Synthesis of 1-Aryl-1*H*-indazoles via a Ligand-Free Copper-Catalyzed Intramolecular Amination Reaction

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A general synthesis of 1-aryl-1-*H*-indazoles from *o*-halogenated aryl aldehydes or ketones and aryl hydrazines was described. This protocol included an intermolecular condensation and a ligand-free copper-catalyzed intramolecular Ullmann-type coupling reaction. This method was applied to a wide range of substrates to produce the indazole products in good yields.

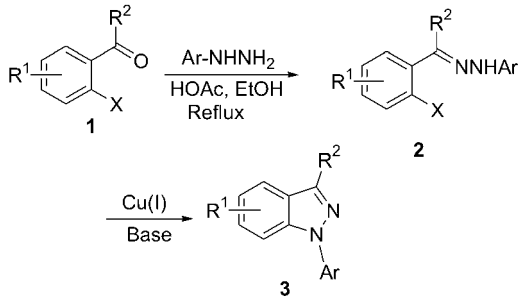
Keywords copper, amination, ligand free

Introduction

The 1-aryl-1*H*-indazole fragment is well recognized in many biologically active and pharmaceutically important compounds which exhibit potent antitumor,[1] antidepressant,[2] anti-HIV,[3] anti-inflammatory[4] or contraceptive activity.[5] Great efforts have been devoted to the development of method for synthesizing this kind of compounds.[6] Classical methods included intramolecular reduction of *o*-nitrobenzylamin,[7] Pd-catalyzed cyclization of arylhydrazones or arylhadrzines with *o*-haloaryl aldehyde,[8] and condensation-nucleophilic substitution cascade process of 2-haloarylcarbonylic compounds with hydrazines *etc*.[9]

In the past years, Ullmann-type C-N coupling reactions have been extensively studied and applied for the preparation of highly diversified heterocycles.[10] Copper-catalyzed *N*-arylation has been successfully adapted to the synthesis of 1*H*-indazole derivatives.[11] For instance, Olmo *et al*.[11b] have reported a CuO-promoted synthesis of 1-aryl or 1-alkyl-1*H*-indazoles through an amination-dehydration cascade process of 2-chloro or 2-fluoroarylcarbonylic compounds with hydrazines at 110 ℃. Liu and colleagues[11c] also reported that 1-aryl-1*H*-indazoles could be efficiently synthesized from a CuI (5 mol%) catalyzed intramolecular amination reaction of arylhydrazones with the assistance of 10 mol% of 1,10-phenanthroline. Furthermore, copper-catalyzed construction of heterocycles under ligand-free conditions has recently attracted much attention due to its environmental benignity and atom economy.[12] Herein we reported a simple and efficient two-step synthesis of 1-aryl-1*H* indazoles from *o*-halo arylaldehydes or ketones with aryl hydrazines under the catalysis of 0.1 mol% of CuI without a supporting ligand (Scheme 1).

Scheme 1 Two-step synthesis of 1-aryl-1*H* indazoles



Results and discussion

The investigation was initiated by the preparation of 1-phenyl-1*H*-indazole (**5**) using *o*-bromobenzaldehyde and phenyl hydrazine as starting materials (Table 1). Firstly, the condensation of *o*-bromobenzaldehyde and phenyl hydrazine in the presence of HOAc almost quantitatively yielded arylhydrazone intermediate **4**. After removing the solvent, the intermediate was successfully transformed to 1-phenyl-1*H*-indazole (**5**) in about 68% yield, under the catalysis of 1.0 mol% CuI at 80 ℃ (Table 1, Etnry 2). The results also indicated that CuI was essential for the cyclizaton, and no desired product

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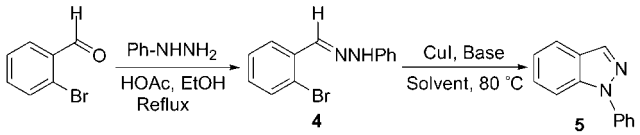
Received October 11, 2010; revised January 14, 2011; accepted February 21, 2011.
Project supported by the National Natural Science Foundation of China (No. 21002102), and State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (No. 10184).

Table 1 Optimization of reaction conditions of *o*-bromobenzaldehyde with benzene hydrazine[a]



Entry	CuI/mol%	Solvent	Base	Yield[b]/%
1	—	DMF	Cs_2CO_3	n.d.[c]
2	1.0	DMF	Cs_2CO_3	68
3	1.0	DMF	K_2CO_3	45
4	1.0	DMF	NaOH	24
5	1.0	DMF	K_3PO_4	63
6	1.0	DMSO	K_3PO_4	67
7	1.0	Dioxane	K_3PO_4	n.d.[c]
8	1.0	Toluene	K_3PO_4	n.d.[c]
9	0.1	DMSO	K_3PO_4	84[d]

[a] Reaction conditions: *o*-bromobenzaldehyde (1.0 mmol), benzene hydrazine (1.0 mmol), CuI, base (2.0 mmol), solvent (1.0 mL), 80 ℃. [b] Isolated yields. [c] No desired products. [d] 100 ℃.

was detected in the absence of copper catalysts (Table 1, Entry 1). Other copper salts such as CuBr and CuCl gave significantly worse results. The reaction condition screen suggested that K_3PO_4 and DMSO were the optimal base and solvent respectively (Table 1, Entries 3—6). More significantly, further investigation revealed that 0.1 mol% of CuI was sufficient to catalyze the cyclization with an excellent yield at a slightly elevated temperature (Table 1, Entry 9). Thus, the combination of 0.1 mol% of CuI, K_3PO_4 in DMSO was chosen as the optimal conditions for further exploration at 100 ℃.

The scope of this new protocol was further explored by using a variety of combinations of *o*-halophenyl aldehydes or ketones with hydrazines under the optimized conditions. As showed in Table 2, the electronic properties of *o*-halophenyl aldehydes or ketones seemed to have little influence on the reacting efficiency. Both the electron-rich and electron-deficient *o*-bromobenzaldedyes could deliver the corresponding products with excellent yields (Table 2, Entries 1—4), except that 1-bromo-2-naph-aldehyde gave a much lower yield (Table 2, Entry 5), which might be due to a steric hindrance of 8-H in the 1-bromo-2-naph-aldehyde substrate. The protocol also worked well for the other aryl hydrazines with *o*-bromophenyl aldehydes or ketones (Table 2, Entries 6—9). It was noteworthy that 3-substituted indazoles were also produced with excellent yields when using 2-bromophenyl ketones as the starting materials (Table 2, Entries 10 and 11).

It is well known that aryl chlorides are highly challenging substrates for most of Ullmann-type coupling reactions.[10] We also wished to investigate if our new protocol worked well for *o*-chlorobenzaldehyde substrates. Only a trace amount of the desired product was detected when the reaction was carried out at 100 ℃ with 1.0 mol% CuI as catalyst. However, a moderate yield was obtained when elevating the reacting temperature to 120 ℃ with an increasing catalyst loading (Table 2, Entry 12). The reacting efficiency of 1-(2-chlorophenyl)ethanone was also evaluated, and no desired product was detected even if the reaction was performed under much more harsh conditions.

Heterocyclic fused pyrazoles are especially attractive compounds because of their unique structures and pharmaceutical importance. Therefore we further investigated the potential application of this new method for the synthesis of the heterocyclic fused pyrazoles. As shown in Table 3, the protocol worked well for *o*-bromo or *o*-chloro heteroaryl aldehydes and ketones. For instance, 2-bromo-3-pyridine aldehyde easily yielded the desired products with satisfactory yields by reacting with different aryl hydrazines under the catalysis of 0.1 mol% CuI at 100 ℃ (Table 3, Entries 1 and 2). 3-Bromofuran-2-carbaldehyde gave a similar result (Table 3, Entry 3). More importantly, the method was highly efficient for the *o*-chloro ketone substrates when the reactions were performed at 120 ℃ with 10 mol% CuI as catalyst (Table 3, Entry 4).

Conclusion

In summary, a simple and efficient protocol for the synthesis of 1-aryl-1*H*-indazoles was developed. This method involved an intermolecular condensation followed by a ligand-free copper-catalyzed intramolecular Ullmann-type coupling reaction, and could be applied to a wide range of substrates to produce the indazole products in good yields. Most importantly, only 0.1 mol% CuI catalyst was needed for the reaction systems of aryl bromide substrates. Our effort may become an attractive addition to the synthesis of biological important 1-aryl-1*H*-indazole analogues.

Experimental

All reagents and solvents were purchased from commercial sources and were used without further purification. ^{1}H and ^{13}C NMR spectra were measured at 400 MHz.

Typical experiment procedure for the two-step synthesis of indazoles

The mixture of aryl halide (1 mmol), aryl hydrazine (1 mmol) and acetic acid (trace) was refluxed in EtOH until the transformation to aryl hydrazone was completed (monitored by TLC, about 2 h). The solvent was evacuated. CuI, K_3PO_4 (2.0 mmol) and DMSO (1.0 mL) were added, and the mixture was heated under the indicated temperature for about 12 h in Ar atmosphere. After cooling to room temperature, the mixture was partioned between water and ethyl acetate. The organic phase was separated and washed with brine, then dried over Na_2SO_4 and concentrated under vacuum. The residue was loaded on the silic gel column to give the

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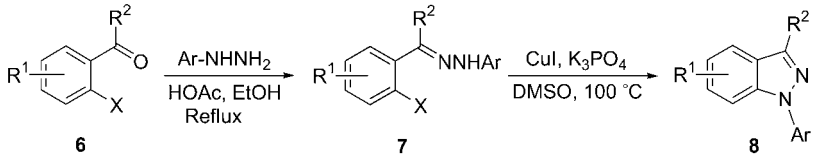
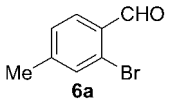
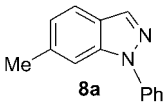
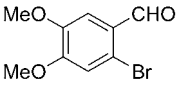
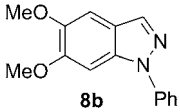
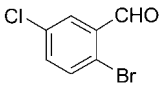
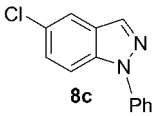
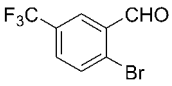
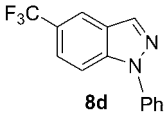
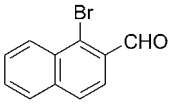
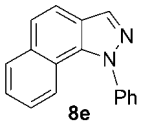
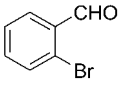
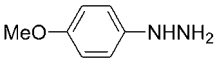
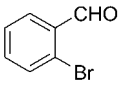
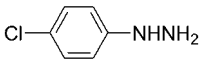
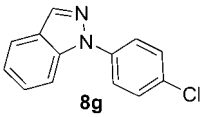
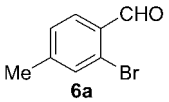
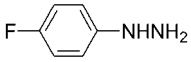
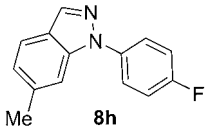
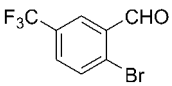
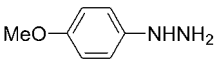
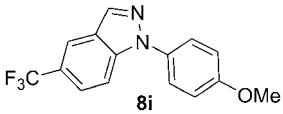
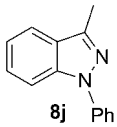
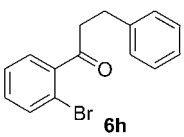
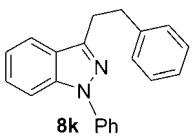
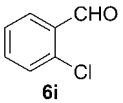
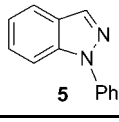
Table 2 Synthesis of indazoles from *o*-halogenated aryl aldehydes or ketones with aryl hydrazines[a]

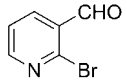
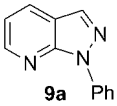
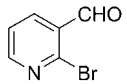
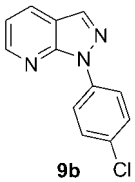
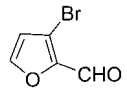
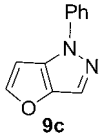
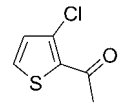
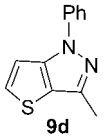
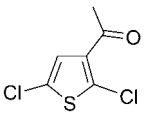
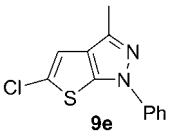


6 **7** **8**

Entry	Aryl halide	Hydrazine	Product	Yield[b]/%
1	 **6a**	$PhNHNH_2$	 **8a**	85
2	 **6b**	$PhNHNH_2$	 **8b**	81
3	 **6c**	$PhNHNH_2$	 **8c**	93
4	 **6d**	$PhNHNH_2$	 **8d**	96
5	 **6e**	$PhNHNH_2$	 **8e**	36
6	 **6f**		 **8f**	52
7	 **6f**		 **8g**	75
8	 **6a**		 **8h**	64
9	 **6d**		 **8i**	70
10	 **6g**	$PhNHNH_2$	 **8j**	81
11	 **6h**	$PhNHNH_2$	 **8k**	82
12	 **6i**	$PhNHNH_2$	 **5**	50[c]

[a] CuI (0.1 mol%), K_3PO_4 2.0 mmol, DMSO 1 mL, 100 ℃. [b] Isolated yield. [c] 10 mol% CuI, 120 ℃, only trace amount of product was found at 100 ℃ with 1 mol% CuI.

Table 3 Reactions of *o*-halogenated heteroaryl aldehydes or ketones with aryl hydrazines[a]

Entry	Aryl halide	Hydrazine	Product	Yield[b]/%
1		$PhNHNH_2$	 **9a**	85
2		4-Cl-$PhNHNH_2$	 **9b**	57
3		$PhNHNH_2$	 **9c**	50
4		$PhNHNH_2$	 **9d**	86
5		$PhNHNH_2$	 **9e**	90

[a] Reaction conditions: for aryl bromides, CuI (0.1 mol%), K_3PO_4 (2.0 mmol), DMSO (1 mL), 100 ℃; for aryl chlorides CuI (10 mol%), 120 ℃. [b] Isolated yields.

product.

1-Phenyl-1*H*-indazole (5) White solid, m.p.78—80 ℃ (lit.[8a] 76—78 ℃); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.21 (s, 1H), 7.82 (d, J=8.0 Hz, 1H), 7.75 (t, J=8.0 Hz, 3H), 7.54 (t, J=8.0 Hz, 2H), 7.44 (t, J=7.2 Hz, 1H), 7.37 (t, J=7.2 Hz, 1H), 7.23—7.21 (m, 1H); ESI-MS *m/z*: 195.0 $[M+H]^+$.

1-Phenyl-6-methyl-1*H*-indazole (8a) White solid, m.p. 86—87 ℃ (lit.[8a] 84—86 ℃); ^{1}H NMR (DMSO, 400 MHz) δ: 8.29 (d, J=0.4 Hz, 1H), 7.77—7.74 (m, 3H), 7.64 (s, 1H), 7.57 (t, J=7.4 Hz, 2H), 7.41 (t, J=7.4 Hz, 1H), 7.11 (dd, J=8.0, 0.4 Hz, 1H), 2.47 (s, 3H); ESI-MS *m/z*: 255.1 $[M+H]^+$.

5,6-Dimethoxy-1-phenyl-1*H*-indazole (8b) White solid, m.p. 91—92 ℃; ^{1}H NMR (DMSO, 400 MHz) δ: 8.14 (d, J=0.8 Hz, 1H), 7.79 (d, J=8.0 Hz, 2H), 7.58 (t, J=8.0 Hz, 2H), 7.38 (t, J=8.0 Hz, 1H), 7.28 (s, 1H), 7.21 (s, 1H), 3.87 (s, 3H), 3.82 (s, 3H); ESI-MS *m/z*: 209.1 $[M+H]^+$.

5-Chloro-1-phenyl-1*H*-indazole (8c) White solid, m.p. 116—117 ℃; ^{1}H NMR (DMSO, 400 MHz) δ: 8.37 (s, 1H), 8.00 (s, 1H), 7.87 (d, J=8.8 Hz, 1H), 7.77 (d, J=7.2 Hz, 2H), 7.61 (t, J=7.2 Hz, 2H), 7.51 (d, J=8.8 Hz, 1H), 7.46 (t, J=7.2 Hz, 1H); ^{13}C NMR (DMSO, 100 MHz) δ: 139.71, 137.19, 135.64, 130.22, 128.15, 127.46, 126.46, 122.75, 121.09, 112.71; ESI-MS *m/z* (%): 229.1 ($[M+H]^+$, 100), 231.1 ($[M+3]^+$, 32.0); HRMS (ESI) calcd for $C_{13}H_9ClN_2$ $[M+H]^+$ 229.0537, found 229.0532.

1-Phenyl-5-(trifluoromethyl)-1*H*-indazole (8d) White solid, m.p. 102—104 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.30 (s, 1H), 8.13 (s, 1H), 7.83 (d, J=7.2 Hz, 1H), 7.73 (d, J=8.8 Hz, 2H), 7.66 (d, J=7.2 Hz, 1H), 7.57 (t, J=8.8 Hz, 2H), 7.42 (t, J=8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 139.73, 139.55, 136.14, 129.66, 127.43, 124.48, 123.75, 123.72, 123.05, 119.55, 119.50, 111.06; ESI-MS *m/z*: 263.1 $[M+H]^+$; HRMS (ESI) calcd for $C_{14}H_9F_3N_2$ $[M+H]^+$ 263.0791, found 263.0787.

1-Phenyl-1*H*-benzo[*g*]indazole (8e) White solid, m.p. 107—109 ℃; ^{1}H NMR (DMSO, 400 MHz) δ: 8.37 (s, 1H), 8.07 (d, J=8.0 Hz, 1H), 7.87 (d, J=8.8 Hz, 1H), 7.86—7.62 (m, 6H), 7.55 (t, J=8.0 Hz, 1H), 7.46 (d, J=8.4 Hz, 1H), 7.38 (t, J=7.2 Hz, 1H); ^{13}C NMR (DMSO, 100 MHz) δ: 141.87, 136.00, 135.85, 133.35, 130.23, 129.86, 129.59, 127.69, 126.86, 126.48, 123.50, 121.77, 121.74, 120.51, 119.79; ESI-MS *m/z*: 245.1 $[M+H]^+$; HRMS (ESI) calcd for $C_{17}H_{12}N_2$ $[M+H]^+$ 245.1073, found 245.1075.

1-(4-Methoxyphenyl)-1*H*-indazole (8f) White solid, m.p. 34—36 ℃ (lit.[8a] 35—38 ℃); ^{1}H NMR (DMSO, 400 MHz) δ: 8.32 (d, J=0.8 Hz, 1H), 7.88 (d, J=8.1 Hz, 1H), 7.77 (d, J=8.1 Hz, 1H), 7.66 (d, J=2.0 Hz, 1H), 7.46 (t, J=7.2 Hz, 1H), 7.24 (d, J=7.2 Hz, 1H), 7.16 (d, J=2.0 Hz, 1H), 3.85 (s, 3H); ESI-MS *m/z*: 225.1 $[M+H]^+$.

1-(4-Chlorophenyl)-1*H*-indazole (8g) Yellow oil; ^{1}H NMR (DMSO, 400 MHz) δ: 8.41 (s, 1H), 7.92 (d, J=8.0 Hz, 1H), 7.87 (d, J=8.0 Hz, 1H), 7.83 (d, J=8.8 Hz, 2H), 7.66 (d, J=8.8 Hz, 2H), 7.52 (t, J=7.6 Hz, 1H), 7.29 (t, J=7.6 Hz, 1H); ESI-MS *m/z*: 229.0 $[M+H]^+$ (100), 231.0 $[M+3]^+$ (32.0).

1-(4-Fluorophenyl)-6-methyl-1*H*-indazole (8h) White solid, m.p. 56—58 ℃ (lit.[8a] 52—54 ℃); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.13 (d, J = 0.8 Hz, 1H), 7.69—7.66 (m, 3H), 7.45 (s, 1H), 7.25—7.21 (m, 2H), 7.06 (dd, J=8.4, 0.8 Hz, 1H), 2.51 (s, 3H); ESI-MS *m/z*: 227.1 $[M+H]^+$.

1-(4-Methoxyphenyl)-5-(trifluoromethyl)-1*H*-indazole (8i) White solid, m.p. 115—117 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.27 (s, 1H), 8.11 (s, 1H), 7.71 (d, J=0.4 Hz , 1H), 7.62—7.57 (m, 3H), 7.09 (dd, J=6.8, 2.0 Hz , 2H), 3.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 158.94, 139.95, 135.59. 132.60, 124.83, 124.05, 124.00, 123.52, 123.49, 119.47, 119.42, 114.78, 110.88, 55.64; ESI-MS *m/z*: 293.1 $[M+H]^+$; HRMS (ESI) calcd for $C_{15}H_{11}F_3N_2O$ $[M+H]^+$ 292.0896, found 293.0899.

1-Phenyl-3-methyl-1*H*-indazole (8j) White solid, m.p. 73—74 ℃ (lit.[13] 73—74 ℃); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.74 (dd, J=8.8, 1.2 Hz, 4H), 7.52 (t, J=7.6 Hz, 2H), 7.43 (m, 1H), 7.33 (t, J=7.6 Hz, 1H), 7.21

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(t, J=7.6 Hz, 1H), 2.67 (s, 3H); ESI-MS *m*/*z*: 208.7 [M+H]$^+$.

3-Phenethyl-1-phenyl-1*H*-indazole (8k) Pale yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.74 (d, J=8.4 Hz, 3H), 7.70 (d, J=8.0 Hz, 1H), 7.54 (t, J=7.6 Hz, 2H), 7.44—7.30 (m, 6H), 7.26—7.18 (m, 2H), 3.39—3.35 (m, 2H), 3.24—3.20 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 147.23, 141.77, 140.31, 139.50, 129.40, 128.49, 128.43, 127.06, 126.19, 126.05, 124.31, 122.54, 120.84, 120.52, 110.40,35.39, 29.18; ESI-MS *m*/*z*: 299.1 [M+H]$^+$; HRMS (ESI) calcd for $C_{21}H_{18}N_2$ [M+H]$^+$ 298.1453, found 299.1542.

1-Phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (9a) White solid, m.p. 53—55 ℃ (lit.[14] 53 ℃); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.63 (dd, J=4.8, 1.6 Hz, 1H), 8.29 (d, J=7.2 Hz, 2H), 8.12 (s, 1H), 8.10 (dd, J=7.2, 1.6 Hz, 1H), 7.56 (t, J=7.2 Hz, 2H), 7.32 (t, J=6.4 Hz, 1H), 7.21 (dd, J=8.4, 4.8 Hz, 1H); ESI-MS *m*/*z*: 196.1 [M+H]$^+$.

1-(4-Chlorphenyl)-1*H*-pyrazolo[3,4-*b*]pyridine (9b) White solid, m.p. 100—101 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.63 (dd, J=4.4, 1.6 Hz, 1H), 8.31 (dt, J=8.8, 2.8 Hz, 2H), 8.20 (s, 1H), 8.15 (dd, J=8.0, 1.6 Hz, 1H), 7.51 (dt, J=8.8, 2.8 Hz, 2H), 7.25 (dd, J=8.0, 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 150.13, 149.23, 138.12, 134.12, 131.34, 130.30, 129.15, 122.18, 117.81, 117.32; ESI-MS *m*/*z* (%): 230.0 ([M+H]$^+$, 100), 232.0 ([M+3]$^+$, 32.1); HRMS (ESI) calcd for $C_{12}H_8ClN_3$ [M+H]$^+$ 230.0480, found 230.0484.

1-Phenyl-1-*H*-furo[3,2-*c*]pyrazole (9c) White solid, m.p. 39—40 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.65 (d, J=2.0 Hz, 2H), 7.52 (s, 1H), 7.48 (d, J=2.4 Hz, 1H), 7.38 (t, J=2.4 Hz, 2H), 7.15 (t, J=2.4 Hz, 1H), 6.67 (d, J=2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 150.28, 148.83, 140.36, 135.02, 129.45, 125.42, 121.05, 117.74, 99.36; ESI-MS *m*/*z*: 185.0 [M+H]$^+$; HRMS (ESI) calcd for $C_{11}H_8N_2O$ [M+H]$^+$ 185.0797, found 185.0713.

3-Methyl-1-phenyl-1*H*-thieno[3, 2-*c*]pyrazole (9d) Black soild, m.p. 45—47 ℃ (lit.[15] 46—47 ℃); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.77 (d, J = 2.0 Hz, 2H), 7.54—7.48 (m, 3H), 7.31—7.25 (m, 2H), 2.57 (s, 3H); ESI-MS *m*/*z*: 215.1 [M+H]$^+$.

5-Chloro-3-methyl-1-phenyl-1*H*-thieno[2,3-*c*]pyrazole (9e) White solid, m.p. 53—54 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.67 (d, J=8.8 Hz, 2H), 7.48 (t, J=8.8 Hz, 2H), 7.27—7.23 (m, 1H), 6.93 (s, 1H), 2.50 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 142.27, 139.33, 137.98, 129.61, 127.68, 125.47, 117.45, 115.05, 13.02; ESI-MS *m*/*z* (%): 249.9 ([M+H]$^+$, 100), 251.9 ([M+3]$^+$, 36.5); HRMS (ESI) calcd for $C_{12}H_9ClN_2S$ [M+H]$^+$ 249.0248, found 249.0248.

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(E1010111 Zhao, C.; Dong, H.)

