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I_2-Mediated Oxidative C−N Bond Formation for Metal-Free One-Pot Synthesis of Di-, Tri-, and Tetrasubstituted Pyrazoles from α,β-Unsaturated Aldehydes/Ketones and Hydrazines

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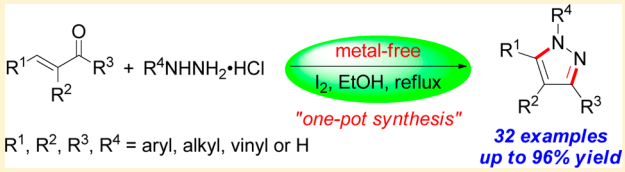
Supporting Information

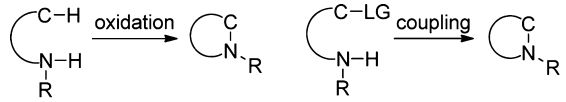
ABSTRACT: An I_2-mediated metal-free oxidative C−N bond formation methodology has been established for the regioselective pyrazole synthesis. This practical and eco-friendly one-pot protocol requires no isolation of the less stable intermediates hydrazones and provides a facile access to a variety of di-, tri-, and tetrasubstituted (aryl, alkyl, and/or vinyl) pyrazoles from readily available α,β-unsaturated aldehydes/ketones and hydrazine salts.



1. INTRODUCTION

The intramolecular C−N bond formation via oxidation of C−H and N−H bonds is a valuable tool for the construction of a nitrogen-containing heterocycle ring system (Scheme 1). It has advantages, such as (1) direct functionalization of C−H bonds with NHR groups without preactivation of the reaction centers; (2) facilitative preparation of structurally diverse substrates; and (3) no generation of the unwanted stoichiometric amounts of byproducts derived from the leaving groups (LGs) in substrates for the classic coupling reaction. Therefore, this synthetic strategy has drawn considerable attention from organic chemists and resulted in the discovery of numerous new synthetic methods for the preparation of indoles/carbazoles,[1] pyrazoles/indazoles,[2] benzoimidazole,[3] and other nitrogen-containing heterocycles.[4] Many recent developments in the literature, however, require the use of hypervalent iodine,[1a,b,2a,4] iodobenzene/oxidants,[2f,3] and DDQ,[2b] or via transition-metal-catalyzed aerobic oxidative cyclization.[1c,d,2c−e] In this paper, we developed a molecular iodine-mediated metal-free methodology for the oxidative intramolecular C−N bond formation to synthesize pyrazole derivatives.

Scheme 1. Oxidation and Coupling Strategies for the Intramolecular C−N Bond Formation



Pyrazole, a five-membered heterocycle with two adjacent nitrogen atoms, is an important structural motif, which widely exists in natural products[5] and synthetic biologically active compounds,[6] such as cyclooxygenase-2 (Cox-2),[7] protein kinase,[8] and HIV-1 reverse transcriptase[9] inhibitors, as well as antibacterial and antifungal compounds.[10] Moreover, substituted pyrazoles have also been applied in agrochemistry[11] and as ligands for cross-coupling reactions.[12] Consequently, a variety of methodologies have been developed for the preparation of pyrazole derivatives.[13] Among them, two general and classical pyrazole synthesis strategies are cyclocondensation of 1,3-dicarbonyl compounds with hydrazines and 1,3-dipolar cycloaddition of dipolarophiles with appropriate dipoles. For the cyclocondensation, when substituted hydrazines and 1,3-dicarbonyl substrates are used, the corresponding pyrazoles are formed as mixtures of two regioisomers. 1,3-Dipolar cycloaddition reaction could afford substituted pyrazoles with better regioselectivity, which, however, needs to use dangerous reagents (e.g., diazo compounds). Besides the above two strategies, another straightforward approach to construct the pyrazole ring is from hydrazones **4**, the advantages of which include that (1) no regioisomers will be form during the reaction,[2a−e] and (2) the required substrates could be readily prepared via condensation of a variety of easily accessible α,β-unsaturated carbonyl compounds **2** and hydrazines **3**. Oxidative cyclization of hydrazones **4** by hypervalent iodine(III)[2a] or DDQ[2b] could provide substituted pyrazoles **1**. Recently, this transformation was also achieved by transition-metal-catalyzed aerobic oxidation (eq 1).[2c−e] However, there are still limitations

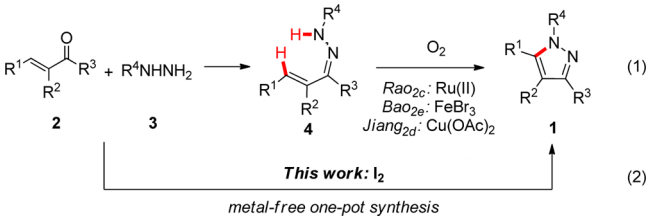


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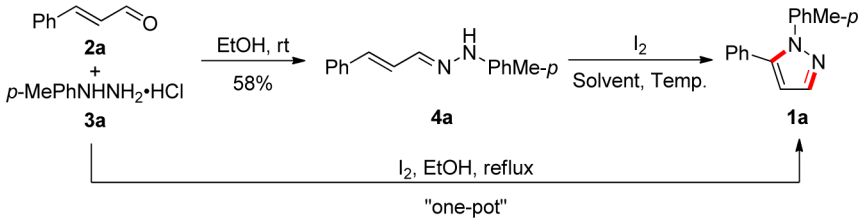
Table 1. Optimization of the Reaction Conditions for the Synthesis of Pyrazole 1a[a]



entry	substrates	equiv of I_2	solvent	temp	yield[b]
1[c]	**4a**	1.2	DMSO	100 °C	trace
2	**4a**	1.2	EtOH	reflux	67%
3[d]	**2a** + **3a**	1.5	EtOH	reflux	80%
4[e]	**2a** + **3a**	1.2	EtOH	reflux	62%
5[e]	**2a** + **3a**	1.5	EtOH	reflux	82%
6[e]	**2a** + **3a**	2.0	EtOH	reflux	78%

[a]Optimal reaction conditions (entry 5): **2a** (0.5 mmol), **3a** (0.75 mmol), I_2 (0.75 mmol), EtOH, reflux, 1 h. [b]Isolated yields after silica gel column chromatography. [c]The reaction was carried out in the presence of K_2CO_3 (3 equiv). [d]First, a mixture of **2a** and **3a** in EtOH was stirred at rt for 1 h, then treated with I_2, and heated to reflux for 1 h. [e]A reaction mixture of **2a**, **3a**, and I_2 in EtOH was directly heated to reflux for 1 h.

associated with these methods, such as limited substrate scope and unsatisfactory overall yields due to the low stability of the intermediates hydrazones **4**. Thus, more general and efficient procedures for pyrazole synthesis are still highly desirable. Previously, we have successfully developed a facile 1,3,4-oxadiazole synthesis protocol through I_2-mediated oxidative intramolecular C−O bond formation strategy.[14] As a part of our continuing research on the oxidative C−X (X = O, N, etc.) bond construction, herein, we report a practical and regioselective one-pot pyrazole synthesis methodology via the oxidative annulation of *α,β*-unsaturated aldehydes/ketones and hydrazines (eq 2).

2. RESULTS AND DISCUSSION

Initially, we investigated the transformation from isolated hydrozone **4a** to pyrazole **1a** under the oxidative cyclization conditions for 1,3,4-oxadiazole synthesis described in our previous work.[14a] However, only a trace amount of the pyrazole **1a** was formed (indicated by TLC, entry 1, Table 1). After the screening of a series of laboratory commonly used solvents, we found that this conversion proceeded well in ethanol at refluxing temperature in the absence of base (entry 2). As the condensation of cinnamaldehyde (**2a**) and *p*-tolylhydrazine hydrochloride (**3a**) was also carried out in ethanol, we continued to optimize the reaction conditions by using crude hydrazone **4a** formed in ethanol without isolation from the reaction system. After the first-step condensation was complete (1 h at room temperature), the reaction mixture was directly treated with molecular iodine (1.5 equiv) and then heated to reflux for another hour, which provided the desired pyrazole **1a** in 80% yield (entry 3). In further optimization of the reaction procedure, a mixture of **2a** and **3a** in the presence of molecular iodine (1.5 equiv) in ethanol was directly heated to reflux. To our delight, the reaction was also complete within 1 h and afforded the product in equally good yield (82%, entry 5). However, either increasing or decreasing the amount of iodine affected the yield of pyrazole **1a** (entry 4 or 6).

With the optimal one-pot reaction conditions (1.0 equiv of **2**, 1.5 equiv of **3**, and 1.5 equiv of iodine in ethanol at refluxing temperature) in hand, we sought to probe the scope and generality of this method for pyrazole synthesis (Table 2). A series of substituted arylhydrazine salts (**3a**−**f**) and cinnamaldehyde (**2a**) were subjected to the above reaction conditions, which afforded the corresponding 1,5-disubstituted pyrazoles (**1a**−**f**, entries 1−6) in 64−92% yield. The structure of 1-(4-cyanophenyl)-substituted pyrazole **1e** was further confirmed by X-ray crystallography (See Supporting Information). Cinnamaldehydes bearing both electron-donating (EDG) and electron-withdrawing (EWG) groups on the benzene ring (**2g**,**h**) were converted to the desired products (**1g**,**h**, entries 7 and 8) in 74% and 79% yields via the reaction with *p*-tolylhydrazine hydrochloride (**3a**). In addition, this methodology is compatible with both cinnamaldehyde with a substituent on the carbon−carbon double bond (**2i**) and crotonaldehyde (**2j**). The low yield of pyrazole **1j** might be due to the poor stability of the condensation intermediate **4j** (which decomposed quickly on the TLC plate).

In light of these encouraging results, we initiated further investigation of this one-pot protocol with *α,β*-unsaturated ketones[15] (Table 3). It is noteworthy to mention that the condensation products of these enones and hydrazines are relatively less stable (decomposing in silica gel column, usually purified through recrystallization), which will decrease the overall efficiency of pyrazole synthesis via step-by-step reaction. Under the optimal oxidative annulation conditions, a series of chalcones (**2k** and **2q**−**v**) and the corresponding arylhydrazine salts were directly converted into 1,3,5-trisubstituted pyrazoles (**1k**−**v**) in good yields, without separation of the corresponding intermediates hydrazones. The structure of 1-(4-chlorophenyl)-substituted pyrazole **1m** was further confirmed by X-ray crystallography (See Supporting Information). This methodology worked well with both EDG (**2k** and **2r**) and EWG (**2s**−**u**) substituted chalcones, as well as the one containing furyl group (**2v**). Moreover, 1,3,4,5-tetrasubstituted pyrazole **1w** could be prepared via the reaction of enone **2w** and *p*-tolylhydrazine hydrochloride (**3a**). While, the brominated chalcone **2x** led to 1,4,5-trisubstituted pyrazole **1k**, with the bromine reduced to hydrogen under the cyclization conditions.[16] Interestingly, the reaction of chalcones (**2k** and **2s**) and *tert*-butylhydrazine salt (**3y**) gave the de-*tert*-butyl products (**1y** and **1z**) in 69−75% yield (Scheme 2). The de-*tert*-butylation process might be promoted by hydroiodide (HI) formed during the reaction (Scheme 3).

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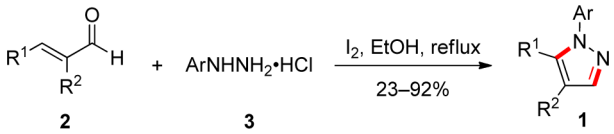
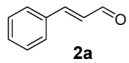
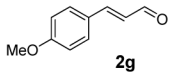
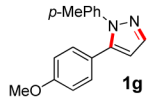
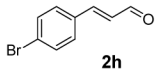
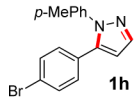
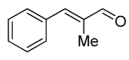
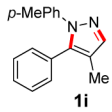
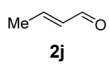
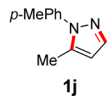
Table 2. Scope of α,β-Unsaturated Aldehydes 2 and Hydrazines 3[a,b]

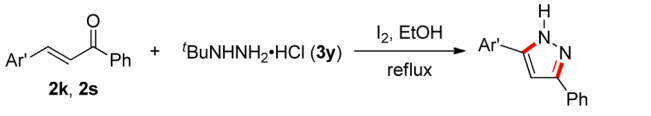


2 3 1

entry	aldehyde (**2**)	product (**1**)	yield[b]
1–6	 **2a**	 **1a**, R^5 = *p*-Me	82%
		1b, R^5 = H	64%
		1c, R^5 = *p*-Cl	82%
		1d, R^5 = *p*-CF_3	90%
		1e, R^5 = *p*-CN	92%
		1f, R^5 = 2,4-di-Cl	85%
7	 **2g**	 **1g**	74%
8	 **2h**	 **1h**	79%
9	 **2i**	 **1i**	77%
10	 **2j**	 **1j**	23%

[a]Optimal reaction conditions: **2** (0.5 mmol), **3** (0.75 mmol), I_2 (0.75 mmol), EtOH, reflux, 1 h; [b]Isolated yields after silica gel column chromatography.

Scheme 2. Synthesis of 3,5-Disubstituted Pyrazoles (1y and 1z) Using *tert*-Butylhydrazine Hydrochloride (3y)



2k, **2s**

1y, Ar' = *p*-MePh (75%)

1z, Ar' = *p*-ClPh (69%)

To further explore the substrate scope, we replaced the phenyl moiety in chalcone **2k** with aliphatic or vinyl substituents (R^3, Table 4). Under the optimal one-pot oxidative cyclization conditions, all of these α,β-unsaturated ketones (**2aa–af**) were also converted to the desired pyrazoles (**1aa–af**) in 67–92% yield via the reaction with *p*-tolylhydrazine hydrochloride (**3a**). It is worth to notice that substrates with *tert*-butyl (**2ad**) and vinyl (**2af**) substituents gave the desired pyrazoles in better yields than substrates **2aa–ac** and **1ae** did. This could be owing to the higher stability of the corresponding intermediates, hydrazones **4ad** and **4af**, which could be converted into pyrazoles **1ad** and **1af** more efficiently with less byproducts formed.

A plausible reaction mechanism for the formation of pyrazole **1** is proposed. As shown in Scheme 3, the oxidative iodination

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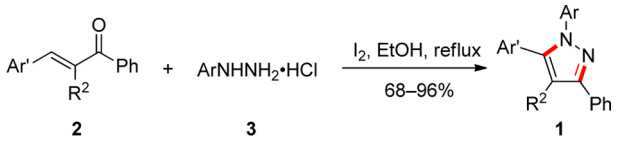
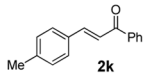
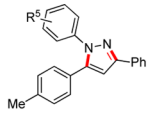
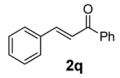
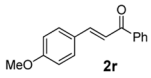
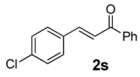
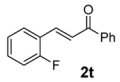
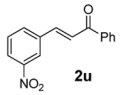
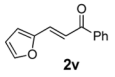
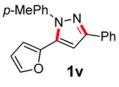
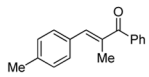
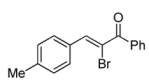
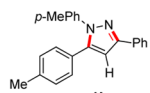
Table 3. Scope of α,β-Unsaturated Ketones 2 and Hydrazines 3[a,b]



2 3 1

entry	ketone (**2**)	product (**1**)	yield[b]
1–6	 **2k**	 **1k**, R^5 = *p*-Me,	91%
		1l, R^5 = H,	85%
		1m, R^5 = *p*-Cl	90%
		1n, R^5 = *p*-CF_3	96%
		1o, R^5 = *p*-CN	93%
		1p, R^5 = 2,4-di-Cl	95%
7	 **2q**	 **1q**	95%
8	 **2r**	 **1r**	90%
9	 **2s**	 **1s**	89%
10	 **2t**	 **1t**	93%
11	 **2u**	 **1u**	94%
12	 **2v**	 **1v**	74%
13	 **2w**	 **1w**	68%
14	 **2x**	 **1k**	71%

[a]Optimal reaction conditions: **2** (0.5 mmol), **3** (1 mmol), I_2 (1 mmol), EtOH, reflux, 1 h. [b]Isolated yields after silica gel column chromatography.

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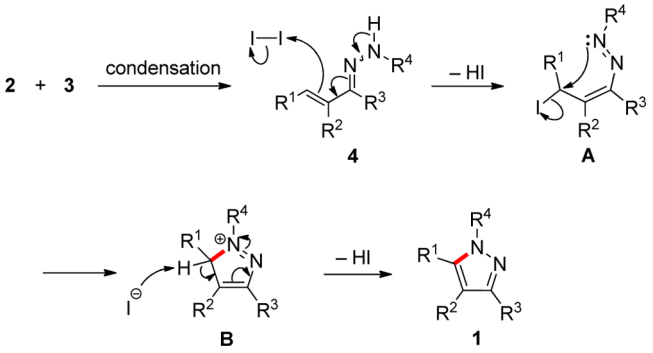
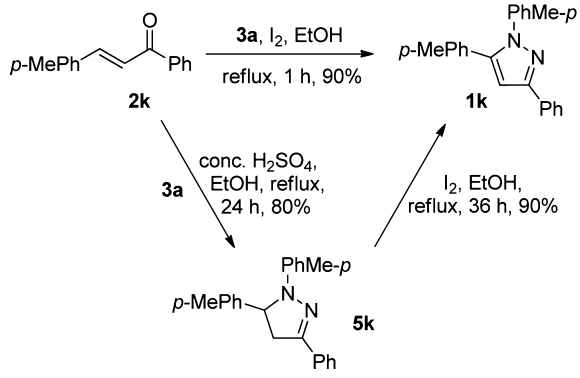
Scheme 3. Proposed Mechanism for the Formation of Pyrazole 1



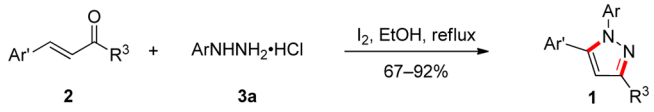
of hydrazone **4** generates an iodide intermediate **A**. Consequently, intemediate **B** is formed via an S_N2'-type cyclization of compound **A**, with a new C–N bond formed. Finally, the subsequent deprotonation affords the pyrazole framework **1**. Furthermore, another possible intermediate pyrazoline **5k** was synthesized via the cyclocondensation of chalcone **2k** and hydrazine **3a** in the presence of conc. sulfuric acid (Scheme 4).[17] It was then subjected to the standard I_2-mediated reaction conditions, which also afforded pyrazole **1k**

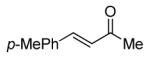
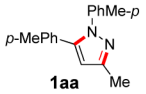
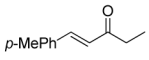
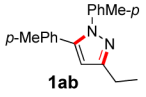
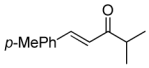
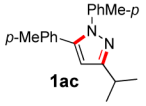
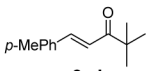
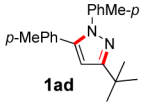
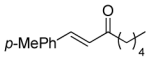
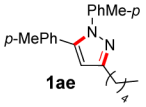
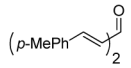
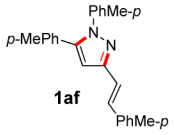
Scheme 4. Synthesis of Pyrazole 1k via Pyrazoline 5k



in 90% yield; however, the conversion rate is quite slow (over 36 h). This result suggested that the oxidative aromatization of pyrazoline **5k** pathway is unlikely to be involved in this one-pot oxidative annulation reaction.[18]

Table 4. Scope of R^3 on α,β-Unsaturated Ketones 2[a,b]



entry	ketone (**2**)	product (**1**)	yield[b]
1	 **2aa**	 **1aa**	80%
2	 **2ab**	 **1ab**	71%
3	 **2ac**	 **1ac**	71%
4	 **2ad**	 **1ad**	92%
5	 **2ae**	 **1ae**	67%
6	 **2af**	 **1af**	88%

[a]Optimal reaction conditions: **2** (0.5 mmol), **3** (1 mmol), I_2 (1 mmol), EtOH, reflux, 1 h. [b]Isolated yields after silica gel column chromatography.

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3. CONCLUSIONS

In summary, we have established an efficient and eco-friendly methodology for regioselective pyrazole synthesis through I_2-mediated oxidative intramolecular C−N bond formation. This practical one-pot protocol is metal-free and requires no isolation of the less stable intermediates hydrazones. Under the optimal reaction conditions, a variety of di-, tri-, and tetrasubstituted (aryl, alkyl, and/or vinyl) pyrazole derivatives were prepared from a broad substrate scope of readily available α,β-unsaturated carbonyl compounds (both aldehydes and ketones) and hydrazine salts.

4. EXPERIMENTAL SECTION

4.1. General Information. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz (100 MHz for ^{13}C NMR) spectrometer. Chemical shift values are given in ppm (parts per million) with tetramethylsilane (TMS) as an internal standard. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sext, sextet; m, multiplet; dd, doublet of doublets; dt, doublet of triplets. The coupling constants (J) are reported in hertz (Hz). Melting points were determined on a micromelting point apparatus without corrections. Flash column chromatography was performed over silica gel 200−300 mesh, and the eluent was a mixture of ethyl acetate (EA) and petroleum ether (PE). High-resolution mass spectra (HRMS-ESI) were obtained on a Q-TOF mass spectrometer. Ethanol was refluxed with magnesium and iodine, followed by distillation, before being used for the synthesis of pyrazoles **1**. All the α,β-unsaturated aldehydes (**2a** and **2g**−**j**) were purchased from commercial sources and were used without further purification. All the α,β-unsaturated ketones (**2k**, **2q**−**x**, and **2aa**−**af**) were prepared as follows.

4.2. Preparation of α,β-Unsaturated Ketones 2. *4.2.1. Preparation of Ketones **2k** and **2q**−**w** (General Procedure A).*[19] To a stirred solution of acetophenone (10 mmol) in methanol (5 mL) was added dropwise a solution of sodium hydroxide (13 mmol) in methanol (10 mL). Fifteen minutes later, the resulting mixture was further treated with substituted benzaldehydes (10 mmol) and stirred at room temperature (for the preparation of **2w**, the reaction was heated to reflux) until the conversion was complete (disappearance of acetophenone, monitored by TLC). The solvent was removed by evaporation, and the residue was treated with water (40 mL) and extracted with ethyl acetate (30 mL × 3). The combined organic layer was dried over anhydrous sodium sulfate, concentrated, and purified through silica gel column chromatography using a mixture of EA and PE as eluent to afford the corresponding α,β-unsaturated ketones in 38−95% yield.

*4.2.2. Preparation of Ketone **2x**.*[20] To a solution of chalcone **2k** (222 mg, 1.0 mmol) in dry dichloromethane (3 mL) at 0 °C was added bromine (192 mg, 1.2 mmol) dropwise. The obtained orange solution was stirred for 1 h at room temperature and then quenched with an ammonium chloride solution (1 M, 5 mL). It was extracted with dichloromethane (5 mL × 2), and the combined organic layer was dried over anhydrous sodium sulfate and concentrated. The resulting residue was redissolved in chloroform (3 mL) and then treated with triethylamine (172 mg, 1.7 mmol). The obtained mixture was stirred overnight at room temperature. After the conversion was complete (monitored by TLC), it was quenched with 5% HCl solution (5 mL) and extracted with dichloromethane (5 mL × 2). The combined organic layer was dried over anhydrous sodium sulfate, concentrated, and purified through silica gel column chromatography (EA/PE 0:100−3:97) to afford the desired ketone **2x** as a colorless oil (232 mg, 77%).

*4.2.3. Preparation of Ketone **2aa**.*[21] A solution of 4-methyl benzaldehyde (600 mg, 5 mmol) in acetone (10 mL) and water (1 mL) was heated to reflux and then treated with 10% NaOH (1 mL) slowly. After addition, the reaction mixture was stirred for 6 h at room temperature (TLC indicated the conversion was complete) and acidified with 1 M HCl to pH = 2. The product was extracted with ethyl acetate (20 mL × 3). The combined organic layer was dried over anhydrous sodium sulfate, concentrated, and purified through silica gel column chromatography (EA/PE 0:100−3:97) to afford the desired ketone **2aa** as a yellow oil (509 mg, 65%).

*4.2.4. Preparation of Ketones **2ab**−**ad** and **2af**.*[22] To a stirred solution of 4-methyl benzaldehyde (1.73 g, 14.4 mmol) and methyl *tert*-butyl ketone (1.20 g, 12.0 mmol) in ethanol (40 mL) at 0 °C was treated with 10% NaOH (1 mL) slowly over 30 min. After addition, the reaction was stirred at 0 °C for several hours and then allowed to warm up to room temperature (overnight, TLC indicated the conversion was complete). The solvent was removed by evaporation, and the residue was treated with water (40 mL) and extracted with ethyl acetate (30 mL × 3). The combined organic layer was dried over anhydrous sodium sulfate, concentrated, and purified through silica gel column chromatography (EA/PE 1:99) to afford the desired ketone **2ad** as a white solid (2.14 g, 88%). Similarly, ketones **2ab**, **2ac**, and **2af** were prepared using methyl ethyl ketone, methyl isopropyl ketone, and acetone, respectively.

*4.2.5. Preparation of Ketone **2ae**.*[23] A reaction mixture of the 4-methyl benzaldehyde (1.22 g, 10 mmol) and 2-heptanone (3.57g, 31.3 mmol) in 3 M NaOH (12 mL) was heated to reflux for 16 h (TLC indicated the conversion was complete). The cooled mixture was diluted with water (24 mL) and extracted with ethyl ether (20 mL × 3). The combined organic layer was dried over anhydrous sodium sulfate, concentrated, and purified through silica gel column chromatography (EA/PE 5:95) to afford the desired ketone **2ae** as a white solid (1.95 g, 90%).

4.3. Synthesis of Pyrazoles 1. *4.3.1. General Procedure.* To a stirred solution of α,β-unsaturated aldehydes/ketones **2** (0.50 mmol) and hydrazine HCl salts **3** (0.75 mmol when **2** was aldehyde; 1 mmol when **2** was ketone) in ethanol (10 mL) was added molecular iodine (0.75 mmol when **2** was aldehyde; 1 mmol when **2** was ketone), and then the reaction was heated to reflux for 1 h under a nitrogen atmosphere. The reaction mixture was concentrated, quenched with 5% $Na_2S_2O_3$, and then extracted with ethyl acetate (15 mL × 3). The combined organic layer was dried over anhydrous sodium sulfate, concentrated, and purified through silica gel column chromatography using a mixture of EA and PE as eluent to afford the corresponding pyrazoles **1**.

*5-Phenyl-1-(p-tolyl)-1H-pyrazole (**1a**).*[24] Yield: 96 mg, 82%; white solid, mp 74−76 °C; R_f = 0.40 (EA/PE 10:90); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 2.0 Hz, 1H), 7.30−7.28 (m, 3H), 7.25−7.22 (m, 2H, overlaps with the peak of chloroform), 7.19−7.11 (m, 4H), 6.49 (d, J = 2.0 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 140.0, 137.7, 137.2, 130.7, 129.4, 128.7, 128.4, 128.0, 125.0, 107.5, 21.0; HRMS (m/z) (M + H) calcd for $C_{16}H_{15}N_2$ 235.1230, found 235.1232.

*1,5-Diphenyl-1H-pyrazole (**1b**).*[25] Yield: 70 mg, 64%; yellow oil; R_f = 0.52 (EA/PE 10:90); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 1.6 Hz, 1H), 7.34−7.21 (m, 10H, overlaps with the peak of chloroform), 6.51 (d, J = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 140.3, 140.1, 130.6, 128.9, 128.7, 128.4, 128.2, 127.4, 125.2, 107.8; HRMS (m/z) (M + H) calcd for $C_{15}H_{13}N_2$ 221.1073, found 221.1076.

*1-(4-Chlorophenyl)-5-phenyl-1H-pyrazole (**1c**).*[26] Yield: 104 mg, 82%; yellow semisolid; R_f = 0.45 (EA/PE 5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 1.6 Hz, 1H), 7.33−7.28 (m, 5H), 7.25−7.21 (m, 4H, overlaps with the peak of chloroform), 6.50 (d, J = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 140.6, 138.6, 133.0, 130.3, 129.0, 128.7, 128.6, 128.4, 126.2, 108.2; HRMS (m/z) (M + H) calcd for $C_{15}H_{12}ClN_2$ 255.0683, found 255.0686.

*5-Phenyl-1-(4-(trifluoromethyl)phenyl)-1H-pyrazole (**1d**).*[25] Yield: 130 mg, 90%; white solid, mp 51−53 °C; R_f = 0.42 (EA/PE 5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 2.0 Hz, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.36−7.33 (m, 3H), 7.25−7.23 (m, 2H, overlaps with the peak of chloroform), 6.53 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 142.8, 141.1, 130.2, 129.0 (q, J_{C-F} = 32.6 Hz), 128.8, 128.7, 128.6, 126.0 (q, J_{C-F} = 3.8 Hz), 124.8, 123.8 (d, J_{C-F} = 270.6 Hz), 108.8; HRMS (m/z) (M + H) calcd for $C_{16}H_{12}F_3N_2$ 289.0947, found 289.0950.

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*4-(5-Phenyl-1H-pyrazol-1-yl)benzonitrile (**1e**).* Yield: 113 mg, 92%; white solid, mp 82−83 °C; R_f = 0.29 (EA/PE 10:90); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77(d, J = 1.6 Hz, 1H), 7.61 (dt, J = 8.8, 2.0 Hz, 2H), 7.43 (dt, J = 8.8, 2.0 Hz, 2H), 7.39−7.34 (m, 3H), 7.25−7.22 (m, 2H), 6.54 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 143.3, 141.5, 132.9, 130.0, 128.9, 128.81, 128.78, 124.9, 118.2, 110.5, 109.3; HRMS (m/z) (M + H) calcd for $C_{16}H_{12}N_3$ 246.1026, found 246.1030.

*1-(2,4-Dichlorophenyl)-5-phenyl-1H-pyrazole (**1f**).*[26] Yield: 123 mg, 85%; white solid, mp 60−62 °C; R_f = 0.48 (EA/PE 10:90); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 1.6 Hz, 1H), 7.46 (d, J = 2.0 Hz, 1H), 7.35−7.26 (m, 5H), 7.20−7.17 (m, 2H), 6.55 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 141.0, 136.8, 135.3, 133.1, 130.6, 130.2, 129.8, 128.5, 128.4, 127.9, 127.8, 106.6; HRMS (m/z) (M + H) calcd for $C_{15}H_{11}Cl_2N_2$ 289.0294, found 289.0297.

*5-(4-Methoxyphenyl)-1-(p-tolyl)-1H-pyrazole (**1g**).* Yield: 98 mg, 74%; yellow syrup; R_f = 0.46 (EA/PE 15:85); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 2.0 Hz, 1H), 7.19−7.12 (m, 6H), 6.84−6.80 (m, 2H), 6.43 (d, J = 2.0 Hz, 1H), 3.79 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 142.7, 140.0, 137.8, 137.1, 130.0, 129.4, 125.0, 123.1, 113.8, 107.0, 55.2, 21.1; HRMS (m/z) (M + H) calcd for $C_{17}H_{17}N_2O$ 265.1335, found 265.1343.

*5-(4-Bromophenyl)-1-(p-tolyl)-1H-pyrazole (**1h**).* Yield: 123 mg, 79%; white solid, mp 115−117 °C; R_f = 0.36 (EA/PE 10:90); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 2.0 Hz, 1H), 7.43−7.41 (m, 2H), 7.15 (s, 4H), 7.11−7.07 (m, 2H), 6.49 (d, J = 2.0 Hz, 1H), 2.37 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 140.1, 137.6, 137.4, 131.6, 130.2, 129.59, 129.55, 125.0, 122.3, 107.6, 21.1; HRMS (m/z) (M + H) calcd for $C_{16}H_{14}BrN_2$ 313.0335, found 313.0339.

*4-Methyl-5-phenyl-1-(p-tolyl)-1H-pyrazole (**1i**).* Yield: 95 mg, 77%; yellow syrup; R_f = 0.40 (EA/PE 10:90); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.35−7.29 (m, 3H), 7.18−7.15 (m, 2H), 7.11−7.04 (m, 4H), 2.30 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 139.7, 137.9, 136.5, 130.7, 129.8, 129.2, 128.4, 127.9, 124.5, 116.1, 21.0, 9.2; HRMS (m/z) (M + H) calcd for $C_{17}H_{17}N_2$ 249.1386, found 249.1395.

*5-Methyl-1-(p-tolyl)-1H-pyrazole (**1j**).*[27] Yield: 40 mg, 23% (1 mmol scale); white semisolid; R_f = 0.58 (EA/PE 10:90); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 2.4 Hz, 1H), 7.51 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 6.21 (d, J = 2.4 Hz, 1H), 2.37(s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 138.0, 135.6, 129.8, 127.3, 118.8, 107.1, 20.8, 13.7; HRMS (m/z) (M +H) calcd for $C_{11}H_{13}N_2$ 173.1073, found 173.1077.

*3-Phenyl-1,5-di-p-tolyl-1H-pyrazole (**1k**).* Yield: 147 mg, 91%; white solid, mp 91−93 °C; R_f = 0.48 (EA/PE 7:93); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92−7.90 (m, 2H), 7.43−7.39 (m, 2H), 7.34−7.30 (m, 1H), 7.26−7.24 (m, 2H, overlaps with the peak of chloroform), 7.18−7.10 (m, 6H), 6.77 (s, 1H), 2.35 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 144.3, 138.1, 137.8, 137.2, 133.2, 129.4, 129.1, 128.56, 128.55, 127.8, 127.7, 125.8, 125.1, 104.7, 21.3, 21.1; HRMS (m/z) (M + H) calcd for $C_{23}H_{21}N_2$ 325.1699, found 325.1706.

*1,3-Diphenyl-5-(p-tolyl)-1H-pyrazole (**1l**).*[2e] Yield: 132 mg, 85%; white solid, mp 110−112 °C; R_f = 0.55 (EA/PE 8:92); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93−7.91 (m, 2H), 7.44−7.27 (m, 8H), 7.17−7.10 (m, 4H), 6.79 (s, 1H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 144.4, 140.2, 138.2, 133.1, 129.2, 128.9, 128.59, 128.58, 127.9, 127.7, 127.3, 125.8, 125.3, 104.9, 21.3; HRMS (m/z) (M + H) calcd for $C_{22}H_{19}N_2$ 311.1543, found 311.1550.

*1-(4-Chlorophenyl)-3-phenyl-5-(p-tolyl)-1H-pyrazole (**1m**).* Yield: 155 mg, 90%; white solid, mp 129−130 °C; R_f = 0.55 (EA/PE 7:93); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91−7.89 (m, 2H), 7.44−7.41 (m, 2H), 7.36−7.31 (m, 5H), 7.15 (t, J = 9.2 Hz, 4H), 6.78 (s, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 144.5, 138.7, 138.5, 132.9, 129.3, 129.0, 128.63, 128.60, 128.1, 127.4, 126.3, 125.8, 105.3, 21.3; HRMS (m/z) (M + H) calcd for $C_{22}H_{18}ClN_2$ 345.1153, found 345.1160.

*3-Phenyl-5-(p-tolyl)-1-(4-(trifluoromethyl)phenyl)-1H-pyrazole (**1n**).* Yield: 181 mg, 96%; white solid, mp 121−122 °C; R_f = 0.60 (EA/PE 5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92−7.90 (m, 2H), 7.59 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 7.45−7.41 (m, 2H), 7.37−7.33 (m, 1H), 7.17 (s, 4H), 6.80 (s, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 144.7, 142.9, 138.8, 132.7, 129.4, 129.0, 128.68, 128.65, 128.2, 127.3, 126.0 (q, J_{C-F} = 4.0 Hz), 125.8, 124.8, 123.9 (d, J_{C-F} = 270.8 Hz), 106.0, 21.3; HRMS (m/z) (M + H) calcd for $C_{23}H_{18}F_3N_2$ 379.1417, found 379.1425.

*4-(3-Phenyl-5-(p-tolyl)-1H-pyrazol-1-yl)benzonitrile (**1o**).* Yield: 150 mg, 93%; white solid, mp 150−152 °C; R_f = 0.56 (EA/PE 15:85); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91−7.89 (m, 2H), 7.62−7.59 (m, 2H), 7.51−7.42 (m, 4H), 7.38−7.34 (m, 1H), 7.20−7.15 (m, 4H), 6.80 (s, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 144.8, 143.5, 139.1, 132.8, 132.4, 129.5, 128.7, 128.65, 128.4, 127.1, 125.9, 124.8, 118.4, 110.2, 106.6, 21.3; HRMS (m/z) (M + H) calcd for $C_{23}H_{18}N_3$ 336.1495, found 336.1503.

*1-(2,4-Dichlorophenyl)-3-phenyl-5-(p-tolyl)-1H-pyrazole (**1p**).* Yield: 180 mg, 95%; white solid, mp 136−138 °C; R_f = 0.55 (EA/PE 8:92); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90−7.88 (m, 2H), 7.45−7.40 (m, 4H), 7.36−7.31 (m, 2H), 7.13−7.08 (m, 4H), 6.82 (s, 1H), 2.32(s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 146.4, 138.5, 137.0, 135.3, 133.3, 132.8, 130.8, 130.2, 129.3, 128.6, 128.1, 127.83, 127.75, 126.9, 125.9, 103.6, 21.2; HRMS (m/z) (M + H) calcd for $C_{22}H_{17}Cl_2N_2$ 379.0763, found 379.0767.

*3,5-Diphenyl-1-(p-tolyl)-1H-pyrazole (**1q**).*[28] Yield: 147 mg, 95%; white solid, mp 106−108 °C; R_f = 0.50 (EA/PE 7:93); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93−7.91 (m, 2H), 7.42 (t, J = 7.6 Hz, 2H), 7.34−7.23 (m, 8H, overlaps with the peak of chloroform), 7.14 (d, J = 8.0 Hz, 2H), 6.81 (s, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 144.2, 137.7, 137.3, 133.1, 130.7, 129.5, 128.7, 128.6, 128.4, 128.2, 127.9, 125.8, 125.1, 104.9, 21.1; HRMS (m/z) (M + H) calcd for $C_{22}H_{19}N_2$ 311.1543, found 311.1545.

*5-(4-Methoxyphenyl)-3-phenyl-1-(p-tolyl)-1H-pyrazole (**1r**).* Yield: 153 mg, 90%; white solid, mp 41−43 °C; R_f = 0.42 (EA/PE 10:90); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92−7.90 (m, 2H), 7.43−7.39 (m, 2H), 7.32(t, J = 7.2 Hz, 1H), 7.26−7.24 (m, 2H, overlaps with the peak of chloroform), 7.21−7.19 (m, 2H), 7.15−7.13 (m, 2H), 6.86−6.83 (m, 2H), 6.75 (s, 1H), 3.81 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 151.6, 144.1, 137.8, 137.2, 133.2, 130.0, 129.4, 128.6, 127.8, 125.7, 125.1, 123.1, 113.8, 104.4, 55.2, 21.1; HRMS (m/z) (M + H) calcd for $C_{23}H_{21}N_2O$ 341.1648, found 341.1652.

*5-(4-Chlorophenyl)-3-phenyl-1-(p-tolyl)-1H-pyrazole (**1s**).* Yield: 153 mg, 89%; white solid, mp 126−127 °C; R_f = 0.48 (EA/PE 7:93); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91−7.89 (m, 2H), 7.42 (t, J = 7.6 Hz, 2H), 7.35−7.27 (m, 3H), 7.24−7.15 (m, 6H), 6.79 (s, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 143.0, 137.6, 137.5, 134.2, 132.9, 129.9, 129.6, 129.1, 128.7, 128.6, 128.0, 125.7, 125.2, 105.0, 21.1; HRMS (m/z) (M + H) calcd for $C_{22}H_{18}ClN_2$ 345.1153, found 345.1158.

*5-(2-Fluorophenyl)-3-phenyl-1-(p-tolyl)-1H-pyrazole (**1t**).* Yield: 153 mg, 93%; white semisolid; R_f = 0.42 (EA/PE 7:93); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93−7.91 (m, 2H), 7.42 (t, J = 8.0 Hz, 2H), 7.35−7.30 (m, 2H), 7.25−7.21 (m, 3H, overlaps with the peak of chloroform), 7.13−7.04 (m, 4H), 6.86 (s, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4 (d, J_{C-F} = 249 Hz), 151.8, 137.9, 137.8, 137.2, 133.0, 131.3 (d, J_{C-F} = 2.4 Hz), 130.4 (d, J_{C-F} = 8.1 Hz), 129.4, 128.6, 127.9, 125.8, 124.2, 124.1 (d, J_{C-F} = 3.7 Hz), 118.9 (d, J_{C-F} = 14.6 Hz), 116.1 (d, J_{C-F} = 21.6 Hz), 106.5 (d, J_{C-F} = 2.0 Hz), 21.0; HRMS (m/z) (M + H) calcd for $C_{22}H_{18}FN_2$ 329.1448, found 329.1452.

*5-(3-Nitrophenyl)-3-phenyl-1-(p-tolyl)-1H-pyrazole (**1u**).* Yield: 167 mg, 94%; white solid, mp 141−143 °C; R_f = 0.38 (EA/PE 10:90); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (t, J = 2.0 Hz, 1H), 8.17−8.14 (m, 1H), 7.93−7.90 (m, 2H), 7.52−7.50 (m, 1H), 7.47−7.41 (m, 3H), 7.37−7.33 (m, 1H), 7.24−7.16 (m, 4H), 6.92 (s, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 148.2, 141.7, 138.2, 137.0, 134.3, 132.6, 132.2, 129.8, 129.4, 128.7, 128.2, 125.8, 125.3, 123.3, 122.8, 105.5, 21.1; HRMS (m/z) (M + H) calcd for $C_{22}H_{18}N_3O_2$ 356.1394, found 356.1402.

*5-(Furan-2-yl)-3-phenyl-1-(p-tolyl)-1H-pyrazole (**1v**).* Yield: 111 mg, 74%; white semisolid; R_f = 0.44 (EA/PE 7:93); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 7.6 Hz, 2H), 7.43−7.24 (m, 8H, overlaps with the peak of chloroform), 6.97 (s, 1H), 6.33 (q, J = 2.0 Hz, 1H),

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5.96 (d, J = 3.2 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 144.6, 142.4, 138.6, 137.8, 135.8, 132.9, 129.7, 128.6, 128.0, 125.9, 125.8, 111.2, 108.7, 103.0, 21.2; HRMS (m/z) (M + Na) calcd for $C_{20}H_{16}N_2ONa$ 323.1155, found 323.1161.

*4-Methyl-3-phenyl-1,5-di-p-tolyl-1H-pyrazole (**1w**).* Yield: 115 mg, 68%; white solid, mp 115−116 °C; R_f = 0.45 (EA/PE 7:93); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82−7.79 (m, 2H), 7.44 (t, J = 7.6 Hz, 2H), 7.36−7.32 (m, 1H), 7.19−7.06 (m, 8H), 2.37 (s, 3H), 2.31 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.9, 141.4, 137.9, 136.4, 134.0, 129.9, 129.2, 129.1, 128.3, 127.9, 127.8, 127.4, 124.6, 113.7, 21.3, 21.0, 10.2; HRMS (m/z) (M + H) calcd for $C_{24}H_{23}N_2$ 339.1856, found 339.1858.

*3-Phenyl-5-(p-tolyl)-1H-pyrazole (**1y**).*[13e] Yield: 88 mg, 75%; white solid, mp 174−176 °C; R_f = 0.55 (EA/PE 30:70); ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.26 (s, 1H), 7.80 (d, J = 7.6 Hz, 2H), 7.69 (d, J = 8.0 Hz, 2H), 7.40 (t, J = 7.6 Hz, 2H), 7.29 (t, J = 7.6 Hz, 1H), 7.22 (d, J = 7.6 Hz, 2H), 7.09 (s, 1H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 137.5, 129.8, 129.2, 128.1, 125.50, 125.45, 99.7, 21.2; HRMS (m/z) (M + H) calcd for $C_{16}H_{15}N_2$ 235.1230, found 235.1233.

*5-(4-Chlorophenyl)-3-phenyl-1H-pyrazole (**1z**).* Yield: 88 mg, 69%; white solid, mp 212−214 °C; R_f = 0.65 (EA/PE 30:70); ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.42 (s, 1H), 7.84−7.78 (m, 4H), 7.48−7.40 (m, 4H), 7.32−7.31 (m, 1H), 7.19 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 132.6, 129.3, 129.2, 128.4, 127.2, 125.5, 100.3; HRMS (m/z) (M + H) calcd for $C_{15}H_{12}ClN_2$ 255.0684, found 255.0691.

*3-Methyl-1,5-di-p-tolyl-1H-pyrazole (**1aa**).* Yield: 105 mg, 80%; white solid, mp 46−48 °C; R_f = 0.40 (EA/PE 10:90); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16−7.14 (m, 2H), 7.12−7.07 (m, 6H), 6.26 (s, 1H), 2.37 (s, 3H), 2.335 (s, 3H), 2.328 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 143.7, 137.9, 137.6, 136.9, 129.4, 129.0, 128.4, 127.8, 125.0, 107.2, 21.2, 21.0, 13.5; HRMS (m/z) (M + H) calcd for $C_{18}H_{19}N_2$ 263.1543, found 263.1547.

*3-Ethyl-1,5-di-p-tolyl-1H-pyrazole (**1ab**).* Yield: 98 mg, 71%; white solid, mp 56−58 °C; R_f = 0.50 (EA/PE 10:90); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17−7.06 (m, 8H), 6.29 (s, 1H), 2.75 (q, J = 7.6 Hz, 2H), 2.32 (d, J = 2.4 Hz, 6H), 1.33 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 143.5, 137.81, 137.76, 136.8, 129.4, 129.0, 128.5, 128.0, 125.0, 105.7, 21.5, 21.2, 21.0, 13.9; HRMS (m/z) (M + H) calcd for $C_{19}H_{21}N_2$ 277.1699, found 277.1702.

*3-Isopropyl-1,5-di-p-tolyl-1H-pyrazole (**1ac**).* Yield: 103 mg, 71%; white solid, mp 76−78 °C; R_f = 0.46 (EA/PE 5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18−7.15 (m, 2H), 7.12−7.06 (m, 6H), 6.29 (s, 1H), 3.08 (heptet, J = 6.8 Hz, 1H), 2.33 (s, 3H), 2.32 (s, 3H), 1.34 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 143.2, 137.9, 137.7, 136.7, 129.3, 129.0, 128.5, 128.1, 125.0, 104.2, 27.9, 22.9, 21.2, 21.0; HRMS (m/z) (M + H) calcd for $C_{20}H_{23}N_2$ 291.1856, found 291.1859.

*3-(tert-Butyl)-1,5-di-p-tolyl-1H-pyrazole (**1ad**).* Yield: 140 mg, 92%; white solid, mp 106−108 °C; R_f = 0.67 (EA/PE 5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19−7.16 (m, 2H), 7.12−7.06 (m, 6H), 6.31 (s, 1H), 2.32 (s, 6H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 142.9, 138.1, 137.6, 136.6, 129.3, 129.0, 128.5, 128.3, 125.1, 104.1, 32.2, 30.6, 21.2, 21.0; HRMS (m/z) (M + H) calcd for $C_{21}H_{25}N_2$ 305.2012, found 305.2021.

*3-Pentyl-1,5-di-p-tolyl-1H-pyrazole (**1ae**).* Yield: 107 mg, 67%; yellow syrup; R_f = 0.50 (EA/PE 5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17−7.15 (m, 2H), 7.12−7.06 (m, 6H), 6.27 (s, 1H), 2.70 (t, J = 8.0 Hz, 2H), 2.33 (d, J = 2.4 Hz, 6H), 1.73 (quint, J = 7.6 Hz, 2H), 1.43−1.35 (m, 4H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 143.4, 137.9, 137.7, 136.7, 129.3, 129.0, 128.4, 128.1, 125.0, 106.1, 31.8, 29.4, 28.3, 22.5, 21.2, 21.0, 14.1; HRMS (m/z) (M + H) calcd for $C_{22}H_{27}N_2$ 319.2169, found 319.2173.

*(E)-3-(4-Methylstyryl)-1,5-di-p-tolyl-1H-pyrazole (**1af**).* Yield: 160 mg, 88%; white solid, mp 174−176 °C; R_f = 0.50 (EA/PE 10:90); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.4 Hz, 2H), 7.21−7.09 (m, 12H), 6.67 (s, 1H), 2.35 (s, 6H), 2.34(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.0, 144.1, 138.1, 137.7, 137.5, 137.1, 134.4, 130.3, 129.43, 129.36, 129.1, 128.5, 127.6, 126.4, 125.0, 119.6, 104.4, 21.3, 21.1; HRMS (m/z) (M + H) calcd for $C_{26}H_{25}N_2$ 365.2012, found 365.2019.

4.4. Synthesis of Pyrazoles 1k via Pyrazoline 5k. A solution of chalcone **2k** (222 mg, 1 mmol) and hydrazine HCl salts **3a** (476 mg, 3 mmol) in methanol (10 mL) was treated with conc. sulfuric acid (1 mL) slowly and then heated to reflux for 24 h.[17] After it cooled to room temperature, the reaction mixture was neutralized with saturated aq. sodium bicarbonate and extracted with ethyl acetate (15 mL × 3). The combined organic layer was dried over anhydrous sodium sulfate, concentrated, and purified through silica gel column chromatography using a mixture of EA and PE (5:95) as eluent to afford pyrazoline **5k** as a light-yellow solid (261 mg, 80%). mp 117−118 °C; R_f = 0.67 (EA/PE 5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 7.6 Hz, 2H), 7.34 (t, J = 7.6 Hz, 2H), 7.29−7.26 (m, 1H, overlapped with the peak of chloroform), 7.18 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 6.97 (t, J = 9.2 Hz, 4H), 5.16 (dd, J = 12.4, 7.6 Hz, 1H), 3.74 (dd, J = 17.2, 12.4 Hz, 1H), 3.06 (dd, J = 17.2, 7.6 Hz, 1H), 2.29 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.3, 142.9, 139.8, 137.2, 133.0, 129.8, 129.5, 128.6, 128.4, 128.3, 125.9, 125.7, 113.6, 64.7, 43.7, 21.2, 20.6. MS (m/z) (M +H) calcd for $C_{23}H_{23}N_2$ 327, found 327.

To a stirred solution of pyrazoline **5k** (163 mg, 0.5 mmol) in ethanol (10 mL) was added molecular iodine (1 mmol), and then the reaction was heated to reflux under a nitrogen atmosphere until TLC indicated that the conversion was complete (36 h). The reaction mixture was concentrated, quenched with sat. 5% $Na_2S_2O_3$, and then extracted with ethyl acetate (15 mL × 3). The combined organic layer was dried over anhydrous sodium sulfate, concentrated, and purified through silica gel column chromatography using a mixture of EA and PE as eluent to afford pyrazole **1k** as a white solid (146 mg, 90%).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of pyrazoles **1**, and crystallographic data of pyrazoles **1e** and **1m** in CIF (CCDC 1016873−1016874). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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