Synthesis and Reactions of Some New Heterocyclic Compounds

ALI ALDALBAHI and YAHIA N. MABKHOT*

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

*Corresponding author: Fax: +966 1 4675992; Tel: +966 1 4675898; E-mail: yahia@ksu.edu.sa

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Synthesis and reactions of some new heterocyclic compounds containing a thieno[2,3-*b*]thiophene *e.g.*, *bis*-thieno[2,3-*b*]thiophene derivatives **3a-d**, **6** and **7** are described. The structures of all newly synthesized compounds have been elucidated by ¹H, ¹³C NMR, GCMS and IR spectrometry. These compounds represent a new class of nitrogen and sulfur containing heterocycles that should also be of interest as new materials.

Keywords: *bis*-Heterocycles, *bis*-Thieno[2,3-*b*]thiophene, Five-membered, Pyrazoles.

INTRODUCTION

bis-(Pyrazole) derivatives are in general well-known five-membered *N*-containing heterocyclic compounds¹⁻³. Compounds with pyrazole ring are of interest due to their broad spectrum of biological activities as NOS inhibitors, monoamine oxidase inhibitor, antibacterial and antiamoebic compounds⁴⁻⁷. Moreover, *N*-phenylpyrazole derivatives play an important role in antitumor screening as well as potent antimicrobial products^{8,9}. On the other hand, many thiophene-containing compounds, including annulated compounds, exhibit biological activities¹⁰⁻¹². 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 aggregation¹³⁻¹⁷. In addition, thienothiophenes have potential applications in a wide variety of optical and electronic systems¹⁸⁻²⁰. Furthermore, *bis*-heterocyclic have received great attention as being model compounds for main chain polymers²¹⁻²⁵. It is also reported that many biologically active natural and synthetic products have molecular symmetry²⁶. Keeping the above facts in mind and in continuation of our interest in the synthesis of *bis*-heterocycles²⁷⁻³⁰, we described herein a simple and efficient route for the synthesis of novel *bis*-(enaminones) and studied their synthetic utilities as key intermediates for the synthesis of novel *bis*-heterocycles pyrazoles derivatives.

EXPERIMENTAL

Melting point were measured on Gallenkamp melting point apparatus in open glass capillaries and are uncorrected. IR spectra were measured as KBr pellets on a Perkin Elmer

FT 1000 spectrophotometer. The NMR spectra were recorded on a Varian Mercury Jeol-400 NMR spectrometer. ¹H NMR (400 MHz) and ¹³C NMR (100 MHz) were run in (DMSO-*d*₆). Chemical shifts (δ) are referred in ppm and coupling constants *J* are given in Hz. 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.

General procedure of compounds 3a-d: To a solution of compound **2** (0.5 mmol, 0.18 g) in dry benzene (20 mL), ethyl 2-chloro-2-(2-arylhydrazono) acetate and arylpropane-hydrazonoyl chloride derivatives (2 equiv., 1 mmol) was added in the presence of few drops of Et₃N, thus the reaction mixture was heated under reflux for 8 h. The solid product was collected by filtration and recrystallized from EtOH (**Scheme-I**).

Diethyl 4,4'-(3,4-dimethylthieno[2,3-*b*]thiophene-2,5-dicarbonyl)*bis*-(1-phenyl-1*H*-pyrazole-3-carboxylate) (3a): Compound **3a** was prepared from ethyl 2-chloro-2-(2-phenylhydrazono) acetate following general procedure, yellow crystals, yield (63 %); m.p. 206-209 °C; IR (KBr, ν_{max}, cm⁻¹): 1731, 1718 2(C=O), 1627 (C=N); ¹H NMR (400 MHz, DMSO-*d*₆): 1.39 (t, 3H, *J* = 6.9 Hz, CH₃, ester), 1.96 (s, 3H, CH₃), 4.31 (q, 2H, *J* = 9.6 Hz, CH₂, ester), 7.03 -7.53 (m, 5 H, Ar-H), 9.35 (s, 1H, pyrazolo-H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ (ppm): 14.49, 21.70, 66.25, 119.34, 120.22, 123.67, 129.56, 146.69, 168.27, 192.12; MS *m/z* (%): 652.74 [M⁺, 57 %], 240 (74), 166 (100), 98 (72); Anal. Calcd. for C₃₄H₂₈N₄O₆S₂: C, 62.56; H, 4.32; N, 8.58; S, 9.82; found: C, 62.44; H, 4.52; N, 8.54; S, 9.75.

Diethyl 4,4'-(3,4-dimethylthieno[2,3-*b*]thiophene-2,5-dicarbonyl)*bis*-[1-(4-chlorophenyl)-1*H*-pyrazole-3-carboxylate] (3b): Compound **3b** was prepared from ethyl 2-chloro-

Scheme-I

2-(2-(4-chlorophenyl)hydrazono) acetate following general procedure, yellow crystal, yield (72 %); m.p. 237-240 °C; IR (KBr, $\nu_{\max}$, cm^{-1}): 1731, 1718 2(C=O), 1634 (C=N); ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 1.30 (t, 3H, J = 6.9 Hz, CH₃, ester), 1.96 (s, 3H, CH₃), 4.25 (q, 2H, J = 16.6 Hz, CH₂, ester), 7.36-7.96 (m, 4H, Ar-H), 9.35 (s, 1H, pyrazolo-H); ^{13}C NMR (100 MHz, DMSO- d_6): 14.49, 21.70, 66.25, 119.34, 120.22, 123.67, 129.56, 146.69, 168.27, 192.12; MS m/z (%): 721.63 [M^+ , 72 %]; Anal. Calcd. for: C₃₄H₂₆N₄O₆S₂Cl₂: C, 56.59; H, 3.63; Cl, 9.83; N, 7.76; S, 8.89; found: C, 56.62; H, 3.97; Cl, 9.58; N, 7.76; S, 8.76.

1,1'-(4,4'-(3,4-Dimethylthieno[2,3-*b*]thiophene-2,5-dicarbonyl)bis(1-(4-chlorophenyl)-1*H*-pyrazole-4,3-diyl))diethanone (3c): Compound 3c was prepared from *N*-(4-chlorophenyl)-2-oxopropanehydrazonoyl chloride following general procedure, yellow crystal, yield (82 %); m.p. 271-273 °C; IR (KBr, $\nu_{\max}$, cm^{-1}): 1731, 1728, 2(C=O), 1624 (C=N); ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 1.03 (s, 3H, CH₃), 1.96 (s, 3H, CH₃), 7.07-7.56 (m, 4H, Ar-H), 9.35 (s, 1H, pyrazolo-H); ^{13}C NMR (100 MHz, DMSO- d_6) δ (ppm): 8.2,

14.49, 21.70, 66.25, 119.34, 120.22, 123.67, 129.56, 146.69, 168.27, 192.12; MS m/z (%): 661.58 [M^+ , 65 %]; Anal. Calcd. for C₃₂H₂₂N₄O₄SCl₂: C, 58.09; H, 3.35; Cl, 10.72; N, 8.47; S, 9.69; found: C, 58.17; H, 3.39; Cl, 10.78; N, 8.57; S, 9.62.

1,1'-(4,4'-(3,4-Dimethylthieno[2,3-*b*]thiophene-2,5-dicarbonyl)bis(1-phenyl-1*H*-pyrazole-4,3-diyl))diethanone (3d): Compound 3d was prepared from 2-oxo-*N*'-phenylpropanehydrazonoyl chloride following general procedure, as a yellow crystal, yield (70 %); m.p. 211-214 °C; IR (KBr, $\nu_{\max}$, cm^{-1}): 1731, 1717, 2(C=O), 1622 (C=N); ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 1.03 (s, 3H, CH₃), 1.96 (s, 3H, CH₃), 7.17-7.65 (m, 5H, Ar-H), 9.35 (s, 1H, pyrazolo-H); ^{13}C NMR (100 MHz, DMSO- d_6) δ (ppm): 8.2, 14.49, 21.70, 66.25, 119.34, 120.22, 123.67, 129.56, 146.69, 168.27, 192.12; MS m/z (%): 592.69 [M^+ , 65 %]; Anal. Calcd. for C₃₂H₂₄N₄O₄S₂: C, 64.85; H, 4.08; N, 9.45; S, 10.82; found: C, 64.75; H, 4.00; N, 9.66; S, 10.65.

5,5'-(3,4-Dimethylthieno[2,3-*b*]thiophene-2,5-diyl)bis(2-cyano-5-(dimethylamino)penta-2,4-dienamide) (6): To a solution of 1 (0.5 mmol, 0.18 g) in EtOH (10 mL),

malononitrile (1 mmol, 0.07 g) was added in the presence of catalytic amount of piperidine. The reaction mixture was heated under reflux for 1 h. The solid product was collected by filtration, **8** was obtained as red crystal, yield (78 %); m.p. 175–177 °C; IR (KBr, $\nu_{\max}$, cm^{-1}): 1616 (C=O), 2123 (CN), 3364 (NH_2); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 1.96 (s, 3H, CH_3), 2.99–3 (s, 6H, N- CH_3), 5.91 (d, 1H, $J = 12$ Hz, CH), 7.15 (d, 1H, $J = 12$ Hz, CH), 4.2 (s, 2H, NH_2); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ (ppm): 180.04, 176.68, 160.58, 149.18, 148.6, 133.6, 129.98, 128.80, 128.68, 119.20, 103, 79.12, 43.2, 14.85; MS m/z (%): 494 [M^+ , 48], 221 (6.1), 149 (100), 73 (34); Anal. Calcd. for $\text{C}_{24}\text{H}_{26}\text{N}_6\text{O}_2\text{S}_2$: C, 58.28; H, 5.30; N, 16.99; S, 12.97; found: 57.99; H, 5.34; N, 16.88; S, 12.76.

6,6'-(3,4-Dimethylthieno[2,3-*b*]thiophene-2,5-diyl)-bis(2-ethoxynicotinonitrile) (7): To a solution of **1** (0.5 mmol, 0.18 g) in EtONa (Na 0.02g/EtOH 10 mL), malononitrile (1 mmol, 0.07 g) was added and the resulting reaction mixture was heated under reflux for 4 h. The solid product was collected by filtration, **5** was obtained as red crystal, yield (78 %); m.p. > 300 °C; IR (KBr, $\nu_{\max}$, cm^{-1}): 1573 (C=N), 2222 (CN); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 1.32 (t, 3H, $J = 8$ Hz, CH_3), 1.96 (s, 3H, CH_3), 4.15–4.90 (q, 2H, $J = 8$ Hz, CH_2), 7.22 (d, 1H, $J = 7.5$ Hz, CH), 8.44 (d, 1H, $J = 7.5$ Hz, CH). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ (ppm): 14.8, 29.58, 69.92, 103, 115, 119, 128.68, 128.81, 129.98, 133.61, 143.8, 149.1, 176, 180; MS m/z (%): 460 [M^+ , 78 %], 382 (6), 203 (14), 149 (100), 91 (64); Anal. Calcd. for $\text{C}_{24}\text{H}_{20}\text{N}_4\text{O}_2\text{S}_2$: C, 62.59; H, 4.38; N, 12.16; S, 13.92; found: C, 62.46; H, 4.28; N, 12; S, 13.87.

RESULTS AND DISCUSSION

Enaminone (**2**) was prepared by different synthetic approaches and their use as building blocks for the synthesis of a wide variety of heterocycles has been investigated^{3,31,32}. The new *bis*-(enaminones) (**2**) being now prompted us to study its synthetic utility as key intermediate for novel *bis*-(5-membered) heterocycles with the thieno[2,3-*b*]thiophene core. Thus, heating the *bis*-(enaminone) with ethyl 2-chloro-2-(2-arylhydrazono) acetate and arylpropane-hydrazonoyl chloride derivatives which are commercially available in dry benzene and triethyl amine resulted in the formation of the *bis*-(1-*H*-pyrazole) derivatives (**3a-d**) in high yields as depicted in Scheme-I. The structure of compounds **3a-d** were determined from its elemental and spectroscopic analyses. Its IR spectrum revealed three absorption bands at 1731–1718 and 1624 cm^{-1} due to two C=O groups and C=N group, respectively. For example, the ^1H NMR spectrum of compound **3a** showed a singlet at 9.35 ppm due to the pyrazole ring (5-CH). It is noteworthy to mention that the *bis*-(pyrazoles) (**3a-d**) could also be prepared from compound **1** in high yields, respectively, using the above synthetic methodology. The formation of the *bis*-(pyrazole) (**3a-d**) is supposed to proceed through the formation of the nonisolable intermediates followed by the elimination of two molecules of the secondary amines.

When enaminone (**2**) was treated with malononitrile in ethanolic piperidine under reflux for 1 h which was a red crystalline product, *bis*-dienamide derivatives **4** was obtained in 78 % yield (Scheme-II).

Scheme-II

We assume that malononitrile initially undergoes 1,4 addition to the double bond in compound **2** yielding the adduct compound **4** that cyclizes into aminopyran (**5**) before undergoing a rearrangement to compound **6** via a 1,3-nitrogen shift. Its IR spectrum revealed three absorption bands at 1616, 2123 and 3364 cm^{-1} due to C=O, CN and NH_2 groups, respectively. The ^1H NMR spectrum of compound **6** showed a 1.96 (s, 3H, CH_3), 2.99–3.00 (s, 6H, N- CH_3), 5.91 (d, 1H, $J = 12$ Hz, CH), 7.15 (d, 1H, $J = 12$ Hz, CH), 4.2 (s, 2H, NH_2). It is noteworthy to (Scheme-II). While reacting compound **2** with malononitrile in ethanolic sodium ethoxide afforded compound **7** in good yield (78 %)³³.

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REFERENCES

1. D. Shen, M. Shu and K.T. Chapman, *Org. Lett.*, **2**, 2789 (2000).
2. S. Dadiboyena, E.J. Valente and A.T. Hamme II, *Tetrahedron Lett.*, **50**, 291 (2009).
3. Y.N. Mabkhot, A.M. Al-Majid and A.S. Alamar, *Molecules*, **16**, 7706 (2011).

4. M.D. Carrion, L.C. Lopez Cara, E.V. Camacho, M. Tapias, G. Escames, D. Acuña-Castroviejo, A. Espinosa, M.A. Gallo and A. Entrena, *Eur. J. Med. Chem.*, **43**, 2579 (2008).
5. N. Gokhan-Kelekçi, S. Koyunoglu, S. Yabanoglu, K. Yelekçi, Ö. Özgen, G. Uçar, K. Erol, E. Kendi and A. Yesilada, *Bioorg. Med. Chem.*, **17**, 675 (2009).
6. X.H. Liu, L.P. Zhi, B.A. Song and H.L. Xu, *Chem. Res.*, **24**, 454 (2008).
7. M. Abid, A.R. Bhat, F. Athar and A. Azam, *Eur. J. Med. Chem.*, **44**, 417 (2009).
8. A.M. Farag, A.S. Mayhoub, S.E. Barakat and A.H. Bayomi, *Bioorg. Med. Chem.*, **16**, 881 (2008).
9. A.M. Farag, A.M. Mayhoub, A.S. Barakat and S.E. Bayomi, *Bioorg. Med. Chem.*, **16**, 4569 (2008).
10. Y. Hui, R. Ptak, R. Paulman, M. Pallansch and C.W.T. Chang, *Tetrahedron Lett.*, **43**, 9255 (2002).
11. J.K. Chakrabarti, L. Horsman, T.M. Hotten, I.A. Pullar, D.E. Tupper and F.C. Wright, *J. Med. Chem.*, **23**, 878 (1980).
12. V.J. Ram, H.K. Pandey and A.J. Vlietinck, *J. Heterocycl. Chem.*, **18**, 55 (1981).
13. I. Jarak, M. Kralj, I. Piantanida, L. Suman, M. Zinic, K. Pavelic and G. Karminski-Zamola, *Bioorg. Med. Chem.*, **14**, 2859 (2006).
14. D. Peters, A.B. Hornfeldt and S. Gronowitz, *J. Heterocycl. Chem.*, **27**, 2165 (1990).
15. S. Kukolja, S.E. Draheim, B.J. Graves, D.C. Hunden, J.L. Pfeil, R.D.G. Cooper, J.L. Ott and F.T. Counter, *J. Med. Chem.*, **28**, 1896 (1985).
16. 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 and M.F. Surgrue, *J. Med. Chem.*, **34**, 1805 (1991).
17. G.D. Hartman and P.A. Ansdale, U.S. Patent 4,806,562, 21 February (1989).
18. V.P. Litvinov, *Russ. Chem. Rev.*, **74**, 217 (2005).
19. M.C. Gather, M. Heeney, W. Zhang, K.S. Whitehead, D.D.C. Bradley, I. McCulloch and A.J. Campbell, *Chem. Commun.*, 1079 (2008).
20. M. He, J. Li, M.L. Sorensen, F. Zhang, R.R. Hancock, H.H. Fong, V.A. Pozdin, D. Smilgies and G.G. Malliaras, *J. Am. Chem. Soc.*, **131**, 11930 (2009).
21. A.G. Griffin and T.R. Britt, *J. Am. Chem. Soc.*, **103**, 4957 (1981).
22. G. Galli, M. Laus and A.S. Angeloni, *Makromol. Chem.*, **187**, 289 (1986).
23. H. Finkelmann, *Angew. Chem. Int. Ed. Engl.*, **26**, 816 (1987).
24. C. Aguilera, M. Parra and G. Fuentes, *Z. Naturforsch.*, **53b**, 367 (1998).
25. D. Braun, R. Langendorf and I. Vitrigens, *J. Prakt. Chem.*, **341**, 128 (1999).
26. E.J. Ariens, *Drug Design*, Academic Press: New York, NY, USA (1971).
27. A.H.M. Elwahy and A.A. Abbas, *Synth. Commun.*, **30**, 2903 (2000).
28. A.A. Abbas, M.A.A. Elneairy and Y.N. Mabkhot, *J. Chem. Res.*, 124 (2001).
29. M.A.A. Elneairy, A.A. Abbas and Y.N. Mabkhout, *Phosphorus Sulfur Silicon Rel. Elem.*, **178**, 1747 (2003).
30. A.A. Abbas and N.M. Rateb, *Phosphorus Sulfur Silicon Rel. Elem.*, **180**, 497 (2005).
31. A.A. Elassar and A.A. El-Khair, *Tetrahedron*, **59**, 8463 (2003).
32. Y. Nasser Mabkhot, A. Barakat, A.M. Al-Majid, Z. Al-Othman and A.S. Alamar, *Int. J. Mol. Sci.*, **12**, 7824 (2011).
33. F. Al-Omran, N. Al-Awadi, A.A. El-Khair and M.H. Elnagdi, *Org. Prep. Proced. Int.*, **29**, 285 (1997).