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ORIGINAL PAPER

A simple procedure for the synthesis of novel 3-(benzofur-2-yl)pyrazole-based heterocycles

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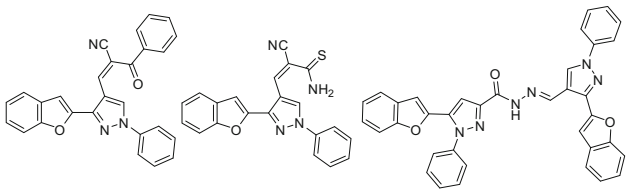
Abstract 3-(Benzofuran-2-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde was used, as a precursor for the synthesis of a series of novel heterocycles by facile reactions with 3-oxo-3-phenylpropanenitrile, 2-cyanoethanethioamide, and various hydrazides such as cyanoacetohydrazide, acetohydrazide, and carbohydrazide derivatives. The structures of the products were confirmed by various spectroscopic methods along with the X-ray crystal structures.

Graphical Abstract



Keywords 2-Substituted benzofuran · Pyrazole-4-carbaldehyde · Carbohydrazide · Heterocycles · Synthesis

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Introduction

Compounds containing benzofuran moieties are important constituent of many fused heterocycles in which many derivatives have been isolated from natural sources and show various biological activities (Abdel-Wahab et al. 2009; Asif 2016; Dawood et al. 2006; Hiranita et al. 2010; Hiremathad et al. 2015; Khanam 2015; Naik et al. 2015; Rickli et al. 2015; Saha et al. 2011). Various synthetic approaches are known to afford substituted benzofurans (Abdel-Aziem 2015; Abd El-Wahab et al. 2011; Abu-Hashem et al. 2014; Kadieva and Oganesyan 1997; Kumar and Sharma 2016; Liu et al. 2016; Weissberger and Taylor 1974; Wu et al. 2016; Yeung 2012; Zhou et al. 2010). The most common traditional methods involve the reaction of salicylaldehyde and chloroacetic acid (Burgstahler and Worden 1966), Perkin rearrangement of coumarin (Perkin 1871), and cyclization of 2-alkyne phenols (Fürstner and Davies 2005). The most recent examples of high yielding synthesis of 2-alkyl/benzyl benzofurans involve the cyclization of 2-styryl phenols at room temperature in acetonitrile for 1–3 h in the presence of stoichiometric amounts of (diacetoxyiodo) benzene (Singh and Wirth 2012), cyclization of 1-allyl-2-allyloxybenzenes at 90 °C in toluene for 3 h in the presence of a ruthenium catalyst (van Otterlo et al. 2005), cross-coupling of 2-iodophenols and substituted acetylene in the presence of palladium nanoparticles in a mixture of methanol and acetonitrile at 60 °C (Mandali and Chand 2015), and cyclization of 2-(1-hydroxyprop-2-ynyl)phenols in the presence of palladium acetate and cesium carbonate as catalysts in acetonitrile (Rajesh et al. 2015). In addition, 2-arylbenzofurans can be obtained in high yields from the reaction of arylboronic acids or potassium aryl trifluoroborates (two mole equivalents) and aliphatic nitriles in aqueous tetrahydrofuran in

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the presence of palladium acetate as a catalyst and excess trifluoroacetic acid (Wang et al. 2013a, b). Moreover, the reaction of phenols with diols or bromoalkynes at high temperatures in the presence of a catalyst gave high yields of 2-substituted benzo[*b*]furans (Lee et al. 2012; Wang et al. 2011).

Recently, we have reported the synthesis of a variety of heterocycles (Abdel-Wahab et al. 2016; Abdel-Megeed et al. 2012a, b; Baashen et al. 2016; Bekheit et al. 2016) as a part of our program in preparation of bioactive heterocycles. The current work deals with the synthesis of novel benzofur-2-ylpyrazoles in which 3-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde was used as the starting material.

Results and discussion

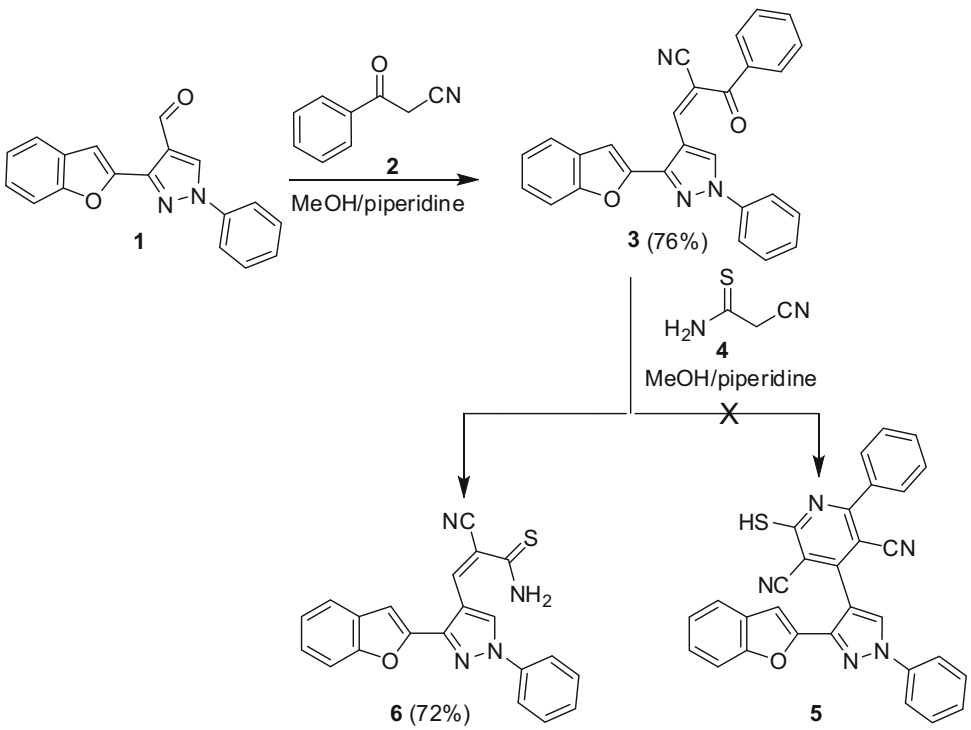
The reaction of equimolar quantities of **1** (Kumar et al. 2007; El-Zahar et al. 2009) with a molar equivalent of **2** in dry ethanol under reflux condition for 3 h, in the presence of piperidine as a base, gave the corresponding benzofuran **3** in 76% yield (Scheme 1). In an attempt to synthesize pyridine-3,5-dicarbonitrile derivative **5** through Michael addition of 2-cyanoethanethioamide (**4**) to **3**, the unexpected product **6** was obtained instead in 72% yield (Scheme 1). In addition, product **6** was obtained in 84% yield from direct reaction between **1** and **4**.

IR spectrum of **6** shows a characteristic absorption band (2213 cm^{-1}) due to the nitrile group. In addition, its ^1H NMR spectrum shows an exchangeable singlet corresponding to the NH_2 protons (10.22 ppm). The structure of **6** was established further by the X-ray crystallography (Fig. 1).

Formation of **6** could involve a retro-aldol reaction that takes place first for **3** to produce intermediates **7** and **8**. Intermediate **8** yields the anion of **2** as a leaving group along with intermediate **9**. Reaction of **9** with the thioamide anion, in the sense of an aldol reaction, affords **6** via intermediate **10** (Scheme 2).

Reaction of **1** with 2-cyanoacetohydrazide (**11**; two mole equivalents) in dry, boiling methanol containing acetic acid gave benzofuran **12** in 83% yield (Scheme 3). Compound **12** was previously synthesized under similar reaction condition but in acetic acid (Abdel-Aziem 2015). However, the physical and spectroscopic data for compound **12** are not exactly the same as the reported ones. For example, the ^1H NMR spectrum of **12** shows a characteristic singlet (4.21 ppm) due to the methylene protons compared to 3.98 ppm for the reported one. In addition, the electron impact mass spectrum of **12** shows an intense molecular ion peak at *m/z* 369 compared to *m/z* 368 (M − 1) for the reported one Condensation of **12** with **1** in boiling methanol in the presence of piperidine gave substituted benzofuran **13** in 80% yield (Scheme 3). The

Scheme 1 Synthetic routes to new thioamide derivative 6



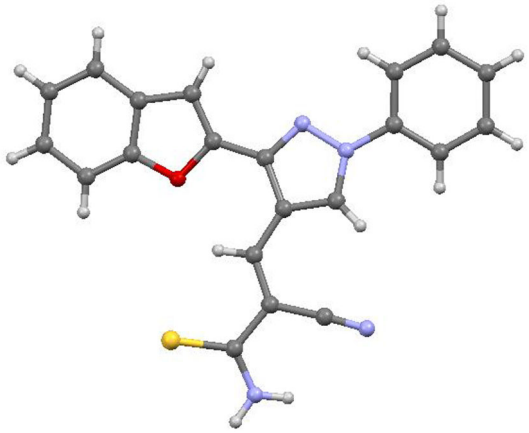


Fig. 1 X-ray structure of compound 6

electron impact mass spectrum of **13** shows an intense molecular ion peak at *m/z* 639 .

In a similar manner, reaction of **1** with cyanoacetohydrazides **14a–c** in boiling methanol containing piperidine afforded acrylohydrazides **15a–c** in 84–87% yields (Scheme 4). The IR spectra of **15** show the presence of the carbonitrile groups that appear within the 2217–2220 cm^{-1} region. The ^1H NMR spectra of **15** show singlet signals (2.10–2.36 ppm) due to the methyl protons .

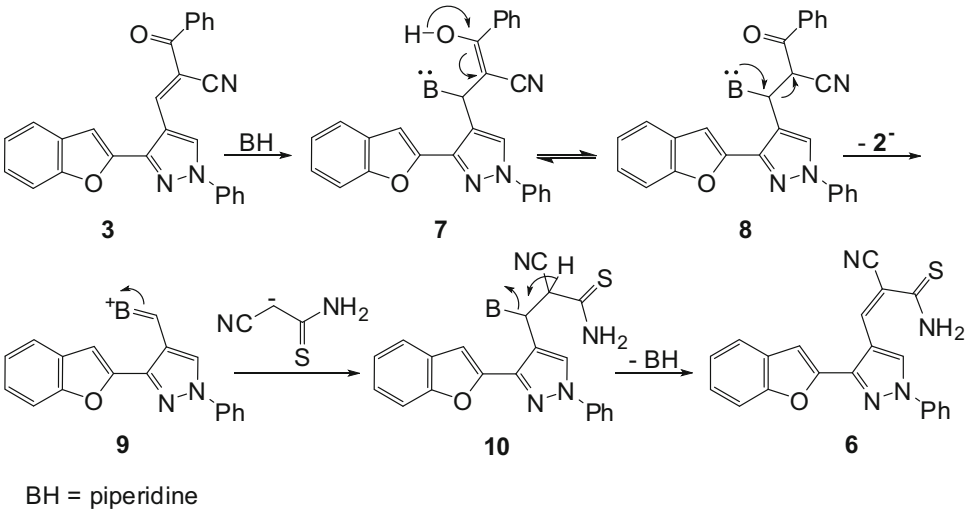
Reaction of **1** with acetohydrazide **16** gave the corresponding hydrazone **17** in 86% yield (Scheme 5). The ^1H NMR spectrum of **17** shows a characteristic singlet (8.74 ppm) and an exchangeable singlet (11.43 ppm) due to the CH=N and NH protons, respectively.

Finally, the reaction of **1** with carbohydrazide **18** gave the corresponding hydrazone **19** in 85% yield (Scheme 6). The ^1H NMR spectrum of **19** shows a singlet (8.87 ppm) and an exchangeable singlet (10.22 ppm) due to the CH=N proton and NH proton, respectively. In addition, the X-ray crystallography (Fig. 2) confirmed the structure of **19**.

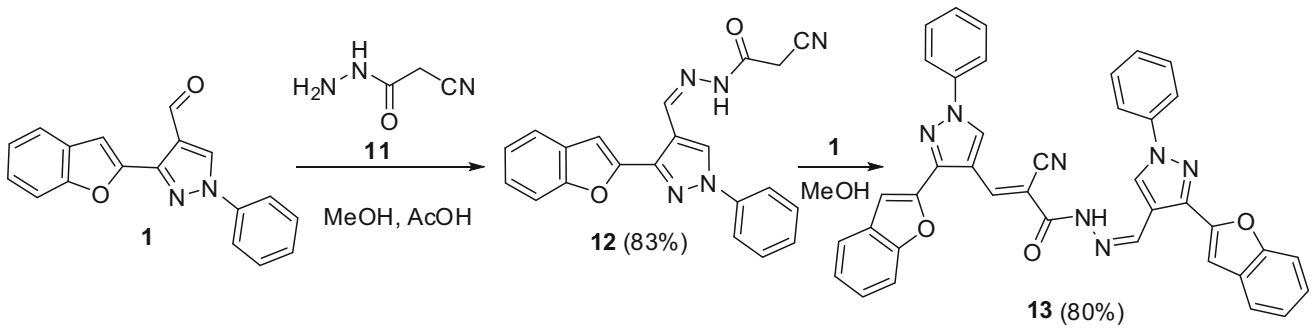
Experimental

General

The melting points were taken on Electrothermal IA 9000 series digital melting point apparatus. The IR spectra (KBr) were recorded on a Shimadzu CVT-04 spectrophotometer. The ^1H NMR spectra were measured in DMSO-d_6 on a JEOL E.C.A-500 MHz spectrometer in which tetramethylsilane was used as internal standard. The mass spectra were determined using a Varian MAT CH-5 spectrometer (70 eV). Compounds **1** (Kumar et al. 2007), **14a** (Mohareb

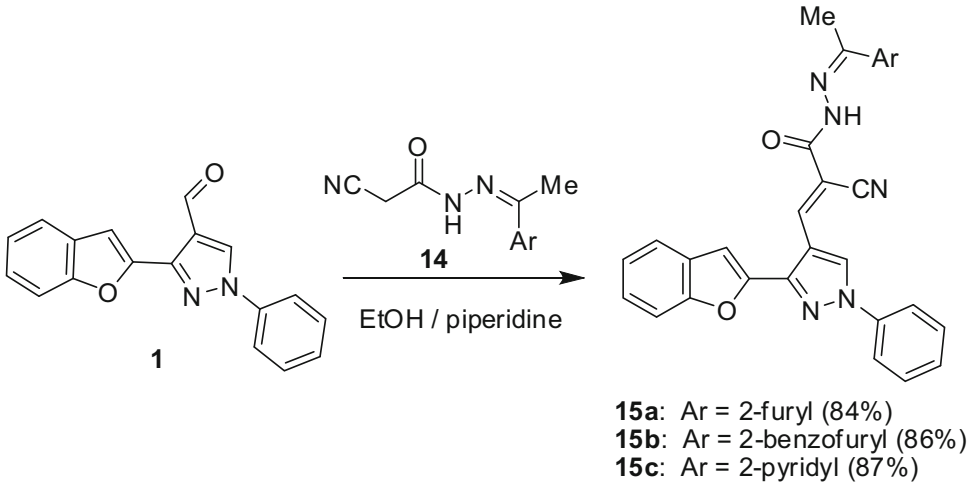


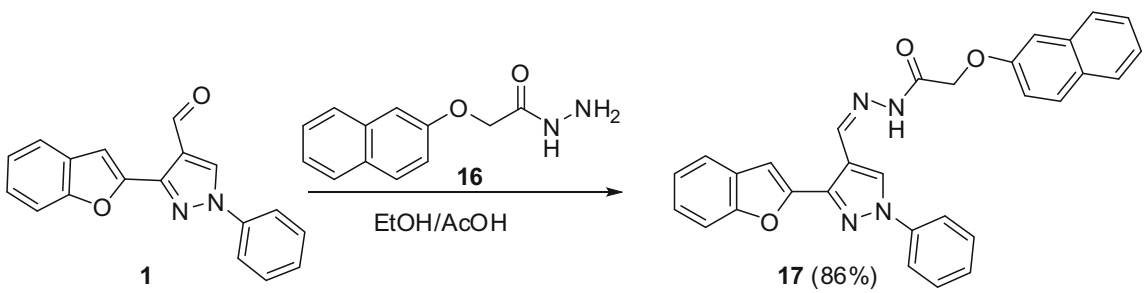
Scheme 2 Proposed mechanism for the formation of compound 6



Scheme 3 Synthetic access to new 2-cyanoacrylohydrazide 10

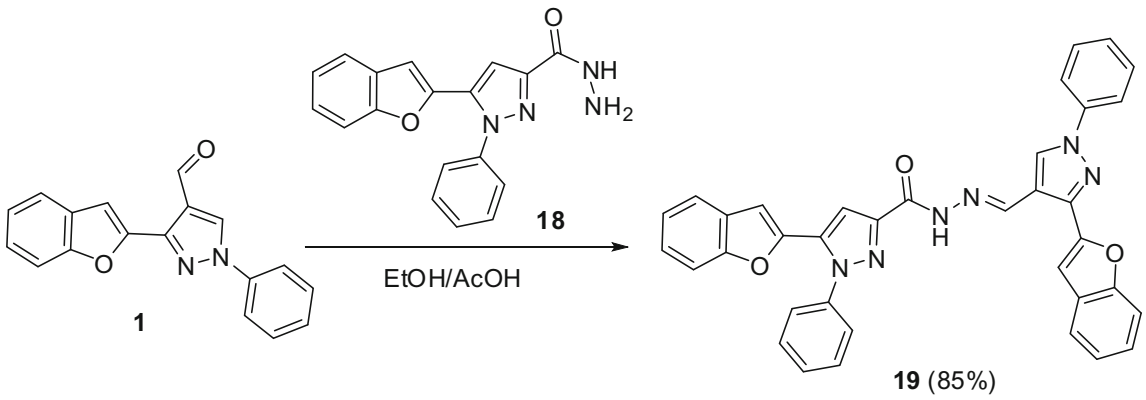
Scheme 4 Synthesis of novel acrylohydrazides 12a–c





Scheme 5 Synthetic route to novel acetohydrazide 15

et al. 2009), **14b** (Rida et al. 2005), **14c** (Zhang et al. 2012), **16** (Mullican et al. 1993), **18** (Abdel-Wahab et al. 2008) were synthesized based on the reported procedures. The Crystallographic data for compounds **6** and **19** were deposited at the Cambridge Crystallographic Data Center as CCDC1531680 and CCDC1531681, respectively.



Scheme 6 Synthetic access to novel carbohydrazide 16

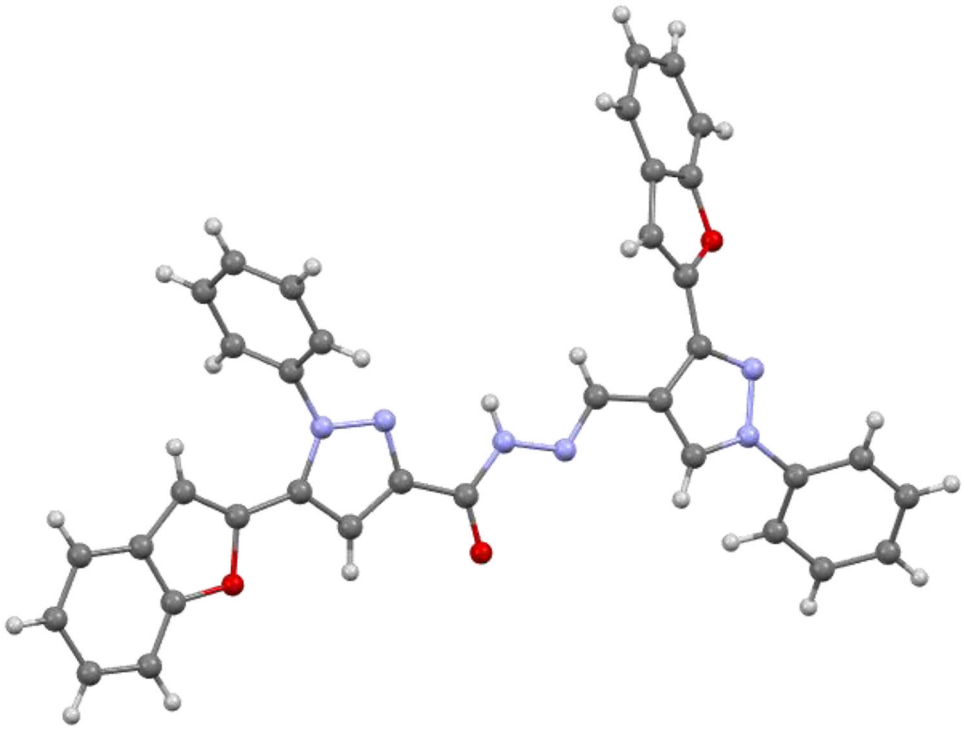


Fig. 2 X-ray structure of compound 16

*Synthesis of 3-(benzofuran-2-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde (**1**)*

Phosphorus oxychloride (20 mL) was added dropwise to a stirred dimethyl formamide (150 mL) at 0–5 °C. (1-Benzofuran-2-yl)ethylidene-2-phenyl hydrazine (23.53 g, 0.0940 mol) was added to the mixture in a portion-wise manner. The mixture was stirred overnight at room temperature, poured onto ice-cold water and neutralized with ammonium hydroxide solution (5%). The solid produced was filtered, dried, and crystallized from acetic acid to give **1** (24.39 g, 0.0846 mmol; 90%), Mp 160–162 °C (lit. 116–118 °C; Kumar et al. 2007; lit. 160–162 °C; El-Zahar et al. 2009).

*Synthesis of 3-(3-(benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)-2-benzoylacrylonitrile (**3**)*

A mixture of **1** (1.44 g, 5.00 mmol) and **2** (0.72 g, 5.00 mmol), piperidine (0.3 mL, 3.04 mmol), and dry EtOH (30 mL) was refluxed for 3 h. The solid obtained was filtrated, dried, and crystallized from EtOH to give pure **3** (1.58 g, 3.80 mmol; 76%). Mp 255–256 °C. IR (KBr) ν_{max}/cm^{-1} 1650 (C=O), 2227 (CN). ^{1}H NMR: δ 7.41–7.98 (m, 15H, Ar–H), 8.60 (s, 1H, CH), 9.31 (s, 1H, CH-pyrazole). ^{13}C NMR: δ 106.6, 109.3, 111.2, 114.9, 116.8, 119.9, 121.9, 123.8, 125.8, 127.6, 128.6, 129.1, 129.9, 130.0, 132.9, 134.6, 136.0, 138.3, 145.8, 146.6, 148.0, 154.4, 190.2. MS (EI) *m/z* (%): 415 (M^{+}, 32), 57

(100). Anal. Calcd. for $C_{27}H_{17}N_3O_2$ (415.44): C, 78.06; H, 4.12; N, 10.11%. Found: C, 78.23; H, 4.40; N, 10.35%.

*Synthesis of 3-(3-(benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)-2-cyanoprop-2-enethioamide (**6**)*

Method A A mixture of **3** (0.83 g, 2.00 mmol), **4** (0.2 g, 2.00 mmol), piperidine (0.3 mL, 3.04 mmol), and dry EtOH (30 mL) was refluxed for 5 h. The solid obtained was filtrated, dried, and crystallized from DMF to give pure **6** (0.53 g, 1.44 mmol; 72%). Mp 205–206 °C. IR (KBr) ν_{max}/cm^{-1} 1342 (C=S), 2213 (CN), 3286–3343 (NH_2). ^1H NMR: δ 7.34–8.00 (m, 10H, Ar–H), 8.48 (s, 1H, CH), 9.43 (s, 1H, CH-pyrazole), 10.22 (s, exch., 2H, NH_2). ^{13}C NMR: δ 106.9, 111.6, 114.8, 116.8, 119.4, 119.7, 121.9, 123.7, 125.7, 127.9, 127.9, 128.3, 129.5, 129.8, 129.9, 137.8, 138.5, 144.9, 147.7, 154.5, 191.4. MS (EI) *m/z* (%): 371 ($M^+ + 1$, 43), 370 (M^+, 56), 57 (100). Anal. Calcd. for $C_{21}H_{14}N_4OS$ (370.43): C, 68.09; H, 3.81; N, 15.12%. Found: C, 68.32; H, 3.98; N, 15.53%. Selected crystallographic data: orange plates, $C_{21}H_{14}N_4OS$, FW = 370.42, T = 296(2) k, λ = 0.71073 Å, triclinic, space group P1, a = 5.8807(8) Å, b = 9.2390(11) Å, c = 16.4270(2) Å, α = 89.882(10)°, β = 82.806(10)°, γ = 77.795(11)°, V = 865.2(2) Å^3, Z = 2, $\rho_{calc.}$ = 1.421 Mg/m^{-3}, crystal size = 0.45 × 0.29 × 0.03 mm, m = 0.021 mm^{-1}, reflections collected = 3550, independent reflections = 5319, R = 0.075, wR = 0.196, R(int) = 0.033. CDC1531680.

Method B A mixture of **1** (0.57 g, 2.00 mmol), **4** (0.2 g, 2.00 mmol), piperidine (0.3 mL, 3.04 mmol), and dry EtOH (30 mL) was refluxed for 3 h. The solid obtained was filtrated, dried, and crystallized from EtOH to give pure **6** (0.61 g, 1.64 mmol; 84%). The spectroscopic and analytical data were similar to those obtained for **6** using method A.

*N'-((3-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-2-cyanoacetohydrazide (**12**)*

A mixture of **1** (1.44 g, 5.00 mmol), **11** (0.50 g, 5.00 mmol), glacial AcOH (0.5 mL, 8.74 mmol), and dry MeOH (20 mL) was refluxed for 1 h. The formed solid was collected by filtration and dried to give pure **12** (1.53 g, 4.14 mmol; 83%). Mp 215–217 °C (lit 228–230 °C; Abdel-Aziem 2015). IR (KBr) ν_{max}/cm^{-1} 1686 (C=O), 1612 (C=N), 2215 (CN), 3282 (NH). ^1H NMR: δ 4.21 (s, 2H, CH_2), 7.39–8.10 (m, 10H, Ar–H), 8.61 (s, 1H, CH), 9.33 (s, 1H, CH-pyrazole), 11.78 (s, exch., 1H, NH). MS (EI) *m/z* (%): 370 ($M^+ + 1$, 100), 369 (M^+, 85). Anal. Calcd. for $C_{21}H_{15}N_5O_2$ (369.38): C, 68.28; H, 4.09; N, 18.96%. Found: C, 68.39; H, 4.18; N, 19.21%.

*3-(3-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)-N'-((3-(benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-2-cyanoacrylohydrazide (**13**)*

A mixture of **12** (0.37 g, 1.00 mmol), **1** (0.29 g, 1.00 mmol), piperidine (0.3 mL, 3.04 mmol), and dry EtOH (30 mL) was refluxed for 1 h. The solid product formed on cooling was collected by filtration and dried to give pure **13** (0.51 g, 0.80 mmol; 80%). Mp 237–238 °C. IR (KBr) ν_{max}/cm^{-1} 1598 (C=O), 2223 (CN), 3280 (NH). ^1H NMR: δ 7.41–8.10 (m, 20H, Ar–H), 8.45 (s, 1H, CH), 8.56 (s, 1H, CH), 8.95 (s, 1H, CH-pyrazole), 9.34 (s, 1H, CH-pyrazole), 11.13 (s, exch., 1H, NH). ^{13}C NMR: 158.0, 155.2, 154.9, 150.2, 147.4, 145.7, 143.0, 141.4, 140.4, 139.9, 136.3, 130.3, 130.23, 130.19, 129.0, 128.8, 128.0, 126.9, 126.2, 125.7, 125.5, 123.9, 123.3, 119.5, 118.8, 111.7, 108.3, 106.7, 106.6. MS (EI) *m/z* (%): 640 ($M^+ + 1$, 42), 639 (M^+, 100). Anal. Calcd. for $C_{39}H_{25}N_7O_3$ (639.66): C, 73.23; H, 3.94; N, 15.33%. Found: C, 73.47; H, 4.09; N, 15.52%.

*Synthesis of **15*** A mixture of **1** (0.29 g, 1.00 mmol), **14** (1.00 mmol), piperidine (0.3 mL, 3.04 mmol), and dry EtOH (30 mL) was refluxed for 2 h. The solid formed on cooling was filtrated and dried to give pure **15**.

*3-(3-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)-2-cyano-N'-(1-(furan-2-yl)ethylidene)acrylohydrazide (**15a**)*

Yield 84% (0.39 g, 0.84 mmol); Mp 235–237 °C. IR (KBr) ν_{max}/cm^{-1} 1608 (C=O), 2220 (CN), 3240 (NH). ^1H NMR: δ 2.36 (s, 3H, CH_3), 6.89–7.97 (m, 13H, Ar–H), 8.53 (s, 1H, CH), 9.35 (s, 1H, CH-pyrazole), 10.55 (s, exch., 1H, NH).^{13}C NMR: δ 11.7, 103.9, 106.2, 109.1, 110.8, 115.8, 111.6, 112.9, 119.3, 121.3, 123.3,124.6, 125.1, 126.2, 127.2, 127.8, 129.4, 137.9, 139.7, 141.6, 143.2, 144.9, 147.4 153.9, 190.2. MS (EI) *m/z* (%): 462 ($M^+ + 1$, 100), 461 (M^+, 35). Anal. Calcd. for $C_{27}H_{19}N_5O_3$ (461.47): C, 70.27; H, 4.15; N, 15.18%. Found: C, 70.38; H, 4.31; N, 15.37%.

*3-(3-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)-N'-(1-(benzofuran-2-yl)ethylidene)-2-cyanoacrylohydrazide (**15b**)*

Yield 86% (0.41 g, 0.86 mmol); Mp 240-242 °C. IR (KBr) ν_{max}/cm^{-1} 1605 (Cld=O), 2218 (CN), 3228 (NH). ^1H NMR: δ 2.35 (s, 3H, CH_3), 7.28–8.00 (m, 15H, Ar–H), 8.67 (s, 1H, CH), 9.30 (s, 1H, CH-pyrazole), 11.05 (s, exch., 1H, NH). ^{13}C NMR: δ 11.9, 103.8, 106.3, 110.8, 114.3, 119.3, 121.3, 122.9, 123.1, 123.1, 125.1, 127.2, 127.3, 127.8, 129.0, 129.4, 137.9, 144.2, 147.2, 147.4, 152.8, 159.9, 190.4. MS (EI) *m/z* (%): 512 ($M^+ + 1$, 100). Anal. Calcd. for $C_{31}H_{21}N_5O_3$ (511.53): C, 72.79; H, 4.14; N, 13.69%. Found: C, 72.99; H, 4.37; N, 13.96%.

*3-(3-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)-2-cyano-N'-(1-(pyridin-2-yl)ethylidene)acrylohydrazide (**15c**)*

Yield 87% (0.39 g, 0.87 mmol); Mp 262–263 °C. IR (KBr) ν_{max}/cm^{-1} 1608 (C=O), 2227 (CN), 3228 (NH). ^1H NMR: δ 2.10 (s, 3H, CH_3), 7.31-8.35 (m, 14H, Ar–H), 8.73 (s, 1H, CH), 9.29 (s, 1H, CH-pyrazole), 11.13 (s, exch., 1H, NH). MS (EI) *m/z* (%): 472 (M^+, 45), 191 (100). Anal. Calcd. for $C_{28}H_{20}N_6O_2$ (472.50): C, 71.17; H, 4.27; N, 17.79%. Found: C, 71.29; H, 4.42; N, 17.96%.

*Synthesis of **17** and **19*** A mixture of **1** (0.29 g, 1.00 mmol), appropriate carbohydrazide **16** or **18** (1.00 mmol), glacial AcOH (0.5 mL, 8.74 mmol), and dry MeOH (20 mL) was refluxed for 1 h. The formed solid was filtrated, dried, and crystallized from DMF.

*N'-((3-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-2-(naphthalen-2-yloxy)acetohydrazide (**17**)*

Yield 86% (0.42 g, 0.86 mmol); Mp 208–210 °C. ^1H NMR: δ 4.62 (s, 2H, CH_2), 7.31–7.98 (m, 17H, Ar–H), 8.74 (s, 1H, CH), 9.13 (s, 1H, CH-pyrazole), 11.43 (s, exch., 1H, NH).MS (EI) *m/z* (%): 486 (M^+, 100). Anal. Calcd. for $C_{30}H_{22}N_4O_3$ (486.52): C, 74.06; H, 4.56; N, 11.52%. Found: C, 74.31; H, 4.67; N, 11.75%.

*5-(Benzofuran-2-yl)-N'-((3-(benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-1-phenyl-1H-pyrazole-3-carbohydrazide (**19**)*

Yield 85% (0.50 g, 0.85 mmol); Mp 270–271 °C. ^1H NMR: 7.12–7.91 (m, 20H, Ar–H), 8.87 (s, 1H, CH), 9.13 (s, 1H, CH-pyrazole), 9.35(s, 1H, CH-pyrazole), 10.22 (s, exch., 1H, NH). MS (EI) *m/z* (%): 588 (M^+, 100). Anal. Calcd. for $C_{36}H_{24}N_6O_3$ (588.61): C, 73.46; H, 4.11; N, 14.28%. Found: C, 73.62; H, 4.37; N, 14.64%. Selected crystallographic data: orange plates, $C_{39}H_{31}N_7O_4$, FW = 661.71, $T = 293(2)$ K, $\lambda = 0.71073$ Å, triclinic, space group P1, $a = 9.8227(5)$ Å, $b = 11.4055(6)$ Å, $c = 29.4496(14)$ Å, $\alpha = 91.753(4)°$, $\beta = 97.043(4)°$, $\gamma = 93.894(4)°$, $V = 3264.3(3)$ $Å^3$, $Z = 4$, $\rho_{calc.} = 1.346$ Mg/m^{-3}, crystal size = 0.38 × 0.24 × 0.12 mm, $m = 0.090$ mm^{-1}, reflections collected = 28397, independent reflections = 15581, $R = 0.058$, wR = 0.149, R(int) = 0.030. CCDC1531681.

Conclusion

Several novel heterocycles having a 3-(benzofur-2-yl)pyrazole moiety were synthesized in high yields using simple and convenient procedures. Moreover, the synthetic processes involved required only commercially available starting materials.

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