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Efficient synthesis of polyfunctionalized thiophene-2,3-diones and thiophen-3(2H)-ones using β-oxodithioesters

Sridhar Madabhushi, a,b Srinivas Kurva, a Vinodkumar Sriramoju, a Jagadeesh Babu Nanubolu b and Suresh Reddy Cirandur c

Efficient methods for the preparation of polyfunctionalized thiophene-2,3-diones and thiophen-3(2H)-ones using β-oxodithioesters were described. In this study, β-oxodithioesters were found to react directly with oxalyl chloride producing 4-aroyl-5-(methylthio)thiophene-2,3-diones in 96-98% yields. However, β-oxodithioesters were found to react efficiently with chloroacetic anhydride in the presence of a base catalyst such as DMAP, which gave 4-aroyl-5-(methylthio)thiophen-3(2H)-ones in 61-77% yields.

Biologically active compounds containing thiophenone as the pharmacophore are scarcely found in nature. Thiocremone (2,4-dihydroxy-2,5-dimethyl-thiophene-3-one) and thialactomycin (E)-4-hydroxy-3,5-dimethyl-5-(2-methylbuta-1,3-dien-1-yl)thiophen-2(5H)-one) are the important natural products, which contain the thiophenone core structure (Figure 1) and the recent studies unveiled many of the potential pharmacological applications of these compounds. For example, thiocremone, which occurs in garlic, was found to possess potent antioxidant, anticancer, antiinflammatory, antiobesity properties. Thialactomycin was isolated from the fermentation broth of a strain of actinomycetes (Nocardioides sp.) and has potent antibacterial properties against in vitro Gram positive, Gram negative and anaerobic bacteria. Hence, these compounds emerged as lead molecules in recent drug discovery studies and several thiophenone derivatives were identified to be potential therapeutics for the treatment of cancer, tuberculosis and the virulent malaria caused by the parasite Plasmodium falciparum.

In literature, efficient methods for the construction of thiophen-3(2H)-one ring structure are scarcely discussed. In recent years, studies were extensively focused on the applications of β-oxodithioesters in organic synthesis as versatile building blocks for the construction of a variety of biologically interesting heterocycles such as pyrazoles, isoxazoles, pyrimidines, coumarins, thiophenes, thiopyrans etc., and methods for the synthesis of thiophenone heterocycles using β-oxodithioesters are so far not known in literature. Here, we report for the first time that β-oxodithioesters directly react with oxalyl chloride to give 4-aroyl-5-(methylthio)thiophene-2,3-diones in 96-98% yields and they also react with chloroacetic anhydride in the presence of a base catalyst such as 4-dimethylaminopyridine(DMAP) to give 4-aroyl-5-(methylthio)thiophen-3(2H)-ones in 61-77% yields as shown in Scheme 1.
In this study, we prepared a variety of β-oxodithioesters 1a-h by reacting dimethyl trithiocarbonate with a corresponding arylmethyl ketone using sodium hydride as the base.\(^{17}\)

Next, we studied the scope of reaction of methyl 3-oxo-3-phenylpropanedithioate 1a with oxalyl chloride and found that they react smoothly under neat condition at room temperature producing 4-benzoyl-5-(methylthio)thiophene-2,3-dione 2a in 96% yield. We found this reaction to proceed well also with the other β-oxodithioesters 1b-h under similar conditions producing corresponding 4-aryloxy-5-(methylthio)thiophene-2,3-diones 2b-h in >96% yields as shown in Table 1.

We characterized the compounds 2a-h based on their \(^1H,\(^13C\) NMR, IR and HRMS data as given in the supplementary file. Figure 2 shows the ORTEP view of the single crystal X-ray analysis of 2f (CCDC 1402850) with atomic numbering.

We also studied the reaction of chloroacetic anhydride with β-oxodithioesters 1a-h. Here, unlike oxalyl chloride, chloroacetic anhydride was found to react with a β-oxodithioester only in the presence of a base catalyst producing 4-aryloxy-5-(methylthio)thiophene-3(2H)-ones. Initially we screened a variety of base catalysts by reacting β-oxodithioester 1a with chloroacetic anhydride using dichloromethane as the solvent. In this study, the best results were found with DMAP, which gave 4-benzoyl-5-(methylthio)thiophen-3(2H)-one 3a in 71% yield in 4h as shown in Table 2.
Next, we studied the reaction of β-oxodithioesters 1b-h with chloroacetic anhydride using DMAP as the catalyst in dichloromethane at room temperature.

Under these conditions, except 1h, the β-oxodithioesters 1b-g gave corresponding 4-aryloxy2-(methylthio)thiophen-3(2H)-ones 2b-g in 61-77% yields as shown in Table 3. However, the reaction of 1h with chloroacetic anhydride was messy producing several unidentified products. The characterization data (1H, 13C NMR, IR and HRMS) obtained for 3a-g were given in supplementary file and the ORTEP view of the single crystal X-ray analysis of 3b (CCDC 1402849) with atomic numbering is shown in Figure 3.

Table 3: Synthesis of 4-aryloxy2-(methylthio)thiophen-3(2H)-ones.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate 1</th>
<th>Product 3</th>
<th>Reaction time (hrs)</th>
<th>% Yield</th>
<th>m.p. (°C)</th>
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<tbody>
<tr>
<td>a</td>
<td>1a</td>
<td>3a</td>
<td>4</td>
<td>71</td>
<td>138-140</td>
</tr>
<tr>
<td>b</td>
<td>1b</td>
<td>3b</td>
<td>4</td>
<td>77</td>
<td>115-116</td>
</tr>
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<tr>
<td>d</td>
<td>1d</td>
<td>3d</td>
<td>6</td>
<td>66</td>
<td>118-120</td>
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<tr>
<td>e</td>
<td>1e</td>
<td>3e</td>
<td>4.5</td>
<td>62</td>
<td>180-181</td>
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<tr>
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<td>1f</td>
<td>3f</td>
<td>6</td>
<td>61</td>
<td>197-198</td>
</tr>
<tr>
<td>g</td>
<td>1g</td>
<td>3g</td>
<td>4.5</td>
<td>72</td>
<td>124-126</td>
</tr>
</tbody>
</table>

*Isolated yields.

The plausible reaction pathways involved in the formation of a thiophene-2,3-dione 2 and thiophen-3(2H)-one 3 by reaction of a β-

oxodithioester with oxalyl chloride and chloroacetic anhydride respectively are shown in Scheme 2 and Scheme 3 respectively.

Conclusions

In summary, this study shows the first application of β-oxodithioesters for preparation of several new polyfunctionalized thiophenone derivatives. A variety of β-oxodithioesters were prepared and reacted with oxalyl chloride and chloroacetic anhydride to obtain 4-aryloxy2-(methylthio)thiophene-2,3-diones and 4-aryloxy2-(methylthio)thiophen-3(2H)-ones respectively in good to excellent yields under mild conditions.

Acknowledgments

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Experimental section

Typical procedure for the synthesis of 4-benzoyloxy2-(methylthio)thiophene-2,3-dione 2a: methyl 3-oxo-3-phenylpropanedithioate 1a (500 mg, 2.37 mmol) was added to oxalyl chloride (362 mg, 2.85 mmol) and reaction mixture was stirred at room temperature for 2 minutes. After completion of the reaction (monitored by TLC), the product formed was separated by filtration, washed with hexane (3×5 ml) to afford the pure 4-benzoyloxy2-(methylthio)thiophene-2,3-dione 2a (600 mg, 96%, brown solid, m.p. 107-109°C). 1H NMR (300 MHz, CDCl3): δ = 7.65 (d, J = 7.1 Hz, 2H), 7.56 (t, J = 7.4, 7.4 Hz, 1H), 7.43 (t, J = 7.7, 7.7 Hz, 2H), 2.68 (s, 3H); 13C NMR (75 MHz, CDCl3): δ = 190.7, 188.7, 180.8, 174.9, 136.7, 132.9, 129.1, 128.0, 123.2, 17.7. IR (KBr): ν 3439, 3058, 1742, 1685, 1620, 1404, 1294, 1229, 949 cm⁻¹; MS (ESI): 287 (M+Na). ESI-HRMS obtained for C12H9O3S2 (M+H) = 264.9983 (calculated: 264.9987).

Typical procedure for the synthesis of 4-benzoyloxy2-(methylthio)thiophen-3(2H)-one 3a: Chloroacetic anhydride (485 mg, 2.85 mmol), methyl 3-oxo-3-phenylpropanedithioate 1a (500 mg, 2.38 mmol), DMAP (145 mg, 1.18 mmol) and dichloromethane (10 ml) were taken in a 50 mL round bottom flask and the mixture
was stirred at room temperature for 4 h. After completion of the reaction (monitored by TLC), the reaction mixture was extracted with dichloromethane (2×20 mL) and dried over anhyd. Na₂SO₄. Solvent was removed using a rotavapor and the crude residue obtained was purified by normal column chromatography (silica gel 60-120 mesh, ethyl acetate/hexane gradient mixture) to afford 4-benzoyl-5-(methylthio)thiophen-3(2H)-one 3a (420 mg, 71%, brown solid, m.p. 138-140 °C). ¹H NMR (300 MHz, CDCl₃): δ = 7.67 (d, J = 7.3 Hz, 2H), 7.52 (t, J = 7.3 Hz, 1H), 7.41 (t, J = 7.5 Hz, 2H), 2.64 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ = 196.3, 193.6, 189.9, 137.9, 132.3, 129.0, 127.8, 125.9, 41.7, 16.2; IR (KBr): ν 3424, 189.9, 137.6, 132.3, 129.0, 127.8, 125.9, 41.7, 16.2 cm⁻¹; MS (ESI) ν 3424, 189.9, 137.6, 132.3, 129.0, 127.8, 125.9, 41.7, 16.2. 3a was 251.0195 (calculated: 251.0194). 

Notes and references

18. Crystal data for 2f: C₅H₅O₂S₂, M = 292.36, 0.48 x 0.21 x 0.08 mm³, triclinic, space group P1 (No. 2), a = 5.7321(15), b = 8.7882(2), c = 13.7691(4), α = 99.381(5), β = 101.216(4), γ = 90.696(4), V = 670.6(3) Å³, Z = 2, D = 1.448 g/cm³, Fₒₒₒ = 304, CCD area detector, MoKα radiation, λ = 0.71073 Å, T = 293(2)K, 2θmax = 50.0°, 6310 reflections collected, 2349 unique (fiint = 0.0395), Final Goof = 1.17, R₁ = 0.0726, wR² = 0.2068, R indices based on 2070 reflections with I >2σ(I) (refinement on F²), 194 parameters, μ = 0.397 mm⁻¹.
19. Crystal data for 3b: C₅H₅O₂Cl₂S₂, M = 284.76, block, 0.45 x 0.32 x 0.30 mm³, monoclinic, space group P2₁/c (No. 14), a = 12.2624(8), b = 13.4433(9), c = 7.9968(5), α = 106.6180(10), β = 126.6115(14), γ = 90.387, D = 1.494 g/cm³, Fₒₒₒ = 584, CCD area detector, MoKα radiation, λ = 0.71073 Å, T = 293(2)K, 2θmax = 50.0°, 11867 reflections collected, 2225 unique (fiint = 0.0203), Final Goof = 1.054, R₁ = 0.0354, wR² = 0.0940, R indices based on 2099 reflections with I >2σ(I) (refinement on F²), 155 parameters, μ = 0.616 mm⁻¹.
Graphical Abstract

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R=aryl or hetero aryl

neat, r.t.; 2-5 min

Cl

O

O

R

SMe

O

S

COCl

COCl

61-77%

96-98%

Cl

O

O

DCM; r.t., 4-6 hrs

DMAP

O

S

R

O

SMe

61-77%