Molecules **2011**, *16*, 5142-5148; doi:10.3390/molecules16065142

OPEN ACCESS

molecules

ISSN 1420-3049

www.mdpi.com/journal/molecules

Article

Reactions of Some New Thienothiophene Derivatives

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Received: 30 May 2011; in revised form: 15 June 2011 / Accepted: 15 June 2011 / Published: 21 June 2011

Abstract: Facile and convenient syntheses of bisdimethylthieno[2,3-b]thiophen-2,5-diyl bis(oxazole-2-amine), bis(1*H*-imidazol-2-amine), bis((3a)-*H*-indole),[1,2-a]pyrimidine), bis(1*H*-imidazo[1,2-b][1,2,4]triazole) and bis(9*H*-benzo[d]imidazo[1,2-a]imidazole) derivatives incorporating a thieno[2,3-b]thiophene moiety from the versatile and readily accessible 1,1'(3,4-dimethylthieno[2,3-b]thiophene-2,5-diyl)-bis(2-bromo-ethanone) (**1**) are described.

Keywords: bis(2-bromoethanone); bis-thieno[2,3-b]thiophene; bis(oxazole-2-amine); bis-heterocycles; imidazotriazole

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1. Introduction

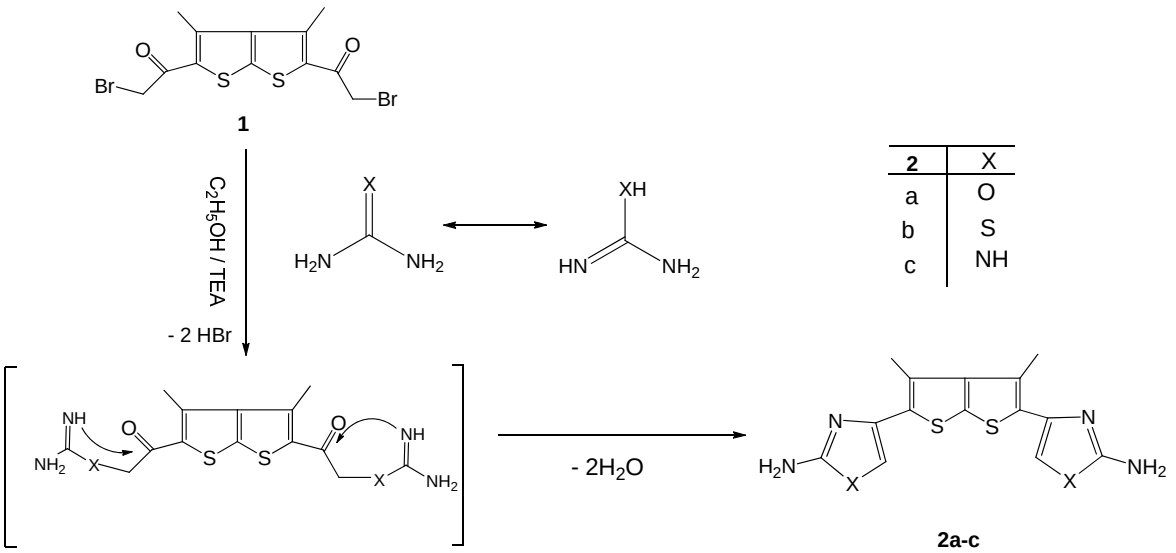
We have been interested for some time in the chemical and biological properties of thienothiophene derivatives [1-3]. Thienothiophenes have been developed for different purposes in the pharmaceutical field and have been tested as potential antitumor, antiviral, antibiotic and antiglaucoma drugs or as inhibitors of platelet aggregation [3-8]. In addition, thienothiophenes find potential applications in a wide variety of optical and electronic systems [9-11]. Recently, some conjugated thienothiophenes, structurally related to several current applications have been reported [12-19]. In continuation of these findings, we report herein the synthesis of some novel bis-heterocycles containing a

thieno[2,3-b]thiophene moiety as a base unit and which are of interest as potential biologically active compounds or pharmaceuticals.

2. Results and Discussion

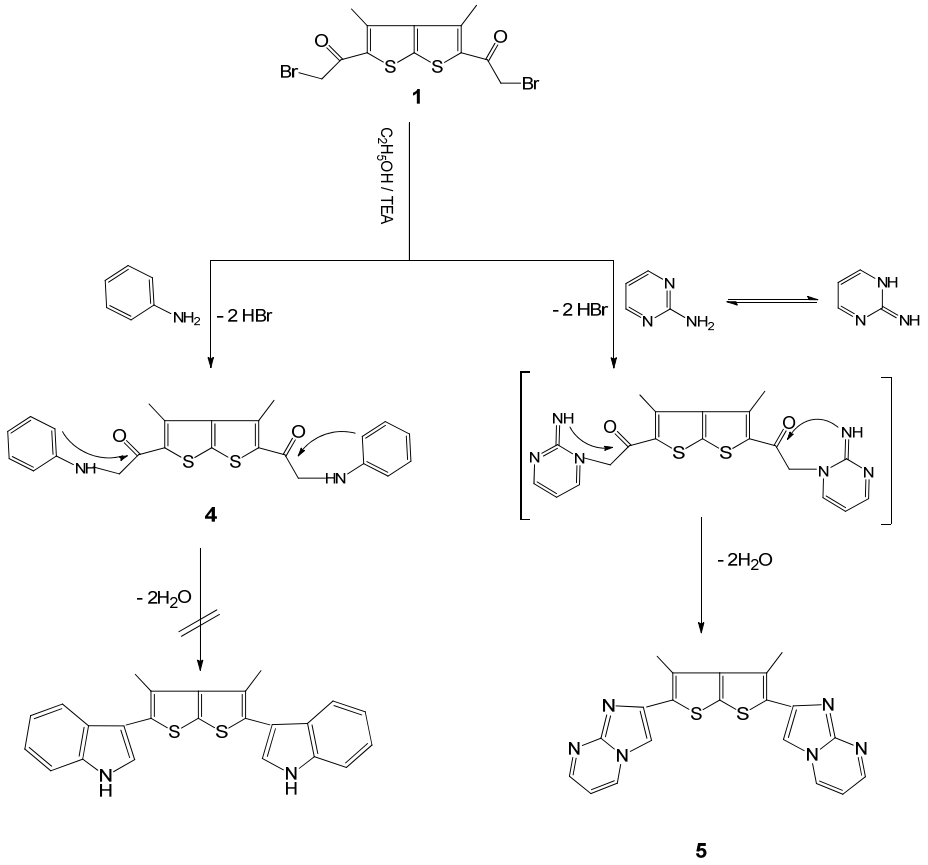
The synthetic procedures adopted to obtain the target compounds are outlined in Schemes 1, 2 and 3. Treatment of bis-2-bromoacetylthieno[2,3-b]thiophene derivative **1** [3] with urea, thiourea or guanidine in refluxing EtOH/TEA gave the novel bisthieno[2,3-b]thiophene derivatives **2a-c**, respectively (Scheme 1). The structures of the products were deduced from their elemental analysis and spectral data. For example, the ^{1}H-NMR spectrum of compound **2a** revealed a singlet at δ 7.19 characteristic of an oxazole CH proton. The IR spectra of **2a-c** showed, in each case, the absence of the carbonyl bands found in **1** and the presence of new bands in the 3422-3385 cm^{-1} region due to NH_2 and NH groups.

Scheme 1. Synthesis of bis-amino heterocycles derivatives **2a-b**.

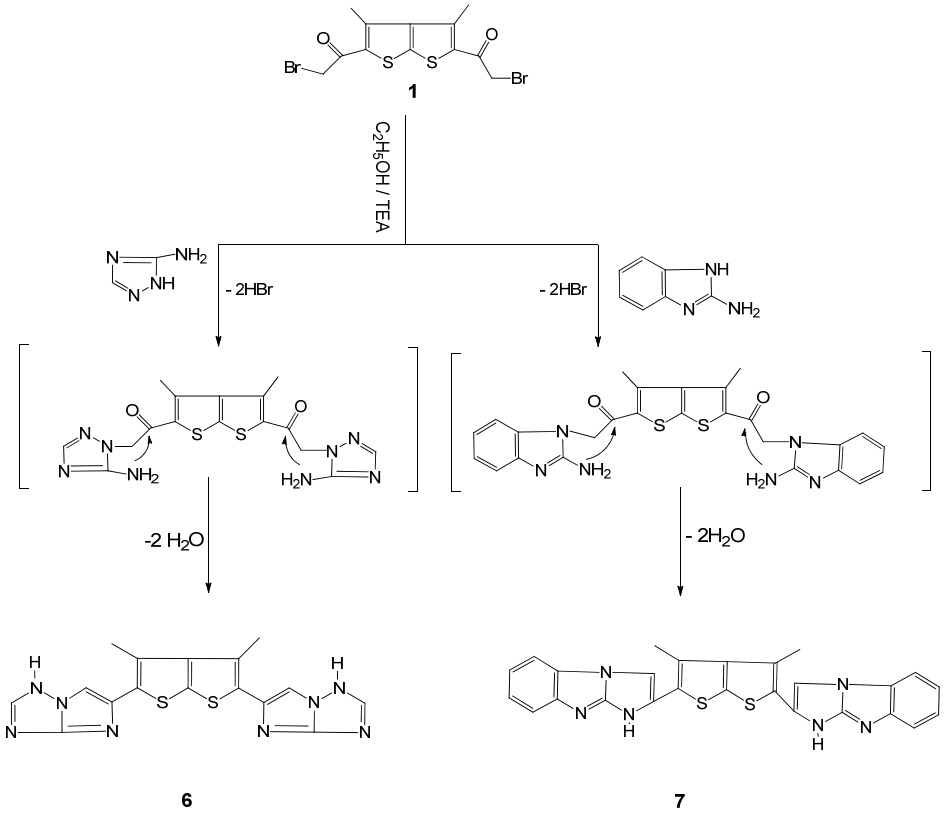


Treatment of compound **1** with aniline or with 2-aminopyrimidine in refluxing EtOH/TEA led to the novel bis-thieno[2,3-b]thiophene derivatives **4** and **5**, respectively (Scheme 2), whose structures were confirmed on the basis of their elemental analyses and spectral data. The ^{1}H-NMR spectrum of compound **5**, for example, revealed signals at δ 7.43-7.80, characteristic of imidazole and pyrimidine CH protons. The IR spectrum of **5** lacked a carbonyl absorption band and the ^{13}C-NMR spectrum revealed eleven types of carbon atoms (*i.e.*, those of half the bisheterocycle), The IR spectrum of compound **4** showed a carbonyl absorption band at 1690 cm^{-1} [20]. Treatment of compound **1** with 4-amino-1,2,4-triazole in refluxing ethanol afforded 5,5'-(3,4-dimethylthieno[2,3-b]thiophene-2,5-diyl)bis(1H-imidazo[1,2-b][1,2,4]triazole) (**6**, Scheme 3). The ^{1}H-NMR spectrum of compound **6** displayed singlets at δ 2.22 (CH_3), δ 7.80 (2H, CH, imidazole), 9.8 (s, 2C, CH, triazole) and 12.4 (2H, NH, triazole). The ^{13}C-NMR spectrum revealed nine types of carbon. The mass spectrum revealed a molecular ion peak at *m/z* 380, corresponding to $C_{16}H_{20}N_8S_2$. In a similar manner, when **1** was treated with 2-aminobenzimidazole, the corresponding compound **7** was obtained in high yield.

Scheme 2. Synthesis of bis- thieno-thiophenes derivatives **4** and **5**.



Scheme 3. Synthesis of bis- imidazole derivatives **6** and **7**.



3. Experimental

3.1. General

All melting points were measured on a Koffler block melting point apparatus. IR spectra were measured as KBr pellets on a Perkin Elmer FT 1000 spectrophotometer. The NMR spectra were recorded in DMSO-d_6 on a Varian Mercury Jeol-(400 MHz) NMR spectrometer. ^{1}H-NMR (400 MHz) and ^{13}C-NMR were run in (DMSO-d_6). Chemical shifts were related to that of the residual solvent peak. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of King Saud University, Riyadh, Saudi Arabia.

3.2. General Procedure for the Reaction of Bis-2-Bromoethanone Derivative **1** *with Urea, Thiourea and Guanidine: Preparation of Compounds* **2a-c**

Compound **1** (0.410 g, 1 mmol) was treated with urea, thiourea or guanidine (2 mmol) in dry ethanol (20 mL, 99.9%) under reflux for 4-6 h. After addition of TEA (0.5 mL) the corresponding derivatives **2a-c** were formed as solids that were filtered off, washed with ethanol, dried and recrystallized (DMF/EtOH) to afford the desired product in pure form.

4,4'-(3,4–Dimethylthieno[2,3-b]thiophen-2,5-diyl)bis(oxazole-2-amine) (**2a**). Dark yellow crystals; yield 77%; mp > 320 °C; IR (KBr) ν_{max} 3417, 3391 (NH_2) cm^{-1}; ^{1}H-NMR: δ 2.23 (s, 6H, CH_3), 7.19 (s, 2H, oxazole), 6.65 (s, 4H, NH_2 aromatic); ^{13}C-NMR: δ 14.8 (2 CH_3, aliphatic), 128.8, 134.3, 148.1, 148.8 (thienothiophene ArC's), 136.1, 140.0, 159.3 (ArC's); MS *m/z* (%): 332 (M^+, 6), 331 (51), 317 (100), 165 (48), 76 (98). Anal. for $C_{14}H_{12}N_4O_2S_2$ (332.40) calcd. C, 50.59; H, 3.64; N, 16.86; S, 19.29. Found: C, 50.48; H, 3.62; N, 16.90; S, 19.20.

4,4'-(3,4-Dimethylthieno[2,3-b]thiophen-2,5-diyl)bis(thiazol-2-amine) (**2b**). Bright brown crystals; yield 89%; mp. 295 °C; IR (KBr) ν_{max} 3420, 3391 (NH_2) cm^{-1}; ^{1}H-NMR: δ 2.37 (s, 6H, CH_3), 8.23 (s, 2H, thiazole), 5.88 (s, 4H, NH_2 aromatic); ^{13}C-NMR: δ 15.2 (2 CH_3, aliphatic), 129.8, 133.8, 147.2, 148.1 (thienothiophene ArC's), 135.6, 140.2, 167.3 (ArC's); MS *m/z* (%): 365 (M + 1,15), 364 (M, 39), 331 (51), 207 (48),79 (98). Anal. for $C_{14}H_{12}N_4S_4$ (364.53) calcd. C, 46.13; H, 3.32; N, 15.37; S, 35.18. Found: C, 46.10; H, 3.34; N, 15.28; S, 35.12.

4,4'-(3,4-Dimethylthieno[2,3-b]thiophen-2,5-diyl)bis(1H-imidazol-2-amine) (**2c**). Light brown crystals; yield 95%; mp. 288 °C; IR (KBr) ν_{max} 3422, 3385 (NH_2), 3220 (NH) cm^{-1}; ^{1}H-NMR: δ 2.33 (s, 6H, CH3), 7.68 (s, 2H, imidazole), 6.51 (s, 4H, NH_2 aromatic), 12.28 (s, 2H,NH imidazole). ^{13}C-NMR: δ 14.8 (2 CH_3, aliphatic), 130.5, 134.3, 148.3, 148.6 (thienothiophene ArC's), 136.3, 141.2, 162.1 (ArC's); MS *m/z* (%): 331 (M + 1, 28), 330 (M, 100), 298 (21), 168 (43), 98 (63), 79 (38). Anal. for $C_{14}H_{14}N_6S_2$ (330.43) calcd. C, 50.89; H, 4.27; N, 25.43; S, 19.41. Found: C, 50.78; H, 4.25; N, 25.38; S, 19.36.

3.3. General Procedure for the Reaction of Bis-2-Bromoethanone Derivative **1** *wih Aniline and 2-Aminopyrimidine*

Treatment of compound **1** (0.410 g, 1 mmol) with aniline or 2-aminopyrimidine (2 mmol) in dry ethanol (20 mL 99.9%) at reflux for 5-8 h afforded the corresponding derivatives **4** and **5**, respectively. The solid products formed were filtered off, washed with ethanol, dried and recrystallized (DMF/EtOH).

2,2'-(3,4-Dimethylthieno[2,3-b]thiophen-2,5-diyl)bis((3a)H-indole)) (**4**). Yellow crystals; yield 95%; mp > 320 °C; IR (KBr) ν_{max} 3390 (NH), 1690 (C=O) cm^{-1}; ^{1}H-NMR: δ 2.83 (s, 6H, CH_3), 7.77-7.83 (s, 10H, ArH's); 6.33 (2H, NH); ^{13}C-NMR: δ 15.1 (2 CH_3, aliphatic), 131.3, 132.3, 144.6, 148.3 (thieno-thiophene ArC's), 34.9, 105.3, 121.2, 122.2, 124.6, 127.2, 166.4 (ArC's); MS *m/z* (%): 399 (M + 1, 41), 398 (M, 89), 397 (84), 383 (24),165 (54). Anal. for $C_{24}H_{18}N_2S_2$ (398.54) calcd. C, 72.33; H, 4.55; N, 7.03; S, 16.09. Found: C, 72.22; H, 4.49; N, 7.13; S, 16.03.

2,2'-(3,4-Dimethylthieno[2,3-b]thiophen-2,5-diyl)bis(imidazo[1,2-a]pyrimidine) (**5**). Brown crystals; yield 78%; mp > 320 °C; IR (KBr) ν_{max} 1600 (C=N) cm^{-1}; ^{1}H-NMR: δ 2.97 (s, 6H, CH_3), 7.78 (s, 2H, CH, imidazole), 7.43, 7.45, 7.80 (s, 6H, CH, pyrimidine); ^{13}C-NMR: δ 14.3 (2 CH_3, aliphatic), 130.2, 133.4, 145.7, 148.4 (thienothiophene ArC's), 103.9, 111.4, 122.2, 127.2, 159.1, 163.2 (ArC's); MS *m/z* (%): 403 (M + 1,46), 402 (M, 100), 387 (29), 284 (12). Anal. for $C_{24}H_{18}N_2S_2$ (402.50) calcd. C, 59.68; H, 3.5; N, 20.88; S, 15.93. Found: C, 59.56; H, 3.48; N, 20.78; S, 15.99.

5,5'-(3,4-Dimethylthieno[2,3-b]thiophen-2,5-diyl)bis(1H-imidazo[1,2-b][1,2,4]triazole (**6**). Compound **1** (0.410 g, 1 mmol), was added to 4-amino-1,2,4-triazole (0.168 g, 2 mmol) in dry ethanol (20 mL, 99.9%) at reflux for 4 h. After adding TEA (0.5 mL), two minutes of heating followed. The solid product formed was filtered off, washed with ethanol, dried and recrystallized (DMF/EtOH). Red crystals; yield 81%; mp. 228-230 °C; IR (KBr) ν_{max} 3385 (NH) 1560 (C=N) cm^{-1}; ^{1}H-NMR: δ 2.22 (s, 6H, 2 CH_3), 8.52 (s, 2H, CH, imidazole) 9.8 (s, 2H, CH, triazole), 12.4 (2H, NH, triazole); ^{13}C-NMR: δ 15.4 (2 CH_3, aliphatic), 137.8, 140.9, 144.4, 148.1 (thienothiophene ArC's), 120.1, 124.1, 156.5, 163.0 (ArC's) MS *m/z* (%): 381 (M + 1, 13), 380 (M, 100), 378 (22), 365 (36), 98 (14). Anal. for $C_{16}H_{20}N_8S_2$ (380.06) calcd. C, 50.51; H, 3.18; N, 29.45; S, 16.86. Found: C, 50.46; H, 3.17; N, 29.22; S, 16.77.

2,2'-(3,4-Dimethylthieno[2,3-b]thiophen-2,5-diyl)bis(9H-benzo[d]imidazo[1,2-a]imidazole) (**7**). Compound **1** (0.410 g, 1 mmol), was added to 2-aminobenzimidazole (0.266 g, 2 mmol) in dry ethanol (20 mL, 99.9%) at reflux for 6 h. After adding TEA (0.5 mL), two minutes of heating followed. The solid product so formed was filtered off, washed with ethanol, dried and recrystallized from (DMF/EtOH). Yellow crystals; yield 78%; mp > 320 °C; IR (KBr) ν_{max} 3414 (NH), 1544 (-C=N) cm^{-1}; ^{1}H-NMR: δ 2.30 (s, 6H, 2 CH_3), 8.86 (2H, imidazole C-H), 12.8 (2H, NH, imidazole), 7.31, 7.33, 7.35 (4H, CH, benzimidazole); ^{13}C-NMR: δ 15.88 (2CH_3, aliphatic), 137.8, 140.9, 144.4, 148.1 (thienothiophene ArC's) 107.1, 112.5, 124.1, 124.5, 124.9, 125.0, 157.2 (ArC's); MS *m/z* (%): 479 (M + 1, 35), 478 (M, 10), 476 (54), 318 (21), 96 (86). Anal. for $C_{26}H_{18}N_6S_2$ (478.59) calcd. C, 65.25; H, 3.79; N, 17.56; S, 13.40. Found: C, 65.22; H, 3.67; N, 17.62; S, 13.33.

4. Conclusions

Syntheses and identification of some bis-heterocycles **2a-c** and **4-7** containing thieno[2,3-b]thiophene moieties *via* the versatile, hitherto unreported reagent 2-bromo-1-[5-(2-bromoacetyl)-3,4-dimethyl-thieno[2,3-b]thiophen-2-yl]-ethanone (**1**) were reported.

Acknowledgements

The authors extend their appreciation to the Deanship of Scientific Research at King Saud University for funding the work through the research group project No. RGP-VPP-007.

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Sample Availability: Samples of compounds **1-7** are available from the authors.