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REACTION OF 1,3-OXATHIIN-6-ONES WITH BASES: SYNTHESIS OF 4-MERCAPTO-2-PYRONE

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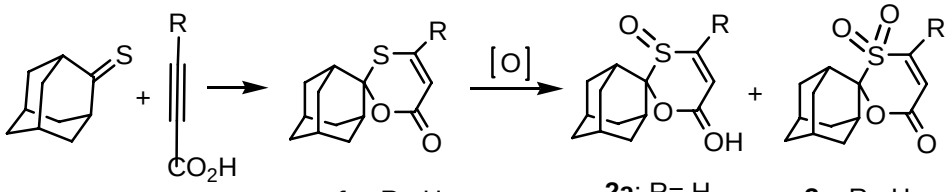
Abstract - The reaction of 4-aryl-1,3-oxathiin-6-one 3,3-dioxide **3c** with secondary amine gave cinnamamides **6** and ammonium sulfinates **7**. On the other hand, the reaction of 4-methyl-1,3-oxathiin-6-one **1b** with LDA, followed by the addition of benzoyl chloride, gave corresponding phenacyldioxenone **8a** and 5-benzoyl-4-methyl-1,3-thiodioxenone **9** in nearly 1:1 ratio, whereas the reaction with 1-benzoyl-1,2,3-benzotriazole gave only **8a** in 78% yield. Thermolysis of **8a** gave the corresponding 4-mercapto-2-pyrone **4a** in 62% yield.

INTRODUCTION

The chemistry of sulfur-containing heterocycles is of current interest. We have reported that the reaction of thioketones with propiolic acid gave corresponding 1,3-oxathiin-6-ones (**1**) in good yields.[1] Oxidation of **1** gave corresponding sulfoxides (**2**) and sulfones (**3**), and acidic methanolysis of **3b** afforded the corresponding ester. Acidic hydrolysis of **1**~**3** generally afforded polymeric products (Scheme 1).[2]



1a: R= H
1b: R= Me
1c: R= Ph

2a: R= H
2b: R= Me
2c: R= Ph

3a: R= H
3b: R= Me
3c: R= Ph

Scheme 1

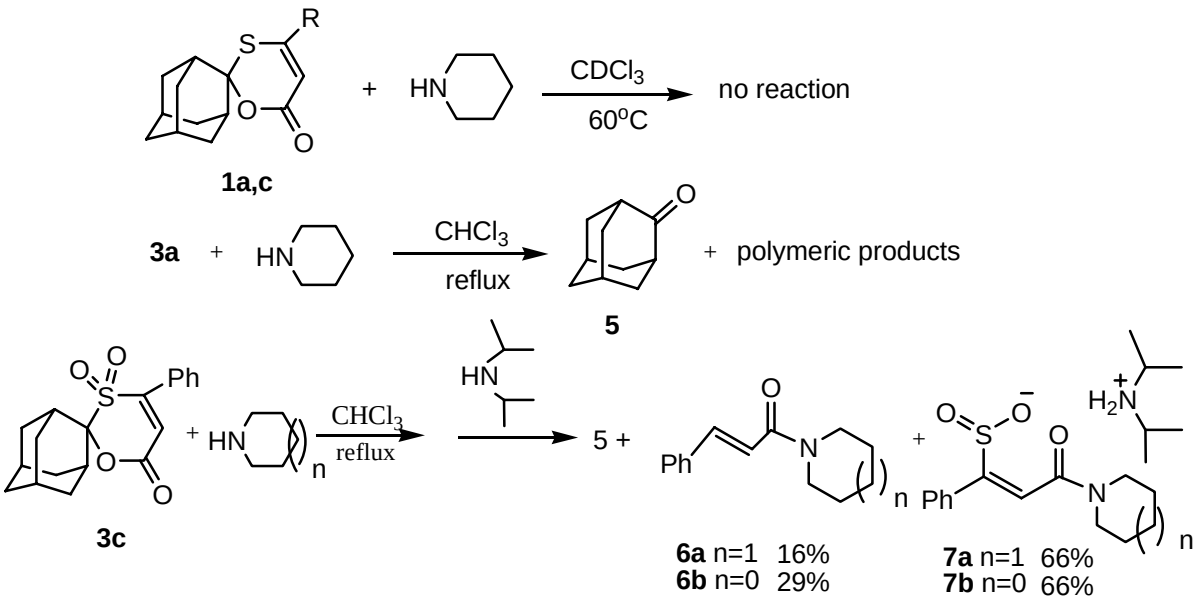
On irradiation in methanol, **1** undergoes both solvent addition to methoxylactone and cycloreversion.[3] The fact that sulfones **3** are more stable than sulfoxides **2** has made their reactivity under basic conditions an intriguing topic of study. Katrizky *et al*. reported the synthesis of 4-hydroxypyrones by thermolysis

of 4-phenacyl-1,3-dioxin-6-one.[4] We have devoted much of our resources to the synthesis 4-mercapto-2-pyrone (**4**) by thermolysis of 4-acyl-1,3-oxathiin-6-one since this compound is a good precursor of bicyclic pyrones.[5] Herein, we report the basic reactivity of 1,3-oxathiin-6-one **1**, sulfoxide **2,** and sulfone **3,** and the synthesis of 4-mercapto-2-pyrone **4** from **1**.

RESULTS AND DISCUSSION

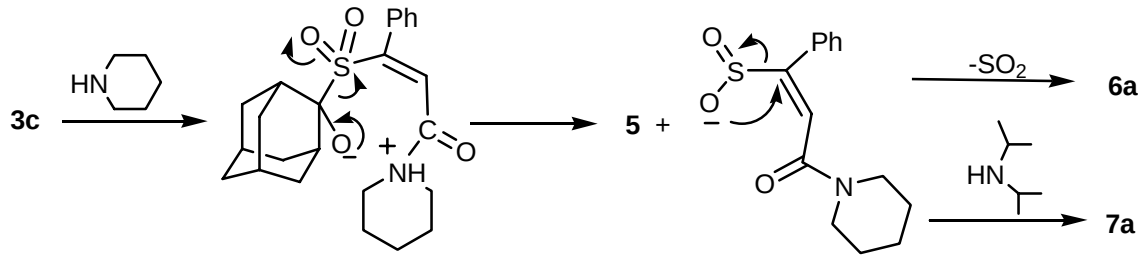
REACTION OF 4-PHENYL-1,3-OXATHIIN-6-ONE 3,3-DIOXIDE 3c WITH BASE

The oxidation of 1,3-oxathiin-6-ones **1a-c** with *m*-CPBA or dimethyldioxirane gave corresponding sulfoxides **2a-c** and sulfones **3a-c** in good yields.[2] The reaction of **1a** with piperidine gave starting **1a** almost quantitatively, whereas the reaction of sulfone **3a** with piperidine afforded adamantan-2-one (**5**) (86%) and polymeric products. The reaction of sulfoxide **2a** and sulfone **3a** with piperidine also gave complex mixtures. On the other hand, treatment of sulfone **3c** with piperidine, followed by the addition of diisopropylamine, resulted in the formation of adamantan-2-one **5**, *trans*-cinnampiperidide (**6a**), and diisopropylammonium sulfinate (**7a**). In the absence of diisopropylamine, the corresponding sulfinate was obtained as impure oily crystals. Similarly, the reaction of **3c** with pyrrolidine gave corresponding sulfinate **7b** in 66% yield along with *trans*-cinnampyrrolidide **6b** (29%) (Scheme 2).



Scheme 2

The reaction is speculated to proceed as follows. The secondary amine attacked the dioxide's ester carbonyl to give **5** and sulfinate intermediate, which further reacted with additional diisopropylamine to give sulfinate **7**. Under refluxing conditions, sulfinate was decomposed to give cinnamamide **6** (Scheme 3).

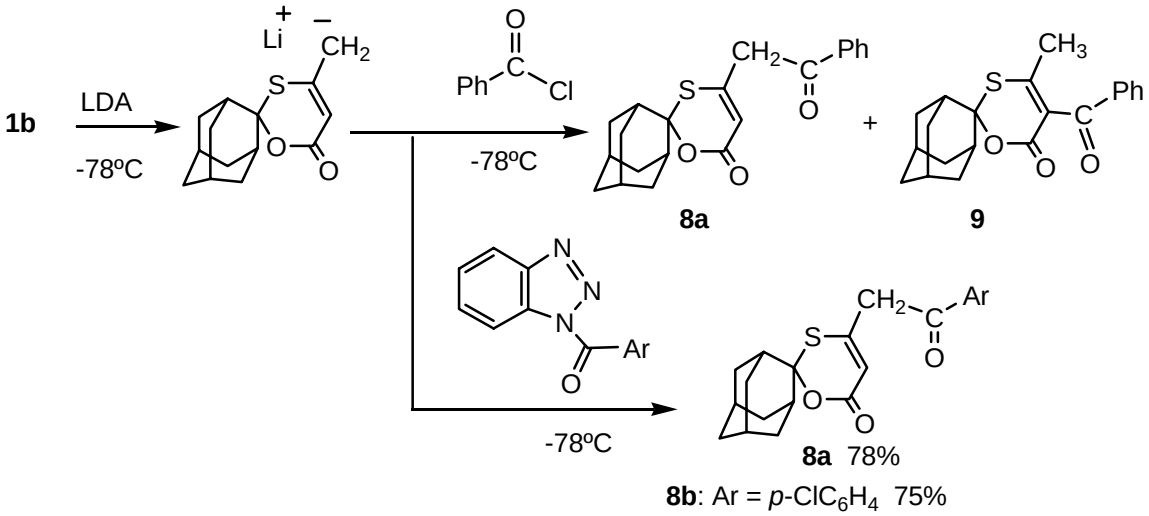


Scheme 3

To confirm this mechanism, we performed the thermolysis of isolated sulfinate **7**. When sulfinate **7a** was refluxed in chloroform for 24 h, cinnamamide **6a** was obtained in 76% yield. The decomposition was completed after 72 h. A similar basic sulfinyl group elimination was observed by Kim and Jeong.[6]

REACTION OF 4-METHYL-1,3-OXATHIIN-6-ONE WITH BENZOYL DERIVATIVES

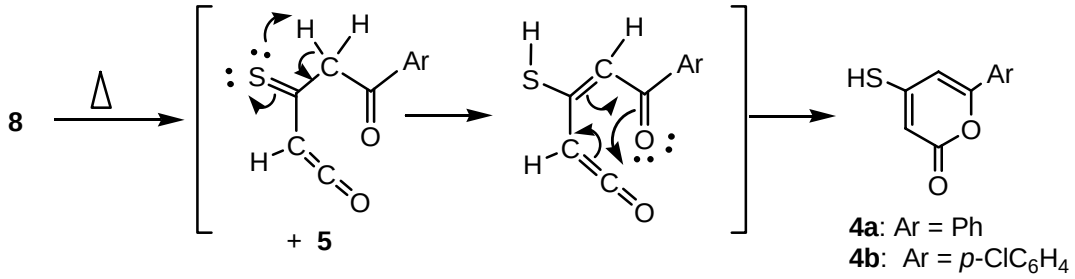
We then tried the synthesis of 4-phenacyl-1,3-oxathiin-6-one (**8a**) to investigate the thermal behavior of this compound. Benzoylation of 4-methyl-1,3-oxathiin-6-one **1b** was initially carried out by using benzoyl chloride. Treatment of **1b** with LDA, followed by the addition of benzoyl chloride at -78 °C, resulted in the formation of two benzoylated products, **8a** (35%) and 5-benzoyl-4-methyl-1,3- oxathiin-6-one (**9**) (36%), indicating that the reaction has no regioselectivity. However, when 1-benzoyl-1,2,3-benzotriazole was used as a benzoylating reagent, **8a** was produced in 78% yield (Scheme 4).



Scheme 4

With the desired **8a** in hand, we proceeded to the thermolysis of this compound. Thermolysis of **8a** in refluxing toluene led to the recovery of starting **8a** in almost quantitative yield. Additionally, **8a** was also recovered in refluxing xylene, suggesting that **8a** is to too stable to react under ordinary solutions. Finally, when the thermolysis was carried out at 220 °C in a glass-tube oven under reduced pressure (50 mmHg), 4-mercapto-6-phenyl-2-pyrone (**4a**) was obtained in 62% yield. 1,3-Oxathiin-6-one **8b** did not afford mercaptan **4b** in pure form, and many side products were formed due to the severe reaction

conditions (Scheme 5).



Scheme 5

Previously, synthesis of 4-mercapto-6-methyl-2-pyrones was reported by Majumdar and Muhuri.[7] However, there is no report on the synthesis of 6-phenyl derivatives. In summary, we have synthesized novel types of ammonium sulfinates **7** and 4-mercapto-2-pyrone **4a** from 1,3-oxathiin-6-one derivatives.

EXPERIMENTAL

Flash chromatography was carried out with Merck Kieselgel 60 (230-400 mesh). Thin layer chromatography (TLC) was carried out on commercially available pre-coated aluminum plates (Merck silica Kieselgel 60F254). All solvents were distilled before use, and no further treatment was carried out. NMR spectra were measured on a Varian Innova-400 (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR). Melting points were uncorrected. 1-Benzoyl-1,2,3-benzotriazole was synthesized according to the reported method.[4]

Reaction of Sulfone 3c with Piperidine

To a solution of sulfone **3c** (0.172 g, 0.5 mmol) in $CHCl_3$ (8 mL) was added piperidine (0.096 g, 1.1 mmol). After refluxing for 10 h, diisopropylamine (0.101 g, 1.0 mmol) was added. After stirring for 1 h, the reaction mixture was evaporated to give a brown oil, which was chromatographed over silica gel by elution with CH_2Cl_2: EtOAc (3:1) and then MeOH: EtOAc (1:2) to give *trans*-cinnampiperidide **6a** (0.018 g, 0.08 mmol) and diisopropylammonium sulfinate **7a** (0.125 g, 0.33 mmol). Compound **6a**: colorless crystals: mp 114-116 ^{o}C (lit.,[8] mp 114-117 ^{o}C). Compound **7a**: Colorless crystals: mp 115-117 ^{o}C. ^{1}H NMR ($CDCl_3$) δ = 1.20 (d, 12H, J = 6.8 Hz, CH_3), 1.55 (br s, 2H, CH_2), 1.64 (br s, 4H, CH_2), 3.15 (sept, 2H, J = 6.8 Hz, CH), 3.55-3.62 (m, 4H, NCH_2), 6.13 (s, 1H, =CH), 7.27-7.33 (m, 3H, Ph), 7.56-7.62 (m, 2H, Ph). ^{13}C NMR ($CDCl_3$) δ = 19.42 (CH_3), 24.76 (CH_2), 24.55 (CH_2), 26.22 (CH_2), 42.47 (NCH_2), 47.04 (NCH), 48.23 (NCH_2), 122.32 (=CH), 127.97, 128.05, 129.08, 135.01 (Ph), 159.14 (=C), 167.01 (C=O). Found: C, 63.43; H, 8.49; N, 7.43. Calcd for $C_{20}H_{32}N_2O_3S$: C, 63.12; H, 8.48; N, 7.36.

Similarly, the reaction of **3c** with pyrrolidine was carried out. Cinnampyrrolidide **6b** (29%): mp 93-94 ^{o}C (lit.,[8] 94-95 ^{o}C). Diisopropylammonium sulfinate **7b** (66%): colorless oil. ^{1}H NMR ($CDCl_3$) δ = 1.15 (d, 6H, J = 6.4 Hz, CH_3), 1.70-1.92 (m, 4H, CH_2), 3.12 (sept, 2H, J = 6.4 Hz, CH), 3.35-3.50 (m, 4H,

NCH_2), 6.08 (s, 1H, =CH), 7.20-7.25 (m, 3H, Ph), 7.41-7.46 (m, 2H, Ph). ^{13}C NMR ($CDCl_3$) δ = 19.09 (CH_3), 24.47 (CH_2), 25.99 (CH_2), 45.77 (NCH_2), 47.04 (NCH), 47.85 (NCH_2), 122.84 (=CH), 127.82, 128.15, 129.19, 134.36 (Ph), 162.34 (=C), 167.07 (C=O). Exact Mass (ESI): Calcd for M^-: $C_{13}H_{14}NO_3S$: 264.0666. Found 264.0694.

Reaction of 4-Methyl-1,3-oxathiin-6-one 1b with LDA followed by Addition of Benzoyl Chloride

To a solution of lithium diisopropylamide prepared from BuLi (1 M solution in hexane, 1.5 mL, 1.5 mmol) and diisopropylamine (0.18 g, 1.8 mmol) in THF (10 mL) was added a solution of **1b** (0.25 g, 1.0 mmol) in THF (5 mL) at -78 ^oC. After stirring for 3 h, benzoyl chloride (0.155 g, 1.1 mmol) in THF (5 mL) was added dropwise. After stirring for 5 h at this temperature, the reaction mixture was warmed to rt and water was added. The water layer was extracted with CH_2Cl_2 (15 mL x 2) and washed with water (10 mL x 2). The combined organic layer was dried over $MgSO_4$, filtered, and evaporated to give pale brown oily crystals, which were chromatographed over silica gel by elution with CH_2Cl_2 to give 4-phenacyl-1,3-oxathiin-6-one **8a** (0.124 g, 0.35 mmol) and 5-benzoyl-4-methyl-1,3-oxathiin-6-one **9** (0.127 g, 0.36 mmol). Compound **8a**: colorless crystals: mp 142-143 ^oC. ^1H NMR ($CDCl_3$) δ = 1.64 (br d, *J* = 12.4 Hz, CH_2), 1.72 (br s, 2H, CH_2), 1.77 (br d, 2H, *J* = 13.2 Hz, CH_2), 1.86 (br d, 2H, *J* = 16.4 Hz, CH_2), 1.98 (br d, 2H, *J* = 13.2 Hz, CH_2), 2.33 (br d, 2H, *J* = 12.4 Hz, CH_2), 2.51 (br s, 2H, CH), 4.01 (s, 2H, CH_2), 6.10 (s, 1H, =CH), 7.49 (dd, 2H, *J* = 7.6 and 7.6 Hz, *m*-Ph), 7.61 (t, 1H, *J* = 7.6 Hz, *p*-Ph), 7.94 (dd, 2H, *J* = 7.6 Hz and 1.2 Hz, *o*-Ph). ^{13}C NMR ($CDCl_3$) δ = 26.69 (CH), 26.90 (CH), 32.65 (CH_2 x 2), 34.93 (CH_2 x 2), 36.72 (CH x 2), 37.77 (CH_2), 46.70 ($COCH_2$), 96.04 (S-C-O), 114.69 (=CH), 128.62 (Ph), 129.11 (Ph), 134.15 (Ph), 136.07 (Ph), 151.76 (=C), 162.75 (COO), 194.01 (C=O). Anal. Calcd for $C_{21}H_{22}O_3S$: C, 71.16; H, 6.26. Found: C, 70.93; H, 6.30. Compound **9**: colorless crystals: mp 112-113 ^oC. ^1H NMR ($CDCl_3$) δ = 1.70 (br d, *J* = 12.4 Hz, CH_2), 1.77 (br s, 2H, CH_2), 1.77 (br d, 2H, *J* = 13.2 Hz, CH_2), 1.82-1.96 (m, 4H, CH_2), 2.09 (br d, 2H, *J* = 9.2 Hz, CH_2), 2.10 (s, 3H, CH_3), 2.40 (br d, 2H, *J* = 12.4 Hz, CH_2), 2.60 (br s, 2H, CH_2), 7.48 (dd, 2H, *J* = 7.6 and 7.6 Hz, *m*-Ph), 7.58 (t, 1H, *J* = 7.6 Hz, *p*-Ph), 7.85 (dd, 2H, *J* = 8.0 Hz and 1.0 Hz, *o*-Ph). ^{13}C NMR ($CDCl_3$) δ = 21.93 (CH_3), 26.60 (CH), 26.87 (CH), 32.55 (CH_2 x 2), 34.91 (CH_2 x 2), 37.25 (CH x 2), 37.70 (CH_2), 94.80 (S-C-O), 123.43 (=C), 128.98 (Ph), 129.47 (Ph), 133.95 (Ph), 137.13 (Ph), 155.24 (=C), 161.40 (COO), 192.27 (C=O). Anal. Calcd for $C_{21}H_{22}O_3S$: C, 71.16; H, 6.26. Found: C, 71.23; H, 6.33.

Reaction of 1b with 1-Benzoyl-1,2,3-Benzotriazole

To a solution of lithium diisopropylamide prepared from BuLi (1 M solution in hexane, 1.5 mL, 1.5 mmol) and diisopropylamine (0.18 g, 1.8 mmol) in THF (10 mL) was added a solution of **1b** (0.25 g, 1.0 mmol) in THF (5 mL) at -78 ^oC. After stirring for 2 h, 1-benzoyl-1,2,3-benzotriazole (0.259 g, 1.1 mmol) in THF (5 mL) was added dropwise. After stirring for 3 h at this temperature, the reaction mixture was warmed to rt and water was added. The water layer was extracted with CH_2Cl_2 (5

mL x 2). The combined organic layer was dried over M_8SO_4, filtered, and evaporated to give pale brown oily crystals, which were chromatographed over silica gel by elution with CH_2Cl_2 to give **8a** (0.276 g, 0.78 mmol). Mp 142-143 ^oC.

Similarly, 4-(4'-chlorophenacyl)-1,3-oxathiin-6-one (**8b**) was obtained in 75% yield. Yellow crystals: mp 154-155 ^oC. ^1H NMR ($CDCl_3$) δ = 1.65 (br d, *J* = 12.8 Hz, CH_2), 1.73 (br s, 2H, CH_2), 1.78 (br d, 2H, *J* = 13.2 Hz, CH_2), 1.87 (br d, 2H, *J* = 15.2 Hz, CH_2), 1.98 (br d, 2H, *J* = 13.2 Hz, CH_2), 2.33 (br d, 2H, *J* = 13.2 Hz, CH_2), 2.51 (br s, 2H, CH), 3.99 (s, 2H, CH_2), 6.09 (s, 1H, =CH), 7.49 (dd, 2H, *J* = 6.8 and 1.6 Hz, ClPh), 7.89 (dd, 2H, *J* = 6.8 Hz and 1.6 Hz, ClPh). ^{13}C NMR ($CDCl_3$) δ = 26.66 (CH), 26.87 (CH), 32.64 (CH_2 x 2), 34.92 (CH_2 x 2), 36.72 (CH x 2), 37.74 (CH_2), 46.62 ($COCH_2$), 96.14 (S-C-O), 114.78 (=CH), 129.48 (Ar), 130.00 (Ar), 134.33 (Ar), 140.07 (Ar), 151.36 =C), 162.66 (COO), 192.84 (C=O). Anal. Calcd for $C_{21}H_{21}ClO_3S$: C, 64.85; H, 5.44. Found: C, 64.97; H, 5.42.

Thermolysis of 4-Phenacyl-1,3-oxathiin-6-one 8a

Compound **8a** (0.177 g, 0.5 mmol) was pipetted into a 5 mL round-bottomed flask that was fitted to a glass-tube oven, and the flask was heated gradually to 250 ^oC under reduced pressure (50 mmHg). At 220 ^oC, a pale yellow oil was obtained. The mixture was cooled to rt by allowing it to stand for 20 min. The mixture was chromatographed over silica gel by elution with CH_2Cl_2 to afford 4-mercapto-6-phenyl-2-pyrone **4a** (0.063 g, 0.31 mmol). Compound **4a**: yellow crystals: mp 194-195 ^oC. ^1H NMR ($CDCl_3$) δ =6.36 (d, 1H, *J* = 1.6 Hz, =CH), 6.64 (d, 1H, *J* = 1.6 Hz, =CH), 7.43-7.55 (m, 3H, Ph), 7.77-7.85 (m, 2H, Ph). ^{13}C NMR ($CDCl_3$) δ = 102.39 (=CH), 113.28 (=CH), 126.20 (Ph), 129.37 (Ph), 130.65 (Ph), 131.95 (Ph), 151.08 (=C), 160.07 (=C), 161.01 (C=O). Anal. Calcd for $C_{11}H_8O_2S$: C, 64.49; H, 3.95. Found: C, 64.14; H, 3.83. Under similar reaction conditions, thermolysis of **8b** was carried out. However, not mercapto-2-pyrone **4b** but a complex reaction mixture was obtained.

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