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Synthesis of Novel Heterocyclic Compounds Containing Benzofuran Moiety

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ABSTRACT

A novel series of benzofuran derivatives were synthesized via treatment of 3-(5-bromobenzofuran-2-yl)-3-oxopropanenitrile **1** with diazonium salts of heterocyclic amines **2a-e** and with aryl diazonium chlorides to give the new **3a-e** and **5a,b** derivatives, respectively . In addition, compound 1 was reacted with hydrazonoyl halides **6a**-c to give pyrazoles **8a-c**. On the other hand, 3-(benzofuran-2-yl)-3-oxopropanenitrile 9 was reacted with phenyl isothiocyanate and each of ethyl chloroacetate, chloroacetone and chloroacetonitrile to give compounds **10-12**, respectively. The structures of the newly synthesized compounds were elucidated based on their spectral data and elemental analysis, whenever possible.

Keywords: Benzofuran derivatives, 3-oxopropanenitrile, Aryldiazonium chloride, Hydrazonoyl halides

INTRODUCTION

Benzofuran derivatives are known to exhibit different pharmacological and biological activities such as antimicrobial [1-3], anti-inflammatory [4], pesticidal and insecticidal [5], anti-convulsant [6] and *in vitro* anti-HIV-1, anti-cancer, anti-microbial activities [7,8].

EXPERIMENTAL

All melting points were determined on an electrothermal apparatus and were uncorrected. IR spectra were recorded (KBr discs) on a Shimadzu FT-IR 8201 PC spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ and $(CD_3)_2SO$ solutions on a Varian Gemini 300 MHz and JNM-LA 400 FT-NMR system spectrometer and chemical shifts are expressed in ppm units using TMS as an internal reference. Mass spectra were recorded on a GC-MS QP1000 EX Shimadzu. Elemental analyses were carried out at the Microanalytical Center of Cairo University.

Synthesis of 3a-e, 5a,b, 11 and 12a-c

A solution of the appropriate diazonium salt of amines (5 mmol) was added to a mixture of 3-(5-bromobenzofuran-2-yl)-3-oxopropanenitrile or 4-(5-bromobenzofuran-2-yl)-thiazole-2-amine **10** (5 mmol) and sodium acetate (0.65 g, 5 mmol) in ethanol (30 mL) at 0-5°C while stirring. The resulting solid which formed after 2 h was collected, washed with water and recrystallized from a proper solvent to give **3a-e**, **5a,b, 11** and **12a-c**, respectively.

(E)-2-(2-(5-phenyl-1H-pyrazol-5-yl)hydrazono)-3-(5-bromobenzofuran-2-yl)-3-oxopropanenitrile 3a

Brown crystals from dioxane, yield (75%), mp: 256-259°C; IR (KBr): 3334, 3166 (2NH), 3065 (CH, aromatic), 2224 (CN), 1640 (C=O); 1H NMR δ=6.46 (s, 1H, pyrazole), 7.21-7.79 (m, 9H, ArH's); 8.81,9.24 (s, 2H, 2NH). Anal. Calcd. for $C_{20}H_{12}BrN_5O_2$ (434.25): C, 55.32; H, 2.79; Br, 18.40; N, 16.13. Found: C, 55.36; H, 2.75; Br, 18.44; N, 16.17.

(E)-2-(2-(4-phenyl-1H-pyrazol-5-yl)hydrazono)-3-(5-bromobenzofuran-2-yl)-3-oxopropanenitrile 3b

Yellow crystals from AcOH, yield (75%), mp: 260-263°C; IR (KBr): 3051 (CH, aromatic), 2230 (CN), 1658 (C=O); 1H NMR δ=6.43 (s, 1H, pyrazole), 7.21-7.72 (m, 9H, ArH's); 8.80, 9.0 (s, 2H, 2NH). Anal. Calcd. For $C_{20}H_{12}BrN_5O_2$ (434.25): C, 55.32; H, 2.79; Br, 18.40; N, 16.13. Found: C, 55.36; H, 2.75; Br, 18.44; N, 16.17.

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(E)-2-(2-(4-cyano-1H-pyrazol-5-yl)hydrazono)-3-(5-bromobenzofuran-2-yl)-3-oxopropanenitrile 3c

Brown crystals from dioxane, yield (84%), mp: >300°C; IR (KBr): 3340 (NH), 2220 (CN); ^{1}H NMR δ=7.20-7.71 (m, 7H, ArH's and 2NH). Anal. Calcd. for $C_{15}H_7BrN_6O_2$ (383.16): C, 47.02; H, 1.84; Br, 20.85; N, 21.93. Found: C, 47.06; H, 1.80; Br, 20.81; N, 21.97.

(E)-2-(2-(1H-1,2,3-triazol-1-yl)hydrazono)-3-(5-bromobenzofuran-2-yl)-3-oxopropanenitrile 3d

Brown crystals from AcOH, yield (84%), mp: 284-86°C; IR (KBr): 3300 (NH), 2215 (CN), 1675 (CO); 1H NMR δ=7.10-7.95 (m, 8H, ArH's+NH). Anal. Calcd. for $C_{13}H_7BrN_6O_2$ (359.14): C, 43.48; H, 1.96; Br, 22.25; N, 23.40. Found: C, 43.44; H, 1.92; Br, 22.21; N, 23.44.

(E)-2-(2-(1H-benzo[d]imidazol-2-yl)hydrazono)-3-(5-bromobenzofuran-2-yl)-3-oxopropanenitrile 3e

Brown powder from AcOH, yield (72%), mp: >300°C; IR (KBr): 3320, 3183 (2NH), 2224 (CN), 1668 (CO); 1H NMR δ=7.07-8.11 (m, 10H, ArH's). Anal. Calcd. For $C_{18}H_{10}BrN_5O_2$ (408.21): C, 52.96; H, 2.47; Br, 19.57; N, 17.16. Found: C, 52.92; H, 2.43; Br, 19.53; N, 17.14.

2-(benzofuran-2-yl)-2-oxo-N'-phenylacetohydrazonoyl cyanide 5a

Brown powder from AcOH, yield 85%, mp: 210-12°C; IR (KBr): 3190 (NH), 3076 (CH, aromatic), 2223 (CN), 1710 (CO): 1H NMR δ=7.20-7.96 (m, 9H, ArH's),12.46 (s,1H, NH). Anal. Calcd. for $C_{17}H_{10}BrN_3O_2$ (368.18): C, 55.46; H, 2.74; Br, 21.70; N, 11.41.

2-(benzofuran-2-yl)-2-oxo-N'-(p-tolyl)phenylacetohydrazonoyl cyanide 5b

Brown powder from EtOH, yield (83%), mp: 195-97°C; IR (KBr): 3205 (NH), 3040 (CH, aromatic), 2209 (CN), 1634 (CO); 1H NMR δ=2.40 (s, 3H, CH_3) 7.23-8.22 (m, 8H, ArH's), 15.44 (s, 1H, NH). Anal. Calcd. for $C_{18}H_{12}BrN_3O_2$ (382.21): C, 56.56; H, 3.16; Br, 20.91; N, 10.99. Found: C, 56.52; H, 3.12; Br, 20.95; N, 10.95.

Synthesis of 3-substituted 5-(benzofuran-2-yl)4-cyano-1-phenyl-1H-pyrazole 8a-c

Compound **1** (5 mmol) was added to a stirred ethanolic sodium ethoxide solution (0.12 g sodium metal in absolute ethanol 20 mL). After 20 min., the appropriate hydrazonoyl halide **6a-c** (5 mmol) was added and the reaction mixture was stirred for 4 h. The resulting solid was collected by filtration, dried and recrystallized from a proper solvent to give **8a-c**, respectively.

Ethyl-5-(bromobenzofuran-2-yl)-4-cyano-1-phenyl-1H-pyrazole-3-carboxylate 8a

Yellow crystals from ethanol. yield (83%), mp.: 193°C. FT-IR (KBr, cm^{-1}): 3066v (CH-aroma.), 2995, 2915v (CH-aliph), 2232v (CN), 1727v (CO), 1585v (C=C). 1H NMR (300 MHz, DMSO-d6, δ, ppm): 1.20 (t, 3H, J=7 Hz, CH2CH3), 4.33 (q, 2H, J=7 Hz, CH_2CH_3), 6.90 (s, 1H, CH-furan), 7.39-7.60 (m, 8H, ArH's). Anal. Calcd. for $C_{21}H_{14}BrN_3O_3$ (436.26): C, 57.82; H, 3.23; Br, 18.32; N, 9.63. Found: C, 57.86; H, 3.27; Br, 18.36; N, 9.67.

3-Acetyl-5-(bromobenzofuran-2-yl)-1-phenyl-1H-pyrazole-4-carbonitrile 8b

Yellow crystals from acetic acid; yield (79%), m.p. 244-246°C. FT-IR (KBr, cm^{-1}): 3060 v (CH-arom.), 2229 v (CN), 1697 v (CO), 1600 v (C=N). 1H NMR (300 MHz, DMSO-d6, δ, ppm): 2.60 (s, 3H, CH3), 7.00 (s, 1H, CH-furan), 7.20-7.65 (m, 8H, ArH's). Anal. Calcd. for $C_{20}H_{12}BrN_3O$ (390.23): C, 61.56; H, 3.10; Br, 20.48; N, 10.77. Found: C, 61.52; H, 3.14; Br, 20.44; N, 10.73.

3-(Bromobenzofuran-2-yl-carbonyl)-5-(benzofuran-2-yl)-1-phenyl-1H-pyrazole-4-carbonitrile 8c

Red crystals from ethanol. Yield: 80%, m.p. 227-230°C. 1H NMR (300 MHz, DMSO-d6, δ, ppm): 7.23-7.55 (m, 14H, ArH's). Anal. Calcd. for $C_{27}H_{14}BrN_3O_3$ (508.32): C, 63.80; H, 2.78; Br, 15.72; N, 8.27. Found: C, 63.84; H, 2.74; Br, 15.68; N, 8.31.

Synthesis of 10, 11a and 11b

A mixture of compound **9** (10 mmol), phenyl isothiocyanate (10 mmol) and potassium hydroxide (10 mmol) in N, N-dimethylformamide (10 mL) was stirred for 2 h at room temperature. The appropriate of ethyl chloroacetate, chloro acetyl chloride, chloroacetone or chloroacetonitrile (10 mmol) was added while stirring. Stirring was continued for 2 h. The resulting solid was collected and crystallized from a proper solvent affording **10**, **11a** and **11b**, respectively.

3-(benzofuran-2-yl)-3-oxo-2-(4-oxo-3-phenylthiazolidin-2-yl)propanenitrile 10

Brown crystals from ethanol. Yield: 81% mp: 283-285°C; FT-IR (KBr, cm^{-1}): 3062 v (CH-aroma.), 2931, 2873 v (CH-aliph.), 2182 v (CN), 1664 v (CO), 1600 v (C=N). 1H NMR (300 MHz, DMSO-d6, δ, ppm): 4.10 (s, 2H, CH_2), 6.90 (s, 1H, CH-furan) and 7.41-7.63 (m, 9H, ArH's). Anal. Calcd. for $C_{20}H_{12}N_2O_3S$ (360.39): C, 66.65; H, 3.36; N, 7.77. Found: C, 66.61; H, 3.32; N, 7.72.

3-Amino-4-(benzofuran-2-yl-carbonyl)-5-phenylamino-thiophen-2-yl)ethanone 11

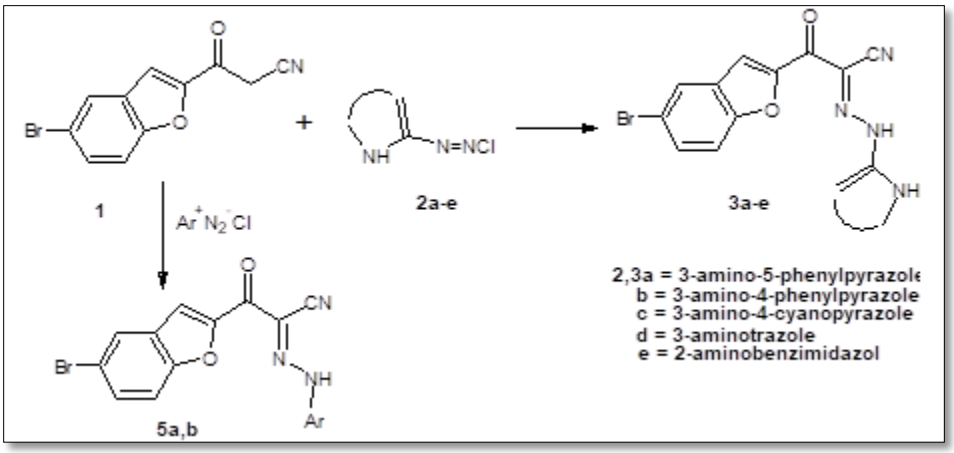
Brown crystals from ethanol. Yield 75% m.p. 280°C; FT-IR (KBr, cm^{-1}): 3240 v (NH), 3031 v (CH-arom.), 1670 (C=O), 1606 v (C=N). 1H NMR (300 MHz, DMSO-d6, δ, ppm): 4.20 (s, 2H, CH_2), 2.40 (s, 3H, CH_3), 4.20 (s, 1H, NH), 4.71 (s, 2H, NH_2), 6.90 (s, 1H, CH-furan), 7.41-7.63 (m, 9H, ArH's). Anal. Calcd. for $C_{21}H_{16}N_2O_3S$ (376.43): C, 67.00; H, 4.28; N, 7.44; S, 8.52. Found: C, 67.13; H, 4.15; N, 7.37; S, 8.67.

2-(benzofuran-2-yl-carbonyl)-3-phenylamino-3(cyanomethylthio)acrylonitrile 12

Brown crystals from ethanol. Yield 75% mp. 160°C; FT-IR (KBr, cm^{-1}): 3128 v (NH), 3058 v (CH-aroma.), 2175 v (CN) 1H NMR (300 MHz, DMSO-d6, δ, ppm): 4.20 (s, 2H, CH2), 4.20 (s, 1H, NH), 6.81 (s, 1H, CH-furan) , 7.40-7.59 (m, 9H, ArH's). Anal. Calcd. for $C_{20}H_{13}N_3O_2S$ (359.4): C, 66.84; H, 3.65; N, 11.69. Found: C, 66.70; H, 3.55; N, 11.59.

RESULTS AND DISCUSSION

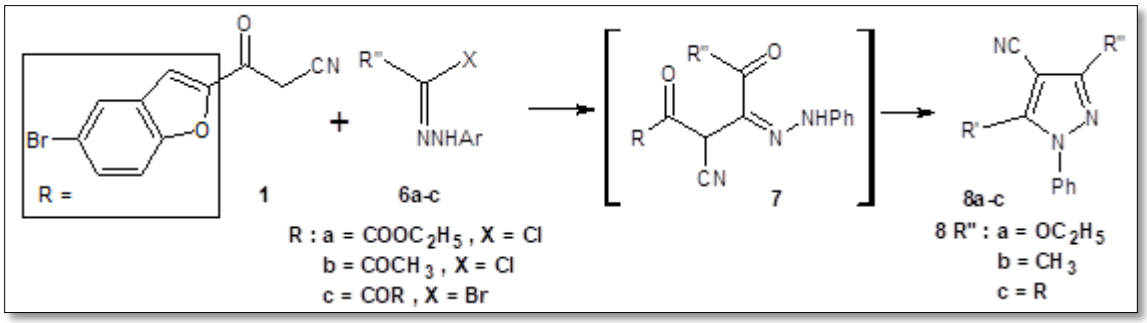
Treatment of 3-(5-bromobenzofuran-2-yl)-3-oxo propanenitrile 1 with diazonium salt of heterocyclic amines **2a-e** in ethanol containing sodium acetate solution under stirring afforded **3a-e**, respectively **(Scheme 1)**. The structures of the products were confirmed on the basis of elemental analysis, spectral data. Thus, 1HNMR of **3a** revealed signals at δ=6.48 (s, 1H, pyrazole), 7.21-7.79 (m, 9H, ArH's); 8.81, 9.24 (s, 2H, 2NH).



Scheme 1. Treatment of 3-(5-bromobenzofuran-2-yl)-3-oxo propanenitrile 1 with diazonium salt of heterocyclic amines.

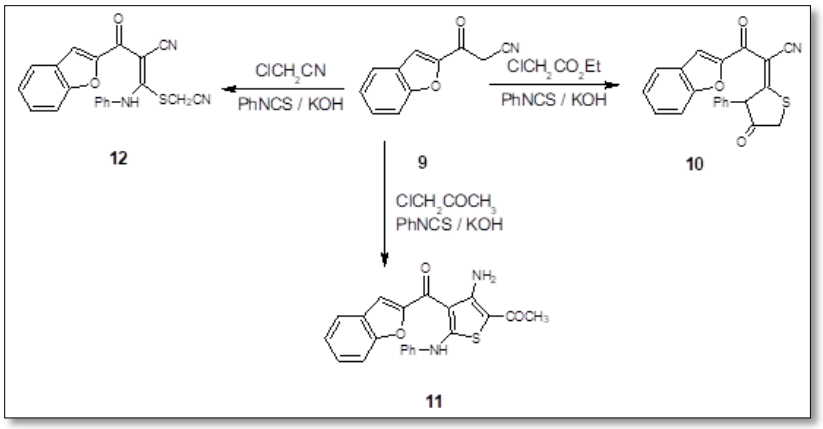
In a similar manner, compound **1** reacted with each of benzenediazonium chloride and 4-methyl benzenediazonium chloride in ethanol containing sodium acetate to afford **5a** and **5b**, respectively **(Scheme 1)**. The structure of **5a,b** were confirmed based on elemental analysis and spectral data.

Furthermore, treatment of compound **1** with three different hydrazonoyl halides [9-12] **6a-c** gave products generally assigned as 3-substituted 5-(5-bromobenzofuran-2-yl)-4-cyano-1-phenyl-1H-pyrazole derivatives **8a-c** on the basis of their analytical and spectral data **(Scheme 2).**



Scheme 2. Treatment of compound 1 with three different hydrazonoyl halides.

On the other hand, 3-(benzofuran-2-yl)-3-oxopropanenitrile [13,14] **9** reacted with phenyl isothiocyanate and ethyl chloroacetate in N,N-dimethylformamide under stirring at room temperature affording 3-(benzofuran-2-yl)-3-oxo-2(4-oxo-3-phenylthiazolidin-2-ylidene)propanenitrile **10 (Scheme 3)**. The IR spectra of **10** displayed an absorption band at 2931, 2873 v (CH-aliph.), 2171 v (CN) and 1660 v (C=O). It's ^1H NMR in (DMSO-d_6) revealed signals at δ 4.10 (s, 2H, CH^2), 6.90 (s, 1H, CH-furan), 7.41-7.63 (m, 9H, ArH's). In a similar manner, compound **9** reacted with phenyl isothiocyanate and each of chloroacetone and chloroacetonitrile yielding 2-(benzofuran-2-yl-carbonyl)-3-phenylamino-3-(acetylmethylthio)propanenitrile **11** and 2-(benzofuran-2-yl-carbonyl)-3-phenyl amino-3(cyanomethylthio) propanenitrile **12**, respectively **(Scheme 3)**.



Scheme 3. Treatment of compound **9** with phenyl isothiocyanate and each of chloroacetone and chloroacetonitrile.

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