

Synthesis of Novel Heterocyclic Compounds Containing Benzofuran Moiety

Basma S Baaue, Khalid M Darwish* and Hussniya Al-Difar

*Department of Chemistry, Faculty of Science, University of Benghazi, Libya.

Received January 10, 2019; Accepted January 21, 2019; Published May 09, 2019

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. ¹H and ¹³C NMR spectra were recorded in CDCl₃ and (CD₃)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 C₂₀H₁₂BrN₅O₂ (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 C₂₀H₁₂BrN₅O₂ (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.

Corresponding author: Khalid M Darwish, Department of Chemistry, Faculty of Science, University of Benghazi, Libya, Tel: 00218945693580; E-mail: kdarwish1962@gmail.com

Citation: Baaue BS, Darwish KM & Al-Difar H. (2019) Synthesis of Novel Heterocyclic Compounds Containing Benzofuran Moiety. J Pharm Drug Res, 2(3): 120-123.

Copyright: ©2019 Baaue BS, Darwish KM & Al-Difar H. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

(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); ¹H NMR δ=7.20-7.71 (m, 7H, ArH's and 2NH). Anal. Calcd. for C₁₅H₇BrN₆O₂ (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 C₁₃H₇BrN₆O₂ (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 C₁₈H₁₀BrN₅O₂ (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 C₁₇H₁₀BrN₃O₂ (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, CH₃), 7.23-8.22 (m, 8H, ArH's), 15.44 (s, 1H, NH). Anal. Calcd. for C₁₈H₁₂BrN₃O₂ (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, CH₂CH₃), 6.90 (s, 1H, CH-furan), 7.39-7.60 (m, 8H, ArH's). Anal. Calcd. for C₂₁H₁₄BrN₃O₃ (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 C₂₀H₁₂BrN₃O (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 C₂₇H₁₄BrN₃O₃ (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, chloroacetyl 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, CH₂), 6.90 (s, 1H, CH-furan) and 7.41-7.63 (m, 9H, ArH's). Anal. Calcd. for C₂₀H₁₂N₂O₃S (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

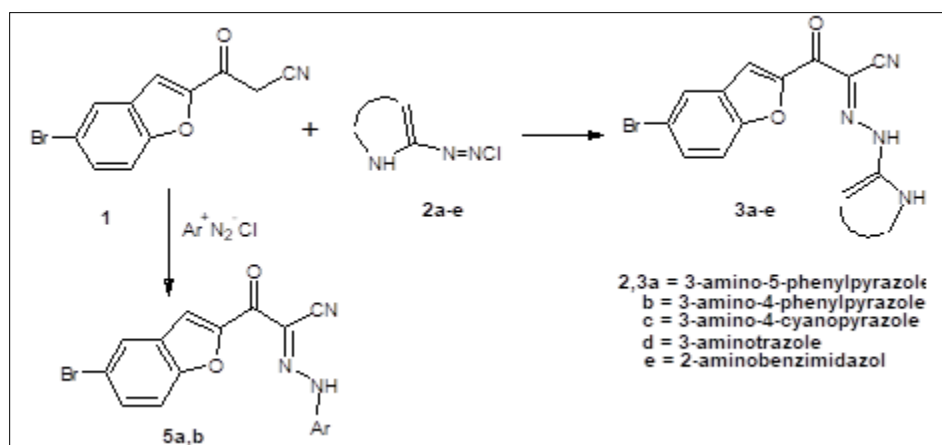
Brown crystals from ethanol. Yield 75% m.p. 280°C; FT-IR (KBr, cm⁻¹): 3240 v (NH), 3031 v (CH-arom.), 1670 (C=O), 1606 v (C=N). ¹H NMR (300 MHz, DMSO-d₆, δ, ppm): 4.20 (s, 2H, CH₂), 2.40 (s, 3H, CH₃), 4.20 (s, 1H, NH), 4.71 (s, 2H, NH₂), 6.90 (s, 1H, CH-furan), 7.41-7.63 (m, 9H, ArH's). Anal. Calcd. for C₂₁H₁₆N₂O₃S (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- d_6 , 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 $\text{C}_{20}\text{H}_{13}\text{N}_3\text{O}_2\text{S}$ (359.4): C, 66.84; H, 3.65; N, 11.69. Found: C, 66.70; H, 3.55; N, 11.59.

RESULTS AND DISCUSSION

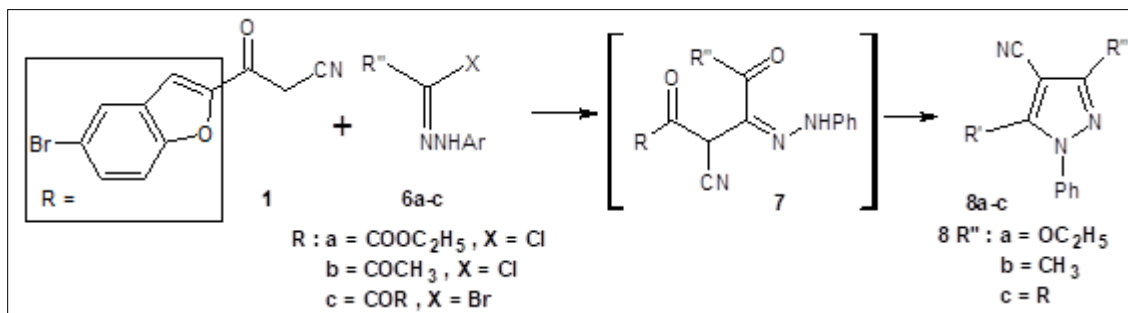
Treatment of 3-(5-bromobenzofuran-2-yl)-3-oxo propanenitrile **1** with diazonium salt of heterocyclic amines **2a-e** in ethanol containing sodium acetate solution under stirring afforded **3a-e**, respectively (Scheme 1). The structures of the products were confirmed on the basis of elemental analysis, spectral data. Thus, ^1H NMR of **3a** revealed signals at $\delta=6.48$ (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.

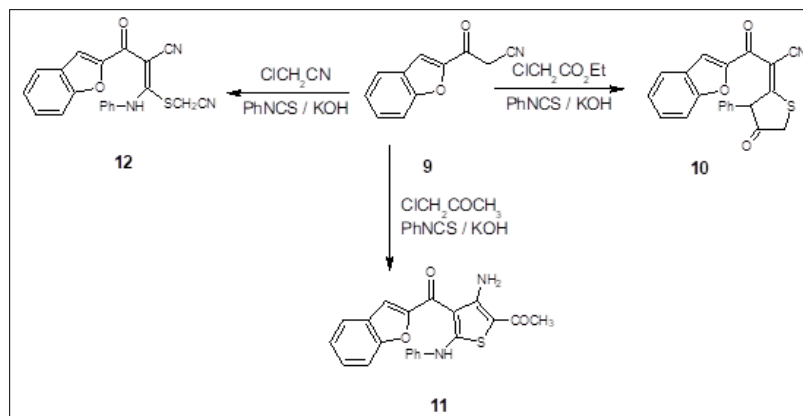
Furthermore, treatment of compound **1** with three different hydrazonoyl halides [9-12] **6a-c** gave products generally assigned as 3-substituted 5-(5-bromobenzofuran-2-yl)-4-cyano-1-phenyl-1H-pyrazole derivatives **8a-c** on the basis of their analytical and spectral data (Scheme 2).



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, CH₂), 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-phenylamino-3(cyanomethylthio) propanenitrile **12**, respectively (Scheme 3).



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

REFERENCES

1. Abdel-Aziem A (2015) An efficient and simple synthesis of 2,3-dihydro-1,3,4-thiadiazoles, pyrazoles and coumarins containing benzofuran moiety using both conventional and grinding methods. *Int J Pharm Sci* 7: 32.
2. Abdel-Aziem A, Abdelhamid A O (2013) One pot synthesis of pyridine, thiazolidine, pyrazole and 2, 3-dihydro-1, 3, 4-thiadiazole derivatives under solvent-free condition. *Int J Adv Res* 9: 717-728.
3. Halawa AH (2014) Synthesis, reactions and biological evaluation of some novel 5-bromobenzofuran-based heterocycles. *World J Org Chem* 2: 9-17.
4. Santana L, Teijeira M, Uriarte E, Teran C, Linares B, et al. (1998) AM1 theoretical study, synthesis and biological evaluation of some benzofuran analogues of anti-inflammatory aryl alcanoic acids. *Eur J Pharm Sci* 7: 161-166.
5. Findlay JA, Buthelezi S, Li G, Seveck M (1997). Insect toxin from an endophytic fungus from wintergreen. *J Nat Prod* 60: 1214-1215.
6. Dawood KM, Abdel-Gawad H, Rageb EA, Ellithey M, Mohamad HA (2006) Synthesis, anti-convulsant and anti-inflammatory evaluation of some new benzotriazole and benzofuran based heterocycles. *Bioorg Med Chem* 14: 3672-3680.
7. Rida SM, El-Hawash SAM, Fahmy HTY, Hazzaa AA, EIMeligy MMM (2006) Synthesis of novel benzofuran and related benzimidazole derivative for evaluation of *in vitro* anti-HIV-1, anticancer and antimicrobial activities. *Arch Pharm Res* 29: 826-833.
8. Raj PA, Suddendra G, Shakeeland AS, Girish M (2012) Synthesis of new benzofuran derivatives and their *in vitro* evaluation for antimicrobial activity. *Inter J Drug Formulation Res* 3: 135-147.
9. Eweiss NE, Osman A (1979) Synthesis of heterocycles. One step synthesis of acetyl thiadiazolines. *Tetrahedron Lett* 13: 1169-1170.
10. Shawali AS, Abdelhamid AO (1976) Reaction of dimethylphenacylsulfonium bromide with N-nitrosoacetarlamides and reactions of the products with nucleophiles. *Bull Soc Chim Jpn* 49: 321-324.
11. Shawali AS, Osman A (1971) Synthesis and reactions of phenylcarbamoxy-arylhydrazidic chlorides. *Tetrahedron* 27: 2517-2528.
12. Abdelhamid AO, Attaby FA, Zaki MY (1990) Reactions with 2-(thiocyanatoacetyl) and 2-(selenacyanoacetyl)-2-benzofuran. Synthesis of some new thiadiazoline, selenadiazoline, thiadiazolo[2,3-b]quinazoline and arylazothiazole derivatives. *Phosphorous, Sulfur, Silicon and Related Element* 53: 403-410.
13. Yilmaz M, Uzunalioglu N, Pekel AT (2005) Manganese (III) acetate based oxidative cyclizations of 3-oxopropanenitriles with conjugated alkenes and synthesis of 4,5-dihydrofuran-3-carbonitriles containing heterocycles. *Tetrahedron* 61: 8860.
14. Yılmaz EVB, Yılmaz M, Oktemer A (2011) Radical cyclizations of conjugated esters and amides with 3-oxopropanenitriles mediated by manganese (III) acetate. *Arkivoc* 2: 363-376.