Research on Chemical Intermediates (2019) 45:4383–4394
https://doi.org/10.1007/s11164-019-03837-w

"On-water" one-pot four-component synthesis of novel 1*H*-furo[2,3-c]pyrazole-4-amine derivatives

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Received: 23 February 2019 / Accepted: 16 April 2019 / Published online: 23 April 2019

Abstract

A catalyst-free, simple and green protocol has been accomplished for the synthesis of novel 1*H*-furo[2,3-c]pyrazole-4-amines in a one-pot four-component domino reaction involving hydrazines, ethyl acetoacetate, aromatic amines and phenylglyoxal monohydrate in water. The protocol presented herein describes in situ generated pyrazolone as intermediate reactants with phenylglyoxal monohydrate in a Knoevenagel condensation followed by a Michael addition of amine, intramolecular cyclization, dehydration and the resulting to the title compound. It was observed that in this protocol bis(pyrazole-5-ols) are formed with amines bearing strong electron withdrawing groups under similar reaction conditions instead of the expected products. The reaction merits the use of water as solvent, no additive catalyst, easy workup, easy purification of products by non-chromatography and provides high yield of products with good purity.

Keywords 1*H*-Furo[2,3-*c*]pyrazole · Hydrazine hydrate · Phenylglyoxal monohydrate · Ethyl acetoacetate · Heteroaryl amine

Introduction

The chemistry of pyrazoles and derivatives, one of the most valuable nitrogen containing heterocyclic compounds, has attracted much attention in recent years. They have been considered very important for pharmaceutical, chemical and agricultural industries [1–3]. Pyrazoles have been reported to possess antimicrobial, anticancer, antileukemic, antidepressant, antiinflammatory, antihelmintic, anticonvulsant, antitubercular, analgesic, antiproliferative agents, angiogenic, antioxidant, antipyretic, antioxidant or herbicidal properties [4–8]. In addition, fused pyrazoles possess a

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wide range of biological properties such as fungicidal [9], herbicidal [10], veridical [11] and insecticidal activity [12, 13] and have been used for the treatment of rheumatoid arthritis [14, 15].

Furans and their derivatives with substituent(s) at C-2 and/or C-3 have attracted strong interest due to their widespread in a large number of natural products and for their useful biological and pharmacological properties [16–18]. Among these compounds, pyrazole-fused ring derivatives such as furopyrazoles have demonstrated antitumour and antimicrobial activities [19]. Therefore, the preparation of furopyrazole derivatives is very important and challenging from a synthetic point of view. In recent years, despite a number of synthetic routs accessible for ring-fused pyrazoles such as dihydrofuro[2,3-*c*]pyrazole derivatives in the literature [20–25], synthesis of furo[2,3-*c*]pyrazole derivatives has received little attention and only few procedures have been reported. Among them, the majority has focused on the preparation of CF_3-substituted furopyrazoles **A** based on Rh catalyzed [3 + 2] cycloaddition of CF_3-substituted diazocarbonyl compound with aromatic alkynes [26], reaction of 4-bromo pyrazolone with malononitrile, cyanoacetamide and/or ethyl cyanoacetate to give furo[2,3-*c*]pyrazoles **B** using chitosan as a green basic catalyst by microwave irradiation technique [27] and synthesis of benzo-bis-furopyrazole **C** an important structural unit of cyanine dyes from *p*-chloranil and 3-methyl-1-phenyl-5-pyrazolone [28] (Fig. 1).

With regard to the exploration of green chemistry, solvent selection is an imperative part of most chemical processes. Organic reactions in water as a solvent without use of any detrimental organic solvents are of immense interest. When water is used as a reaction medium, it leads to some specific interactions such as polarity, hydrogen bonding, hydrophobic effect and trans-phase interactions due to its exclusive structure and incredible physical and chemical assets [29, 30]. However, a clear-cut understanding on the role of water in accelerating organic reactions is yet to be made. Towards this direction various terminologies such as "on water," in water,"in the presence of water" have been coined [31–34]. However, the insolubility of most organic reactants in water makes the reaction mixtures heterogeneous, which proves to be a major difficulty while using water as a solvent. But the effect of water on heterogeneous reactions is precisely opposite. Actually, depending on the nature of the reaction, water was observed to accelerate most reactions appreciably on its interface. The observed rate enhancement in water was explained by the hydrophobic effect [35–38]. In recent years, various reactions have been carried out in water, and mostly when the organic reactants are insoluble in the aqueous phase [39–44].

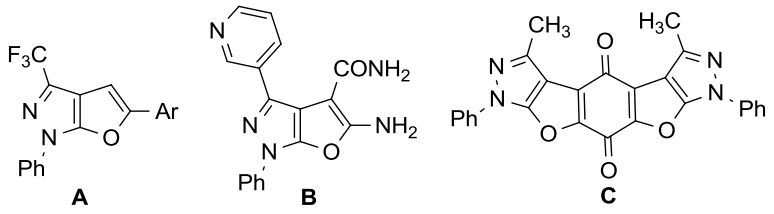


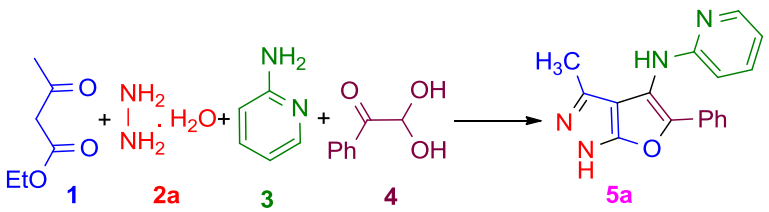
Fig. 1 Fused furopyrazoles (**a**–**c**)

To the best of our knowledge, synthesis of 1*H*-furo[2,3-*c*]pyrazole-4-amines in aqueous medium is not yet reported. In continuation of our ongoing program for the development of sustainable processes the heterocyclic compounds [45–51], herein we wish to report our results for the uncatalyzed domino synthesis of novel highly substituted 1*H*-furo[2,3-*c*]pyrazole derivatives by a one-pot four-component condensation reaction between hydrazines, ethyl acetoacetate, aromatic amines and phenylglyoxal monohydrate in water.

Results and discussion

For our initial study, the reaction of ethyl acetoacetate (**1**, 1.0 mmol), hydrazine hydrate (**2a**, 1.0 mmol), 2-aminopyridine (**3a**, 1.0 mmol) and phenylglyoxal monohydrate (**4**, 1.0 mmol) was chosen as a model reaction (Table 1). This combination in the absence of any catalyst and solvent-free condition at 90 °C provided four-component product **5a** after 60 min in 54% yield (Table 1, entry 1). Next, the same reaction mixture stirred at reflux temperature in water for 40 min gave the desired product **5a** in 88% yield (Table 1, entry 2). Interestingly, the model reaction in water and in the presence of a catalytic amount of guanidine hydrochloride or formic acid was examined. The results indicated that using of the catalyst did not improve the yield of the product. In order to study the solvent effect, the model reaction was carried out in the presence of various polar protic and polar aprotic solvents. It was found that polar protic solvents (EtOH and MeOH) and low boiling aprotic solvents

Table 1 Optimization of the reaction conditions[a]



Entry	Solvent	Temperature (°C)	Time (min)	Yield (%)[b]
1	–	90	60	54
2	H_2O	reflux	40	88
3	EtOH	reflux	120	43
4	MeOH	reflux	120	48
5	CH_3CN	reflux	120	54
6	THF	reflux	120	42

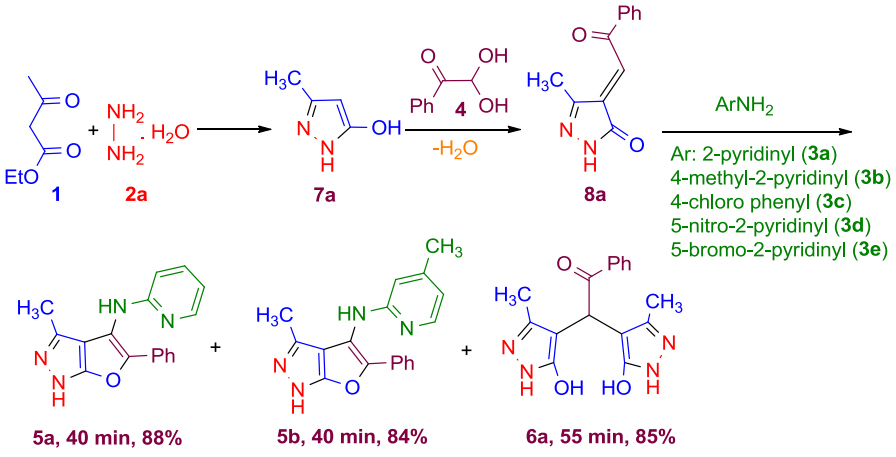
[a]Reaction conditions: ethyl acetoacetate (1.0 mmol), hydrazine hydrate (1 mmol), 2-aminopyridine (1 mmol) and phenylglyoxal monohydrate (1 mmol), solvent 5 mL

[b]Isolated yields

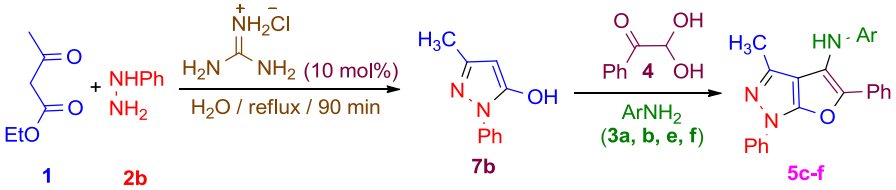
(CH_3CN and THF) under reflux conditions afforded the moderate yields of the product **5a** after 2 h (Table 1, entries 3–6).

With the optimized reaction conditions for the synthesis of amine substituted ring-fused furopyrazoles, we explored the generality of this reaction. Our attention was focused on the use of commercially available aromatic amines such as 2-amino-4-methylpyridine (**3b**), 4-chloroaniline (**3c**), 2-amino-5-nitropyridine (**3d**) and 2-amino-5-bromopyridine (**3e**). The reaction with **3b** gave the corresponding product **5b** in high yield (84%) after 40 min. Interestingly, under similar reaction conditions, the other amines **3c-e** with ethyl acetoacetate, hydrazine hydrate and phenylglyoxal monohydrate gave the corresponding 2,2′-bis(5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)-1-phenylethanone (**6a**) instead of the desired ring-fused furopyrazoles. It is suggested that 3-methyl-1*H*-pyrazol-5-ol (**7a**) generated in situ from the condensation of hydrazine hydrate (**2a**) and ethyl acetoacetate (**1**) is more nucleophilic than amine containing electron-withdrawing group (**3c–e**) and reacts with intermediate **8a** to afford product **6a** (Scheme 1).

Thus, encouraged by the results, we further explored the scope and limitation of the current method. With the optimal conditions in hand, one-pot, two-step domino reaction of phenyl hydrazine (**2b**, 1.0 mmol), ethyl acetoacetate (**1**, 1.0 mmol), 2-aminopyridine (**3a**, 1.0 mmol) and phenylglyoxal monohydrate (**4**, 1.0 mmol) was investigated. Initially, the reaction of phenyl hydrazine (**2b**, 1.0 mmol) and ethyl acetoacetate (**1**, 1.0 mmol) in the presence of a catalytic amount of guanidine hydrochloride (10 mol%) as organocatalyst in water at reflux condition was studied. The reaction gave 3-methyl-1-phenyl-1*H*-pyrazol-5-ol (**7b**) in high yield (90%) after 90 min (Scheme 2). We also evaluated the amount of catalyst required for this reaction. It was found that when we increased the amount of catalyst from 10 mol% to 15 mol% and 20 mol%, the yield did not improve. Moreover, by decreasing the amount of catalyst from 10 mol % to 5 mol%, the yield decreased from 90 to 75%. Also, under the identical condition, the yield of the reaction was not affected in the presence of



Scheme 1 Synthesis of furopyrazole **5a–b** and bis (pyrazole-5-ols) (**6a**)



Scheme 2 One-pot synthesis of 3-methyl-1-phenyl-1*H*-pyrazol-5-ol (**7b**) and furopyrazole **5c–f**

10 mol% catalyst after different time intervals (90 min, 120 min and 150 min). Thus, 10 mol% guanidine hydrochloride was chosen as a quantitative catalyst for this reaction and 90 min was chosen as the reaction time. After determining the optimum reaction condition, to established the synthesis of **7b**, phenylglyoxal monohydrate (**4**, 1.0 mmol) and various aryl amines (1.0 mmol) were added to the reaction mixture for the synthesis of a series of novel furopyrazoles **5c–f** (Scheme 2).

As indicated in Fig. 2, the various aromatic amines such as 2-aminopyridine, 2-amino-4-methylpyridine, 2-amino-5-bromopyridine and 2-amino-3-methylpyridine (**3f**), afforded the corresponding furopyrazole **5c–f** within 50–60 min in high yields (75–85%).

However, when the reaction was performed with 4-chloroaniline (**3c**) or 2-amino-5-nitropyridine (**3d**), 2,2′-bis(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-1-phenylethanone (**6b**) was obtained instead of the expected furopyrazole derivatives. Accordingly, the reaction occurred via initial formation of intermediate **8b** from the reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5-ol (**7b**) and phenylglyoxal monohydrate followed by Michael addition of **7b** to **8b** to give product **6b** because of the higher nucleophilicity of **7b** than amines bearing strong electron-withdrawing group (**3c**–**d**) (Scheme 3).

It should be noted that the purification of the title compounds is very easy. After cooling the reaction mixture to room temperature, the solid that separated out was filtered. The crude product was stirred for 5 min in boiling CH_3CN and the resulting precipitate was filtered to give the pure product. In another study, one-pot three-component reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5-ol (**7b**), phenylglyoxal monohydrate (**4**) and aromatic amines **3a–f** in the absence of catalyst in water under reflux conditions was examined (Scheme 4). In this process, the same products **5c–f** and **6b** as well as yields were obtained after 50–60 min. As a result, guanidine hydrochloride as catalyst in the synthesis of compounds **5c–f** and **6b** is only

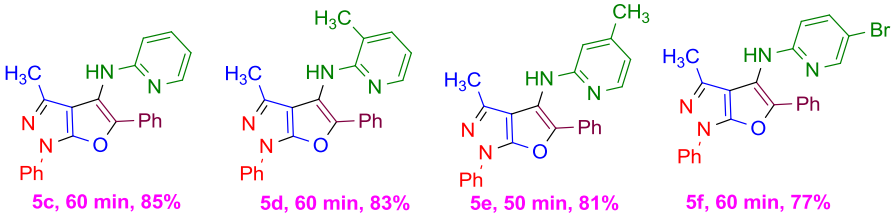
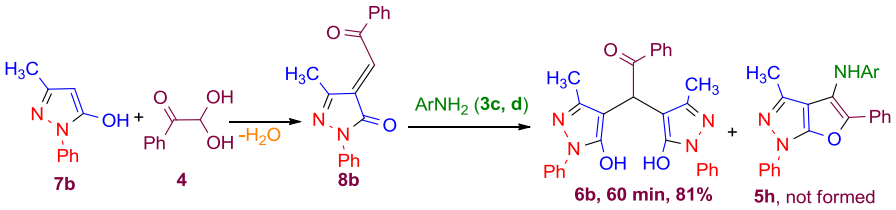
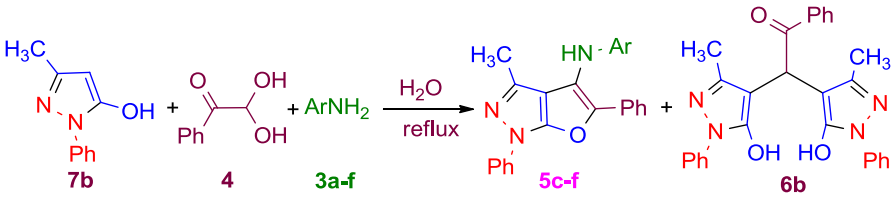


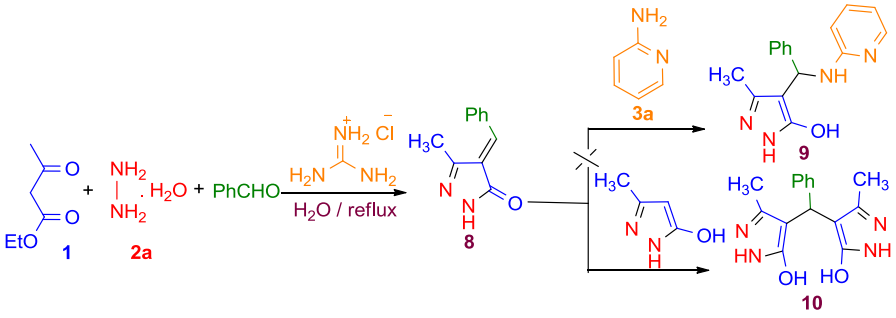
Fig. 2 One-pot, two-step synthesis of furopyrazole **5c–f**



Scheme 3 Synthesis of bis (pyrazole-5-ols) (**6b**)



Scheme 4 One-pot three-component synthesis of compounds **5c**–**f** and **6b**



Scheme 5 Proposal mechanism for the synthesis of compound **10**

effective for the first step of the reaction, in which phenyl hydrazine reacts with ethyl acetoacetate, and has no effect on the second step.

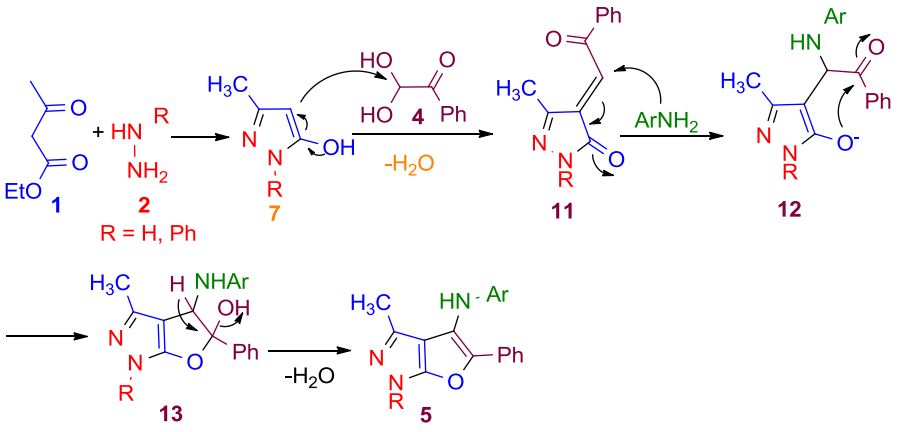
In order to expand the scope of the current method, the reaction of hydrazine hydrate (**2a**, 1.0 mmol), ethyl acetoacetate (**1**, 1.0 mmol), 2-aminopyridine (**3a**, 1.0 mmol) and benzaldehyde (1.0 mmol) was examined to synthesize 3-methyl-4-(phenyl(pyridin-2-ylamino)methyl)-1H-pyrazol-5-ol (**9**). Unfortunately, the attempt to replace phenylglyoxal monohydrate with benzaldehyde failed and 4,4′-(phenylmethylene)bis(3-methyl-1*H*-pyrazol-5-ol) (**10**) was obtained instead of compound **9**. Therefore, it might be concluded that 4-benzylidene-3-methyl-1H-pyrazol-5(4*H*)-one (**8**) is initially formed as an intermediate. Then, the intermediate is attacked by 3-methyl-1*H*-pyrazol-5(4*H*)-one to give the product **10**, which might be due to the higher nucleophilicity of the 3-methyl-1*H*-pyrazol-5(4*H*)-one than 2-aminopyridine (Scheme 5). Also, we examined the reaction of 2-aminopyridine and benzaldehyde in the presence of guanidine hydrochloride

under solvent-free condition at 90 °C for 20 min. Then, 3-methyl-1*H*-pyrazol-5-ol (**7a**) was added to the reaction mixture and stirred at 90 °C for 15 min. As a result, compound **10** obtained instead of the desired product **9**.

The plausible reaction mechanism of formation of compounds **5a–f** is described in Scheme 6. The reaction proceeds through the in situ formation of 1*H*-pyrazol-5-ol **7** by the condensation of hydrazine **2** and ethyl acetoacetate **1**. The last one reacts with the phenylglyoxal monohydrate with loss of a water molecule leading to the formation of intermediate **11**. Next, the Michael addition of amine to intermediates **11** provide to intermediate **12** and subsequent intramolecular cyclization and dehydration, to afford final the corresponding furopyrazole **5**.

Conclusion

In summary, we have developed a protocol for the facile preparation of novel fused 1*H*-furo[2,3-c]pyrazole-4-amines in high yields by a one-pot four-component domino protocol involving Knoevenagel condensation, Michael addition, cyclization and dehydration sequences in an aqueous medium under reflux conditions. In this process, the replacement of the amine bearing electron-donating group or weak electron-withdrawing group moiety with amine bearing strong electron-withdrawing group led to the formation of bis(pyrazole-5-ol) compounds. The advantages of this method include environmental acceptability, easy work-up, easy product separation and purification, short reaction time, no additive catalyst, and finally compliance with green chemistry protocols. Moreover, our products are expected to be of pharmacological interest and may act as potential drug candidates similar to the pyrazoles. To the best of our knowledge, this is the first report on the synthesis of novel 1*H*-furo[2,3-*c*]pyrazole-4-amine derivatives.



Scheme 6 Proposed mechanism pathway for the formation of **5a–f**

Experimental section

General information

All commercially available chemicals and reagents were used without further purification. Melting points were determined with an Electrothermal model 9100 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 4300 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 on Bruker DRX-300 Avance spectrometers. Chemical shifts (δ) are reported in parts per million and are referenced to the NMR solvent. Mass spectra of the products were obtained with an HP (Agilent technologies) 5973 mass selective detector. Elemental analyses were carried out by a CHN–O–Rapid Heraeus elemental analyzer (Wellesley, MA).

General procedure for the synthesis of compounds 5a–b and 6a

Hydrazine hydrate (1.0 mmol), ethylacetoacetate (1.0 mmol), aromatic amine (1.0 mmol), phenylglyoxal monohydrate (1.0 mmol) and 5 mL of H_2O were placed in a 50 mL round bottom flask over a magnetic stirrer and the contents were refluxed for appropriate times (40–55 min). The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was allowed to cool at room temperature and the resulting solid (crude product) filtered and dried. The crude product was stirred for 5 min in boiling CH_3CN and the resulting precipitate was filtered. The products **5a**, **5b** and **6a** thus obtained were found to be pure upon ^{1}H and ^{13}C-NMR, mass spectra, elemental analyses, and TLC examination.

General procedure for the synthesis of compounds 5c–f and 6b

Phenyl hydrazine (1.0 mmol), ethylacetoacetate (1.0 mmol), guanidine hydrochloride (10% mol) and 5 mL of H_2O were placed in a 50 mL round bottom flask over a magnetic stirrer and the contents were refluxed for 90 min (the progress of the reaction was monitored by TLC). Then, aromatic amine (1.0 mmol), phenylglyoxal monohydrate (1.0 mmol) were added to the reaction mixture and the contents were refluxed for appropriate times (50–60 min). The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was allowed to cool at room temperature and the resulting solid (crude product) filtered and dried. The crude product was stirred for 5 min in boiling CH_3CN and the resulting precipitate was filtered. The products **5c**–**f** and **6b** thus obtained were found to be pure upon ^{1}H and ^{13}C-NMR, mass spectra, elemental analyses, and TLC examination.

3-Methyl-5-phenyl-N-(pyridin-2-yl)-1H-furo[2,3-c]pyrazol-4-amine (5a)

Light pink powder; m.p. = 324–325 °C; IR (KBr, cm^{-1}): 3417, 3113, 3030, 2885, 1636, 1617, 1578, 1530, 1505, 1450, 1384, 1340, 1276, 1244, 1154, 1112, 1059; ^{1}H

NMR (300 MHz, DMSO-d_6): $\delta = 1.50$ (*s*, 3H, CH_3), 6.62 (*t*, 1H, $J = 6.6$ Hz, Ar–H), 7.00–7.11 (*m*, 4H, Ar–H), 7.35 (*d*, 1H, $J = 9.0$ Hz, Ar–H), 7.52 (*d*, 2H, $J = 7.8$ Hz, Ar–H), 7.59 (*d*, 1H, $J = 6.6$ Hz, Ar–H), 9.92 (br, 1H, NH), 11.55 (br, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 10.87$, 91.28, 95.45, 112.45, 112.93, 117.12, 125.11, 125.24, 127.02, 127.65, 128.77, 135.37, 142.33, 160.10, 164.61; MS m/z (%): 291 ($M+1$) (100), 290 $(M)^+$, 289, 275, 233, 218, 205, 154, 128, 103, 78; Anal. calcd. for $C_{17}H_{14}N_4O$: C, 70.34; H, 4.82; N, 19.31. Found: C, 70.43; H, 4.75; N, 19.37.

3-Methyl-N-(4-methylpyridin-2-yl)-5-phenyl-1H-furo[2,3-c]pyrazol-4-amine (**5b**)

White powder; m.p. = 332–334 °C; IR (KBr, cm^{-1}): 3219, 3169, 3055, 2913, 1644, 1623, 1561, 1524, 1498, 1382, 1346, 1270, 1243, 1220, 1166, 1112, 1058; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.49$ (*s*, 3H, CH_3), 2.10 (*s*, 3H, CH_3), 6.45–6.47 (dd, 1H, $J = 1.2$, 7.2 Hz, Ar–H), 6.95–7.11 (*m*, 4H, Ar–H), 7.45–7.51 (*m*, 3H, Ar–H), 9.93 (br, 1H, NH), 11.47 (br, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 10.86$, 21.23, 91.44, 112.30, 114.88, 115.37, 124.36, 126.90, 127.46, 128.70, 135.52, 135.64, 140.20, 141.96, 145.08, 164.71; MS m/z (%): 304 $(M)^+$ (100), 289, 275, 247, 232, 219, 205, 169, 152, 128, 115, 92, 78, 65; Anal. calcd. for $C_{18}H_{16}N_4O$: C, 71.05; H, 5.26; N, 18.42. Found: C, 70.97; H, 5.30; N, 18.54.

3-Methyl-1,5-diphenyl-N-(pyridin-2-yl)-1H-furo[2,3-c]pyrazol-4-amine (**5c**)

Light pink powder; m.p. = 310–312 °C; IR (KBr, cm^{-1}): 3430, 3062, 2920, 1595, 1500, 1445, 1389, 1359, 1309,1231, 1029; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.52$ (s, 3H, CH_3), 6.65 (*t*, 1H, $J = 6.6$ Hz, Ar–H), 6.99–7.26 (*m*, 9H, Ar–H, NH), 7.39 (*d*, 1H, $J = 12.0$ Hz, Ar–H), 7.57–7.60 (*m*, 3H, Ar–H), 7.75 (*d*, 1H, $J = 6.9$ Hz, Ar–H); ^{1}H NMR (300 MHz, DMSO-d_6 +D_2O): $\delta = 1.65$ (*s*, 3H, CH_3), 6.86 (*t*, 1H, $J = 6.6$ Hz, Ar–H), 7.15–7.41 (*m*, 8H, Ar–H), 7.54 (*d*, 1H, $J = 8.7$ Hz, Ar–H), 7.66–7.69 (*m*, 3H, Ar–H), 7.90 (*d*, 1H, $J = 6.9$ Hz, Ar–H); ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 23.25$, 112.72, 117.05, 120.48, 120.93, 125.70, 125.89, 125.91, 127.05, 127.88, 128.94, 129.43, 135.14, 138.86, 140.41, 142.71, 144.85, 145.74, 148.62; MS m/z (%): 366 $(M)^+$ (100), 346, 292, 261, 233, 231, 218, 205, 187, 185, 155, 128, 105, 91, 77; Anal. calcd. for $C_{23}H_{18}N_4O$: C, 75.41; H, 4.91; N, 15.30. Found: C, 75.34; H, 4.99; N, 15.33.

3-Methyl-N-(3-methylpyridin-2-yl)-1,5-diphenyl-1H-furo[2,3-c]pyrazol-4-amine (**5d**)

Pink powder; m.p. = 330–331 °C; IR (KBr, cm^{-1}): 3413, 3061, 2948, 2917, 1597, 1548, 1500, 1449, 1347, 1309, 1255, 1031; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.52$ (*s*, 3H, CH_3), 2.32 (*s*, 3H, CH_3), 6.56 (*t*, 1H, $J = 6.6$, Ar–H), 6.87 (*d*, 1H, $J = 6.6$ Hz, Ar–H), 6.95–7.25 (*m*, 7H, Ar–H, NH); 7.57–7.60 (*m*, 5H, Ar–H); ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 13.01$, 16.99, 112.68, 112.75, 120.86, 123.19, 124.21, 125.84, 126.53, 127.14, 127.74, 128.86, 129.40, 135.26, 138.80, 142.30, 145.19, 145.77, 148.62, 148.64; MS m/z (%): 380 $(M)^+$ (100), 351, 310, 275, 260,

247, 245, 231, 219, 208, 190, 168, 128, 105, 92, 77; Anal. calcd. for $C_{24}H_{20}N_4O$: C, 75.79; H, 5.26; N, 14.73. Found: C, 75.84; H, 5.15; N, 14.77.

3-Methyl-N-(4-methylpyridin-2-yl)-1,5-diphenyl-1H-furo[2,3-c]pyrazol-4-amine (**5e**)

Yellowish powder; m.p. = 270–272 °C; IR (KBr, cm^{-1}): 3444, 3069, 2979, 2910, 1596, 1503, 1452, 1359, 1216, 1027; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.50 (*s*, 3H, CH_3), 2.12 (*s*, 3H, CH_3), 6.50 (*d*, 1H, *J* = 6.9 Hz, Ar–H), 6.98–7.25 (*m*, 8H, Ar–H, NH), 7.55–7.64 (*m*, 5H, Ar–H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 13.03, 21.27, 112.11, 114.99, 115.38, 116.65, 117.31, 118.91, 120.74, 124.78, 124.87, 125.69, 126.95, 127.81, 128.88, 129.38, 134.83, 136.71, 144.90, 148.56; MS m/z (%): 380 $(M)^+$ (100), 351, 310, 275, 260, 247, 245, 232, 219, 190, 169, 119, 105, 92, 77; Anal. calcd. for $C_{24}H_{20}N_4O$: C, 75.79; H, 5.26; N, 14.73. Found: C, 75.68; H, 5.20; N, 14.80.

N-(5-Bromopyridin-2-yl)-3-methyl-1,5-diphenyl-1H-furo[2,3-c]pyrazol-4-amine (**5f**)

White powder; m.p. = 313–315 °C; IR (KBr, cm^{-1}): 3430, 3065, 2918, 1594, 1531, 1492, 1440, 1405, 1326, 1223, 1102, 1052; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.52 (*s*, 3H, CH_3), 7.02–7.26 (*m*, 8H, Ar–H), 7.39 (*d*, 1H, *J* = 9.6 Hz, Ar–H), 7.56–7.61 (*m*, 4H, Ar–H), 7.95 (br, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 15.13, 106.65, 113.05, 118.35, 121.18, 122.47, 124.77, 125.93, 127.08, 128.16, 128.48, 129.02, 129.42, 134.73, 143.44, 143.67, 150.83, 152.87, 161.31; MS m/z (%): 446 $(M+2)^+$ (100), 444 $(M)^+$, 380, 365, 339, 313, 311, 283, 285, 260, 247, 231, 218, 204, 185, 158, 156, 128, 105, 92, 77; Anal. calcd. for $C_{23}H_{17}BrN_4O$: C, 62.02; H, 3.82; N, 12.58. Found: C, 62.08; H, 3.75; N, 12.64.

2,2-Bis(5-hydroxy-3-methyl-1H-pyrazol-4-yl)-1-phenylethanone (**6a**)

Yellowish powder; m.p. = 260–262 °C; IR (KBr, cm^{-1}): 3371, 3023, 2896, 1691, 1600, 1529, 1446, 1364, 1291, 1241, 1172, 1076; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.73 (*s*, 6H, 2 × CH_3), 3.11 (2 × OH exchanged with water of DMSO-d_6), 5.13 (*s*, 1H, methine-H), 7.15–7.25 (*m*, 3H, Ar–H), 7.56 (*d*, 2H, *J* = 7.5 Hz, Ar–H), 10.55 (br, 2H, 2 × NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 10.77, 38.08, 100.40, 128.56, 128.73, 132.70, 137.17, 138.93, 160.56, 197.35; MS m/z (%): 312 $(M)^+$, 311, 310, 293, 281, 216, 207, 185, 175, 157, 128, 112, 105 (100), 98, 91, 77; Anal. calcd. for $C_{16}H_{16}N_4O_3$: C, 61.53; H, 5.12; N, 17.94. Found: C, 61.59; H, 5.22; N, 18.01.

2,2-Bis(5-hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)-1-phenylethanone (**6b**)

Pink powder; m.p. = 273–275 °C; IR (KBr, cm^{-1}): 3417, 3062, 2907, 2865, 2782, 1679, 1621, 1566, 1498, 1406, 1368, 1312, 1204, 1136, 1010; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.94 (*s*, 6H, 2 × CH_3), 5.24 (*s*, 1H, methine-H), 6.88 (*t*, 1H, *J* = 7.2 Hz, Ar–H), 7.08–7.35 (*m*, 11H, Ar–H), 7.81–7.86 (*m*, 3H, Ar–H), 10.91 (br, 2H, 2 × OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 11.72, 32.09, 118.75, 125.07, 128.60, 129.21, 129.35, 133.89, 135.95, 136.28, 137.33, 148.06, 163.39, 207.86;

MS m/z (%): 368, 292, 290, 261, 236, 213, 187 (100), 185, 173, 157, 141, 128, 115, 105, 91, 77; Anal. calcd. for $C_{28}H_{24}N_4O_3$: C, 72.41; H, 5.17; N, 12.06. Found: C, 72.33; H, 5.19; N, 12.11.

Acknowledgements The authors thank the Research Council of Payame Noor University and Islamic Azad University, Qaemshahr Branch for financial support.

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