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Pd-catalyzed direct arylation of phenylpyrazole: Synthesis of fipronil derivatives with aryl boronic acids promoted by a stoichiometric amount of NIS

Ting Lv [a], Xiao-Hong Zhang [a,*], Jiang-Sheng Han [a], Ping Zhong [a,b,**]

[a] College of Chemistry and Materials Science, Wenzhou University, Wenzhou 325035, China
[b] Oujiang College, Wenzhou University, Wenzhou 325035, China

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ABSTRACT

The palladium-catalyzed direct arylation of phenylpyrazole with aryl boronic acid promoted by a stoichiometric amount of NIS has been reported. Several phenyl pyrazoles, especially for those with trifluoromethyl groups, can participate in the reaction, providing a series of fipronil derivatives of 4-aryl-phenylpyrazole with potential bioactivity in moderate to good yields. All the compounds were characterized by ^{1}H NMR, ^{13}C NMR and HRMS spectroscopic techniques.

1. Introduction

Phenyl pyrazole is an important class of heterocyclic compounds and has shown a wide range of biological activities [1]. In addition, phenyl pyrazole derivatives possessing fluorine-containing groups, for example, fipronil (**I**, Fig. 1) [5-amino-1-[2,6-dichloro-4-(trifluoromethyl)-phenyl]-4-trifluoromethylsulfinyl-lH-pyrazole-3-carbonitrile] and ethiprole (**II**, Fig. 1), with 4-EtSO replacing with the 4-CF_3SO, are effective against a host of insect pests of crops including grass hoppers, boll weevils, rice insects, termites, houseflies, fruitflies and thrips [2]. The new analog of desulfinylethiprole (**III**, Fig. 1) was surprisingly found to have high insecticidal activity [3]. So we believe that 4-aryl-1-phenylpyrazole compounds (**IV**, Fig. 1) may have the same high insecticidal activity. However, there are relatively few reports for the synthesis of compounds **IV** [4], which was synthesized mainly via the reaction of 4-iodo-1-phenylpyrazole with arylboronic acid [5]. This method requires to prepare substrates to form the electrophiles, and the overall process is neither atom-economical nor green. Therefore, the protocol for novel procedures for the synthesis of 4-aryl-1-phenylpyrazoles containing CF_3 group is still a great challenge.

Recently, great interests have been aroused to develop mild methods for the direct functionalization of C–H to construct C–C [6], C–N [7], C–O [8] and C–S [9] bonds. It is well known that Suzuki–Miyaura reaction is one of the most attractive methods to construct C–C bond [10]. With the development of the Suzuki–Miyaura reaction, boronic acids have been developed as powerful reagents owing to their nontoxicity, stability and compatibility with most functional groups [11]. So we envisioned that 4-aryl-1-phenylpyrazoles can be obtained through the metal-catalyzed direct arylation of phenylpyrazoles with aryl boronic acids. And it is very fortunate that the direct arylation of phenylpyrazole occurred smoothly using $PdCl_2(PPh_3)_2$ as catalyst. Here, we describe the novel synthesis of 4-aryl-1-phenylpyrazole derivatives containing CF_3 group. All the compounds were characterized by ^{1}H NMR, ^{13}C NMR and HRMS spectroscopic techniques.

2. Results and discussion

We choose the reaction of 5-amino-1-[2,6-dichloro-4-trifluoromethylphenyl]-l-H-pyrazole-3-carbonitrile (**1a**) with phenyl boronic acid (**2a**) as a model system to determine the optimal reaction conditions (Table 1). Initially, a series of Pd catalysts, including $PdCl_2$, $Pd(OAc)_2$, $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_2$, were tested for the reaction using 2 equiv $NaHCO_3$ as base, 1 equiv NIS as iodine source, C_2H_5OH:H_2O (3:1) as solvent at 80 °C under N_2 (entries 1–4). Among these catalysts screened, $PdCl_2(PPh_3)_2$ showed the

* Corresponding author. Tel.: +86 0577 86689338; fax: +86 0577 86689338.
** Corresponding author at: College of Chemistry and Materials Science, Wenzhou University, Wenzhou 325035, China. Tel.: +86 0577 86689338; fax: +86 0577 86689338.
E-mail addresses: kamenzxh@163.com (X.-H. Zhang), zhongp0512@163.com (P. Zhong).

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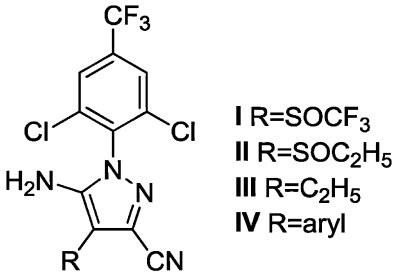


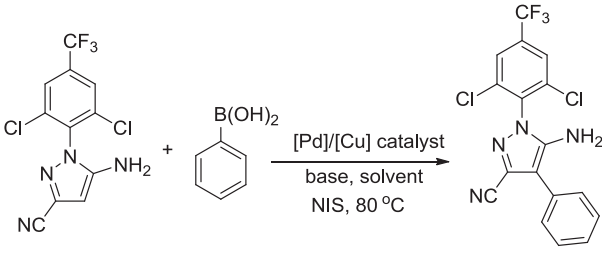
Fig. 1. Fipronil (**I**) and analogs (**II**, **III**, **IV**).

highest efficiency. However, when the reaction was conducted under atmospheric condition, the yield was decreased to 54% (entry 3). Other transition-metal catalyst, $Cu(OAc)_2$ was also measured and the byproduct of 4-iodo-1-phenylpyrazole was found to be obtained in a high yield (entry 5). Next, $NaHCO_3$ was replaced with different bases, such as CH_3ONa, Cs_2CO_3, K_2CO_3, t-BuOK, Na_2CO_3 and CH_3COOK, the results indicated that the identity of base was critical to the success of the direct arylation (entries 6–11). Subsequently, when the amount of $NaHCO_3$ was decreased to 1.5 equiv, the yield of **3** was reduced to 50% (entry 3). Promoted by the help from NIS, other iodide reagents, such as I_2 or ICl, were investigated in the presence of $PdCl_2(PPh_3)_2$ and they are less effective than NIS (entries 12–13). Based on our previous work [12], we think NIS promoted the generation of 4-iodo-1-phenylpyrazole in situ compared to I_2 and ICl, which was then reacted with phenyl boronic acid to give the arylated product **3**. It is noteworthy the slightly excess of NIS affected the yield slightly, but only 75% yield of **3** was obtained when decreasing the amount of NIS to 0.9 equiv (entries 14–15). It was interesting that no arylated product but only the by-product 4-iodo-1-phenylpyrazole can be obtained in high yields (entries 16–17) when the mixture solvent of C_2H_5OH:H_2O was replaced with C_2H_5OH and dioxane.

With the optimal catalytic system in hand, the scope of boronic acids in the reaction with **1a** was next investigated (Table 2). Gratifyingly, aryl boronic acids with electron-rich and electron-poor groups were successfully converted to the corresponding arylated products in moderate to good yields. Generally speaking, the electron-donating groups, such as methoxy, methyl and ethyl, on the phenyl ring of boronic acids were beneficial for the transformation (entries 2–4), whereas electron-withdrawing groups like chloro, fluoro and trifluoromethyl, decreased the efficiency (entries 7–9). Yet, steric hindrance affected the efficiency. For example, 88% yield of compound **4** without ortho substituent was isolated, while the yield of compounds **7** and **8** derived from ortho-substituted boronic acid were decreased to 69% and 60%, respectively (entries 5–6).

Subsequently, the substrate scope was extended to 5-amino-1-[2-chloro-4-trifluoromethylphenyl]-l-H-pyrazole-3-carbonitrile (**1b**) and 5-amino-1-phenyl-3-methylpyrazole (**1c**). With the strong electron-withdrawing group of trifluoromethyl on the phenyl ring, substrate **1a** and **1b** reacted with aryl boronic acids smoothly to give the arylated products in good yields (entries 1–10). However, when CF_3 on the phenyl ring of substrate **1c** disappeared, as well as CH_3 instead of CN on the pyrazole ring, no more than 62% of arylated products can be obtained (entries 11–18). The relatively poor reactivity may largely attribute to absence

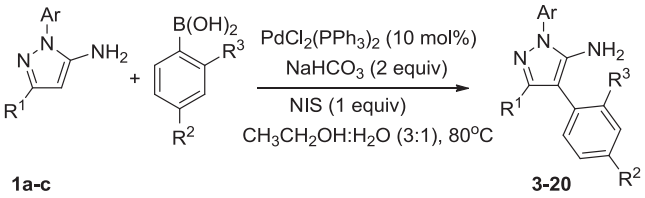
Table 1
Optimization of the arylation conditions.[a]



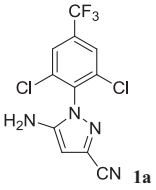
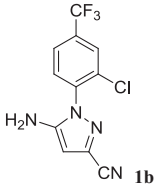
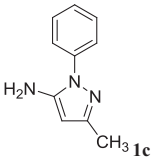
Entry	Catalyst	Base	Iodide source	Solvent	Yield (%)[b]
1	$PdCl_2$	$NaHCO_3$	NIS	C_2H_5OH:H_2O	25
2	$Pd(OAc)_2$	$NaHCO_3$	NIS	C_2H_5OH:H_2O	8
3	$PdCl_2(PPh_3)_2$	$NaHCO_3$	NIS	C_2H_5OH:H_2O	85 (50[c], 54[d])
4	$Pd(PPh_3)_4$	$NaHCO_3$	NIS	C_2H_5OH:H_2O	52
5	$Cu(OAc)_2$	$NaHCO_3$	NIS	C_2H_5OH:H_2O	90[d]
6	$PdCl_2(PPh_3)_2$	CH_3ONa	NIS	C_2H_5OH:H_2O	36
7	$PdCl_2(PPh_3)_2$	Cs_2CO_3	NIS	C_2H_5OH:H_2O	6
8	$PdCl_2(PPh_3)_2$	K_2CO_3	NIS	C_2H_5OH:H_2O	32
9	$PdCl_2(PPh_3)_2$	t-BuOK	NIS	C_2H_5OH:H_2O	30
10	$PdCl_2(PPh_3)_2$	Na_2CO_3	NIS	C_2H_5OH:H_2O	20
11	$PdCl_2(PPh_3)_2$	CH_3COOK	NIS	C_2H_5OH:H_2O	19
12	$PdCl_2(PPh_3)_2$	$NaHCO_3$	I_2	C_2H_5OH:H_2O	36
13	$PdCl_2(PPh_3)_2$	$NaHCO_3$	ICl	C_2H_5OH:H_2O	40
14[e]	$PdCl_2(PPh_3)_2$	$NaHCO_3$	NIS	C_2H_5OH:H_2O	86
15[f]	$PdCl_2(PPh_3)_2$	$NaHCO_3$	NIS	C_2H_5OH:H_2O	75
16	$PdCl_2(PPh_3)_2$	$NaHCO_3$	NIS	C_2H_5OH	96[g]
17	$PdCl_2(PPh_3)_2$	$NaHCO_3$	NIS	Dioxane	93[g]

[a] Reaction conditions: 1a (0.2 mmol), 2a (0.4 mmol), [NIS, I_2 or ICl] (1 equiv), [Pd] or [Cu] (10 mol%), base (0.4 mmol), C_2H_5OH:H_2O (3:1), N_2, 80 °C for 18 h.
[b] Isolated yield.
[c] $NaHCO_3$ (0.3 mmol).
[d] Without N_2.
[e] NIS (1.1 equiv).
[f] NIS (0.9 equiv).
[g] The yield of by-product 4-iodo-1-phenylpyrazole

Table 2
Pd-catalyzed arylation of phenylpyrazole with arylboronic acid.[a]



1a-c **3-20**

Entry	Pyrazole	R^2	R^3	Product (yield %) [b]
1	 **1a**	H	H	**3** (85)
2	**1a**	OCH_3	H	**4** (88)
3	**1a**	CH_3	H	**5** (87)
4	**1a**	CH_2CH_3	H	**6** (86)
5	**1a**	H	OCH_3	**7** (69)
6	**1a**	Cl	OCH_3	**8** (60)
7	**1a**	Cl	H	**9** (75)
8	**1a**	F	H	**10** (71)
9	**1a**	CF_3	H	**11** (68)
10	 **1b**	H	H	**12** (83)
11	 **1c**	H	H	**13** (55)
12	**1c**	OCH_3	H	**14** (62)
13	**1c**	CH_3	H	**15** (60)
14	**1c**	CH_2CH_3	H	**16** (61)
15	**1c**	H	CH_3	**17** (43)
16	**1c**	H	Cl	**18** (41)
17	**1c**	F	H	**19** (50)
18	**1c**	Cl	H	**20** (52)

[a] Reaction conditions: 1a (0.2 mmol), 2a (0.4 mmol), [NIS] (0.2 mmol), [Pd] (10 mol%), $NaHCO_3$ (0.4 mmol), $C_2H_5OH:H_2O$ (3:1), N_2, 80 °C for 18 h.
[b] Isolated yield.

of CN, which displayed the existence of electron-withdrawing substituents on the pyrazole ring benefited the direct arylation of phenylpyrazole. Similarly, the substituent on the phenyl of boronic acids affected the reaction obviously. The electron-donating groups, such as methoxy, methyl and ethyl, on the phenyl ring of boronic acids favored the reaction (entries 12–14) and gave higher yields of products than the electron-withdrawing groups (entries 17–18). Meanwhile, steric hindrance affected the efficiency to give compounds **17** and **18** in lower yields of 43% and 41%, respectively (entries 15–16).

3. Conclusion

In summary, we have presented a novel method for palladium-catalyzed direct arylation of phenylpyrazole with the aid of a stoichiometric amount of NIS. Adopting the method, various substrates can tolerate the conditions and a series of fipronil derivatives of 4-aryl-phenylpyrazole with potential bioactivity were synthesized in moderate to good yields. Undoubtedly, this efficient method will be useful for the synthesis of trifluoromethyl-containing 4-aryl-phenylpyrazole derivatives for drug discovery.

4. Experimental

Chemicals were either purchased or purified by standard techniques. NMR spectroscopy was performed on a Bruker Avance-300 spectrometer operating at 500 MHz (^{1}H NMR) and 125 MHz (^{13}C NMR), using DMSO as the solvent with tetramethylsilane (TMS) as an internal standard at room temperature. The coupling constants *J* are given in Hz. The high resolution mass spectrometer was Bruker micrOTOF-QII (ESI). All reactions are happened under N_2 atmosphere. Column chromatography was performed using EM Silica gel 60 (300–400 mesh).

4.1. Typical experimental procedure for the Pd-catalyzed direct arylation of phenylpyrazole with arylboronic acid

Phenylpyrazole (0.2 mmol), arylboronic acid (0.4 mmol), NIS (0.2 mmol), [Pd] (10 mol%), $NaHCO_3$ (0.4 mmol) and C_2H_5OH:H_2O (3:1, 10 mL), were added to a Schlenk tube. Then the tube was charged with N_2 and the reaction mixture was stirred at 80 °C for 18 h. After the completion of the reaction, as monitored by TLC, the mixture was cooled and filtrated. The filtrate was extracted with ethyl acetate and washed with brine. Then the combined organic extracts were dried over Na_2SO_4, concentrated under vacuum and the resulting residue was purified by silica gel column chromatography to afford the desired products.

5-Amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-phenyl-1H-pyrazole-3-carbonitrile (3)

Light yellow solid; mp 204–206 °C.
^{1}H NMR (500 MHz, DMSO): 8.30 (s, 2H), 7.59–7.55 (m, 5H), 6.29 (s, 2H).
^{13}C NMR (500 MHz, DMSO): 146.3, 135.9, 132.8 (*J* = 33.75 Hz), 129.7, 129.0, 127.2, 126.9, 126.6, 126.5, 124.7, 122.3 (*J* = 271.25 Hz), 114.5, 104.8.
HRMS (EI): calcd. for $C_{17}H_{10}Cl_2F_3N_4$ (M^+): 397.0229; found: 397.0206.

5-Amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-(4-methoxyphenyl)-1H-pyrazole-3-carbonitrile (4)

Light yellow solid; mp 206–208 °C.
^{1}H NMR (500 MHz, DMSO): 8.28 (s, 2H), 7.49 (d, *J* = 10 Hz, 2H), 7.11 (d, *J* = 10 Hz, 2H), 6.10 (s, 2H), 3.85 (s, 3H).
^{13}C NMR (500 MHz, DMSO): 158.3, 146.0, 136.0, 135.9, 132.7 (*J* = 33.75 Hz), 128.7, 126.5, 126.4, 124.6, 122.4 (*J* = 271.25 Hz), 121.9, 114.6, 104.9, 55.2.
HRMS (EI): calcd. for $C_{18}H_{12}Cl_2F_3N_4O$ (M^+): 427.0335; found: 427.0313.

5-Amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-p-tolyl-1H-pyrazole-3-carbonitrile (5)

Light yellow solid; mp 203–205 °C.
^{1}H NMR (500 MHz, DMSO): 8.30 (s, 2H), 7.47 (d, *J* = 5 Hz, 2H), 7.36 (d, *J* = 5 Hz, 2H), 6.22 (s, 2H), 2.41 (s, 3H).
^{13}C NMR (500 MHz, DMSO): 146.2, 136.2, 135.9, 132.7 (*J* = 33.75 Hz), 129.5, 127.2, 126.8, 126.6, 126.5, 124.6, 122.4 (*J* = 271.25 Hz), 114.5, 104.9, 20.7.
HRMS (EI): calcd. for $C_{18}H_{12}Cl_2F_3N_4$ (M^+): 411.0386; found: 411.0368.

5-Amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-(4-ethylphenyl)-1H-pyrazole-3-carbonitrile (6)

Light yellow solid; mp 206–208 °C.
^{1}H NMR (500 MHz, DMSO): 8.24 (s, 2H), 7.44 (d, *J* = 10 Hz, 2H), 7.34 (d, *J* = 10 Hz, 2H), 6.17 (s, 2H), 2.67 (q, 2H), 1.22 (t, 3H).
^{13}C NMR (500 MHz, DMSO): 146.2, 142.6, 135.8, 132.7 (*J* = 33.75 Hz), 128.4, 127.2, 126.9, 126.5, 126.4, 124.6, 123.4 (*J* = 271.25 Hz), 114.5, 104.9, 27.9, 15.5.
HRMS (EI): calcd. for $C_{19}H_{14}Cl_2F_3N_4$ (M^+): 425.0542; found: 425.0533.

5-Amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-(2-methoxyphenyl)-1H-pyrazole-3-carbonitrile (7)

Light yellow solid; mp 206–208 °C.
^{1}H NMR (500 MHz, DMSO): 8.29 (s, 2H), 7.42–7.09 (m, 4H), 5.94 (s, 2H), 3.88 (s, 3H).
^{13}C NMR (500 MHz, DMSO): 156.3, 146.8, 136.1, 135.9, 132.6 (*J* = 33.75 Hz), 130.2, 129.0, 126.5, 126.3, 122.4 (*J* = 275 Hz), 120.6, 118.2, 114.4, 111.7, 101.7, 55.3.
HRMS (EI): calcd. for $C_{18}H_{12}Cl_2F_3N_4O$ (M^+): 427.0335; found: 427.0318.

5-Amino-4-(5-chloro-2-methoxyphenyl)-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-1H-pyrazole-3-carbonitrile (8)

Light yellow solid; mp 209–211 °C.
^{1}H NMR (500 MHz, DMSO): 8.29 (s, 2H), 7.51–7.15 (m, 3H), 6.12 (s, 2H), 3.89 (s, 3H).
^{13}C NMR (500 MHz, DMSO): 155.2, 146.9, 136.0, 135.9, 132.7 (*J* = 33.75 Hz), 129.5, 128.5, 126.5, 126.3, 124.2, 122.4 (*J* = 272.5 Hz), 120.1, 114.1, 113.3, 100.0, 55.7.
HRMS (EI): calcd. for $C_{18}H_{11}Cl_3F_3N_4O$ (M^+): 460.9945; found: 460.9933.

5-Amino-4-(4-chlorophenyl)-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-1H-pyrazole-3-carbonitrile (9)

Light yellow solid; mp 208–210 °C.
^{1}H NMR (500 MHz, DMSO): 8.32 (s, 2H), 7.61–7.60 (m, 4H), 6.38 (s, 2H).
^{13}C NMR (500 MHz, DMSO): 146.5, 135.9, 135.8, 132.8 (*J* = 32.5 Hz), 131.4, 129.0, 128.6, 128.4, 126.6, 124.6, 122.3 (*J* = 257 Hz), 114.2, 103.6.
HRMS (EI): calcd. for $C_{17}H_8Cl_3F_3N_4$ (M^+): 430.9826; found: 430.9830.

5-Amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-(4-fluorophenyl)-1H-pyrazole-3-carbonitrile (10)

Light yellow solid; mp 209–211 °C.
^{1}H NMR (500 MHz, DMSO): 8.21 (s, 2H), 7.55–7.53 (m, 2H), 7.32 (t, *J* = 7.5, 2H) 6.23 (s, 2H).
^{13}C NMR (500 MHz, DMSO): 161.1 (*J* = 242.5), 146.3, 135.9, 135.8, 132.8 (*J* = 33.75), 129.4 (*J* = 7.5), 126.5, 126.0, 124.7, 122.3 (*J* = 271.25), 116 (*J* = 21.25), 114.3, 104.1.
HRMS (EI): calcd. for $C_{17}H_9Cl_2F_4N_4$ (M^+): 415.0135; found: 415.0141.

5-Amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-(4-(trifluoromethyl)phenyl)-1H-pyrazole-3-carbonitrile (11)

Light yellow solid; mp 208–210 °C.
^{1}H NMR (500 MHz, DMSO): 8.26 (s, 2H), 7.85 (d, *J* = 10 Hz, 2H), 7.75 (d, *J* = 10 Hz, 2H), 6.47 (s, 2H).
^{13}C NMR (500 MHz, DMSO): 146.9, 135.9, 134.8 (*J* = 202.5 Hz), 132.9 (*J* = 33.75 Hz), 127.7, 126.1 (*J* = 201.3 Hz), 126.6, 126.5, 125.9, 125.8, 124.7, 123.3 (*J* = 30 Hz), 114.1, 103.4.
HRMS (EI): calcd. for $C_{18}H_9Cl_2F_6N_4$ (M^+): 465.0103; found: 465.0075.

5-Amino-1-(2-chloro-4-(trifluoromethyl)phenyl)-4-phenyl-1H-pyrazole-3-carbonitrile (12)

Light yellow solid; mp 180–182 °C.
^{1}H NMR (500 MHz, DMSO): 8.09–7.96 (m, 3H), 7.54–7.33 (m, 5H), 6.01 (s, 2H).
^{13}C NMR (500 MHz, DMSO): 146.1, 136.3, 135.1, 131.7 (J = 33.75 Hz), 129.7, 129.2, 129.0, 128.6, 127.6, 127.5, 127.2, 126.9, 123.7 (J = 271.25), 114.6, 105.5.
HRMS (EI): calcd. for $C_{17}H_{11}ClF_3N_4$ (M^+): 363.0619; found: 363.0622.

3-Methyl-1, 4-diphenyl-1H-pyrazol-5-amine (13)

Brown oil.
^{1}H NMR (500 MHz, DMSO): 7.60–7.23 (m, 10H), 5.01 (s, 2H), 2.16 (s, 3H).
^{13}C NMR (500 MHz, DMSO): 145.0, 143.2, 138.8, 133.2, 129.1, 128.6, 128.2, 126.3, 125.4, 123.1, 103.7, 13.0.
HRMS (EI): calcd. for $C_{16}H_{16}N_3$ (M^+): 250.1339; found: 250.1342.

4-(4-Methoxyphenyl)-3-methyl-1-phenyl-1H-pyrazol-5-amine (14)

Brown oil.
^{1}H NMR (500 MHz, DMSO): 7.59–6.99 (m, 9H), 4.89 (s, 2H), 3.77 (s, 3H), 2.12 (s, 3H).
^{13}C NMR (500 MHz, DMSO): 157.2, 146.0, 142.9, 138.9, 131.5, 129.6, 129.1, 128.6, 122.9, 114.1, 103.6, 55.0, 13.4.
HRMS (EI): calcd. for $C_{17}H_{18}N_3O$ (M^+): 280.1444; found: 280.1456.

3-Methyl-1-phenyl-4-p-tolyl-1H-pyrazol-5-amine (15)

Brown oil.
^{1}H NMR (500 MHz, DMSO): 7.60–7.22 (m, 9H), 4.94 (s, 2H), 2.32 (s, 3H), 2.14 (s, 3H).
^{13}C NMR (500 MHz, DMSO): 146.0, 143.1, 138.9, 134.5, 130.2, 129.2, 129.1, 128.2, 126.2, 123.0, 103.7, 20.5, 13.0.
HRMS (EI): calcd. for $C_{17}H_{18}N_3$ (M^+): 264.1495; found: 264.1504.

4-(4-Ethylphenyl)-3-methyl-1-phenyl-1H-pyrazol-5-amine (16)

Brown oil.
^{1}H NMR (500 MHz, DMSO): 7.59–7.25 (m, 9H), 4.94 (s, 2H), 2.62 (q, 2H), 1.21 (t, 3H).
^{13}C NMR (500 MHz, DMSO): 146.0, 143.1, 140.9, 138.8, 129.1, 128.5, 128.2, 128.0, 126.3, 123.0, 103.7, 27.8, 15.5, 13.4.
HRMS (EI): calcd. for $C_{18}H_{20}N_3$ (M^+): 278.1652; found: 278.1644.

3-Methyl-1-phenyl-4-o-tolyl-1H-pyrazol-5-amine (17)

Brown oil.
^{1}H NMR (500 MHz, DMSO): 7.63–7.15 (m, 9H), 4.75 (s, 2H), 2.19 (s, 3H), 1.95 (s, 3H).
^{13}C NMR (500 MHz, DMSO): 146.4, 143.2, 139.1, 137.4, 131.9, 131.2, 130.0, 129.1, 127.0, 125.9, 125.7, 122.6, 103.8, 19.5, 12.5.
HRMS (EI): calcd. for $C_{17}H_{18}N_3$ (M^+): 264.1495; found: 264.1508.

4-(2-Chlorophenyl)-3-methyl-1-phenyl-1H-pyrazol-5-amine (18)

Brown oil.
^{1}H NMR (500 MHz, DMSO): 7.62–7.32 (m, 9H), 4.92 (s, 2H), 1.99 (s, 3H).
^{13}C NMR (500 MHz, DMSO): 146.6, 143.8, 133.8, 132.9, 131.6, 131.5, 129.5, 129.1, 128.6, 127.2, 126.1, 122.7, 102.0, 12.7.
HRMS (EI): calcd. for $C_{16}H_{15}ClN_3$ (M^+):284.0949; found: 284.0948.

4-(4-Fluorophenyl)-3-methyl-1-phenyl-1H-pyrazol-5-amine (19)

Brown oil.
^{1}H NMR (500 MHz, DMSO): 7.53–7.22 (m, 9H), 5.03 (s, 2H), 2.14 (s, 3H).
^{13}C NMR (500 MHz, DMSO): 160.3 (J = 240 Hz), 146.0, 143.3, 138.8, 130.2 (J = 7.5 Hz), 129.2, 128.6, 126.4, 123.2, 115.4 (J = 21.3 Hz), 102.9, 13.4.
HRMS (EI): calcd. for $C_{16}H_{15}FN_3$ (M^+): 268.1245; found: 268.1248.

4-(4-Chlorophenyl)-3-methyl-1-phenyl-1H-pyrazol-5-amine (20)

Brown oil.
^{1}H NMR (500 MHz, DMSO): 7.58–7.33 (m, 9H), 5.11 (s, 2H), 2.15 (s, 3H).
^{13}C NMR (500 MHz, DMSO): 146.0, 143.4, 138.7, 132.2, 129.9, 129.2, 128.5, 126.4, 125.9, 123.2, 102.5, 13.0.
HRMS (EI): calcd. for $C_{16}H_{15}ClN_3$ (M^+): 284.0949; found: 284.0946.

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