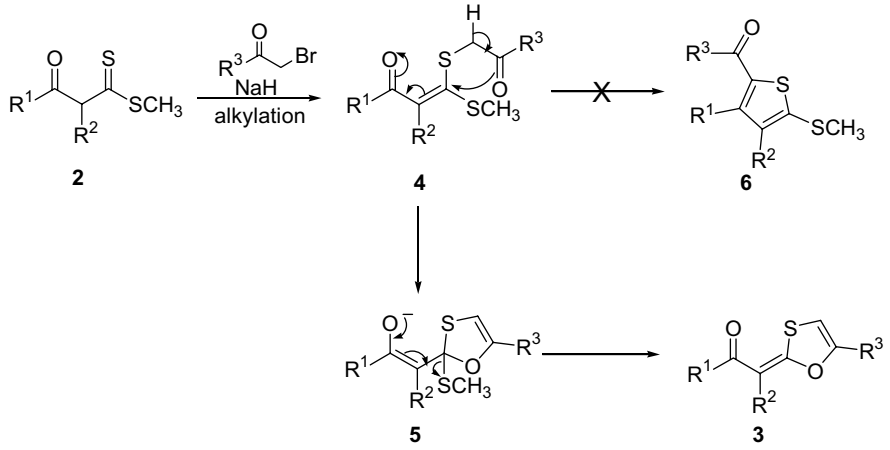


**Scheme 2.**

of Chemistry, Madurai Kamaraj University for providing spectral and analytical data.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.09.076.

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33. *Synthesis of β-Oxodithiocarboxylates; general procedure:* acetophenone **1** (20 mmol) was added to a suspension of NaH (50% suspension in mineral oil, 1.92 g, 40 mmol) in DMF/hexane solvent mixture (50 mL, 1:10; hexane bp 40–65 °C). Trithiocarbonate (20 mmol) was added to the solution and stirred well for 1 h. The reaction formed an interface between the two layers present in the reaction mixture. The reaction was exothermic and the reaction mixture was cooled in a water bath at room temperature. After 1 h, the reaction mixture was acidified with 1 N HCl (20 mL). The precipitated dithiocarboxylates **2** were filtered, dissolved in dichloromethane, dried over anhydrous sodium sulfate and the solvent was evaporated to give the corresponding β-oxodithiocarboxylates in good yields.
34. *Representative experimental procedure for the synthesis of 1-aryl-2-(5-aryl/alkyl-1,3-oxathiol-2-yliden)-1-ethanones*: NaH (50% suspension in mineral oil, 0.48 g, 10 mmol) was washed with petroleum ether (bp 40–65 °C) and suspended in 20 mL of dry toluene. Methyl 3-oxo-3-phenylpropanedithioate **2a** (1.05 g, 5 mmol) was added and the mixture was stirred for 15 min. To this phenacyl bromide (5 mmol) was added and the reaction was stirred at room temperature for 48 h. The reaction mixture was then added to cold water (50 mL) and extracted with diethyl ether ($3 \times 50$ mL). The combined organic layer was washed with water ($3 \times 50$ mL), dried ($Na_2SO_4$) and the solvent was removed under vacuum. The residue was column chromatographed over silica gel using hexane/ethyl acetate (20:1) as eluent to give the title compound **3a** (0.77 g, 55%) as a yellow crystalline solid, mp, 152–154 °C ($C_{17}H_{12}O_2S$ requires C, 72.83; H, 4.31. Found: C, 72.68; H, 4.33.); $\nu_{max}$ (KBr) 1690, 1568, 1480, 1300, 1120, 870 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 6.66 (1H, s, vinylic), 7.20 (1H, s, C-4); 7.41–7.49 (6H, m, ArH), 7.66 (2H, d, $J = 7$ Hz, ArH), 7.98 (2H, d, $J = 7$ Hz, ArH); $^{13}C$ NMR (100.40 MHz, $CDCl_3$): $\delta$ 99.62, 124.90, 127.36, 127.48, 127.88, 128.42, 128.99, 129.50, 131.71, 138.40, 150.48, 175.92, 186.43; EI-MS *m/z*: 280 ($M^+$, 99%), 203 (67), 134 (48), 105 (83), 77 (100).