The Synthesis of Fipronil Derivatives via Pd-Catalyzed Direct Alkynylation of Phenylpyrazole with Terminal Alkynes in Green Solvents

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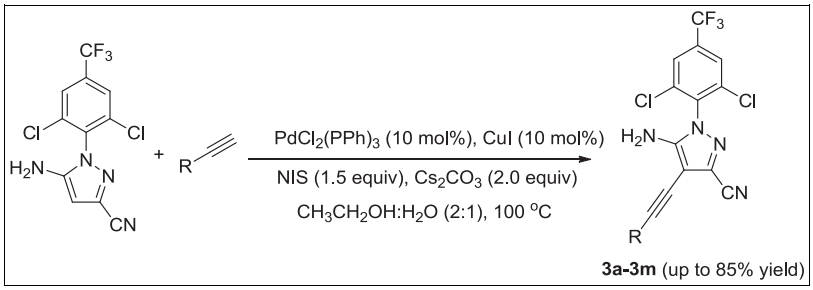


The palladium-catalyzed direct alkynylation of phenylpyrazole (5-amino-1-[2, 6-dichloro-4-trifluoromethylphenyl]-l*H*-pyrazole-3-carbonitrile) with terminal alkynes is being reported. The protocol utilizes EtOH/H_2O as the solvents and does not require the preactivation of phenylpyrazole with halide to form its halide substrate, which exemplifies the ideal condition of green chemistry. Various terminal alkynes such as arylacetylenes and aliphatic alkynes are used in the reaction to afford a series of fipronil derivatives of 4-alkynyl-1-phenylpyrazoles with potential bioactivity in good yields. All the compounds were characterized by ^{1}H NMR, ^{13}C NMR, and HRMS spectroscopic techniques.

INTRODUCTION

Phenylpyrazoles are an important class of heterocycles that are present in many natural products and pharmaceutical intermediates [1–5]. Moreover, phenylpyrazole derivatives containing fluorine groups have been found to exhibit a broad range of biological activities [6,7]. For example, the commercial fipronil (**I**, Fig. 1) (5-amino-1-[2, 6-dichloro-4-trifluoromethylphenyl]-4-trifluoromethylsulfinyl-l*H*-pyrazole-3-carbonitrile) is effective against a host of insect pests of crops including grass hoppers, boll weevils, rice insects, termites, houseflies, fruitflies, and thrips [8–10]. Similar insecticidal activity can be observed in its new analogs such as ethiprole (**II**, Fig. 1) [11], with 4-EtSO replacing the 4-CF_3SO and desulfinylethiprole (**III**, Fig. 1) [12], with 4-Et instead of 4-CF_3SO.

Recently, fipronil was greatly limited to be used as a pesticide because of its harm to animals [13]. In view of the biologically important fipronil, we have been devoted to the structural modification of fipronil parent in order to seek for its new analogs with highly biological activity and low toxicity to animals [14–16]. For example, the compounds of 4-aryl-1-phenylpyrazoles were successfully synthesized via the palladium-catalyzed direct arylation of phenylpyrazoles with boronic acids [17]. These works provided a series of fipronil derivatives with potential bioactivity. However, the direct alkynylation of phenylpyrazole to produce the 4-alkynyl-1-phenylpyrazole derivatives was seldom reported.

It is well known that palladium/copper-catalyzed Sonogashira cross-coupling reactions of aryl hailides with terminal alkynes are the most straightforward and powerful methods for the construction of C(Sp^2)–C(Sp) bonds [18–20]. Since its inception, great developments related to the Sonogashira cross-coupling reaction have been achieved, including the enhancement of catalytic efficiency [21,22], copper- [23–25] and/or solvent-free versions [26], and low reaction temperature [27,28]. However, all these reactions are dependent on preactivation of alkene with halide to form the substrate of vinyl halide, which requires several extrasynthetic steps and results in the production of waste and the low yield. Therefore, there is still a need for developing a direct and novel method to synthesize the 4-alkynyl-1-phenylpyrazole derivatives.

Encouraged by the successful synthesis of 4-aryl-1-phenylpyrazoles, we envisioned that 4-alkynyl-1-phenylpyrazoles can be obtained through the metal-catalyzed direct alkynylation of phenylpyrazoles with terminal alkynes. Fortunately, the direct alkynylation of phenylpyrazoles could be achieved smoothly when using $PdCl_2(PPh_3)_2$ as catalyst in green solvents. Herein, we describe the efficient synthesis of 4-alkynyl-1-phenylpyrazoles bearing CF_3 group. All the compounds were characterized by ^{1}H NMR, ^{13}C NMR, and HRMS spectroscopic techniques.

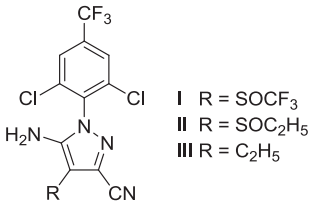


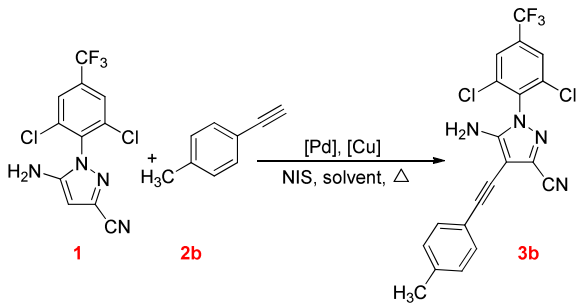
Figure 1. Fipronil (**I**) and analogs (**II**, **III**).

RESULTS AND DISCUSSION

We chose to study the reaction of 5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-l*H*-pyrazole-3-carbonitrile (**1**) with 4-ethynyltoluene (**2b**) as a model system to determine the optimal reaction conditions (Table 1). Initially, in the absence of Cu source, four commonly used catalyst precursors for the direct alkynylation were surveyed when using 2 equiv K_2CO_3 as base, 1.5 equiv *N*-iodosuccinimide (NIS) as iodine source, and $C_2H_5OH:H_2O$ (2:1) as solvent at 100°C. It was found that $PdCl_2(PPh_3)_2$ gave better yield of the product than $PdCl_2$, $Pd(OAc)_2$, and $Pd(PPh_3)_4$ (entries 1–4). Notably, the yield of cross-coupling product 5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-(*p*-tolylethynyl)-1*H*-pyrazole-3-carbonitrile (**3b**) could be dramatically increased in the presence of Cu source. Evaluation of addition of Cu sources such as CuCl and $Cu(OAc)_2$ provided conditions that gave a much lower yield relative to CuI (entries 5–7). Next, K_2CO_3 was replaced with different bases, such as Cs_2CO_3, *t*-BuOK, Na_2CO_3, CH_3COOK, and $NaHCO_3$. The results indicated that the identity of base affected the reaction efficiency, and Cs_2CO_3 was proved to be the optimal base for the direct alkynylation reaction (entries 8–12). It was interesting that no aimed product but only the intermediate 4-iodo-1-phenylpyrazole can be obtained in high yields when the mixture solvent of $C_2H_5OH:H_2O$ was replaced

Table 1

Optimization of the alkynylation conditions[a].



Entry	Pd	Cu source	Base	Iodide source	Solvent	Yield (%) [b]
1	$PdCl_2$	—	K_2CO_3	NIS	$C_2H_5OH:H_2O$	15
2	$Pd(OAc)_2$	—	K_2CO_3	NIS	$C_2H_5OH:H_2O$	10
3	$PdCl_2(PPh_3)_2$	—	K_2CO_3	NIS	$C_2H_5OH:H_2O$	40
4	$Pd(PPh_3)_4$	—	K_2CO_3	NIS	$C_2H_5OH:H_2O$	Trace
5	$PdCl_2(PPh_3)_2$	CuI	K_2CO_3	NIS	$C_2H_5OH:H_2O$	65
6	$PdCl_2(PPh_3)_2$	CuCl	K_2CO_3	NIS	$C_2H_5OH:H_2O$	55
7	$PdCl_2(PPh_3)_2$	$Cu(OAc)_2$	K_2CO_3	NIS	$C_2H_5OH:H_2O$	45
8	$PdCl_2(PPh_3)_2$	CuI	Cs_2CO_3	NIS	$C_2H_5OH:H_2O$	70 (65[c], 40[d])
9	$PdCl_2(PPh_3)_2$	CuI	t-BuOK	NIS	$C_2H_5OH:H_2O$	55
10	$PdCl_2(PPh_3)_2$	CuI	Na_2CO_3	NIS	$C_2H_5OH:H_2O$	60
11	$PdCl_2(PPh_3)_2$	CuI	CH_3COOK	NIS	$C_2H_5OH:H_2O$	20
12	$PdCl_2(PPh_3)_2$	CuI	$NaHCO_3$	NIS	$C_2H_5OH:H_2O$	63
13	$PdCl_2(PPh_3)_2$	CuI	Cs_2CO_3	NIS	DMSO	85[e]
14	$PdCl_2(PPh_3)_2$	CuI	Cs_2CO_3	NIS	C_2H_5OH	65
15	$PdCl_2(PPh_3)_2$	CuI	Cs_2CO_3	NIS	CH_3CN	40
16	$PdCl_2(PPh_3)_2$	CuI	Cs_2CO_3	NIS	DMF	80[e]
17	$PdCl_2(PPh_3)_2$	CuI	Cs_2CO_3	I_2	$C_2H_5OH:H_2O$	47
18	$PdCl_2(PPh_3)_2$	CuI	Cs_2CO_3	ICl	$C_2H_5OH:H_2O$	65

[a]Reaction conditions: 1 (0.2 mmol), 2b (0.4 mmol), [NIS or I_2] (0.3 mmol), [Pd] and [Cu] (10 mol%), base (0.4 mmol), solvent (6 mL), 100°C for 18 h.
[b]Isolated yield.
[c]NIS (0.2 mmol).
[d]80°C.
[e]The yield of intermediate 4-iodo-1-phenylpyrazole.

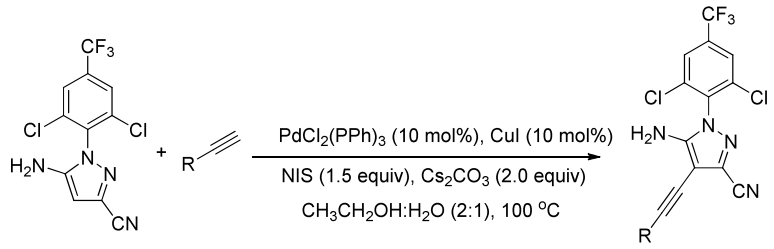
with DMSO and DMF (entries 13, 16), whereas the yield of product **3b** was decreased to 65 and 40% when using C_2H_5OH and CH_3CN as solvent (entries 14–15), respectively. Subsequently, promoted by the beneficial help from NIS, other iodide reagents, such as I_2 and ICl, were investigated to give lower yields than NIS (entries 17–18). Unfortunately, the yields of the product **3b** were dropped when decreasing the amount of NIS to 1 equiv as well as decreasing the reaction temperature to 80°C (entry 8). Thus, the optimal condition was finally identified as follows: 5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-l*H*-pyrazole-3-carbonitrile (**1**) (0.2 mmol), terminal alkyne (0.4 mmol), $PdCl_2(PPh_3)_2$ (10 mmol%), CuI (10 mmol%), NIS (0.3 mmol), Cs_2CO_3 (0.4 mmol), $C_2H_5OH : H_2O$ (2:1, 6 mL), 100°C for 18 h.

With the preliminary optimized reaction in hand, the scope of terminal alkynes was next discussed. The results were summarized in Table 2. As expected, various arylacetylenes worked well under the reaction condition. A series of functional groups, such as methyl, ethyl, *n*-propyl, *n*-butyl, methoxyl, chloro, bromo, fluoro, and the active group NH_2, were tolerated well in this process. Generally, the electron-withdrawing substituents on the phenyl of aryacetylenes were beneficial for the transformation, whereas electron-donating groups decreased the efficiency. For example, the arylacetylenes with fluoro, chloro, and bromo gave the cross-coupling products in more than 80% yields (entries 7–9), while their methyl, ethyl, *n*-propyl, *n*-butyl, and methoxyl equivalents generated the corresponding products in less than 75% (entries 1–6). To our delight, the treatment of 3-aminophenylacetylene with 5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-l*H*-pyrazole-3-carbonitrile (**1**) also afforded product **3k** in 50% yield (entry 11). Meanwhile, the steric hindrance affected the efficiency slightly. Substrates with *para*-methyl and *para*-chloro gave similar yields as their *meta*-methyl and *meta*-chloro equivalents (entries 2, 8, 10, 12). Fortunately, the aliphatic terminal alkyne such as 1-hexyne was also well tolerant to the catalytic system, providing the corresponding product in a moderate yield (entry 13).

The possible mechanism was listed in Figure 2 on the basis of reported mechanism [20,29]. Firstly, 5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-l*H*-pyrazole-3-carbonitrile (**1**) was reacted with NIS, giving the intermediate 4-iodo-1-phenylpyrazole. Then, the oxidative addition of Pd(0) with 4-iodo-1-phenylpyrazole proceed to form intermediate **A**. On the other hand, the copper acetylide was generated by the reaction of terminal alkyne with base. Subsequently, the replacement between

Table 2

Pd-catalyzed direct alkynylation of phenylpyrazole with terminal alkynes[a].



Entry	R	Compounds	Yield (%)[b]
1	C_6H_5	**3a**	75
2	4-MeC_6H_4	**3b**	70
3	4-EtC_6H_4	**3c**	65
4	4-n-PrC_6H_4	**3d**	66
5	4-n-BuC_6H_4	**3e**	71
6	4-$OCH_3C_6H_4$	**3f**	74
7	4-FC_6H_4	**3g**	80
8	4-ClC_6H_4	**3h**	85
9	4-BrC_6H_4	**3i**	83
10	3-MeC_6H_4	**3j**	72
11	3-$NH_2C_6H_4$	**3k**	50
12	3-ClC_6H_4	**3l**	82
13	1-heptyne	**3m**	71

[a]Reaction conditions: 1 (0.2 mmol), terminal alkynes (0.4 mmol), NIS (0.3 mmol), $PdCl_2(PPh_3)_2$ (10 mmol%), CuI (10 mmol%), Cs_2CO_3 (0.4 mmol), $C_2H_5OH : H_2O$ (2:1, 6 mL), 100°C for 18 h.
[b]Isolated yield.

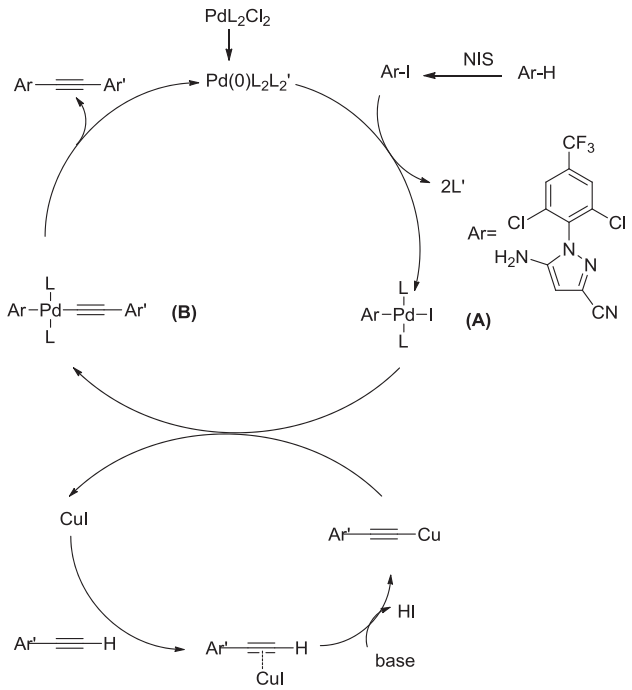


Figure 2. The possible mechanism.

intermediate **A** and the copper acetylide occurred to afford intermediate **B**, which released the aimed product and the active Pd(0) species via the reductive elimination reaction.

In summary, we have developed an efficient method for the palladium-catalyzed direct alkynylation of phenylpyrazole (5-amino-1-[2, 6-dichloro-4-trifluoromethylphenyl]-l*H*-pyrazole-3-carbonitrile) with terminal alkynes. The protocol does not require the preactivation of phenylpyrazole with halide to form its halide substrate, and the reaction adopted EtOH/H_2O as the solvent, which exemplifies the ideal condition of green chemistry. Various terminal alkynes, including arylacetylenes bearing electron-donating or withdrawing groups and aliphatic terminal alkynes, can participate in the reaction, affording a series of fipronil derivatives of 4-alkynyl-1-phenylpyrazole in moderate to good yields. Undoubtedly, this efficient method will be useful for the synthesis of trifluoromethyl-containing 4-alkynyl-1-phenylpyrazole derivatives for drug discovery.

EXPERIMENTAL

Typical experimental procedure for the palladium-catalyzed direct alkynylation of phenylpyrazole with terminal alkynes. 5-Amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-l*H*-pyrazole-3-carbonitrile (**1**) (0.2 mmol), terminal alkyne (0.4 mmol), [NIS] (0.3 mmol), $PdCl_2(PPh_3)_2$ (10 mmol%), CuI (10 mmol%), Cs_2CO_3 (0.4 mmol), and $C_2H_5OH:H_2O$ (2:1, 6 mL) were added to a Schlenk tube. Then, the reaction mixture was stirred at 100°C. 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 and 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-phenylethynyl-1H-pyrazole-3-carbonitrile (3a). Yellow solid, mp 187–189°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (s, 2H), 7.47–7.76 (m, 2H), 7.30–7.29 (m, 3H), 4.41 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.7, 136.8, 135.2, 135.0 (q, J = 34.1 Hz), 131.8, 129.3, 129.0, 128.7, 126.5 (q, J = 3.6 Hz), 122.7, 122.2 (q, J = 274.1 Hz), 112.6, 96.9, 92.4, 75.9. HRMS (ESI) calcd for $C_{19}H_{10}Cl_2F_3N_4^+$([M + H]$^+$) 421.0229, found 421.0247.

5-Amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-(p-tolylethynyl)-1H-pyrazole-3-carbonitrile (3b). Yellow solid, mp 229–230°C. ^{1}H NMR (500 MHz, d_6-acetone) δ 8.11 (s, 2H), 7.44 (d, J = 8.5 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 6.42 (s, 2H), 2.36 (s, 3H); ^{13}C NMR (125 MHz, d_6-acetone) δ 151.9, 139.5, 137.5, 136.6, 134.8 (q, J = 34.0 Hz), 132.1, 130.1, 129.0, 127.4 (q, J = 3.75 Hz), 122.4 (q, J = 271.6 Hz), 120.9, 113.7, 96.3, 89.7, 76.9, 21.4. HRMS (ESI) calcd for $C_{20}H_{12}Cl_2F_3N_4^+$([M + H]$^+$) 435.0386, found 435.0397.

5-Amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-((4-ethylphenyl)ethynyl)-1H-pyrazole-3-carbonitrile (3c). Yellow solid, mp 187–189°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (s, 2H), 7.45 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 4.23 (s, 2H), 2.67 (q, J = 7.5 Hz, 2H), 1.25 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.3, 146.3, 137.4, 135.9, 135.6 (q, J = 34.5 Hz), 132.5, 129.8, 128.9, 127.2 (q, J = 3.5 Hz), 122.9 (q, J = 272.2 Hz), 120.4, 113.3, 97.8, 93.2, 75.8, 29.8, 16.2. HRMS (ESI) calcd for $C_{21}H_{14}Cl_2F_3N_4^+$([M + H]$^+$) 449.0542, found 449.0554.

5-Amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-((4-n-propylphenyl)ethynyl)-1H-pyrazole-3-carbonitrile (3d). White solid, mp 208–209°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 2H), 7.43 (d, J = 8.5 Hz, 2H), 7.15 (d, J = 8.5 Hz, 2H), 4.16 (s, 2H), 2.59 (t, J = 7.5 Hz, 2H), 1.63 (q, J = 7.5 Hz, 2H), 0.93 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.4, 143.9, 136.6, 135.1, 134.8 (q, J = 33.75 Hz), 131.5, 129.0, 128.7, 126.3 (q, J = 3.63 Hz), 122.0 (q, J = 272.5 Hz), 119.6, 112.4, 96.9, 92.4, 74.9, 38.0, 24.3, 13.7. HRMS (ESI) calcd for $C_{22}H_{16}Cl_2F_3N_4^+$([M + H]$^+$) 463.0699, found 463.0717.

5-Amino-4-((4-n-butylphenyl)ethynyl)-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-1H-pyrazole-3-carbonitrile (3e). White solid, mp 171–173°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (s, 2H), 7.42 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 4.18 (s, 2H), 2.61 (t, J = 8.0 Hz, 2H), 1.60–1.57 (m, 2H), 1.36–1.32 (m, 2H), 0.92 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.4, 144.1, 136.6, 135.1, 134.8 (q,

J = 34.6 Hz), 131.5, 128.9, 128.6, 126.3 (q, J = 3.60 Hz), 122.0 (q, J = 272.2 Hz), 119.5, 112.4, 96.9, 92.4, 74.9, 35.6, 33.4, 22.3, 13.9. HRMS (ESI) calcd for $C_{23}H_{18}Cl_2F_3N_4^+$([M + H]$^+$) 477.0855, found 477.0873.

5-Amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-((4-methoxyphenyl)ethynyl)-1H-pyrazole-3-carbonitrile (3f). White solid, mp 138–140°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (s, 2H), 7.45 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 9.0 Hz, 2H), 4.17 (s, 2H), 3.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.3, 148.3, 136.8, 135.3, 134.9 (q, J = 34.4 Hz), 133.4, 129.3, 126.5 (q, J = 3.6 Hz), 122.2 (q, J = 272.3 Hz), 114.7, 114.4, 112.7, 96.8, 92.7, 74.4, 55.6. HRMS (ESI) calcd for $C_{20}H_{12}Cl_2F_3N_4O^+$([M + H]$^+$) 451.0335, found 451.0341.

5-Amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-((4-fluorophenyl)ethynyl)-1H-pyrazole-3-carbonitrile (3g). White solid, mp 219–221°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 2H), 7.52–7.48 (m, 2H), 7.06–7.03 (m, 2H), 4.17 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.8 (d, J = 249.0 Hz), 148.5, 136.6, 135.0, 134.8 (q, J = 30.3 Hz), 133.6 (d, J = 8.1 Hz), 129.0, 126.3 (q, J = 3.6 Hz), 121.9 (q, J = 272.6 Hz), 118.5 (d, J = 3.5 Hz), 115.8 (d, J = 22.1 Hz), 112.4, 95.6, 91.9, 75.4. HRMS (ESI) calcd for $C_{19}H_9Cl_2F_4N_4^+$([M + H]$^+$) 439.0135, found 439.0134.

5-Amino-4-((4-chlorophenyl)ethynyl)-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-1H-pyrazole-3-carbonitrile (3h). White solid, mp 221–223°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 2H), 7.44 (d, J = 9.0 Hz, 2H), 7.32 (d, J = 9.0 Hz, 2H) 4.20 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.5, 136.6, 134.9 (q, J = 34.5 Hz), 134.9, 133.7, 132.7, 129.0, 128.9, 128.8, 126.4 (q, J = 3.6 Hz), 121.9 (q, J = 272.2 Hz), 120.9, 112.3, 95.6, 91.7. HRMS (ESI) calcd for $C_{19}H_9Cl_3F_3N_4^+$([M + H]$^+$) 454.9839, found 454.9857.

5-Amino-4-((4-bromophenyl)ethynyl)-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-1H-pyrazole-3-carbonitrile (3i). White solid, mp 191–193°C. ^{1}H NMR (500 MHz, CD_3COCD_3) δ 8.10 (s, 2H), 7.64–7.62 (m, 2H), 7.53–7.51 (m, 2H), 6.57 (s, 2H); ^{13}C NMR (125 MHz, CD_3COCD_3) δ 152.3, 137.4, 136.5, 134.8 (q, J = 33.8 Hz), 133.8, 132.6, 128.9, 127.4 (q, J = 3.4 Hz), 123.3 (q, J = 272.1 Hz), 123.2, 122.9, 111.6, 95.2, 89.1, 79.1. HRMS (ESI) calcd for $C_{19}H_9BrCl_2F_3N_4^+$([M + H]$^+$) 498.9334, found 498.9363.

5-Amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-(m-tolylethynyl)-1H-pyrazole-3-carbonitrile (3j). White solid, mp 219–220°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 2H), 7.35–7.31 (m, 2H), 7.23–7.22 (m, 1H), 7.16–7.15 (m, 1H), 4.18 (s, 2H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.5, 138.2, 136.6, 135.0, 134.8 (q, J = 34.4 Hz), 132.1, 129.7, 128.9, 128.6, 128.4, 126.3 (q, J = 3.6 Hz), 122.2, 121.9 (q, J = 272.3 Hz), 112.4, 96.9, 92.6, 75.3, 21.2. HRMS (ESI) calcd for $C_{20}H_{12}Cl_2F_3N_4^+$([M + H]$^+$) 435.0386, found 435.0401.

5-Amino-4-((3-aminophenyl)ethynyl)-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-1H-pyrazole-3-carbonitrile (3k). White solid, mp 119–121°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (s, 2H), 7.11 (t, J = 7.5 Hz, 1H), 6.90 (d, J = 7.5 Hz, 1H), 6.83 (s, 1H), 6.67–6.65 (m, 1H), 4.20 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.5, 146.4, 136.6, 135.0, 134.8 (q, J = 36.7 Hz), 129.4, 128.9, 126.3 (q, J = 3.7 Hz), 123.1, 121.9 (q, J = 272.1 Hz), 121.9, 117.7, 115.8, 112.4, 97.0, 92.2, 75.0. HRMS (ESI) calcd for $C_{19}H_{11}Cl_2F_3N_5^+$([M + H]$^+$) 436.0338, found 436.0359.

5-Amino-4-((3-chlorophenyl)ethynyl)-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-1H-pyrazole-3-carbonitrile (3l). White solid, mp 215–217°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 2H), 7.50–7.49 (m, 1H), 7.41–7.39 (m, 1H), 7.33–7.26 (m, 2H), 4.21 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.6, 136.6, 134.9 (q, J = 34.3 Hz), 134.8, 134.4, 131.3, 129.7, 129.6, 129.1, 129.0, 126.4 (q, J = 3.6 Hz), 124.1, 121.9 (q, J = 273.8 Hz), 112.2, 95.3, 91.5. HRMS (ESI) calcd for $C_{19}H_9Cl_3F_3N_4^+$([M + H]$^+$) 454.9839, found 454.9836.

5-Amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-(hept-1-yn-1-yl)-1H-pyrazole-3-carbonitrile (3m). White solid, mp 215–217°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (s, 2H), 4.01 (s, 2H), 2.44 (t, J = 7.0 Hz, 2H), 1.63–1.60 (m, 2H), 1.46–4.41 (m, 2H), 1.39–1.33 (m, 2H), 0.91 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.3, 136.5, 135.2, 134.7 (q, J = 34.4 Hz), 129.1, 126.3 (q, J = 3.7 Hz), 121.9 (q, J = 272.3 Hz), 112.5, 98.2, 93.1, 66.9, 31.1, 28.4, 22.2, 19.7, 14.0. HRMS (ESI) calcd for $C_{18}H_{16}Cl_2F_3N_4^+$([M + H]$^+$) 415.0699, found 415.0697.

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REFERENCES AND NOTES

[1] Akbas, E.; Berber, I.; Sener, A.; Hasanov, B. IL Farmaco 2005, 60, 23.

[2] Kasimogullari, R.; Bulbul, M.; Arslan, B. S.; Gokce, B. Eur J Med Chem 2010, 45, 4769.

[3] Insuasty, B.; Tigreros, A.; Orozco, F.; Quiroga, J.; Abonia, R.; Nogueras, M.; Sanchez, A.; Cobo, J. Bioorg Med Chem 2010, 18, 4965.

[4] Moon, M. W.; Bell, L. T.; Cutting, T. L.; Keyser, H. R.; Tiller, R. H.; Vostral, H. J. J Agric Food Chem 1977, 25, 1039.

[5] Wu, J.; Lin, Y. J.; Lu, J.; Wilson, C. Sci Total Environ 2011, 409, 3482.

[6] Yamamoto, S.; Tomita, N.; Suzuki, Y.; Suzaki, T.; Kaku, T.; Hara, T.; Yamaoka, M.; Kanzaki, N.; Hasuoka, A.; Baba, A.; Ito, M. Bioorg Med Chem 2012, 20, 2338.

[7] Meegalla, S. K.; Doller, D.; Liu, R.; Sha, D. Y.; Lee, Y.; Soll, R. M.; Wisnewski, N.; Silver, G. M.; Dhanoa, D. Bioorg Med Chem Lett 2006, 16, 1702.

[8] Durham, E. W.; Scharf, M. E.; Siegfried, B. D. Pestic Biochem Physiol 2001, 71, 97.

[9] Stevens, M. M.; Helliwell, S.; Warren, G. N. Field Crop Res 1998, 57, 195.

[10] Brennan, A. A.; Harwood, A. D.; You, J.; Landrum, P. F.; Lydy, M. J Chemosphere 2009, 77, 22.

[11] Wu, T. T. US Patent 5,814,652, 1998; Chem Abstr 1998, 129, 256473.

[12] Sammelson, R. E.; Caboni, P.; Durkin, K. A.; Casida, J. E. Bioorg Med Chem 2004, 12, 3345.

[13] Parikshit, C. D.; Yan, C.; Nathan, C.; Ernest, H.; Randy, L. R. Chem Biol Interact 2006, 164, 200.
[14] Xu, M.; Zhang, X. H.; Zhong, P. Synth Commun 2012, 42, 3472.
[15] Zhang, X. H.; He, H.; Xu, M.; Zhong, P. J Chem Res Synop 2011, 6, 23.
[16] Tang, R. Y.; Zhong, P.; Lin, Q. L. J Fluorine Chem 2006, 127, 948.
[17] Lv, T.; Zhang, X. H.; Han, J. S.; Zhong, P. J Fluorine Chem 2012, 137, 44.
[18] Gelman, D.; Buchwald, S. L. Angew Chem Int Ed 2003, 42, 5993.
[19] Eckhardt, M.; Fu, G. C. J Am Chem Soc 2003, 125, 13642.
[20] Liang, Y.; Xie, Y.-X.; Li, J.-H. J Org Chem 2006, 71, 379.
[21] Herrmann, W. A.; BIhm, V. P. W.; Reisinger, C. P. J Organomet Chem 1999, 576, 23.
[22] Alonso, D. A.; Najera, C.; Pacheco, M. C. Tetrahedron Lett 2002, 43, 9365.
[23] Liang, B.; Dai, M.; Chen, J.; Yang, Z. J Org Chem 2005, 70, 391.
[24] Gholap, A. R.; Venkatesan, K.; Pasricha, R.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. J Org Chem 2005, 70, 4869.
[25] Yi, C.; Hua, R. J Org Chem 2006, 71, 2535.
[26] Kabalka, G. W.; Wang, L.; Namboodiri, V.; Pagni, R. M. Tetrahedron Lett 2000, 41, 5151.
[27] BIhm, V. P. W.; Herrmann, W. A. Eur J Org Chem 2000 3679.
[28] Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. Org Lett 2000, 2, 1729.
[29] Yin, L.; Liebscher, J. Chem Rev 2007, 107, 133.