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Oxone-mediated facile access to substituted pyrazoles

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ABSTRACT

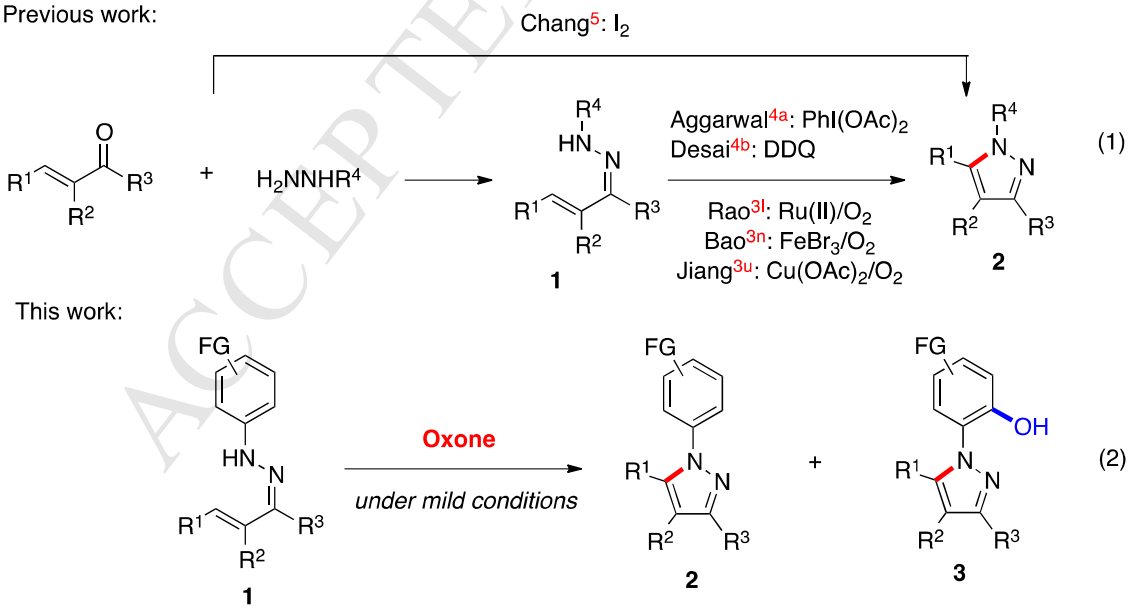
An Oxone-mediated transition-metal-free oxidative C−N bond formation has been achieved for the regioselective synthesis of substituted pyrazoles. The reactions accompany the chelation-controlled ortho-oxidation of *N*-substituted aromatic ring to provide phenol derivatives in some cases. This method displays a facile access to diverse range of substituted pyrazoles from readily accessible hydrazones.

1. Introduction

Pyrazole and its derivatives are well known to be an important structural unit for the development of pharmaceuticals and agrochemicals.[1] For instances, pyrazoles exhibit antimicrobial, ant-inflammatory, analgesic, anticonvulsant, anticancer, and herbicidal activities.[1] To date, huge amount of synthetic methods of pyrazoles have been documented[2,3] including traditional approach based on the condensation of 1,3-dicarbonyl compounds with hydrazines and 1,3-dipolar cycloaddition of dipolarophiles with appropriate dipoles. However, the former affords pyrazoles as mixtures of two regioisomers when substituted hydrazines and 1,3- dicarbonyl

substrates are used. The latter requires the unstable reagents such as diazo compounds.

Recently, oxidative cyclization of hydrazones **1** by hypervalent iodine (III)[4a] or DDQ[4b] to provide substituted pyrazoles **2** have been published (eq 1). This transformation was also achieved by transition-metal-catalyzed aerobic oxidation.[3j,3u,3n] More recently, I_2-mediated one-pot transformations from α,β- unsaturated aldehydes/ketones and hydrazines have also been accomplished.[5] However, there are still limitations associated with these methods, such as limited substrate scope, harsh reaction conditions, and unsatisfactory overall yields. Thus, more general and practical protocols for the synthesis of pyrazole and derivatives are still desirable. Previously, we have developed iodobenzene-catalyzed oxidative C–H amination for the construction of 1*H*-indazole core from arylhydrazones by using Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) as a terminal oxidant under mild reaction conditions.[6] As a part of our continuing research on the oxidative C−N bond formation to access useful heterocycles, herein, we report a practical and regioselective synthesis of pyrazole via the oxidative annulation of allylidene- and butenylidenehydrazones under the presence of Oxone[7] as an single reagent without the use of iodine source (eq 2).

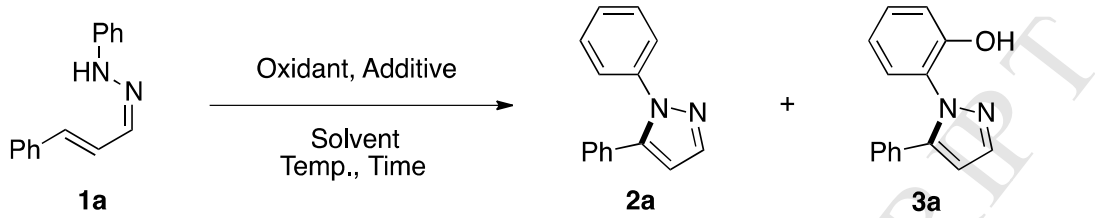


2. Results and discussion

The reaction conditions were evaluated by using (*E*)-1-phenyl-2-((*E*)-3-phenylallylidene)hydrazone **1a** as a model substrate (Table 1). At first we applied the conditions previously utilized for the synthesis of 1*H*-indazoles.[6] Reaction of **1a** in the presence of iodobenzene (30mol%) and Oxone (1.5 equiv.) in trifluoroacetic acid (TFA) at -10 ^{o}C for 30 min afforded the desired pyrazole **2a** in 75% yield (Table 1, run 1). To our surprise, reaction of **1a** without iodobenzene under otherwise same conditions also afforded pyrazole **2a** in 54% yield along with phenol **3a** (24%) (run 2). The formation of phenol **3a** has been reduced when the same reaction was performed at 0 ^{o}C to provide 78% yield of pyrazole **2a** and still 12% of phenol **3a** (run 3). Further lowering the temperature resulted in the remarkable decrease of reactivity (run 4). Less effective results have been observed when 1.0 and 2.0 equivalent of Oxone was introduced (runs 5 and 6). Interestingly, phenol **3a** was formed as a major product with the use of 30% H_2O_2 aq. instead of Oxone to afford pyrazole **2a** (16%) and phenol **3a** (56%), respectively (run 7). The use of other oxidants (*m*CPBA, $K_2S_2O_8$, and TBHP) displayed the unsatisfactory transformations (runs 8-10). In addition, another solvents instead of TFA were found to be less effective (runs 11-15) to afford pyrazole **2a** as a sole product, which indicate the participation of TFA and/or trifluoroperacetic acid derived from TFA with Oxone for the formation of phenol **3a** (*vide infra*). The present method without the use of iodobenzene would be more practical because it can avoid the tedious chromatographic separation to remove organics derived from iodobenzene. The separation of phenol derivative was easy by extractive work-up and/or chromatography.

Table 1

Evaluation of the reaction conditions for the synthesis of pyrazoles[a]



1a **2a** **3a**

Run	Oxidant (equiv)	Additive (equiv)	Solvent	Temp (°C)	Time (h)	Yield **2a** (%)[b]	Yield **3a** (%)[b]
1	Oxone (1.5)	PhI (0.1)	TFA	-10	0.5	75	0
2	Oxone (1.5)	-	TFA	RT	0.5	54	24
3	**Oxone** (1.5)	**-**	TFA	**0**	**2**	**78**	**12**
4	Oxone (1.5)	-	TFA	-10	5	54	16
5	Oxone (1.0)	-	TFA	0	2	50	9
6	Oxone (2.0)	-	TFA	0	2	53	11
7	30% H_2O_2 aq. (1.5)	-	TFA	RT	0.5	16	55
8	*m*CPBA (1.5)	-	TFA	RT	0.5	23	5
9	$K_2S_2O_8$ (1.5)	-	TFA	RT	0.5	trace	0
10	70% TBHP aq. (1.5)	-	TFA	RT	0.5	0	0
11	Oxone (1.5)	TsOH (1.5)	$CHCl_3$	RT	6	28	0
12	Oxone (1.5)	TsOH (1.5)	EtOH	RT	24	25	0
13	Oxone (1.5)	TsOH (1.5)	PhMe	RT	24	22	0
14	Oxone (1.5)	TsOH (1.5)	MeCN	RT	3	27	0
15	Oxone (1.5)	TFA (1.5)	MeCN	RT	3	31	0

TFA=trifluoroacetic acid, TBHP=*tert*-butylhydroperoxide, Oxone=$2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$.

[a] Reaction Conditions: Substrate **1a**, oxidant (1.5 equiv.), in TFA (0.33 M).

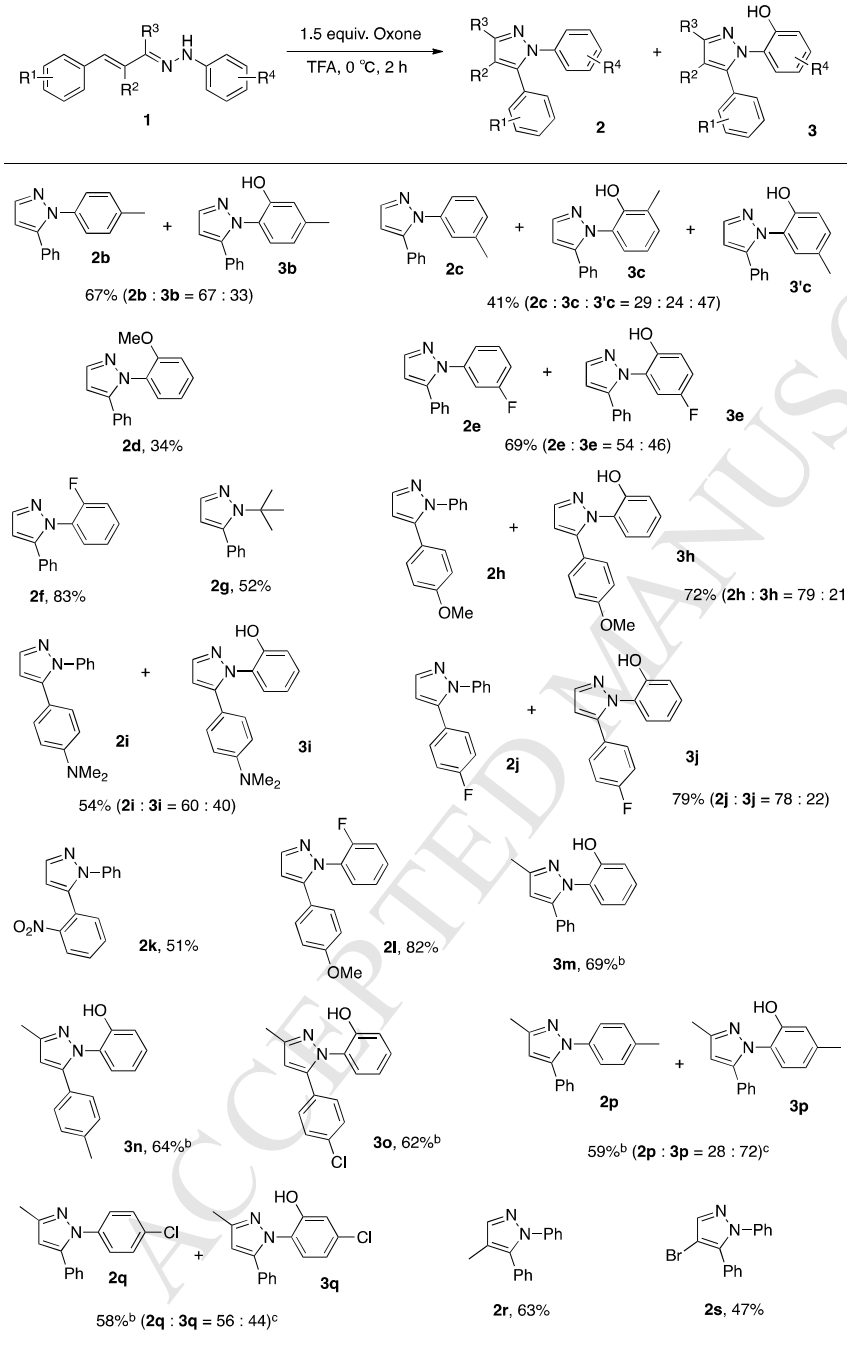
[b] Isolated yield.

Another hydrazones (**1b**-**1s**)[8] were examined for the cyclization reaction under the conditions (Table 1, run 3). Substrates with electron-donating group on the *N*-substituted aromatic ring provided moderate yields of expected pyrazoles (**2b**, **2c**, and **2d**) along with phenols (**3b**, **3c**, and its regioisomer **3'c**). The preferential formation of phenol **3'c** in the transformation of hydrazine **1c** would be attributed to the steric and electronic effects (*para*-position of electron-donating group). Phenol product was not

observed when hydrazine **1d** with *ortho*-substituent was employed to afford pyrazole **2d** in moderate yield, probably due to the steric congestion. Better yields were observed when substrates with electron-deficient benzene ring (**1e** and **1f**) were applied. Interestingly, exclusive formation of pyrazole **2f** was observed with excellent yield (83%) when 2-fluorophenylhydrazone **1f** was applied. Hydrazone **1g** derived from *tert*-butylhydrazine also afforded a corresponding pyrazole **2g** in moderate yield. Pyrazoles with substituted aromatic ring at the 5-position were also formed smoothly in moderate to good yields (51-82%) still as a mixture of pyrazoles (**2h**, **2i**, and **2j**) and phenols (**3h**, **3i**, and **3j**) except for nitro- and fluoro-substituted substrates (**1k** and **1l**). In the case of hydrazine **1k**, the oxidation would be inhibited by the strong inducting effect of electron-withdrawing nitro group, which would lower the electron density of *N*-phenyl group, to afford **2k**, exclusively. Moreover, butenylidenehydrazones (**1m**, **1n**, **1o**, **1p**, and **1q**) were tested to provide corresponding 1,3,5-trisubstituted pyrazoles (**2p** and **2q**) and phenols (**3m**, **3n**, **3o**, **3p**, and **3q**) in good yields. Intriguingly, substrates with *N*-phenyl group (**1m**, **1n**, and **1o**) gave phenols as a sole product (**3m**, **3n**, and **3o**), while the other substrates with substituted *N*-aromatics (**1p** and **1q**) were transferred to the mixtures of pyrazoles and phenols (**2p**+**3p** and **2q**+**3q**). It is assumed that the oxidations of *N*-substituted aryl group would be easier in the case of **1m-1q** due to the additional substitution of methyl group which would enhance the electron density of aromatic ring by its electron-donating nature. Therefore, rich amount of phenol products (**3m**, **3n**, **3o**, **3p**, and **3q**) have been produced. In all cases, mixtures of two classes of compounds (pyrazole **2** and phenol **3**) were separated easily through the work-up process and/or silica gel column chromatography.

Table 2

The reaction substrate scope of di- and tri-substituted pyrazoles[a]

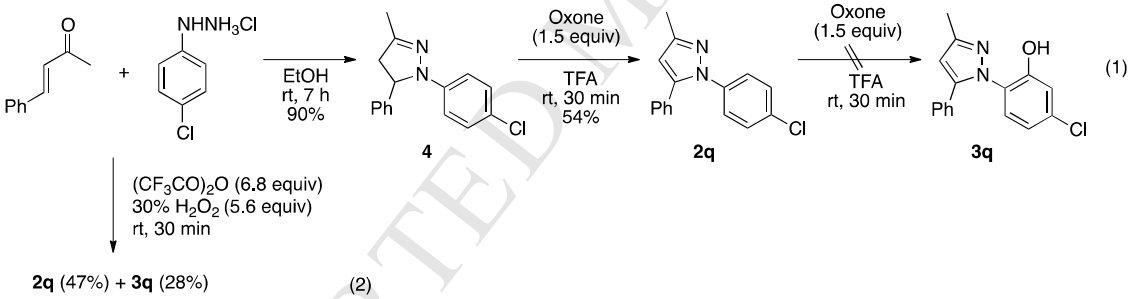


[a] Reaction Conditions: Substrate **1**, Oxone (1.5 equiv.), at 0 ^{o}C in TFA (0.33 M).

[b] Reaction at room temperature for 0.5 h.

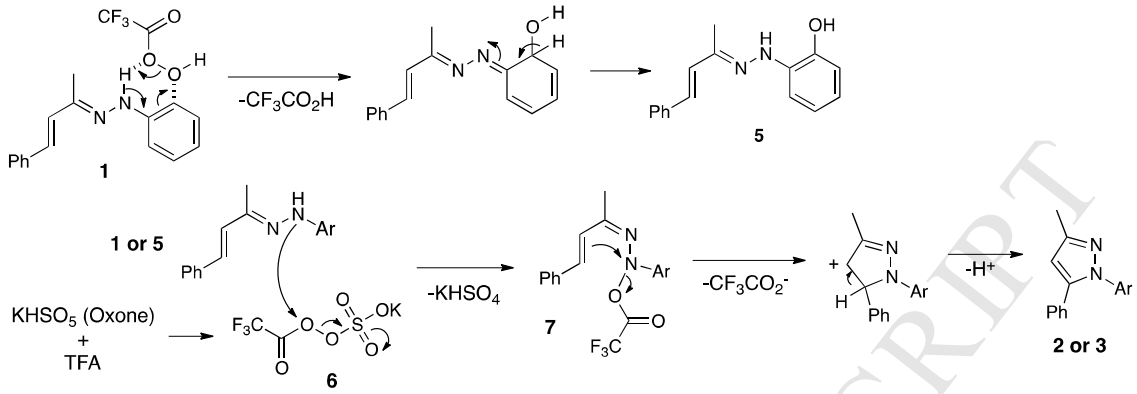
[c] The ratios were determined by ^{1}H-NMR.

To examine the reaction pathway for the formation of pyrazole and phenol, the reaction of benzylideneacetone and 4-chlorophenylhydrazine hydrochloride in ethanol without oxidant was conducted to afford 4,5-dihydro-1*H*-pyrazole **4** in 90% yield,[9] which was subjected to the condition to provide pyrazole **2q** as a sole product (Scheme 1, eq. 1). Furthermore, isolated pyrazole **2q** did not transform to phenol **3q** under the conditions. While hydrazone **1q** gave pyrazole **2q** and phenol **3q** in 58% yield in a ratio of 56:44 (Table 2). On the other hand, the same results was observed when in situ generated trifluoroperacetic acid derived from trifluoroacetic anhydride with hydrogen peroxide[10] was applied to the reaction to form pyrazole **2q** and phenol **3q** in 47 and 28% yield, respectively (Scheme 1, eq. 2), which is close results obtained in Table 2. These results suggested that oxidation of *ortho*-position of nitrogen-substituted aromatic ring could occur prior cyclization and also trifliooperacetic acid would participate the transformation.



Scheme 1. Examination of the reaction pathway.

Considering the phenomenon, a possible reaction pathway for the formation of pyrazole **2** and phenol **3** has been illustrated in Scheme 2. *Ortho*-oxidation of hydrazine **1** would afford intermediate phenol **5** with the aid of trifluoroperacetic acid derived from triflioroacetic acid and Oxone.[9] While the reaction of Oxone and trifluoroacetic acid should form complex **6** which would suffer from nucleophilic attack by nitrogen atom of hydrazine to produce trifluoroacetoxyhydrazone **7** which would cyclize to give phenol **3** after deprotonation.[11] Pyrazole **2** would form directly by skipping the *ortho*-oxidation step.



Scheme 2. Proposed reaction mechanism.

3. Conclusions

In conclusion, we have discovered the first simple and divergent synthesis of pyrazoles and phenols by employing an inexpensive and environmentally benign Oxone as a single oxidant in moderate to excellent yields. A range of functional groups has been tolerated through this transformation. Diverse range of di- and tri-substituted pyrazole derivatives along with phenol compounds has been synthesized from readily accessible starting materials by simple operations. The present method would effectively complement the previous synthesis and serve as combinatorial synthesis of diverse pyrazole scaffolds and drug discovery.

4. Experimental section

4.1. General

Unless stated otherwise, reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F_{254}), visualizing with ultraviolet light or iodine spray. Column chromatography was performed on silica gel (60–120 mesh) using hexane and ethyl acetate. ^{1}H and ^{13}C NMR spectra were determined in $CDCl_3$ solution using 400 and 100 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, d = 0.0) as the internal standard and expressed in parts per million. Spin multiplicities are given as s (singlet), d (doublet), t (triplet), and m (multiplet) as well as b (broad). Coupling constants (*J*) are given in hertz. Infrared spectra were recorded on a FT-IR spectrometer. Melting points were determined by

using a Büchi melting point B-540 apparatus and are uncorrected. MS spectra were obtained on a mass spectrometer. HR-MS was determined using JEOL JNM-AX 500 mass spectrometer.

4.2. General procedures for the synthesis of pyrazoles and phenols

4.2.1. Condition A. Oxone (0.75 mmol, 1.5 equiv) was added to a stirred solution of hydrazine **1** (0.5 mmol, 1.0 equiv) in TFA (1.5 mL) at 0 ºC, and the mixture was stirred for 2 h at the same temperature. The reaction mixture was quenched with water (5 mL) and diluted with $CHCl_3$ (5 mL), and extracted with $CHCl_3$ (3 x 15 mL). The organic layers were washed with water (3 x 15 mL), dried over Na_2SO_4 and the solvent was evaporated in vacuo. The residue was purified by silica gel column chromatography to afford pure substituted pyrazoles **2** and/or **3**.

4.2.2. Condition B. Oxone (0.75 mmol, 1.5 equiv) was added to a solution of hydrazine **1** (0.5 mmol, 1.0 equiv) in TFA (1.5 mL) to stir for 30 min at ambient temperature. The reaction mixture was quenched with water (5 mL) and diluted with $CHCl_3$ (5 mL), and extracted with $CHCl_3$ (3 x 15 mL). The organic layers were washed with water (3 x 15 mL), dried over Na_2SO_4 and the solvent was removed in vacuo. The residue was purified by silica gel column chromatography to afford pure substituted pyrazoles **2** and/or **3**.

If it is required for further purification, the residue was added 1N NaOH aq. (15 mL), and extracted with Et_2O (3 x 15 mL). The organic layers were washed with 1N citric acid aq. (15 mL) and brine (15 mL). Drying over Na_2SO_4 followed by evaporation of the solvent afforded almost pure pyrazoles **2**. The aqueous layer was treated with 1N citric acid aq. (20 mL) to acidify, and extracted with Et_2O (3 x 20 mL) and the layers were washed with sat. $NaHCO_3$ aq. (20 mL) and brine (20 mL). Drying over Na_2SO_4 followed by evaporation of the solvent gave almost pure phenols **3**.

*4.2.3. 1,5-Diphenylpyrazole (**2a**)*[5]. Following the condition A. Pale yellow oil; yield 78%; R*f* 0.50 (hexane : AcOEt = 4 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.72 (d, *J* = 1.7 Hz, 1H), 7.38–7.26 (m, 8H), 7.26–7.19 (m, 2H), 6.51 (d, *J* = 1.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 143.0, 140.3, 140.1, 130.6, 128.9 (2C), 128.7 (2C), 128.4 (2C), 128.2 (2C), 127.4, 125.2, 107.8 ppm.

*4.2.4. 2-(5-Phenylpyrazol-1-yl)phenol (**3a**).* Following the condition A. Pale yellow oil; yield 12%; R*f* 0.39 (hexane : AcOEt = 4 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.79 (d, *J* = 2.0 Hz, 1H), 7.42–7.33 (m, 3H), 7.33–7.27 (m, 2H), 7.20–7.09 (m, 2H), 6.75–6.67 (m, 1H), 6.67–6.58 (m, 1H), 6.53 (d, *J* = 2.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 150.4, 143.6, 140.0, 130.1, 128.8 (2C), 128.6, 128.5, 128.3, 125.3 (2C), 124.4, 119.0, 118.4, 108.1 ppm; HRMS (FAB) calcd for $C_{15}H_{13}N_2O$: 237.1024, $[M+H]^+$ found: 237.1027.

*4.2.5. 1-(4-Tolyl)-5-phenylpyrazole (**2b**)*[5]. Following the condition A. Yellow oil; yield 45%; R*f* 0.50 (hexane : AcOEt = 4 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.70 (d, *J* = 1.5 Hz, 1H), 7.34–7.27 (m, 3H), 7.27–7.20 (m, 2H), 7.18 (d, *J* = 8.3 Hz, 2H), 7.12 (d, *J* = 8.3 Hz, 2H), 6.49 (d, *J* = 1.5 Hz, 1H), 2.35 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 142.8, 140.0, 137.7, 137.3, 130.7, 129.4 (2C), 128.7 (2C), 128.4 (2C), 128.1, 125.0 (2C), 107.6, 21.1 ppm.

*4.2.6. 5-Methyl-2-(5-phenylpyrazol-1-yl)pyrazole (**3b**).* Following the condition A. White solid; yield 22%; R*f* 0.41 (hexane : AcOEt = 4 : 1); mp 119–121 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.76 (d, *J* = 1.2 Hz, 1H), 7.40–7.26 (m, 5H), 6.95 (s, 1H), 6.56 (d, *J* = 8.0 Hz, 1H), 6.50 (d, *J* = 1.2 Hz, 1H), 6.42 (d, *J* = 8.0 Hz, 1H), 2.29 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 150.2, 143.5, 139.9, 138.7, 130.3, 128.9 (2C), 128.64 (2C), 128.58, 124.1, 123.0, 119.9, 118.8, 108.0, 21.1 ppm; HRMS (FAB): *m/z* $[M+H]^+$ calcd for $C_{16}H_{15}ON_2$: 251.1185; found: 251.1157.

*4.2.7. 5-Phenyl-1-(4-tolyl)pyrazole (**2c**).* Following the condition A. Yellow oil; yield 12%; R*f* 0.32 (hexane : AcOEt = 9 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.71 (d, *J* = 1.7 Hz, 1H), 7.37–7.27 (m, 3H), 7.27–7.21 (m, 3H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.10 (d, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.50 (d, *J* = 1.7 Hz, 1H), 2.32 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 142.9, 140.1, 140.0, 139.0, 130.6, 128.7 (2C), 128.5, 128.4 (2C), 128.2, 128.1, 125.8, 122.3, 107.7, 21.3 ppm; IR (NaCl) ν 3445, 3057, 1605, 1493, 760, 694 cm^{-1}; HRMS (FAB): *m/z* $[M+H]^+$ calcd for $C_{16}H_{15}N_2$: 235.1236; found: 235.1292.

*4.2.8. 2-Methyl-6-(5-phenylpyrazol-1-yl)phenol (**3c**).* Following the condition A. Yellow oil; yield 10%; R*f* 0.44 (hexane : AcOEt = 9 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ

= 9.17 (s, 1H), 7.77 (d, *J* = 1.5 Hz, 1H), 7.48–7.31 (m, 3H), 7.31–7.22 (m, 2H), 7.02 (d, *J* = 8.3 Hz, 2H), 6.95 (d, *J* = 8.3 Hz, 1H), 6.52 (d, *J* = 1.5 Hz, 1H), 6.48 (s, 1H), 2.00 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.2, 143.6, 140.0, 130.2, 128.9, 128.8 (2C), 128.6, 128.5 (2C), 127.4, 125.0, 124.9, 118.0, 108.0, 20.3 ppm; IR (NaCl) ν 3058, 2931, 1731, 1604, 1485, 1245, 767, 694 cm^{-1}; HRMS (FAB): *m/z* $[M+H]^+$ calcd for $C_{16}H_{15}ON_2$: 251.1184; found: 251.1182.

*4.2.9. 4-Methyl-2-(5-phenylpyrazol-1-yl)phenol (**3'c**).* Followed the condition A. Yellow solid; yield 19%; R*f* 0.21 (hexane : AcOEt = 9 : 1); mp 108–110 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.45 (s, 1H), 7.78 (d, *J* = 1.5 Hz, 1H), 7.40–7.30 (m, 3H), 7.30–7.22 (m, 2H), 7.03 (t, *J* = 4.4 Hz, 1H), 6.58–6.44 (m, 3H), 2.35 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.7, 143.8, 140.0, 130.2, 129.6, 128.9 (2C), 128.6, 128.5 (2C), 127.7, 124.9, 122.3, 118.4, 108.1, 16.2 ppm; HRMS (FAB): *m/z* $[M+H]^+$ calcd for $C_{16}H_{15}ON_2$: 251.1184; found: 251.1186.

*4.2.10. 1-(2-Methoxyphenyl)-5-phenylpyrazole (**2d**):* Following the condition A. Yellow oil; yield 34%; R*f* 0.23 (hexane : AcOEt = 4 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.74 (d, *J* = 2.0 Hz, 1H), 7.39 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.34 (dt, *J* = 8.3, 1.5 Hz, 1H), 7.28–7.15 (m, 5H), 7.01 (t, *J* = 7.6 Hz, 1H) 6.87 (d, *J* = 8.3 Hz, 1H), 6.52 (d, *J* = 2.0 Hz, 1H), 3.45 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 154.1, 144.7, 140.2, 131.0, 129.9, 129.4, 128.8, 128.1 (2C), 127.8, 127.5, 120.8 (2C), 112.1, 105.9, 55.3 ppm; IR (KBr) ν 3068, 2937, 1711, 1600, 1508, 1278, 1025, 759, 695 cm^{-1};HRMS (FAB): *m/z* $[M+H]^+$ calcd for $C_{16}H_{15}ON_2$: 251.1184; found: 251.1205.

*4.2.11. 1-(3-Fluorophenyl)-5-phenylpyrazole (**2e**):* Following the condition A. Yellow oil; yield 37%; R*f* 0.50 (hexane : AcOEt = 4 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.73 (d, *J* = 1.7 Hz, 1H), 7.38–7.30 (m, 3H), 7.30–7.18 (m, 3H), 7.09 (dd, *J* = 9.8, 4.4 Hz, 1H), 7.05 (d, *J* = 8.3 Hz, 1H), 7.00 (dt, *J* = 8.3, 2.4 Hz, 1H), 6.51 (d, *J* = 1.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.5 (d, $^1J_{CF}$ = 246.2 Hz), 143.1, 141.3, 140.7, 130.2, 130.0 (d, $^3J_{CF}$ = 9.0 Hz), 128.7 (2C), 128.6 (2C), 128.5, 120.6 (d, $^4J_{CF}$ = 3.3 Hz), 114.3 (d, $^2J_{CF}$ = 20.6 Hz), 112.5 (d, $^2J_{CF}$ = 23.8 Hz), 108.3 ppm; IR (NaCl) ν 3071, 1737, 1606, 1494, 1194, 761, 691 cm^{-1}; HRMS (FAB): *m/z* $[M+H]^+$ calcd for $C_{15}H_{12}N_2F$: 239.0985; found: 239.1014.

*4.2.12. 4-Fluoro-2-(5-phenylpyrazol-1-yl)phenol (**3e**):* Following the condition A. Yellow solid; yield 32%; R*f* 0.46 (hexane : AcOEt = 4 : 1); mp 120–122 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.47 (s, 1H), 7.79 (d, *J* = 1.7 Hz, 1H), 7.50–7.34 (m, 3H), 7.34–7.21 (m, 2H), 7.07 (dd, *J* = 9.3, 5.4 Hz, 1H), 6.87 (dt, *J* = 7.8, 2.9 Hz, 1H), 6.53 (d, *J* = 1.7 Hz, 1H), 6.41 (dd, *J* = 9.3, 2.9 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 154.9 (d, $^{1}J_{CF}$ = 255.2 Hz), 153.8, 146.7, 143.9, 140.3, 129.7, 129.1, 128.8 (4C), 119.1 (d, $^{3}J_{CF}$ = 9.1 Hz), 114.9 (d, $^{2}J_{CF}$ = 23.0 Hz), 111.1 (d, $^{2}J_{CF}$ = 26.3 Hz), 108.5 ppm; FT-IR: 3087, 1613, 1451, 1269, 1175, 975, 925, 863, 783, 690 cm^{-1}; HRMS (FAB): *m/z* $[M+H]^+$ calcd for $C_{15}H_{12}ON_2F$: 255.0934, found: 255.0887.

*4.2.13. 1-(2-Fluorophenyl)-5-phenylpyrazole (**2f**):* Following the condition A. Yellow solid; yield 83%; R*f* 0.50 (hexane : AcOEt = 4 : 1); mp 77–78 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.77 (d, *J* = 1.5 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.35 (q, *J* = 6.3 Hz, 1H), 7.31–7.12 (m, 6H), 7.08 (t, *J* = 9.1 Hz, 1H), 6.55 (d, *J* = 1.5 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.6 (d, $^{1}J_{CF}$ = 251.1 Hz), 144.8, 141.0, 130.1 (d, $^{3}J_{CF}$ = 8.2 Hz, 2C), 128.9, 128.4 (2C), 128.3 (2C), 127.8 (2C), 124.6 (d, $^{4}J_{CF}$ = 3.3 Hz), 116.6 (d, $^{2}J_{CF}$ = 19.7 Hz), 106.7 ppm; HRMS (FAB): *m/z* $[M+H]^+$ calcd for $C_{15}H_{12}N_2F$: 239.0985; found: 239.0923.

*4.2.14. 1-tert-Butyl-5-phenylpyrazole (**2g**):* Following the condition A. White solid; yield 52%; R*f* 0.61 (hexane : AcOEt = 4 : 1); mp 97–99 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.47 (d, *J* = 1.7 Hz, 1H), 7.42–7.30 (m, 5H), 6.14 (d, *J* = 1.7 Hz, 1H), 6.14 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 142.6, 136.3, 134.3, 130.4 (2C), 128.3, 127.7 (2C), 109.2, 61.0, 31.1 (3C) ppm; IR (KBr) ν 3052, 2991, 2937, 1652, 1448, 1369, 1347, 771, 709 cm^{-1}; HRMS (FAB): *m/z* $[M+H]^+$ calcd for $C_{13}H_{17}N_2$: 201.1392, found: 201.1353.

*4.2.15. 5-(4-Methoxyphenyl)-1-phenylpyrazole (**2h**)[12]:* Following the condition A. Yellow oil; yield 49%; R*f* 0.32 (hexane : AcOEt = 4 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.70 (d, *J* = 1.8 Hz, 1H), 7.39–7.24 (m, 5H), 7.15 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.45 (d, *J* = 1.8 Hz, 1H), 3.79 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.5, 142.8, 140.2 (2C), 130.0 (2C), 128.8 (2C), 127.3, 125.2 (2C), 113.9, 197.3, 55.2 ppm.

*4.2.16. 2-[5-(4-Methoxyphenyl)pyrazol-1-yl]phenol (**3h**):* Following the condition A. White solid; yield 23%; R*f* 0.27 (hexane : AcOEt = 4 : 1); mp 163–164 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.50 (s, 1H), 7.76 (d, *J* = 1.7 Hz, 1H), 7.21 (d, *J* = 8.5 Hz, 2H), 7.17–7.04 (m, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 6.73 (d, *J* = 8.0 Hz, 1H), 6.64 (dt, *J* = 7.0, 2.4 Hz, 1H), 6.47 (d, *J* = 1.7 Hz, 1H), 3.82 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.9, 150.6, 143.5, 140.0, 130.2 (2C), 128.3, 125.4, 124.4, 122.4, 119.1, 118.5, 114.0 (2C), 107.7, 55.3 ppm; HRMS (FAB): *m/z* $[M+H]^+$ calcd for $C_{16}H_{15}O_2N_2$: 267.1133, found: 267.1062.

*4.2.17. 5-(4-Dimethylaminophenyl)-1-phenylpyrazole (**2i**):* Following the condition A. Yellow oil; yield 32%; R*f* 0.31 (hexane : AcOEt = 4 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.69 (d, *J* = 1.8 Hz, 1H), 7.41–7.22 (m, 5H), 7.08 (d, *J* = 8.4 Hz, 2H), 6.62 (d, *J* = 8.4 Hz, 2H), 6.42 (d, *J* = 1.8 Hz, 1H), 2.95 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 150.0, 143.5, 140.4, 140.1, 129.5 (2C), 128.8 (2C), 127.1, 125.2 (2C), 111.8, 106.6, 104.1, 40.2 ppm; HRMS (FAB): *m/z* $[M+H]^+$ calcd for $C_{17}H_{18}N_3$: 264.1500, found: 264.1566.

*4.2.18. 2-[5-(4-Dimethylaminophenyl) pyrazol-1-yl]phenol (**3i**):* Following the condition A. Yellow oil; yield 22%; R*f* 0.31 (hexane : AcOEt = 4 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.74 (d, *J* = 2.0 Hz, 1H), 7.14 (d, *J* = 9.0 Hz, 2H), 7.20–7.00 (m, 2H), 6.83 (d, *J* = 7.6 Hz, 1H), 6.65 (d, *J* = 9.0 Hz, 2H), 6.67–6.52 (m, 1H), 6.43 (d, *J* = 2.0 Hz, 1H), 2.98 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 150.6, 150.3, 144.3, 139.9, 129.7 (2C), 128.1, 125.8, 124.5, 119.1, 118.3, 117.4, 111.8 (2C), 107.1, 40.2 ppm; HRMS (FAB): *m/z* $[M]^+$ calcd for $C_{17}H_{17}ON_3$: 279.1371, found: 279.1360.

*4.2.19. 5-(4-Fluorophenyl)-1-phenylpyrazole (**2j**):* Following the condition A. Yellow oil; yield 62%; R*f* 0.38 (hexane : AcOEt = 4 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.72 (d, *J* = 1.7 Hz, 1H), 7.40–7.24 (m, 5H), 7.21 (d, *J* = 8.5 Hz, 1H), 7.20 (d, *J* = 8.5 Hz, 1H), 7.01 (d, *J* = 8.5 Hz, 1H), 6.99 (d, *J* = 8.5 Hz, 1H), 6.49 (d, *J* = 1.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.5 (d, $^{1}J_{CF}$ = 247.8 Hz), 141.9, 140.3, 139.9, 130.5 (d, $^{3}J_{CF}$ = 8.3 Hz, 2C), 128.9 (2C), 127.5, 126.7 (d, $^{4}J_{CF}$ = 3.3 Hz), 125.2, 115.6 (d, $^{2}J_{CF}$ = 21.4 Hz, 2C), 107.8 ppm; HRMS (FAB): $[M+H]^+$ calcd. for $C_{15}H_{12}N_2F$: 239.0985, found: 239.0989.

*4.2.20. 2-[5-(4-Fluorophenyl)pyrazol-1-yl]phenol (**3j**):* Following the condition A. White solid; yield 17%; R*f* 0.26 (hexane : AcOEt = 4 : 1); mp 184–186 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.39 (s, 1H), 7.78 (s, 1H), 7.45–7.21 (m, 2H), 7.21–7.10 (m, 2H), 7.10–6.90 (m, 2H), 6.79–6.57 (m, 2H), 6.51 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.8 (d, $^{1}J_{CF}$ = 247.8 Hz), 150.6, 142.6, 140.1, 130.7 (d, $^{3}J_{CF}$ = 8.2 Hz, 2C), 128.6, 126.2 (d, $^{4}J_{CF}$ = 3.3 Hz), 125.2, 124.4, 119.2, 118.6, 115.8 (d, $^{2}J_{CF}$ = 21.5 Hz, 2C), 108.2 ppm; HRMS (FAB): $[M+H]^+$ calcd. for $C_{15}H_{12}ON_2F$: 255.0934, found: 255.0870.

*4.2.21. 5-(2-Nitrophenyl)-1-phenylpyrazole (**2k**)[13]:* Following the condition A. Orange solid; yield 51%; R*f* 0.22 (hexane : toluene = 1 : 1); mp 113–115 ºC (lit.[11] 120–122 ºC); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.90 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.77 (d, *J* = 1.7 Hz, 1H), 7.61 (dt, *J* = 7.6, 1.5 Hz, 1H), 7.72 (dt, *J* = 8.0, 1.2 Hz, 1H), 7.72 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.34–7.16 (m, 5H), 6.48 (d, *J* = 1.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 140.4, 139.2, 137.9, 132.9, 132.6, 129.8, 129.0 (2C), 127.6, 125.9, 125.2, 124.53, 124.45 (2C), 108.4 ppm.

*4.2.22. 1-(2-Fluorophenyl)-5-(4-methoxyphenyl)pyrazole (**2l**):* Following the condition A. Yellow solid; yield 82%; R*f* 0.25 (hexane : AcOEt = 4 : 1); mp 123–125 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.75 (d, *J* = 1.7 Hz, 1H), 7.45 (dt, *J* = 7.6, 1.7 Hz, 1H), 7.40–7.29 (m, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.15–7.01 (m, 1H), 7.14 (d, *J* = 9.0 Hz, 2H), 6.80 (d, *J* = 9.0 Hz, 2H), 6.48 (d, *J* = 1.7 Hz, 1H), 3.78 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.5, 156.6 (d, $^{1}J_{CF}$ = 251.1 Hz), 144.6, 141.0, 130.0 (d, $^{3}J_{CF}$ = 7.5 Hz), 129.1 (2C), 129.0, 128.4 (d, $^{3}J_{CF}$ = 11.5 Hz), 124.5 (d, $^{4}J_{CF}$ = 4.2 Hz), 122.6, 116.7 (d, $^{2}J_{CF}$ = 19.8 Hz), 113.8 (2C), 106.2, 55.2 ppm; HRMS (FAB): $[M]^+$ calcd. for $C_{16}H_{13}ON_2F$: 268.1012, found: 268.0969.

*4.2.23. 2-(3-Methyl-5-phenylpyrazol-1-yl)phenol (**3m**):* Following the condition B. Yellow solid; yield 69%; R*f* 0.47 (hexane : AcOEt = 4 : 1); mp 135–136 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.73 (s, 1H), 7.38–7.31 (m, 3H), 7.30–7.23 (m, 2H), 7.11 (d, *J* = 3.9 Hz, 1H), 6.68–6.55 (m, 2H), 6.30 (s, 1H), 2.39 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 150.4, 149.6, 144.3, 130.3, 128.8 (2C), 128.61 (2C), 128.57, 127.9, 125.4,

124.1, 119.0, 118.3, 180.1, 13.5 ppm; HRMS (FAB): *m/z* $[M+H]^+$ calcd for $C_{16}H_{15}ON_2$: 251.1184, found: 251.1188.

*4.2.24. 2-(3-Methyl-5-p-tolylpyrazol-1-yl)phenol (**3n**):* Following the condition B. White solid; yield 64%; R*f* 0.46 (hexane : AcOEt = 4 : 1); mp 177–179 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.75 (s, 1H), 7.35–7.24 (m, 1H), 7.22–7.05 (m, 5H), 6.67 (d, *J* = 7.8 Hz, 1H), 6.64–6.53 (m, 1H), 6.27 (s, 1H), 2.38 (s, 3H), 2.36 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 150.4, 149.5, 144.4, 138.6, 129.3 (2C), 128.6 (2C), 127.8, 127.4, 125.5, 124.1, 119.0, 118.3, 107.9, 21.3, 13.5 ppm; HRMS (FAB): *m/z* $[M+H]^+$ calcd for $C_{17}H_{17}ON_2$: 265.1340, found: 265.1343.

*4.2.25. 2-[5-(4-Chlorophenyl)-3-Methylpyrazol-1-yl]phenol (**3o**):* Following the condition B. Yellow solid; yield 62%; R*f* 0.38 (hexane : AcOEt = 4 : 1); mp 214–216 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.57 (s, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 7.17–7.08 (m, 2H), 6.63 (d, *J* = 2.9 Hz, 2H), 6.30 (s, 1H), 2.39 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 150.4, 149.8, 143.0, 134.7, 130.0 (2C), 128.9 (2C), 128.8, 128.2, 125.2, 124.1, 119.2, 118.5, 108.2, 13.5 ppm; HRMS (FAB): *m/z* $[M]^+$ calcd for $C_{16}H_{13}ON_2Cl$: 284.0717, found: 284.0707.

*4.2.26. 3-Methyl-5-phenyl-1-p-tolylpyrazole (**2p**):* Following the condition B. Yellow oil; yield 16%; R*f* 0.44 (hexane : AcOEt = 4 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.33–7.16 (m, 5H), 7.15 (d, *J* = 8.8 Hz, 2H), 7.10 (d, *J* = 8.8 Hz, 2H), 6.29 (s, 1H), 2.38 (s, 3H), 2.33 (s, 3H) ppm; IR (NaCl) ν 3016, 2925, 1670, 1607, 1516, 1450, 1199, 975, 761, 698 cm^{-1}; HRMS (FAB): *m/z* $[M]^+$ calcd for $C_{17}H_{16}N_2$: 248.1313, found: 248.1320.

*4.2.27. 5-Methyl-2-(3-Methyl-5-phenylpyrazol-1-yl)phenol (**3p**):* Following the condition B. Yellow oil; yield 43%; R*f* 0.44 (hexane : AcOEt = 4 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.58 (s, 1H), 7.40–7.31 (m, 3H), 7.31–7.24 (m, 2H), 6.92 (s, 1H), 6.51 (d, *J* = 7.6 Hz, 1H), 6.39 (d, *J* = 7.6 Hz, 1H), 6.28 (s, 1H), 2.38 (s, 3H), 2.27 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 151.5, 147.9, 146.4, 141.1, 129.6, 128.7 (2C), 128.6 (2C), 128.4, 128.2, 126.0, 120.8, 119.3, 107.3, 21.3, 12.4 ppm; IR (NaCl) ν 3060, 2920, 1738, 1592, 1517, 1244, 763, 697 cm^{-1}; HRMS (FAB): *m/z* $[M+H]^+$ calcd for $C_{17}H_{17}ON_2$: 265.1341, found: 265.1341.

*4.2.28. 1-(4-Chlorophenyl)-3-methyl-5-phenylpyrazole (**2q**)[14]:* Following the condition B. Yellow oil; yield 78%; R*f* 0.57 (hexane : AcOEt = 4 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34–7.23 (m, 5H), 7.23–7.10 (m, 4H), 2.38 (s, 3H) ppm.

*4.2.29. 5-Chloro-2-(3-Methyl-5-phenylpyrazol-1-yl)phenol (**3q**):* Following the condition B. White oil; yield 12%; R*f* 0.54 (hexane : AcOEt = 4 : 1); mp 133–135 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42–7.30 (m, 3H), 7.30–7.18 (dd, *J* = 7.2, 2.0 Hz, 2H), 7.12 (d, *J* = 2.0 Hz, 1H), 6.60–6.46 (m, 2H), 6.30 (s, 1H), 2.38 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 151.3, 149.8, 144.4, 132.8, 130.1, 128.9, 128.76 (2C), 128.74 (2C), 124.4, 124.1, 119.1, 118.6, 108.4, 14.2, 13.5 ppm; IR (KBr) ν 3038, 2930, 1597, 1511, 1424, 1264, 1091, 767, 701 cm^{-1}; HRMS (FAB): *m/z* $[M+H]^+$ calcd for $C_{16}H_{13}ON_2Cl$: 284.0717, found: 284.0733.

*4.2.30. 4-Methyl-1,5-diphenylpyrazole (**2r**)[15]:* Following the condition A. Pale yellow oil; yield 63%; R*f* 0.44 (hexane : AcOEt = 4 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.61 (s, 1H), 7.38–7.30 (m, 3H), 7.29–7.24 (m, 2H), 7.24–7.20 (m, 3H), 7.20–7.13 (m, 2H), 2.12 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 141.1, 140.2, 139.8, 130.5, 129.8 (2C), 128.7, 128.4 (2C), 127.9 (2C), 126.7, 124.6 (2C), 116.3, 9.2 ppm.

*4.2.31. 4-Bromo-1,5-diphenylpyrazole (**2s**):* Following the condition A. Pale yellow oil; yield 47%; R*f* 0.38 (hexane : AcOEt = 4 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.76 (s, 1H), 7.39–7.33 (m, 3H), 7.31–7.24 (m, 5H), 7.24–7.18 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 141.0, 140.4, 139.8, 130.0 (2C), 128.89, 128.87 (2C), 128.5 (2C), 127.6, 124.7 (2C), 95.8 ppm; IR (NaCl) ν 3059, 1596, 1498, 1381, 1068, 950, 764, 696 cm^{-1}; HRMS (FAB): *m/z* $[M]^+$ calcd for $C_{15}H_{11}N_2Br$: 298.0106, found: 298.0103.

*4.2.32. The procedure for synthesis of pyrazoline **4**.* Benzylideneacetone (5.0 mmol, 1.0 equiv) and *p*-chlorophenylhydrazine hydrochloride (5.0 mmol, 1.0 equiv) was mixed in EtOH (6 mL) to stir at ambient temperature for 7 h. After the reaction mixture was quenched with sat. $NaHCO_3$ aq. (5 mL), a lot of solid precipitated from the solution. The solid was collected by filtration and washed with EtOH, to give the pure 1-(4-chloro-phenyl)-3-methyl-5-phenylpyrazoline **4**[16].

White solid; yield 90%; R*f* 0.63 (hexane : AcOEt = 4 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.43–7.17 (m, 5H), 7.06 (d, *J* = 9.0 Hz, 2H), 6.82 (d, *J* = 9.0 Hz, 2H), 4.98 (dd, *J* = 11.9, 8.0 Hz, 1H), 3.42 (dd, *J* = 17.6, 11.9 Hz, 1H), 2.72 (dd, *J* = 17.6, 8.0 Hz, 1H), 2.06 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 149.0, 144.4, 142.4, 129.1 (2C), 128.7 (2C), 127.5, 125.8 (2C), 123.2, 114.1 (2C), 64.6, 47.9, 15.9 ppm.

4.2.33. The procedure for synthesis of ***2q*** *and* ***3q*** *by* $(CF_3CO)_2O$ *and* H_2O_2. 30% Hydrgen peroxide (0.085 mL, 2.8 mmol, 5.6 eq) was added slowly at 0 °C to trifluoroacetic anhydride (0.48 mL, 3.4 mmol, 6.8 eq.), then the mixuture was stirred at room temperature for 1 hour. After hydrazone **1q** (135 mg, 0.5 mmol) was added little by little to the mixture, the reaction mixture was stirred at the same temperature for 30 min. The reaction mixture was quenched with water (5 mL) and diluted with $CHCl_3$ (5 mL), and extracted with $CHCl_3$ (3 x 15 mL). The organic layers were washed with water (3 x 15 mL), dried over Na_2SO_4 and the solvent was evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane:EtOAc=19:1) to afford the mixture of pyrazoles **2q** and phenol **3q**. For further purification, the mixture was added 1N NaOH aq. (15 mL), and extracted with Et_2O (3 x 15 mL). The organic layers were washed with 1N citric acid aq. (15 mL) and brine (15 mL). Drying over Na_2SO_4 followed by evaporation of the solvent afforded almost pure pyrazoles **2** (63 mg, 47%). The aqueous layer was treated with 1N citric acid aq. (20 mL) to acidify, and extracted with Et_2O (3 x 20 mL) and the layers were washed with sat. $NaHCO_3$ aq. (20 mL) and brine (20 mL). Drying over Na_2SO_4 followed by evaporation of the solvent gave almost pure phenols **3** (40 mg, 28%).

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References and notes

1. Reviews and reports for biological activities of pyrazoles: (a) Jamwal, A.; Javed, A.; Bhardwaj, V. *J. Pharm. BioSci.* **2013**, *3*, 114−123. (b) Chauhan, A.; Sharma, P. K.; Kaushik, N. *Int. J. ChemTech Res.* **2011**, *3*, 11−17. (c) Datar, P. A.; Jadhav, S. R. *Letters in Drug Design & Discovery* **2014**, *11*, 686−703. (d) Pal, D.; Saha, S.; Singh, S. *Int. J. Pharm. Sci.* **2012**, *4*, 98−104. (e) Wu, H.; Feng, J.-T.; Lin, K.-C.; Zhang, X. *Molecules* **2012**, *17*, 12187−12196.

2. Reviews on pyrazole synthesis: (a) Elkanzi, A. A. *Int. J. Res. Pharm. Biomed. Sci.* **2013**, *4*, 17−26. (b) Aggarwal, R.; Kumar, V.; Kumar, R.; Singh, S. P. *Beilstein J. Org. Chem.* **2011**, *7*, 179−197.

3. For recent synthesis of pyrazoles: (a) Lefebvre, V.; Cailly, T.; Fabis, F.; Rault, S. *J. Org. Chem.* **2010**, *75*, 2730−2732. (b) Wu, C.; Fang, Y.; Larock, R. C.; Shi, F. *Org. Lett.* **2010**, *12*, 2171−2173. (c) Kumar, M. R.; Park, A.; Park, N.; Lee, S. *Org. Lett.* **2011**, *13*, 3542−3545. (d) Ma, C.; Li, Y.; Wen, P.; Yan, R.; Ren, Z.; Huang, G. *Synlett* **2011**, 1321−1323. (e) Jackowski, O.; Lecourt, T.; Micouin, L. *Org. Lett.* **2011**, *13*, 5664−5667. (f) Babinski, D. J.; Aguilar, H. R.; Still, R.; Frantz, D. E. *J. Org. Chem.* **2011**, *76*, 5915−5923. (g) Li, P.; Zhao, J.; Wu, C.; Larock, R. C.; Shi, F. *Org. Lett.* **2011**, *13*, 3340−3343. (h) Li, P.; Wu, C.; Zhao, J.; Rogness, D. C.; Shi, F. *J. Org. Chem.* **2012**, *77*, 3127−3133. (i) Xiong, X.; Jiang, Y.; Ma, D. *Org. Lett.* **2012**, *14*, 2552−2555. (j) Panda, N.; Jena, A. K. *J. Org. Chem.* **2012**, *77*, 9401−9406. (k) Wu, L.-L.; Ge, Y.-C.; He, T.; Zhang, L.; Fu, X.-L.; Fu, H.-Y.; Chen, H.; Li, R.-X. *Synthesis* **2012**, *44*, 1577−1583. (l) Hu, J.; Chen, S.; Sun, Y.; Yang, J.; Rao, Y. *Org. Lett.* **2012**, *14*, 5030−5033. (m) Jiang, J.-A. Du, C.-Y.; Gu, C.-H.; Ji, Y.-F. *Synlett* **2012**, *23*, 2965−2968. (n) Zhang, T.; Bao, W. *J. Org. Chem.* **2013**, *78*, 1317-1322. (o) Xu, L.; Peng, Y.; Pan, Q.; Jiang, Y.; Ma, D. *J. Org. Chem.* **2013**, *78*, 3400−3401. (p) Stepaniuk, O. O.; Matviienko, V. O.; Kontratov, I. S.; Vitruk, I. V.; Tolmachev, A. O. *Synthesis* **2013**, *45*, 925−930. (q) Moustafa, A. H.; Malakar, C. C.; Aljaar, N.; Merisor, E.; Conrad, J.; Beifuss, U. *Synlett* **2013**, *24*, 1573−1577. (r) Reddy, C. R.; Vijaykumar, J.; Grée, R. *Synthesis* **2013**, *45*, 830−836. (s) Li, H.; Li, P.; Wang, L. *Org. Lett.* **2013**, *15*, 620−623. (t) Zhang, G.; Ni, H.; Chen, W.; Shao, J.; Liu, H.; Chen, B.; Yu, Y. *Org. Lett.* **2013**, *15*, 5967−5969. (u) Li, X.; He, L.; Chen, H.; Wu, W.; Jiang, H. *J. Org. Chem.* **2013**, *78*, 3636-3646. (v) Kumar, S. V.; Yadav, S. K.; Raghava, B.; Saraiah, B.; Ila, H.; Ragappa, K. S.; Hazra, A.

J. Org. Chem. **2013**, *78*, 4960−4973. (w) Sha, Q.; Wei, Y. *Synthesis* **2013**, *45*, 413−420. (x) Guo, C.; Sahoo, B.; Daniliuc, C. G.; Glorius, F. *J. Am. Chem. Soc.* **2014**, *136*, 17402−17405. (y) Wen, J.-J.; Tang, H.-T.; Xiong, K.; Ding, Z.-C.; Zhan, Z.-P. *Org. Lett.* **2014**, *16*, 5940−5943. (z) Merchant, R. R.; Allwood, D. M.; Blakemore, D. C.; Ley, S. V. *J. Org. Chem.* **2014**, *79*, 8800−8811. (aa) Specklin, S.; Decuypere, E.; Plougastel, L.; Aliani, S.; Taran, F. *J. Org. Chem.* **2014**, *79*, 7772−7777. (ab) Zhang, J.; Shao, Y.; Wang, H.; Luo, Q.; Chen, J.; Xu, D.; Wan, X. *Org. Lett.* **2014**, *16*, 3312−3315. (ac) Zhang, F.-G.; Wei, Y.; Yi, Y.-P.; Nie, J.; Ma, J.-A. *Org. Lett.* **2014**, *16*, 3122−3125. (ad) Harigae, R.; Moriyama, K.; Togo, H. *J. Org. Chem.* **2014**, *79*, 2049−2058. (ae) Venkateswarlu, V.; Aravinda Kumar, K. A.; Balgotra, S.; Lakshma Reddy, G.; Srinivas, M.; Vishwakarma, R. A.; Sawant, S. D. *Chem. Eur. J.* **2014**, *20*, 6641−6645.

4. (a) Aggarwal, R.; Kumar, R. *Synth. Commun.* **2009**, *39*, 2169−2177. (b) Desai, V. G.; Satardekar, P. C.; Polo, S.; Dhumaskar, K. *Synth. Commun.* **2012**, *42*, 836−842.

5. Zhang, X.; Kang, J.; Niu, P.; Wu, J.; Yu, W.; Chang, J. *J. Org. Chem.*, **2014**, *79*, 10170−10178.

6. Kashiwa, M.; Sonoda, M.; Tanimori, S. *Eur. J. Org. Chem.* **2014**, 4720–4723.

7. Selected examples for organic synthesis using Oxone, see: (a) Clark, J. H.; Cork, D. G. *J. Chem. Soc., Chem. Commun.* **1982**, 635−636. (b) Abu-Omar, M. M.; Espenson, J. H. *Organometallics* **1996**, *15*, 3543−3549. (c) Denmark, S. E.; Forbes, D. C.; Hays, D. S.; DePue, J. S.; Wilde, R. G. *J. Org. Chem.* **1995**, *60*, 1391−1407. (d) Woźniak, L. A.; Stec, W. J. *Tetrahedron Lett.* **1999**, *40*, 2637−2640. (e) Webb, K. S.; Levy, D. *Tetrahedron Lett.* **1995**, *36*, 5117−5118. (f) Webb, K. S. *Tetrahedron Lett.* **1994**, *35*, 3457−3460. (g) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 1287−1290. (h) Davis, F. A.; Lal, S. G.; Durst, H. D. *J. Org. Chem.* **1988**, *53*, 5004−5007. (i) Davis, F. A.; Chattopadhyay, S.; Towson, J. C.; Lal, S.; Reddy, T. *J. Org. Chem.* **1988**, *53*, 2087−2089. (j) Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O. *Synlett* **1999**, 777−779. (k) Travis, B. R.; Narayan, R. S.; Borhan, B. *J. Am. Chem. Soc.* **2002**, *124*, 3824−3825. (l) Travis, B.; Borhan, B. *Tetrahedron Lett.* **2001**, *42*, 7741−7745. (m) Webster, F. X.; Rivas-Enterrios, J.; Silverstein, R. M. *J. Org. Chem.* **1987**, *52*, 689−691.

8. Synthesis of hydrazones, please see supplementary content.

9. McClure, J, D. *J. Org. Chem.* **1963**, *28*, 69−71.

10. Itoh, Y.; Yamanaka, M.; Mikami, K. *Org. Lett.*, **2003**, *5*, 4803–4806.

11. Venkateswarlu, V.; Kumar, K. A. A.; Balgotra, S.; Reddy, G. L.; Srinivas, M.; Vishwakarma, R. A.; Sawant, S. D. *Chem. Eur. J.* **2014**, *20*, 6641−6645.

12. Zora, M.; Kivrak, A. *J. Org. Chem.* **2011**, *76*, 9379–9390.

13. Janjic, M.; Prebil, R.; Groselj, U.; Kralj, D.; Malavasic, C.; Golobic, A.; Stare, K.; Dahmann, G.; Stanovnik, B.; Svete, J. *Helv. Chim. Acta* **2011**, *94*, 1703–1717.

14. Ananthnag, G. S.; Adhikari, A.; Balakrishna, M. S. *Cat. Comm.* **2014**, *43*, 240–243.

15. Cho, C. S.; Patel, D. B. *Tetrahedron* **2006**, *62*, 6388–6391.

16. Bercovici, D. A.; Brewer, M. *J. Am. Chem. Soc.* **2012**, *134*, 9890–9893.

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