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Note

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Fe-catalyzed one-pot Synthesis of 1,3- and 1,3,4-substituted pyrazoles from hydrazones and vicinal diols

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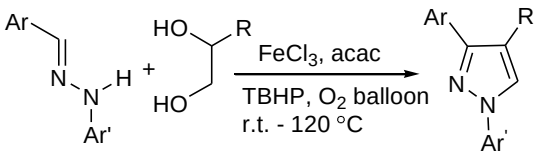
Abstract



R = H, CH_3; 24 examples; 51-85 % yield

An iron-catalyzed route for the regioselective synthesis of 1,3- and 1,3,4-substituted pyrazoles from the reaction of diarylhydrazones and vicinal diols has been developed. This method was found to be practical with wide substrate scope.

Keywords: Pyrazoles; oxidation; hydrazone; vicinal diol.

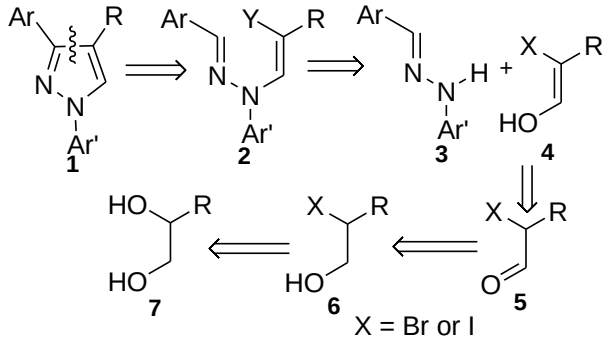
The presence of pyrazole motif in several blockbuster drugs and pesticides including sildenafil (Viagra), celecoxib (Celebrex), rimonabant (Acomplia), Fipronil and Pyracolfos made this heterocycle a popular synthetic target to pharmaceutical and agrochemical industries.[1] Furthermore, substituted pyrazoles are privileged structural units in many functional materials including optical brightener,[2] ultraviolet stabilizer[3] etc. The rising usage of pyrazoles stimulates the development of new and complementary methods for their synthesis. The most powerful tool is undoubtedly the Knorr reaction of hydrazine derivatives with 1,3-dicarbonyl compounds or their derivatives.[4] However, the multistep access of appropriately functionalized 1,3-dicarbonyl compounds and the formation of regioisomeric mixture are the inevitable drawbacks

of this reaction.[5] The replacement of 1,3-diketones with acetylenic or olefinic ketones somewhat improves the selectivity of the synthesis.[6] In recent years, 1,3-dipolar cycloaddition of diazoalkanes or nitrile imines with olefins or alkynes has been emerged as a complementary approach towards the regioselective synthesis of substituted pyrazoles.[7] Moreover, in this method the question of regioselectivity is transferred to the preparation and handling of 1,3-dipoles.[8] Intriguingly, transition metal-catalyzed C-C/C-N/N-N bond formation reactions using Pd- and Cu-based catalysts are efficiently used for the synthesis of 1,3- 1,3,4-, 1,3,5- and 1,3,4,5-substituted pyrazoles.[9] However, the high cost and toxicity of these catalysts often vitiate their synthetic utility. Thus, development of efficient, less expensive and environmental friendly catalysts has been found to be attractive for regioselective synthesis of pyrazoles. Undeniably, among the myriad of important transition metal catalysts, iron catalysts are particularly attractive in modern organic synthesis in terms of economical and ecological point of view.[10] As such, a number of iron-catalyzed Friedel-Crafts reactions,[11] Aldol condensation reactions,[12] carbometalation reactions,[13] cycloaddition reactions[14] have been disclosed. Fe-catalysts are also successfully used for the oxidation of alcohols to the corresponding carbonyl compounds in presence of peroxide as an oxidant.[15-17] However, the use of iron catalysts in heterocycle synthesis particularly substituted pyrazoles with controlled selectivity has been less literature precedent.[18] In turn, here we report a simple and efficient Fe^{III}-catalyzed one-pot route to access 1,3- and 1,3,4-substituted pyrazoles regioselectively. To the best of our knowledge this is the first report on the regioselective synthesis of substituted pyrazoles from the one-pot reaction of simple vicinal diols and diarylhydrazones.

Our strategy towards the synthesis of pyrazoles is outlined in Scheme 1. This involves the condensation of α-hydroxy carbonyl compounds (**5**) with diarylhydrazones (**3**) to give **2**; the

latter may undergo transition-metal-catalyzed reductive coupling to afford the desired pyrazoles (**1**). We envisioned that the intermediate α-hydroxy carbonyl compounds (**5**) can be achieved in-situ by the oxidation of vicinal diols (**7**). Indeed, our anticipation to access **5** from **7** is based on the pioneering work of Bolm,[15] Beller[16] and Repo.[17] They used nontoxic and inexpensive iron-based catalysts for the oxidation of alcohols to carbonyl compounds by peroxide oxidants.

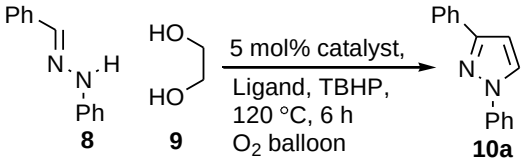
Scheme 1. Retrosynthetic analysis



To test the viability of our strategy, we took diphenylhydrazone (**8**) and ethylene glycol (**9**) as model substrates. To synthesize **2**, when the reaction was carried out in presence of $FeCl_3$, TBHP and pyridine no desired product was formed even at elevated temperature (120°C). Interestingly on addition of ligand such as acetylacetone (acac) resulted 1,3-disubstituted pyrazole directly (Table 1, entry 6). From the systematic screening of a range of iron sources, ligands and solvents at different temperature, we found that tandem oxidation and cyclization occurred at 120 °C in the presence of 5 mol % $FeCl_3$ and provided 1,3-disubstituted pyrazole (**10a**) in 75% yield within 6 h (Table 1). Among the tested ligands, acetylacetone (acac) was found to be more effective to afford **10a** in good yield. Notably, the reaction was sluggish in N_2 as well as in air and led to **10a** in 10 and 25 % yield respectively whereas under O_2 atmosphere reaction proceeds rapidly and resulted **10a** in 75% yield. The reaction did not lead to any pyrazole in absence

TBHP or $FeCl_3$. Moreover, optimum yield of 1,2-disubstituted pyrazole (**10a**) was obtained when diphenylhydrazone and ethylene glycol were heated at 120 °C in presence of 5 mol% of $FeCl_3$, 2 equiv. of acac and 1 equiv. of TBHP under O_2 atmosphere. In line with the pioneering work of Barton[19] and Bolm,[12c] it may be hypothesized that in presence of $FeCl_3$/TBHP/O_2, acac initially oxidized in an analogous manner to an intermediate that oxidizes the diol to α-hydroxy aldehyde. Subsequently, $FeCl_3$ activates the in-situ generated aldehyde through coordination of the carbonyl oxygen to the iron (III) center[20] to form activated intermediate which then reacts with hydrazone and leads to **10a**.

Table 1. Optimization of reaction conditions[a]



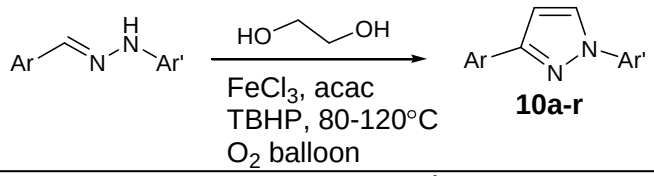
Entry	Catalyst	Ligand	Yield (%)
1	$FeCl_3$	EAA	13
2	$FeCl_3$	DMEDA	10
3	$FeCl_3$	TMEDA	0
4	$FeCl_3$	1,10-phen	0
5	$FeCl_3$	DEM	≤5
6	$FeCl_3$	acac	75
7	--	acac	0
8	$FeCl_3$	--	13
9	$FeCl_2.2H_2O$	acac	40
10	$Fe(acac)_3$	acac	≤5
11	Fe_3O_4	acac	20

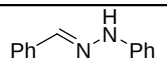
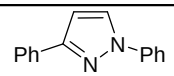
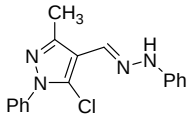
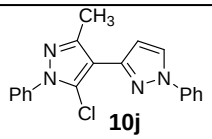
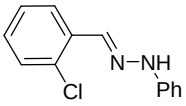
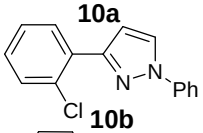
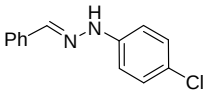
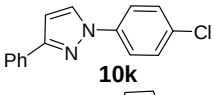
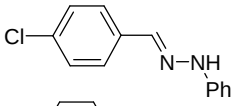
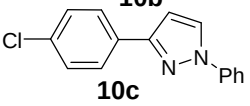
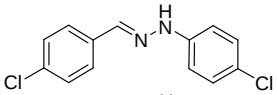
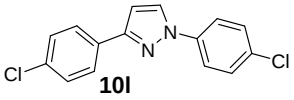
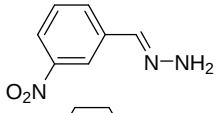
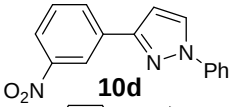
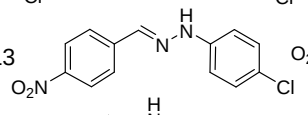
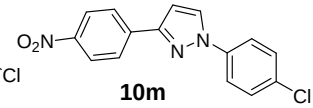
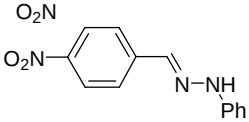
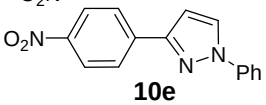
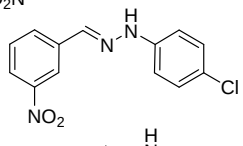
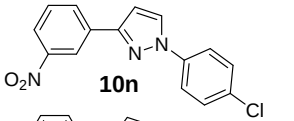
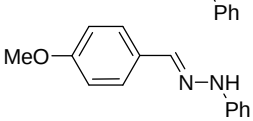
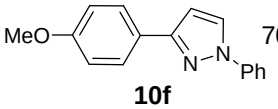
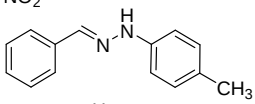
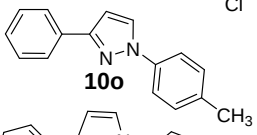
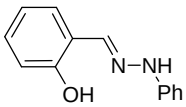
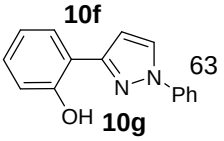
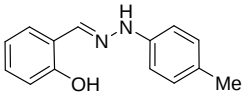
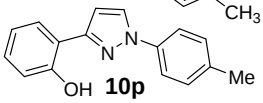
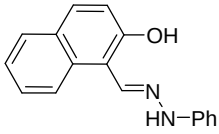
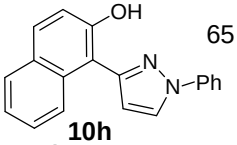
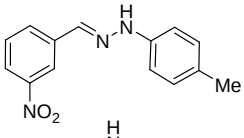
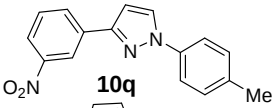
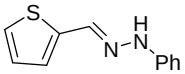
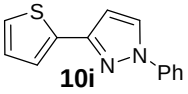
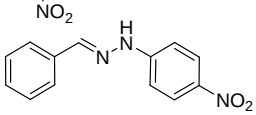
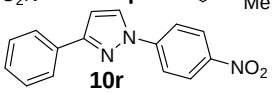
[a]Reaction conditions: diphenylhydrazone (100 mg, 0.51 mmol), ethylene glycol (2 mL), catalyst (5 mol %), ligand (1 mmol), TBHP (0.51 mmol), heated at 120 °C, 6 h, O_2 balloon.

Next we exploited the scope of the reaction with varieties of hydrazones. A number of substituted hydrazones were synthesized by the reaction of corresponding aldehydes and hydrazines following the standard protocol. When diarylhydrazones were treated with ethylene

glycol under optimum reaction conditions, 1,3-disubstituted pyrazoles (**10a-q**) were obtained selectively in good yield (Table 2). Notably, the presence of electron donating substituents to N-aryl group increases the reactivity of the hydrazone by increasing the nucleophilicity of the nitrogen and hence the reaction completes at lower temperature (< 120°C). However, the

Table 2. Synthesis of 1,3-diaryl pyrazoles[a]



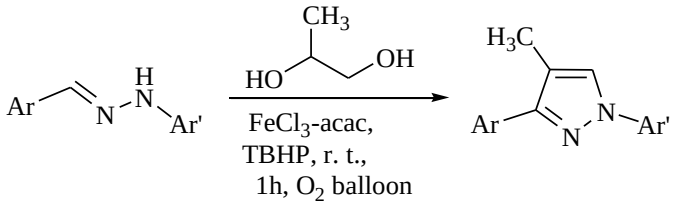
Entry	Hydrazone	Product	Yield (%)[b]	Entry	Hydrazone	Product	Yield (%)
1		 **10a**	75	10		 **10j**	65
2		 **10b**	62	11		 **10k**	77
3		 **10c**	68	12		 **10l**	85
4		 **10d**	62	13		 **10m**	71
5		 **10e**	73	14		 **10n**	74
6		 **10f**	70	15		 **10o**	61
7		 **10g**	63	16		 **10p**	58
8		 **10h**	65	17		 **10q**	60
9		 **10i**	68	18		 **10r**	00

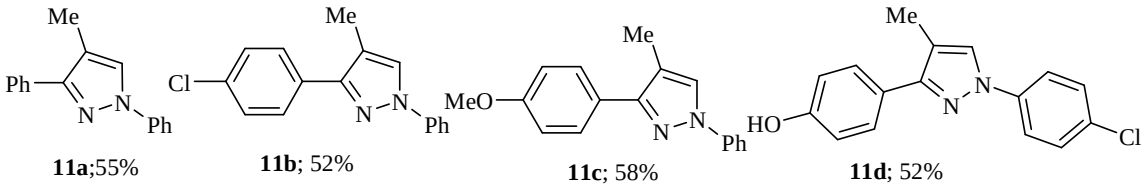
[a]Reaction conditions: diarylhydrazone (100 mg), ethylene glycol (2 mL), anhyd. $FeCl_3$ (5 mol %), acac (2 equiv.), TBHP (1 equiv.), 6 h, O_2 balloon.

presence of electron-withdrawing groups such as $–NO_2$ to the N-phenyl ring retards the reaction and desired pyrazole was not formed even at elevated temperature (entry 18). Furthermore, this protocol was found to be tolerant to both electron-donating and –withdrawing groups at the C_3-aryl ring and afforded the pyrazoles in moderate to good yield.

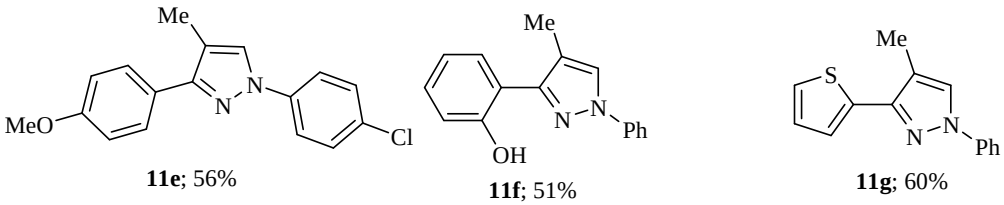
Having the proved efficiency of our catalytic protocol with ethylene glycol, the scope of the reaction was subsequently extended towards the regioselective synthesis of 1,3,4-trisubstituted pyrazoles. Thus, when diarylhyrazones were reacted with 1,2-propane diol, 1,3,4-trisubstituted pyrazoles were resulted in moderate to good yield (Table 3). Interestingly, these reactions proceed at room temperature in absence of any solvent although excess of diol is required. Several 1,3,4-trisubstituted pyrazoles (**11a-g**) have been prepared by varying the substituents to the aromatic ring of diarylhydrazone.

Table 3. Synthesis of 1,3,4-substituted pyrazoles[a]





11a;55% **11b**; 52% **11c**; 58% **11d**; 52%



11e; 56% **11f**; 51% **11g**; 60%

[a]Reaction conditions: diarylhydrazone (100 mg), 1,2-propanediol (2 mL), anhyd. $FeCl_3$ (5 mol %), acac (2 equiv.), TBHP (1 equiv.), 1 h, O_2 balloon.

In summary, we first developed iron-catalyzed one-pot synthesis of substituted pyrazoles from the reaction of simple vicinal diols and diarylhydrazones. This protocol was found to be tolerant to varieties electron-donating and -withdrawing substitutions to the aromatic rings. This reaction is simple and affords a new route for the regioselective synthesis of 1,3- and 1,3,4-substituted pyrazoles.

Experimental

General Procedure for the synthesis of substituted 1,3-disubstituted pyrazoles (method A)

A mixture of diarylhydrazones (100 mg), $FeCl_3$ (5 mol %) and ethylene glycol **9** (2 mL) was stirred under O_2 atmosphere at RT. To the resulting mixture acetyl acetone (2 equiv.) followed by TBHP (1 equiv.) was added dropwise and the temperature was slowly increased to 80-120 ^{0}C. After stirring at appropriate temperature for 6 h (completion of the reaction was monitored by TLC), the reaction mixture was cooled to room temperature. Dichloromethane was added. The organic layer was washed with water, dried over Na_2SO_4 and then evaporated under reduced pressure. The crude product was purified by flash column chromatography using ethyl acetate and petroleum ether as eluent to afford **10a-q**.

General procedure for the synthesis of 1,3,4-trisubstituted pyrazoles 11a-g (method B)

A mixture of diaryl hydrazones **8** (100 mg) and $FeCl_3$ (5 mol %) in propane1,2-diol (2 mL) was stirred under O_2 atmosphere. To the resulting mixture acetyl acetone (2 equiv.) followed by TBHP (1 equiv.) was added dropwise at room temperature. After stirring for 1 h at r. t. dichloromethane was added. The organic layer was washed with water, dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography using ethyl acetate and petroleum ether as eluent to afford 1,3,4-trisubstituted pyrazoles **11a-g**.

1,3-Diphenyl-1H-pyrazole (10a)[21]

Following method A, the reaction was carried out at 120 °C to give 83 mg (75 %) of **10a** as a white solid. M. P.: 80-82 °C. IR (KBr): 1597, 1527, 1504, 1456, 1361 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96-7.90 (m, 3H), 7.80-7.76 (m, 2H), 7.51-7.40 (m, 4H), 7.38-7.26 (m, 2H), 6.79 (d, 1H, *J* = 2.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.9 (s), 140.2 (s), 133.1 (s), 129.4 (d), 128.6 (d), 128.0 (d), 128.0 (d), 126.3 (d), 125.8 (d), 119.0 (d), 105.0 (d). MS (ESI): *m/z* (relative intensity) 243 ($[M+Na]^+$, 100 %), 221 ($[M+H]^+$, 37 %).

3-(2-chlorophenyl)-1-phenyl-1H-pyrazole (10b)[22]

Following method A, the reaction was stirred at 120 °C to give 68 mg (62 %) of **10b** as a white solid. M. P.: 134-136 °C. IR (KBr): 3050, 1597, 1503, 1448, 1386, 1348 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, 1H, *J* = 2.4 Hz), 7.99-7.95 (m, 1H), 7.80 (d, 2H, *J* = 8 Hz), 7.49 (t, 3H, *J* = 7.6 Hz), 7.39-7.29 (m, 3H), 7.03 (d, 1H, *J* = 2.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.6 (s), 140.1 (s), 132.4 (s), 132.1 (s), 130.7 (d), 130.3 (d), 129.4 (d), 129.0 (d), 127.1 (d), 126.8 (d), 126.5 (d), 119.1 (d), 109.0 (d). MS (ESI): *m/z* (relative intensity) 277 ($[M+Na]^+$, 100 %), 255 ($[M+H]^+$, 45 %).

3-(4-chlorophenyl)-1-phenyl-1H-pyrazole (10c)[21]

Following method A, the reaction was stirred at 120 °C to give 75 mg (68 %) of **10c** as a white solid. M. P.: 118 °C. IR (KBr) : 3052, 2924, 1596, 1507, 1442, 1410, 1262 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, 1H, *J* = 2.8 Hz), 7.87 (d, 2H, *J* = 8.4 Hz), 7.78 (d, 2H, *J* = 7.6 Hz), 7.52-7.46 (m, 2H), 7.42 (d, 2H, *J* = 8.4 Hz), 7.35-7.30 (m, 1H), 6.77 (d, 1H, *J* = 2.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.8 (s), 140.1 (s), 133.7 (s), 131.6 (s), 129.4 (d), 128.8 (d), 128.1 (d), 127.0 (d), 126.5 (d), 119.0 (d), 104.9 (d). MS (ESI): *m/z* (relative intensity) 277 ($[M+Na]^+$, 100 %), 255 ($[M+H]^+$, 39 %).

3-(3-nitrophenyl)-1-phenyl-1H-pyrazole (10d)

Following method A, the reaction was stirred at 100 °C to give 68 mg (62 %) of **10d** as a yellow solid. M. P.: 110-112 °C. IR (KBr) : 1596, 1518, 1455, 1345 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, 1H, *J* = 0.8 Hz), 8.22-8.18 (m, 2H), 8.03 (d, 1H, *J* = 2.8 Hz), 7.80 (d, 2H, *J* = 7.6 Hz), 7.64-7.48 (m, 3H), 7.38-7.32 (m, 1H), 6.88 (d, 1H, *J* = 2.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.5 (s), 148.7 (s), 139.9 (s), 135.0 (s), 131.4 (d), 129.5 (d), 128.5 (d), 126.8 (d), 122.4 (d), 120.6 (d), 119.1 (d), 105.2 (d). MS (ESI): *m/z* (relative intensity) 288 ($[M+Na]^+$, 100 %), 266 ($[M+H]^+$, 23 %).

Anal. Calcd for $C_{15}H_{11}N_3O_2$: C, 67.92; H, 4.18; N, 15.84. Found: C, 67.89; H, 3.99; N, 15.74.

3-(4-nitrophenyl)-1-phenyl-1H-pyrazole (10e)[22]

Following method A, the reaction was stirred at 120 °C to give 80 mg (73 %) of **10e** as a yellow solid. M. P.: 138-140 °C. IR (KBr): 1597, 1557, 1506, 1457, 1418, 1334 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, 2H, *J* = 8.8 Hz), 8.09 (d, 2H, *J* = 8.8 Hz), 8.03 (d, 1H, *J* = 2.4 Hz), 7.80 (d, 2H, *J* = 7.6 Hz), 7.55-7.49 (m, 2H), 7.39-7.34 (m, 1H), 6.89 (d, 1H, *J* = 2.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.5 (s), 147.3 (s), 139.9 (s), 139.4 (s), 129.5 (d), 128.6 (d), 127.0 (d), 126.2 (d), 124.0 (d), 119.2 (d), 105.8 (d). MS (ESI): *m/z* (relative intensity) 288 ($[M+Na]^+$, 100 %), 266 ($[M+H]^+$, 24 %).

3-(4-methoxyphenyl)-1-phenyl-1H-pyrazole (10f)[21]

Following method A, the reaction was stirred at 120 °C to give 77 mg (70 %) of **10f** as a white solid. M. P.: 102-104 °C. IR (KBr): 3141, 3059, 2959, 1596, 1510, 1452, 1389, 1358 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, 1H, *J* = 2.4 Hz), 7.89-7.85 (m, 2H), 7.80-7.76 (m, 2H),

7.51-7.45 (m, 2H), 7.32-7.30 (m, 1H), 7.01-6.97 (m, 2H), 6.72 (d, 1H, *J* = 2.4 Hz), 3.87 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6 (s), 152.7 (s), 140.3 (s), 129.3 (d), 127.8 (d), 127.1 (d), 126.1 (d), 125.9 (s), 118.9 (d), 114.0 (d), 104.5 (d), 55.3 (q). MS (ESI): *m/z* (relative intensity) 273 ($[M+Na]^+$, 100 %), 251 ($[M+H]^+$, 70 %).

2-(1-phenyl-1H-pyrazol-3-yl)phenol (10g)[22]

Following method A, the reaction was stirred at 120 °C to give 70 mg (63 %) of **10g** as a white solid. M. P.: 102 °C. IR (KBr) : 3142, 3050, 2951, 2920, 2854, 1621, 1599, 1523, 1506, 1451, 1403, 1362, cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.87 (s), 7.99 (d, 1H, *J* = 2.8 Hz), 7.70 (d, 1H, *J* = 8 Hz), 7.64 (d, 1H, *J* = 8 Hz), 7.54-7.48 (m, 2H), 7.38-7.26 (m, 2H), 7.10 (d, 1H, *J* = 8 Hz), 6.99-6.94 (m, 1H), 6.88 (d, 1H, *J* = 2.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.0 (s), 152.9 (s), 139.2 (s), 129.6 (d), 129.6 (d), 127.7 (d), 126.8 (d), 126.5 (d), 119.3 (d), 118.8 (d), 117.2 (d), 116.2 (s), 104.5 (d). MS (ESI): *m/z* (relative intensity) 259 ($[M+Na]^+$, 100 %), 237 ($[M+H]^+$, 55 %).

1-(1-phenyl-1H-pyrazol-3-yl)naphthalen-2-ol (10h)

Following method A, the reaction was stirred at 120 °C to give 71 mg (65 %) of **10h** as a white solid. M. P.: 74-76 °C. IR (KBr) : 3145, 3048, 2912, 1598, 1547, 1528, 1509, 1464, 1391, 1368, 1336 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.53 (s, 1H), 8.33 (d, 1H, *J* = 8.8 Hz), 8.15 (d, 1H, *J* = 2.4 Hz), 7.86-7.77 (m, 4H), 7.56-7.48 (m, 3H), 7.41-7.31 (m, 3H), 7.04 (d, 1H, *J* = 2.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.7 (s), 150.4 (s), 139.4 (s), 132.0 (s), 130.4 (d), 129.6 (d), 129.0 (s), 128.7 (d), 127.9 (d), 126.8 (d), 126.7 (d), 123.8 (d), 123.0 (d), 118.9 (d), 118.8 (d), 109.8 (s), 109.5 (d). MS (ESI): *m/z* (relative intensity) 309 ($[M+Na]^+$, 100 %), 287 ($[M+H]^+$, 30 %). Anal. Calcd for $C_{19}H_{14}N_2O$: C, 79.70; H, 4.93; N, 9.78. Found: C, 79.80; H, 4.82; N, 9.80.

1-phenyl(3-thiophen-2-yl)-1H-pyrazole (10i)[23]

Following method A, the reaction was stirred at 120 °C to give 75 mg (68 %) of **10i** as a white solid. M. P.: 65 °C. IR (KBr) : 3066, 2920, 1597, 1559, 1506, 1460, 1375 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.76 (d, 2H, *J* = 8 Hz), 7.51-7.44 (m, 3H), 7.34-7.29 (m, 2H), 7.13-7.10 (m, 1H), 6.70 (d, 1H, *J* = 2.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.2 (s), 139.9 (s), 136.3 (s), 129.4 (d), 128.0 (d), 127.4 (d), 126.4 (d), 124.9 (d), 124.2 (d), 119.0 (d), 105.0 (d). MS (ESI): *m/z* (relative intensity) 249 ($[M+Na]^+$, 100 %), 227 ($[M+H]^+$, 56 %).

3-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-1-phenyl-1H-pyrazole (10j)

Following method A, the reaction was stirred at 100 °C to give 70 mg (65 %) of **10j** as a white solid. M. P.: 110-112 °C. IR (KBr) : 3048, 2922, 1595, 1506, 1450, 1408, 1378, 1337 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, 1H, *J* = 2.4 Hz), 7.82-7.78 (m, 2H), 7.63-7.59 (m, 2H), 7.55-7.42 (m, 5H), 7.34-7.29 (m, 1H), 6.87 (d, 1H, *J* = 2.8 Hz), 2.65 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.9 (s), 144.9 (s), 140.1 (s), 138.2 (s), 129.4 (d), 129.2 (s), 129.0 (d), 128.1 (d), 126.9 (d), 126.2 (d), 125.2 (d), 118.7 (d), 112.2 (s), 106.6 (d), 14.6 (q). MS (ESI) *m/z* (relative intensity) 357 ($[M+Na]^+$, 100 %), 335 ($[M+H]^+$, 68 %). Anal. Calcd for $C_{19}H_{15}ClN_4$: C, 68.16; H, 4.52; N, 16.73. Found: C, 68.32; H, 4.41; N, 16.75.

1-(4-chlorophenyl)-3-phenyl-1H-pyrazole (10k)[24]

Following method A, the reaction was stirred at 100 °C to give 85 mg (77 %) of **10k** as a white solid. M. P. : 132-133 °C. IR (KBr) : 3059, 1594, 1530, 1505, 1491, 1451, 1385 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96-7.90 (m, 3H), 7.76-7.72 (m, 2H,), 7.48-7.44 (m, 4H), 7.40-7.34 (m, 1H), 6.80 (d, 1H, *J* = 2.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2 (s), 138.7 (s), 132.8 (s),

131.7 (s), 129.4 (d), 128.7 (d), 128.2 (d), 127.9 (d), 125.8 (d), 120.0 (d), 105.4 (d). MS (ESI) *m/z* (relative intensity) 277 ($[M+Na]^+$, 54 %), 255 ($[M+H]^+$, 30 %).

1,3-bis(4-chlorophenyl)-1H-pyrazole (10l)

Following method A, the reaction was stirred at 100 °C to give 92 mg (85 %) of **10l** as a white solid. M. P.: 136 °C. IR (KBr) : 3145, 3048, 1594, 1565, 1501, 1443, 1419, 1381 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, 1H, *J* = 2.4 Hz), 7.88-7.82 (m, 2H), 7.75-7.69 (m, 2H), 7.48-7.40 (m, 4H), 6.76 (d, 1H, *J* = 2.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.0 (s), 138.6 (s), 133.9 (s), 131.9 (s), 131.4 (s), 129.5 (d), 128.8 (d), 128.0 (d), 127.0 (d), 120.1 (d), 105.3 (d). MS (ESI) *m/z* relative intensity 289 ($[M+H]^+$, 40%). Anal. Calcd for $C_{15}H_{10}Cl_2N_2$: C, 62.30; H, 3.49; Cl, 24.52; N, 9.69. Found: C, 62.33; H, 3.35; N, 9.65.

1-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazole (10m)[25]

Following method A, the reaction was stirred at 80 °C to give 77 mg (71 %) of the 1,3-diarylpyrazole **10m** as a yellow solid. M. P.: 168-170 °C. IR (KBr) : 2920, 1598, 1555, 1511, 1449, 1422, 1343 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.33-8.29 (d, 2H, *J* = 8.8 Hz), 8.10-8.06 (d, 2H, *J* = 8.8 Hz), 8.00 (d, 1H, *J* = 2.4 Hz), 7.77-7.73 (d, 2H, *J* = 8.4 Hz), 7.51-7.46 (d, 2H, *J* = 8.8 Hz), 6.90 (d, 1H, *J* = 2.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.8 (s), 147.4 (s), 139.1 (s), 138.4 (s), 132.5 (s), 129.6 (d), 128.5 (d), 126.2 (d), 124.1 (d), 120.3 (d), 106.2 (d).

1-(4-chlorophenyl)-3-(3-nitrophenyl)-1H-pyrazole (10n)

Following method A, the reaction was stirred at 90 °C to give 80 mg (74 %) of **10n** as a yellow solid. M. P.: 144-146 °C. IR (KBr) : 3083, 1594, 1519, 1501, 1433, 1416, 1346, 1308 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.74 (s, 1H), 8.28-8.18 (m, 2H), 8.00 (d, 1H, *J* = 2.8 Hz), 7.77-7.72

(m, 2H), 7.62 (t, 1H, *J* = 8 Hz), 7.51-7.45 (m, 2H), 6.89 (d, 1H, *J* = 2.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.8 (s), 148.7 (s), 138.4 (s), 134.7 (s), 132.3 (s), 131.5 (d), 129.6 (d), 128.4 (d), 122.6 (d), 120.6 (d), 120.2 (d), 105.6 (d). MS (ESI): *m/z* (relative intensity) 300 ($[M+H]^+$, 48 %). Anal. Calcd for $C_{15}H_{10}ClN_3O_2$: C, 60.11; H, 3.36; Cl, 11.83; N, 14.02. Found: C, 60.21; H, 3.21; N, 14.25.

3-phenyl-1-p-tolyl-1H-pyrazole (10o)[21]

Following method A, the reaction was stirred at 90 °C to give 67 mg (61 %) of **10o** as a white solid. M. P.: 110-111 °C. IR (KBr) : 3145, 3029, 1605, 1521, 1453, 1389, 1364 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95-7.91 (m, 3H), 7.69-7.64 (m, 2H,), 7.48-7.42 (m, 2H), 7.38-7.32 (m, 1H), 7.30-7.26 (m, 2H), 6.78 (d, 1H, *J* = 2.8 Hz), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.6 (s), 138.0 (s), 136.1 (s), 133.2 (s), 129.9 (d), 128.6 (d), 127.9 (d), 125.8 (d), 119.0 (d), 104.7 (d), 20.9 (q). MS (ESI): *m/z* (relative intensity) 257 ($[M+Na]^+$, 69 %), 235 ($[M+H]^+$, 100 %).

2-(1-p-tolyl-1H-pyrazol-3-yl)phenol (10p)

Following method A, the reaction was stirred at 90 °C to give 64 mg (58 %) of **10p** as a white solid. M. P.: 117-119 °C. IR (KBr) : 3152, 3044, 2955, 1619, 1584, 1519, 1454, 1402, 1365, 1299 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.87 (s, 1H), 7.95 (d, 1H, *J* = 2.8 Hz), 7.66-7.56 (m, 3H), 7.32-7.24 (m, 4H), 7.08 (d, 1H, *J* = 8 Hz), 7.07-6.93 (m, 1H), 6.86 (d, 1H, *J* = 3.2 Hz), 2.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.9 (s), 152.6 (s), 137.1 (s), 136.7 (s), 130.1 (d), 129.5 (d), 127.6 (d), 126.5 (d), 119.3 (d), 118.8 (d), 117.1 (d), 116.3 (s), 104.2 (d), 20.9 (q). MS (ESI): *m/z* (relative intensity) 273 ($[M+Na]^+$, 60 %), 250 ($[M+H]^+$, 100 %). Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.67; H, 5.48; N, 11.35.

3-(3-nitrophenyl)-1-p-tolyl-1H-pyrazole (10q)

Following method A, the reaction was stirred at 80 °C to give 65 mg (60 %) of **10q** as a yellow solid. M. P.: 113-115 °C. IR (KBr) : 3032, 2921, 2854, 1609, 1580, 1522, 1455, 1347 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.76-8.74 (m, 1H), 8.26 (d, 1H, *J* = 8 Hz), 8.20-8.16 (m, 1H), 7.97 (d, 1H, *J* = 2.4 Hz),7.67 (d, 2H, *J* = 8.4 Hz), 7.59 (t, 1H, *J* = 8.0 Hz), 7.30 (d, 2H, *J* = 8.4 Hz), 6.84 (d, 1H, *J* = 2.4 Hz), 2.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.2 (s), 148.7 (s), 137.7 (s), 136.7 (s), 135.0 (s), 131.4 (d), 130.0 (d), 129.5 (d), 128.4 (d), 122.4 (d), 120.5 (d), 119.1 (d), 105.0 (d), 20.9 (q). MS (ESI) *m/z* (relative intensity) 302 ($[M+Na]^+$, 100 %), 280 ($[M+H]^+$, 43 %). Anal. Calcd for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.05. Found: C, 68.75; H, 4.52; N, 15.14.

4-methyl-1,3-diphenyl-1H-pyrazole (11a)

Following method B, the reaction was stirred at r. t. to give 66 mg (55 %) of the 1,3-diaryl-4-methylpyrazole **11a** as a liquid. IR (neat): 3060, 2924, 1597, 1549, 1500, 1456, 1412, 1365 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91-7.86 (m, 2H), 7.57-7.48 (m, 4H), 7.45-7.39 (m, 3H), 7.36-7.32 (m, 1H), 6.55 (s, 1H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.5 (s), 140.1 (s), 139.9 (s), 133.3 (s), 129.0 (d), 128.5 (d), 127.7 (d), 127.6 (d), 125.7 (d), 125.0 (d), 104.3 (d), 12.5 (q). MS (ESI): *m/z* (relative intensity) 257 ($[M+Na]^+$, 100 %), 235 ($[M+H]^+$, 88 %). Anal. Calcd for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96. Found: C, 82.21; H, 5.87; N, 11.87.

3-(4-chlorophenyl)-4-methyl-1-phenyl-1H-pyrazole (11b)

Following method B, the reaction was stirred at r. t. to give 60 mg (52 %) of **11b** as a white crystaline solid. M. P.: 80 °C. IR (KBr) : 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), 2.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.4 (s), 140.4 (s), 139.8 (s), 133.4 (s), 131.9 (s), 129.1 (d), 128.7 (d), 127.7 (d), 126.9 (d), 124.9 (d), 104.3 (d), 12.5 (q). MS (ESI): *m/z* (relative intensity) 291 ($[M+Na]^+$, 97 %), 269 ($[M+H]^+$, 100 %). Anal. Calcd for $C_{16}H_{13}ClN_2$: C, 71.51; H, 4.88; N, 10.42. Found: C, 71.45; H, 4.69; N, 10.56.

3-(4-methoxyphenyl)-4-methyl-1-phenyl-1H-pyrazole (11c)

Following method B, the reaction was stirred at r. t. and gave 68 mg (58 %) of **11c** as a white solid. M. P.: 102-104 °C. IR (KBr): 3059, 2956, 1597, 1523, 1500, 1453, 1432, 1404, 1362, 1292 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82-7.78 (m, 2H), 7.56-7.47 (m, 4H), 7.42-7.37 (m, 1H), 6.98-6.93 (m, 2H), 6.47 (s, 1H), 3.85 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4 (s), 151.3 (s), 140.0 (s), 139.9 (s), 129.0 (d), 127.4 (d), 126.9 (d), 126.1 (s), 124.9 (d), 113.9 (d), 103.9 (d), 55.2 (q), 12.5 (q). MS (ESI): *m/z* (relative intensity) 287 ($[M+Na]^+$, 100 %), 265 ($[M+H]^+$, 85 %). Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.32; H, 5.97; N, 10.72.

4-(1-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl)phenol (11d)

Following method B, the reaction was stirred at r. t. to give 61 mg (52 %) of **11d** as a white solid. M. P. : 176-178 °C. IR (KBr): 2984, 1611, 1551, 1524, 1496, 1466, 1435, 1404, 1362 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71-7.67 (m, 2H), 7.46 (m, 4H), 6.85-6.81 (m, 2H), 6.46 (s, 1H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.7 (s), 151.7 (s), 140.2 (s), 138.3 (s), 133.2 (s), 129.2 (d), 127.2 (d), 126.0 (d), 125.6 (s), 115.5 (d), 104.3 (d), 12.5 (q). MS (ESI): *m/z* (relative intensity) 307 ($[M+Na]^+$, 51 %), 285 ($[M+H]^+$, 46 %). Anal. Calcd for $C_{16}H_{13}ClN_2O$: C, 67.49; H, 4.60; N, 9.84. Found: C, 67.32; H, 4.47; N, 10.02.

1-(4-chlorophenyl)-3-(4-methoxyphenyl)-4-methyl-1H-pyrazole (11e)

Following method B, the reaction was stirred at r. t. to give 64 mg (56 %) of **11e** as a colourless solid. M. P.: 97 °C. IR (KBr) : 3063, 2998, 2959, 2932, 2833, 1612, 1523, 1497, 1462, 1434, 1401, 1363 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80-7.76 (m, 2H), 7.49-7.46 (m, 4H), 6.98-6.93 (m, 2H), 6.47 (s, 1H), 3.86 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.5 (s), 151.6 (s), 140.0 (s), 138.5 (s), 133.1 (s), 129.2 (d), 126.9 (d), 125.9 (s), 114.0 (d), 104.3 (d), 55.2 (q), 12.5 (q). MS (ESI): *m/z* (relative intensity) 321 ($[M+Na]^+$, 91 %), 299 ($[M+H]^+$, 100 %). Anal. Calcd for $C_{17}H_{15}ClN_2O$: C, 68.34; H, 5.06; Cl, 11.87; N, 9.38. Found: C, 68.44; H, 5.03; N, 9.39.

2-(4-methyl-1-phenyl-1H-pyrazol-3-yl)phenol (11f)

Following method B, the reaction was stirred at r. t. to give 60 mg (51 %) of **11f** as a colourless liquid. IR (neat): 3133, 3102, 3056, 1619, 1596, 1548, 1501, 1458, 1367, 1295 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.94 (s, 1H), 7.60 (d, 1H, J = 1.6 Hz), 7.59-7.49 (m, 4H), 7.47-7.41 (m, 1H), 7.27-7.21 (m, 1H), 7.06-7.02 (m, 1H), 6.97-6.91 (m, 1H), 6.61 (s, 1H), 2.44 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.1 (s), 151.6 (s), 139.9 (s), 139.1 (s), 129.2 (d), 129.1 (d), 127.9 (d), 126.3 (d), 124.6 (d), 119.1 (d), 117.0 (d), 116.4 (s), 103.8 (d), 12.4 (q). MS (ESI): *m/z* (relative intensity) 273 ($[M+Na]^+$, 91 %), 251 ($[M+H]^+$, 100 %). Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.88; H, 5.58; N, 11.29.

4-methyl-1-phenyl-3-(thiophen-2-yl)-1H-pyrazole (11g)

Following method B, the reaction was stirred at r. t. to give 71 mg (60 %) of **11g** as a colourless liquid. IR (neat): 3067, 2962, 1596, 1565, 1532, 1500, 1424, 1375, 1327 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54-7.46 (m, 4H), 7.43-7.37 (m, 2H), 7.28-7.26 (m, 1H), 7.10-7.06 (m, 1H), 6.45 (s, 1H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.8 (s), 140.2 (s), 139.6 (s), 136.6

(s), 129.1 (d), 127.7 (d), 127.4 (d), 125.0 (d), 124.5 (d), 123.8 (d), 104.3 (d), 12.5 (q). MS (ESI) *m/z* (relative intensity) 263 ($[M+Na]^+$, 100 %), 241 ($[M+H]^+$, 55 %). Anal. Calcd for $C_{14}H_{12}N_2S$: C, 69.97; H, 5.03; N, 11.66; S, 13.34. Found: C, 70.00; H, 4.90; N, 11.56; S, 13.25.

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Supporting Information Available. NMR spectra of compounds **10a-q** and **11a-g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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