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

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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, 2θ_{max} = 50.0º, 2225 reflections collected, 2225 unique (R_{int} = 0.0203), Final GooF = 1.054, R1 = 0.0354, wR2 = 0.0940, R indices based on 2099 reflections with I >2σ(I) (refinement on F^2), 155 parameters, μ = 0.616 mm^-1.

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\overline{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, 2θ_{max} = 50.0º, 6310 reflections collected, 2349 unique (R_{int} = 0.0395), Final GooF = 1.177, R1 = 0.0726, wR2 = 0.2068, R indices based on 2070 reflections with I >2σ(I) (refinement on F^2), 194 parameters, μ = 0.397 mm^-1.

CCDC 1402849 (3b) and CCDC 1402850 (2f) contain the supplementary crystallographic data for this paper which can be obtained free of charge at https://summary.ccdc.cam.ac.uk/structure-summary-form or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223 336 033; email: deposit@ccdc.cam.ac.uk.

Crystal structure determination: X-ray data for the compounds were collected at room temperature using a Bruker Smart Apex CCD diffractometer with graphite monochromated Mo-Kα radiation (λ=0.71073Å) with ω-scan method. Preliminary lattice parameters and orientation matrices were obtained from four sets of frames. Unit cell dimensions were determined using 9189 reflections for 3b and 2233 reflections for 2f data sets. Integration and scaling of intensity data were accomplished using SAINT program. The structures were solved by Direct Methods using SHELXS97 and refinement was carried out by full-matrix
least-squares technique using SHELXL97.  

Anisotropic displacement parameters were included for all non-hydrogen atoms. All H atoms were positioned geometrically and treated as riding on their parent C atoms, with C-H distances of 0.93--0.97 Å, and with $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$ or $1.5U_{\text{eq}}$ for methyl atoms. Two atoms of ethyl group of 2f were disordered over two sites with site occupancy factor of 0.77 for C1/C2 atoms (major component) and 0.23 for C1D/C2D atoms (minor component). The anisotropic displacement parameters of the disordered carbon atoms were restrained to be similar (SIMU instruction) and the direction of motion along the axis between the atoms was also restrained (DELU instruction). The C-C bond distances were restrained to a set target value of 1.50-1.55 Å.

2. Sheldrick, G. M. SHELXS97 and SHELXL97, Programs for crystal structure solution and refinement; University of Gottingen: Germany, 1997.

**General Information:** Melting points of all the compounds were recorded on Veego programmable melting point apparatus and are uncorrected. IR spectra were recorded on a PerkineElmer FT-IR 240-C spectrophotometer using KBr optics. $^1$H NMR spectra were recorded on Bruker AV 300 MHz in CDCl$_3$ using TMS as internal standard. Electron Spray Ionization (ESI) and high-resolution spectra were recorded on QSTARXL hybrid MS/MS system (Applied Biosystems, USA) under electrospray ionization. All the reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F254 (mesh)
plates; spots were visualized with UV light. Merck silica gel (60-120 mesh) was used for column chromatography.

**Typical procedure for 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 precipitate was washed with 3×5 ml of hexane to afford the pure 4-benzoyl-5-(methylthio)thiophene-2,3-dione 2a.

**Typical procedure for synthesis of 4-benzoyl-5-(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 rotavapor, and the crude residue obtained was purified by normal column chromatography (silica gel 60-120 mesh, ethylacetate/hexane gradient mixture as eluent to afford 4-benzoyl-5-(methylthio)thiophen-3(2H)-one 3a.
Characterization data obtained for polyfunctionalized 4-benzoyl-5-(methylthio) thiophene-2,3-diones 2a-2h:

4-Benzoyl-5-(methylthio)thiophene-2,3-dione (2a): Yield 96% (0.60 g), brown solid, m.p. 107-109 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta = 7.65 \) (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\(_3\)) \(\delta = 190.7, 188.7, 180.8, 174.9, 136.7, 132.9, 129.1, 128.0, 123.2, 17.7\); IR (KBr): \(\nu = 3439, 3058, 1742, 1685, 1620, 1404, 1299, 949\) cm\(^{-1}\); MS (ESI) 287 (M+Na). ESI-HRMS obtained for C\(_{12}\)H\(_9\)O\(_3\)S\(_2\) (M+H) = 264.9983 (calculated: 264.9987).

4-(4-Chlorobenzoyl)-5-(methylthio)thiophene-2,3-dione (2b): Yield 98 % (0.60 g), orange solid, m.p. 182 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta = 7.60 \) (d, \(J = 8.5\) Hz, 2H), 7.4 (d, \(J = 8.5\) Hz, 2H), 2.71 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta = 191.7, 187.4, 180.6, 174.9, 139.3, 135.1, 130.6, 128.4, 122.9, 17.9\); IR (KBr): \(\nu = 3424, 3082, 2932, 1720, 1685, 1617, 1396, 1299, 1239, 976\) cm\(^{-1}\); MS (ESI) 321 (M+Na). ESI-HRMS obtained for C\(_{12}\)H\(_7\)ClO\(_3\)NaS\(_2\) (M+Na) = 321.0154 (calculated: 321.0151).
4-(4-Methoxybenzoyl)-5-(methylthio)thiophene-2,3-dione (2c): Yield 96% (0.59 g), yellow solid, m.p. 148 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 7.70\) (d, \(J = 8.8\) Hz, 2H), 6.93 (d, \(J = 8.8\) Hz, 2H), 3.87 (s, 3H), 2.68 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 188.9, 187.0, 181.0, 175.1, 163.8, 131.9, 129.2, 124.1, 113.5, 55.4, 17.5\); IR (KBr): \(\nu = 3458, 2983, 2838, 1748, 1680, 1594, 1424, 1304, 1245, 1177\) cm\(^{-1}\); MS (ESI) 317 (M+Na). ESI-HRMS obtained for C\(_{13}\)H\(_{10}\)O\(_4\)NaS\(_2\) (M+Na) = 317.0357 (calculated: 317.0353).

5-(Methylthio)-4-(4-(trifluoromethyl)benzoyl)thiophene-2,3-dione (2d): Yield 98% (0.58 g), yellow solid, m.p. 172-174 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 7.74-7.68\) (q, \(J = 9.0, 9.8\) Hz, 4H), 2.74 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 193.0, 187.7, 180.4, 174.8, 139.9, 133.6, 129.2, 126.6, 125.5, 125.07, 125.04, 124.9, 122.3, 122.2, 18.0\); IR (KBr): \(\nu = 3458, 3354, 1739, 1688, 1620, 1414, 1322, 1134, 1065\) cm\(^{-1}\); MS (ESI) 355 (M+Na). ESI-HRMS obtained for C\(_{13}\)H\(_7\)F\(_3\)O\(_3\)NaS\(_2\) (M+Na) = 355.0078 (calculated: 355.0082)

5-(Methylthio)-4-(thiophene-2-carbonyl)thiophene-2,3-dione (2e): Yield 97% (0.61 g), yellow solid, m.p. 135-137 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = \ldots\)
7.87-7.86 (dd, \( J = 1.0, 3.9 \) Hz, 1H), 7.72-7.71 (dd, \( J = 1.0, 3.9 \) Hz, 1H), 7.15-7.13 (dd, \( J = 3.9, 3.9 \) Hz, 1H), 2.68 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta = 190.5, 180.6, 179.2, 174.6, 142.6, 135.0, 134.6, 128.1, 123.5, 18.0 \); IR (KBr): \( \nu = 3449, 2922, 1745, 1675, 1615, 1458, 1414, 1305, 1242, 723 \) cm\(^{-1}\); MS (ESI) 293 (M+Na). ESI-HRMS obtained for C\(_{16}\)H\(_6\)O\(_3\)NaS\(_3\) (M+Na) = 293.0177 (calculated: 293.0181).

4-(4-Ethylbenzoyl)-5-(methylthio)thiophene-2,3-dione (2f): Yield 98 % (0.60 g), yellow solid, m.p. 143 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta = 7.61 (d, \( J = 8.0 \) Hz, 2H), 7.26 (d, \( J = 8.0 \) Hz, 2H), 2.73-2.69 (q, \( J = 7.6, 7.4 \) Hz, 2H), 2.68 (s, 3H), 1.26 (t, \( J = 7.6, 7.6 \) Hz, 3H ); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta = 189.7, 188.3, 181.0, 175.0, 150.2, 134.2, 129.5, 127.6, 123.8, 28.9, 17.6, 15.0 \); IR (KBr): \( \nu = 3476, 2960, 2361, 1749, 1694, 1606, 1425, 1293, 1238, 950 \) cm\(^{-1}\); MS (ESI) 315 (M+Na). ESI-HRMS obtained for C\(_{14}\)H\(_{12}\)O\(_3\)NaS\(_2\) (M+Na) = 315.0229 (calculated: 315.0232).

4-(Benzo[d][1,3]dioxole-5-carbonyl)-5-(methylthio)thiophene-2,3-dione (2g): Yield 98 % (0.59 g), brown solid, m.p. 166-168 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta = 7.29-7.27 (dd, \( J = 1.8, 1.6 \) Hz, 1H), 7.21 (d, \( J = 1.5 \) Hz, 1H), 6.84 (d, \( J = 8.2 \) Hz, 1H ), 6.05 (s, 2H), 2.69 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta = 188.9, 186.7, 180.8, 175.0, 152.2, 147.8, 130.9, 126.3, 124.1, 109.1, 107.7, 101.9, 17.6 \); IR (KBr): \( \nu = 3462, 3005, 2921,
2621, 1741, 1665, 1425, 1259, 1030 cm\(^{-1}\); MS (ESI) 331 (M+Na). ESI-HRMS obtained for 
\(\text{C}_{13}\text{H}_{8}\text{O}_{5}\text{NaS}_{2} \text{(M+Na)} = 330.9915\) (calculated: 330.9920).

\[\text{4-(3,4-Difluorobenzoyl)-5-(methylthio)thiophene-2,3-dione (2h):}\] Yield 97% (0.58 g), orange solid, m.p. 152 \(^{\circ}\)C; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 7.45-7.41\) (dd, \(J = 1.5, 1.7\) Hz, 1H), 7.38-7.34 (dd, \(J = 1.5, 1.5\) Hz, 1H), 7.20 (t, \(J = 7.5, 7.9\) Hz, 1H), 2.71 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 189.5, 185.5, 180.2, 174.3, 159.7, 159.0, 133.7, 133.7, 132.3, 132.1, 125.9, 124.8, 124.4, 124.3, 122.2, 114.5, 114.2, 112.7, 112.4, 16.8; IR (KBr): \(\nu = 3447, 2925, 2361, 1732, 1676, 1618, 1422, 1304, 1228, 960\) cm\(^{-1}\); MS (ESI) 323 (M+Na). ESI-HRMS obtained for \(\text{C}_{12}\text{H}_{6}\text{F}_{2}\text{O}_{3}\text{NaS}_{2} \text{(M+Na)} = 323.0015\) (calculated: 323.0011).

Characterization data obtained for polyfunctionalized 4-benzoyl-5-(methylthio) thiophen-3(2\(H\))-ones 3a-3g:

\[\text{4-Benzoyl-5-(methylthio)thiophen-3(2\(H\))-one (3a):}\] Yield 71% (0.42 g), brown solid, m.p 138-140 \(^{\circ}\)C; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 7.67\) (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\(_3\)): \(\delta = 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 C₁₂H₁₁O₂S₂ (M+H) = 251.0194 (calculated: 251.0195).

**4-(4-Chlorobenzoyl)-5-(methylthio)thiophen-3(2H)-one (3b):**

Yield 77% (0.45 g), brown solid, m.p. 116 °C; ¹H NMR (300 MHz, CDCl₃): δ = 7.61 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 8.5 Hz, 2H), 3.87 (s, 2H), 2.64 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ = 197.4, 193.5, 188.5, 138.4, 135.9, 130.4, 128.1, 125.4, 41.8, 16.2; IR (KBr): ν 3059, 2976, 2928, 1664, 1607, 1429, 1298, 1232, 1087 cm⁻¹; MS (ESI) 307 (M+Na). ESI-HRMS obtained for C₁₂H₁₀O₂ClS₂ (M+H) = 284.9807 (calculated: 284.9805).

**4-(4-Methoxybenzoyl)-5-(methylthio)thiophen-3(2H)-one (3c):**

Yield 68% (0.4 g), brown solid, m.p. 178-180 °C; ¹H NMR (300 MHz, CDCl₃): δ = 7.72 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 3.87 (s, 2H), 3.85 (s, 3H), 2.62 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ = 194.4, 193.8, 188.4, 163.3, 131.7, 129.9, 126.6, 113.2, 55.3, 41.6, 16.0; IR (KBr): ν 3327, 2928, 2850, 1625, 1600, 1431, 1241, 1175, 1024 cm⁻¹; MS (ESI) 303 (M+Na). ESI-HRMS obtained for C₁₃H₁₂O₃NaS₂ (M+Na) = 303.0115 (calculated: 303.0120).
5-(Methylthio)-4-(4-(trifluoromethyl)benzoyl)thiophen-3(2H)-one (3d): Yield 66% (0.38 g), pale yellow solid, m.p. 118-120 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 7.73-7.64 \text{ (q, } J = 8.3, 8.3 \text{ Hz, 4H), 3.88 (s, 2H), 2.67 (s, 3H);} \) \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 198.7, 193.4, 188.7, 140.9, 133.2, 133.0, 129.0, 128.1, 127.9, 125.9, 125.4, 124.9, 124.8, 124.7, 122.6, 41.9, 16.4; \) IR (KBr): \(\nu = 3314, 3063, 2979, 2931, 1668, 1614, 1435, 1329, 1112 \text{ cm}^{-1}; \) MS (ESI) 341 (M+Na). ESI-HRMS obtained for C\(_{13}\)H\(_9\)F\(_3\)O\(_2\)S\(_2\) (M+Na) = 341.0030 (calculated: 341.0031).

5-(Methylthio)-4-(thiophene-2-carbonyl)thiophen-3(2H)-one (3e): Yield 62% (0.37 g), brown solid, m.p. 181 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 7.87 \text{ (d, } J = 2.4 \text{ Hz, 1H), 7.65 (d, } J = 4.8 \text{ Hz, 1H), 7.10 (t, } J = 4.8, 3.9 \text{ Hz, 1H) 3.90 (s, 2H), 2.62 (s, 3H);} \) \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 195.9, 193.4, 180.5, 153.0, 143.3, 134.1, 127.7, 126.3, 41.7, 16.3; \) IR (KBr): \(\nu = 3295, 2937, 2857, 1710, 1658, 1419, 1231, 1054 \text{ cm}^{-1}; \) MS (ESI) 279 (M+Na). ESI-HRMS obtained for C\(_{10}\)H\(_8\)O\(_2\)NaS\(_3\) (M+Na) = 278.9985 (calculated: 278.9987).

4-(Benzo[d][1,3]dioxole-5-carbonyl)-5-(methylthio)thiophen-3(2H)-one (3f): Yield 61% (0.35 g), pale yellow solid, m.p. 198 °C; \(^1\)H NMR (300 MHz,
CDCl$_3$+DMSO): $\delta$ =7.31 (d, $J$ = 8.1 Hz, 1H), 7.19 (s, 1H), 6.82 (d, $J$ = 8.1 Hz, 1H), 6.05 (s, 2H), 3.92 (s, 2H), 2.65 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$+DMSO): $\delta$ = 197.6, 193.2, 187.3, 156.7, 150.8, 146.8, 130.9, 125.0, 108.2, 106.8, 101.0, 41.0, 15.2; IR (KBr): $\nu$ 3327, 2929, 2851, 1625, 1626, 1575, 1447, 1250, 1035 cm$^{-1}$; MS (ESI) 307 (M+Na). ESI-HRMS obtained for C$_{13}$H$_{10}$O$_4$NaS$_2$ (M+Na) = 307.0174(calculated: 307.0177).

![Chemical Structure](image)

4-(4-Ethylbenzoyl)-5-(methylthio)thiophen-3(2H)-one (3g):
Yield 72% (0.42 g), pale pink solid; m.p. 124-126°C $^{1}$H NMR (300 MHz, CDCl$_3$): $\delta$ = 7.63 (d, $J$ = 8.0 Hz, 2H), 7.24 (d, $J$ = 8.0 Hz, 2H), 3.87 (s, 2H), 2.71-2.67 (q, $J$ = 7.6, 7.6 Hz, 2H), 2.63 (s, 3H), 1.25 (t, $J$ = 7.6, 7.6 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 195.2, 193.7, 189.5, 149.3, 134.9, 129.4, 127.4, 126.3, 41.7, 28.9, 16.0, 15.0; IR (KBr): $\nu$ 3312, 2929, 2363, 1656, 1605, 1427, 1235, 846 cm$^{-1}$; MS (ESI) 301 (M+Na). ESI-HRMS obtained for C$_{14}$H$_{15}$O$_2$S$_2$ (M+H) = 279.0505 (calculated: 279.0508).
$^1$H NMR CDCl$_3$ 500 MHz

$^{13}$C NMR CDCl$_3$ 75 MHz