Synthesis of novel 1,4,5-trisubstituted 3-trifluoromethylpyrazoles via microwave-assisted Stille coupling reactions

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Abstract

1,5-Disubstituted 3-trifluoromethylpyrazoles were reacted with *N*-bromosuccinimide in DMF at room temperature or 70–80 °C for 1–2 h to afford the corresponding 4-bromo-substituted pyrazoles **2** in 95–99% yields. The microwave-assisted Stille coupling reactions of **2** with arylstannanes having a substituent on the benzene ring and allylstannane in refluxing CH_3CN in the presence of $Pd(PPh_3)_4$ provided the corresponding 1,4,5-trisubstituted 3-trifluoromethylpyrazoles **3** in 75–98% yields.
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Keywords: Bromination; 1,5-Disubstituted 3-trifluoromethylpyrazoles; Arylstannanes; Allystannane; Microwave-assisted Stille coupling reactions; 1,4,5-Trisubstituted 3-trifluoromethylpyrazoles

1. Introduction

The pyrazole ring has been known as an important framework in a large number of compounds possessing pharmaceutical and agrochemical properties [1–6]. Numerous methods for the synthesis of this family of compounds have been well documented in the previous literatures [7–15], but methods are mostly related to the synthesis of nonfluorinated pyrazoles. However, to our knowledge, there have been limited methodologies for the preparation of trifluoromethylated pyrazoles. Since the introduction of a trifluoromethyl group into the pyrazole ring system has often increased the biological properties [16,17], many efforts have been devoted to the development of synthetic methodologies for the preparation of trifluoromethylated pyrazoles. General methods for the preparation of these compounds involve the reactions of hydrazine derivatives with trifluoromethylated precursors such as 1-trifluoromethylated 1,3-diketones [16,18,19], trifluoro-methylacetylenic esters [20], pentafluoroethylacetylenes [21], trifluoroacetyl acetylenes [22], β-alkoxyvinyl trifluoromethyl ketones [23,24], β-trifluoromethyl enaminones [25,26], *N*-aryl-

1-trifluoromethyl acetylenic imines [27] and 1-pentafluoro-ethyl-2-iodoalkenes [28,29]. 1,3-Dipolar cycloaddition reaction of 2-bromo-3,3,3-trifluoropropene with diazomethane followed by dehydration also afforded the corresponding 3-trifluoromethylpyrazole [30]. Recently, a direct preparation of 5-tributylstannyl-4-trifluoromethylpyrazole was accomplished by 1,3-dipolar cycloaddition reaction of tributyl(3,3,3-trifluoro-1-propynyl)stannane with diazomethane [31,32]. Dipolarophiles such as phenylacetylene, vinylsulfone and 2-bromoacrylate were also reacted with trifluoroacetyl-triphenylsilane 2,4,6-triisopropylbenzenesulfonyl hydrazone to give the corresponding 3-trifluoromethylpyrazoles [33]. However, the most of these methods focused on the preparation of mono- and disubstituted trifluoromethylpyrazole derivatives. In spite of importance of trisubstituted trifluoromethylpyrazole in recent years, the methods for the preparation of trisubstituted trifluoromethylpyrazoles have been quite limited in the previous literatures [16,34–36]. Moreover, these methods have some drawbacks such as a lack of generality and uneasy availability of starting materials. Herein, we wish to report a novel and general approach to 1,4,5-trisubstituted 3-trifluor-omethylpyrazoles via the microwave-assisted Stille coupling reactions of the corresponding 1,5-disubstituted 4-bromo-3-trifluoromethylpyrazoles with arylstannanes or allylstannane in the presence of palladium catalyst.

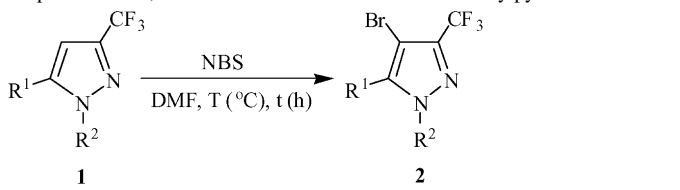* Corresponding author. Tel.: +82 33 760 2240; fax: +82 33 763 4323.
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2. Results and discussion

The starting materials, 1,5-disubstituted 3-trifluoromethyl-pyrazoles **1a–f**, were prepared in 92–98% isolated yields from the condensation reaction of 1-trifluoromethylated 1,3-dicarbonyl compounds with hydrazine derivatives in 1,4-dioxane, except for methylhydrazine, followed by dehydration reaction in refluxing toluene. Small quantities of undesired regioisomer, 1,3-disubstituted 5-trifluoromethylpyrazoles, were separated by column chromatographic purification. A recent study has established that this high regioselectivity was due to electron-withdrawing group such as CF$_3$ on C-1 of 1,3-dicarbonyl compounds [37]. In order to install the aryl or allyl substituent onto the 4-position of fully assembled pyrazoles **1**, we chose to explore a carbon–carbon bond-forming reaction in the presence of transition-metal catalysis. Therefore, we carried out the bromination reaction with the corresponding bromo succinimide to introduce a bromo substituent as a reacting site of the coupling reaction. We found 1,5-disubstituted 4-bromo-3-trifluoromethylpyrazoles **2a–g** were prepared in 95–99% isolated yields from the reaction of **1** with N-bromosuccinimide in DMF at room temperature or 70–80 °C. The results of these reactions were summarized in Table 1. The use of other solvents such as CH$_2$Cl$_2$, CCl$_4$ or CH$_3$CN in this bromination reaction caused not only to retard the reaction, but also to decrease the yield of **2**. The previous method using sodium acetate and bromine did not provide a satisfied result for the formation of **2** [38].
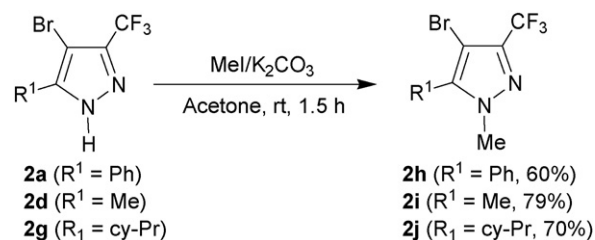
Since 5-substituted 3-trifluoromethyl-1-methylpyrazoles were not directly synthesized from the reaction of 1-trifluoromethylated 1,3-dicarbonyl compounds with methyl-hydrizine, 5-substituted 4-bromo-3-trifluoromethyl-1-methyl-pyrazoles **2h–j** were prepared regiospecifically from the methylation reaction of **2a**, **2d** and **2g** with methyl iodide in the presence of K$_2$CO$_3$ (Scheme 1). The assignment of regioisomers **2h–j** was based on ^{1}H NMR chemical shifts. The ^{1}H NMR spectrum of **2h–j** showed that the peaks of N-methyl protons appeared at $\delta = 3.84$–3.95 ppm which is consistent with the range of chemical shift of a similar structure, 4-substituted

Table 1
Preparation of 1,5-disubstituted 4-bromo-3-trifluoromethylpyrazoles **2**

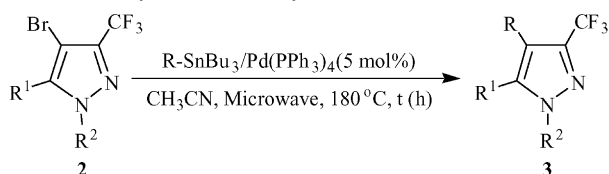| Compound no.	R^1	R^2	T (°C)	t (h)	Yield (%)[a]
2a	Ph	H	70–80	2	96
2b	Ph	PhCH$_2$	70–80	2	98
2c	Ph	Ph	70–80	2	99
2d	Me	H	25	1	99
2e	Me	PhCH$_2$	25	1	95
2f	cy-Pr	Ph	25	1	98
2g	cy-Pr	H	25	1	99

[a] Isolated yield.

Scheme 1.

3-trifluoromethyl-1-methylpyrazoles [39]. The resonance of N-methyl protons of regioisomer, 4-substituted 5-trifluoro-methyl-1-methylpyrazoles, appeared at $\delta = 4.07$–4.11 ppm. Regiospecificity on N-methylation of **2a**, **2d** and **2g** to give 5-substituted 4-bromo-3-trifluoromethyl-1-methylpyrazole **2h–j** can be explained by the steric effect of trifluoromethyl group in the formation of regioisomer, 3-substituted 4-bromo-5-trifluoromethyl-1-methylpyrazole. A similar result was established in the formation of 1-methyl-3-trimethylsilylpyr-azole and 1-methyl-3,4-bis(trimethylsilyl)pyrazole [40].

Although several previous literature reports described the coupling reactions, such as Suzuki, Stille, and Sonogashira couplings, performed on nonfluorinated 5-bromopyrazoles [10,41] and pyrazole triflates [42], there has been only one example (Sonogashira reaction) in the coupling reactions on trifluoromethylated halopyrazoles [38]. Among the coupling reactions, we investigated Stille coupling reaction of **2** with arylstannane or allylstannane. We carried out the cross-coupling reaction of **2c** with phenylstannane as a standard reaction to find out an optimized reaction condition. When **2c** was reacted with phenylstannane in the presence of Pd(PPh$_3$)$_4$ (5 mol%) at refluxing CH$_3$CN for 24 h, the cross-coupled product **3a** was obtained in 76% isolated yield based on the only 15% conversion of the starting material. The use of DMF as a solvent under the same reaction condition caused to enhance the conversion of the starting material up to 40%, but reaction was still sluggish. Recently, we reported that microwave-assisted cross-coupling reaction of trifluoromethylated chlor-opyrimidines with arylstannanes afforded the corresponding coupled product in high yields [43]. We applied this reaction condition to explore the coupling reaction of **2** with arylstannane or allylstannane. It was found that microwave-assisted coupling reaction of **2c** with phenylstannane in CH$_3$CN at 180 °C for 1 h afforded the coupled product **3a** in 97% isolated yield based on the 100% conversion of **2c**. The arylstannane having a substituent on the benzene ring and allylstannane also underwent the coupling reactions with **2c** to give **3b–e** in 92–98% isolated yields under the same reaction condition. The reactions between **2b** and arylstannane also afforded the corresponding coupled products **3f–i** in 91–92% isolated yields, but the reactions were more sluggish than that of **2c** with phenylstannane and a prolong reaction time (1.5 h) was required. A small amount of reduced product was obtained in less than 5% yield for each case. The reaction of **2b** with allylstannane under the same reaction condition afforded the corresponding coupled product **3j** in 97% isolated yield. Similarly, **2g** underwent the coupling reaction with

Table 2
The coupling reactions of 1,5-disubstituted 4-bromo-3-trifluoromethylpyrazoles **2** with arylstannanes or allystannane

$$R\text{-SnBu}_3/\text{Pd(PPh}_3)_4\,(5\,\text{mol}\%) \quad \xrightarrow{\text{CH}_3\text{CN, Microwave, } 180\,^\circ\text{C, } t\,(\text{h})}$$

Compound no.	R^1	R^2	R	t (h)	Yield (%)[a]
3a	Ph	Ph	C_6H_5	1	97
3b	Ph	Ph	p-MeO–C_6H_4	1	96
3c	Ph	Ph	p-F–C_6H_4	1	98
3d	Ph	Ph	p-CF$_3$–C_6H_4	1	92
3e	Ph	Ph	CH_2=CH–CH_2	1	97
3f	Ph	Bn	C_6H_5	1.5	92
3g	Ph	Bn	p-MeO–C_6H_4	1.5	92
3h	Ph	Bn	p-F–C_6H_4	1.5	91
3i	Ph	Bn	p-CF$_3$–C_6H_4	1.5	92
3j	Ph	Bn	CH_2=CH–CH_2	1.5	97
3k	Ph	Me	C_6H_5	1.5	81
3l	Ph	Me	p-MeO–C_6H_4	1.5	82
3m	Ph	Me	p-F–C_6H_4	1.5	84
3n	Ph	Me	p-CF$_3$–C_6H_4	1.5	82
3o	Ph	Me	CH_2=CH–CH_2	1.5	90
3p	cy-Pr	Ph	C_6H_5	2.5	91
3q	cy-Pr	Ph	CH_2=CH–CH_2	2.5	93
3r	cy-Pr	Me	C_6H_5	2.5	75
3s	cy-Pr	Me	CH_2=CH–CH_2	2.5	80

[a] Isolated yield.

arylstannanes or allylstannane to give the coupled products **3k–o** in 81–90% isolated yields. The coupling reactions of 5-cyclopropyl substituted pyrazole derivative **2f** with phenylstannane or allylstannane were much sluggish under the same reaction condition and a prolong reaction time (2.5 h) was required. The results of these coupling reactions were summarized in Table 2.

3. Conclusion

In conclusion, we synthesized 1,4,5-trisubstituted 3-trifluoromethylpyrazoles in excellent yields via the microwave-assisted Stille coupling reactions of 1,5-disubstituted 4-bromo-3-trifluoromethylpyrazoles with arylstannane or allylstannane in the presence of Pd(PPh$_3$)$_4$ catalyst. 1,5-Disubstituted 4-bromo-3-trifluoromethylpyrazoles were easily prepared by bromination of 1,5-disubstituted 3-trifluoromethylpyrazoles with NBS. The present method provided an efficient and facile approach to novel 1,4,5-trisubstituted 3-trifluoromethylpyrazoles.

4. Experimental

^{1}H NMR spectra were recorded on a 200 MHz Gemini-200 NMR spectrometer and ^{19}F NMR spectra were recorded on a 100 MHz Bruker AC-100F NMR spectrometer with tetramethylsilane (TMS) and CFCl$_3$ as an internal standard, respectively and the upfield as negative. All chemical shifts (δ) are expressed in parts per million and coupling constant (J) are given in Hertz. Infrared spectra were determined on a

Mattson Genesis series FT High Resolution Spectrophotometer. Mass spectra were obtained by using GC/MS-Qp1000-Shimadzu (EI, 70 eV). Microwave-assisted coupling reactions were carried by using Biotage Microwave Organic Synthesizer. Melting points were determined in open capillary tubes and are uncorrected.

Commercially available reagents were purchased from Aldrich, Lancaster, Tokyo Kasei and Fluorochem. All solvents were dried by general purification method. Flash chromatography was performed on 40–60 μm silica gel (230–400 mesh).

4.1. General procedure for the preparation of 4-brominated pyrazoles 2a–2g

A 50 mL two-neck round bottom flask equipped with a magnetic stirrer bar, a septum and reflux condenser connected to an argon source was charged with 3-trifluoromethylated pyrazoles **1** (2.0 mmol), NBS (4.0 mmol) and 10 mL of DMF. After the reaction mixture was stirred at room temperature for 1 h or heated at 70–80 °C for 2 h, the reaction mixture was quenched with water. The reaction mixture was extracted with methylene chloride twice, dried over anhydrous MgSO$_4$ and chromatographed on SiO$_2$ column. Elution with a mixture of hexane and ethyl acetate (9:1) provided 4-brominated pyrazoles **2a–2g**.

4.1.1. 4-Bromo-3-trifluoromethyl-5-phenylpyrazole (2a)

2a was prepared in 96% yield (0.559 g) according to the general procedure (the reaction mixture was heated at 70–80 °C for 2 h). **2a**: mp 173–175 °C; ^{1}H NMR (CDCl$_3$) δ 11.06 (bs, 1H), 7.69–7.50 (m, 5H); ^{19}F NMR (CDCl$_3$, internal standard CFCl$_3$) δ −63.22 (s, 3F); MS, m/z (relative intensity) 292 ($M^+ + 1$, 52), 290 ($M^+ - 1$, 53), 182 (12), 163 (31), 142 (100), 133 (35), 89 (19), 77 (30). Anal. Calcd for $C_{10}H_6BrF_3N_2$: C, 41.26; H, 2.08. Found: C, 41.10; H, 2.05.

4.1.2. 1-Benzyl-4-bromo-3-trifluoromethyl-5-phenylpyrazole (2b)

2b was prepared in 98% yield (0.747 g) according to the general procedure (the reaction mixture was heated at 70–80 °C for 2 h). **2b**: oil; ^{1}H NMR (CDCl$_3$) δ 7.50–7.44 (m, 3H), 7.27–7.23 (m, 5H), 7.00–6.97 (m, 2H), 5.28 (s, 2H); ^{19}F NMR (CDCl$_3$, internal standard CFCl$_3$) δ −62.65 (s, 3F); MS, m/z (relative intensity) 382 ($M^+ + 1$, 10), 380 ($M^+ - 1$, 11), 91 (100), 65 (17). Anal. Calcd for $C_{17}H_{12}BrF_3N_2$: C, 53.57; H, 3.17. Found: C, 53.43; H, 3.12.

4.1.3. 4-Bromo-3-trifluoromethyl-1,5-diphenylpyrazole (2c)

2c was prepared in 99% yield (0.727 g) according to the general procedure (the reaction mixture was heated at 70–80 °C for 2 h). **2c**: mp 102–104 °C; ^{1}H NMR (CDCl$_3$) δ 7.43–7.20 (m, 10H); ^{19}F NMR (CDCl$_3$, internal standard CFCl$_3$) δ −62.92 (s, 3F); MS, m/z (relative intensity) 368 ($M^+ + 1$, 64), 366 ($M^+ - 1$, 66), 347 (24), 286 (23), 218 (13), 120 (24), 89 (23), 77 (100). Anal. Calcd for $C_{16}H_{10}BrF_3N_2$: C, 52.34; H, 2.75. Found: C, 52.11; H, 2.70.

4.1.4. 4-Bromo-3-trifluoromethyl-5-methylpyrazole (2d)

2d was prepared in 99% yield (0.453 g) according to the general procedure (the reaction mixture was stirred at room temperature for 1 h). **2d**: mp 89–90 °C; ^{1}H NMR (CDCl$_3$) δ 11.88 (bs, 1H), 2.33 (s, 3H); ^{19}F NMR (CDCl$_3$, internal standard CFCl$_3$) δ −63.15 (s, 3F); MS, m/z (relative intensity) 230 ($M^+ + 1$, 14), 228 ($M^+ − 1$, 15), 211 (4), 149 (19), 101 (69), 69 (100). Anal. Calcd for C$_5$H$_4$BrF$_3$N$_2$: C, 26.22; H, 1.76. Found: C, 26.18; H, 1.74.

4.1.5. 1-Benzyl-4-bromo-3-trifluoromethyl-5-methylpyrazole (2e)

2e was prepared in 95% yield (0.606 g) according to the general procedure (the reaction mixture was stirred at room temperature for 1 h). **2e**: oil; ^{1}H NMR (CDCl$_3$) δ 7.38–7.30 (m, 3H), 7.15–7.11 (m, 2H), 5.34 (s, 2H), 2.19 (s, 3H); ^{19}F NMR (CDCl$_3$, internal standard CFCl$_3$) δ −63.29 (s, 3F); MS, m/z (relative intensity) 320 ($M^+ + 1$, 14), 318 ($M^+ − 1$, 13), 305 (10), 249 (7), 149 (5), 91 (100), 65 (19). Anal. Calcd for C$_{12}$H$_{10}$BrF$_3$N$_2$: C, 45.16; H, 3.16. Found: C, 44.99; H, 3.11.

4.1.6. 4-Bromo-5-cyclopropyl-3-trifluoromethyl-1-phenylpyrazole (2f)

2f was prepared in 98% yield (0.649 g) according to the general procedure (the reaction mixture was stirred at room temperature for 1 h). **2f**: oil; ^{1}H NMR (CDCl$_3$) δ 7.53–7.43 (m, 5H), 1.80–1.74 (m, 1H), 0.96–0.88 (m, 2H), 0.75–0.69 (m, 2H); ^{19}F NMR (CDCl$_3$, internal standard CFCl$_3$) δ −63.18 (s, 3F); MS, m/z (relative intensity) 332 ($M^+ + 1$, 8), 330 ($M^+ − 1$, 9), 295 (10), 236 (16), 128 (13), 77 (100). Anal. Calcd for C$_{13}$H$_{10}$BrF$_3$N$_2$: C, 47.15; H, 3.04. Found: C, 47.42; H, 2.99.

4.1.7. 4-Bromo-5-cyclopropyl-3-trifluoromethylpyrazole (2g)

2g was prepared in 99% yield (0.505 g) according to the general procedure (the reaction mixture was stirred at room temperature for 1 h). **2g**: mp 112–114 °C; ^{1}H NMR (CDCl$_3$) δ 11.88 (bs, 1H), 1.90–1.76 (m, 1H), 1.16–0.99 (m, 2H), 0.84–0.76 (m, 2H); ^{19}F NMR (CDCl$_3$, internal standard CFCl$_3$) δ −63.16 (s, 3F); MS, m/z (relative intensity) 256 ($M^+ + 1$, 17), 354 ($M^+ − 1$, 18), 155 (18), 105 (22), 69 (23), 40 (100). Anal. Calcd for C$_{17}$H$_6$BrF$_3$N$_2$: C, 32.97; H, 2.37. Found: C, 32.85; H, 2.34.

4.2. General procedure for the preparation of 4-brominated pyrazoles 2h–2j

A 50 mL two-neck round bottom flask equipped with a magnetic stirrer bar, a septum and reflux condenser connected to an argon source was charged with 3-trifluoromethylated 4-bromopyrazoles **2a**, **2d** or **2g** (1.5 mmol), K$_2$CO$_3$ (1.7 mmol) and 10 mL of dry Acetone. After the reaction mixture was stirred at room temperature for 1 h, CH$_3$I (2.0 mmol) was added into the reaction and then the reaction mixture was stirred at room temperature for 1.5 h. After removal of solvent, water was added. The reaction mixture was extracted with ethyl acetate twice, dried over anhydrous MgSO$_4$ and chromatographed on SiO$_2$ column. Elution with a mixture of hexane and ethyl acetate (9:1) provided 4-brominated pyrazoles **2h**–**2j**.

4.2.1. 4-Bromo-3-trifluoromethyl-1-methyl-5-phenylpyrazole (2h)

2h was prepared in 60% yield (0.275 g) according to the general procedure. **2h**: mp 66–67 °C; ^{1}H NMR (CDCl$_3$) δ 7.56–7.51 (m, 3H), 7.49–7.36 (m, 2H), 3.84 (s, 3H); ^{19}F NMR (CDCl$_3$, internal standard CFCl$_3$) δ −62.71 (s, 3F); MS, m/z (relative intensity) 306 ($M^+ + 1$, 28), 304 ($M^+ − 1$, 29), 223 (47), 153 (64), 127 (95), 104 (100), 77 (42). Anal. Calcd for C$_{11}$H$_8$BrF$_3$N$_2$: C, 43.30; H, 2.64. Found: C, 43.11; H, 2.69.

4.2.2. 4-Bromo-3-trifluoromethyl-1,5-dimethylpyrazole (2i)

2i was prepared in 79% yield (0.288 g) according to the general procedure. **2i**: mp 42–44 °C; ^{1}H NMR (CDCl$_3$) δ 3.85 (s, 3H), 2.27 (s, 3H); ^{19}F NMR (CDCl$_3$, internal standard CFCl$_3$) δ −62.55 (s, 3F); MS, m/z (relative intensity) 244 ($M^+ + 1$, 25), 242 ($M^+ − 1$, 27), 223 (11), 163 (48), 99 (17), 69 (72), 56 (73), 43 (100). Anal. Calcd for C$_6$H$_6$BrF$_3$N$_2$: C, 29.65; H, 2.49. Found: C, 29.49; H, 2.51.

4.2.3. 4-Bromo-5-cyclopropyl-3-trifluoromethyl-1-methylpyrazole (2j)

2j was prepared in 70% yield (0.377 g) according to the general procedure. **2j**: oil; ^{1}H NMR (CDCl$_3$) δ 3.94 (s, 3H), 1.72–1.57 (m, 1H), 1.15–1.05 (m, 2H), 0.99–0.86 (m, 2H); ^{19}F NMR (CDCl$_3$, internal standard CFCl$_3$) δ −62.53 (s, 3F); MS, m/z (relative intensity) 270 ($M^+ + 1$, 92), 268 ($M^+ − 1$, 91), 169 (95), 91 (74), 58 (93), 44 (100). Anal. Calcd for C$_8$H$_8$BrF$_3$N$_2$: C, 35.71; H, 3.00. Found: C, 35.60; H, 2.95.

4.3. General procedure for the preparation of 1,4,5-trisubstituted 3-trifluoromethylpyrazoles 3a–3s

A 2 mL microwave reactor was charged with **2** (0.1 mmol), Pd(PPh$_3$)$_4$ (5 mol%) and 1.5 mL of dry CH$_3$CN. After bubbling with air gas, arylstannane or allylstannane (0.13 mmol) was added into the reactor. The reactor was heated at 180 °C for 1–2.5 h. After quenching with 10% KF solution at room temperature, the reaction mixture was extracted with CH$_2$Cl$_2$ twice. The CH$_2$Cl$_2$ solution was dried over anhydrous MgSO$_4$ and chromatographed on SiO$_2$ column. Elution with a mixture of hexane and ethyl acetate (9:1) provided **3a**–**3s**.

4.3.1. 3-Trifluoromethyl-1,4,5-triphenylpyrazole (3a)

3a was prepared in 97% yield (0.035 g) according to the general procedure (the reactor was heated at 180 °C for 1 h). **3a**: mp 159–161 °C; ^{1}H NMR (CDCl$_3$) δ 7.35–7.14 (m, 13H), 7.03–6.98 (m, 2H); ^{19}F NMR (CDCl$_3$, internal standard CFCl$_3$) δ −59.98 (s, 3F); MS, m/z (relative intensity) 364 (M^+, 22), 267 (10), 190 (12), 165 (12), 89 (11), 77 (100); IR (KBr) 3047, 2920, 1595, 1502, 1155, 1122, 755, 692 cm^{-1}. Anal. Calcd for C$_{22}$H$_{15}$F$_3$N$_2$: C, 72.52; H, 4.15. Found: C, 72.37; H, 4.09.

4.3.2. 3-Trifluoromethyl-4-(p-methoxy)phenyl-1,5-diphenylpyrazole (3b)

3b was prepared in 96% yield (0.038 g) according to the general procedure (the reactor was heated at 180 °C for 1 h). **3b**: mp 124–125 °C; ^{1}H NMR (CDCl$_3$) δ 7.31–7.11 (m, 10H), 7.03–6.98 (m, 2H), 6.84–6.80 (m, 2H), 3.79 (s, 3H); ^{19}F NMR (CDCl$_3$, internal standard CFCl$_3$) δ −60.05 (s, 3F); MS, m/z (relative intensity) 394 (M^+, 90), 379 (16), 254 (10), 152 (13), 77 (100); IR (KBr) 3064, 2935, 1614, 1520, 1252, 1153, 1126, 825, 747, 697 cm^{-1}. Anal. Calcd for C$_{23}$H$_{17}$F$_3$N$_2$O: C, 70.04; H, 4.34. Found: C, 70.23; H, 4.27.

4.3.3. 3-Trifluoromethyl-4-(p-fluoro)phenyl-1,5-diphenylpyrazole (3c)

3c was prepared in 98% yield (0.037 g) according to the general procedure (the reactor was heated at 180 °C for 1 h). **3c**: mp 161–162 °C; ^{1}H NMR (CDCl$_3$) δ 7.36–7.15 (m, 10H), 7.03–6.92 (m, 4H); ^{19}F NMR (CDCl$_3$, internal standard CFCl$_3$) δ −60.06 (s, 3F), −114.90 (s, 1F); MS, m/z (relative intensity) 382 (M^+, 25), 341 (11), 285 (9), 183 (9), 107 (10), 77 (100); IR (KBr) 3064, 2918, 1520, 1153, 1126, 817, 752, 691 cm^{-1}. Anal. Calcd for C$_{22}$H$_{14}$F$_4$N$_2$: C, 69.11; H, 3.69. Found: C, 69.33; H, 3.74.

4.3.4. 3-Trifluoromethyl-4-(p-trifluoromethyl)phenyl-1,5-diphenylpyrazole (3d)

3d was prepared in 92% yield (0.040 g) according to the general procedure (the reactor was heated at 180 °C for 1 h). **3d**: mp 121–123 °C; ^{1}H NMR (CDCl$_3$) δ 7.57–7.52 (m, 2H), 7.38–7.17 (m, 10H), 7.03–6.97 (m, 2H); ^{19}F NMR (CDCl$_3$, internal standard CFCl$_3$) δ −59.90 (s, 3F), −63.11 (s, 3F); MS, m/z (relative intensity) 432 (M^+, 100), 391 (10), 363 (9), 267 (8), 146 (15), 77 (91); IR (KBr) 3060, 2924, 1600, 1487, 1327, 1169, 1128, 809, 750, 689 cm^{-1}. Anal. Calcd for C$_{23}$H$_{14}$F$_6$N$_2$: C, 63.89; H, 3.26. Found: C, 63.67; H, 3.20.

4.3.5. 4-Allyl-3-trifluoromethyl-1,5-diphenylpyrazole (3e)

3e was prepared in 97% yield (0.032 g) according to the general procedure (the reactor was heated at 180 °C for 1 h). **3e**: oil; ^{1}H NMR (CDCl$_3$) δ 7.40–7.16 (m, 10H), 6.01–5.82 (m, 1H), 5.08–4.91 (m, 2H), 3.29 (d, J = 5.9 Hz, 2H); ^{19}F NMR (CDCl$_3$, internal standard CFCl$_3$) δ −61.51 (s, 3F); MS, m/z (relative intensity) 328 (M^+, 53), 313 (42), 259 (15), 115 (22), 77 (100); IR (neat) 3064, 2922, 1641, 1599, 1493, 1277, 1165, 1128, 991, 915, 755, 694 cm^{-1}. Anal. Calcd for C$_{19}$H$_{15}$F$_3$N$_2$: C, 69.50; H, 4.60. Found: C, 69.27; H, 4.53.

4.3.6. 1-Benzyl-3-trifluoromethyl-4,5-diphenylpyrazole (3f)

3f was prepared in 92% yield (0.035 g) according to the general procedure (the reactor was heated at 180 °C for 1.5 h). **3f**: oil; ^{1}H NMR (CDCl$_3$) δ 7.43–7.01 (m, 15H), 5.30 (s, 2H); ^{19}F NMR (CDCl$_3$, internal standard CFCl$_3$) δ −59.65 (s, 3F); MS, m/z (relative intensity) 378 (M^+, 15), 301 (5), 189 (5), 91 (100), 77 (5); IR (neat) 3064, 2922, 1454, 1223, 1182, 1134, 753, 696 cm^{-1}. Anal. Calcd for C$_{23}$H$_{17}$F$_3$N$_2$: C, 73.01; H, 4.53. Found: C, 72.78; H, 4.59.

4.3.7. 1-Benzyl-3-trifluoromethyl-4-(p-methoxy)phenyl-5-phenylpyrazole (3g)

3g was prepared in 92% yield (0.038 g) according to the general procedure (the reactor was heated at 180 °C for 1.5 h). **3g**: mp 74–76 °C; ^{1}H NMR (CDCl$_3$) δ 7.35–7.24 (m, 6H), 7.09–7.02 (m, 6H), 6.78–6.74 (m, 2H), 5.30 (s, 2H), 3.75 (s, 3H); ^{19}F NMR (CDCl$_3$, internal standard CFCl$_3$) δ −59.74 (s, 3F); MS, m/z (relative intensity) 408 (M^+, 29), 339 (5), 176 (3), 151 (3), 91 (100); IR (KBr) 3032, 2920, 1520, 1250, 1178, 1134, 820, 749, 694 cm^{-1}. Anal. Calcd for C$_{24}$H$_{19}$F$_3$N$_2$O: C, 70.58; H, 4.69. Found: C, 70.39; H, 4.64.

4.3.8. 1-Benzyl-3-trifluoromethyl-4-(p-fluoro)phenyl-5-phenylpyrazole (3h)

3h was prepared in 91% yield (0.036 g) according to the general procedure (the reactor was heated at 180 °C for 1.5 h). **3h**: oil; ^{1}H NMR (CDCl$_3$) δ 7.41–6.85 (m, 14H), 5.30 (s, 2H); ^{19}F NMR (CDCl$_3$, internal standard CFCl$_3$) δ −59.76 (s, 3F), −115.28 (s, 1F); MS, m/z (relative intensity) 396 (M^+, 44), 377 (4), 319 (8), 207 (4), 103 (3), 91 (100); IR (neat) 3043, 2920, 1520, 1225, 1157, 1134, 825, 749, 688 cm^{-1}. Anal. Calcd for C$_{23}$H$_{16}$F$_4$N$_2$: C, 69.69; H, 4.07. Found: C, 69.48; H, 4.02.

4.3.9. 1-Benzyl-3-trifluoromethyl-4-(p-trifluoromethyl)phenyl-5-phenylpyrazole (3i)

3i was prepared in 92% yield (0.041 g) according to the general procedure (the reactor was heated at 180 °C for 1.5 h). **3i**: oil; ^{1}H NMR (CDCl$_3$) δ 7.50–7.46 (m, 2H), 7.40–7.24 (m, 8H), 7.08–7.04 (m, 4H), 5.30 (s, 2H); ^{19}F NMR (CDCl$_3$, internal standard CFCl$_3$) δ −59.62 (s, 3F), −63.13 (s, 3F); MS, m/z (relative intensity) 446 (M^+, 11), 377 (7), 189 (6), 91 (100), 65 (3); IR (neat) 3039, 2922, 1454, 1325, 1126, 828, 748, 685 cm^{-1}. Anal. Calcd for C$_{24}$H$_{16}$F$_6$N$_2$: C, 64.58; H, 3.61. Found: C, 64.27; H, 3.55.

4.3.10. 4-Allyl-1-benzyl-3-trifluoromethyl-5-phenylpyrazole (3j)

3j was prepared in 97% yield (0.033 g) according to the general procedure (the reactor was heated at 180 °C for 1.5 h). **3j**: mp 62–63 °C; ^{1}H NMR (CDCl$_3$) δ 7.45–7.34 (m, 3H), 7.27–7.13 (m, 5H), 6.98–6.94 (m, 2H), 5.91–5.71 (m, 1H), 5.22 (s, 2H), 4.94 (d, J = 10.3 Hz, 1H), 4.83 (d, J = 16.8 Hz, 1H), 3.17 (d, J = 5.9 Hz, 2H); ^{19}F NMR (CDCl$_3$, internal standard CFCl$_3$) δ −61.27 (s, 3F); MS, m/z (relative intensity) 342 (M^+, 3), 251 (5), 183 (4), 91 (100), 65 (26); IR (KBr) 3081, 2922, 1641, 1495, 1454, 1275, 1149, 1126, 989, 909, 752, 690 cm^{-1}. Anal. Calcd for C$_{20}$H$_{17}$F$_3$N$_2$: C, 70.17; H, 5.00. Found: C, 69.89; H, 4.93.

4.3.11. 3-Trifluoromethyl-1-methyl-4,5-diphenylpyrazole (3k)

3k was prepared in 81% yield (0.025 g) according to the general procedure (the reactor was heated at 180 °C for 1.5 h). **3k**: mp 108–110 °C; ^{1}H NMR (CDCl$_3$) δ 7.40–7.34 (m, 4H), 7.27–7.12 (m, 6H), 3.87 (s, 3H); ^{19}F NMR (CDCl$_3$, internal standard CFCl$_3$) δ −59.76 (s, 3F); MS, m/z (relative intensity) 302 (M^+, 100), 287 (22), 233 (11), 140 (21); IR (KBr) 3072,

2922, 1477, 1173, 1124, 755, 698 cm^{-1}. Anal. Calcd for C$_{17}$H$_{13}$F$_3$N$_2$: C, 67.54; H, 4.33. Found: C, 67.80; H, 4.40.

4.3.12. 3-Trifluoromethyl-4-(p-methoxy)phenyl-1-methyl-5-phenylpyrazole (3l)

3l was prepared in 82% yield (0.027 g) according to the general procedure (the reactor was heated at 180 °C for 1.5 h). **3l**: mp 98–99 °C; ^{1}H NMR (CDCl$_3$) δ 7.39–7.35 (m, 3H), 7.22–7.17 (m, 2H), 7.09–7.03 (m, 2H), 6.81–6.75 (m, 2H), 3.85 (s, 3H), 3.76 (s, 3H); ^{19}F NMR (CDCl$_3$, internal standard CFCl$_3$) δ −59.84 (s, 3F); MS, m/z (relative intensity) 332 (M$^+$, 100), 317 (34), 269 (12), 205 (9), 148 (10), 76 (7); IR (KBr) 3064, 2927, 1522, 1250, 1171, 1124, 817, 745, 690 cm^{-1}. Anal. Calcd for C$_{18}$H$_{15}$F$_3$N$_2$O: C, 65.06; H, 4.55. Found: C, 64.88; H, 4.51.

4.3.13. 3-Trifluoromethyl-4-(p-fluoro)phenyl-1-methyl-5-phenylpyrazole (3m)

3m was prepared in 84% yield (0.027 g) according to the general procedure (the reactor was heated at 180 °C for 1.5 h). **3m**: oil; ^{1}H NMR (CDCl$_3$) δ 7.43–6.89 (m, 9H), 3.87 (s, 3H); ^{19}F NMR (CDCl$_3$, internal standard CFCl$_3$) δ −59.85 (s, 3F), −115.31 (s, 1F); MS, m/z (relative intensity) 320 (M$^+$, 100), 299 (17), 251 (8), 140 (11); IR (neat) 3062, 2920, 1522, 1323, 1174, 1140, 1134, 831, 747, 695 cm^{-1}. Anal. Calcd for C$_{17}$H$_{12}$F$_4$N$_2$: C, 63.75; H, 3.78. Found: C, 63.69; H, 3.75.

4.3.14. 3-Trifluoromethyl-4-(p-trifluoromethyl)phenyl-1-methyl-5-phenylpyrazole (3n)

3n was prepared in 82% yield (0.030 g) according to the general procedure (the reactor was heated at 180 °C for 1.5 h). **3n**: oil; ^{1}H NMR (CDCl$_3$) δ 7.52–7.16 (m, 9H), 3.87 (s, 3H); ^{19}F NMR (CDCl$_3$, internal standard CFCl$_3$) δ −59.71 (s, 3F), −63.12 (s, 3F); MS, m/z (relative intensity) 370 (M$^+$, 100), 349 (14), 301 (22), 281 (24), 165 (7), 118 (8), 77 (10); IR (neat) 3064, 2922, 1491, 1327, 1173, 1126, 809, 753, 692 cm^{-1}. Anal. Calcd for C$_{18}$H$_{12}$F$_6$N$_2$: C, 58.39; H, 3.27. Found: C, 58.51; H, 3.23.

4.3.15. 4-Allyl-3-trifluoromethyl-1-methyl-5-phenylpyrazole (3o)

3o was prepared in 90% yield (0.024 g) according to the general procedure (the reactor was heated at 180 °C for 1.5 h). **3o**: oil; ^{1}H NMR (CDCl$_3$) δ 7.55–7.45 (m, 3H), 7.39–7.28 (m, 2H), 5.83 (ddt, J = 17.2, 9.9, 6.2 Hz, 1H), 4.97 (d, J = 9.9 Hz, 1H), 4.86 (d, J = 17.2 Hz, 1H), 3.78 (s, 3H), 3.18 (d, J = 6.2 Hz, 2H); ^{19}F NMR (CDCl$_3$, internal standard CFCl$_3$) δ −61.34 (s, 3F); MS, m/z (relative intensity) 266 (M$^+$, 100), 251 (71), 231 (58), 197 (22), 115 (31), 77 (23); IR (neat) 3082, 2918, 1641, 1490, 1277, 1167, 1124, 979, 911, 755, 693 cm^{-1}. Anal. Calcd for C$_{14}$H$_{13}$F$_3$N$_2$: C, 63.15; H, 4.92. Found: C, 62.89; H, 4.86.

4.3.16. 5-Cyclopropyl-3-trifluoromethyl-1,4-diphenylpyrazole (3p)

3p was prepared in 91% yield (0.030 g) according to the general procedure (the reactor was heated at 180 °C for 2.5 h). **3p**: mp 78–80 °C; ^{1}H NMR (CDCl$_3$) δ 7.65–7.36 (m, 10H), 1.88–1.77 (m, 1H), 0.69–0.60 (m, 2H), 0.25–0.16 (m, 2H); ^{19}F NMR (CDCl$_3$, internal standard CFCl$_3$) δ −59.73 (s, 3F); MS, m/z (relative intensity) 328 (M$^+$, 59), 313 (29), 217 (13), 115 (26), 91 (23), 77 (100). Anal. Calcd for C$_{19}$H$_{15}$F$_3$N$_2$: C, 69.50; H, 4.60. Found: C, 69.23; H, 4.55.

4.3.17. 4-Allyl-5-cyclopropyl-3-trifluoromethyl-1-phenylpyrazole (3q)

3q was prepared in 93% yield (0.027 g) according to the general procedure (the reactor was heated at 180 °C for 2.5 h). **3q**: oil; ^{1}H NMR (CDCl$_3$) δ 7.56–7.36 (m, 5H), 6.04–5.85 (m, 1H), 5.08–4.98 (m, 2H), 3.42 (d, J = 6.0 Hz, 2H), 1.80–1.67 (m, 1H), 0.87–0.76 (m, 2H), 0.50–0.42 (m, 2H); ^{19}F NMR (CDCl$_3$, internal standard CFCl$_3$) δ −61.21 (s, 3F); MS, m/z (relative intensity) 292 (M$^+$, 13), 127 (11), 105 (13), 77 (44), 40 (100). Anal. Calcd for C$_{16}$H$_{15}$F$_3$N$_2$: C, 65.75; H, 5.17. Found: C, 65.48; H, 5.15.

4.3.18. 5-Cyclopropyl-3-trifluoromethyl-1-methyl-4-phenylpyrazole (3r)

3r was prepared in 75% yield (0.020 g) according to the general procedure (the reactor was heated at 180 °C for 2.5 h). **3r**: mp 65–66 °C; ^{1}H NMR (CDCl$_3$) δ 7.43–7.28 (m, 5H), 3.99 (s, 3H), 1.79–1.65 (m, 1H), 0.88–0.78 (m, 2H), 0.37–0.29 (m, 2H); ^{19}F NMR (CDCl$_3$, internal standard CFCl$_3$) δ −59.78 (s, 3F); MS, m/z (relative intensity) 266 (M$^+$, 100), 251 (40), 231 (72), 152 (24), 115 (40), 76 (33). Anal. Calcd for C$_{14}$H$_{13}$F$_3$N$_2$: C, 63.15; H, 4.92. Found: C, 62.91; H, 4.84.

4.3.19. 4-Allyl-5-cyclopropyl-3-trifluoromethyl-1-methylpyrazole (3s)

3s was prepared in 80% yield (0.019 g) according to the general procedure (the reactor was heated at 180 °C for 2.5 h). **3s**: oil; ^{1}H NMR (CDCl$_3$) δ 5.97–5.78 (m, 1H), 5.03–4.86 (m, 2H), 3.92 (s, 3H), 3.32 (d, J = 5.5 Hz, 2H), 1.66–1.52 (m, 1H), 1.06–0.95 (m, 2H), 0.75–0.67 (m, 2H); ^{19}F NMR (CDCl$_3$, internal standard CFCl$_3$) δ −61.24 (s, 3F); MS, m/z (relative intensity) 230 (M$^+$, 72), 189 (100), 120 (20), 69 (8). Anal. Calcd for C$_{11}$H$_{13}$F$_3$N$_2$: C, 57.39; H, 5.69. Found: C, 57.20; H, 5.72.

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