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## ONE-POT SYNTHESIS OF 3,5-DIPHENYL-1H-PYRAZOLES FROM CHALCONES AND HYDRAZINE UNDER MECHANOCHEMICAL BALL MILLING

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**Abstract** – A highly efficient and environmentally friendly method has been developed for facile synthesis of 3,5-diphenyl-1H-pyrazoles under mechanochemical ball-milling conditions. The advantages of short reaction time, high efficiency, no separation of *in situ* generated intermediate, using cheap sodium persulfate as the oxidant, together with very simple work-up procedure, make this one-pot and solvent-free protocol a green and powerful alternative to traditional methods for the synthesis of these kinds of compounds.

### INTRODUCTION

It is well known that pyrazole scaffold has been contributing more and more in biological,<sup>1</sup> pharmacological,<sup>2</sup> food,<sup>3</sup> agrochemical fields<sup>4</sup> and so on. Due to its scarcity in nature, various methods have been developed for the synthesis of pyrazoles, among which the most commonly used strategies are: (a) condensation of 1,3-diketones with hydrazines; (b) 1,3-dipolar cycloadditions of terminal alkynes onto diazo compounds generated from aldehyde and tosyl hydrazide; (c) reaction of  $\alpha,\beta$ -unsaturated carbonyl compounds with hydrazines followed by further oxidation. But if a diversity-oriented synthesis of pyrazoles is desired, method (a) would be somewhat cumbersome as each 1,3-diketone must be purified and such obtained pyrazole is often a mixture of condensation products. As to method (b), the process involves diazo compounds, which are well known to be toxic and potentially explosive. Although various examples have been reported for the synthesis of pyrazoles from  $\alpha,\beta$ -unsaturated carbonyl compounds by method (c), there are still drawbacks such as rigorous or hazardous conditions, intractable side reactions, use of organic solvent, long reaction time, tedious procedures and so on. To circumvent these problems, one of the best alternatives is to carry out this kind of reactions under solvent-free conditions. Among current solvent-free techniques, mechanical ball-milling has recently been contributing more and more for efficient promotion of various organic reactions in a greener way.<sup>5,6</sup>

Considering the requirement of green chemistry, we have also successfully applied the mechanochemistry technique in some organic transformation in recent years.<sup>7</sup> Herein, we want to report a one-pot and solvent-free mechanochemical synthesis of various 3,5-diphenyl-1*H*-pyrazoles from chalcones and hydrazine, which can be used as a molecular scaffold for the synthesis of apoptosis-inducing agents<sup>8</sup> or as inhibitors of monoamine oxidases.<sup>9</sup>

## RESULTS AND DISCUSSION

We firstly chose chalcone **1a** as the model substrate to optimize the best reaction condition. A series of experiments were carried out in solution and under ball milling by varying the oxidant, the solvent and the reaction temperature, and the results are summarized in Table 1.

**Table 1.** Optimization of the reaction conditions for synthesis of 3,5-diphenyl-1*H*-pyrazole **2a** from chalcone **1a** and hydrazine<sup>a</sup>

Entry	Solvent	Oxidant	Temperature <sup>c</sup> (°C)	Time 1/Time 2 (min)	Product (Yield) <sup>d</sup>
1	no solvent <sup>b</sup>	KMnO <sub>4</sub>	rt (20~25)	40/60	<b>3</b> (trace) + <b>2a</b> (45%)
2	no solvent <sup>b</sup>	I <sub>2</sub>	rt (20~25)	40/60	<b>3</b> (35%) + <b>2a</b> (30%)
3	no solvent <sup>b</sup>	Mn(OAc) <sub>3</sub> ·2H <sub>2</sub> O	rt (20~25)	40/60	<b>3</b> (67%) + <b>2a</b> (15%)
4	no solvent <sup>b</sup>	Cu(OAc) <sub>2</sub>	rt (20~25)	40/60	<b>3</b> (83%) + <b>2a</b> (trace)
5	no solvent <sup>b</sup>	Ce(NH <sub>4</sub> ) <sub>2</sub> (NO <sub>3</sub> ) <sub>6</sub>	rt (20~25)	40/60	<b>3</b> (trace) + <b>2a</b> (85%)
6	no solvent <sup>b</sup>	Na <sub>2</sub> S <sub>2</sub> O <sub>8</sub>	rt (20~25)	40/60	<b>3</b> (trace) + <b>2a</b> (95%)
7	CH <sub>2</sub> Cl <sub>2</sub>	Na <sub>2</sub> S <sub>2</sub> O <sub>8</sub>	rt (20~25)	120/120	<b>1a</b> (22%) + <b>3</b> (35%) + <b>2a</b> (37%)
8	CH <sub>2</sub> Cl <sub>2</sub>	Na <sub>2</sub> S <sub>2</sub> O <sub>8</sub>	Refluxing	30/60	<b>3</b> (62%) + <b>2a</b> (29%)
9	THF	Na <sub>2</sub> S <sub>2</sub> O <sub>8</sub>	rt (20~25)	120/120	<b>1</b> (trace) + <b>3</b> (41%) + <b>2a</b> (48%)
10	THF	Na <sub>2</sub> S <sub>2</sub> O <sub>8</sub>	Refluxing	30/60	<b>3</b> (58%) + <b>2a</b> (40%)
11	DMF	Na <sub>2</sub> S <sub>2</sub> O <sub>8</sub>	rt (20~25)	120/120	<b>3</b> (20%) + <b>2a</b> (75%)
12	DMF	Na <sub>2</sub> S <sub>2</sub> O <sub>8</sub>	80	30/60	<b>3</b> (24%) + <b>2a</b> (70%)
13	DMSO	Na <sub>2</sub> S <sub>2</sub> O <sub>8</sub>	rt (20~25)	120/120	<b>3</b> (18%) + <b>2a</b> (79%)
14	DMSO	Na <sub>2</sub> S <sub>2</sub> O <sub>8</sub>	80	30/60	<b>3</b> (23%) + <b>2a</b> (73%)
15	EtOH	Na <sub>2</sub> S <sub>2</sub> O <sub>8</sub>	rt (20~25)	120/120	<b>1</b> (trace) + <b>3</b> (27%) + <b>2a</b> (68%)
16	EtOH	Na <sub>2</sub> S <sub>2</sub> O <sub>8</sub>	Refluxing	30/60	<b>3</b> (36%) + <b>2a</b> (53%)
17	EtOH	none	Refluxing	12 h	<b>3</b> (30%) + <b>2a</b> (56%)

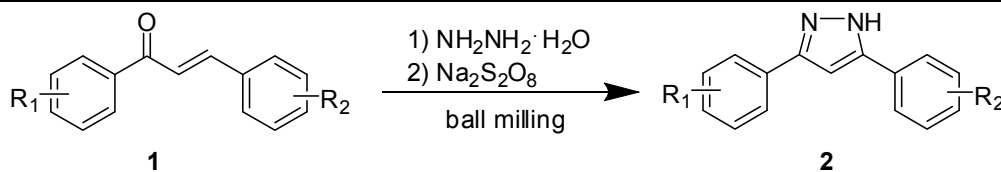
<sup>a</sup>All reactions were carried out with **1a** (2.0 mmol), hydrazine hydrate (2.2 mmol) and second-stepwise added oxidant (2.5 mmol) unless noted; For ball-milling: 1800 rpm (30 Hz) at room temperature; For stirring in solution: 15 mL solvent was employed at room temperature or under refluxing. <sup>b</sup>Carried out under ball-milling. <sup>c</sup>In fact, the temperature in the ball-milling reaction vessel reached up to 40-50 °C after the reaction, varying according to the reaction time.

<sup>d</sup>Determined by HPLC analysis.

Under the condition of ball milling at room temperature, the addition-cyclization of hydrazine with chalcone **1a** to form intermediate pyrazoline **3** can be almost completely accomplished within 40 minutes. Then we explored several oxidants to convert the *in situ* generated pyrazoline **3** into pyrazole **2a**, and found that potassium permanganate and iodine afforded rather low chemoselectivity, in which pyrazoline **3** was essentially consumed but the yield of the desired product pyrazole **2a** was very poor (entries 1, 2). This may be ascribed to side reactions resulted from too strong oxidizing capability of the oxidants. As to  $\text{Mn}(\text{OAc})_3$  and  $\text{Cu}(\text{OAc})_2$ , they cannot promote the conversion of pyrazoline **3** into pyrazole **2a** efficiently (entries 3, 4). In contrast,  $\text{Ce}(\text{NH}_4)_2(\text{NO}_3)_6$  and  $\text{Na}_2\text{S}_2\text{O}_8$  gave a relatively good result, producing pyrazole **2a** in good to excellent yield (entries 5, 6). But with a view to green synthesis including the factors such as yield, atom economy and cost,  $\text{Na}_2\text{S}_2\text{O}_8$  is undoubtedly the best oxidant for this transformation.

Using the optimized  $\text{Na}_2\text{S}_2\text{O}_8$  as the oxidant, we also performed several control experiments for this reaction in various solvents. At room temperature in all these solution cases, a relatively long time of two hours was needed for complete conversion of starting materials chalcone **1a** into pyrazoline **3**, which was obviously slower than that under ball milling condition. When  $\text{Na}_2\text{S}_2\text{O}_8$  was afterward added and further stirring was kept for two hours, the *in situ* generated pyrazoline **3** still remained in some extent. It was noted that strong polarity of the solvent favored the formation of the product pyrazole **2a**. For example, DMF and DMSO (entries 11-14) gave better conversion than that of  $\text{CH}_2\text{Cl}_2$  and THF. Under heating, the first addition-cyclization step became significantly rapid, in which chalcone **1a** was consumed within 30 minutes. When  $\text{Na}_2\text{S}_2\text{O}_8$  was added and heating was kept for another hour, both the conversion of pyrazoline **3** and the yield of pyrazole **2a** decreased to a certain extent. The reason may be that  $\text{Na}_2\text{S}_2\text{O}_8$  would decompose when heated in solution, making the desired usage amount of the oxidant insufficient. On the other hand, we found that even in the absence of any oxidant, pyrazoline **3** can be slowly converted into pyrazole **2a** just by heating in solution. For example, when a mixture of chalcone **1a** and hydrazine was directly refluxed for 12 hours in EtOH, chalcone **1a** was also completely consumed, forming 30% pyrazoline **3** and 56% pyrazole **2a** (entry 17). In general, the solvent-free condition of ball milling at room temperature has obvious advantages including short reaction time, high chemoselectivity and yield.

Inspired by the results as shown in Table 1, we then employed  $\text{Na}_2\text{S}_2\text{O}_8$  as the oxidant and applied the ball milling technique to access a wide variety of 3,5-diphenyl-1*H*-pyrazoles from various chalcones in a one-pot pathway. Under this mechanically promoted condition, the reactions proceeded cleanly without intermediate work-up and left no, or only traces of byproducts. The detailed results are outlined in Table 2.

**Table 2.** Results for mechanochemical synthesis of 3,5-diphenyl-1*H*-pyrazoles **2** from chalcones **1**

	Chalcone <b>1</b>	R <sub>1</sub>	R <sub>2</sub>	Pyrazole <b>2</b> <sup>a</sup>	Time 1/Time 2 (min)	Yield <sup>b</sup> (%)
1	<b>1a</b>	H	H	<b>2a</b>	40/60	92
2	<b>1b</b>	H	4-OMe	<b>2b</b>	40/50	92
3	<b>1c</b>	H	4-Cl	<b>2c</b>	45/60	85
4	<b>1d</b>	H	3, 4-Cl	<b>2d</b>	50/65	88
5	<b>1e</b>	H	4-Br	<b>2e</b>	50/60	93
6	<b>1f</b>	H	4-NO <sub>2</sub>	<b>2f</b>	50/65	80
7	<b>1g</b>	H	3-NO <sub>2</sub>	<b>2g</b>	50/65	88
8	<b>1h</b>	4-OMe	H	<b>2h</b>	40/50	92
9	<b>1i</b>	4-OMe	4-OMe	<b>2i</b>	40/50	90
10	<b>1j</b>	4-OMe	4-Cl	<b>2j</b>	50/60	88
11	<b>1k</b>	4-OMe	4-NO <sub>2</sub>	<b>2k</b>	45/65	83
12	<b>1l</b>	4-OMe	3-NO <sub>2</sub>	<b>2l</b>	50/65	89
13	<b>1m</b>	4-NO <sub>2</sub>	4-Br	<b>2m</b>	50/75	90
14	<b>1n</b>	4-NO <sub>2</sub>	4-Cl	<b>2n</b>	50/70	82
15	<b>1o</b>	4-NO <sub>2</sub>	4-NO <sub>2</sub>	<b>2o</b>	50/90	86

<sup>a</sup>Characterized by mp, IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR and HRMS analysis.

<sup>b</sup>Isolated yield combined from two parallel runs.

From Table 2 it can be seen that the first addition-cyclization step proceeded very smoothly within one hour in all cases, and substituents in chalcones **1** have no significant effect on this step. This may be explained that the  $\alpha,\beta$ -unsaturated carbonyl moiety in chalcone exhibits very strong electrophilicity, and hydrazine has both very strong nucleophilicity and basicity. These facts make the addition-cyclization of chalcone with hydrazine fairly easy whether the substituent is electron-donating or electron-withdrawing. But during the second step for oxidation of *in situ* generated intermediate pyrazoline into pyrazole, those cases bearing electron-donating groups exhibited obviously higher reaction activity, thus the reaction time for full conversion of intermediate pyrazoline into pyrazole was much shorter than those bearing electron-withdrawing groups. This point is easy to be understood that electron-donating groups cause electron density in pyrazoline ring very high, which favors the dehydrogenation in the presence of an oxidant.

In general, all these cases could afford good to excellent yields for the corresponding 3,5-diphenyl-1*H*-pyrazoles, which were obtained just through immersing the resulted reaction mixtures

into diluted HCl with the aid of ultrasonic irradiation and Büchner filtration. Furthermore, the reaction process involves no use of organic solvent, and only 10% excessive hydrazine was employed to achieve complete conversion of chalcone, which is much less than most traditional methods carried out in solution. All the products were well characterized by mp, IR,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR and HRMS analysis. It is noteworthy that tautomerism was evident in  $^{13}\text{C}$  NMR experiments of the 3,5-substituted pyrazoles as reported,<sup>9,10,12</sup> thus sometimes led to difficulty in assigning the corresponding  $^{13}\text{C}$  NMR signals.

In conclusion, we have successfully developed a facile, efficient and environmentally friendly method for synthesis of various 3,5-diphenyl-1*H*-pyrazoles using mechanochemical ball-milling technique. This one-pot protocol exhibits the advantages of short reaction time, free use of organic solvent, no separation of intermediates, low cost, simple work-up procedure, which make it a very efficient and green alternative to traditional methods for the synthesis of these kinds of compounds.

## EXPERIMENTAL

NMR spectra were recorded on a Bruker AV300 or AV400 NMR spectrometer in  $\text{CDCl}_3$  or  $\text{DMSO-}d_6$ . IR spectra were recorded on a Bruker VECTOR-22 instrument in KBr pellet. All melting points were determined on a XT-4 binocular microscope (Beijing Tech Instrument Co., China) and are not corrected. High resolution mass spectra (HR-MS) were recorded on a Micromass GCT-MS spectrometer with ESI mode. HPLC was conducted on an Agilent 1100 liquid chromatograph with a diode-array detector using a Zorbax Eclipse XDB-C18 (4.6 mm  $\times$  250 mm) with  $\text{MeCN:H}_2\text{O}$  (4:1) as the eluent (2 mL/min), and was monitored at 254 nm. All ball-milling reactions were performed on mixer mill MM 400 (Retsch GmbH, Germany). TLC and column chromatography were performed on silica gel GF254, and silica gel H60, respectively. All other chemicals used in this study were commercially available.

**Starting Materials.** Chalcones were prepared according to reported method,<sup>11</sup> and hydrazine (>99%) was purchased from Acros.

### Typical Procedure for the Preparation of Products 2

Chalcone **1** (2.0 mmol), hydrazine (2.2 mmol) and a stainless ball of 7.0 mm in diameter, were introduced into a stainless jar (25 mL). The same mixture was also introduced into a second parallel jar. The two reaction vessels were sealed with screw caps, fixed on the vibration arms of a ball-milling apparatus (mixer mill MM400, Retsch GmbH, Haan, Germany) and were vibrated vigorously at a rate of 1800 rounds per minute (30 Hz) at room temperature for designated time (Time 1). Then the vessels were opened and  $\text{Na}_2\text{S}_2\text{O}_8$  (2.5 mmol) were added into the resulted mixtures, and the sealed vessels were continued to vibrate for designated time (Time 2). The reaction mixtures were immersed in 30 mL water with the aid of ultrasonic irradiation, and the desired solid products were collected by Büchner filtration, washed with  $\text{EtOH/H}_2\text{O}$  (5 mL/5 mL) and dried in a desiccator.

**3-Phenyl-5-phenyl-1H-pyrazole (2a).** Mp 194–196 °C (lit.,<sup>12</sup> 197–199 °C); IR (KBr)  $\nu$  3241, 2834, 1462, 1274, 1182, 1075, 978, 750, 688  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  10.40 (brs, 1H, NH), 7.84 (brs, 4H, ArH), 7.45 (brs, 4H, ArH), 7.34 (brs, 2H, ArH), 7.21 (s, 1H, CH); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  147.4, 131.3, 128.9, 128.0, 125.2, 99.8; HRMS (ESI) *m/z* calcd for C<sub>15</sub>H<sub>13</sub>N<sub>2</sub> (M+H)<sup>+</sup>: 221.1079, found: 221.1068.

**5-(4-Methoxyphenyl)-3-phenyl-1H-pyrazole (2b).** Mp 164–166 °C (lit.,<sup>13</sup> 166–168 °C); IR (KBr)  $\nu$  3029, 2836, 1612, 1510, 1461, 1251, 1169, 1033, 976, 833, 765  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.71 (d, *J* = 6.9 Hz, 2H, ArH), 7.62 (d, *J* = 8.4 Hz, 2H, ArH), 7.31–7.40 (m, 1H, ArH), 7.36 (d, *J* = 7.5 Hz, 2H, ArH), 6.90 (d, *J* = 8.4 Hz, 2H, ArH), 6.74 (s, 1H, CH), 3.82 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  159.0, 143.8, 143.4, 133.8, 128.7, 127.9, 127.6, 126.4, 125.0, 114.2, 98.8, 55.1; HRMS (ESI) *m/z* calcd for C<sub>16</sub>H<sub>15</sub>N<sub>2</sub>O (M+H)<sup>+</sup>: 251.1184, found: 251.1157.

**5-(4-Chlorophenyl)-3-phenyl-1H-pyrazole (2c).** Mp 212–213 °C (lit.,<sup>9</sup> 217–219 °C); IR (KBr)  $\nu$  3217, 2920, 2850, 1588, 1491, 1448, 1182, 1097, 970, 758, 688  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  13.44 (brs, 1H, NH), 7.87 (brs, 2H, ArH), 7.83 (brs, 2H, ArH), 7.52 (brs, 2H, ArH), 7.47 (brs, 2H, ArH), 7.36 (brs, 1H, ArH), 7.23 (s, 1H, CH), 7.13–7.16 (m, 1H, ArH), 6.90–6.96 (m, 2H, ArH), 3.94 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  147.2, 142.1, 132.2, 128.8 (3C overlapped), 128.1, 128.0, 126.8, 125.1, 99.9; HRMS (ESI) *m/z* calcd for C<sub>15</sub>H<sub>12</sub>ClN<sub>2</sub> (M+H)<sup>+</sup>: 255.0689, found: 255.0673.

**5-(3,4-Dichlorophenyl)-3-phenyl-1H-pyrazole (2d).** Mp 194–195 °C; IR (KBr)  $\nu$  3045, 2913, 2845, 1603, 1432, 1038, 956, 865, 743, 691  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  13.51 (brs, 1H, NH), 8.07 (s, 1H, ArH), 7.77–7.83 (m, 3H, ArH), 7.68 (s, 1H, ArH), 7.38–7.47 (m, 2H, ArH), 7.31 (s, 1H, ArH), 7.20 (s, 1H, ArH); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  149.0, 143.8, 134.3, 130.9, 129.7, 129.0, 128.6, 128.3, 127.6, 126.8, 126.6, 125.1, 100.3; HRMS (ESI) *m/z* calcd for C<sub>15</sub>H<sub>11</sub>Cl<sub>2</sub>N<sub>2</sub> (M+H)<sup>+</sup>: 289.0299, found: 289.0292; Anal. Calcd for C<sub>15</sub>H<sub>10</sub>Cl<sub>2</sub>N<sub>2</sub>: C, 62.30; H, 3.49; N, 9.69. Found: C, 62.46; H, 3.53; N, 9.58.

**5-(4-Bromophenyl)-3-phenyl-1H-pyrazole (2e).** Mp 232–233 °C (lit.,<sup>14</sup> 219–220 °C); IR (KBr)  $\nu$  3042, 2910, 2844, 1601, 1232, 1057, 955, 793, 689  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  13.45 (brs, 1H, NH), 7.82 (brs, 4H, ArH), 7.64 (brs, 2H, ArH), 7.48 (brs, 2H, ArH), 7.37 (brs, 1H, ArH), 7.24 (s, 1H, CH); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  150.3, 143.7, 131.6, 129.0, 128.8, 128.2, 128.0, 127.1, 125.1, 120.6, 99.9; HRMS (ESI) *m/z* calcd for C<sub>15</sub>H<sub>12</sub>BrN<sub>2</sub> (M+H)<sup>+</sup>: 299.0184, found: 299.0175.

**5-(4-Nitrophenyl)-3-phenyl-1H-pyrazole (2f).** Mp 259–261 °C (lit.,<sup>8</sup> 281 °C); IR (KBr)  $\nu$  3348, 2916, 2848, 1604, 1516, 1346, 856, 768, 698  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  13.72 (brs, 1H, NH), 8.29 (d, *J* = 8.4 Hz, 2H, ArH), 8.12 (d, *J* = 8.4 Hz, 2H, ArH), 7.81 (d, *J* = 7.5 Hz, 2H, ArH), 7.37–7.51 (m, 3H, ArH), 7.34 (s, 1H, CH); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  146.9, 145.2, 142.0, 129.5, 128.9, 126.3, 125.6, 124.6, 101.5; HRMS (ESI) *m/z* calcd for C<sub>15</sub>H<sub>12</sub>N<sub>3</sub>O<sub>2</sub> (M+H)<sup>+</sup>: 266.0930, found: 266.0924.

**5-(3-Nitrophenyl)-3-phenyl-1H-pyrazole (2g).** Mp 199–201 °C (lit.,<sup>15</sup> 204–205 °C); IR (KBr)  $\nu$  3125, 2918, 2849, 1604, 1513, 1356, 1093, 930, 813, 791  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  8.68 (s, 1H, ArH), 8.31 (d,  $J = 7.8$  Hz, 1H, ArH), 8.18–8.21 (m, 1H, ArH), 7.79–7.87 (m, 2H, ArH), 7.74–7.77 (m, 1H, ArH), 7.37–7.52 (m, 4H, ArH), 4.58 (brs, 1H, NH);  $^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ )  $\delta$  148.8, 147.6, 146.4, 134.5, 131.8, 130.9, 130.5, 129.4, 128.6, 125.6, 122.6, 119.7, 101.0; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{15}\text{H}_{12}\text{N}_3\text{O}_2$  (M+H) $^+$ : 266.0930, found: 266.0928.

**3-(4-Methoxyphenyl)-5-phenyl-1H-pyrazole (2h).** Mp 158–160 °C (lit.,<sup>16</sup> 160–162 °C); IR (KBr)  $\nu$  3128, 2921, 2832, 1603, 1504, 1383, 1297, 1034, 931, 828  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  13.04 (brs, 1H, NH), 7.83 (d,  $J = 7.3$  Hz, 2H, ArH), 7.76 (d,  $J = 8.8$  Hz, 2H, ArH), 7.43 (t,  $J = 7.5$  Hz, 2H, ArH), 7.32 (t,  $J = 7.4$  Hz, 1H, ArH), 7.02 (d,  $J = 8.8$  Hz, 2H, ArH), 6.99 (s, 1H, CH), 3.81 (s, 3H, OCH<sub>3</sub>);  $^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ )  $\delta$  158.8, 128.3, 127.2, 126.2, 124.8, 114.0, 98.5, 54.9; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{16}\text{H}_{15}\text{N}_2\text{O}$  (M+H) $^+$ : 251.1184, found: 251.1169.

**3,5-Bis(4-methoxyphenyl)-1H-pyrazole (2i).** Mp 156–157 °C (lit.,<sup>17</sup> 153 °C); IR (KBr)  $\nu$  3417, 2964, 2937, 2840, 1610, 1496, 1440, 1303, 1246, 1110, 1022, 962, 835, 792, 642  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  12.89 (brs, 1H, NH), 7.43 (d,  $J = 8.8$  Hz, 4H, ArH), 7.01 (d,  $J = 8.8$  Hz, 4H, ArH), 6.88 (s, 1H, CH), 3.81 (s, 6H, OCH<sub>3</sub>);  $^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ )  $\delta$  158.7, 126.1, 113.9, 97.9, 54.9; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{17}\text{H}_{17}\text{N}_2\text{O}_2$  (M+H) $^+$ : 281.1290, found: 281.1283.

**5-(4-Chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazole (2j).** Mp 164–166 °C; IR (KBr)  $\nu$  3230, 2919, 2838, 1666, 1601, 1504, 1255, 1169, 1095, 968, 835, 789  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  13.27 (brs, 1H, NH), 7.82 (brs, 2H, ArH), 7.71 (brs, 2H, ArH), 7.53 (brs, 2H, ArH), 7.09 (s, 1H, CH), 7.02 (brs, 2H, ArH), 3.77 (s, 3H, OCH<sub>3</sub>);  $^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ )  $\delta$  159.5, 141.5, 141.2, 132.0, 130.5, 129.2, 128.5, 127.2, 126.9, 114.7, 99.5, 55.6; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{16}\text{H}_{14}\text{ClN}_2\text{O}$  (M+H) $^+$ : 285.0795, found: 285.0782; Anal. Calcd for  $\text{C}_{16}\text{H}_{13}\text{ClN}_2\text{O}$ : C, 67.49; H, 4.60; N, 9.84. Found: C, 67.46; H, 4.65; N, 9.77.

**5-(4-Nitrophenyl)-3-(4-methoxyphenyl)-1H-pyrazole (2k).** Mp 174–175 °C; IR (KBr)  $\nu$  3233, 2902, 2861, 1612, 1523, 1374, 1078, 930, 813, 749  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  13.57 (brs, 1H, NH), 8.31 (d,  $J = 8.1$  Hz, 2H, ArH), 8.13 (d,  $J = 8.1$  Hz, 2H, ArH), 7.77 (d,  $J = 7.8$  Hz, 2H, ArH), 7.32 (s, 1H, CH), 7.07 (d,  $J = 8.1$  Hz, 2H, ArH), 3.82 (s, 3H, OCH<sub>3</sub>);  $^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ )  $\delta$  159.7, 149.6, 146.8, 144.5, 140.6, 127.0, 126.2, 124.6, 122.0, 114.8, 100.6, 55.6; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{16}\text{H}_{14}\text{N}_3\text{O}_3$  (M+H) $^+$ : 296.1035, found: 296.1031; Anal. Calcd for  $\text{C}_{16}\text{H}_{13}\text{N}_3\text{O}_3$ : C, 65.08; H, 4.44; N, 14.23. Found: C, 65.15; H, 4.51; N, 14.19.

**5-(3-Nitrophenyl)-3-(4-methoxyphenyl)-1H-pyrazole (2l).** Mp 195–196 °C; IR (KBr)  $\nu$  3337, 2898, 2832, 1608, 1511, 1392, 1338, 1108, 938, 846, 754  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  13.45 (brs, 1H,

NH), 8.62 (s, 1H, ArH), 8.28 (d,  $J = 7.8$  Hz, 1H, ArH), 8.15 (d,  $J = 8.1$  Hz, 1H, ArH), 7.69–7.76 (m, 3H, ArH), 7.30 (s, 1H, CH), 7.04 (d,  $J = 8.7$  Hz, 2H, ArH), 3.79 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) 159.8, 148.8, 144.0, 142.5, 136.7, 131.7, 130.7, 127.0, 122.4, 122.1, 119.6, 114.9, 99.9, 55.6; HRMS (ESI)  $m/z$  calcd for C<sub>16</sub>H<sub>14</sub>N<sub>3</sub>O<sub>3</sub> (M+H)<sup>+</sup>: 296.1035, found: 296.1027; Anal. Calcd for C<sub>16</sub>H<sub>13</sub>N<sub>3</sub>O<sub>3</sub>: C, 65.08; H, 4.44; N, 14.23. Found: C, 65.17; H, 4.52; N, 14.16.

**5-(4-Bromophenyl)-3-(4-nitrophenyl)-1H-pyrazole (2m).** Mp 243–244 °C; IR (KBr)  $\nu$  3277, 3001, 2938, 2844, 1597, 1515, 1487, 1351, 1237, 1055, 936, 742 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) 13.75 (brs, 1H, NH), 8.27–8.35 (m, 2H, ArH), 8.06–8.12 (m, 2H, ArH), 7.61–7.84 (m, 4H, ArH), 7.45 (s, 1H, CH); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) 149.5, 146.4, 142.9, 139.8, 131.6, 128.1, 127.1, 125.8, 124.1, 121.5, 101.4; HRMS (ESI)  $m/z$  calcd for C<sub>15</sub>H<sub>11</sub>BrN<sub>3</sub>O<sub>2</sub> (M+H)<sup>+</sup>: 344.0035, found: 344.0024; Anal. Calcd for C<sub>15</sub>H<sub>10</sub>BrN<sub>3</sub>O<sub>2</sub>: C, 52.35; H, 2.93; N, 12.21. Found: C, 52.39; H, 2.94; N, 12.24.

**5-(4-Chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazole (2n).** Mp 234–236 °C; IR (KBr)  $\nu$  3431, 2916, 2850, 1602, 1516, 1491, 1344, 976, 852 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) 8.31 (d,  $J = 9.0$  Hz, 2H, ArH), 7.96 (d,  $J = 8.7$  Hz, 2H, ArH), 7.60 (d,  $J = 8.4$  Hz, 2H, ArH), 7.46 (d,  $J = 8.7$  Hz, 2H, ArH), 6.94 (s, 1H, CH); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) 146.5, 144.3, 143.8, 143.6, 129.6, 129.1, 128.5, 126.9, 125.8, 121.4, 101.5; HRMS (ESI)  $m/z$  calcd for C<sub>15</sub>H<sub>11</sub>ClN<sub>3</sub>O<sub>2</sub> (M+H)<sup>+</sup>: 300.0540, found: 300.0531; Anal. Calcd for C<sub>15</sub>H<sub>10</sub>ClN<sub>3</sub>O<sub>2</sub>: C, 60.11; H, 3.36; N, 14.02. Found: C, 60.20; H, 3.31; N, 13.93.

**3,5-Bis(4-nitrophenyl)-1H-pyrazole (2o).** Mp 257–258 °C (lit.,<sup>18</sup> 266 °C); IR (KBr)  $\nu$  3273, 2925, 2843, 1597, 1516, 1478, 1355, 1237, 1074, 915, 707 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  14.07 (brs, 1H, NH), 8.30–8.39 (m, 4H, ArH), 8.07–8.16 (m, 4H, ArH), 7.69 (s, 1H, CH); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  147.0, 139.1, 129.5, 124.6, 101.5; HRMS (ESI)  $m/z$  calcd for C<sub>15</sub>H<sub>11</sub>N<sub>4</sub>O<sub>4</sub> (M+H)<sup>+</sup>: 311.0780, found: 311.0773.

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