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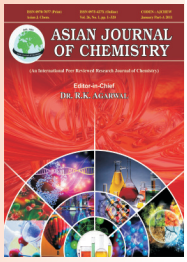

Synthesis and Reactions of Some New Heterocyclic Compounds

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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 ^{1}H, ^{13}C 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 compounds[1-3]. Compounds with pyrazole ring are of interest due to their broad spectrum of biological activities as NOS inhibitors, monoamine oxidase inhibitor, antibacterial and antiamoebic compounds[4-7]. 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 activities[10-12]. 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 aggregation[13-17]. In addition, thienothiophenes have potential applications in a wide variety of optical and electronic systems[18-20]. Furthermore, *bis*-heterocyclic have received great attention as being model compounds for main chain polymers[21-25]. It is also reported that many biologically active natural and synthetic products have molecular symmetry[26]. Keeping the above facts in mind and in continuation of our interest in the synthesis of *bis*-hetrocycles[27-30], 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

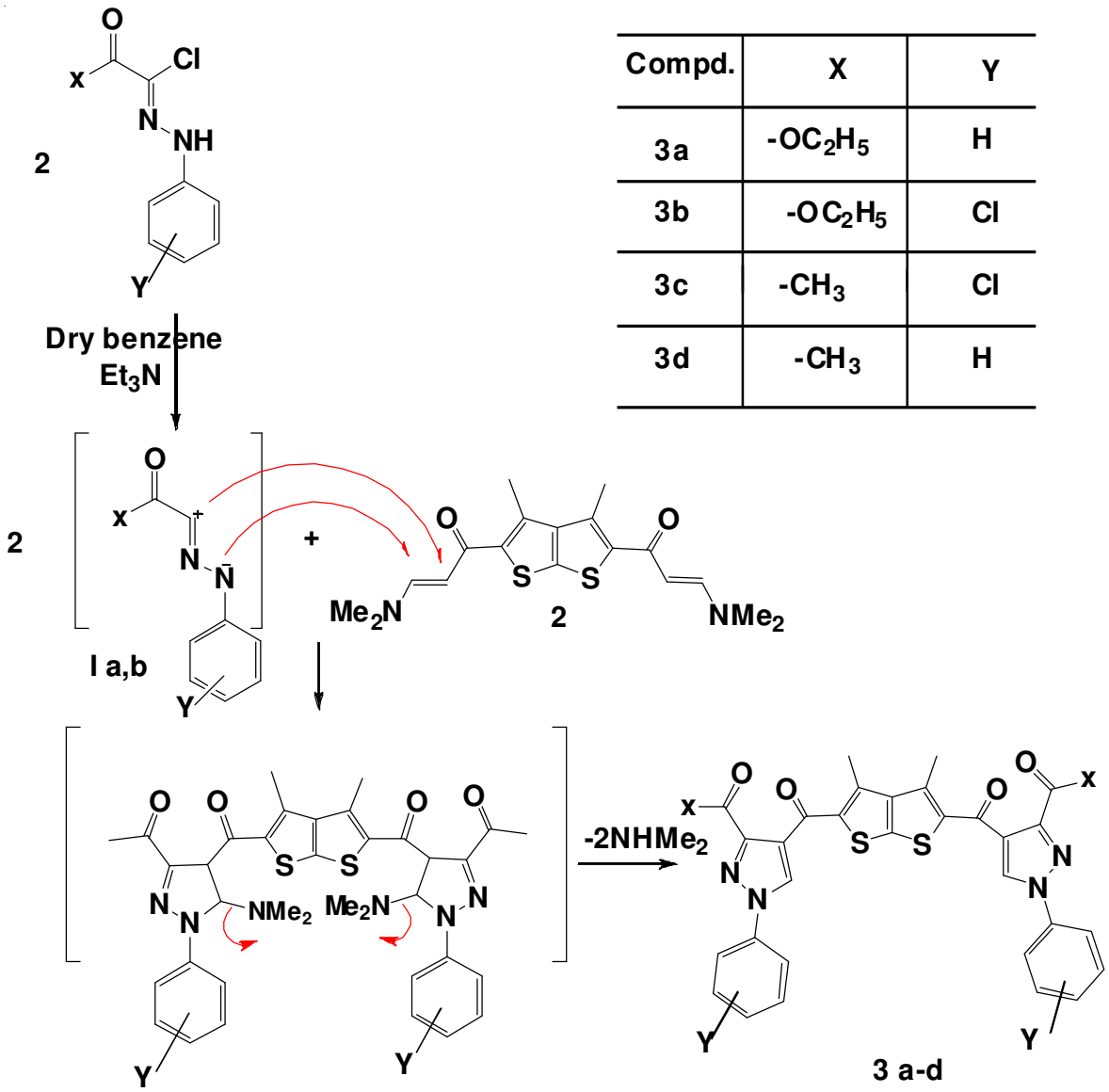
Melting point were measured on Gallenkamp melting point apparatus in open glass capillaries and are uncorrected. IR spectra were measured as KBr pellets on a Perkin Elmer FT 1000 spectrophotometer. The NMR spectra were recorded on a Varian Mercury Jeol-400 NMR spectrometer. ^{1}H NMR (400 MHz) and ^{13}C 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 arylpropanehydrazonoyl chloride derivatives (2 equiv., 1 mmol) was added in the presence of few drops of Et_3N, 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); ^{1}H NMR (400 MHz, DMSO-d_6): 1.39 (t, 3H, *J* = 6.9 Hz, CH_3, ester), 1.96 (s, 3H, CH_3), 4.31 (q, 2H, *J* = 9.6 Hz, CH_2, ester), 7.03 -7.53 (m, 5 H, Ar-H), 9.35 (s, 1H, pyrazolo-H); ^{13}C 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 $C_{34}H_{28}N_4O_6S_2$: 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-

Compd.	X	Y
3a	$-OC_2H_5$	H
3b	$-OC_2H_5$	Cl
3c	$-CH_3$	Cl
3d	$-CH_3$	H



Scheme-I

2-(2-(4-chlorophenyl)hydrazono) acetate following general procedure, yellow crystal, yield (72 %); m.p. 237-240 °C; IR (KBr, ν_{max}, cm^{-1}): 1731, 1718 2(C=O), 1634 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.30 (t, 3H, J = 6.9 Hz, CH_3, ester), 1.96 (s, 3H, CH_3), 4.25 (q, 2H, J = 16.6 Hz, CH_2, 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: $C_{34}H_{26}N_4O_6S_2Cl_2$: 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, ν_{max}, cm^{-1}): 1731, 1728, 2(C=O), 1624 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.03 (s, 3H, CH_3), 1.96 (s, 3H, CH_3), 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 $C_{32}H_{22}N_4O_4SCl_2$: 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*'-phenyl-propanehydrazonoyl chloride following general procedure, as a yellow crystal, yield (70 %); m.p. 211-214 °C; IR (KBr, ν_{max}, cm^{-1}): 1731, 1717, 2(C=O), 1622 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.03 (s, 3H, CH_3), 1.96 (s, 3H, CH_3), 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 $C_{32}H_{24}N_4O_4S_2$: 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),

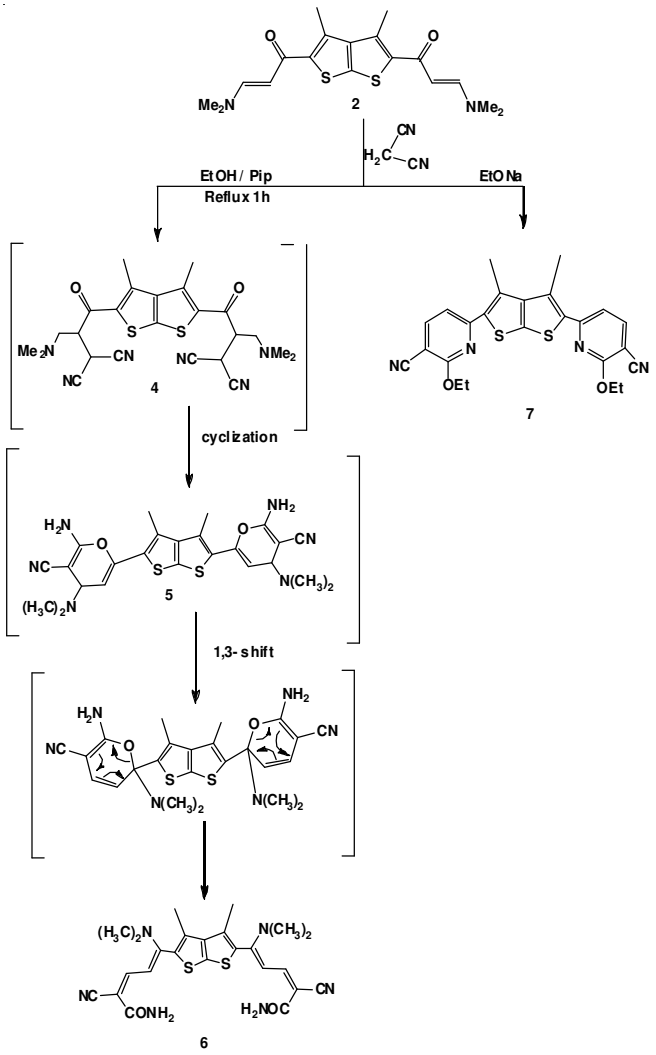
malononitrile (1 mmol, 0.07 g) was added in the presence of catalytic amount of piperidine. The reaction mixture was heated under reflux for 1 h. The solid product was collected by filtration, 8 was obtained as red crystal, yield (78 %); m.p. 175-177 °C; IR (KBr, ν_{max}, cm^{-1}): 1616 (C=O), 2123 (CN), 3364 (NH_2); ^{1}H NMR (400 MHz, 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, 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 $C_{24}H_{26}N_6O_2S_2$: 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, ν_{max}, cm^{-1}): 1573 (C=N), 2222 (CN); ^{1}H NMR (400 MHz, 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, 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 $C_{24}H_{20}N_4O_2S_2$: 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 ^{1}H 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 ^{1}H 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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