An Efficient Synthesis of Isoxazoles and Pyrazoles under Ultrasound Irradiation

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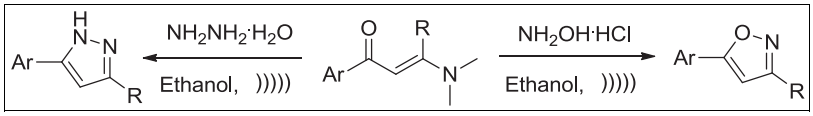

A series of 5-arylisoxazole and 5-aryl-1*H*-pyrazole derivatives was synthesized by the reaction of 3-(dimethylamino)-1-arylprop-2-en-1-one with hydroxylamine hydrochloride or hydrazine hydrate under ultrasound irradiation without using any catalyst. This method has the advantages of easier work-up, mild reaction condition, high yields, shorter reaction time, and environmentally benign procedure.

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INTRODUCTION

Ultrasonic irradiation, as a powerful tool in modern chemistry for the organic synthesis, has attracted more attention from organic chemists [1–3]. The ultrasonic irradiation with its advantages of convenient operation, mild reaction conditions, short reaction times, and high efficiency has become particularly popular in recent years, and numerous examples under this condition for constructing heterocyclic compounds have been reported in the literatures [4–8].

Nitrogen-containing heterocyclic building blocks are of great importance to both medical and organic chemists, and their synthesis continues to represent a challenge from both academic and industrial perspectives [9]. The isoxazole derivatives are an important class of heterocyclic pharmaceuticals and bioactive natural products because of their significant and wide spectrum of biological activities. Isoxazole derivatives display a broad range of pharmacological activities including the potent and selective antagonism of N-methyl-D-aspartate (NMDA) receptor [10] and anti-HIV activity [11]. Pyrazole and its derivatives are shown to possess important biological and pharmaceutical activities such as antimicrobial, antiviral, antitumor, anti-inflammatory, antifungal, and antidepressant [12–17].

Isoxazole and pyrazole derivatives have been synthesized by several methods [18–22] including the following: (1) reaction of 3-(dimethylamino)-1-arylprop-2-en-1-one with an aminating agent such as hydroxylamine-*O*-sulfonic acid; (2) condensation of α,β-unsaturated carbonyl compounds with hydrazine; (3) 1,3-dipolar cycloaddition of diazo compounds onto triple bonds; (4) nucleophilic attack of hydrazines to chromones, flavones, or isoxazoles and other methods. However, these methods possess some weakness: (1) require unavailable aminating agent, (2) need long reaction time, (3) require a large excess of aminating agent, (4) result in a mixture of regioisomeric dihydropyrazole, and (5) require the reaction to be carried in a sealed vial. It is urgent to further develop an efficient and convenient method to construct such scaffold. As a part of our current studies on the development of new routes to heterocyclic systems [23–30], we herein would like to report an ultrasound that assisted the efficient synthesis of isoxazole and pyrazole derivatives.

RESULTS AND DISCUSSION

The choice of an appropriate reaction medium is of crucial importance for the successful organic synthesis. To achieve suitable conditions, we selected the reaction of 1-(4-chlorophenyl)-3-(dimethylamino)but-2-en-1-one **1a** and hydroxylamine hydrochloride **2** as a model reaction (Scheme 1). The reaction was examined under both thermal (method A) and ultrasound irradiation (method B) conditions using different solvents such as EtOH, MeOH, acetonitrile, 1,4-dioxane, toluene, and THF, respectively. The results are summarized in Table 1. It can be seen from Table 1 that the reaction performed under traditional reaction without ultrasonic irradiation afforded comparatively lower yields in 1 h. In all cases, the experimental results show that the yields of the products are higher under sonication. The reaction could be efficiently carried out in the aforementioned solvents, and the reaction in EtOH gave the best result. It is apparent that the ultrasound can accelerate the reaction significantly, and EtOH is the solvent of choice for this reaction under ultrasound irradiation.

With this optimum condition in hand, we smoothly synthesized 5-arylisoxazole derivatives in EtOH under sonication (Scheme 2). The results are summarized in Table 2. The reaction proceeded smoothly, and a variety of the desired 5-arylisoxazole derivatives products **3** were obtained in good yields whether the aromatic ring of 3-(dimethylamino)-1-arylprop-2-en-1-one **1** is the one

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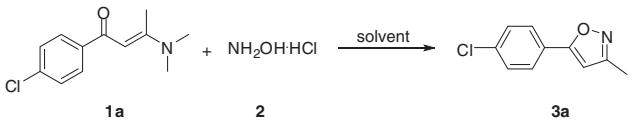
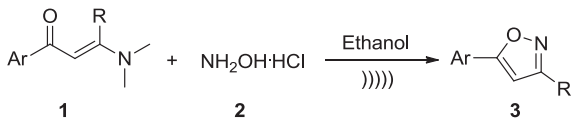
Scheme 1. Model reaction.



Scheme 2. The synthesis of 5-arylisoxazol derivatives **3** under ultrasound irradiation.



bearing electron-withdrawing substituents or electron-donating substituents. To verify the effect of ultrasound irradiation, all previously mentioned reactions were carried out under the same conditions in the absence of ultrasound irradiation. The desired products were produced in lower yields (56–80%) and with much longer reaction time (1–2.5 h), whereas under ultrasound irradiation, the products were obtained in 30–45 min with the yields of 84–96%.

To expand the scope of the current method, hydrazine hydrate **4** was examined as a replacement for the hydroxylamine hydrochloride **2**, and another series of 3-arylpyrazole derivatives **5** were obtained in good yields (Scheme 3). The results are summarized in Table 3.

The structures of all the products **3** and **5** were identified from their IR, ^{1}H NMR, and HRMS spectra.

Although the detailed mechanism of the aforementioned reaction remains to be fully clarified, the formation of 5-aryl-1*H*-pyrazoles **5** could be explained by a reaction sequence presented in Scheme 4. We propose that the reaction proceeded via a reaction sequence of Michael addition, elimination, cyclization, and dehydration. First, the Michael addition of 3-(dimethylamino)-1-arylprop-2-en-1-ones **1** and hydrazine **3** gave the intermediate product **6**. The intermediate **6** eliminated one molecule dimethylamine to give the intermediate product **7**, which upon intramolecular cyclization and dehydration gave rise to product **5**.

In conclusion, we have developed an efficient synthesis of isoxazole and pyrazole derivatives via the reaction of 3-(dimethylamino)-1-arylprop-2-en-1-one with hydroxylamine hydrochloride and hydrazine hydrate, respectively, under ultrasound irradiation without using any catalyst. This method has the advantages of easier work-up, mild reaction condition, high yields, shorter reaction time, and environmentally benign procedure.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded on F-1000 spectrometer (Varian Inc., Palo Alto, CA) in KBr with absorptions in cm^{-1}. ^{1}H NMR and ^{13}C NMR were determined on Varian Inova-300 or Inova 400-MHz spectrometers in $CDCl_3$ or DMSO-d_6 solution. *J* values are in hertz. Chemical shifts are expressed in parts per million downfield from internal standard TMS. HRMS data were obtained using micrOTOF-Q instrument (Bruker Daltonics Inc., Billerica, MA). Ultrasonication was performed in a KQ-250E medical ultrasound cleaner with a frequency of 40 kHz and an output power of 250 W (Built-in heating, 30–110°C thermostatically adjustable). The reaction flask was located at the maximum energy area in the cleaner, and the surface of the reactions was placed slightly lower than the level of the water. The observation of the surface of the reaction solution during vertical adjustment of vessel depth will show the optimum position by the point at which maximum surface disturbance occurs. The reaction temperature was controlled by the addition or removal of water from ultrasonic bath.

General procedure for the synthesis of 5-arylisoxazole 3 and 5-aryl-1*H*-pyrazole under sonochemical conditions. A dry 50-mL flask was charged with 3-(dimethylamino)-1-arylprop- 2-en-1-one **1** (0.5 mmol), hydroxylamine hydrochloride **2** (0.5 mmol) or hydrazine hydrate **4** (0.5 mmol), and EtOH (5 mL). The mixture was sonicated in the water bath of an ultrasonic cleaner under air condition at 25°C to complete the reaction (monitored by TLC), and then, the solid was filtered off. The crude product was purified by recrystallization from EtOH to give products **3** or **5**.

Table 1

Optimization of the solvent in the synthesis of **3a** under thermal condition and ultrasound irradiation.[a]

		Method A (without US[b])		Method B (with US[c])	
Entry	Solvent	Time (h)	Isolated yield (%)	Time (h)	Isolated yield (%)
1	EtOH	1	45	1	93
2	MeOH	1	49	1	84
3	Acetonitrile	1	33	1	72
4	1,4-Dioxane	1	48	1	50
5	Toluene	1	16	1	20
6	THF	1	35	1	46

US, ultrasonication.
[a]Reaction conditions: 1-(4-chlorophenyl)-3-(dimethylamino)but-2-en-1-one **1a** (0.5 mmol) and hydroxylamine hydrochloride **2** in a 5-mL solvent.
[b]Reaction under thermal condition.
[c]Reaction under ultrasonic waves at room temperature, ultrasonic power 250 W, and irradiation frequency 40 kHz.

Table 2

The synthesis of 5-arylisoxazol derivatives **3**.

				With US		Without US	
Entry	Product	Ar	R	Time (min)	Yield (%)	Time (h)	Yield (%)
1	**3a**	4-ClC_6H_4	CH_3	45	93	2	80
2	**3b**	4-BrC_6H_4	CH_3	45	95	1.5	76
3	**3c**	2,4-$Cl_2C_6H_3$	CH_3	30	91	1.5	75
4	**3d**	4-$CH_3OC_6H_4$	CH_3	35	87	2	69
5	**3e**	4-$CH_3OCOC_6H_4$	CH_3	30	96	1	80
6	**3f**	4-$BocNHC_6H_4$	CH_3	40	84	2	56
7	**3g**	4-ClC_6H_4	H	30	89	1.5	70
8	**3h**	4-$CH_3OC_6H_4$	H	35	87	2	72
9	**3i**	Naphthalene-1-yl	H	40	85	2.5	68
10	**3j**	4-$CH_3C_6H_4$	CH_3	30	90	1	67
11	**3k**	C_6H_5	CH_3	45	89	2	65
12	**3l**	4-BrC_6H_4	H	40	86	2.5	69

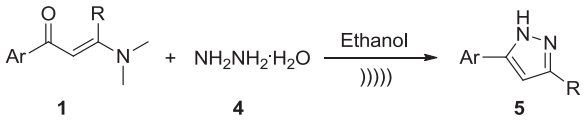
US, ultrasonication.

General procedure for the synthesis of 5-arylisoxazole 3 and 5-aryl-1*H*-pyrazole under thermal conditions. A dry 50-mL flask was charged with 3-(dimethylamino)-1-arylprop-2-en-1-one **1** (0.5 mmol), hydroxylamine hydrochloride **1** (0.5 mmol) or hydrazine hydrate **3** (0.5 mmol), and EtOH (5 mL), The mixture was stirred at room temperature. After the completion of the reaction (monitored by TLC), the solid was filtered off. The crude product was purified by recrystallization from EtOH to give products **3** or **5**.

5-(4-Chlorophenyl)-3-methylisoxazole (3a). mp 80–81°C; IR (KBr, cm^{-1}): 1601, 1517, 1454, 1249, 1092, 832, 662; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.35 (s, 3H, CH_3), 6.35 (s, 1H, CH), 7.42 (d, $J = 8.7$ Hz, 2H, ArH), 7.68 (d, $J = 8.4$ Hz, 2H, ArH); HRMS Calcd for $C_{10}H_9ClNO$ $[M+H]^+$: 194.0373; Found: 194.0378.

5-(4-Bromophenyl)-3-methylisoxazole (3b). mp 126–128°C; IR (KBr, cm^{-1}): 1604, 1467, 1258, 1068, 790, 655; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.36 (s, 3H, CH_3), 6.37 (s, 1H, CH),

Scheme 3. The synthesis of 3-arylpyrazole derivatives **5** under ultrasound irradiation.



Scheme 4. The proposed mechanism for the synthesis of 5-aryl-1*H*-pyrazole derivatives.

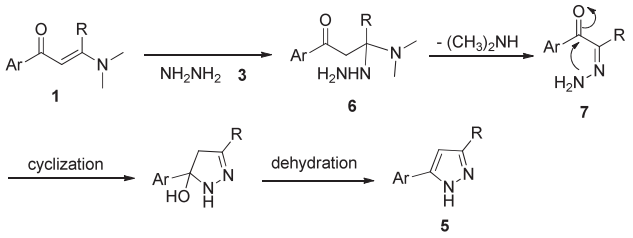


Table 3

The synthesis of 5-arylpyrazole derivatives **5**.

				With US		Without US	
Entry	Product	Ar	R	Time (min)	Yield (%)	Time (h)	Yield (%)
1	**5a**	4-ClC_6H_4	CH_3	35	90	2	81
2	**5b**	4-BrC_6H_4	CH_3	40	92	2.5	79
3	**5c**	2,4-$Cl_2C_6H_3$	CH_3	40	86	2.5	63
4	**5d**	4-$CH_3OC_6H_4$	CH_3	30	93	1.5	75
5	**5e**	4-$CH_3OCOC_6H_4$	CH_3	45	87	2	72
6	**5f**	4-$BocNHC_6H_4$	CH_3	35	89	2	68
7	**5g**	4-ClC_6H_4	H	40	84	2.5	65
8	**5h**	4-$CH_3OC_6H_4$	H	30	86	2	71
9	**5i**	4-BrC_6H_4	H	35	89	2	64
10	**5j**	C_6H_4	CH_3	40	87	2.5	68

US, ultrasonication.

7.58 (d, J = 8.7 Hz, 2H, ArH), 7.63 (d, J = 9.0 Hz, 2H, ArH); HRMS Calcd for $C_{10}H_9BrNO$ $[M+H]^+$: 237.9868; Found: 237.9857.

5-(2,4-Dichlorophenyl)-3-methylisoxazole (3c). mp 79–80°C; IR (KBr, cm^{-1}): 1609, 1450, 1230, 1078, 789, 672; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.39 (s, 3H, CH_3), 6.79 (s, 1H, CH), 7.37 (d, J = 8.8 Hz, 1H, ArH), 7.52 (d, J = 2.0 Hz, 1H, ArH), 7.88 (d, J = 8.4 Hz, 1H, ArH); HRMS Calcd for $C_{10}H_8Cl_2NO$ $[M+H]^+$: 227.9983; Found: 227.9986.

5-(4-Methoxyphenyl)-3-methylisoxazole (3d). mp 98–99°C; IR (KBr, cm^{-1}): 1612, 1520, 1443, 1240, 1178, 1100, 835; ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 2.33 (s, 3H, CH_3), 3.87 (s, 3H, CH_3O), 6.25 (s, 1H, CH), 6.97 (d, J = 8.7 Hz, 2H, ArH), 7.70 (d, J = 8.7 Hz, 2H, ArH); HRMS Calcd for $C_{11}H_{12}NO_2$ $[M+H]^+$: 190.0868; Found: 190.0872.

Methyl 4-(3-methylisoxazol-5-yl)benzoate (3e). mp 82–83°C; IR (KBr, cm^{-1}): 1722, 1594, 1282, 1184, 1044, 874, 773; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.36 (s, 3H, CH_3), 3.93 (s, 3H, CH_3O), 6.46 (s, 1H, CH), 7.81 (d, J = 8.0 Hz, 2H, ArH), 8.10 (d, J = 8.4 Hz, 2H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 11.7, 52.6, 101.9, 125.8, 130.4, 131.4, 160.7, 166.5, 168.6; HRMS Calcd for $C_{12}H_{12}NO_3$ $[M+H]^+$: 218.0817; Found: 218.0827.

tert-Butyl 4-(3-methylisoxazol-5-yl)phenylcarbamate (3f). mp 120–121°C; IR (KBr, cm^{-1}): 1701, 1520, 1413, 1237, 1160, 835, 772, 625; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.48 (s, 9H, $(CH_3)_3C$), 2.25 (s, 3H, CH_3), 6.71 (s, 1H, CH), 7.59 (d, J = 8.8 Hz, 2H, ArH), 7.71 (d, J = 8.4 Hz, 2H, ArH), 9.65 (s, 1H, NH); HRMS Calcd for $C_{15}H_{19}N_2O_3$ $[M+H]^+$: 275.1396; Found: 275.1392.

5-(4-Chlorophenyl)isoxazole (3g). mp 85–87°C (Lit. [18] 84–85°C); IR (KBr, cm^{-1}): 1648, 1447, 1256, 1128, 1109, 826; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.52 (d, J = 2.0 Hz, 1H, CH), 7.45 (d, J = 8.4 Hz, 2H, ArH), 7.73 (d, J = 8.4 Hz, 2H, ArH), 8.30 (d, J = 2.0 Hz, 1H, CH); HRMS Calcd for C_9H_7ClNO $[M+H]^+$: 180.0216; Found: 180.0215.

5-(4-Methoxyphenyl)isoxazole (3h). mp 60–61°C (Lit. [18] 64–65°C); IR (KBr, cm^{-1}): 1669, 1454, 1289, 1200, 1096, 812; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.85 (s, 3H, CH_3O), 6.39 (s, 1H, CH), 6.95 (d, J = 8.7 Hz, 2H, ArH), 7.73 (d, J = 8.7 Hz, 2H, ArH), 8.25 (s, 1H, CH); HRMS Calcd for $C_{10}H_{10}NO_2$ $[M+H]^+$: 176.0712; Found: 176.0715.

5-(Naphthalen-1-yl)isoxazole (3i). mp 91–92°C; IR (KBr, cm^{-1}): 1679, 1426, 1257, 1235, 1091, 843; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 6.63 (s, 1H, CH), 7.53-7.56 (m, 2H, ArH), 7.84–7.93 (m, 4H, ArH), 8.32 (d, J = 1.5 Hz, 2H, CH and ArH); HRMS Calcd for $C_{13}H_{10}NO$ $[M+H]^+$: 196.0762; found: 196.0768.

3-Methyl-5-(4-methylphenyl)isoxazole (3j). mp 90–91°C; IR (KBr, cm^{-1}): 1607, 1414, 1114, 1045, 956, 793; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.13 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 6.09 (s, 1H, CH), 7.04 (d, J = 8.8 Hz, 2H, ArH), 7.43 (d, J = 8.0 Hz, 2H, ArH); HRMS Calcd for $C_{11}H_{12}NO$ $[M+H]^+$: 174.0919; Found: 174.0914.

3-Methyl-5-phenylisoxazole (3k). mp 68–70°C; IR (KBr, cm^{-1}): 1601, 1424, 1087, 1037, 767, 686; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.36 (s, 3H, CH_3), 6.37 (s, 1H, CH), 7.41–7.47 (m, 3H, ArH), 7.76 (dd, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 2H, ArH); HRMS Calcd for $C_{10}H_{10}NO$ $[M+H]^+$: 160.0762; Found: 160.0770.

5-(4-Bromophenyl)isoxazole (3l). mp 110–112°C (Lit. [18] 114–116°C); IR (KBr, cm^{-1}): 1629, 1427, 1077, 1021, 846, 775; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.53 (d, J = 1.6 Hz, 1H, CH), 7.59–7.67 (m, 4H, ArH), 8.30 (s, 1H, CH). HRMS Calcd for C_9H_7BrNO $[M+H]^+$: 223.9711; Found: 223.9716.

5-(4-Chlorophenyl)-3-methyl-1H-pyrazole (5a). mp 142–144°C; IR (KBr, cm^{-1}): 3458, 1579, 1433, 1198, 1093, 1017, 834; ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.25 (s, 3H, CH_3), 6.46 (s, 1H, CH), 7.43 (d, J = 7.2 Hz, 2H, ArH), 7.76 (d, J = 7.6 Hz, 2H, ArH), 12.63 (s, 1H, NH); HRMS Calcd for $C_{10}H_{10}ClN_2$ $[M+H]^+$: 193.0532; Found: 193.0530.

5-(4-Bromophenyl)-3-methyl-1H-pyrazole (5b). mp 152–153°C; IR (KBr, cm^{-1}): 3443, 1584, 1433, 1288, 1074, 827; ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 2.24 (s, 3H, CH_3), 6.45 (s, 1H, CH), 7.57–7.70 (m, 4H, ArH), 12.68 (s, 1H, NH); HRMS Calcd for $C_{10}H_{10}BrN_2$ $[M+H]^+$: 237.0027; Found: 237.0025.

5-(2,4-Dichlorophenyl)-3-methyl-1H-pyrazole (5c). mp 100–102°C; IR (KBr, cm^{-1}): 3427, 1629, 1397, 1098, 1069, 804; ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.27 (s, 3H, CH_3), 6.50 (s, 1H, CH), 7.45 (d, J = 8.0 Hz, 1H, ArH), 7.64 (s, 1H, ArH), 7.79 (s, 1H, ArH), 12.83 (s, 1H, NH); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 11.6, 106.0, 127.3, 130.3, 130.5, 131.4, 133.1, 134.2, 142.4, 146.5; HRMS Calcd for $C_{10}H_9Cl_2N_2$ $[M+H]^+$: 227.0143; Found: 227.0125.

5-(4-Methoxyphenyl)-3-methyl-1H-pyrazole (5d). mp 130–131°C; IR (KBr, cm^{-1}): 3123, 2910, 1612, 1440, 1258, 1022, 835; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.23 (s, 3H, CH_3), 3.80 (s, 3H, CH_3O), 6.23 (s, 1H, CH), 6.84 (d, J = 8.4 Hz, 2H, ArH), 7.60 (d, J = 8.0 Hz, 2H, ArH), 9.74 (s, 1H, NH); HRMS Calcd for $C_{11}H_{13}N_2O$ $[M+H]^+$: 189.1028; Found: 189.1025.

Methyl 4-(5-methyl-2H-pyrazol-3-yl)benzoate (5e). mp 194–195°C; IR (KBr, cm^{-1}): 3139, 2856, 1634, 1276, 1038, 827; ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.28 (s, 3H, CH_3), 3.85 (s, 3H, CH_3O), 6.55 (s, 1H, CH), 7.90 (d, J = 8.0 Hz, 2H, ArH), 7.96 (d, J = 8.0 Hz, 2H, ArH), 12.77 (s, 1H, NH); HRMS Calcd for $C_{12}H_{13}N_2O_2$ $[M+H]^+$: 217.0977; Found: 217.0972.

tert-Butyl 4-(5-methyl-2H-pyrazol-3-yl)-phenylcarbamate (5f). mp 160–161°C; IR (KBr, cm^{-1}): 3116, 2902, 1643, 1028, 937, 827; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.52 (s, 9H, $(CH_3)_3C$), 2.28 (s, 3H, CH_3), 6.27 (s, 1H, CH), 6.75 (s, 1H, NH), 7.34 (d, J = 7.2 Hz, 2H, ArH), 7.59 (d, J = 8.4 Hz, 2H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 12.0, 28.6, 80.8, 101.9, 119.1, 126.5, 138.2, 153.1; HRMS Calcd for $C_{15}H_{20}N_3O_2$ $[M+H]^+$: 274.1556; Found: 274.1559.

5-(4-Chlorophenyl)-1H-pyrazole (5g). mp 99–100°C; IR (KBr, cm^{-1}): 3057, 2923, 1491, 1185, 1089, 957, 817; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 6.62 (s, 1H, CH), 7.38 (d, J = 8.4 Hz, 2H, ArH), 7.62 (s, 1H, CH), 7.71 (d, J = 8.1 Hz, 2H, ArH), 11.65 (s, 1H, NH); HRMS Calcd for $C_9H_8ClN_2$ $[M+H]^+$: 179.0376; Found: 179.0364.

5-(4-Methoxyphenyl)-1H-pyrazole (5h). mp 120–123°C; IR (KBr, cm^{-1}): 3088, 2932, 1486, 1089, 987, 839, 753, 676; ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 3.77 (s, 3H, CH_3O), 6.60 (s, 1H, CH), 6.93–7.00 (m, 2H, ArH), 7.49–7.72 (m, 3H, CH and ArH), 12.76 (s, 1H, NH); HRMS Calcd for $C_{10}H_{11}N_2O$ $[M+H]^+$: 175.0871; Found: 175.0866.

5-(4-Bromophenyl)-1H-pyrazole (5i). mp 128–129°C (Lit. [31] 132–134°C); IR (KBr, cm^{-1}): 3162, 2910, 1426, 1189, 1024, 998, 862; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.59 (d, J = 2.0 Hz, 1H, CH), 7.50 (d, J = 8.4 Hz, 2H, ArH), 7.56–7.62 (m, 3H, CH and ArH), 10.70 (s, 1H, NH); HRMS Calcd for $C_{10}H_{11}N_2$ $[M+H]^+$: 159.0922; Found: 159.0931.

3-Methyl-5-phenyl-1H-pyrazole (5j). mp 104–105°C (Lit. [32] 98–100°C); IR (KBr, cm^{-1}): 3125, 2920, 1612, 1528, 1434, 1126, 1001, 842; ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.24 (s, 3H, CH_3), 6.43 (s, 1H, CH), 7.25–7.28 (m, 1H, ArH), 7.36–7.40 (m, 2H, ArH), 7.73 (d, J = 7.6 Hz, 2H, ArH), 12.56 (s, 1H, NH); HRMS Calcd for $C_9H_8BrN_2$ $[M+H]^+$: 222.9871; Found: 222.9867.

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