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

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Efficient methods for the preparation of polyfunctionalized thiophene-2,3-diones and thiophen-3(2*H*)-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(2*H*)-ones in 61-77% yields.

Biologically active compounds containing thiophenone as the pharmacophore are scarcely found in nature. Thiocremonone (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(5*H*)-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, thiocremonone, which occurs in garlic,[1] was found to possess potent antioxidant,[2] anticancer,[3] antiinflammatory,[4] antiobesity[5] properties. Thialactomycin was isolated from the fermentation broth of a strain of actinomycetes (*Nocradia Sp.*)[6a,b] and has potent antibacterial properties against *in vitro* Gram positive, Gram negative and anaerobic bacteria.[7a-d] 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,[8] tuberculosis[9] and the virulent malaria caused by the parasite *Plasmodium falciparum*.[10]

In literature, efficient methods for the construction of thiophen-3(2*H*)-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,[11a-c] isoxazoles,[12] pyrimidines,[13] coumarins,[14]

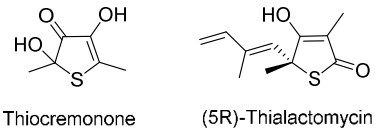
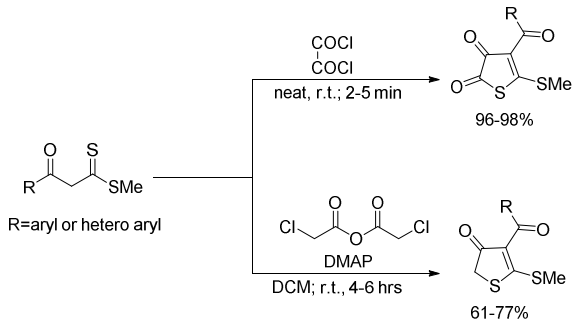


Figure 1: Some bioactive natural products containing thiophenone core structure.

thiophenes,[15a,b] thiopyrans[16] 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(2*H*)-ones in 61-77% yields as shown in Scheme 1.



Scheme 1: Reaction of a β-oxodithioester with oxalyl chloride and chloroacetic anhydride.

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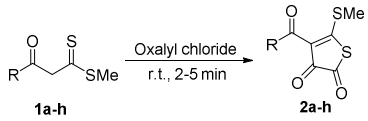
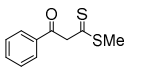
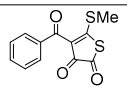
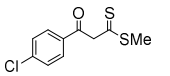
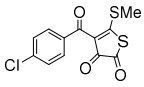
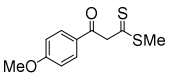
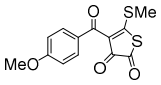
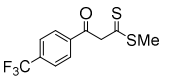
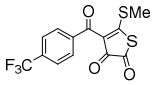
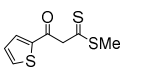
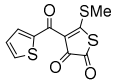
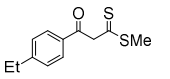
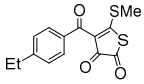
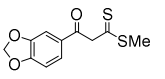
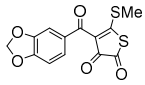
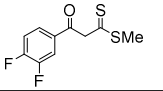
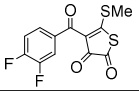
In this study, we prepared a variety of β-oxodithioesters **1a-h** by reacting dimethyl trithiocarbonate with a corresponding arylmethyl ketone using sodium hydride as the base.[17]

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-aroyl-5-(methylthio)thiophene-2,3-diones **2b-h** in >96% yields as shown in Table 1.

Table 1: Synthesis of 4-benzoyl-5-(methylthio)thiophene-2,3-diones.



1a-h **2a-h**

Entry	Substrate **1**	Product **2**	Reaction time (min)	%Yield[a]	m.p. (^{0}C)
a			2	96	107-109
b			3	98	181-182
c			3	96	147-148
d			4	97	172-174
e			2	98	135-137
f			2	98	142-143
g			4	98	166-168
h			5	97	151-152

[a]Isolated yields.

We characterized the compounds **2a-h** based on their ^{1}H, ^{13}C 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-aroyl-5-(methylthio)thiophen-3(2*H*)-ones. Initially we screened a variety of base catalysts by reacting β-oxodithioester **1a** with chloroacetic anhydride using dichlromethane as the solvent. In this study, the best results were found with DMAP, which gave 4-benzoyl-5-(methylthio)thiophen-3(2*H*)-one **3a** in 71% yield in 4h as shown in Table 2.

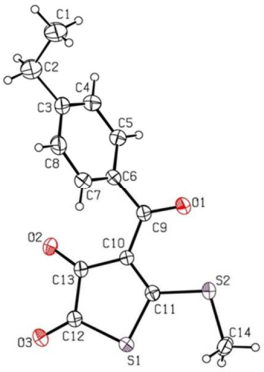
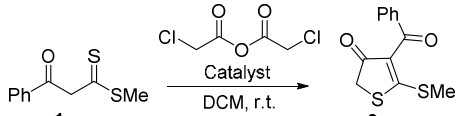


Figure 2: ORTEP diagram of **2f**[18]. Displacement ellipsoids are drawn at the 30% probability level and the H atoms are shown as small spheres of arbitrary radius. Only major component of the disordered ethyl group is shown for clarity.

Table 2: Screening of the base catalysts.



1a **3a**

entry	catalyst	reaction time (hrs)	**3a** % yield[a]	entry	catalyst	reaction time (hrs)	**3a** % yield[a]
1	DMAP	4	71	5	piperidine	8	45
2	DABCO	8	65	6	DBU	12	42
3	Et_3N	5	52	7	piperizine	8	40
4	K_2CO_3	8	50	8	pyrrolidine	8	35

[a]Isolated yields

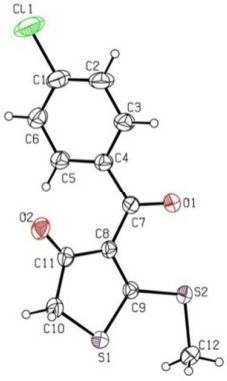
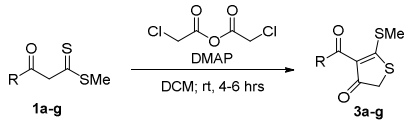


Figure 3: ORTEP diagram of **3b**[19]. Displacement ellipsoids are drawn at the 30% probability level and the H atoms are shown as small spheres of arbitrary radius.

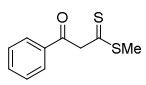
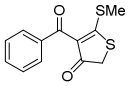
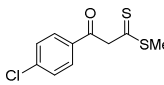
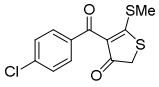
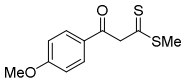
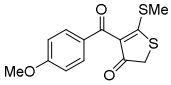
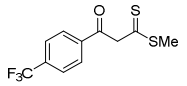
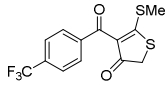
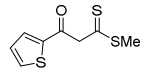
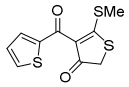
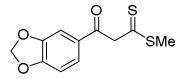
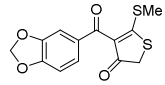
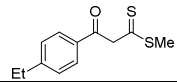
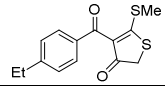
Next, we studied the reaction of β-oxodithioesters **1b-h** with chloroacetic anhydride using DMAP as the catalyst in dichloromethane at room temperature.

Under these conditions, except **1h**, the β-oxodithioesters **1b-g** gave corresponding 4-aroyl-5-(methylthio)thiophen-3(2*H*)-ones **2b-g** in 61-77% yields as shown in Table 3. However, the reaction of **1h** with chloroacetic anhydride was messy producing several unidentifiable products. The characterization data (^{1}H, ^{13}C 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-aroyl-5-(methylthio)thiophen-3(2*H*)-ones.

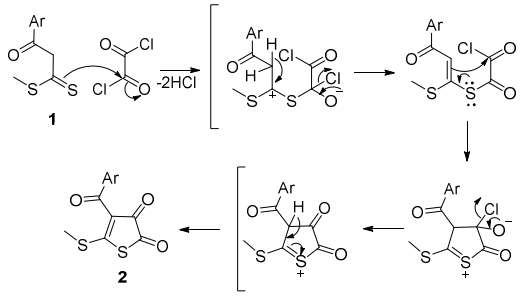


1a-g 3a-g

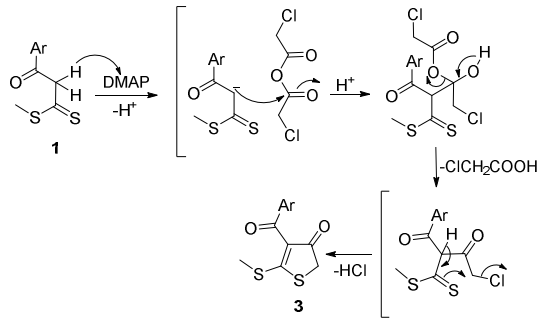
Entry	Substrate **1**	Product **3**	Reaction time (hrs)	%Yield[a]	m.p. (°C)
a			4	71	138-140
b			4	77	115-116
c			5	68	178-180
d			6	66	118-120
e			4.5	62	180-181
f			6	61	197-198
g			4.5	72	124-126

[a]Isolated yields.

The plausible reaction pathways involved in the formation of a thiophene-2,3-dione **2** and thiophen-3(2*H*)-one **3** by reaction of a β-oxodithioester with oxalyl chloride and chloroacetic anhydride respectively are shown in Scheme 2 and Scheme 3 respectively.



Scheme 2: Plausible mechanism for the formation of **2** from a β-oxodithioester.



Scheme 3: Plausible reaction mechanism for the formation of **3** from a β-oxodithioester.

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-aroyl-5-(methylthio)thiophene-2,3-diones and 4-aroyl-5-(methylthio)thiophen-3(2*H*)-ones respectively in good to excellent yields under mild conditions.

Acknowledgments

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Experimental section

Typical procedure for the synthesis of 4-benzoyl-5-(methylthio)thiophene-2,3-dione 2a: methyl 3-oxo-3-phenylpropanedithioate **1a** (500 mg, 2.37 mmol) was added to oxalylchloride (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-benzoyl-5-(methylthio)thiophene-2,3-dione **2a** (600 mg, 96%, brown solid, m.p. 107-109^{0}C). ^{1}H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{12}H_9O_3S_2$ (M+H) = 264.9983 (calculated: 264.9987).

Typical procedure for the synthesis of 4-benzoyl-5-(methylthio)thiophen-3(2*H*)-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. Na_2SO_4. 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(2*H*)-one **3a** (420 mg, 71%, brown solid, m.p. 138-140 ^{0}C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 7.3 Hz, 2H), 7.52 (t, *J* = 7.3, 7.2 Hz, 1H), 7.41 (t, *J* = 7.5, 7.3 Hz, 2H), 3.87 (s, 2H), 2.64 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.3, 193.6, 189.9, 137.6, 132.3, 129.0, 127.8, 125.9, 41.7, 16.2; IR (KBr): ν 3424, 3052, 2974, 2924, 1671, 1624, 1458, 1286, 1231 cm^{-1}; MS (ESI) 251 (M+H).ESI-HRMS obtained for $C_{12}H_{11}O_2S_2$ (M+H) = 251.0194 (calculated: 251.0195).

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18 *Crystal data for* **2f***:* $C_{14}H_{12}O_3S_2$, *M* = 292.36, 0.48 x 0.21 x 0.08 mm^3, triclinic, space group $P\bar{1}$ (No. 2), a = 5.7321(15), b = 8.788(2), c = 13.769(4) Å, *α* = 99.381(5), *β* = 101.216(4), *γ* = 90.696(4)º, *V* = 670.6(3) Å^3, *Z* = 2, D_c = 1.448 g/cm^3, F_{000} = 304, CCD area detector, MoKα radiation, λ = 0.71073 Å, *T* = 293(2)K, $2\vartheta_{max}$ = 50.0º, 6310 reflections collected, 2349 unique (*R*int = 0.0395), Final *GooF* = 1.177, *R*1 = 0.0726, *wR*2 = 0.2068, *R* indices based on 2070 reflections with I >2*σ*(I) (refinement on F^2), 194 parameters, μ = 0.397 mm^{-1}.

19 *Crystal data for* **3b**: $C_{12}H_9ClO_2S_2$, *M* = 284.76, block, 0.45 x 0.32 x 0.30 mm^3, monoclinic, space group $P2_1/c$ (No. 14), a = 12.2624(8), b = 13.4433(9), c = 7.9968(5) Å, *β* = 106.1680(10)º, *V* = 1266.11(14) Å^3, *Z* = 4, D_c = 1.494 g/cm^3, F_{000} = 584, CCD area detector, MoKα radiation, λ = 0.71073 Å, *T* = 293(2)K, $2\vartheta_{max}$ = 50.0º, 11867 reflections collected, 2225 unique (R_{int} = 0.0203), Final *GooF* = 1.054, *R*1 = 0.0354, *wR*2 = 0.0940, *R* indices based on 2099 reflections with I >2*σ*(I) (refinement on F^2), 155 parameters, μ = 0.616 mm^{-1}.

Graphical Abstract

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

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