



Expeditious and highly efficient protocol for the synthesis of novel diversely substituted thieno[2,3-*b*]thiophene

Yahia Nasser Mabkhot*, Assem Barakat*, Saeed Alshahrani

Department of Chemistry, Faculty of Science, King Saud University, P.O. Box 2455, Riyadh 11451, Saudi Arabia

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ABSTRACT

1,1'-(3-Methyl-4-phenylthieno[2,3-*b*]thiophene-2,5-diyl)bis(4,4,4 triethoxybut-2-en-1-one)-3 has been reported by one-pot reaction of enaminone derivative **2** with triethylorthoformate in fairly high yields. The hitherto unknown bis-hydroxyl amine derivatives **4** via *N*-nucleophile under basic conditions is described. Additionally, the novel Compound **5** were synthesized by the cyclization of enaminone derivative **2** using AcOH with the aid of catalytic amount of AcONH₄. Nevertheless, facile reaction sequences for the preparation of **6**, **7**, **8a-c**, and **9a-c** starting with 1,1'-(3-methyl-4-phenylthieno[2,3-*b*]thiophene-2,5-diyl)diethanone **1** have been developed. Finally, several bis-heterocycles 10a-f were synthesized through a stepwise formation of hydrazone followed by a Michael 1,4-addition of the nucleophile nitrogen atom and provides a convenient access to an important class of nitrogen heterocycles.

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1. Introduction

More recently thienothiophene, in particular the thieno[2,3-*b*]thiophene scaffold, have attracted considerable attention as the moieties comprise some significant advantages. Thienothiophene derivatives represent important building blocks in organic and medicinal chemistry. They have been developed for different pharmaceutical purposes and have been tested as potential antitumor, antiviral, antibiotic, and antiglaucoma drugs, or as inhibitors of platelet aggregation [1,2]. On the other hand, hydrazone derivatives are reported to possess antimicrobial [3], antitubercular [4], anticonvulsant [5] and anti-inflammatory [6] activities. Mabkhot and others [7–22] have reported a variety of syntheses of heteroaromatics developed using functionally substituted thieno[2,3-*b*]thiophenes as readily obtainable building blocks possessing multiple electrophilic and nucleophilic moieties. Nitrogen-containing heterocycles are undoubtedly one of the most important fundamentals in organic chemistry. They are widely distributed in natural products and in pharmaceuticals, and numerous studies for their chemistry and synthesis have been reported. Pyrazole derivatives are a very interesting class of heterocyclic compounds that have remarkable pharmacological activities as antibacterial, antifungal, and hypoglycemic compounds, as tumor necrosis inhibitor, and in the treatment of thromboembolic disorders [23–29]. In continuation of these findings, we report herein the synthesis of analogs of thieno[2,3-*b*]thiophene moiety as a base unit which

are of interest as potential biologically active compounds or pharmaceuticals. To the best of our knowledge, no such any of those molecules had been reported so far.

2. General experimental

General: All melting points were measured on a Gallenkamp melting point apparatus. IR spectra were measured as KBr pellets on a perking elmer FT 1000 spectrophotometer. The NMR spectra were recorded on a Varian Mercury Jeol-400 NMR spectrometer. ¹H NMR (400 MHz) and ¹³C NMR were run in dimethylsulfoxide (DMSO-*d*₆). Chemical shifts (δ) are referred in terms of ppm and *J*-coupling constants are given in Hz. Abbreviations for multiplicity is as follows: s (singulet), d (doublet), t (triplet), q (quadruplet), m (multiplet). Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 eV. Elemental analysis was carried out on an Elementar Vario EL analyzer.

2.1. 1,1'-(3-Methyl-4-phenylthieno[2,3-*b*]thiophene-2,5-diyl)bis(4,4,4-triethoxybut-2-en-1-one) (**3**)

Compound **3** was prepared by fusion of enaminone derivative **2** (212 mg, 0.5 mmol) with triethylorthoformate (TEOF) (148 mg, 1 mmol). Ethanol was added and then the formed solid product was filtered off affording **3** as pale red crystals. Yield: 57%; m.p. 315–317 °C; IR ν_{max} (KBr): 1641 (C=O) cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) (ppm): 1.05 (t, 3H, *J* = 6.6 Hz, CH₃), 1.96 (s, 3H, CH₃), 2.84–3.13 (q, 2H, *J* = 8.0 Hz, CH₂), 5.69 (d, 1H, *J* = 12 Hz, ^αCH), 6.53 (d, 1H, *J* = 12 Hz, ^βCH), 7.42–7.52 (m, 5H, Ar-H); ¹³C NMR

* Corresponding authors. Tel.: +966 14675884; fax: +966 14675992.

E-mail addresses: Yahia@ksu.edu.sa (Y.N. Mabkhot), ambarakat@ksu.edu.sa (A. Barakat).

(100 MHz, DMSO-*d*₆) (ppm): 14.2, 22.3, 44.0, 129.3, 129.8, 130.4, 131.5, 133.3, 142.0, 182.41; MS *m/z* (%): 630 [M⁺, 35%]; Anal. calcd. for C₃₃H₄₂O₈S₂: C, 62.83; H, 6.71; O, 20.21; S, 10.17; Found: C, 62.80; H, 6.75; S, 20.18.

2.2. 1,1'-(3-Methyl-4-phenylthieno[2,3-*b*]thiophene-2,5-diyl)bis(3-(hydroxyamino)prop-2-en-1-one) (**4**)

A mixture of compound **2** (212 mg, 0.5 mmol) with (NH₂OH·HCl) (70 mg, 1 mmol) in dioxan (15 mL) was refluxed for 7 h in the presence of TEA (triethyl amine). The reaction mixture was left to cool to RT. The formed solid product was filtered off, washed with ethanol, dried and recrystallized from (EtOH) to afford the corresponding hydroxyl mine derivatives **4** as white crystal. Yield (59%); m.p. 165–166 °C; IR *v*_{max} (KBr): 1653 (C=O), 3420 (OH) cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) (ppm): 2.2 (brs, 2H, OH&NH), 1.96 (s, 3H, CH₃), 4.53 (d, 1H, *J* = 12 Hz, CH), 5.38 (d, 1H, *J* = 12 Hz, CH), 7.41–7.65 (m, 5H, C₆H₅); ¹³C NMR (100 MHz, DMSO-*d*₆) (ppm): 180, 153.9, 109.8, 44.79, 14.9; MS *m/z* (%): 400 [M⁺, 15%]; Anal. calcd. for C₁₉H₁₆N₂O₄S₂: C, 56.98; H, 4.03; N, 7.00; O, 15.98; S, 16.01; Found: C, 56.91; H, 4.09; N, 7.02; S, 16.04.

2.3. 3-(Dimethylamino)-1-(5-(6-(5-(*E*)-3-(dimethylamino)acryloyl)-3-methyl-4-phenylthieno[2,3-*b*]thiophen-2-yl)nicotinoyl)-3-methyl-4-phenylthieno[2,3-*b*]thiophen-2-yl)prop-2-en-1-one (**5**)

A mixture of compound **2** (212 mg, 0.5 mmol) with acetic acid glacial (15 mL) was refluxed for 3 h in the presence of ammonium acetate. The solid product formed was filtered off, washed with ethanol, dried and recrystallized from (DMF/EtOH) to afford **5** as deep yellow powder crystal. Yield (77%); m.p. >330 °C; IR *v*_{max} (KBr): 1640 (C=O) cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) (ppm): 1.96 (s, 3H, CH₃), 2.2 (s, 3H, CH₃), 3.00 (s, 12H, CH₃), 4.55 (d, 1H, *J* = 12 Hz, CH), 5.43 (d, 1H, *J* = 12 Hz, CH), 7.41–7.65 (m, 5H, C₆H₅), 7.98–8.10 (m, 3H, C₅H₃N), ¹³C NMR (100 MHz, DMSO-*d*₆) (ppm): 14.2, 22.3, 44.0, 129.3, 129.8, 130.4, 131.5, 133.3, 142.0, 182.41, 183.5; MS *m/z* (%): 758 [M⁺, 1.2%]; Anal. calcd. for C₄₂H₃₅N₃O₃S₄: C, 66.55; H, 4.65; N, 5.54; O, 6.33; S, 16.92; Found: C, 66.58; H, 4.60; N, 5.58; S, 16.89.

2.4. 2,2'-(1,1'-(3-Methyl-4-phenylthieno[2,3-*b*]thiophene-2,5-diyl)bis(ethan-1-yl-1-ylidene)) dimalononitrile (**6**)

A mixture of compound **1** (314 mg, 1 mmol) (with malononitrile (132 mg, 2 mmol, 2.0 equiv.) in absolute ethanol (15 mL) was heated under reflux for 4 h. The solid product was collected by filtration afford **6** as a deep red crystals; Yield (65%); m.p. >320 °C; IR *v*_{max} (KBr): 2191 (CN) cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) (ppm): 1.63 (s, 6H, CH₃), 1.84 (s, 3H, CH₃), 7.29–7.55 (m, 5H, Ar–H); ¹³C NMR (100 MHz, DMSO-*d*₆) (ppm): 178.6, 137.0, 136.5, 135.2, 132.1, 129.0, 128.1, 125.4, 112.4, 45.5, 22.2; MS *m/z* (%): 410 [M⁺, 2%]; Anal. calcd. for C₂₃H₁₄N₄S₂: C, 67.29; H, 3.44; N, 13.65; S, 15.62; Found: C, 67.12; H, 3.49; N, 13.68; S, 15.59.

2.5. 2,2'-1,1'-(3-Methyl-4-phenylthieno[2,3-*b*]thiophene-2,5-diyl)bis(3-(dimethylamino) prop-2-ene-1-yl-1-ylidene)dimalononitrile (**7**)

A mixture of compound **6** (205 mg, 0.5 mmol) (with (DMF–DMA) (1 mmol, 2 equiv.) in absolute ethanol (15 mL) was heated under reflux for 4 h. The formed solid product was collected by filtration afford **7** as a deep brown powder crystals; Yield (64%); m.p. >320 °C; IR *v*_{max} (KBr): 2193 (CN) cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) (ppm): 1.83 (s, 3H, CH₃), 3.24–3.13 (s, 12H, CH₃), 7.90–7.95 (d, 1H, *J* = 12.0 Hz, ^αCH), 7.39–7.52 (m, 5H, Ar–H), 8.15 (d, 1H, *J* = 12.0 Hz, ^βCH); ¹³C NMR (100 MHz, DMSO-*d*₆) (ppm):

179.7, 140.6, 137.0, 135.0, 134.2, 129.1, 128.4, 115.8, 100.8, 72.5, 44.7, 13.9; MS *m/z* (%): 520 [M⁺, 5%]; Anal. calcd. for C₂₉H₂₄N₆S₂: C, 66.90; H, 4.65; N, 16.14; S, 12.32; Found: C, 66.85; H, 4.72; N, 16.17; S, 12.39.

2.6. General procedure for the synthesis of compounds **8a,b** (GP1)

A mixture of compound **1** (157 mg, 0.5 mmol) with hydrazine derivatives (1 mL) in absolute ethanol (15 mL) was heated under reflux for 8 h afforded the corresponding derivatives **8a,b** respectively. The solid product was collected by filtration and recrystallized from (EtOH).

2.6.1. 1,1'-(1,1'-(3-Methyl-4-phenylthieno[2,3-*b*]thiophene-2,5-diyl)bis(ethan-1-yl-1-ylidene))bis(hydrazine) (**8a**)

Compound **8a** was prepared from hydrazine hydrate (1 mL) followed GP1 as a deep yellow crystals; Yield (89%); m.p. 186–187 °C; IR *v*_{max} (KBr): 3350–3385 (NH₂), 1598 (C=N) cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) (ppm): 1.34–1.71–2.01 (s, 9H, CH₃), 6.38–6.39 (s, 2H, NH₂), 7.36–7.45 (m, 5H, Ar–H); ¹³C NMR (100 MHz, DMSO-*d*₆) (ppm): 148.3, 141.7, 140.1, 132.6, 129.8, 129.2, 126.8, 15.1, 12.0; MS *m/z* (%): 342 [M⁺, 43%]; Anal. calcd. for C₁₇H₁₈N₄S₂: C, 59.62; H, 5.30; N, 16.36; S, 18.73; Found: C, 59.65; H, 5.26; N, 16.31; S, 18.76.

2.6.2. 2,2'-(1,1'-(3-Methyl-4-phenylthieno[2,3-*b*]thiophene-2,5-diyl)bis(ethan-1-yl-1-ylidene))bis(1-phenylhydrazine) (**8b**)

Compound **8b** was prepared from phenyl hydrazine (1 mL) followed GP1 as a yellow crystals; Yield (88%); m.p. 192–193 °C; IR *v*_{max} (KBr): 3442 (N–H), 1598 (C=N) cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) (ppm): 1.30–1.67–1.98 (s, 9H, CH₃), 7.67 (s, 1H, NH), 7.24–7.57 (m, 15H, Ar–H); ¹³C NMR (100 MHz, DMSO-*d*₆) (ppm): 148.2, 141.7, 140.2, 132.6, 129.2, 127.6, 122.4, 113.2, 15.1, 14.0; MS *m/z* (%): 494 [M⁺, 1%]; Anal. calcd. for C₂₉H₂₆N₄S₂: C, 70.41; H, 5.30; N, 11.33; S, 12.96; Found: C, 70.36; H, 5.33; N, 11.40; S, 12.93.

2.7. General procedure for the synthesis of compounds **9a-c** (GP2)

A mixture of compound **1** (314 mg, 1 mmol) with aromatic aldehyde derivatives (2 mmol, 2 equiv.) in absolute ethanol (15 mL) was heated under reflux for 6–7 h in the presence of mixture of (TEA) and ZnCl₂. The reaction mixture was cooled to RT and the formed solid product was collected by filtration, and recrystallized from (EtOH) afford the corresponding derivatives **9a-c**.

2.7.1. 1,1'-(3-Methyl-4-phenylthieno[2,3-*b*]thiophene-2,5-diyl)bis(3-phenylprop-2-en-1-one) (**9a**)

Compound **9a** was prepared from benzaldehyde followed GP2 as a white fine needles crystals; yield (76%); m.p. 239–240 °C; IR *v*_{max} (KBr): 1699 (C=O) cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) (ppm): 2.40 (s, 3H, CH₃), 6.89 (d, 1H, *J* = 8.8 Hz, ^αCH), 7.00–7.77 (m, 15H, Ar–H), 7.87 (d, 1H, *J* = 8.8 Hz, ^βCH); ¹³C NMR (100 MHz, DMSO-*d*₆) (ppm): 183.9, 144.8, 141.0, 137.5, 136.2, 131.2, 130.3, 129.6, 128.8, 128.6, 127.7, 124.8, 122.0, 114.1, 113.2, 15.2; MS *m/z* (%): 490 [M⁺, 1%]; Anal. calcd. for C₃₁H₂₂O₂S₂: C, 75.89; H, 4.52; O, 6.52; S, 13.07; Found: C, 75.94; H, 4.49; S, 13.10.

2.7.2. 1,1'-(3-Methyl-4-phenylthieno[2,3-*b*]thiophene-2,5-diyl)bis(3-(4-chlorophenyl)prop-2-en-1-one) (**9b**)

Compound **9b** was prepared from *p*-chlorobenzaldehyde followed GP2 as a yellow crystals; yield (82%); m.p. 222–223 °C; IR *v*_{max} (KBr): 1654 (C=O) cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) (ppm): 2.40 (s, 3H, CH₃), 6.35 (d, 1H, *J* = 8.8 Hz, ^αCH), 7.34–7.56 (m, 15H, Ar–H), 7.85 (d, 1H, *J* = 8.8 Hz, ^βCH); ¹³C NMR (100 MHz, DMSO-*d*₆) (ppm): 183.9, 144.8, 141.1, 137.5, 136.2, 131.2, 130.3,

129.7, 128.8, 127.7, 124.8, 122.1, 114.1, 113.3, 15.2; MS *m/z* (%): 559[M⁺, 1.5%]; Anal. calcd. for C₃₁H₂₀Cl₂O₃S₂: C, 66.54; H, 3.60; O, 5.72; S, 11.46; Found: C, 66.63; H, 3.57; S, 11.43.

2.7.3. 1,1'-(3-Methyl-4-phenylthieno[2,3-*b*]thiophene-2,5-diyl)bis(3-(4-methoxyphenyl)prop-2-en-1-one). (**9c**)

Compound **9c** was prepared from *p*-methoxybenzaldehyde followed GP2 as a yellow crystals; yield (48%); m.p. >320 °C; IR ν_{\max} (KBr): 1636 (C=O cm⁻¹); ¹H NMR(400 MHz, DMSO-*d*₆) (ppm): 2.40 (s, 3H, CH₃) 6.88 (d, 1H, *J* = 8.8 Hz, ^αCH), 7.12–7.57 (m, 15H, Ar–H), 7.86 (d, 1H, *J* = 8.8 Hz, ^βCH); ¹³C NMR(100 MHz, DMSO-*d*₆) (ppm): 183.9, 144.8, 141.1, 137.5, 136.2, 131.2, 130.3, 129.6, 128.6, 127.7, 124.8, 122.0, 114.1, 113.3, 15.2; MS *m/z* (%): 550[M⁺, 1.8%]; Anal. calcd. for C₃₃H₂₆O₄S₂: C, 71.97; H, 4.76; O, 11.62; S, 11.65; Found: C, 71.90; H, 4.73; S, 11.69.

2.8. General procedure for the synthesis of compounds **10a–f** (GP3)

A mixture of compound **9a–c** (0.25 mmol) with hydrazine derivatives (0.5 mmol) in absolute ethanol (10 mL) was heated under reflux for 6–8 h. The reaction mixture was cooled to RT and the formed solid product was collected by filtration, and recrystallized from (MeOH) afford the corresponding derivatives **10a–f**.

2.8.1. 5,5'-(3-Methyl-4-phenylthieno[2,3-*b*]thiophene-2,5-diyl)bis(3-phenyl-1H-pyrazole). (**10a**)

Compound **10a** was prepared from **9a** and hydrazine hydrate followed GP3 as a yellow crystals; yield (57%); m.p. 202–203 °C; IR ν_{\max} (KBr): 3283 (N–H), 1605 (C=N) cm⁻¹; ¹H NMR(400 MHz, DMSO-*d*₆) (ppm): 1.81 (s, 3H, CH₃), 3.7 (d, 4H, *J* = 4.5 Hz, 2CH₂), 4.8 (t, 2H, *J* = 7.1 Hz, 2CH), 6.95–7.40 (m, 15H, Ar–H), 9.12 (s, 1H, NH); ¹³C NMR(100 MHz, DMSO-*d*₆) (ppm): 151.7, 141.6, 129.5, 128.4, 128.3, 62.8, 44.1, 14.3; MS *m/z* (%): 518[M⁺, 3%]; Anal. calcd. for C₃₁H₂₆N₄S₂: C, 71.78; H, 5.05; N, 10.80; S, 12.36; Found: C, 71.69; H, 5.10; N, 10.78; S, 12.39.

2.8.2. 5,5'-(3-Methyl-4-phenylthieno[2,3-*b*]thiophene-2,5-diyl)bis(1,3-diphenyl-1H-pyrazole). (**10b**)

Compound **10b** was prepared from **9a** and phenyl hydrazine hydrate followed GP3 as a yellow crystals; yield (62%); m.p. 301 °C; IR ν_{\max} (KBr): 1598 (C=N) cm⁻¹; ¹H NMR(400 MHz, DMSO-*d*₆) (ppm): 1.83 (s, 3H, CH₃), 3.5 (d, 4H, *J* = 8.6 Hz, CH₂), 4.8 (t, 2H, *J* = 7.1 Hz, CH), 6.85–7.40 (m, 25H, Ar–H); ¹³C NMR(100 MHz, DMSO-*d*₆) (ppm): 151.2, 141.2, 129.5, 126, 128.1, 61.8, 42.1, 13.8; MS *m/z* (%): 670[M⁺, 8%]; Anal. calcd. for C₄₃H₃₄N₄S₂: C, 76.98; H, 5.11; N, 8.35; S, 9.56; Found: C, 76.91; H, 5.15; N, 8.30; S, 9.49.

2.8.3. 5,5'-(3-Methyl-4-phenylthieno[2,3-*b*]thiophene-2,5-diyl)bis(3-(4-chlorophenyl)-1H-pyrazole). (**10c**)

Compound **10c** was prepared from **9b** and hydrazine hydrate followed GP3 as a yellow crystals; yield (67%); m.p. 315–316 °C; IR ν_{\max} (KBr): 3284 (N–H), 1608 (C=N) cm⁻¹; ¹H NMR(400 MHz, DMSO-*d*₆) (ppm): 1.82 (s, 3H, CH₃), 3.82 (d, 2H, *J* = 4.5 Hz, CH₂), 4.9 (t, 1H, *J* = 7.1 Hz, CH), 6.96–7.49 (m, 25H, Ar–H), 9.10 (s, 1H, NH); ¹³C NMR(100 MHz, DMSO-*d*₆) (ppm): 151.7, 141.6, 129.5, 128.4, 128.3, 62.8, 44.1, 14.3; MS *m/z* (%): 587[M⁺, 3%]; Anal. calcd. for C₃₁H₂₄Cl₂N₄S₂: C, 63.37; H, 4.12; N, 9.54; S, 10.91; Found: C, 63.31; H, 4.16; N, 9.58; S, 10.89.

2.8.4. 5,5'-(3-Methyl-4-phenylthieno[2,3-*b*]thiophene-2,5-diyl)bis(3-(4-chlorophenyl)-1-phenyl-1H-pyrazole). (**10d**)

Compound **10d** was prepared from **9b** and phenyl hydrazine hydrate followed GP3 as a pale brown crystals; yield (59%); m.p. 176–177 °C; IR (ν_{\max}): 1596 (C=N) cm⁻¹; ¹H NMR(400 MHz, DMSO-*d*₆) (ppm): 1.83 (s, 3H, CH₃), 3.5 (d, 4H, *J* = 8.6 Hz, CH₂), 4.8 (t, 2H, *J* = 7.1 Hz, CH), 6.85–7.49 (m, 23H, Ar–H); ¹³C

NMR(100 MHz, DMSO-*d*₆) (ppm): 151.2, 141.2, 129.5, 126, 128.1, 61.8, 42.1, 13.8; MS *m/z* (%): 739[M⁺, 3%]; Anal. calcd. for C₄₃H₃₂Cl₂N₄S₂: C, 69.81; H, 4.36; N, 7.57; S, 8.67; Found: C, 69.89; H, 4.29; N, 7.61; S, 8.62.

2.8.5. 5,5'-(3-Methyl-4-phenylthieno[2,3-*b*]thiophene-2,5-diyl)bis(3-(4-methoxyphenyl)-1H-pyrazole). (**10e**)

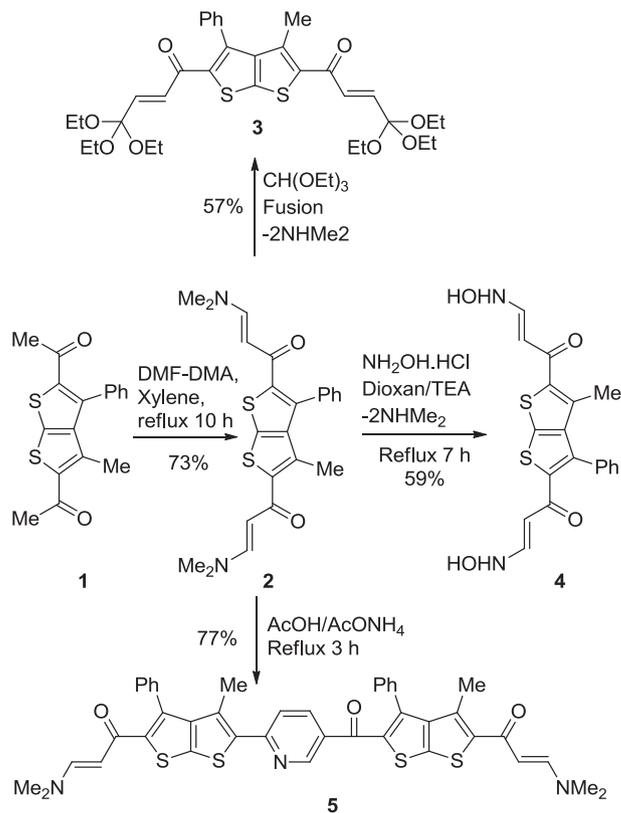
Compound **10e** was prepared from **9c** and hydrazine hydrate followed GP3 as a white crystals; yield (60%); m.p. >320 °C; ν_{\max} (KBr): 3417 (N–H), 1571 (C=N) cm⁻¹; ¹H NMR(400 MHz, DMSO-*d*₆) (ppm): 1.83 (s, 3H, CH₃), 3.5 (d, 4H, *J* = 8.6 Hz, 2CH₂), 3.90 (s, 6H, 2CH₃) 4.8 (t, 2H, *J* = 7.1 Hz, 2CH), 6.85–7.4 (m, 25H, Ar–H), 9.12 (s, 1H, NH), ¹³C NMR(100 MHz, DMSO-*d*₆) (ppm): 151.2, 141.2, 129.5, 126, 128.1, 61.8, 42.1, 13.8; MS *m/z* (%): 578[M⁺, 3%]; Anal. calcd. for C₃₃H₃₀N₄O₂S₂: C, 68.48; H, 5.22; N, 9.68; O, 5.53; S, 11.08; Found: C, 68.54; H, 5.29; N, 9.60; S, 11.03.

2.8.6. 5,5'-(3-Methyl-4-phenylthieno[2,3-*b*]thiophene-2,5-diyl)bis(3-(4-methoxyphenyl)-1-phenyl-1H-pyrazole). (**10f**)

Compound **10f** was prepared from **9c** and phenyl hydrazine hydrate followed GP3 as a pale brown crystals; yield (57%); m.p. 222–224 °C; ν_{\max} (KBr): 1589 (C=N) cm⁻¹; ¹H NMR(400 MHz, DMSO-*d*₆) (ppm): 1.83 (s, 3H, CH₃), 3.5 (d, 4H, *J* = 8.6 Hz, 2CH₂), 3.90 (s, 6H, 2CH₃) 4.8 (t, 2H, *J* = 7.1 Hz, 2CH), 6.85–7.4 (m, 25H, Ar–H); ¹³C NMR(100 MHz, DMSO-*d*₆) (ppm): 151.2, 141.2, 129.5, 126, 128.1, 61.8, 42.1, 13.8; MS *m/z* (%): 730[M⁺, 3%]; Anal. calcd. for C₄₅H₃₈N₄O₂S₂: C, 73.94; H, 5.24; N, 7.67; O, 4.38; S, 8.77; Found: C, 73.88; H, 5.30; N, 7.61; S, 8.71.

3. Results and discussion

The new 1,1'-(3-methyl-4-phenylthieno[2,3-*b*]thiophene-2,5-diyl)diethanone **1** and its bis(enaminones) derivatives **2** [30] being



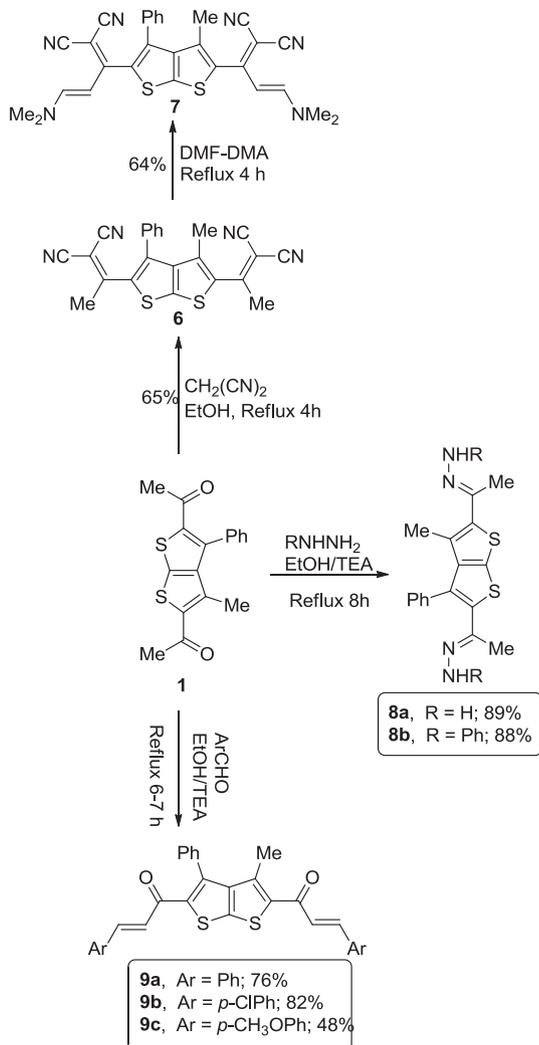
Scheme 1. Synthesis of **3**, **4**, and **5**.

now available in our hand prompted us to study their synthetic utility as key intermediate for a new class of molecules as well as bis(5-membered) heterocycles with the thieno[2,3-*b*]thiophene core. Thus, fusion the bis(enaminone) **2** with neat triethoxymethane which is commercially available resulted in the formation of the (2*E*,2'*E*)-1,1'-(3-methyl-4-phenylthieno[2,3-*b*]thiophene-2,5-diyl)bis(4,4,4-triethoxybut-2-en-1-one) **3** after washing with EtOH in 57% yield as depicted in Scheme 1.

The structure of compound **3** was determined from its elemental and spectroscopic analyses. The ¹H NMR spectrum strongly supported this assignment where disappeared of singlet signal of NMe₂. Furthermore, the appearance two characteristic signals of CH₃CH₂ group.

Our study is now extended to include the synthesis of new bis-hydroxyl amine derivatives **4**. Thus, reaction of **2** with hydroxyl amine hydrochloride in refluxing dioxan for 7 h in the presence of TEA afforded the corresponding bis-hydroxyl amine derivatives **4** in 59% yields. The formation of compound **4** would involve an initial addition of the amino group in hydroxylamine to the activated double bond in enaminone derivative **2**, followed by deamination of NMe₂ affording the final isolable product (Scheme 1).

When bis enaminone **2** was refluxed in AcOH 3 h in the presence of a catalytic amount of AcONH₄ afforded **5** (Scheme 1). The structure of the product was confirmed by elemental analysis were consistent with isolated product **5** [31].

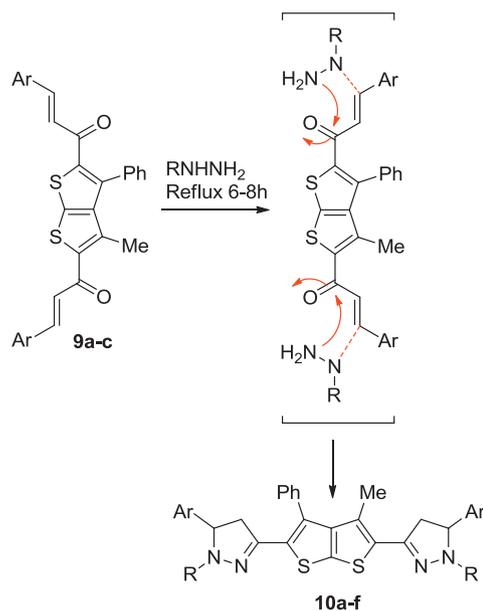


Scheme 2. Synthesis of **6**, **7**, **8a,b**, and **9a-c**.

Refluxing of equimolar amounts of the 1,1'-(3-methyl-4-phenylthieno[2,3-*b*]thiophene-2,5-diyl)diethanone **1** and malononitrile in ethanol afforded the corresponding dimalononitrile derivatives **6** (Scheme 2). The structure of the isolated product was identified as 2,2'-((3-methyl-4-phenylthieno[2,3-*b*]thiophene-2,5-diyl)bis(ethan-1-yl-1-ylidene))dimalononitrile **6** on the basis of its elemental analyses and spectral data. The IR spectrum of the reaction product exhibited absorption bands at 2191 cm⁻¹ due to the nitrile group. The reactivity of compound **6** towards DMF–DMA was also investigated. Thus, the treatment of compound **6** with DMF–DMA in ethanol and refluxed for 4 h afforded bis-enamine derivatives **7**. The ¹H NMR spectrum of compound **7** revealed two singlets at δ 1.83, and 3.24 due to methyl, and NMe₂ protons, respectively. Furthermore, the appearance two doublets at δ 7.90, and 8.15 due to CH=CH protons.

Nevertheless, Phenylhydrazones **8a,b** were next synthesized in almost quantitative yields by the reaction between the hydrazine derivatives and **1**. The structure of hydrazone derivatives **8a,b** was established on the basis of their elemental analysis and spectral data.

The reactivity of compound **1** towards some heterocyclic aldehydes was also investigated. Thus, the treatment of compound **1**



| # | R | Ar | Yield % |
|------------|----|-------------------------------|---------|
| 10a | H | Ph | 57 |
| 10b | Ph | Ph | 62 |
| 10c | H | <i>p</i> -ClPh | 67 |
| 10d | Ph | <i>p</i> -ClPh | 59 |
| 10e | H | <i>p</i> -CH ₃ OPh | 60 |
| 10f | Ph | <i>p</i> -CH ₃ OPh | 57 |

Scheme 3. Synthesis of **10a-f**.

with aldehyde derivatives in ethanol and in the presence of a catalytic amount of TEA afforded *bis*- α,β -enone derivatives **9a–c**. The ^1H NMR spectrum of **9a** showed two doublets at δ 6.89 and 7.87 due to $\text{CH}=\text{CH}$ protons, in addition to an aromatic multiplet in the region 6.99–7.40.

Another approach has been investigated which would afford the pyrazole after an elimination/aromatization of the cycloadduct intermediate. On the basis of these studies in the present work we utilized simple and convenient method for the synthesis of pyrazoles derivatives from α,β -unsaturated carbonyl compounds. Pyrazoles derivatives **10a–f** were prepared following the classical procedure (ketone plus hydrazine derivatives in ethanol at reflux in very good yield as depicted in (Scheme 3). The novel bis pyrazoles **10a–f** were assumed to be formed *via* a stepwise formation of hydrazone followed by a Michael 1,4-addition of the nucleophile nitrogen atom [32]. We then decided to investigate the generality of this strategy and focused on the preparation of thieno[2,3-*b*]thiophenes pyrazole derivatives **10a–f**.

4. Conclusions

In conclusion, the reactivity of 1,1'-(3-methyl-4-phenylthieno[2,3-*b*]thiophene-2,5-diyl)diethanone (**1**) and (2*E*,2'*E*)-1,1'-(3-methyl-4-phenylthieno[2,3-*b*]thiophene-2,5-diyl)bis(3 (dimethylamino)prop-2-en-1-one) (**2**) were investigated as a versatile and readily accessible building block for the synthesis of new molecules incorporating thieno[2,3-*b*]thiophene moiety, many of which may display potentially interesting biological activity in the field of medicinal chemistry.

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References

- [1] I. Jarak, M. Kralj, I. Piantanida, L. Suman, M. Zinic, K. Pavelic, G. Karminski-Zamola, *Bioorg. Med. Chem.* 14 (2006) 2859–2868.
- [2] J.D. Prugh, G.D. Hartman, P.J. Mallorga, B.M. McKeever, S.R. Michelson, M.A. Murcko, H. Schwam, R.L. Smith, J.M. Sondey, J.P. Springer, M.F. Surgue, *J. Med. Chem.* 34 (1991) 1805–1818.
- [3] M.S. Egbertson, J.J. Cook, B. Bednar, J.D. Prugh, R.A. Bednar, S.L. Gaul, R.J. Gould, G.D. Hartman, C.F. Homnick, M.A. Holahan, L.A. Libby Jr., J.J. Lynch, R.J. Lynch, G.R. Sitko, M.T. Stranieri, L.M. Vassallo, *J. Med. Chem.* 42 (1999) 2409–2421.
- [4] H.M. Eisa, A.S. Tantawy, M.M. El-Kerdawy, *Pharmazie* 46 (1991) 182–184.
- [5] P.P.T. Sah, S.A. Peoples, *J. Am. Pharm. Ass. Sci. Ed.* 43 (1954) 513–524.
- [6] S.S. Parmar, A.K. Gupta, T.K. Gupta, V.I. Stenberg, *J. Pharm. Sci.* 64 (1975) 154–157.
- [7] R. Kalsi, K. Pande, T.N. Bhalla, J.P. Bartwall, G.P. Gupta, S.S. Parmar, *J. Pharm. Sci.* 79 (1990) 317–320.
- [8] Y.N. Mabkhot, N.A. Kheder, A.M. Al-Majid, *Molecules* 15 (2010) 9418–9426.
- [9] Y.N. Mabkhot, *Molecules* 15 (2010) 3329–3337.
- [10] Mabkhot, *Molecules* 14 (2009) 1904–1914.
- [11] Y.N. Mabkhot, A.M. Al-Majid, A.S. Alamar, I. Warad, Y. Sedigi, *Molecules* 16 (2011) 5142–5148.
- [12] N.A. Kheder, Y.N. Mabkhot, *Int. J. Mol. Sci.* 13 (2012) 3661–3670.
- [13] Y.N. Mabkhot, A. Barakat, A.M. Al-Majid, S.A. Alshahrani, *Int. J. Mol. Sci.* 13 (2012) 2263–2275.
- [14] H.M. Sabir, Y.S. Sangvikar, S.G. Ghadigaonkar, M. Ashraf, A. Meetsma, *Tetrahedron* 64 (2008) 8837–8842.
- [15] H.M. Sabir, M. Ashraf, H. Hariharasubrahmanian, R.M. Kellogg, A. Meetsma, *J. Mol. Struct.* 689 (2004) 107–113.
- [16] A. Bugge, *Acta Chem. Scand.* 23 (1969) 2704–2710.
- [17] S.H. Mashraqui, Y.S. Sangvikar, M. Ashraf, S. Kumar, E. Daub, *Tetrahedron* 61 (2005) 3507–3513.
- [18] M.-G. Liu, Y.-G. Hu, M.-W. Ding, *Tetrahedron* 64 (2008) 9052–9059.
- [19] Y.X. Wu, J. Cao, H.Y. Deng, J.X. Feng, *Spectrochim. Acta Part A* 82 (2011) 340–344.
- [20] I. McCulloch, M. Heeney, M.L. Chabiny, D. DeLongchamp, R.J. Kline, M. Cölle, W. Duffy, D. Fischer, D. Gundlach, B. Hamadani, R. Hamilton, L. Richter, A. Salles, M. Shkunov, D. Sparrowe, S. Tierney, W. Zhang, *Adv. Mater.* 21 (2009) 1091–1109.
- [21] H.M. Sabir, Y. Sanghvikar, S. Ghadhigaonkar, S. Kumar, A. Meetsma, E. Trần Huu Dâu, *J. Org. Chem.* 5 (2009) 1–8.
- [22] M. Heeney, C. Bailey, K. Genevicius, M. Shkunov, D. Sparrowe, S. Tierney, I. McCulloch, *J. Am. Chem. Soc.* 127 (2005) 1078–1079.
- [23] Y.N. Mabkhot, A. Barakat, A.M. Al-Majid, A.S. Alamar, T.T. Al-Nahary, *Int. J. Mol. Sci.* 13 (2012) 5035–5047.
- [24] Y.N. Mabkhot, A.M. Al-Majid, A.S. Alamar, *Molecules* 16 (2011) 7706–7714.
- [25] B.F. Abdel-Wahab, H. Abdel-Aziz, E.M. Ahmed, *Eur. J. Med. Chem.* 44 (2009) 2632–2635.
- [26] B.F. Abdel-Wahab, H.A. Abdel-Aziz, E.M. Ahmed, *Monatsh. Chem.* 341 (2009) 734–739.
- [27] A.E. Amr, N.M. Sabrry, M.M. Abdalla, B.F. Abdel-Wahab, *Eur. J. Med. Chem.* 44 (2009) 725–735.
- [28] B.F. Abdel-Wahab, A.E. Amr, M.M. Abdalla, *Monatsh. Chem.* 140 (2009) 601–605.
- [29] A.M. Farag, N.A. Kheder, Y.N. Mabkhot, *Heterocycles* 78 (2009) 1787–1798.
- [30] Y.N. Mabkhot, A.M. Al-Majid, A. Barakat, S. Alshahrani, Y. Siddiqui, *Molecules* 16 (2011) 6502–6511.
- [31] A.-A. Alnajjar, M.M. Abdelkhalik, A. Al-Enezi, M.H. Elnagdi, *Molecules* 14 (2009) 68–77.
- [32] Y.N. Mabkhot, A. Barakat, A.M. Al-Majid, Z.A. Al-Othman, A.S. Alamar, *Int. J. Mol. Sci.* 12 (2011) 7824–7834.