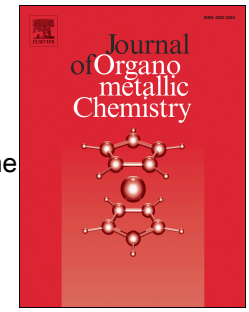
Accepted Manuscript



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Facile Synthesis of Pyrazoles by Iron-catalyzed Regioselective Cyclization of Hydrazone and 1,2-diol under Ligand-free Conditions

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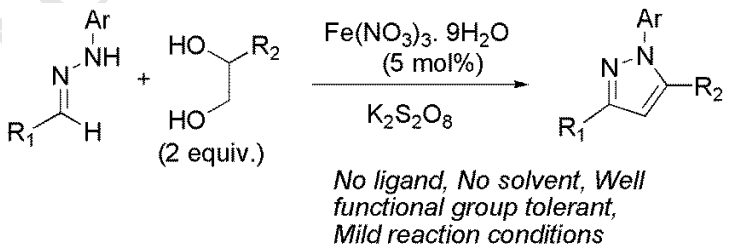
KEYWORDS: Pyrazoles, Iron-catalysis, 1,2-diol, hydrazones, ligand-free condition

ABSTRACT: A facile synthesis of pyrazoles by the cyclization of hydrazones and 1,2-diols was described. In the presence of ferric nitrate, the reaction occurs under neat conditions and makes the use of potassium persulfate to oxidize the diol to α-hydroxy carbaldehyde for the reaction with hydrazones to produce 1,3- and 1,3,5-substituted pyrazoles selectively. The overall regioselective transformation occurs in one-pot under ligand-free, mild conditions even in the presence of air.

Graphical Abstract



Highlights

- An iron-catalyzed protocol for the synthesis of N-aryl pyrazoles starting from hydrazone and 1,2-diol was described.
- This reaction proceeds under mild reaction conditions in the absence of any ligand
- This protocol eliminates the regioselective issue that usually associated with 1,3,5-trisubstituted pyrazoles.

1.1 Introduction

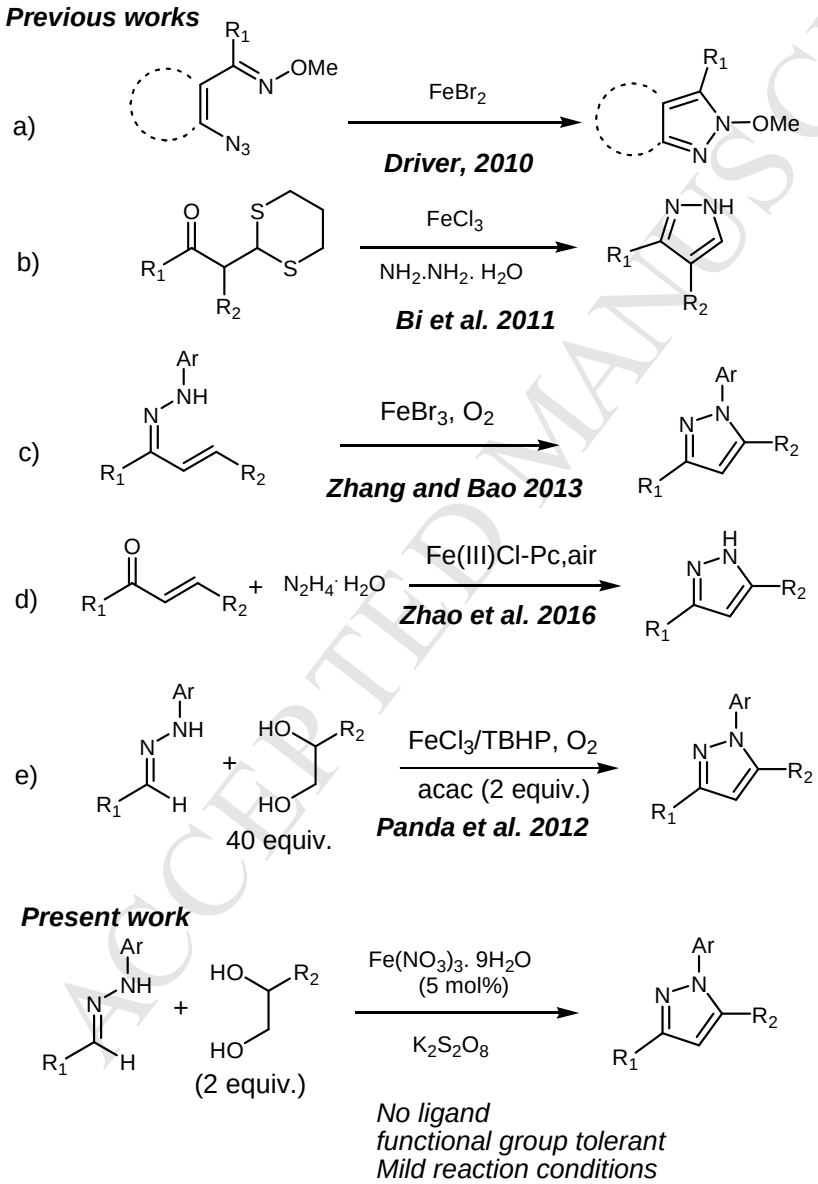
Pyrazoles are privileged structural motifs abundant in numerous agrochemicals and pharmaceuticals.[1] Substituted pyrazoles show a broad spectrum of biological activities, including anti-inflammatory, antipyretic, analgesic, sedative, and hypnotic properties.[2] They are also often realized as optical brighteners,[3] ultraviolet stabilizers,[4] and building blocks in supramolecular assemblies.[5] Of the many methods developed, acid-catalyzed cyclocondensation of hydrazines with 1, 3- dicarbonyl compounds (known as Knorr pyrazole synthesis) has been adapted as the standard method to achieve pyrazoles.[6,7] However, multistep access to appropriately substituted dicarbonyl compounds and lack of regiospecificity of the product greatly reduce the attractiveness of this method.[8] 1,3-dipolar cycloaddition of diazoalkanes or nitrile imines with olefins or alkynes is another increasingly used method to synthesize pyrazoles.[7,9] Notably, though the later method somewhat overcomes the regioselectivity problem; difficulty in preparation and explosive nature of diazonium salt vitiate the large scale use.[10] As a result, development of other alternative synthetic methods has been received considerable attention. Indeed, several prevalent miscellaneous methods, including transition-metal-catalyzed cyclocondensation and functionalization of pyrazole core-structure leading to the target molecule have been emerged. For this purpose, several transition metal catalysts including Pd, Cu, Rh, Ru and Co have been employed.[11] Moreover, these catalysts are expensive and have their inherent toxicity. Thus, the use of an efficient, environmentally benign and less expensive commercially viable catalysts, such Fe for the construction of pyrazole structure is stimulating.[12] Evidently, there appear scattered precedents on the Fe-catalyzed synthesis of pyrazole derivatives.[13] For instance, iron(II) bromide catalyzed reaction of azides with methyl oxime substituents led to pyrazoles through the formation of an N-O or N-N bond was developed by Driver and co-

workers (Scheme 1a).[13a] In 2011, Bi et al. reported an iron-catalyzed method for the aminolysis of β-carbonyl 1,3-dithianes with hydrazine hydrate to produce 3,4-disubstituted pyrazoles in good yields (Scheme 1b).[13b] Zhang and Bao reported $FeBr_3/O_2$ mediated facile synthesis of substituted pyrazoles from arylhydrazones via C−H activation/C−N bond formation reactions (Scheme 1c).[13c] Very recently, Zhao and co-workers developed an iron(III) phthalocyanine chloride-catalyzed oxidation–aromatization protocol for the synthesis of 3,5-disubstituted 1H-pyrazoles by the reaction of α, β-unsaturated ketones with hydrazine hydrate (Scheme 1d).[13d] Besides, previously, we have developed a strategically different, ligand-mediated $FeCl_3/O_2$-catalyzed method for the regioselective synthesis of 1,3- and 1,3,5-substituted pyrazoles from the reaction of diarylhydrazones and vicinal diols under neat conditions (Scheme 1e).[14] Although our method merits over complete regioselectivity control, necessities for stoichiometric excess amounts of diol (liquid) and optimal ligand (i.e., acetylacetone, 2 equiv), which is quite wasteful, are striking shortcomings. Within this context, in continuation of our earlier work[15] here we report a more simple iron-catalyzed outcompeted method for the synthesis of 3- and 3,5-substituted N-arylpyrazoles from the reaction of diaryl hydrazones and diols under ligand-free conditions using less expensive oxidant.

In our earlier report,[14] we have proposed that the ligand-mediated selective oxidation of vicinal diol by Fe^{+3}/TBHP produces α-hydroxy carbonyl compound; which subsequently reacts with hydrazone of carbaldehyde affords pyrazole in-situ. Evidently, in the absence of ligand (i.e. acetyl acetone) the reaction produces only 13% of the required pyrazole, while the use of the stoichiometric excess of ligand (2 equiv.) improves the yield. Indeed, the excess of ligand is not only wasteful but also somewhat poses difficulty in purification. Therefore, development of a simple and economical method for the regioselective synthesis of pyrazoles seems to be worthy.

In this context, we speculated that if the overall oxidation of diol can be achieved by any other oxidant under ligand-free conditions in-situ, then the desired pyrazoles could be obtained regioselectively from the reaction of hydrazone in the presence of less expensive eco-friendly Fe-catalyst.

Scheme 1. ***Fe-catalyzed pyrazole synthesis***

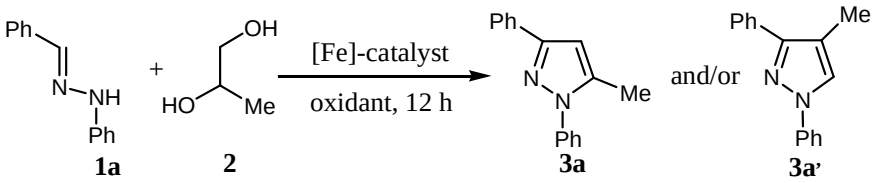


1.2 Results and Discussion

We, therefore, began our study with the screening of various oxidants in the presence of Fe-catalysts for the reaction of phenyl hydrazone of benzaldehyde (**1**) and 1,2-propane diol (**2**) (Table 1). To our dismay when the reactions were conducted with the oxidants such as CAN, BQ, H_2O_2 in the presence $Fe(NO_3)_3.9H_2O$ (5 mol%) catalyst, desired pyrazole **3a** was not formed rather hydrazone (**1a**) decomposed completely (entries 1-3). Moreover, similar reactions in the presence of other oxidants such as TBHP, MnO_2, DDQ, Ag_2CO_3, Ag_2O, AgOAc, oxone and $(NH_4)_2S_2O_8$ produce **3a** in 13-44% yield (entries 4-11) under neat conditions (hydrazone 1 equiv., diol 15 equiv. and oxidant 1 equiv. at 60°C). Moreover, an improved yield of 47% was achieved when 1 equiv. of potassium persulfate ($K_2S_2O_8$) was used as the terminal oxidant (entry 12). Notably, lowering the temperature to room temperature and decreasing the concentration of diol to 2 equiv. increases the yield of the reaction further to 52% (entry 13). Additionally, the optimum yield of 68% was obtained when hydrazone (**1a**) was treated with propane diol (**2**) (2 equiv.) in the presence of 2 equiv. of potassium persulfate at room temperature for 12 h (entry 14). Further rise in the concentration of $K_2S_2O_8$ or prolonged stirring for 24h did not afford better yield. To test the catalytic efficiency of other iron salts such as $FeCl_2$, $FeBr_3$, $Fe(acac)_2$, $FeCl_3$, $FeSO_4$, the similar reaction was performed (entries 15-21). However, $Fe(NO_3)_3$ furnished the best yield. Addition of acetyl acetone (2 equiv.) as ligand[14] did not improve the yield of **3a**, rather detrimental effect (39% yield) was observed. Under controlled experimental condition when the reaction was carried out in the absence of any oxidant, i.e., treatment of **1a** with **2** in the presence of ferric nitrate did not produce any pyrazole **3a** with complete recovery of starting material (entry 22). While similar reaction in the absence of iron salt and the presence peroxosulfate afforded **3a** in 13% yield (entry 23). Surprisingly, in the presence of any polar as well as non-polar solvents no or trace amount of product forms with the decomposition of

hydrazone **1a**. Additionally, we have not identified any 3, 4-substituted N-aryl pyrazole (**3a'**) from the reaction mixture.

Table 1. Optimization of reaction conditions[a]



Entry	Oxidant	Catalyst	Yield (%)[b]
1	CAN	$Fe(NO_3)_3.9H_2O$	0
2	BQ	$Fe(NO_3)_3.9H_2O$	0
3	H_2O_2	$Fe(NO_3)_3.9H_2O$	0
4	TBHP	$Fe(NO_3)_3.9H_2O$	21
5	MnO_2	$Fe(NO_3)_3.9H_2O$	13
6	DDQ	$Fe(NO_3)_3.9H_2O$	44
7	Ag_2CO_3	$Fe(NO_3)_3.9H_2O$	23
8	AgOAc	$Fe(NO_3)_3.9H_2O$	41
9	Ag_2O	$Fe(NO_3)_3.9H_2O$	49
10	Oxone	$Fe(NO_3)_3.9H_2O$	47
11	$(NH_4)_2S_2O_8$	$Fe(NO_3)_3.9H_2O$	33
12	$K_2S_2O_8$	$Fe(NO_3)_3.9H_2O$	47
13	$K_2S_2O_8$	$Fe(NO_3)_3.9H_2O$	52[c]
14	**$K_2S_2O_8$**	**$Fe(NO_3)_3.9H_2O$**	**68**[d]
15	$K_2S_2O_8$	$FeCl_2$	36[d]
16	$K_2S_2O_8$	$FeBr_3$	51[d]

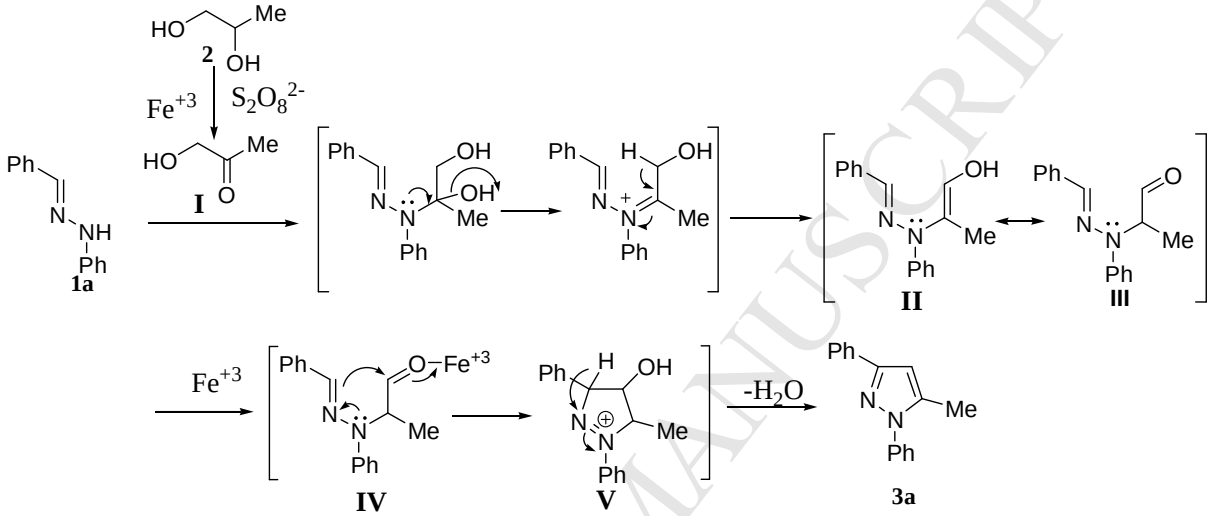
17	$K_2S_2O_8$	Fe_3O_4	49[d]
18	$K_2S_2O_8$	$Fe(acac)_3$	47[d]
19	$K_2S_2O_8$	$FeCl_3$	38[d]
20	$K_2S_2O_8$	$FeCl_3.6H_2O$	32[d]
21	$K_2S_2O_8$	$FeSO_4.7H_2O$	27[d]
22	--	$Fe(NO_3)_3.9H_2O$	N.R.
23	$K_2S_2O_8$	-	13

[a] Reaction conditions: Hydrazone **1a** (100 mg, 0.51 mmol), diol **2** (15 equiv), oxidant (0.51 mmol, 1 equiv), catalyst (5 mol%), 60°C. [b]GC yield. [c] Hydrazone **1a** (100 mg, 0.51 mmol), diol **2** (2 equiv), oxidant (0.51 mmol, 1 equiv), catalyst (5 mol%), rt. [d] Hydrazone **1a** (100 mg, 0.51 mmol), diol **2** (2 equiv), oxidant (1.02 mmol, 2 equiv), catalyst (5 mol%), rt.

To explain the reaction pathway and regioselectivity, some experiments were performed. For instance when benzyl alcohol (0.51 mmol) was treated with 1 equiv. of $K_2S_2O_8$ in the presence of $Fe(NO_3)_3.9H_2O$, benzaldehyde was produced (50% yield) with complete consumption of the starting material at room temperature. While the similar reaction of 1-phenylethane-1,2-diol (0.36 mmol) afforded 2-hydroxy-1-phenylethanone[16] (24% yield) along with some other unidentified impurities; which indicates that the catalytic protocol initially oxidizes the secondary alcoholic group preferentially than the primary alcoholic –OH group though the exact reason is not known yet.[17] A plausible mechanism for overall transformation is described in Scheme 2. Thus, in the presence of $K_2S_2O_8$ and $Fe(NO_3)_3.9H_2O$, 1,2-propane diol (**2**) oxidized to 1-hydroxypropan-2-one (**I**), which subsequently reacts with hydrazone **1a** to produce the enol **II** via the iminium ion intermediate. **II** might be tautomerized to the corresponding carbonyl

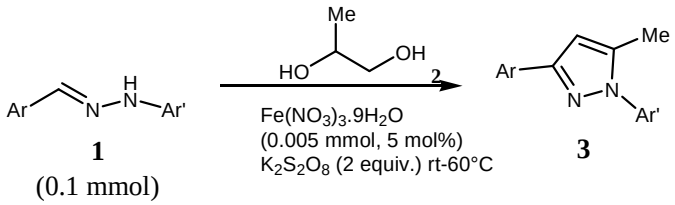
compound **III**. Co-ordination of iron to the carbonyl group and subsequent intramolecular annulation leads to the intermediate **V**. Removal of water as well aromatization produces the desired pyrazole **3a**.

Scheme 2. Plausible mechanism

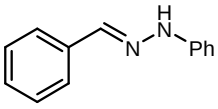
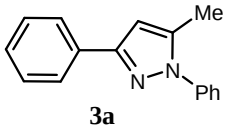
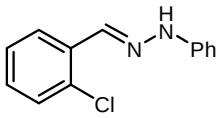
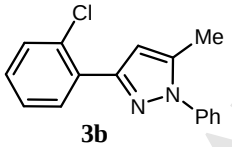
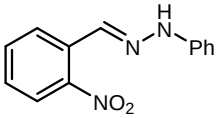
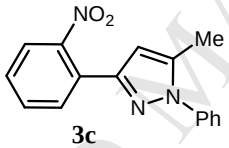
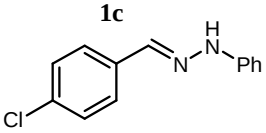
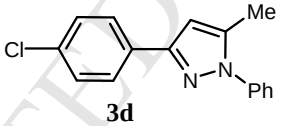
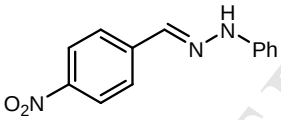
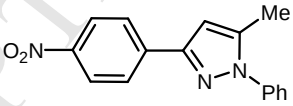
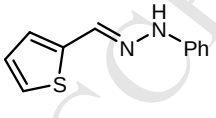
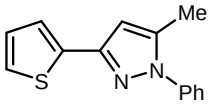
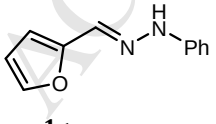
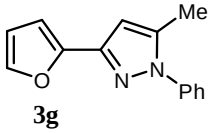


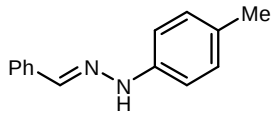
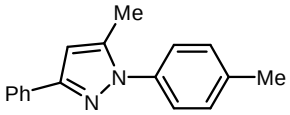
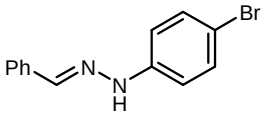
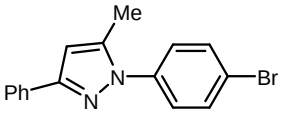
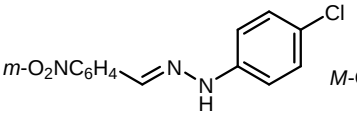
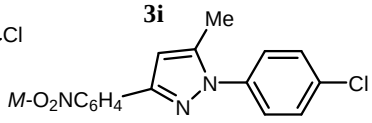
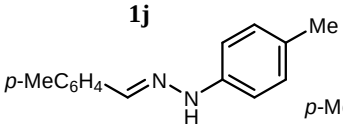
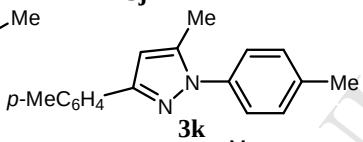
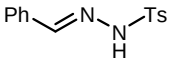
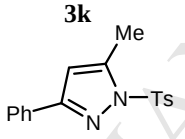
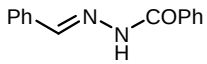
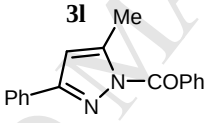
With the optimum condition in hand, scope and limitation of the reaction were investigated (Table 2). Thus, when phenyl hydrazones of differently substituted aryl carbaldehyde react with the 1,2-propane diol, the corresponding 1,3,5-trisubstituted pyrazoles were produced smoothly in moderate yield. Hydrazones having both electron-donating and -withdrawing groups attached to hydrazones (**1a**-**1e**) afforded the desired pyrazoles **3a**-**3e** in moderate yield. Hydrazones derived from thiophene 2-carbaldehyde produces the substituted pyrazoles (**3f**), while the similar reaction of furfural failed with the complete decomposition of starting material (**3g**). Besides, hydrazones derived from the differently substituted aryl hydrazines (i.e., -Me, –Cl, -Br) produces the corresponding 1,3,5-substituted pyrazoles in appreciable yield. However, hydrazones with the corresponding electron-withdrawing groups (**1l**, **1m**) were failed to give pyrazole (i.e., **3l** and **3m**) probably due to the poor nucleophilicity of nitrogen (e.g., **1** → **II**).

Table 2. Synthesis of 1,3,5-substituted pyrazoles



1 (0.1 mmol) **3**

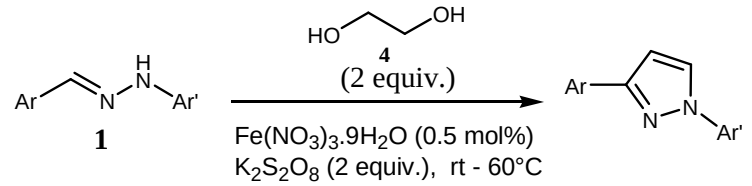
Entry	substrate	product	yield (%)
1	 **1a**	 **3a**	68
2	 **1b**	 **3b**	32
3	 **1c**	 **3c**	45[b]
4	 **1d**	 **3d**	66
5	 **1e**	 **3e**	39[b]
6	 **1f**	 **3f**	38
7	 **1g**	 **3g**	0

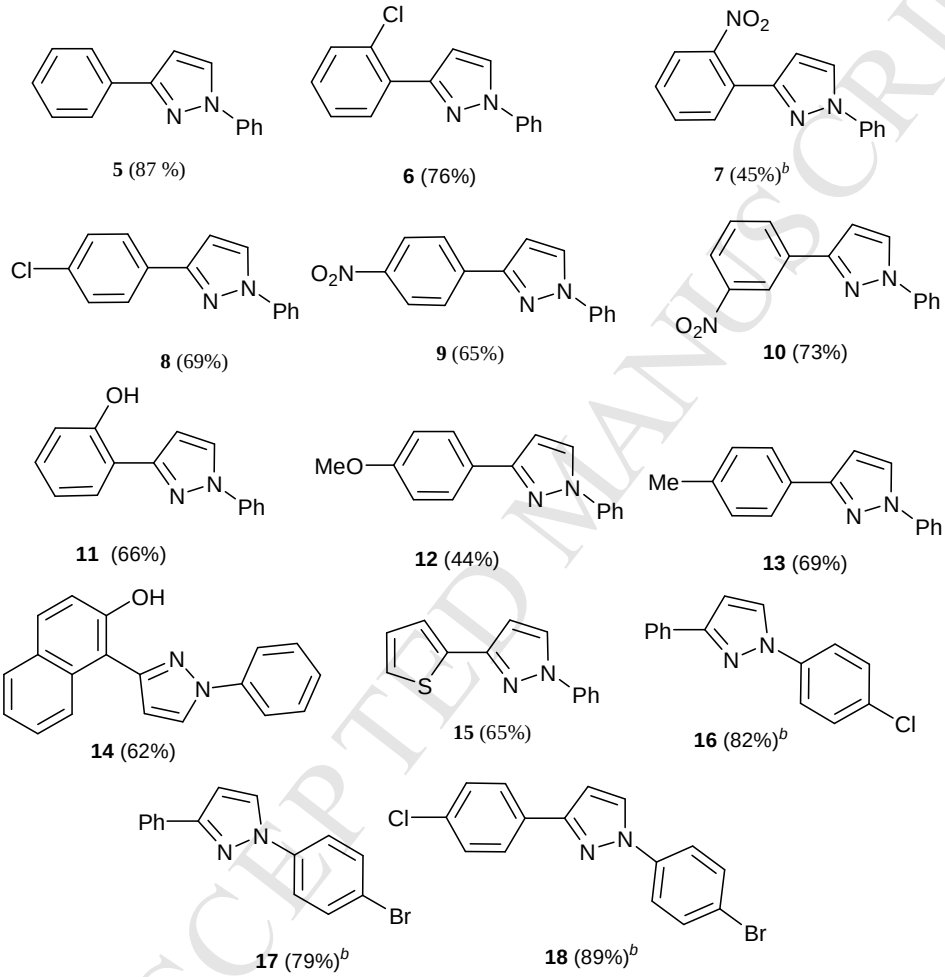
Entry	substrate	product	yield (%)
8	 **1h**	 **3h**	42 *b*
9	 **1i**	 **3i**	48 *b*
10	 **1j**	 **3j**	68 *b*
11	 **1k**	 **3k**	65 *b*
12	 **1l**	 **3l**	0
13	 **1m**	 **3m**	0

[a] **Reaction conditions: 1** (0.51 mmol), **2** (1.02 mmol, 2 equiv), oxidant (1.02 mmol, 2.0 equiv), $Fe(NO_3)_3.9H_2O$ (5 mol %), rt, 12h. [b] similar condition but heated at 60°C.

Next, we surveyed the suitability of this protocol for the synthesis of 1,3-substituted pyrazoles (Scheme 3) from the reaction of hydrazone from the carbaldehyde (**1**) and ethylene glycol (**4**). Interestingly, under similar reaction conditions, various 1,3-disubstituted pyrazoles (**5-18**) were produced readily even at room temperature in moderate to good yield.

Scheme 3. Synthesis of 1,3-diaryl pyrazoles





[a]*Reaction conditions*: **1** (0.51 mmol), **4** (1.02 mmol, 2 equiv), $K_2S_2O_8$ (1.02 mmol , 2.0 equiv), $Fe(NO_3)_3.9H_2O$ (5 mol %), rt, 12h. [b] similar condition but heated at 60°C.

In conclusion, we have developed a simple and economical method for the regioselective synthesis of 1,3,5-trisubstituted pyrazoles from the reaction of hydrazones of aryl carbaldehyde

and 1,2-propane diol. Low concentration of inexpensive ferric nitrate salt was employed as the catalyst along with oxidant potassium persulfate to catalyze the reaction. It is expected that in the presence of Fe^{+3} peroxosulfate oxidizes the diol to 1-hydroxypropan-2-one, which subsequently reacts with hydrazone to produce the required pyrazoles. Additionally, when ethylene glycol was employed instead of 1,2-propane diol, 1,3-disubstituted pyrazoles are generated efficiently. Application of this strategy to the synthesis of natural products is going on in our laboratory.

Experimental

General Information: Unless otherwise noted, the reagents (chemicals) were purchased from commercial sources and used without further purification. Hydrazones were prepared by following the literature procedure from the reaction of carbaldehyde and hydrazine in methanol at room temperature. The reactions were monitored by TLC, and the residue was chromatographed on a pad of silica gel (mesh 80-120) (Merck, India), using an ethyl acetate-petroleum ether (60-80 °C) mixture as eluent. All NMR spectra were recorded on a 400 MHz (for ^{1}H NMR) and 100 MHz (for ^{13}C NMR) NMR spectrometer (Bruker, Avance III), and chemical shifts were expressed in δ units (ppm). Multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet, when multiplicity is complex) for 1H NMR. Coupling constants, *J* were reported in Hz. High-resolution mass spectrometry (ESI-HRMS) (Agilent 6520 Q-TOF) was used to determine the elemental composition.

General procedure for the Synthesis of substituted Pyrazoles

Method A: A mixture of diaryl hydrazones (0.51 mmol), $K_2S_2O_8$ (2 equiv.), $Fe(NO_3)_3.9H_2O$ (5 mol%) and diol (1.02 mmol, 2 equiv.) was stirred at room temperature for 12h. After complete

consumption of hydrazone, the reaction mixture was poured into water (20 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic layer was washed with water (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography using ethyl acetate and petroleum ether as eluent to afford the desired pyrazoles.

Method B: Similar to method A, but the reaction mixture was stirred at room temperature instead of heating at 60°C for 12h stirring.

Synthesis and Analytical Data

5-Methyl-1,3-diphenyl-1H-pyrazole[14] (**3a**). Following method A, the reaction was carried out at rt to give 75 mg (68% yield) of **3a** as a yellow liquid. IR: 3060, 2924, 1597, 1549, 1500, 1456, 1412, 1365 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.91-7.85 (m, 2H), 7.58-7.47 (m, 5H), 7.46-7.37 (m, 4H), 6.55 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.5, 140.1, 139.9, 133.3, 129.1, 128.5, 127.7, 127.6, 125.7, 125.0, 104.3, 12.6.

3-(2-Chlorophenyl)-5-methyl-1-phenyl-1H-pyrazole (**3b**). Following method A, the reaction was carried out at rt to give 35 mg (32% yield) of **3b** as a yellow liquid. IR: 3063, 2925, 1598, 1547, 1503, 1459, 1349 cm^{-1} .^1H NMR (400 MHz, $CDCl_3$): δ 7.94-7.88 (m, 1H), 7.59-7.44 (m, 5H), 7.45-7.39 (m, 1H), 7.36-7.25 (m, 3H), 6.78 (s, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 149.1, 139.6, 139.1, 132.2, 132.1, 130.5, 130.1, 128.9, 128.6, 127.6, 126.7, 124.8, 108.1, 12.5. HRMS (ESI) calcd for $C_{16}H_{14}ClN_2^+$ $[M+H]^+$ 269.0846; found 269.0840.

5-Methyl-3-(2-nitrophenyl)-1-phenyl-1H-pyrazole (**3c**). Following method B, the reaction mixture was heated at 60°C to give 56 mg (45% yield) of **3c** as a red liquid. IR: 2983, 2355, 1511, 1541, 1370, 1237 cm^1 .^{1}H NMR (400 MHz, $CDCl_3$): δ 7.7.86-7.80 (m, 1H), 7.76-7.70 (m, 1H), 7.7.64-7.56 (m, 1H), 7.53-7.38 (m, 5H), 6.36 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.8, 140.1, 139.5, 131.8, 130.7, 129.1, 128.4, 127.8, 127.5, 124.8, 123.5, 106.2, 12.5. HRMS (ESI) calcd for $C_{16}H_{14}N_3O_2^+$ $[M+H]^+$ 280.1086.

5-Methyl-3-(4-chlorophenyl)-1-phenyl-1H-pyrazole [14] (**3d**). Following method A, the reaction was carried out at rt to give 69 mg (66% yield) of **3d** as a colorless liquid. IR: 3059, 2920, 1597, 1547, 1501, 1453, 1431, 1397, 1360 cm^{-1} .^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (t, 2H, J = 2 Hz), 7.55-7.48 (m, 4H), 7.45-7.36 (m, 3H), 6.51 (s, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.4, 140.4, 139.7, 133.4, 131.8, 129.1, 128.7, 127.8, 126.9, 125.0, 104.2, 12.5.

5-Methyl-3-(4-nitrophenyl)-1-phenyl-1H-pyrazole [18] (**3e**). Following method A, the reaction was carried out at rt to give 45 mg (39% yield) of **3e** as a white crystalline solid. M.P.: 130°C .IR: 2928, 1594, 1502, 1416, 1320, 1261 cm^{-1} .^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, 2H, J = 1.6 Hz), 8.02 (dd, 2H, J_1 = 2 Hz, J_2 = 7.2 Hz), 7.54 (d, 4H, J = 4 Hz), 7.49-7.44 (m, 1H), 6.64 (s, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.0, 139.6, 129.4, 129.1, 128.0, 125.9, 124.9, 124.0, 123.9, 118.9, 105.0, 12.4.

5-Methyl-1-phenyl-3-(thiophene-2-yl)-1H-pyrazole [14] (**3f**). Following method A, the reaction was carried out at rt to give 46 mg (38% yield) of **3f** as a colorless liquid. IR: 3067, 2962, 1596, 1565, 1532, 1500, 1424, 1375, 1327 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53-7.47 (m, 4H),

7.41-7.36 (m, 2H), 7.29-7.24 (m, 1H), 8.01-7.05 (m, 1H), 6.45 (s, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.7, 140.1, 139.5, 128.9, 127.6, 127.2, 124.9, 124.4, 123.6, 104.2, 12.3.

5-Methyl-3-Phenyl-1-(p-tolyl)-1H-pyrazole [19] (**3h**). Following method B, the reaction mixture was heated at 60°C to give 47 mg (42% yield) of **3h** as a white gummy liquid. IR: 2968, 1518, 1466, 1372, 248 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00-7.84 (m, 2H), 7.45-7.38 (m, 4H), 7.36-7.27 (m, 3H), 6.53 (s, 1H), 2.44 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.2, 140.2, 137.7, 133.3, 129.6, 128.5, 127.6, 125.7, 124.9, 122.2, 104.0, 21.1, 12.5.

1-(4-Bromo-phenyl)-5-methyl-3 -phenyl-1H-pyrazole [20] (**3i**). Following method B, the reaction mixture was heated at 60°C to give 54 mg (48%) of **3i** as a yellow gummy liquid. IR: 3063, 2917, 1583, 1554, 1488, 1364 cm^{-1} .^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89-7.83 (m, 2H), 7.66-7.60 (m, 2H), 7.47-7.39 (m, 4H), 7.35 (d, 1H, *J* = 7.6 Hz), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.8, 140.1, 138.9, 133.0, 132.2, 128.6, 127.9, 126.3, 125.7, 121.1, 104.8, 12.6.

1-(4-Chloro-phenyl)-5-methyl-3-(3-nitro-phenyl)-1H-pyrazole (**3j**). Following method B, the reaction was heated at 60°C to give 77 mg (68%) of **3j** as a white crystalline solid. M.P.: 130-132°C. IR: 3092, 1882, 1590, 1496, 1394, 1350 cm^{-1} .^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69-8.64 (m, 1H), 8.23-8.14 (m, 2H), 7.62-7.54 (m, 1H), 7.50 (s, 3H), 6.63 (s, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.4, 148.6, 140.9, 138.0, 134.9, 133.8, 131.4, 129.5, 129.4, 126.0, 122.4, 120.5, 104.9, 12.6. HRMS (ESI) calcd for $C_{16}H_{13}ClN_3O_2$ $[M+H]^+$ 314.0696; found 314.0692.

5-Methyl-1,3-di-p-tolyl-1H-pyrazole (**3k**). Following method B, the reaction mixture was heated at 60°C to give 74 mg (65%) of **3k** as a yellow liquid. IR: 3569, 1560, 1456, 1436, 1363 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, 2H, *J* = 8 Hz), 7.41 (d, 2H, *J* = 8.4 Hz), 7.29 (d, 2H, *J* = 8.4

Hz), 7.22 (d, 2H, *J* = 8 Hz), 6.50 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.3, 140.0, 137.5, 137.3, 130.6, 129.6, 129.2, 128.9, 128.8, 125.5, 124.9, 103.9, 21.3, 21.1, 12.5. HRMS (ESI) calcd for $C_{18}H_{19}N_2$ $[M+H]^+$ 263.1548; found 263.1539.

1,3-Diphenyl-1H-pyrazole [14] (**5**). Following method A, the reaction was carried out at rt to give 97 mg (87% yield) of **5** as a white crystalline solid. M. P: 80-82°C. IR: 1597, 1527, 1504, 1456, 1361 cm^{1} .^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, 1H, *J* = 2.4 Hz), 7.86-7.76 (m, 4H), 7.52-7.44 (m, 2H), 7.34-7.23 (m, 4H), 6.77 (d, 1H, *J* = 2.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.9, 140.2, 133.1, 129.4, 128.6, 128.0, 128.0, 126.3, 125.8, 119.0, 105.0.

3-(2-Chlorophenyl)-1-phenyl-1H-pyrazole [14] (**6**). Following method A, the reaction was carried out at rt to give 84 mg (76% yield) of **6** as a colorless crystalline solid. M.P: 134-136°C. IR: 3050, 1597, 1503, 1448, 1386, 1348 cm^{-1} .^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (t, 2H, *J* = 1.6 Hz), 7.82 (t, 2H, *J* = 8 Hz), 7.56-7.46 (m, 3H), 7.41-7.04 (m, 3H), 7.05 (d, 1H, *J* = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.6, 140.0, 132.4, 132.1, 130.8, 130.4, 129.4, 129.1, 127.2, 126.9, 126.5, 119.1, 109.0.

3-(2-Nitrophenyl)-1-phenyl-1H-pyrazole [21] (**7**). Following method B, the reaction mixture was heated at 60°C to give 84 mg (76% yield) of **7** as a red crystalline solid. M.P.: 80-82°C. IR: 1599, 1503, 1343, 1271, 1038 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, 1H, *J* = 2.8 Hz), 7.88 - 7.82 (m, 1H), 7.78 - 7.70 (m, 3H), 7.62 (t, 1H, *J* = 6.8 Hz), 7.53 - 7.43 (m, 3H), 7.32 - 7.29 (m, 1H), 6.63 (d, 1H, *J* = 2.4Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.2, 139.8, 131.8, 130.7, 129.4, 128.7, 127.9, 126.7, 124.4, 123.7, 119.1, 106.9, 65.3.

1-(4-Chlorophenyl)-3-phenyl-1H-pyrazole [14] (**8**). Following method A, the reaction mixture was stirred at rt for 12h to give 76 mg (69% yield) of **8** as colorless crystalline solid. M.P.: 118°C. IR: 3052, 2924, 1596, 1507, 1442, 1410, 1262 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, 1H, *J* = 2.4 Hz), 7.88 (t, 2H, *J* = 6.8 Hz), 7.78 (d, 2H, *J* = 7.6 Hz), 7.49 (t, 2H, *J* = 8.4 Hz), 7.42 (d, 2H, *J* = 8.4 Hz), 7.38-7.28 (m, 1H), 6.77 (d, 1H, *J* = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.8, 140.0, 133.7, 131.6, 129.4, 128.8, 128.2, 127.0, 126.5, 119.0, 104.9.

3-(4-Nitrophenyl)-1-phenyl-1H-pyrazole [14] (**9**). Following method A, the reaction was carried out at rt to give 71 mg (65% yield) of **9** as a yellow crystalline solid. M.P.: 138-140°C. IR: 1597, 1557, 1506, 1457, 1418, 1334 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, 2H, *J* = 8.8 Hz), 8.10 (t, 2H, *J* = 8.8 Hz), 8.04 (d, 1H, *J* = 2.4 Hz), 7.81 (t, 2H, *J* = 7.6 Hz), 7.52 (t, 2H, *J* = 8.4 Hz), 7.41-7.35 (m, 1H), 6.90 (d, 1H, *J* = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.5, 147.2, 139.8, 139.3, 129.5, 128.6, 127.0, 126.2, 124.1, 119.2, 105.9.

3-(3-Nitrophenyl)-1-phenyl-1H-pyrazole [14] (**10**). Following method A, the reaction was carried out at rt to give 86 mg (73% yield) of **10** as a yellow crystalline solid. M.P.: 110-11°C. IR: 1596, 1518, 1455, 1345 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.76 (d, 1H, *J* = 1.6 Hz), 8.31-8.24 (m, 2H), 8.23-8.17 (m, 1H), 7.03 (d, 1H, *J* = 2.4 Hz), 7.84-7.78 (m, 2H), 7.62 (t, 1H, *J* = 8 Hz), 7.56-7.48 (d, 2H), 7.39-7.32 (m, 1H), 6.88 (s, 1H, *J* = 2.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.5, 148.7, 139.9, 134.9, 131.5, 129.5, 129.5, 128.5, 126.8, 122.5, 120.6, 119.1, 105.3.

2-(1-Phenyl-1H-pyrazol-3-yl) phenol [14] (**11**). Following method A, the reaction was carried out at rt to give 73 mg (66% yield) of **11** as a colorless crystalline solid. M.P.: 102°C. IR: 3142, 3050, 2951, 2920, 2854, 1621, 1599, 1523, 1506, 1451, 1403, 1362 cm^{-1}.^{1}H NMR (400 MHz,

$CDCl_3$): δ 10.86 (s, 1H), 8.01 (d, 1H, *J* = 2.4 Hz), 7.74-7.68 (m, 2H), 7.67-7.62 (m, 1H,), 7.55-7.48 (m, 2H), 7.35 (t, 1H, *J* = 7.2 Hz), 7.33-7.24 (m, 2H), 7.10 (m, 1H), 7.01-6.93 (m, 1H), 6.89 (d, 1H, *J* = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.9, 152.9, 139.2, 129.6, 127.7, 126.8, 126.5, 119.3, 118.8, 117.2, 116.2, 104.6.

3-(4-Methoxyphenyl)-1-phenyl-1H-pyrazole [14] (**12**). Following method A, the reaction was carried out at rt to give 49 mg (44% yield) of **12** as a colorless crystalline solid. M.P.: 102-104°C. IR: 3141, 3059, 2959, 1596, 1510, 1452, 1389, 1358 cm^{-1} .^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, 1H, *J* = 2.4 Hz), 8.02-7.84 (m, 2H), 7.82-7.75 (m, 2H), 7.48. (t, 2H, J = 8 Hz), 7.30 (t, 2H, J = 7.6 Hz), 7.00 (t, 2H, J = 7.2 Hz), 6.73 (d, 1H, J = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6, 152.7, 140.2, 129.4, 128.1, 127.9, 127.6, 127.1, 126.1, 125.9, 118.9, 114.0, 104.6, 55.3.

1-Phenyl-3-p-tolyl-1H-pyrazole [22](**13**). Following method A, the reaction was carried out at rt to give 77 mg (69% yield) of **13** as a white crystalline solid. M.P.: 78°C. IR: 3036, 2926, 1599, 1511, 1446, 1387, 1351 cm^{-1} .^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, 1H, *J* = 2.8 Hz), 7.85-7.73 (m, 4H), 7.50-7.42 (m, 2H), 7.32-7.21 (m, 3H), 6.75 (d, 1H, *J* = 2.4 Hz), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.9, 140.1, 137.8, 130.2, 129.3, 129.3, 127.8, 126.1, 125.6, 118.9, 104.9, 104.8, 21.2.

1-(1-Phenyl-1H-pyrazol-3-yl)-naphthalen-2-ol [14] (**14**). Following method A, the reaction was carried out at rt to give 57 mg (62% yield) of **14** as a colorless crystalline solid. M.P.: 74-76°C. IR: 3145, 3048, 2912, 1598, 1547, 1528, 1509, 1464, 1391, 1368, 1336 cm^{-1} .^{1}H NMR (400 MHz, $CDCl_3$): δ 12.09 (s, 1H), 8.79 (s, 1H), 8.02 (d, 1H, *J* = 8.8 Hz), 7.84-7.74 (m, 2H), 7.65 (s, 1H), 7.53 (t, 1H, *J* = 8 Hz), 7.42-7.31 (m, 3H), 7.25(S, 1H), 7.07 (d, 2H, *J* = 8 Hz), 6.97 (t, 1H, *J*

= 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.8, 143.4, 137.8, 131.3, 131.2, 129.6, 129.1, 128.3, 127.1, 123.3, 120.9, 119.9, 118.9, 112.6, 108.9, 29.7.

1-Phenyl (3-thiophene-2-yl)-1H-pyrazole [14] (**15**). Following method A, the reaction was carried out at rt to give 72 mg (65% yield) of **15** as a colorless crystalline solid. M.P: 64-66°C. IR: 3066, 2920, 1597, 1559, 1506, 1460, 1375 1351 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, 1H, J = 2.8 Hz), 7.76 (dd, 2H, J_1 = 1.2 Hz, J_2 = 8 Hz), 7.52-7.41 (m, 3H), 7.35-7.27 (m, 2H), 7.14-7.08 (m, 1H), 6.70 (d, 1H, J= 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.2, 139.9, 136.3, 129.4, 128.0, 127.4, 126.4, 124.9, 124.2, 119.0, 105.1.

1-(4-Chloro-phenyl)-3-phenyl-1H-pyrazole [14] (**16**). Following method B, the reaction mixture was heated at 60°C to give 91 mg (82% yield) of **16** as a colorless crystalline solid. M.P: 131-133°C. IR: 3059, 1594, 1530, 1505, 1491, 1451, 1385 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, 3H, J = 7.2 Hz), 7.74 (d, 2H, J = 8.8 Hz), 7.50-7.42 (m, 4H), 7.41-7.34 (m, 1H), 6.80 (d, 1H, J = 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2, 138.7, 132.8, 131.7, 129.5, 128.7, 128.2, 127.9, 125.8, 120.0, 105.4.

1-(4-Bromo-phenyl)-3-phenyl-1H-pyrazole [22] (**17**). Following method B, the reaction mixture was heated at 60 °C to give 73 mg (79% yield) of **17** as a white crystalline solid. M.P: 112-123°C. IR: 3152, 3050, 2467, 1592, 1504, 1453, 1366, 1271 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, 1H, J = 2.4 Hz), 7.95-7.89 (m, 2H), 7.72-7.89 (m, 2H), 7.63-7.57 (m, 2H), 7.49-7.42 (m, 2H), 7.41-7.35 (m, 1H), 6.81 (d, 1H, J = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.1, 139.0, 132.7, 132.3, 128.6, 128.1, 127.7, 125.7, 120.2, 119.3, 105.3.

1-(4-Bromo-phenyl)-3-(4-chloro-phenyl)-1H-pyrazole (**18**). Following method B, the reaction mixture was heated at 60 °C to give 96 mg (89% yield) of **18** as a white crystalline solid. M.P: 134-136°C. IR: 3152, 2314, 1592, 1497, 1417, 1387 cm^{-1} .^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, 1H, *J* = 2.4 Hz), 7.88 - 7.82 (m, 2H), 7.70 - 7.64 (m, 2H), 7.64 - 7.57 (m, 2H), 7.45 - 7.39 (m, 2H), 6.77 (d, 1H, *J* = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.0, 138.9, 133.8, 132.3, 131.2, 128.7, 127.9, 126.9, 120.2, 119.5, 105.3. HRMS (ESI) calcd for $C_{15}H_{11}BrClN_2^+$ $[M+H]^+$ 332.9794; found 332.9788.

ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C NMR of unknown compounds.

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Conflicts of interest

Authors ensure there is no conflict of interest.

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Highlights

- An iron-catalyzed protocol for the synthesis of pyrazoles starting from hydrazone and 1,2-diol was described.
- This reaction proceeds under mild reaction conditions in the absence of any ligand
- This protocol eliminates the regioselective issue that usually associated with 1,3,5-trisubstituted pyrazoles.