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One-pot synthesis of functionalized pyrazolo[3,4-*c*]pyrazoles by reaction of 2-cyano-*N*-methyl-acrylamide, aryl aldehyde, and hydrazine hydrate

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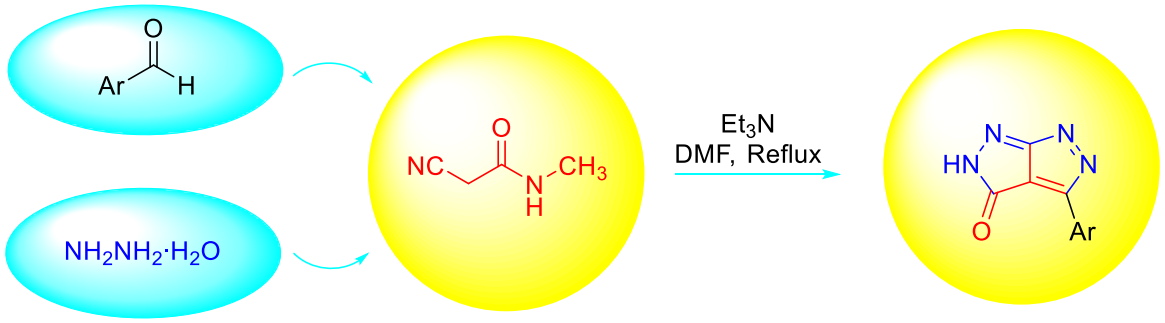
Abstract

A simple and efficient procedure for the synthesis of novel 4-aryl pyrazolo[3,4-*c*]pyrazol-3(2*H*)-ones *via* a one-pot, three-component reaction between 2-cyano-*N*-methylacetamide, aryl aldehydes, and hydrazine hydrate in the presence of Et_3N in DMF is reported. Products are obtained in good yields and their structures are supported by their spectroscopic data and combustion analysis.



Keywords: Aryl aldehyde, 2-Cyano-*N*-methylacetamide, Hydrazine hydrate, Pyrazolo[3,4-*c*]pyrazole-3(2*H*)-one

Introduction

Pyrazoles are five-membered heterocycles that contain nitrogen-nitrogen (N-N) bonds. Pyrazoles are relatively rare in the nature but can be found widely in the pharmaceutical and biochemical industries.[1,2] Also, monocyclic pyrazoles are useful scaffolds for the synthesis of larger fused heterocyclic systems. Among them, we can mention pyrazolo-fused pyrimidines,[3] quinolines,[4] pyridines,[5] thiazoles,[6] isoquinolines,[7] imidazoles,[8] diazepines,[9] and triazines.[10] Fused pyrazoles are important classes of heterocycles with effective biological activity such as antitumor,[11] antioxidant,[2] antimicrobial,[12] antiviral,[13] and as immunostimulatory agents.[14] Moreover, some of these bicyclic heterocycles are used for treatment of autoimmune/inflammatory diseases,[1] useful for treatment of esophageal and gastrointestinal mucosa injury,[14] and potent inhibitors of hGSK-3a.[15]

Among the fused pyrazoles are pyrazolo[3,4-*c*]pyrazoles, which are important owing to their various pharmacological and biological activities such as adenosine mimics (A),[16] antibiotics (B),[17] and anticancer (C),[18] which have inhibitory activity against liver cancer (HepG2) Cell Category (D) [19] (Figure 1).

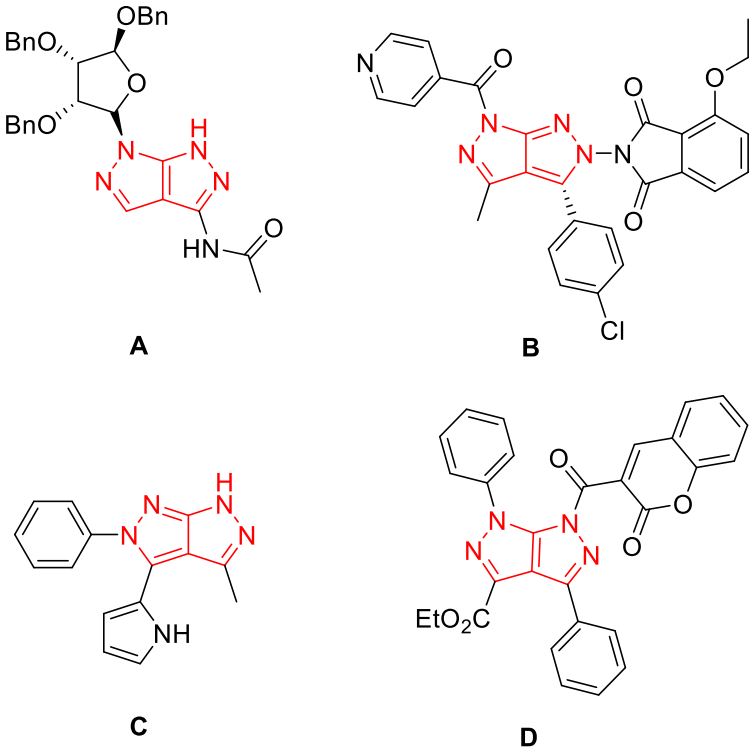


Figure 1. Selected examples of bioactive pyrazolo[3,4-*c*]pyrazoles.

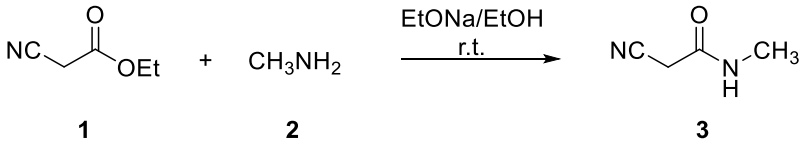
Several successful methods for the synthesis of pyrazolo[3,4-*c*]pyrazoles have been reported by diverse procedures, such as from the: (a) intermolecular cyclization of hydrazono-2,4-dixobutanoic acids,[20] and arylidene pyrazolinone with hydrazine hydrate;[21] (b) condensation of 2-isonicotinoyl-pyrazol-3-one in the presence of hydrazine hydrate;[18] (c) reaction of 5-chloropyrazole-4-carbaldehydes with hydrazine hydrate or phenyl hydrazine;[22] and, (d) the three-component reaction of 2,4-dihydro-3*H*-pyrazol-3-ones, aryl aldehydes, and hydrazine hydrate.[23,24] Also for some of these synthesis the use of catalysts are reported.[25,26]

This encouraged us to focus on the synthesis of this potential biologically active core as part of our ongoing efforts to develop multicomponent reactions for the synthesis of nitrogen-containing heterocycles.[27,28] Herein, we describe a new and efficient strategy for the synthesis of 4-arylpyrazolo[3,4-*c*]pyrazol-3(2*H*)-ones *via* a

one-pot, three-component reaction of 2-cyano-*N*-methylacrylamide, aryl aldehyde, and hydrazine hydrate in the presence of Et_3N in DMF heated at reflux.

Results and Discussion

Our study began with reaction of ethyl 2-caynoacetate **1** and methylamine **2** to give 2-cyano-*N*-methylacetamide **3** following a literature procedure (Scheme 1).[29]

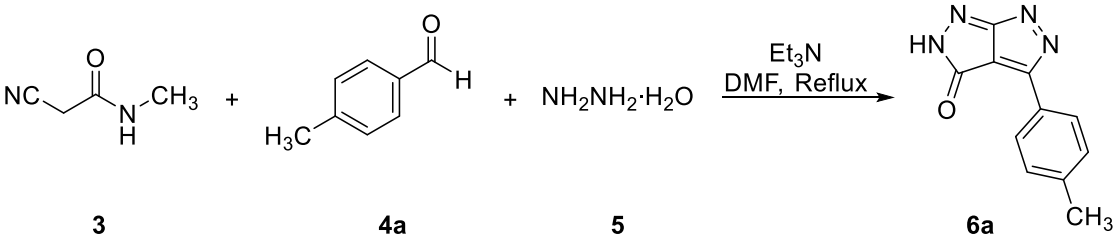


1 **2** **3**

Scheme 1. Synthesis of 2-cyano-*N*-methylacetamide.

To find the optimized conditions, we studied the synthesis of 4-(*p*-tolyl)pyrazolo[3,4-*c*]pyrazol-3(2*H*)-one **6a** *via* the three-component reaction of 2-cyano-*N*-methylacetamide **3**, 4-methylbenzaldehyde **4a**, and hydrazine hydrate **5** under a variety of conditions (Table 1).

Table 1. Optimization of the reaction conditions in the synthesis of4-(*p*-tolyl)pyrazolo[3,4-*c*]pyrazol-3(2*H*)-one **6a**



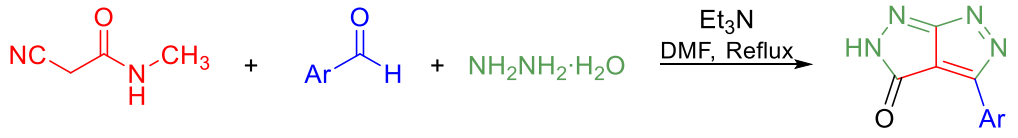
3 **4a** **5** **6a**

Entry	Solvent	Temp.[a]	mmol of **3:4a:5**	Yield (%)[b]
1	DMF	r.t.	1:1:2	25
2	MeOH	r.t.	1:1:2	N.R.
3	THF	r.t.	1:1:2	N.R.
4	EtOH	r.t.	1:1:2	N.R.
5	CH_3CN	r.t.	1:1:2	N.R.
6	DMF	Reflux	1:1:2	40
7	DMF	Reflux	1:1:2.5	40
8	DMF	Reflux	1:1.5:3	45
9	DMF	Reflux	1:1:3	49
10	DMF	Reflux	1.5:1:3	55
11	DMF	Reflux	1:1:5	78
12	DMF	Reflux[c]	1:1:5	78

[a] Reaction conditions: solvent was 5 mL, with 0.27 mL (2.0 mmol) Et_3N, reaction time was 3 h. [b] Isolated yields. [c] Reaction time was 12 h.

The optimization of the reaction conditions, including the reaction solvent, the reaction temperature, and the equivalents of starting materials were investigated. First, various solvents were examined (Table 1, entries 1–5), and DMF was shown to be the preeminent solvent for this reaction. Then, we examined the influence of different temperatures on this reaction. The product yield at room temperature for 5 h was 25% and in the reflux conditions during the same time was 40% (Table 1, entries 1 and 6). Finally, we observed that the molar ration of reactants also have important influence on the reaction (Table 1, entries 7–11). More molar equivalents of hydrazine hydrate **5** (for example, 5.0 mmol) in DMF at reflux conditions led to a higher yield, 78% (Table 1, entry 11). Also, increasing the reaction time in DMF under reflux conditions did not improve the yield (Table 1, entry 12). This series of experiments reveal that the optimal results were obtained when the reaction of 2-cyano-*N*-methylacetamide **3** (0.09 g, 1.0 mmol) was conducted with 4-methylbenzaldehyde **4a** (0.12 mL, 1.0 mmol), in the presence of Et_3N (0.27 mL, 2.0 mmol) and hydrazine hydrate **5** (0.20 mL, 5.0 mmol) in DMF (5 mL) under reflux conditions. These optimized reaction conditions (Table 1, entry 11) were then used to synthesize and explore the scope of this novel transformation with various aryl aldehydes to give one series 4-arylpyrazolo[3,4-*c*]pyrazol-3(2*H*)-ones **6a-k** (Table 2) in good yields. As can be seen from Table 2, the nature of the aryl aldehyde was important: aryl aldehydes bearing electron-withdrawing groups gave higher yields.

Table 2. Synthesis of 4-arylpyrazolo[3,4-*c*]pyrazol-3(2*H*)-ones



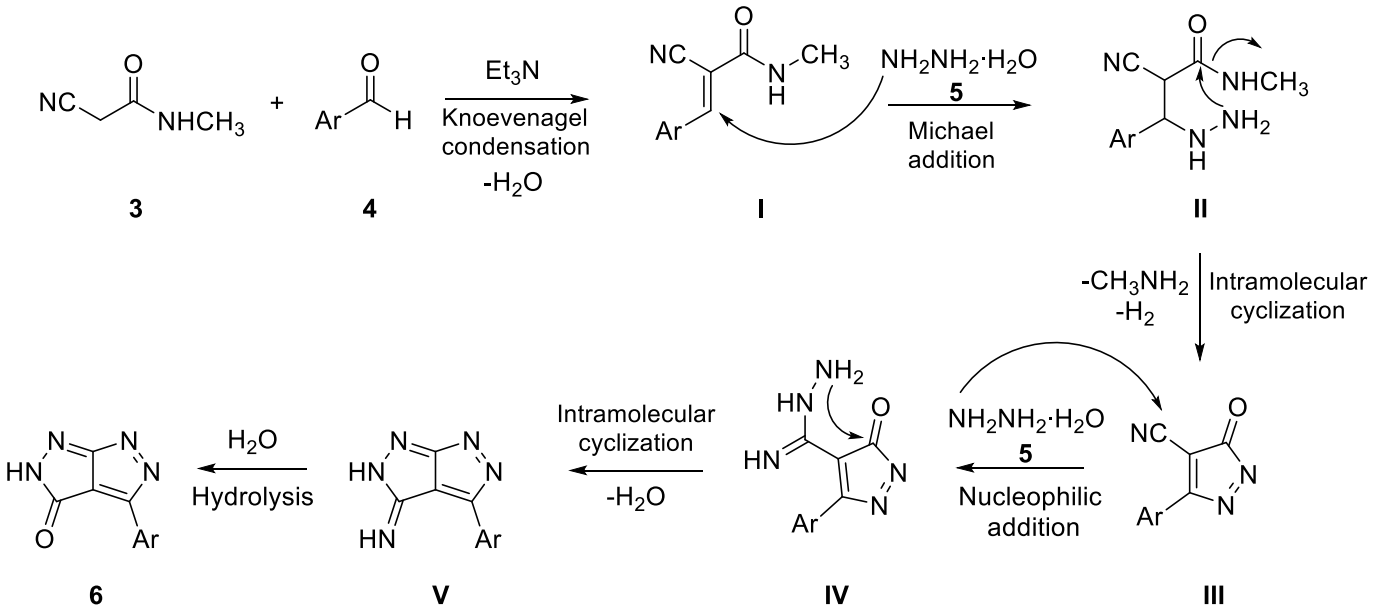
3 **4** **5** **6a-k**

Entry	Product	Ar	Yield (%)[a]
1	**6a**	4-Tol	78
2	**6b**	3-Tol	75
3	**6c**	4-ClC_6H_4	88
4	**6d**	4-$MeOC_6H_4$	70
5	**6e**	4-BrC_6H_4	80
6	**6f**	3-FC_6H_4	90
7	**6g**	4-$Me_2NC_6H_4$	65
8	**6h**	2-Tol	74
9	**6i**	2-ClC_6H_4	85
10	**6j**	2-$MeOC_6H_4$	68
11	**6k**	Ph	62

[a] Isolated yield.

To the best of our knowledge, all the synthesized compounds were new and their structures were supported by ^1H and ^{13}C NMR, IR, and CHN analysis. For instance, the ^1H NMR spectrum of the compound **6a** consisted of one singlet at δ_H 2.35 for the three hydrogens of the methyl group. Also, two doublet signals at δ_H 7.34 and 7.55 with coupling constant of 8.0 Hz for the aromatic protons of the phenyl ring and a broad singlet signal at δ_H 8.65 for the proton of the NH were also observed. The ^{13}C NMR spectrum of compound **6a** exhibited 9 distinct signals in agreement with the proposed structure.

A proposed mechanism for the synthesis of 4-arylpyrazolo[3,4-*c*]pyrazol-3(2*H*)-ones is illustrated in Scheme 2. Firstly, intermediates **I** are formed by means of a Knoevenagel condensation between 2-cyano-*N*-methylacetamide **3** and aryl aldehydes **4** in presence of Et_3N. Then, the Michael addition of hydrazine hydrate **5** to intermediates **I** afforded intermediates **II**, which subsequently undergo an intramolecular cyclization reaction and loss of one molecule of H_2 and CH_3NH_2 to form intermediates **III**. Then, the nucleophilic addition of another equivalent of hydrazine hydrate **5** to intermediates **III** afforded intermediates **IV**, which subsequently undergo an intramolecular cyclization reaction to form intermediates **V**. In the last step, 4-arylpyrazolo[3,4-*c*]pyrazol-3(2*H*)-ones **6** are formed by hydrolysis of intermediates **V** in DMF under reflux conditions.



Scheme 2. The proposed mechanism for the synthesis of 4-arylpyrazolo[3,4-*c*]pyrazol-3(2*H*)-ones.

Conclusions

In conclusion, 4-arylpyrazolo[3,4-*c*]pyrazol-3(2*H*)-ones can be synthesized from the reaction of 2-cyano-*N*-methylacetamide, aryl aldehydes, and hydrazine hydrate in the presence of Et_3N in DMF under reflux conditions. The mild reaction conditions, low cost of the starting materials, operational simplicity and good yields are the advantages of the protocol.

Experimental Section

General. All commercially available reagents and other solvents were purchased and used without further purification. Melting points were obtained on a Bamslead Electrothermal 9200 melting point apparatus and are uncorrected. IR spectra were acquired on a Bruker FT-IR Equinax-55 spectrometer. Peaks are reported in wavenumbers (cm^{-1}). All of the NMR spectra were recorded on a Varian model UNITY Inova 500 MHz (^1H: 500, ^{13}C: 125 MHz) NMR spectrometer. Chemical shifts of ^1H and ^{13}C NMR are reported in δ or parts per million

(ppm) from tetramethylsilane (TMS) as an internal standard in DMSO-d_6 as solvents. Elemental analyses were performed using a Carlo Erba EA 1108 instrument. All products were characterized by their spectral and physical data.

General procedure for the preparation of compounds 6a–k. A mixture of 2-cyano-*N*-methylacetamide **3** (0.09 g, 1.0 mmol), aryl aldehyde **4** (1.0 mmol), in the presence of Et_3N (0.27 mL, 2.0 mmol) was stirred in DMF (5 mL) for 2 h at reflux conditions to give 2-cyano-*N*-methylacrylamide **I**. Then, hydrazine hydrate **5** (0.2 mL, 5.0 mmol) was added, and obtained mixture was stirred for more 3 h at reflux conditions. After completion of the reaction determined by TLC, the reaction product was extracted with ethyl acetate (3 × 5 mL), the solvent was removed under reduced pressure and the isolated compounds **6a–k** (62–90%) were purified by plate chromatography (20 × 20 cm) (SiO_2, eluent *n*-hexane/EtOAc, 25:75).

4-(4-Tolyl)pyrazolo[3,4-*c*]pyrazol-3(2*H*)-one (6a). Colorless powder; mp 171-173 °C. IR υ/cm^{-1} (KBr): 3420, 1630 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ_H 2.35 (s, 3H, CH_3), 7.34 (d, *J* 8.0 Hz, 2H, ArH), 7.75 (d, *J* 8.0 Hz, 2H, ArH), 8.65 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ_C 21.1, 119.6, 128.4, 129.5, 153.0, 155.6, 160.5, 170.1, 174.4. Anal. Calcd for $C_{11}H_8N_4O$ (212.21): C, 62.26; H, 3.80; N, 26.40. Found: C, 62.41; H, 3.84; N, 26.32%.

4-(3-Tolyl)pyrazolo[3,4-*c*]pyrazol-3(2*H*)-one (6b). Colorless powder; mp 167-169 °C. IR υ/cm^{-1} (KBr): 3308, 1625 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.36 (s, 3H, CH_3), 7.34-7.43 (m, 4H, ArH), 8.12 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ_C 21.25, 124.5, 127.5, 129.0, 130.9, 134.3, 138.4, 145.6, 148.2, 157.5, 165.2. Anal. Calcd for $C_{11}H_8N_4O$ (212.21): C, 62.26; H, 3.80; N, 26.40. Found: C, 62.09; H, 3.82; N, 26.51%.

4-(4-Chlorophenyl)pyrazolo[3,4-*c*]pyrazol-3(2*H*)-one (6c). Colorless powder; mp 111-113 °C. IR υ/cm^{-1} (KBr): 3448, 1639 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.51 (d, *J* 8.0 Hz, 2H, ArH), 7.75 (d, *J* 8.0 Hz, 2H, ArH), 8.30 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ_C 129.3, 130.0, 130.4, 133.7, 135.6, 156.6, 167.3, 174.9. Anal. Calcd for $C_{10}H_5ClN_4O$ (232.63): C, 51.63; H, 2.17; N, 24.08. Found: C, 51.87; H, 2.21; N, 24.15%.

4-(4-Methoxyphenyl)pyrazolo[3,4-*c*]pyrazol-3(2*H*)-one (6d). Colorless powder; mp 183-185 °C. IR υ/cm^{-1} (KBr): 3430, 1621 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.81 (s, 3H, OCH_3), 7.02 (d, *J* 8.5 Hz, 2H, ArH), 7.79 (d, *J* 8.5 Hz, 2H, ArH), 8.59 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ_C 55.7, 114.7, 115.6, 127.0, 129.2, 160.9, 162.1, 167.4, 170.8. Anal. Calcd for $C_{11}H_8N_4O_2$ (228.21): C, 57.89; H, 3.53; N, 24.55. Found: C, 58.04; H, 3.59; N, 24.47%.

4-(4-Bromophenyl)pyrazolo[3,4-*c*]pyrazol-3(2*H*)-one (6e). Colorless powder; mp 216-218 °C. IR υ/cm^{-1} (KBr): 3423, 1625 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.71 (d, *J* 8.0 Hz, 2H, ArH), 7.82 (d, *J* 8.0 Hz, 2H, ArH), 8.68 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ_C 123.7, 125.0, 130.6, 132.5, 160.3, 161.0, 163.0, 173.2. Anal. Calcd for $C_{10}H_5BrN_4O$ (277.08): C, 43.35; H, 1.82; N, 20.22. Found: C, 43.54; H, 1.84; N, 20.17%.

4-(3-Fluorophenyl)pyrazolo[3,4-*c*]pyrazol-3(2*H*)-one (6f). Colorless powder; mp 180-182 °C. IR υ/cm^{-1} (KBr): 3413, 1626 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.45-7.52 (m, 3H, ArH), 8.05 (s, 1H, ArH), 8.68 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ_C 114.7, 114.8, 118.6, 118.8, 125.2, 125.7, 131.5, 160.6, 163.7, 168.1. Anal. Calcd for $C_{10}H_5FN_4O$ (216.18): C, 55.56; H, 2.33; N, 25.92. Found: C, 55.69; H, 2.38; N, 26.03%.

4-(4-(Dimethylamino)phenyl)pyrazolo[3,4-*c*]pyrazol-3(2*H*)-one (6g). Colorless powder; mp 168-170 °C. IR υ/cm^{-1} (KBr): 3410, 1619 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.98 (s, 6H, $N(CH_3)_2$), 6.76 (d, *J* 8.5 Hz, 2H, ArH), 7.63 (d, *J* 8.5 Hz, 2H, ArH), 8.48 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ_C 50.3, 54.4, 112.1, 122.1, 129.9, 151.9, 154.3, 160.1, 170.6, 172.2. Anal. Calcd for $C_{12}H_{11}N_5O$ (241.25): C, 59.74; H, 4.60; N, 29.03. Found: C, 59.62; H, 4.58; N, 29.11%.

4-(2-Tolyl)pyrazolo[3,4-*c*]pyrazol-3(2*H*)-one (6h). Colorless powder; mp 165-167 °C. IR υ/cm^{-1} (KBr): 3422, 1632 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ_H 2.30 (s, 3H, CH_3), 7.19-7.42 (m, 4H, ArH), 8.65 (s, 1H, NH). ^{13}C NMR

(125 MHz, DMSO-d_6): δ_C 21.6, 124.5, 127.9, 129.1, 131.4, 133.9, 138.5, 145.7, 148.3, 157.5, 166.2. Anal. Calcd for $C_{11}H_8N_4O$ (212.21): C, 62.26; H, 3.80; N, 26.40. Found: C, 62.50; H, 3.83; N, 26.34%.

4-(2-Chlorophenyl)pyrazolo[3,4-*c*]pyrazol-3(2*H*)-one (6i). Colorless powder; mp 122-124 °C. IR υ/cm^{-1} (KBr): 3435, 1632 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ_H 7.39 (t, 1H, ArH), 7.42 (t, 1H, ArH), 7.50 (d, *J* 8.0 Hz, 1H, ArH), 7.90 (d, *J* 8.0 Hz, 1H, ArH), 8.69 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ_C 126.9, 128.0, 130.3, 131.6, 131.8, 133.4, 134.7, 141.5, 157.7, 166.0. Anal. Calcd for $C_{10}H_5ClN_4O$ (232.63): C, 51.63; H, 2.17; N, 24.08. Found: C, 51.79; H, 2.24; N, 23.97%.

4-(2-Methoxyphenyl)pyrazolo[3,4-*c*]pyrazol-3(2*H*)-one (6j). Colorless powder; mp 145-147 °C. IR υ/cm^{-1} (KBr): 3424, 1615 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ_H 3.87 (s, 3H, OCH_3), 7.03 (t, *J* 8.0 Hz, 1H, ArH), 7.14 (d, *J* 8.5 Hz, 1H, ArH), 7.50 (t, *J* 7.5 Hz, 1H, ArH), 7.96 (d, *J* 8.5 Hz, 1H, ArH), 8.94 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ_C 57.3, 114.7, 114.9, 127.0, 130.4, 148.6, 157.5, 160.9, 162.1, 166.2, 170.9. Anal. Calcd for $C_{11}H_8N_4O_2$ (228.21): C, 57.89; H, 3.53; N, 24.55. Found: C, 57.68; H, 3.57; N, 24.47%.

4-Phenylpyrazolo[3,4-*c*]pyrazol-3(2*H*)-one (6k). Yellow powder; mp 175-177 °C. IR υ/cm^{-1} (KBr): 3450, 1663 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ_H 7.20-7.75 (m, 5H, ArH), 8.12 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ_C 127.1, 127.6, 129.2, 130.3, 134.3, 145.5, 157.5, 165.3. Anal. Calcd for $C_{10}H_6N_4O$ (198.19): C, 60.60; H, 3.05; N, 28.27. Found: C, 60.47; H, 3.02; N, 28.34%.

Supplementary Material

^{1}H and ^{13}C NMR spectra of compounds **6a-6k** are available in the Supplementary Material.

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