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

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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 $AcONH_4$. 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.

1. Introduction

More recently thienothoiphene, 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. ^{1}H NMR (400 MHz) and ^{13}C 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}; ^{1}H NMR (400 MHz, DMSO-d_6) (ppm): 1.05 (t, 3H, J = 6.6 Hz, CH_3), 1.96 (s, 3H, CH_3), 2.84–3.13 (q, 2H, J = 8.0 Hz, CH_2), 5.69 (d, 1H, J = 12 Hz, $^{\alpha}$CH), 6.53 (d, 1H, J = 12 Hz, $^{\beta}$CH), 7.42–7.52 (m, 5H, Ar—H); ^{13}C NMR

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(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 $C_{33}H_{42}O_8S_2$: 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 (NH_2OH·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 ν_{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, CH_3), 4.53 (d, 1H, *J* = 12 Hz, CH), 5.38 (d, 1H, *J* = 12 Hz, CH), 7.41–7.65 (m, 5H, C_6H_5); 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 $C_{19}H_{16}N_2O_4S_2$: 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 ν_{max} (KBr): 1640 (C=O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (ppm): 1.96 (s, 3H, CH_3), 2.2 (s, 3H, CH_3), 3.00 (s, 12H, CH_3), 4.55 (d, 1H, *J* = 12 Hz, CH), 5.43 (d, 1H, *J* = 12 Hz, CH), 7.41–7.65 (m, 5H, C_6H_5), 7.98–8.10 (m, 3H, C_5H_3N), ^{13}C 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 $C_{42}H_{35}N_3O_3S_4$: 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 malononitril (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 ν_{max} (KBr): 2191 (CN) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (ppm): 1.63 (s, 6H, CH_3), 1.84 (s, 3H, CH_3), 7.29–7.55 (m, 5H, Ar—H); ^{13}C 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 $C_{23}H_{14}N_4S_2$: 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 ν_{max} (KBr): 2193 (CN) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (ppm): 1.83 (s, 3H, CH_3), 3.24–3.13 (s, 12H, CH_3), 7.90–7.95 (d, 1H, *J* = 12.0 Hz, $^{\alpha}CH$), 7.39–7.52 (m, 5H, Ar—H), 8.15 (d, 1H, *J* = 12.0 Hz, $^{\beta}CH$); ^{13}C 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 $C_{29}H_{24}N_6S_2$: 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 ν_{max} (KBr): 3350–3385 (NH_2), 1598 (C=N) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (ppm): 1.34–1.71–2.01 (s, 9H, CH_3), 6.38–6.39 (s, 2H, NH_2) 7.36–7.45 (m, 5H, Ar—H); ^{13}C 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 $C_{17}H_{18}N_4S_2$: 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 ν_{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, CH_3), 7.67 (s, 1H, NH) 7.24–7.57 (m, 15H, Ar—H); ^{13}C 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 $C_{29}H_{26}N_4S_2$: 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 $ZnCl_2$. 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 ν_{max} (KBr): 1699 (C=O) cm^{-1}; ^1H NMR(400 MHz, DMSO-d_6) (ppm): 2.40 (s, 3H, CH_3), 6.89 (d, 1H, *J* = 8.8 Hz, $^{\alpha}CH$), 7.00–7.77 (m, 15H, Ar—H), 7.87 (d, 1H, *J* = 8.8 Hz, $^{\beta}CH$); ^{13}C 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 $C_{31}H_{22}O_2S_2$: 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 ν_{max} (KBr): 1654 (C=O cm^{-1}; ^1H NMR(400 MHz, DMSO-d_6) (ppm): 2.40 (s, 3H, CH_3), 6.35(d, 1H, *J* = 8.8 Hz, $^{\alpha}CH$), 7.34–7.56 (m, 15H, Ar—H), 7.85 (d, 1H, *J* = 8.8 Hz, $^{\beta}CH$); ^{13}C NMR(100 MHz, DMSO-d_6) (ppm): 183.9, 144.8, 141.1, 137.5, 136.2, 131.2, 130.3,