

Article

Facile and Convenient Synthesis of New Thieno[2,3-b]-Thiophene Derivatives

Yahia Nasser Mabkhot ^{1,*}, Nabila abd Elshafy Kheder ^{2,†} and Abdullah Mohammad Al-Majid ¹

¹ Department of Chemistry, Faculty of Science, King Saud University, P. O. Box 2455, Riyadh 11451, Saudi Arabia

² Department of Chemistry, Faculty of Science, Cairo University, Giza 12613, Egypt

[†] Current Address: Department of Pharmaceutical Chemistry, Faculty of Pharmacy, King Khalid University, Abha, Saudi Arabia; E-Mail: nabila_abdelshafy@yahoo.com.

* Author to whom correspondence should be addressed; E-Mail: yahia@ksu.edu.sa.

Received: 12 October 2010; in revised form: 15 December 2010 / Accepted: 16 December 2010 / Published: 20 December 2010

Abstract: A facile and convenient synthesis of bis(2-(1H-benzo[d]imidazol-2(3H)-ylidene)-3-oxopropanenitrile), bis((3-amino-5-(methylthio)-1H-pyrazol-4-yl)methanone) and bis(2-thioxo-1,2-dihydropyrimidine-5-carbonitrile) derivatives incorporating a thieno[2,3-b]thiophene moiety *via* versatile, readily accessible diethyl 3,4-dimethylthieno[2,3-b]thiophene-2,5-dicarboxylate (**1**) is described.

Keywords: thieno[2,3-b]thiophene; bis-heterocycles; nucleophilic addition; 2-bromo-1-phenylethanone

1. Introduction

Recently, bis(heterocycles) have received a great deal of attention, not only as model compounds for main chain polymers but also because many biologically active natural and synthetic products have molecular symmetry [1-8]. On the other hand, many thiophene-containing compounds, including annulated compounds, exhibit biological activities [9,10]. Thienothiophene derivatives have been developed for different purposes in the pharmaceutical field and have been tested as potential antitumor, antiviral and antibiotic, antiglaucoma drugs, or as inhibitors of platelet aggregation [11-15]. In addition, thienothiophenes have potential applications in a wide variety of optical and electronic

systems [16-18]. Encouraged by all these findings and in continuation of our ongoing research program investigating the utilisation of compound **1** as a versatile and useful building block for the synthesis of a wide variety of bis-heterocyclic systems [19,20], we report herein a convenient route to some novel bis-heterocycles derivatives.

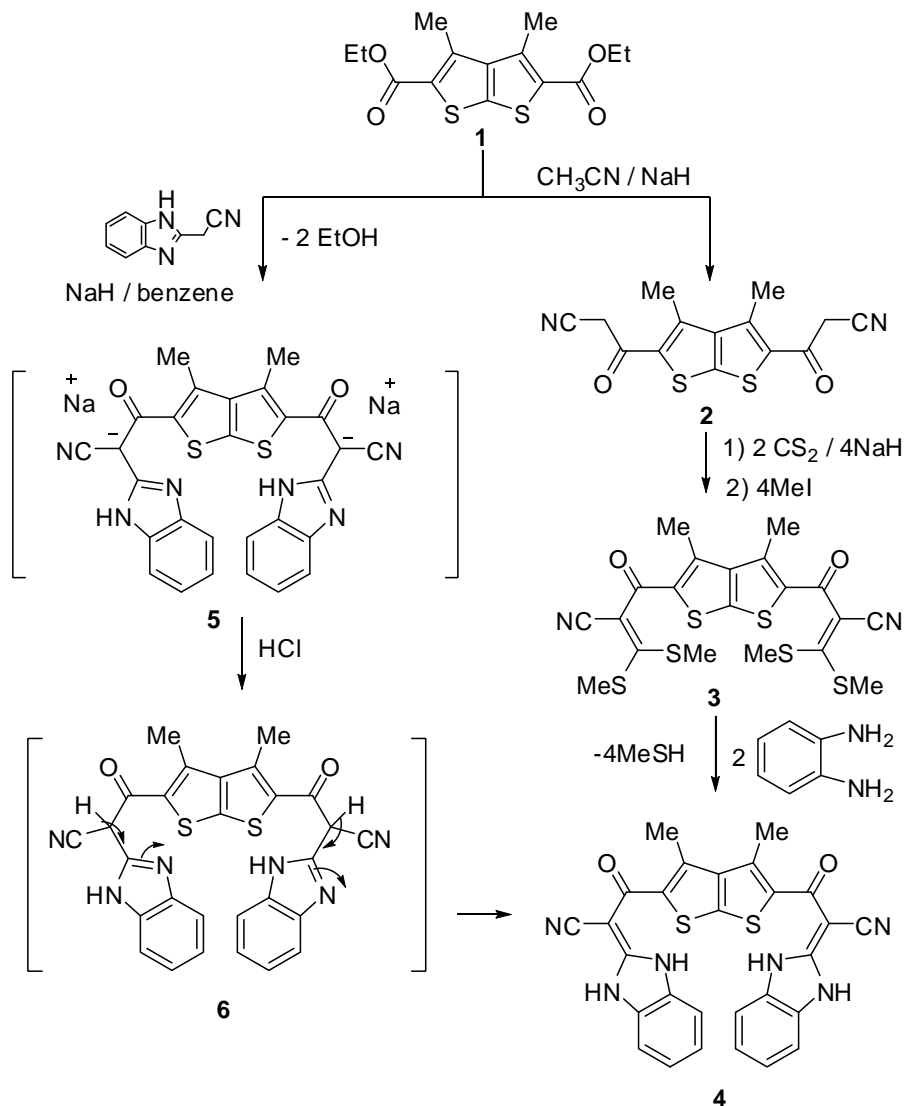
2. Results and Discussion

Treatment of 3,3'-(3,4-dimethylthieno[2,3-b]thiophene-2,5-diyl)bis(3-oxopropanenitrile) (**2**) [20] with sodium hydride and carbon disulfide followed by methyl iodide afforded compound **3**, which reacted with *o*-phenylenediamine in refluxing ethanol to give 3,3'-(3,4-dimethylthieno[2,3-b]thiophene-2,5-diyl)bis(2-(1H-benzo[d]imidazol-2(3H)-ylidene)-3-oxopropanenitrile) (**4**, Scheme 1). Its IR spectrum revealed two absorption bands at 3,214 and 3,177 cm^{-1} due to two NH groups and two bands at 2,195 and 1,670 cm^{-1} assignable to nitrile and carbonyl functions, respectively. The $^1\text{H-NMR}$ spectrum of the reaction product displayed singlets at δ 2.49 and 13.1 due to methyls and two NH protons, respectively, in addition to an aromatic multiplet in the δ 7.28–7.59 region. The lack of an active methine proton signal in the $^1\text{H-NMR}$ spectrum indicates that it exists exclusively in the 1,3-dihydrobenzimidazol-2-ylidene structure **4**, and rules out the isomeric **6**. Further evidence for the structure of compound **4** was provided by its alternative synthesis shown in Scheme 1. Thus, treatment of ester **1** [21] with an equimolar quantity of 2-cyanomethyl-1H-benzimidazole in the presence of sodium hydride in benzene under refluxing conditions, followed by neutralisation of the formed salt, afforded a product identical in all respects (mp., mixed mp., IR and MS spectra) with compound **4**.

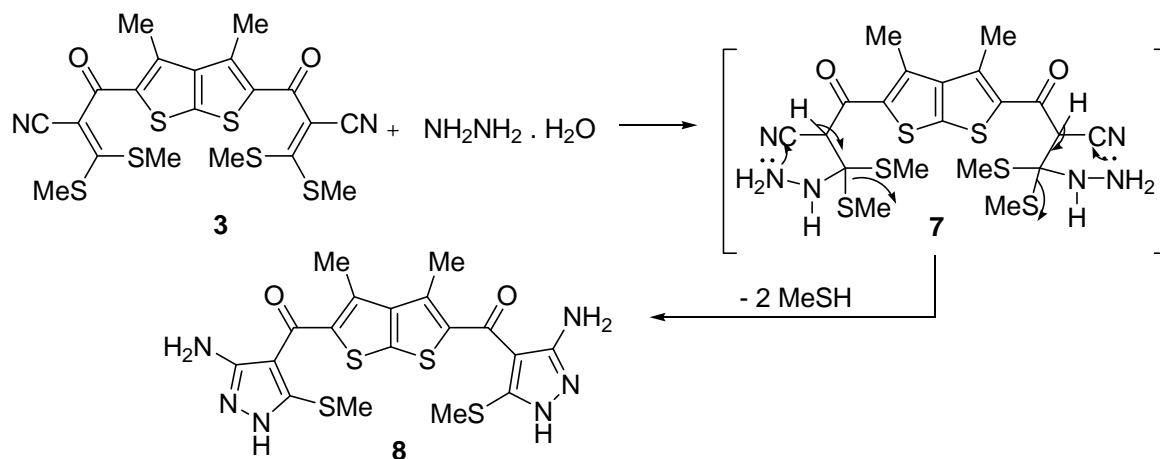
Reaction of the product **3** with hydrazine hydrate gave 3,4-dimethylthieno[2,3-b]thiophene-2,5-diyl-bis-(3-amino-5-(methylthio)-1H-pyrazol-4-yl)methanone (**8**, Scheme 2). The $^1\text{H-NMR}$ spectrum of compound **8** revealed two signals at δ 2.49 and 2.89 due to two CH_3 groups, in addition to two D_2O -exchangeable signals at δ 5.50 and 7.95 due to NH_2 and NH protons, respectively.

Treatment of compound **2** with dimethylformamide-dimethylacetal (DMF-DMA) in refluxing xylene afforded 2-(5-[2-cyano-3-(dimethylamino)-2-propenoyl]-3,4-dimethylthieno[2,3-b]thiophen-2-yl)carbonyl)-3-(dimethylamino)-2-propenenitrile (**9**) [20]. When compound **9** was treated with thiourea in refluxing ethanol, the novel 4,4'-(3,4-dimethylthieno[2,3-b]thiophene-2,5-diyl)bis(2-thioxo-1,2-dihydropyrimidine-5-carbonitrile) (**12**) was produced (Scheme 3). The structure of the obtained product was assigned as **12** and not the other expected derivative **14** based on its spectral data. For example, the IR spectrum of the reaction product revealed no absorption bands due to amino groups and revealed absorption bands at 3,200 and 2,210 cm^{-1} assignable to NH groups and nitrile functions, respectively. The formation of compound **12** is assumed to take place *via* nucleophilic addition of NH_2 in thiourea to the double bond in the enaminone **9** to give the acyclic non-isolable intermediate **10**, which underwent intramolecular cyclization with subsequent aromatization *via* loss of water and dimethylamine molecules to afford the final product **12** (Scheme 3).

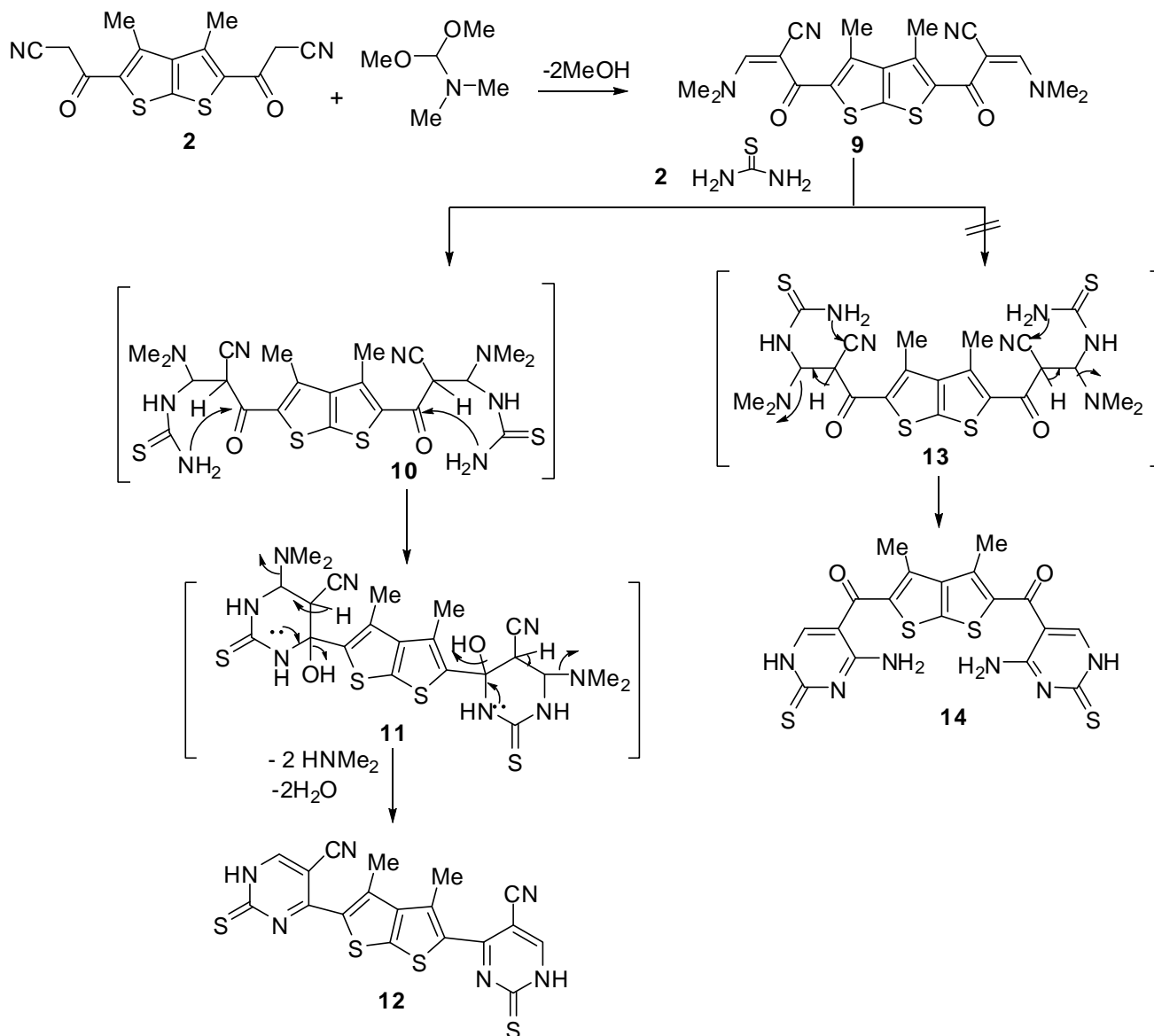
Scheme 1. Synthesis of 3,3'-(3,4-dimethylthieno[2,3-b]thiophene-2,5-diyl)bis(2-(1H-benzo[d]imidazol-2(3H)-ylidene)-3-oxopropanenitrile) (4).



Scheme 2. Synthesis of (3,4-dimethylthieno[2,3-b]thiophene-2,5-diyl)bis((3-amino-5-(methylthio)-1H-pyrazol-4-yl)methanone) (8).

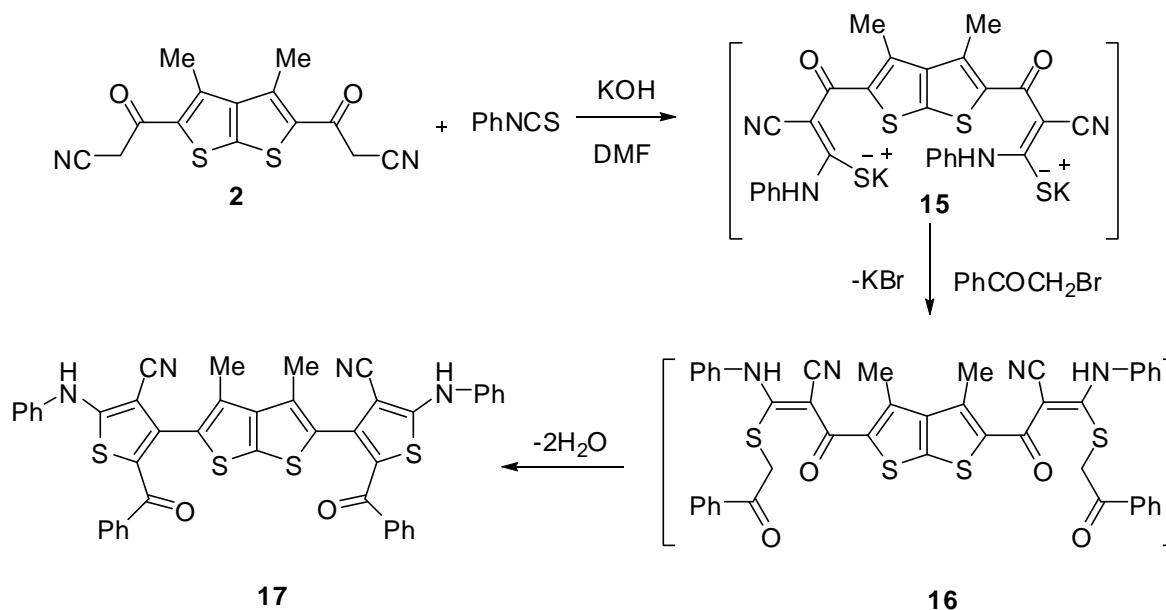


Scheme 3. Synthesis of 4,4'-(3,4-dimethylthieno[2,3-b]thiophene-2,5-diyl)bis(2-thioxo-1,2-dihydropyrimidine-5-carbonitrile) (**12**).



The nucleophilic addition of the thieno[2,3-b]thiophene **2** to phenyl isothiocyanate in DMF, in the presence of potassium hydroxide, afforded the corresponding potassium salt **15**. Heterocyclisation of the intermediate **15** with an equimolar amount of the 2-bromo-1-phenylethanone [22] furnished one isolable product (as verified by TLC analysis). The reaction product was identified as 4,4'-(3,4-dimethylthieno[2,3-b]thiophene-2,5-diyl)bis(5-benzoyl-2-(phenylamino)thiophene-3-carbonitrile) (**17**, Scheme 4). The IR spectrum of compound **17** revealed absorption bands at 1,618, 2,212 and 3,277 cm^{-1} due to carbonyl group, nitrile and NH functions, respectively. Its $^1\text{H-NMR}$ spectrum showed signals at δ 2.07 due to two CH_3 groups and a D_2O -exchangeable peak at δ 10.6 due to two NH protons, in addition to an aromatic multiplet in the δ 7.09–7.53 region. The aforementioned results indicate that the reaction of the intermediate **15** with 2-bromo-1-phenylethanone proceeds *via* loss of two water molecules from the non-isolable intermediate **16** (Scheme 4).

Scheme 4. Synthesis of 4,4'-(3,4-dimethylthieno[2,3-b]thiophene-2,5-diyl)bis(5-benzoyl-2-(phenyl-amino)thiophene-3-carbonitrile) (**17**).



3. Experimental

General

All melting points were measured on a Gallenkamp melting point apparatus. The infrared spectra were recorded in potassium bromide disks on a Pye Unicam SP 3300 or Shimadzu FT IR 8101 PC infrared spectrophotometers. The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer. ^1H spectra were run at 300 MHz and ^{13}C spectra were run at 75.46 MHz in deuterated dimethyl sulfoxide ($\text{DMSO}-d_6$). Chemical shifts were related to that of the solvent. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 e.V. Elemental analyses were carried out at the Microanalytical Center of Cairo University, Giza, Egypt.

2-({5-[2-Cyano-3-(1,1-bis-methylthio)-2-propenoyl]-3,4-dimethylthieno[2,3-b]thiophen-2-yl}carbonyl)-3-(1,1-bis-methylthio)-2-propenenitrile (3). To a stirred solution of sodium hydride (0.96 g, 40 mmol) in dimethylsulfoxide (20 mL), compound **2** (3.02 g, 10 mmol) was added. The resulting mixture was stirred for 30 min, and then carbon disulfide (1.52 g, 20 mmol) was added. After 2 h of stirring, methyl iodide (5.68 g, 40 mmol) was added and the stirring was continued for additional 4 h. The resulting reaction mixture was then poured over crushed ice and the solid product was filtered off, washed with water, dried and finally recrystallised from ethanol to afford bis(methylthio)methylene derivative **3** in 60% yield, mp 170 °C; IR (KBr) ν_{max} : 1,698 (C=O), 2,210 (C≡N), 2,985 (aliphatic CH) cm^{-1} . ^1H -NMR ($\text{DMSO}-d_6$): δ 2.23 (s, 6H, CH_3), 2.53 (s, 12H, CH_3). Anal. Calcd for $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_2\text{S}_6$ (510.76): C, 47.03; H, 3.55; N, 5.48. Found: C, 47.13; H, 3.48; N, 5.40%.

3,3'-(3,4-Dimethylthieno[2,3-b]thiophene-2,5-diyl)bis(2-(1H-benzo[d]imidazol-2(3H)-ylidene)-3-oxo-propanenitrile) (4) **Method A.** *o*-Phenylenediamine (0.22 g, 2 mmol) was added to a solution of bis(methylthio)methylene derivative **3** (0.51 g, 1 mmol) in ethanol (20 mL). The mixture was refluxed

for 3 h and then allowed to cool. The solid formed was filtered off, washed with ethanol and recrystallised from DMF/water to afford compound **4** in 72% yield, mp > 320 °C; IR (KBr) ν_{\max} : 1,670 (C=O), 2,195 (C≡N), 3,214 and 3,177 (NH) cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6): δ 2.49 (s, 6H, 2CH₃), 7.28–7.32 (d, 4H, $J = 8.7$ Hz), 7.56–7.59 (t, 4H, $J = 8.7$ Hz), 13.1 (s, 4H, D₂O-exchangeable, 4NH); $^{13}\text{C-NMR}$ (DMSO- d_6): δ 8.3 (2CH₃), 111.0 (2=C-C), 115.3 (2CN), 117.6, 118.9, 142.2, 156.0 (benzimidazole ArC), 130.4, 131.8, 138.8, 140.1, (thienothiophene ArC), 185.9 (2C=O). Anal. Calcd for C₂₈H₁₈N₆O₂S₂ (534.61): C, 62.91; H, 3.39; N, 15.72. Found: C, 62.81; H, 3.32; N, 15.67%.

Method B. To a mixture of diethyl 3,4-dimethylthieno[2,3-*b*]thiophene-2,5-dicarboxylate (**1**, 3.12 g, 10 mmol) and 2-(1H-benzo[*d*]imidazol-2-yl)acetonitrile (3.14 g, 20 mmol) in dry benzene (25 mL) and dimethylformamide (1 mL) was added sodium hydride (0.96 g, 60%). The reaction mixture was refluxed for 4 h, then allowed to cool. The solid that precipitated was collected by filtration, washed with ether and dried. The solid product was dissolved in water and the resulting solution was neutralised to pH 7 with concentrated hydrochloric acid. The precipitated solid was collected by filtration, washed with water and dried. Recrystallisation of the crude product from DMF/water gave a product (60% yield) identical in all respects (TLC, IR spectrum) with that obtained by method A.

*Synthesis of (3,4-dimethylthieno[2,3-*b*]thiophene-2,5-diyl)bis((3-amino-5-(methylthio)-1H-pyrazol-4-yl)methanone) (8).* To a solution of compound **3** (0.51 g, 1 mmol) in EtOH (20 mL), hydrazine hydrate (80%, 0.2 mL, 2 mmol) was added and the reaction mixture was refluxed for 4 h, and then left to cool. The solid product so formed was filtered off, washed with EtOH and dried. Recrystallization from DMF/ EtOH afforded **8** in 55% yield; mp 302 °C; IR (KBr) ν_{\max} : 3,427, 3,214 and 3,177 (NH, NH₂), 1,675 (C=O) cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6): δ 2.49 (s, 6H, 2CH₃), 2.89 (s, 6H, 2CH₃), 5.5 (s, 4H, D₂O-exchangeable, 2NH₂), 7.95 (s, 2H, D₂O-exchangeable, 2NH); $^{13}\text{C-NMR}$ (DMSO- d_6): δ 8.3 (2CH₃), 11.7 (2CH₃-SH), 87.8, 115.3, 142.2, (pyrazole ArC), 130.4, 131.8, 136.3, 140.1, (thienothiophene ArC), 185.9 (2C=O). Anal. Calcd for C₁₈H₁₈N₆O₂S₄(478.63): C, 45.17; H, 3.79; N, 17.56. Found: C, 45.27; H, 3.86; N, 17.51%

*Synthesis of 4,4'-(3,4-dimethylthieno[2,3-*b*]thiophene-2,5-diyl)bis(2-thioxo-1,2-dihydropyrimidine-5-carbonitrile) (12).* To a mixture of compound **9** (0.41 g, 1 mmol) and thiourea (0.15 g, 2.0 mmol) in ethanol (30 mL), a few drops of piperidine was added and the reaction mixture was refluxed for 8 h, then left to cool to room temperature. The precipitated product was filtered off, washed with EtOH, dried and finally recrystallized from DMF to afford compound **12** in 78% yield; mp. 318 °C; IR (KBr) 3,200 (NH), 2,210 (C≡N), cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6): δ 2.49 (s, 6H, 2CH₃), 6.37 (s, 2H, 2CH pyrimidine), 11.62 (s, 2H, D₂O-exchangeable, 2NH). Anal. Calcd. for C₁₈H₁₀N₆S₄(438.57): C, 49.29; H, 2.30; N, 19.16. Found: C, 49.20; H, 2.22; N, 19.106%.

*Synthesis of 4,4'-(3,4-dimethylthieno[2,3-*b*]thiophene-2,5-diyl)bis(5-benzoyl-2-(phenylamino)-thiophene-3-carbonitrile) (17).* To a stirred solution of potassium hydroxide (0.11 g, 2 mmol) in DMF (20 mL) was added compound **2** (0.30 g, 1 mmol). After stirring for 30 min, phenyl isothiocyanate (0.27 g, 2 mmol) was added to the resulting mixture. Stirring was continued for 6 h, and then 2-bromo-1-phenylethanone (0.40 g, 2 mmol) was added portionwise over a period of 30 min. After the addition was complete, the reaction mixture was stirred for additional 12 h, during which the 2-bromo-1-

phenylethanone went into solution and a yellow product precipitated. The solid product was filtered off, washed with EtOH and dried, Recrystallization from EtOH/DMF afforded **17** in 86% yield, mp > 320 °C; IR (KBr) ν_{\max} : 3,277 (NH), 2,212 (C≡N), 1618 (C=O) cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6): δ 2.07 (s, 6H, 2CH₃), 7.09–7.53 (m, 20H, ArH), 10.6 (s, 2H, D₂O-exchangeable, 2NH); $^{13}\text{C-NMR}$ (DMSO- d_6): δ 8.3 (2CH₃), 115.3 (2CN), 116.3, 117.6, 118.9, 125.3, 126.6, 127.9, 129.1, 136.7 (ArC's), 130.4, 131.8, 138.8, 140.1 (thienothiophene ArC), 111.0, 133.3, 145.8, 156.0 (thiophene ArC), 187.9 (2C=O). MS m/z (%) 774 (M^++1 , 88.6%), 773 (M^+ , 100%), 351 (80.6%), 212 (16.2%), 63(30.3%). Anal. Calcd for C₄₄H₂₈N₄O₂S₄ (772.98): C, 68.37; H, 3.65; N, 7.25. Found: C, 68.31; H, 3.69; N, 7.20%.

4. Conclusions

In summary, the reactivity of diethyl 3,4-dimethylthieno[2,3-b]thiophene-2,5-dicarboxylate (**1**) as a versatile and readily accessible building block for the synthesis of new bis-heterocycles incorporating thieno[2,3-b]thiophene moieties of potential biological and pharmaceutical importance was investigated.

Acknowledgements

Project (Chem/2010/2) was supported by King Saud University, Deanship of Scientific Research, College of Science Research Center.

References

1. Li, J.T.; Sun, M.X.; He, G.Y.; Xu, X.Y. Efficient and green synthesis of bis(indolyl)methanes catalyzed by ABS in aqueous media under ultrasound irradiation. *Ultrason. Sonochem.* **2011**, *18*, 412-414.
2. Wang, Z.; Zhao, C.; Zhao, D.; Li, C.; Ahang, J.; Wang, H. The preparation of substituted bithiophenyl aldehydes via the ring opening of dithieno[2,3-b:3',2'-d]thiophene in the presence of n-BuLi. *Tetrahedron* **2010**, *66*, 2168-2174.
3. Diana, P.; Carbone, A.; Barraja, P.; Kelter, G.; Herbert Fiebig, H.; Cirrincione, G. Synthesis and antitumor activity of 2,5-bis(3'-indolyl)-furans and 3,5-bis(3'-indolyl)-isoxazoles, nortopsentin analogues. *Bioorg. Med. Chem.* **2010**, *18*, 4524-4529.
4. Toyota, K.; Okada, K.; Katsuta, H.; Morita, N. Preparations of bis[2-(2-arylethynyl)-3-thienyl]arenes and bis[2-{2-(trimethylsilyl)ethynyl}-3-thienyl]arenes. *Tetrahedron* **2009**, *65*, 145-151.
5. Todd, E.M.; Zimmerman, S.C. Bis-ureidodeazapterin (Bis-DeAP) as a general route to supramolecular star polymers. *Tetrahedron* **2008**, *64*, 8558-8570.
6. Diana, P.; Carbone, A.; Barraja, P.; Montalbano, A.; Martorana, A.; Dattolo, G.; Gia, O.; Dalla Via, L.; Cirrincione, G. Synthesis and antitumor properties of 2,5-bis(3'-indolyl)thiophenes: Analogues of marine alkaloid nortopsentin. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2342-2346.
7. Blanco, G.; Quintela, J.M.; Peinador, C. Efficient one-pot preparation of bis(pyrazino[2',3':4,5]thieno-[3,2-d]pyrimidin-4-yl)benzenes based on an aza-Wittig/mediated annulation strategy. *Tetrahedron* **2007**, *63*, 2034-2041.

8. Promarak, V.; Punkvuang, A.; Jungstittiwong, S.; Saengsuwan, S.; Sudyoadsuk, T.; Keawin, T. Synthesis, optical, electrochemical, and thermal properties of α,α' -bis(9,9-bis-n-hexylfluorenyl) substituted oligothiophenes. *Tetrahedron Lett.* **2007**, *48*, 3661-3665.
9. Chakrabarti, J.K.; Horsman, L.; Hotten, T.M.; Pullar, I.A.; Tupper, D.E.; Wright, F.C. 4-Piperazinyl-10H-thieno[2,3-b][1,5]benzodiazepines as potential neuroleptics. *J. Med. Chem.* **1980**, *23*, 878-884.
10. Ram, V.J.; Pandey, H. K.; Vlientick, A.J. Thieno[2,3-d]pyrimidines as potential chemotherapeutic agents. II. *J. Heterocycl. Chem.* **1981**, *18*, 1277-1280.
11. Jarak, I.; Kralj, M.; Piantanida, I.; Suman, L.; Zinic, M.; Pavelic, K.; Karminski-Zamola, G. Novel cyano- and amidino-substituted derivatives of thieno[2,3-b]- and thieno[3,2-b]thiophene-2-carboxanilides and thieno[3',2':4,5]thieno and thieno[2',3':4,5] thieno[2,3-c]quinolones: Synthesis, photochemical synthesis, DNA binding, and antitumor evaluation. *Bioorg. Med. Chem.* **2006**, *14*, 2859-2868.
12. Peters, D.; Hornfeldt, A.B.; Gronowitz, S. Synthesis of various 5-substituted uracils. *J. Heterocycl. Chem.* **1990**, *27*, 2165-2173.
13. Kukulja, S.; Draheim, S.E.; Graves, B.J.; Hunden, D.C.; Pfeil, J.L.; Cooper, R.D.G.; Ott, J.L.; Couter, F.T. Orally absorbable cephalosporin antibiotics. 2. Structure-activity studies of bicyclic glycine derivatives of 7-aminodeacetoxycephalosporanic acid. *J. Med. Chem.* **1985**, *28*, 1896-1903.
14. Prugh, J.D.; Hartman, G.D.; Mallorga, P.J.; McKeever, B.M.; Michelson, S.R.; Murcko, M.A.; Schwam, H.; Smith, R.L.; Sondey, J.M.; Springer, J.P.; Surgrue, M.F. New isomeric classes of topically active ocular hypotensive carbonic anhydrase inhibitors: 5-substituted thieno[2,3-b]thiophene-2-sulfonamides and 5-substituted thieno[3,2-b]thiophene-2-sulfonamides. *J. Med. Chem.* **1991**, *34*, 1805-1818.
15. Hartman, G.D.; Ansdale, P.A. Substituted thieno[2,3-b]thiophene-2-sulfonamides as antiglaucoma agents. *U.S. Patent 4,806,562*, 21 February 1989.
16. Litvinov, V.P. The latest achievements in thienothiophene chemistry. *Russ. Chem. Rev.* **2005**, *74*, 217-248.
17. Gather, M.C.; Heeny, M.; Zhang, W.; Whitehead, K.S.; Bradley, D.D.C.; McCulloch, I.; Campbell, A. J. An alignable fluorene thienothiophene copolymer with deep-blue electroluminescent emission at 410 nm. *Chem. Commun.* **2008**, 1079-1081.
18. He, M.; Li, J.; Sorensen, M. L.; Zhang, F.; Hancock, R.R.; Fong, H.H.; Pozdin, V.A.; Smilgies, D.; Malliaras, G.G. Alkylsubstituted thienothiophene semiconducting materials: structure property relationships. *J. Am. Chem. Soc.* **2009**, *131*, 11930-8.
19. Mabkhoot, Y.N. Synthesis and Chemical Characterisation of New Bis-Thieno[2,3-b]thiophene Derivatives. *Molecules* **2010**, *15*, 3329-3337.
20. Mabkhoot, Y.N. Synthesis and Analysis of Some Bis-Heterocyclic Compounds Containing Sulphur. *Molecules* **2009**, *14*, 1904-1914.
21. Comel, A.; Kirsch, G. Efficient one pot preparation of variously substituted thieno[2,3-b]thiophene. *J. Heterocycl. Chem.* **2001**, *38*, 1167-1171.

22. Cowper, R.M.; Davidson, L.H. Phenacyl bromide. *Org. Synth. Coll.* **1943**, *II*, 480.

Sample Availability: Samples of compounds **3-17** are available from the authors.

© 2010 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution license (<http://creativecommons.org/licenses/by/3.0/>).