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Nitroketene dithioacetal chemistry: Synthesis of coumarins incorporating nitrothiophene moiety

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Abstract. Alkylation of dipotassium 2-nitro-1,1-ethylenedithiolate **1** with ethyl 4-chloroacetoacetate **6** in a mixture of MeOH-H_2O (2:1) furnished highly functionalized 3-nitrothiophene **5**. Pechmann condensation of **5** with 2-hydroxybenzaldehydes **8a–i**, **10** furnished coumarin-3-nitrothiophene conjugates **9a–i**, **11**.

Keywords. Nitroketenedithioacetals; 3-nitrothiophenes; 2-hydroxy benzaldehydes; coumarins; Pechmann condensation.

1. Introduction

Nitroketene dithioacetals **2**, prepared from carbon disulfide, nitromethane and alkylating agents in a two-step process, are extremely useful two carbon synthons for the synthesis of heterocyclic compounds incorporating diverse functional groups.[1] We have been investigating on the alkylation of dipotassium salt of 2-nitro-1, 1-ethylenedithiolate **1** with a variety of alkyl halides and found that product formation is critically dependent on the nature of the alkyl halide and conditions. We found that while alkylation of the salt **1** with simple alkyl halides provided *bis*-alkylated products of the type **2** (route a, scheme 1),[2] alkylation with sterically hindered alkyl halides or with propargyl bromide provided 1,3-dithioles of the type **3** (route b, scheme 1) and **4** (route c, scheme 1) respectively.[3,4] Recently we found that alkylation of the salt **1** with acyl methyl chlorides furnished 3-nitrothiophenes of the type **5** (route d, scheme 1).[5]

In continuation of above studies, we considered the reaction of the salt **1** with an alkyl halide having multiple functionalities, like ethyl 4-chloroacetoacetate **6**, which is having two carbonyls, two active methylenes and two leaving groups namely chloro and ethoxy. The reaction could produce thiophene **5** going via the route d in analogy with our previous findings involving acyl methyl chlorides or it could produce mono- or *bis*-alkylated products (route a or b) followed by cyclization. To evaluate these interesting possibilities, we performed alkylation of **6** with the salt **1**. The reaction provided a single product, ethyl 4-{[4-(2-ethoxy-2-oxoethyl)-3-nitrothiophen-2-yl]sulfanyl}-3-oxobutanoate **5** (R = COOEt; scheme 1). The product was obviously formed via route d (scheme 1). In this paper, we give details of this study for the synthesis of highly functionalized 3-nitrothiophene **5**. Thiophenes in general[6] and 3-nitrothiophenes[7] in particular have found several applications in pharmaceutical and technological fields. Further to isolation and characterization of 3-nitrothiophene **5**, we describe its transformation into two more 3-nitrothiophene derivatives and nine coumarin 3-nitrothiophene conjugates.

2. Experimental

2.1 *General*

Reactions were performed in oven-dried glassware (150°C). Dichloromethane, tetrahydrofuran, hexanes, ethyl acetate obtained commercially were distilled before use. Thin layer chromatography (TLC) was carried out using silica gel 60 F_{254} plates. The developed chromatogram was analysed by UV lamp (254 nm) or iodine vapors. The crude compounds were purified by flash chromatography on silica gel (230–400 mesh) using hexanes-EtOAc mixture (10% to 50% EtOAc) as eluent. Ethyl 4-chloroacetoacetate, 2-hydroxybenzaldehyde (salicylaldehyde) and piperidine were purchased from Sigma Aldrich and used as received. Substituted 2-hydroxybenzaldehydes **8b–i** were prepared following the procedure described by Wynberg.[8] The ^{1}H NMR (400 MHz/300 MHz/60 MHz)

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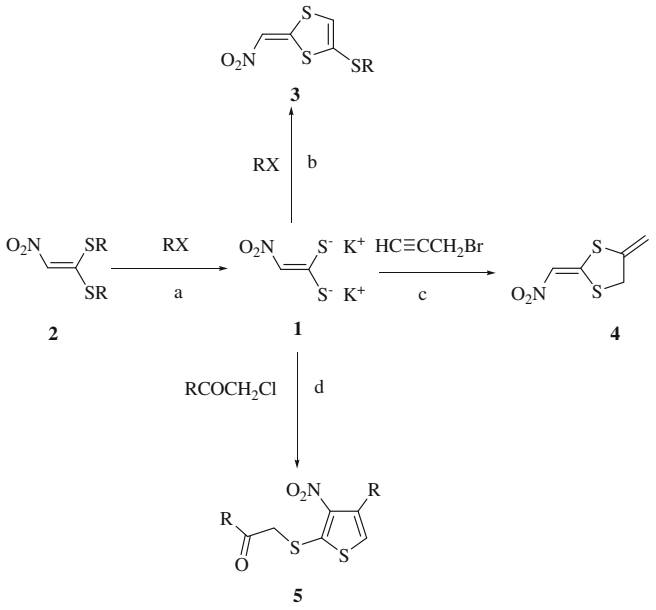
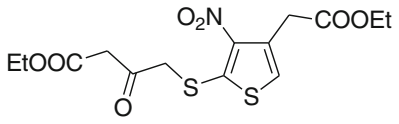


Scheme 1. Reaction of dipotassium salt **1** with different alkyl halides.

and ^{13}C NMR (100 MHz / 75 MHz), DEPT spectra were recorded in $CDCl_3$/$CDCl_3$:CCl_4 (1:1)/DMSO-d_6:CCl_4 (1:1) on Bruker 400 MHz, JEOL 300 MHz or JEOL 60 MHz FT-NMR spectrometers with tetramethylsilane (TMS; 0 ppm) as internal standard. CHN analysis were performed on PerkinElmer elemental analyzer.

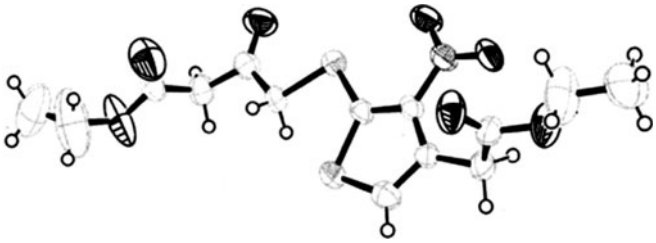
2.2 *Preparation of ethyl 4-{[4-(2-ethoxy-2-oxoethyl)-3-nitro-2-thienyl]sulfanyl}-3-oxobutanoate* **5a**



5a

To a stirred suspension of freshly prepared dipotassium salt of nitroketene dithioacetate **1** (0.5 g, 2.35 mmol) in a mixtureof MeOH and water (2:1; 10 mL) at 0°C a dilute solution of ethyl 4-chloro-3-oxobutanoate **6** (0.77 g, 4.70 mmol) in aqueous MeOH (15 mL) was added by using pressure equalizer funnel at 0°C during 45 min. The resulting reaction mixture was then stirred vigorously at room temperature (rt) for 6 h. After the completion of the reaction (TLC; hexanes − EtOAc = 6:4), the mixture was transferred into a beaker containing 20 g of crushed ice. The acidic (pH = 5) reaction mixture was carefully neutralized with 0.1 *N* $NaHCO_3$. The contents of the reaction mixture separated into two phases on dilution with dichloromethane (45 mL). The organic layer was washed with water (3 × 25 mL) and brine (2 × 15 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure resulted in the crude product as dark brown pasty mass. The crude product was subjected to column chromatography on silica gel by using increasing amounts of EtOAc (5% to 40%) in hexanes as eluent. Evaporation of the pooled fraction having required 3-nitrothiophene furnished 1.14 g of ethyl 4-{[4-(2-ethoxy-2-oxoethyl)-3-nitro-2-thienyl]sulfanyl}-3-oxobutanoate **5a** as yellow crystalline solid in 57% yield. Mp: 79–80°C (MeOH); UV λ_{max} (MeOH): 281 nm (log ε = 4.1), 370 nm (log ε = 3.6); IR ν_{max} (KBr): 1722 (CO), 1547, 1489, 1370 (NO_2), 1081, 768 cm^{-1}. ^{1}H NMR δ (400 MHz; $CDCl_3$; Me_4Si): 7.01 (s, 1H, CH), 4.23–4.14 (m, 4H, OCH_2), 4.11 (s, 2H, CH_2), 3.85 (s, 2H, CH_2), 3.66 (s, 2H, CH_2), 1.29 (t, *J* = 7.2 Hz, 3H, CH_3), 1.27 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR δ (100 MHz; $CDCl_3$; Me_4Si): 195.7 (C), 169.7 (C), 166.4 (C), 147.5 (C), 141.8 (C), 131.5 (C), 121.5 (CH), 61.7 (CH_2), 61.1 (CH_2), 47.3 (CH_2), 44.9 (CH_2), 36.2 (CH_2), 14.2 (CH_3), 14.1 (CH_3); HRMS (ESI^+): calcd for $C_{14}H_{17}NNaO_7S_2$ (MNa^+), 398.0344; found, 398.0344. Anal. Calcd. for $C_{14}H_{17}NO_7S_2$: C 44.71; H, 4.56; N, 3.71; S, 17.08; found: C 44.68; H, 4.52; N, 3.69; S, 17.06.

2.2a *X-ray crystal structure of ethyl 4-[4-(2-ethoxy-2-oxoethyl)-3-nitro-2-thienyl]sulfanyl-3-oxobutanoate* **5a**:

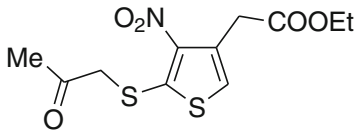


Crystal data and structure refinement data for **5a**.

Identification code	: **CCDC 633059**
Empirical formula	: '$C_{14}H_{17}NO_7S_2$'
Formula weight	: 375.41
Temperature	: 273(2)
Wavelength	: 0.71073 Å
Crystal system, space group	: Monoclinic $P2_1$

Unit cell dimensions	: a = 14.9609(16) Å; α = 90 deg.
	: b = 4.9763(5) Å; β = 92.706(4) deg.
	: c = 23.301(3) Å; γ = 90.00 deg.
Volume	: 1732.8(3) Å^3
Z, Calculated density	: 4, 1.525 Mg/m^3
Absorption coefficient	: 0.342 mm^{-1}
F(000)	: 784
Crystal size	: 0.26 × 0.11 × 0.08 mm
Theta range for data collection	: 2.63 to 18.97 deg.
Limiting indices	: −16 <= h <= 20, −4 <= k <= 6, −33 <= *l* <= 31
Reflections collected / unique	: 16260 / 2949 [R (int) = 0.0338]
Completeness to theta = 25.00	: 99.9 %
Absorption correction	: Semi-empirical from equivalents
Max. and min. transmission	: 0.9112 and 0.8730
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 6821/1/437
Goodness-of-fit on F^2	: 0.971
Final R indices [I>2sigma(I)]	:R1 = 0.0715, wR2 = 0.1752
R indices (all data)	:R1 = 0.0765, wR2 = 0.1772
Largest diff. peak and hole	: 1.152 and −0.425 e.Å^{-3}

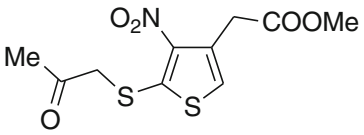
2.2b *Ethyl 2-{4-nitro-5-[(2-oxopropyl)sulfanyl]-3-thienyl}acetate* **7**:



7

To a stirred solution of ethyl 4-{[4-(2-ethoxy-2-oxoethyl)-3-nitro-2-thienyl]sulfanyl}-3-oxobutanoate **5a** (0.05 g, 0.13 mmol) in EtOH (1 mL), 1 drop of dil. H_2SO_4 (1 drop of conc. H_2SO_4 in 1 mL EtOH) was added. The resulting reaction mixture was refluxed on a pre-heated oil bath maintained at 100°C for 18 h for complete transformation (TLC hexanes - EtOAc 7:3). Excess acid was quenched with Na_2CO_3. Evaporation of the solvent under reduced pressure furnished 0.04 g of ethyl 2-{4-nitro-5-[(2-oxopropyl)sulfanyl]-3-thienyl}acetate **7** in 99% yield. Mp: 134–136°C (MeOH); UV λ_{max} (MeOH): 238 nm (log ε = 4.1), 377 nm (log ε = 3.6); IR ν_{max} (KBr): 1735 (CO), 1718 (CO), 1546, 1492, 1319 (NO_2), 1093, 863, 738 cm^{-1}. ^{1}H NMR δ (400 MHz; $CDCl_3$; Me_4Si): 6.99 (s, 1H, CH), 4.17 (q, *J* = 7.2 Hz, 2H, CH_2), 3.92 (s, 1H, OH), 3.87 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 1.27 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR δ (100 MHz; $CDCl_3$; Me_4Si): 200.6 (C), 169.8 (C), 154.0 (C), 148.2 (C), 131.6 (C), 121.3 (CH), 61.2 (CH_2), 45.6 (CH_2), 36.3 (CH_2), 28.6 (CH_3) 14.2 (CH_3). HRMS (ESI$^+$): calcd for $C_{11}H_{13}NNaO_5S_2$ (MNa^+), 326.0133; found, 326.0132. Anal. Calcd. for $C_{11}H_{13}NO_5S_2$: C, 43.50; H, 4.32; N, 4.62; S, 21.14; found: C 43.49; H, 4.30; N, 4.60; S, 21.12.

2.2c *Methyl 2-{4-nitro-5-[(2-oxopropyl)sulfanyl]-3-thienyl}acetate* **7a**:

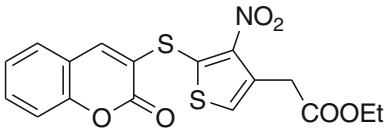


7a

Following the above procedure ethyl 4-{[4-(2-ethoxy-2-oxoethyl)-3-nitro-2-thienyl]sulfanyl}-3-oxobutanoate **5a** (0.13 mmol) in MeOH (1 mL), was transformed into 0.036 g of methyl 2-{4-nitro-5-[(2-oxopropyl)sulfanyl]-3-thienyl}acetate **7a** in 96% yield with dil. H_2SO_4. Mp: 108–110°C (MeOH); UV λ_{max} (MeOH): 238 nm (log ε = 4.1), 377 nm (log ε = 3.6); IR ν_{max} (KBr): 1735 (*CO*OEt), 1718 (CO), 1546, 1492, 1319 (NO_2), 1093, 863, 738 cm^{-1}. ^{1}H NMR δ (400 MHz; $CDCl_3$; Me_4Si): 6.98 (s, 1H, CH), 3.89 (s, 2H, CH_2), 3.87 (s, 2H, CH_2), 3.72 (s, 3H, CH_3), 2.37 (s, 3H, CH_3); ^{13}C NMR δ (100 MHz; $CDCl_3$; Me_4Si): 200.2 (C), 170.0 (C × 2), 147.7 (C), 131.4 (C), 121.2 (CH), 52.2 (OCH_3), 45.5 (CH_2), 36.0 (CH_2), 28.5 (CH_3). HRMS (ESI$^+$): calcd for $C_{10}H_{11}NNaO_5S_2$ (MNa^+), 311.9976; found, 311.9976. Anal. Calcd. for

$C_{10}H_{11}NO_5S_2$: C, 41.51; H, 3.83; N, 4.84; S, 22.17; found: C 41.49; H, 3.80; N, 4.82; S, 22.12.

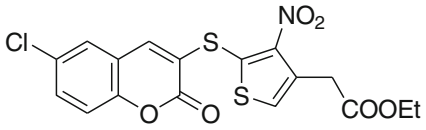
2.3 *Representative procedure for the synthesis of coumarins: Preparation of ethyl 2-{4-nitro-5-[(2-oxo-2H-3-chromenyl)sulfanyl]-3-thienyl}acetate* **9a**



9a

To a homogenous solution of 2-hydroxybenzaldehyde **8a** (0.02 g, 0.16 mmol) in THF, piperidine (0.001 g, 0.1 mol%) was added and stirred for 10 min at rt. The reaction mixture became brown in colour. To this solution, ethyl 4-{[4-(2-ethoxy-2-oxoethyl)-3-nitro-2-thienyl]sulfanyl}-3-oxobutanoate **5a** (0.05 g, 0.13 mmol) was added and the reaction mixture was allowed to stir at rt for 32 h for completion of the reaction (TLC: hexanes- EtOAc 8:2). The reaction mixture was then diluted with dichloromethane (25 mL) and the organic layer was washed sequentially with water (3 × 25 mL), brine and dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure resulted in crude ethyl 2-{4-nitro-5-[(2-oxo-2*H*-3-chromenyl)sulfanyl]-3-thienyl}acetate **9a** as gummy liquid. The crude product was subjected to column chromatography on SiO_2 (35 g, 15 cm × 1 cm) using increasing amounts of ethyl acetate in hexanes as eluent. Evaporation of the pooled fractions having the required product resulted in 0.042 g of **9a** as a light yellow colour solid in 69% yield. M.p.: 188–190°C (MeOH); R_f: 0.68 (hexanes − EtOAc; 8:2); UV λ_{max} (MeOH): 278 nm (log ε = 4.2), 374 nm (log ε = 3.4); IR ν_{max} (KBr): 1735 (CO), 1541, 1492, 1319 (NO_2), 1096, 881, 729 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$; Me_4Si): δ 8.22 (s, 1H, CH), 7.68–7.35 (m, 4H, CH), 7.02 (s, 1H, CH), 4.18 (q, J = 7.2 Hz, 2H, OCH_2), 3.89 (s, 2H, CH_2), 1.27 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$; Me_4Si): δ 169.8 (C), 158.2 (C), 154.5 (C), 150.5 (CH), 148.7 (C), 142.2 (C), 133.6 (CH), 131.2 (C), 128.5 (CH), 125.1 (CH), 123.1 (CH), 120.8 (C), 118.7 (C), 117.0 (CH), 61.3 (CH_2), 36.2 (CH_2), 14.1 (CH_3). HRMS (ESI^+): calcd for $C_{17}H_{13}NNaO_6S_2$ (MNa^+), 414.0082; found, 414.0079. Anal. calcd. for $C_{17}H_{13}NO_6S_2$: C, 52.16; H, 3.35; N, 3.58; S, 16.38; found: C 52.19; H, 3.31; N, 3.59; S, 16.36.

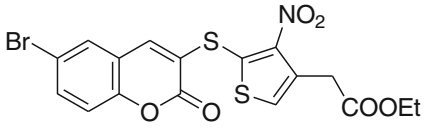
2.3a *Ethyl 2-{5-[(6-chloro-2-oxo-2H-3-chromenyl) sulfanyl]-4-nitro-3-thienyl}acetate* **9b**:



9b

Following the general procedure described above, the reaction of 5-chloro-2-hydroxybenzaldehyde **8b** (0.024 g, 0.16 mmol) and ethyl 4-{[4-(2-ethoxy-2-oxoethyl)-3-nitro-2-thienyl]sulfanyl}-3-oxobutanoate **5a** (0.05 g, 0.13 mmol) in the presence of piperidine (0.001 g, 0.1 mol%) stirred at rt for 34 h furnished 0.037 g of ethyl 2-{5-[(6-chloro-2-oxo-2*H*-3-chromenyl)sulfanyl]-4-nitro-3-thienyl}acetate **9b** as yellow colour solid in 66% yield. Mp: 160–161°C (MeOH); UV λ_{max}(MeOH): 271 nm (log ε = 4.3), 379 nm (log ε = 3.8); IR ν_{max} (KBr): 1740 (CO), 1546, 1492, 1319 (NO_2), 1091, 883, 740 cm^{-1}. ^1H NMR δ (300 MHz, $CDCl_3$: DMSO-d_6; Me_4Si): 8.35 (s, 1H, CH), 7.72 (s, 1H, CH), 7.63 (d, J = 8.7 Hz, 1H, CH), 7.39 (d, J = 9 Hz, 1H, CH), 7.27 (s, 1H, CH), 4.15 (q, J = 7.2 Hz, 2H, OCH_2), 3.90 (s, 2H, CH_2), 1.26 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR δ (300 MHz, $CDCl_3$: DMSO-d_6; Me_4Si): 169.3 (C), 157.4 (C), 152.2 (C), 148.6 (CH), 143.7 (C), 142.5 (C), 132.9 (CH), 130.7 (C), 129.7 (C), 127.6 (CH), 124.2 (CH), 121.7 (C), 119.5 (C), 117.9 (CH), 60.6 (CH_2), 35.6 (CH_3), 13.8 (CH_3). HRMS (ESI^+): calcd for $C_{17}H_{12}ClNNaO_6S_2$ (MNa^+), 447.9692; found, 447.9677. Anal. Calcd. for $C_{17}H_{12}ClNO_6S_2$: C, 47.95; H, 2.84; Cl, 8.32; N, 3.29; S, 15.06; found: C, 47.91; H, 2.79; Cl, 8.30; N, 3.31; S, 15.09.

2.3b *Ethyl 2-{5-[(6-bromo-2-oxo-2H-3-chromenyl) sulfanyl]-4-nitro-3-thienyl}acetate* **9c**:

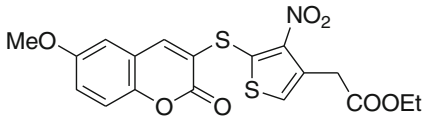


9c

Following the general procedure described above, the reaction of 5-bromo-2-hydroxybenzaldehyde **8c** (0.032 g, 0.16 mmol) and ethyl 4-{[4-(2-ethoxy-2-oxoethyl)-3-nitro-2-thienyl]sulfanyl}-3-oxobutanoate **5a** (0.05 g, 0.13 mmol) in the presence of piperidine (0.001 g, 0.1 mol%) stirred at rt for 34 h furnished 0.028 g of ethyl 2-{5-[(6-bromo-2-oxo-2H-3-chromenyl)

sulfanyl]-4-nitro-3-thienyl}acetate **9c** as yellow colour solid in 48 % yield. Mp: 170–172°C (MeOH); UV λ_{max} (MeOH): 276 nm (log $\varepsilon = 4.3$), 374 nm (log $\varepsilon = 3.8$); IR ν_{max} (KBr): 1740 (CO), 1546, 1492, 1319 (NO_2), 1091, 883, 740 cm^{-1}. ^1H NMR δ (300 MHz, $CDCl_3$: DMSO-d_6; Me_4Si): 8.2 (s, 1H, CH), 7.73 (d, $J = 9.0$ Hz, 1H, CH), 7.53 (s, 1H, CH), 7.32 (d, $J = 8.4$ Hz, 1H, CH), 7.19 (s, 1H, CH), 4.17 (q, $J = 7.2$ Hz, 2H, CH_2), 3.91 (s, 2H, CH_2), 1.27 (t, $J = 7.2$ Hz, 3H, CH_3); ^{13}C NMR δ (300 MHz, $CDCl_3$; Me_4Si): 169.9 (C), 157.6 (C), 153.0 (C), 150.9 (CH), 146.4 (C), 141.3 (C), 136.2 (CH), 131.6 (CH), 130.7 (C), 128.6 (CH), 125.0 (CH), 120.4 (C), 120.3 (C), 118.7 (CH), 60.5 (OCH_2), 35.4 (CH_2), 13.8 (CH_3). HRMS (ESI^+): calcd for $C_{17}H_{12}BrNNaO_6S_2$ (MNa^+), 491.9187; found, 491.9172. Anal. Calcd. for $C_{17}H_{12}BrNO_6S_2$: C, 43.41; H, 2.57; Br, 16.99; N, 2.98; S, 13.64; found: C, 43.40; H, 2.59; Br, 17.01; N, 2.99; S, 13.68.

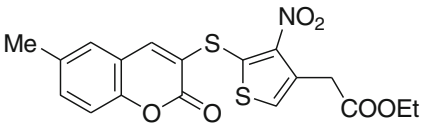
2.3c *Ethyl 2-{5-[(6-methoxy-2-oxo-2H-3-chromenyl) sulfanyl]-4-nitro-3-thienyl}acetate* **9d**:



9d

Following the general procedure described above, the reaction of 5-methoxy-2-hydroxybenzaldehyde **8d** (0.025 g, 0.17 mmol) and ethyl 4-{[4-(2-ethoxy-2-oxoethyl)-3-nitro-2-thienyl]sulfanyl}-3-oxobutanoate **5a** (0.052 g, 0.14 mmol) in the presence of piperidine (0.001 g, 0.1 mol%) stirred at rt for 32 h furnished 0.032 g of Ethyl 2-{5-[(6-methoxy-2-oxo-2H-3-chromenyl)sulfanyl]-4-nitro-3-thienyl}acetate **9d** as yellow colour solid in 53% yield. Mp: 170–172°C (MeOH); UV λ_{max} (MeOH): 273 nm (log $\varepsilon = 4.3$), 374 nm (log $\varepsilon = 3.8$); IR ν_{max} (KBr): 1736 (CO), 1546, 1492, 1319, 1091, 883, 740 cm^{-1}. ^1H NMR δ (400 MHz, $CDCl_3$; Me_4Si): 8.17 (s, 1H, CH), 7.27 (s, 1H, CH), 7.18 (d, $J = 8.0$ Hz, 1H, CH), 7.11 (d, $J = 7.8$ Hz, 1H, CH), 7.0 (s, 1H, CH), 4.17 (q, $J = 7.2$ Hz, 2H, CH_2), 4.0 (s, 3H, CH_3), 3.88 (s, 2H, CH_2), 1.27 (t, $J = 7.2$ Hz, 3H, CH_3) ; ^{13}C NMR δ (300 MHz, $CDCl_3$; Me_4Si): 169.7 (C), 157.7 (C), 150.4 (CH), 147.3 (C), 145.4 (C), 144.2 (C), 142.9 (C), 131.2 (C), 125.0 (CH), 123.0 (CH), 121.3 (C), 119.6 (CH), 119.3 (C), 115.2 (CH), 61.2 (CH_2), 56.3 (OCH_3), 36.1 (CH_2), 14.1 (CH_3). HRMS (ESI^+): calcd for $C_{18}H_{15}NNaO_7S_2$ (MNa^+), 444.0188; found, 444.0179. Anal. Calcd. for $C_{18}H_{15}NO_7S_2$: C, 51.30; H, 3.59; N, 3.32; S, 15.22; found: C, 50.29; H, 3.62; N, 3.35; S, 15.19.

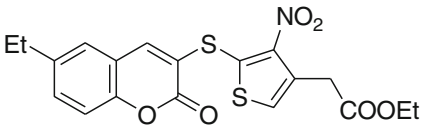
2.3d *Ethyl 2-{5-[(6-methyl-2-oxo-2H-3-chromenyl) sulfanyl]-4-nitro-3-thienyl}acetate* **9e**:



9e

Following the general procedure described above, the reaction of 5-methyl-2-hydroxybenzaldehyde **8e** (0.044 g, 0.32 mmol) and ethyl 4-{[4-(2-ethoxy-2-oxoethyl)-3-nitro-2-thienyl]sulfanyl}-3-oxobutanoate **5a** (0.1 g, 0.27 mmol) in the presence of piperidine (0.001 g, 0.1 mol%) stirred at rt for 36 h furnished 0.078 g of ethyl 2-{5-[(6-methyl-2-oxo-2H-3-chromenyl)sulfanyl]-4-nitro-3-thienyl}acetate **9e** as yellow colour solid in 67% yield. Mp: 186–188°C (MeOH); UV λ_{max} (MeOH): 276 nm (log $\varepsilon = 4.3$), 374 nm (log $\varepsilon = 3.8$); IR ν_{max} (KBr): 1740 (CO), 1546, 1492, 1319, 1091, 883, 740 cm^{-1}. ^1H NMR δ (400 MHz, $CDCl_3$; Me_4Si): 8.2 (s, 1H, CH), 7.46 (d, $J = 8.1$ Hz, 1H, CH), 7.33 (d, $J = 8.7$ Hz, 1H, CH), 7.28 (d, $J = 6.6$ Hz, 1H, CH), 7.0 (s, 1H, CH), 4.15 (q, $J = 7.2$ Hz, 2H,OCH_2), 3.97 (s, 2H, CH_2), 2.44 (s, 3H, CH_3), 1.23 (t, $J = 7.2$ Hz, 3H, CH_3) ; ^{13}C NMR δ (100 MHz, $CDCl_3$; Me_4Si): 169.9 (C), 158.1 (C), 152.3 (CH), 148.2 (C), 140.7 (C), 135.0 (CH), 134.6 (C × 2), 130.8 (C), 128.8 (CH), 124.6 (CH), 118.5 (C), 118.4 (C), 116.2 (CH), 60.4 (OCH_2), 35.4 (CH_2), 20.1 (CH_3), 14.1 (CH_3). HRMS (ESI^+): calcd for $C_{18}H_{15}NNaO_6S_2$ (MNa^+), 428.0238; found, 428.0229. Anal. Calcd. for $C_{18}H_{15}NO_6S_2$: C, 53.32; H, 3.73; N, 3.43; S, 15.82; found: C, 53.34; H, 3.71; N, 3.39; S, 15.79.

2.3e *Ethyl 2-{5-[(6-ethyl-2-oxo-2H-3-chromenyl) sulfanyl]-4-nitro-3-thienyl}acetate* **9f**:

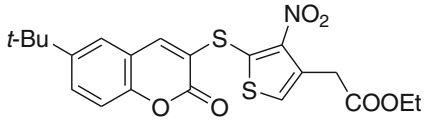


9f

Following the general procedure described above, the reaction of 5-ethyl-2-hydroxybenzaldehyde **8f** (0.024 g, 0.16 mmol) and ethyl 4-{[4-(2-ethoxy-2-oxoethyl)-3-nitro-2-thienyl]sulfanyl}-3-oxobutanoate **5a** (0.05 g,

0.13 mmol) in the presence of piperidine (0.001 g, 0.1 mol%) stirred at rt for 36 h furnished 0.04 g of ethyl 2-{5-[(6-ethyl-2-oxo-2H-3-chromenyl)sulfanyl]-4-nitro-3-thienyl}acetate **9f** as yellow colour solid in 69% yield. Mp: 174–176°C (MeOH); UV λ_{max} (MeOH): 274 nm (log $\varepsilon = 4.1$), 372 nm (log $\varepsilon = 3.6$); IR ν_{max} (KBr): 1738 (CO), 1546, 1492, 1319 (NO_2), 1091, 883, 740 cm^{-1}. ^1H NMR δ (400 MHz, $CDCl_3$; Me_4Si): 8.17 (s, 1H, CH), 7.48 (d, $J = 8.0$ Hz, 1H, CH), 7.35 (d, $J = 8.0$ Hz, 1H, CH), 7.32 (d, $J = 8.0$ Hz, 1H, CH), 7.0 (s, 1H, CH), 4.18 (q, $J = 7.2$ Hz, 2H, OCH_2), 3.88 (s, 2H, CH_2), 2.73 (q, $J = 7.6$ Hz, 2H, CH_2), 1.29 (t, $J = 6.0$ Hz, 3H, CH_3), 1.27 (t, $J = 5.2$ Hz, 3H, CH_3); ^{13}C NMR δ (100 MHz, $CDCl_3$; Me_4Si): 169.7 (C), 158.5 (C), 152.9 (C × 2), 150.7 (CH), 141.3 (C), 133.7 (CH), 131.2 (C), 127.0 (CH), 122.9 (CH), 120.6 (C), 118.6 (C × 2), 116.8 (CH), 61.2 (OCH_2), 36.2 (CH_2), 28.1 (CH_2), 15.5 (CH_3), 14.2 (CH_3). HRMS (ESI^+): calcd for $C_{19}H_{17}NNaO_6S_2$ (MNa^+), 442.0395; found, 442.0382. Anal. Calcd. for $C_{19}H_{17}NO_6S_2$: C, 54.40; H, 4.08; N, 3.34; S, 15.29; found: C, 54.42; H, 4.11; N, 3.37; S, 15.26.

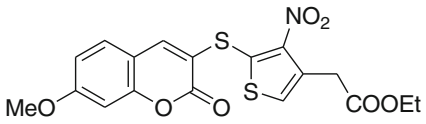
2.3f *Ethyl 2-(5-{[6-(tert-butyl)-2-oxo-2H-3-chromenyl] sulfanyl}-4-nitro-3-thienyl)acetate* **9g**:



9g

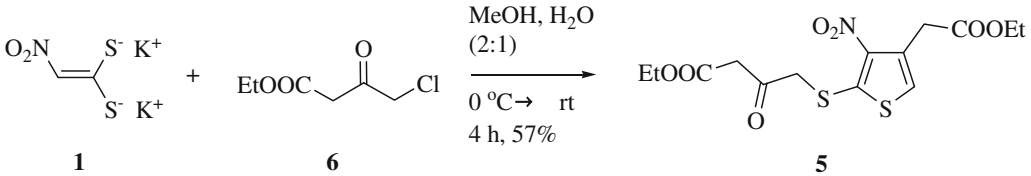
Following the general procedure described above, the reaction of 5-*tert*-butyl-2-hydroxybenzaldehyde **8g** (0.057 g, 0.32 mmol) and ethyl 4-{[4-(2-ethoxy-2-oxoethyl)-3-nitro-2-thienyl]sulfanyl}-3-oxobutanoate **5a** (0.1 g, 0.27 mmol) in the presence of piperidine (0.001 g, 0.1 mol%) stirred at rt for 36 h furnished 0.076 g of ethyl 2-(5-{[6-(*tert*-butyl)-2-oxo-2H-3-chromenyl]sulfanyl}-4-nitro-3-thienyl)acetate **9g** as yellow colour solid in 64% yield. Mp: 154–156°C (MeOH); UV λ_{max} (MeOH): 274 nm (log $\varepsilon = 4.1$), 372 nm (log $\varepsilon = 3.7$); IR ν_{max} (KBr): 1738 (CO), 1546, 1492, 1319 (NO_2), 1091, 883, 740 cm^{-1}. ^1H NMR δ (400 MHz, $CDCl_3$; Me_4Si): 8.21 (s, 1H, CH), 7.48 (d, $J = 8.1$ Hz, 1H, CH), 7.32 (d, $J = 8.7$ Hz, 1H, CH), 7.29 (d, $J = 8.6$ Hz, 1H, CH), 6.98 (s, 1H, CH), 4.14 (q, $J = 7.2$ Hz, 2H, OCH_2), 3.98 (s, 2H, CH_2), 1.27 (s, 9H, CH_3), 1.23 (t, $J = 7.2$ Hz, 3H, CH_3); ^{13}C NMR δ (100 MHz, $CDCl_3$; Me_4Si): 169.9 (C), 158.1 (C), 153.1 (CH), 152.3 (C), 148.2 (C), 140.7 (C), 135.0 (CH), 134.6 (C), 130.8 (C), 128.8 (CH), 124.6 (CH), 118.5 (C), 118.4 (C), 116.2 (CH), 60.4 (OCH_2), 35.4 (CH_2), 31.6 ($CH_3 \times 3$), 26.3 (C), 14.0 (CH_3). HRMS (ESI^+): calcd for $C_{21}H_{21}NNaO_6S_2$ (MNa^+), 470.0708; found, 470.0699. Anal. Calcd. for $C_{21}H_{21}NO_6S_2$: C, 56.36; H, 4.73; N, 3.13; S, 14.33; found: C, 56.33; H, 4.72; N, 3.09; S, 14.31

2.3g *Ethyl 2-{5-[(7-methoxy-2-oxo-2H-3-chromenyl) sulfanyl]-4-nitro-3-thienyl}acetate* **9h**:



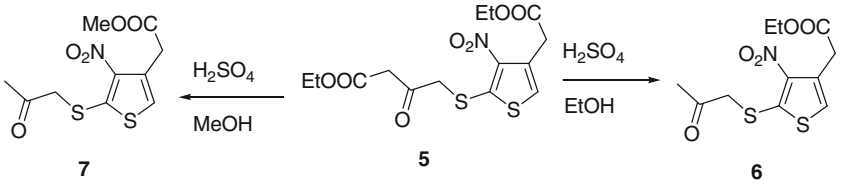
9h

Following the general procedure described above, the reaction of 4-methoxy-2-hydroxybenzaldehyde **8h** (0.049 g, 0.32 mmol) and ethyl 4-{[4-(2-ethoxy-2-oxoethyl)-3-nitro-2-thienyl]sulfanyl}-3-oxobutanoate **5a** (0.1 g, 0.27 mmol) in the presence of piperidine (0.001 g, 0.1 mol%) stirred at rt for 34 h furnished 0.085 g of ethyl 2-{5-[(7-methoxy-2-oxo-2*H*-3-chromenyl)sulfanyl]-4-nitro-3-thienyl}acetate **9h** as yellow colour solid in 73% yield. Mp: 182–183°C (MeOH); UV λ_{max} (MeOH): 276 nm (log $\varepsilon = 4.3$), 372 nm (log $\varepsilon = 3.8$); IR ν_{max} (KBr): 1740 (CO), 1546, 1492, 1319 (NO_2), 1091, 883, 740 cm^{-1}. ^1H NMR δ (400 MHz, $CDCl_3$; Me_4Si): 8.14 (s, 1H, CH), 7.34 (d, $J = 8.8$ Hz, 1H, CH), 7.21 (d, $J = 6.4$ Hz, 1H, CH), 7.0 (s, 1H, CH), 6.95 (s, 1H, CH), 4.18 (q, $J = 7.2$ Hz, 2H, OCH_2), 3.89 (s, 2H, CH_2), 3.87 (s, 3H, CH_3), 1.28 (t, $J = 7.2$ Hz, 3H, CH_3); ^{13}C NMR δ (100 MHz, $CDCl_3$; Me_4Si): 171.7 (C), 169.8 (C), 158.7



1 **6** **5**

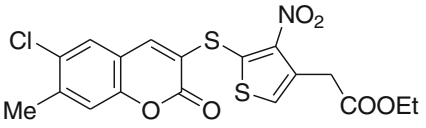
Scheme 2. Reaction of dipotassium salt **1** with ethyl 4-chloroacetoacetate **6**.



Scheme 3. Solvolysis of 3-nitrothiophene **5**.

(C), 156.5 (C), 149.9 (CH), 149.0 (C), 131.2 (C), 123.2 (CH), 121.7 (CH), 120.9 (C), 119.0 (C), 118.1 (CH), 109.9 (CH), 106.8 (C), 61.3 (OCH_2), 55.9 (OCH_3), 36.2 (CH_2), 14.2 (CH_3). HRMS (ESI^+): calcd for $C_{18}H_{15}NNaO_7S_2$ (MNa^+), 444.0188; found, 444.0179. Anal. Calcd. for $C_{18}H_{15}NO_7S_2$: C, 51.30; H, 3.59; N, 3.32; S, 15.22; found: C, 50.29; H, 3.62; N, 3.35; S, 15.19.

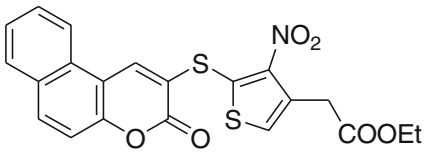
2.3h *Ethyl 2-{5-[(6-chloro-7-methyl-2-oxo-2H-3-chromenyl)sulfanyl]-4-nitro-3-thienyl}acetate* **9i**:



9i

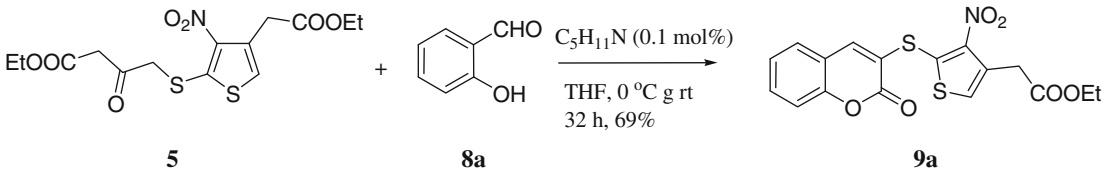
Following the general procedure described above, the reaction of 3-chloro-6-hydroxy-2-methylbenzaldehyde **8i** (0.024 g, 0.16 mmol) and ethyl 4-{[4-(2-ethoxy-2-oxoethyl)-3-nitro-2-thienyl]sulfanyl}-3-oxobutanoate **5a** (0.05 g, 0.13 mmol) in the presence of piperidine (0.001 g, 0.1 mol%) stirred at rt for 36 h furnished 0.026 g of ethyl 2-{5-[(6-chloro-7-methyl-2-oxo-2*H*-3-chromenyl)sulfanyl]-4-nitro-3-thienyl}acetate **9i** as yellow colour solid in 43% yield. Mp: 189–190°C (MeOH); UV λ_{max} (MeOH): 275 nm (log $\varepsilon = 4.3$), 382 nm (log $\varepsilon = 3.8$); IR ν_{max} (KBr): 1740 (CO), 1546, 1492, 1319 (NO_2), 1091, 883, 740 cm^{-1}. ^1H NMR δ (400 MHz, $CDCl_3$; Me_4Si): 8.4 (s, 1H, CH), 7.59 (d, $J = 9.2$ Hz, 1H, CH), 7.21 (d, $J = 8.8$ Hz, 1H, CH), 7.0 (s, 1H, CH), 4.18 (q, $J = 7.2$ Hz, 2H, OCH_2), 3.89 (s, 2H, CH_2), 2.59 (s, 3H, CH_3), 1.28 (t, $J = 7.2$ Hz, 3H, CH_3); ^{13}C NMR δ (100 MHz, $CDCl_3$; Me_4Si): 169.7 (C), 157.6 (C), 153.5 (C), 146.6 (CH), 144.5 (C), 134.4 (C), 133.9 (CH), 131.3 (C), 130.9 (C), 130.5 (C), 123.4 (CH), 121.6 (C), 118.8 (C), 115.9 (CH), 61.3 (OCH_2), 36.1 (CH_2), 15.6 (CH_3), 14.2 (CH_3). HRMS (ESI^+): calcd for $C_{18}H_{14}ClNNaO_6S_2$ (MNa^+), 461.9849; found, 461.9832. Anal. Calcd. for $C_{18}H_{14}ClNO_6S_2$: C, 49.15; H, 3.21; Cl, 8.06; N, 3.18; O, 21.82; S, 14.58; found: C, 49.11; H, 3.20; Cl, 8.07; N, 3.19; O, 21.78; S, 14.56.

2.3i *Ethyl 2-{4-nitro-5-[(3-oxo-3H-benzo[f]chromen-2-yl)sulfanyl]-3-thienyl}acetate* **11**:



11

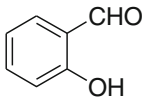
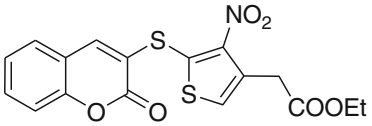
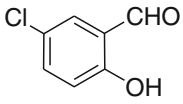
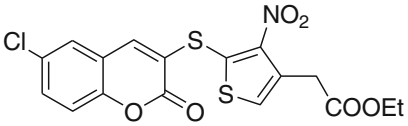
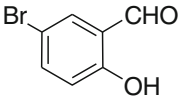
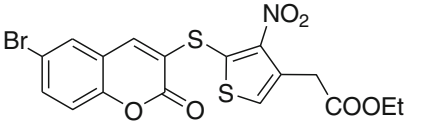
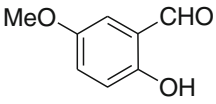
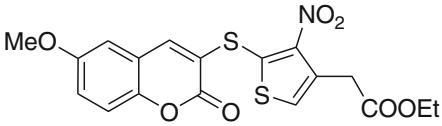
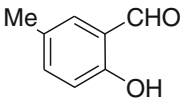
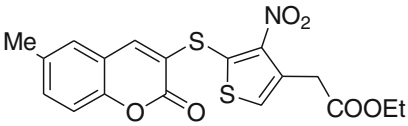
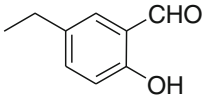
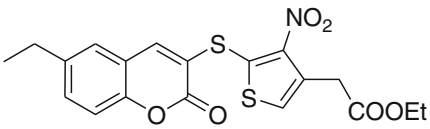
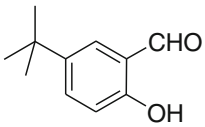
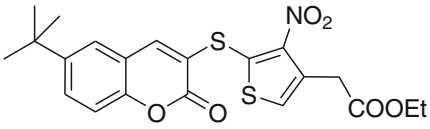
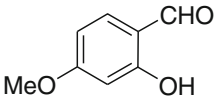
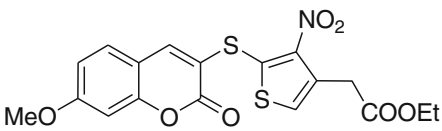
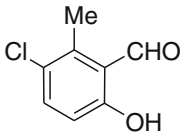
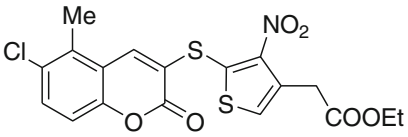
Following the general procedure described above, the reaction of 2- hydroxy-1-napthaldehyde **10** (0.055 g, 0.32 mmol) and ethyl 4-{[4-(2-ethoxy-2-oxoethyl)-3-nitro-2-thienyl]sulfanyl}-3-oxobutanoate **5a** (0.1 g, 0.27 mmol) in the presence of piperidine (0.001 g, 0.1 mol%) stirred at rt for 36 h furnished 0.067 g of ethyl 2-{4-nitro-5-[(3-oxo-3*H*-benzo[*f*]chromen-2-yl)sulfanyl]-3-thienyl}acetate **11** as yellow colour solid in 57% yield. Mp: 196–198°C (MeOH); UV λ_{max} (MeOH): 276 nm (log $\varepsilon = 4.3$), 394 nm (log $\varepsilon = 3.8$); IR ν_{max} (KBr): 1740 (CO), 1546, 1492, 1319 (NO_2), 1091, 883, 740 cm^{-1}. ^1H NMR δ (400 MHz, $CDCl_3$; Me_4Si): 9.0 (s, 1H, CH), 8.26 (d, $J = 8.0$ Hz, 1H, CH), 8.11 (d, $J = 12.0$ Hz, 1H, CH), 8.0 (d, $J = 8.0$ Hz, 1H, CH), 7.76 (t, $J = 8.0$ Hz, 1H, CH), 7.64 (t, $J = 8.0$ Hz, 1H, CH),

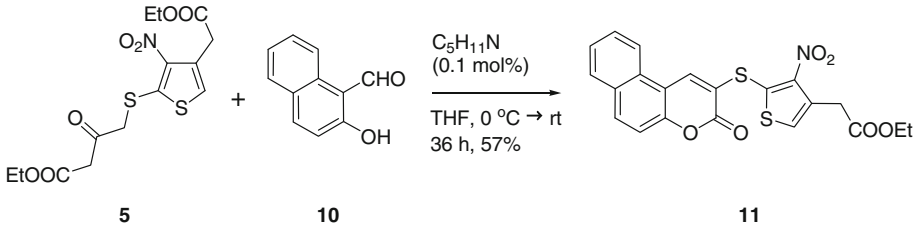


5 **8a** **9a**

Scheme 4. Reaction of 2-hydroxybenzaldehyde **8a** with β-keto ester unit in parent thiophene **5a**.

Table 1. Transformation of β-keto ester **5a** to coumarins **9a–i**.

Entry	2-Hydroxy benzaldehydes **8a-i**	4-Nitro-3-thienyl-2*H*-chromenes **9a-i**	Time (h)	Yield (%)
1	 **8a**	 **9a**	32	69
2	 **8b**	 **9b**	34	66
3	 **8c**	 **9c**	34	48
4	 **8d**	 **9d**	34	53
5	 **8e**	 **9e**	36	67
6	 **8f**	 **9f**	38	69
7	 **8g**	 **9g**	36	64
8	 **8h**	 **9h**	32	73
9	 **8i**	 **9i**	34	42



5 10 11

Scheme 5. Reaction of 2-hydroxy-1-napthaldehyde **10** with β-keto ester unit in parent thiophene **5a**.

7.52 (t, J = 8.0 Hz, 1H, CH), 6.99 (s, 1H, CH), 4.19 (q, J = 8.0 Hz, 2H, OCH_2), 3.90 (s, 2H, CH_2), 1.28 (t, J = 8.0 Hz, 3H, CH_3); ^{13}C NMR δ (100 MHz, $CDCl_3$; Me_4Si): 169.9 (C), 158.6 (C), 155.2 (C), 147.1 (CH), 146.8 (C), 135.5 (CH), 131.3 (C × 2), 130.4 (C), 129.3 (CH), 129.2 (CH), 128.8 (C), 126.8 (CH), 122.8 (CH), 121.4 (CH), 119.1 (C), 116.8 (CH), 113.2 (C), 61.3 (OCH_2), 36.3 (CH_2), 14.2 (CH_3). HRMS (ESI^+): calcd for $C_{21}H_{15}NNaO_6S_2$ (MNa^+), 464.0238; found, 464.0224. Anal. Calcd. for $C_{21}H_{15}NO_6S_2$: C, 57.13; H, 3.42; N, 3.17; S, 14.53; found: C, 57.11; H, 3.39; N, 3.14; S, 14.49.

3. Results and discussion

The reaction of ethyl chloroacetoacetate **6** with dipotassium nitroketenedithioacetate **1** provided 3-nitrothiopene **5a** as the only product in 57% yield (scheme 2). The structure of the thiophene **5a** was established on the basis of spectroscopic (IR, ^{1}H NMR, ^{13}C NMR, 2D NMR and HRMS), analytical data and single crystal X-ray structure determination.[9] As anticipated from the assigned structure, ^{1}H NMR spectrum of **5a** displayed four singlets for three methylenes (δ 3.66, 3.85, 4.11 ppm) and one for C5H (δ 7.01 ppm). The ^{1}H NMR spectrum also revealed occurrence of the keto-enol tautomerism to the extent of 85:15 where keto-form predominated.

The thiophene **5a**, prepared in this study possesses multiple functional groups like ketone, ester and nitrogroups. Particularly, there are three active methylenes flanked by three carbonyl carbons. Initially, we treated thiophene **5a** with EtOH in presence of a catalytic amount of H_2SO_4. The product was the anticipated methyl ketone **7** (scheme 3). Reaction of with MeOH in presence of catalytic amount of H_2SO_4 provided **7a**, the decarboethoxylated and trans-esterification product (scheme 3).

Next, we considered transformation of **5a** into coumarin and 3-nitrothiophene conjugates by reaction of the β-keto ester moiety in **5a** with 2-hydroxybenzaldehyde. Many natural products with coumarin (benzopyrone) motif have been isolated from plant sources and such molecules show immense biological activity.[10] In addition, coumarin and its C3-substitution products found clinical medical applications as blood thinners or as anticoagulants.[11] Some coumarin derivatives are triplet sensitizers and are in use as dye lasers.[12] Classical routes to coumarins include Pechmann,[13,14] Knoevenagel,[15] Perkin,[16] Reformatsky[17] and Wittig[18] condensation reactions. Thus, thiophene **5a** was subjected to Pechmann condensation with 2-hydroxybenzaldehyde (salicylaldehyde) **8a** to produce a C3-nitrothiophene substituted coumarin **9a**. The reaction conducted in presence of piperidine in THF produced the coumarin, ethyl 2-{4-nitro-5-[(2-oxo-2*H*-3-chromenyl)sulfanyl]-3-thienylacetate **9a** as the only product in 69% yield (scheme 4). By changing solvents and bases systematically, we found that the transformation works well in presence of a catalytic amount of piperidine (0.1 mol %) in THF at rt. Even though catalytic amount of piperidine demanded longer reaction time (table 1), the reaction was cleaner and product isolation was facile. The coumarin **9a** was characterized on the basis of spectroscopic (IR, ^{1}H NMR, ^{13}C NMR, 2D NMR and HRMS) and analytical data. Three singlets at δ 3.89 ppm for two hydrogens, at δ 7.02 for one hydrogen and at 8.22 ppm for one hydrogen assignable to methylene, thiophene C5H and coumarin C4H respectively, were notable signals in the ^{1}H NMR spectrum.

The Pechmann transformation of thiophene **5a** into coumarin **9a** proved to be quite general for nine 2-hydroxybenzaldehydes **8a–i** and the coumarin products **9a–i** were obtained in 42–73% yield (table 1).

Scope of the present 3-nitrothiophene substituted coumarin synthesis could be further extended by making 2-hydroxy-1-naphthaldehyde **10** participate in the condensation reaction (scheme 5). This reaction provided coumarin **11** in 57% yield. Spectroscopic data supported structure. Particularly noteworthy is the singlet for C4H of the coumarin ring in the ^{1}H NMR spectrum which appeared at δ 9.1 ppm.

Mechanistically, the transformation is interesting as one acetate unit in **5a** was lost during coumarin formation.[19] Moreover, the active methylene adjacent to C2S, instead of that of the β-keto ester moiety was utilized in the coumarin synthesis. This is in contrast to general expectation that β-keto ester moiety in **5a** would react in preference over the methylene flanked by C2S and CO groups during coumarin formation. Perhaps, under the reaction conditions, the carbanion generated on C2S methylene is more reactive than the carbanion generated on the β-keto ester moiety.

4. Conclusions

Our studies clearly delineated the alkylation of the salt **1** with ethyl 4-chloroacetoacetate **6** to provide the thiophene **5a** which could be utilized for the synthesis of novel coumarins **9** and **11** with 3-nitrothiophene moiety at C3 position. Overall, we have demonstrated a facile two-step synthesis of hybrid heterocyles incorporating biologically important 3-nitrothiophene and coumarin units starting from inexpensive and readily available chemicals and reagents. Furthermore, we have demonstrated that the one of the two esters in **5a** can be selectively decarboethoxylated to provide methyl ketones as well trans-esterification products.

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