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Regioselective Synthesis of 5-Trifluoromethylpyrazoles by [3 + 2] Cycloaddition of Nitrile Imines and 2-Bromo-3,3,3-trifluoropropene

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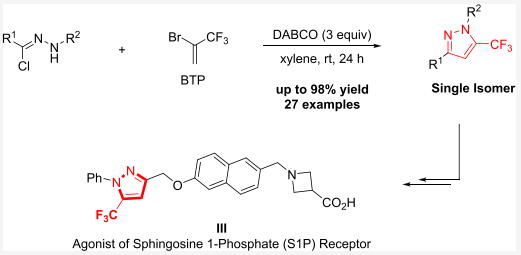
ABSTRACT: A general and practical method for the synthesis of 5-trifluoromethylpyrazoles is reported that occurs by the coupling of hydrazonyl chlorides with environmentally friendly and large-tonnage industrial feedstock 2-bromo-3,3,3-trifluoropropene (BTP). This exclusively regioselective [3 + 2] cycloaddition of nitrile imines and with BTP is catalyst-free and operationally simple and features mild conditions, high yields, gram-scalable, a broad substrate scope, and valuable functional group tolerance. Significantly, our method has been applied for the synthesis of the key intermediate of an active agonist of sphingosine 1-phosphate receptor.



INTRODUCTION

Compounds with a trifluoromethylpyrazole skeleton have been found with broad applications in many pharmaceutials, agrochemicals, and bioactive compounds.[1] For example, celecoxib and mavacoxib (COX-2 inhibitors),[2a,b] SC-560 (human lung cancer inhibitor),[2c] AS-136A (measles virus inhibitor),[2d] DPC-602 (arterial thrombosis),[2e] Razaxaban (anticoagulant),[2f] and DP-23 (insecticidal activity)[2g] have a 3-trifluoromethylpyrazole core. Fluazolate (herbicide),[3a] compound **I** (soluble epoxide hydrolase inhibitor),[3b] compound **II** (store operated calcium entry modulator),[3c] and compound **III** (active agonist of sphingosine 1-phosphate (S1P) receptor)[3d] feature a 5-trifluoromethylpyrazole skeleton (Figure 1). Traditionally, the dehydrative condensation between hydrazines and 1,3-dicarbonyl compounds could lead to the formation of trifluoromethylpyrazole frameworks. However, this strategy suffers from the formation of regioisomeric mixtures of both 3- and 5-trifluoromethylpyrazole isomers.[4] Although considerable progress has been achieved on the regioselective synthesis of 3-trifluoromethylpyrazoles,[5] in sharp contrast, the methods for the regioselective construction of 5-trifluoromethylpyrazoles are still underdeveloped. The early study for the regioselective synthesis of 5-trifluoromethylpyrazoles was documented by Harrity via a [3 + 2] cycloaddition of 4-trifluoromethylsydnones and alkynes, which needed a six-step synthesis for the preparation of the starting material 4-trifluoromethylsydnones and suffered from high reaction temperature (140 or 180 °C), long reaction time, and also with the generation of two regioisomers (Scheme 1, a).[6a] Later, the groups of Hsieh[6b] and Nenajdenko[6c] independently reported the elegant one pot, two-step protocols for the regioselective synthesis of 5-trifluoromethylpyrazoles by the [3 + 2] dehydrative condensation of trifluoromethylated ynones and hydrazines (Scheme 1, b). However, the corresponding 3-trifluoromethylpyrazole isomer was still unavoidably generated during the transformation. In this context, the development of efficient methods for the regioselective construction of 5-trifluoromethylpyrazoles from simple raw materials is always highly demanded.

2-Bromo-3,3,3-trifluoropropene (BTP) is an environmentally benign and large-tonnage industry feedstock, which is a stable liquid at room temperature. Especially, it is not recognized as an ozone depletion molecule and is supposed to be an attractive alternative to halon fire suppressants[7] as well as a useful and attractive raw material in synthetic chemistry.[5h,8] Recently, we utilized it as a C2 synthon in the regioselective synthesis of 3-trifluoromethylpyrazoles (Scheme 1, c).[5h] Inspired by it, we envision that the regioselective [3 + 2] cycloaddition of a C1N2 synthon with BTP might become a straightforward and efficient method for the synthesis of 5-trifluoromethylpyrazoles. Nitrile imines, generally *in situ* generated by a base-induced dehydrodechlorination of hydrazonyl chlorides,[9] could serve as the attractive C1N2 synthons in [3 + 2] cycloaddition reactions;[10] however, their [3 + 2] cycloaddition reactions with alkenes usually give pyrazoline derivatives as the products.[10f−h] As our recent interest in exploiting the synthetic application of BTP,[5h] as well as our continuous effort in the synthesis of trifluoromethylated compounds,[11] herein we report the exclusively regioselective [3 + 2] cycloaddition reaction of nitrile imines with BTP under mild conditions, delivering various 5-trifluoromethylpyrazoles in high yields (Scheme 1, d).

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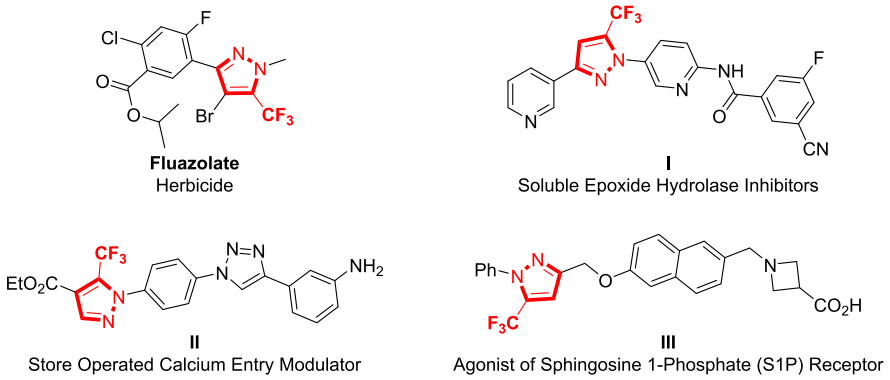
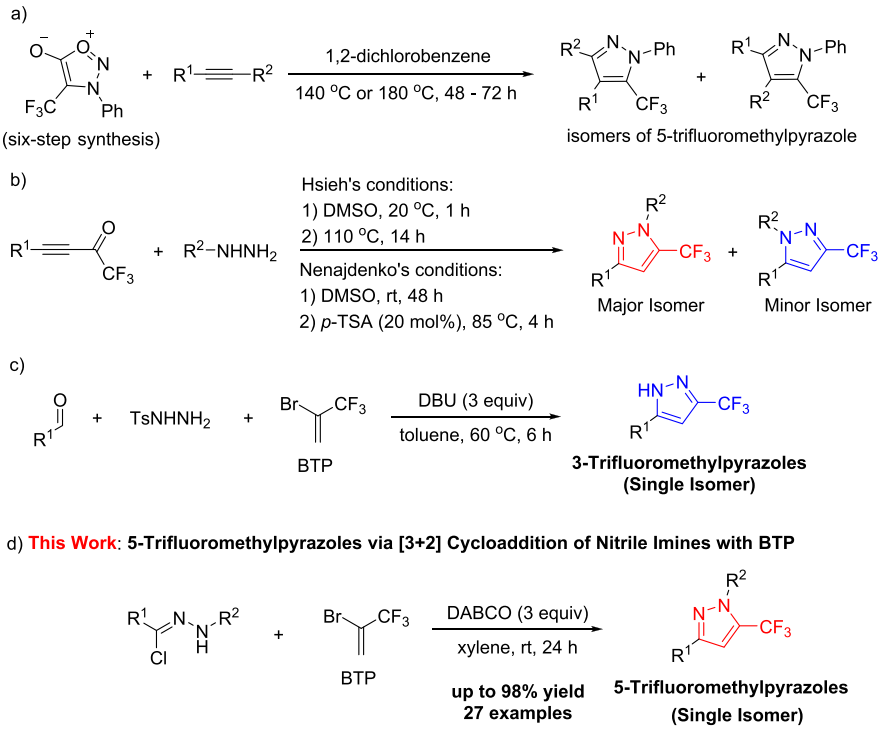


Figure 1. Selected examples of bioactive 5-trifluoromethylpyrazole derivatives.

Scheme 1. Background and Reaction Design for Regioselective Synthesis of 5-Trifluoromethylpyrazoles



RESULTS AND DISCUSSION

By using hydrazonyl chloride **1a** as the precursor of the nitrile imine, the initial experiment was carried out with **1a** and BTP in the presence of Cs_2CO_3 in toluene at room temperature (Table 1, entry 1). We are delighted that this regioselective [3 + 2] cycloaddition reaction could give the desired product **2a** in 72% isolated yield. Next, different types of inorganic bases such as K_2CO_3, Na_2CO_3, Li_2CO_3, *t*-BuOLi, *t*-BuOK, and MeONa and organic bases such as Et_3N, DABCO (triethylenediamine), and DBU (1,8-diazabicyclo[5.4.0]-undec-7-ene) were screened (Table 1, entries 2−10). A base of DABCO gave product **2a** in 93% yield. Owing to the failure to generate the reactive nitrile imine from its precursor **1a**, no reaction happened in the absence of a base (Table 1, entry 11). Furthermore, different types of solvents were investigated (Table 1, entries 12−19). A solvent of xylene further enhanced the isolated yield of **2a** to 98%, which might be related to the efficient generation and the stability of the nitrile imine intermediate in low-polar aprotic solvent. In addition, performing the reaction in anhydrous xylene under N_2 did not further improve the yield of **2a** (Table 1, entry 20). Remarkably, no other regioselective isomers were detected under all these conditions.

With the optimized reaction conditions in hand, we then examined the scope of hydrazonyl chlorides **1** (Scheme 2). Generally, this reaction could tolerate a broad scope of hydrazonyl chlorides bearing different R^1 substituents, delivering products **2a−2v** in high to excellent yields with exclusive regioselectivity. Regardless of the electronic properties (electron-neutral, electron-donating, and electron-withdrawing) of the substituents on the phenyl ring, the corresponding products **2a−2p** were isolated in high to excellent yields (71−98%). Valuable functional groups such as alkyl, alkoxyl, fluoro, chloro, bromo, iodo, trifluoromethyl, and cyano at *para*-, *meta*-, and *ortho*-positions of the phenyl ring could be well tolerated, providing ample potential for further synthetic applications of the products. Significantly, product **2a** proved to be crystalline; thus its structure was further confirmed by X-ray crystallographic analysis.[12] Symmetric 5-trifluoromethyl pyrazole **2q** derived from the corresponding

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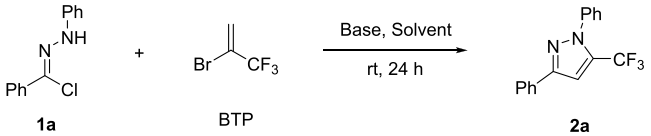
J. Org. Chem. 2021, 86, 2810−2819

Table 1. Optimization of the Reaction Conditions[a]



entry	base	solvent	yield (%)[b]
1	Cs_2CO_3	toluene	72
2	K_2CO_3	toluene	69
3	Na_2CO_3	toluene	<10
4	Li_2CO_3	toluene	0
5	*t*-BuOLi	toluene	<10
6	*t*-BuOK	toluene	<10
7	MeONa	toluene	16
8	Et_3N	toluene	90
9	DABCO	toluene	93
10	DBU	toluene	0
11		toluene	0
12	DABCO	xylene	98
13	DABCO	DCE	14
14	DABCO	MeCN	35
15	DABCO	1,4-dioxane	19
16	DABCO	THF	70
17	DABCO	DMF	30
18	DABCO	DMSO	<10
19	DABCO	EtOH	20
20[c]	DABCO	xylene	98

[a]Unless otherwise noted, all reactions were carried out with **1a** (1 mmol), BTP (2 mmol), base (3 mmol), and solvent (10 mL) in a 25 mL test tube at room temperature for 24 h. [b]Isolated yields. [c]Under N_2 with anhydrous xylene.

symmetric hydrazonyl chloride was obtained in 85% yield. Hydrazonyl chloride derived from *α,β*-unsaturated (*S*)-perillaldehyde afforded product **2r** in 87% yield. Heteroaromatic hydrazonyl chlorides such as thienyl-, and furanyl hydrazonyl chlorides were also found to be good substrates and delivered products **2s** and **2t** in high yields. Ethyl 2-oxoacetate derived hydrazonyl chloride also gave the desired product **2u** in 90% yield. Additionally, different R^2-substituted hydrazonyl chlorides also worked well to give the 5-trifluoromethyl pyrazole products **2v**−**2x**.

Hydrazonyl chlorides **1** with an alkyl R^1 substitutent are quite unstable and have usually been found to be more difficult to synthesize, isolate, and store in the laboratory. Then, a one pot, two-step procedure was developed for the synthesis of the corresponding 5-trifluoromethyl pyrazole products by directly using hydrazones **3** as the reactant (Scheme 3). Gratifyingly, hydrazones **3** derived from tertiary, secondary, and primary aliphatic aldehydes were all found to be suitable substrates in this one pot, two-step procedure to afford products **2y**−**2aa** in moderate to high yields. Additionally, hydrazone **3d** derived from benzaldehyde also delivered **2a** in 83% yield under these one pot, two-step procedure conditions.

Intrigued by this unique [3 + 2] cyclization reaction, a 10 mmol scale experiment was performed with **1u** and BTP as the reaction partners, delivering the corresponding product **2u** in 87% yield (2.471 g) (Scheme 4). Further reduction of **2u** gave alcohol product **4** in 85% yield. Bromination of the alcohol **4** in the presence of PBr_3 afforded the brominated compound **5** in 75% yield, which was a key intermediate for the synthesis of an active agonist of sphingosine 1-phosphate receptor.[3d]

On the basis of the previous literatures,[9,10] the possible reaction mechanism is illustrated in Scheme 5. Dehydrodechlorination of hydrazonyl chloride **1a** in the presence of the base afforded the reactive nitrile imine intermediates with two resonance forms as **A** and **A′**, of which **A′** underwent the regioselective [3 + 2] cycloaddition with BTP to give the pyrazoline intermediate **B**. The subsequent aromatization of intermediate **B** via HBr elimination under basic conditions delivered the desired 5-trifluoromethylpyrazole product **2a**.[3]

CONCLUSION

In summary, we have reported a general and practical method for the synthesis of 5-trifluoromethylpyrazoles by the coupling of hydrazonyl chlorides with environmentally friendly and large-tonnage industrial feedstock 2-bromo-3,3,3-trifluoropropene (BTP). This exclusively regioselective [3 + 2] cycloaddition of nitrile imines and with BTP is catalyst-free and operationally simple and features mild conditions, high yields, gram-scalable, a broad substrate scope, and valuable functional group tolerance. Significantly, our method has been applied for the synthesis of the key intermediate of an active agonist of sphingosine 1-phosphate (S1P) receptor.

EXPERIMENTAL SECTION

General Information. Toluene and THF were distilled from sodium/benzophenone, 1,2-dichloroethane (DCE) was distilled from calcium hydride, and acetonitrile (MeCN) was distilled from phosphorus pentoxide. Other commercially available reagents were purchased and used without further purification. Analytical thin-layer chromatography was performed on 0.20 mm silica gel plates (GF_{254}) using UV light as a visualizing agent. Flash column chromatography was carried out using silica gel (200−300 mesh) with the indicated solvent system. All reactions were conducted in oven-dried test tubes. All the reaction temperatures reported are oil bath temperatures. Melting points were measured using a melting point instrument and are uncorrected. Chemical shifts were reported in ppm from the solvent resonance as the internal standard ($CDCl_3$ δ_H = 7.26 ppm, δ_C = 77.16 ppm). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Coupling constants were reported in hertz (Hz). IR spectra were obtained with an infrared spectrometer on either potassium bromide pellets or liquid films between two potassium bromide pellets. HRMS was carried out on a high-resolution mass spectrometer (LCMS-IT-TOF). X-ray structural analyses were conducted on a Bruker APEX-II CCD diffractometer. TLC was performed using commercially available 100−400 mesh silica gel plates (GF_{254}). These known compounds **1a**,[10c] **1b**,[10c] **1c**,[10c] **1d**,[10e] **1e**,[10c] **1f**,[10c] **1g**,[10c] **1h**,[10e] **1i**,[13a] **1j**,[10c] **1k**,[10h] **1l**,[10c] **1m**,[13b] **1n**,[10h] **1o**,[13c] **1p**,[13d] **1q**,[13e] **1s**,[13f] **1t**,[13g] **1u**,[10c] **1v**,[10g] **1w**,[10e] **1x**,[10e] **3a**,[13h] **3b**,[13i] **3c**,[13h] and **3d**[13i] were synthesized according to the reported literatures.

Procedure for the Synthesis of Hydrazonyl Chloride 1r. An oven-dried clean round-bottom flask equipped with a magnetic stirring bar, (*S*)-(−)-perillaldehyde (750.0 mg, 5.0 mmol), phenylhydrazine (540.0 mg, 5.0 mmol), and MeOH (15 mL) was vigorously stirred at 60 °C for 4 h. Then the mixture was stopped stirring, water was added (15 mL), and the mixture was extracted with EtOAc (20 mL × 3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to obtain crude product. The crude was added into the suspension of TCCA (trichloroisocyanuric acid, 0.8 equiv), CH_2Cl_2 (20 mL), and dimethyl sulfide (2.4 equiv) at 0 °C, and then the mixture was vigorously stirred at room temperature for 1 h. Then the mixture was stopped stirring, water was added (20 mL), and the mixture was extracted with EtOAc (20 mL × 3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Further purification by flash column chromatography on silica gel (eluting with petroleum ether/

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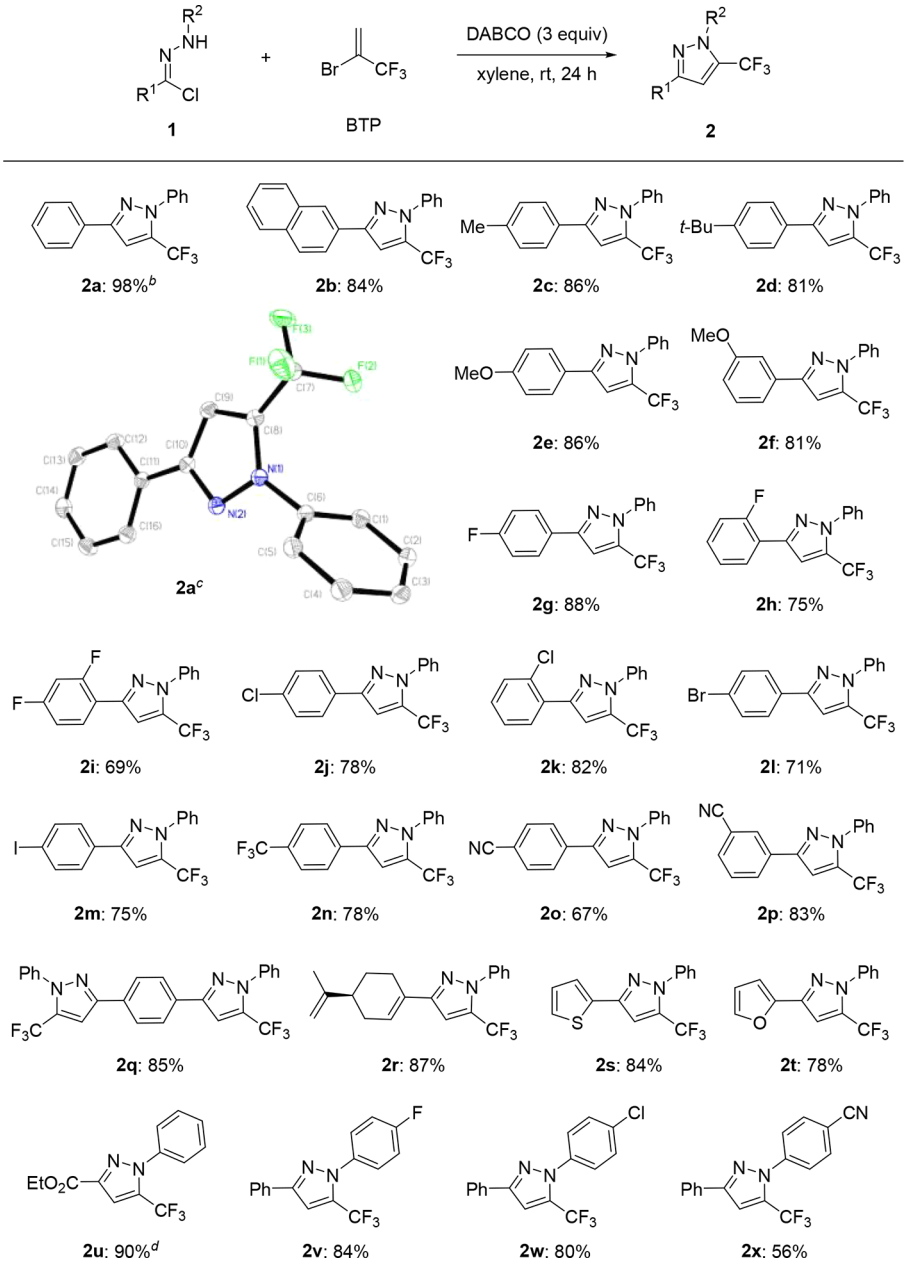
J. Org. Chem. 2021, 86, 2810−2819

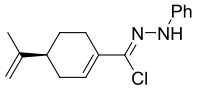
Scheme 2. Scope of Hydrazonyl Chlorides[a]



[a]Unless otherwise noticed, the reaction conditions were: hydrazonyl chlorides **1** (1 mmol), BTP (2 mmol), DABCO (3 mmol), and xylene (10 mL) in a 25 mL test tube at room temperature for 24 h. [b]Isolated yield. [c]ORTEP representation with 50% probability thermal ellipsoids of a crystal structure of **2a**; H atoms were omitted for clarity. [d]At 90 °C.

ethyl acetate = 30:1) provided the product **1r** in 52% isolated yield (719.7 mg).

*(S,Z)-N-Phenyl-4-(prop-1-en-2-yl)cyclohex-1-ene-1-carbohydrazonoyl Chloride (**1r**).*



719.7 mg, 52%, brown solid, mp: 110−111 °C; eluting with petroleum ether/ethyl acetate = 30:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.26−7.29 (m, 2H), 7.06−7.08 (m, 2H), 6.87−6.91 (m, 1H), 6.47 (s, 1H), 4.77 (d, J = 9.5 Hz, 2H), 2.76 (d, J = 17.0 Hz, 1H), 2.36−2.44 (m, 2H), 2.12−2.24 (m, 2H), 1.93 (d, J = 13.0 Hz, 1H), 1.77 (s, 3H), 1.50−1.58 (m, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 149.2, 143.7, 132.7, 130.3, 129.3, 127.0, 120.8, 113.2, 109.1, 40.9, 31.3, 27.5, 26.4, 20.8. IR (KBr): 3062, 2928, 1596, 1504, 1138, 745 cm^{-1}; HRMS (APCI-TOF, m/z): [M + H]$^+$ Calcd for $C_{16}H_{20}ClN_2$, 275.1309; found, 275.1306.

General Procedure for the Synthesis of 5-Trifluoromethylpyrazoles 2. An oven-dried clean round-bottom flask was charged with a magnetic stirring bar, hydrazonyl chlorides **1** (1.0 mmol) diluted in xylene (10 mL), 2-bromo-3,3,3-trifluoropropene (BTP) (349.9 mg, 2.0 mmol), and DABCO (336.5 mg, 3.0 mmol), and the mixture was vigorously stirred at room temperature for 24 h. Then the mixture was stopped stirring, water was added (15 mL), and the mixture was extracted with EtOAc (15 mL × 3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Further purification by flash column chromatography on silica gel (eluting with petroleum ether/ethyl acetate) provided the product **2**.

One Pot, Two-Step Transformation Directly from Hydrazones 3. An oven-dried clean 25 mL round-bottom flask was charged

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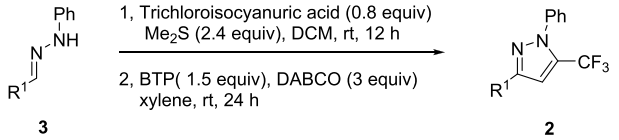
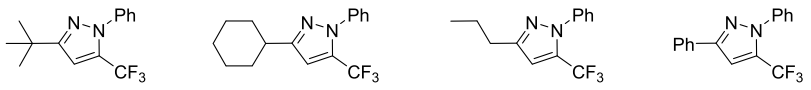
J. Org. Chem. 2021, 86, 2810−2819

Scheme 3. One Pot, Two-Step Transformation Directly from Hydrazones 3[a]



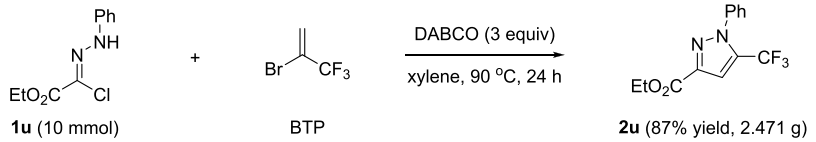
3 2



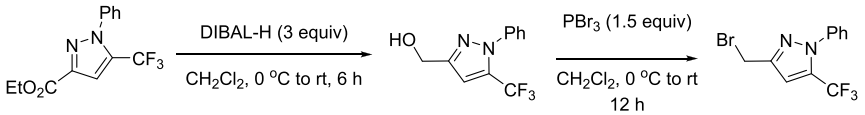
2y: 80%[b] **2z**: 60% **2aa**: 48% **2a**: 83%

[a]Unless otherwise noted, the reaction conditions were: Step (1): hydrazone **3** (1 mmol), trichloroisocyanuric acid (185.6 mg, 0.8 mmol), Me_2S (148.8 mg, 2.4 mmol), and DCM (8 mL) in a 25 mL test tube at room temperature for 12 h. Removal of the volatiles under reduced pressure. Step (2): BTP (349.9 mg, 2 mmol), DABCO (336.5 mg, 3 mmol), and xylene (10 mL) in a 25 mL test tube at room temperature for 24 h. [b]Isolated yield.

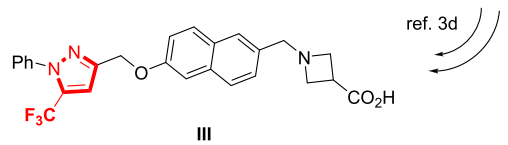
Scheme 4. Gram-Scale Experiment and Transformation of 2u



1u (10 mmol) BTP **2u** (87% yield, 2.471 g)

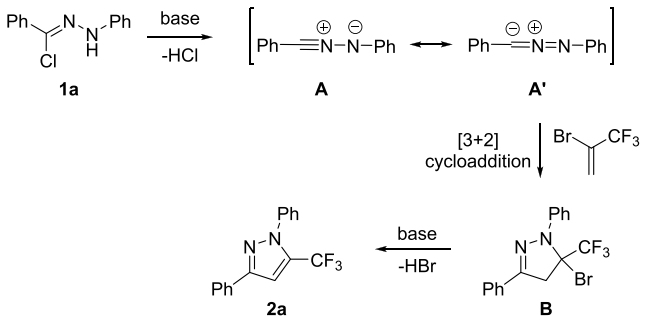


2u **4**: 85% **5**: 75%



III
Agonist of Sphingosine 1-Phosphate (S1P) Receptor

Scheme 5. Proposed Mechanism



1a **A** **A'** **2a** **B**

with a magnetic stirring bar, hydrazone **3** (1 mmol), trichloroisocyanuric acid (185.6 mg, 0.8 mmol), Me_2S (148.8 mg, 2.4 mmol), and DCM (8 mL), and the mixture was stirred at room temperature for 12 h. The volatiles were removed under reduced pressure. Then BTP (349.9 mg, 2 mmol), DABCO (336.5 mg, 3 mmol), and xylene (10 mL) were added, and the resulting mixture was vigorously stirred at room temperature for 24 h. Then the mixture was stopped stirring, water was added (15 mL), and the mixture was extracted with EtOAc (15 mL × 3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Further purification by flash column chromatography on silica gel (eluting with petroleum ether/ethyl acetate) provided the product **2**.

1,3-Diphenyl-5-(trifluoromethyl)-1H-pyrazole (***2a***). 282.5 mg, 98% yield, light yellow solid, mp: 70−71 °C; eluting with petroleum ether/ethyl acetate = 20:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85−7.86 (m, 2H), 7.54 (d, J = 7.5 Hz, 2H), 7.45−7.50 (m, 3H), 7.42 (t, J = 7.0 Hz, 2H), 7.35 (t, J = 7.5 Hz, 1H), 7.09 (s, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 151.8, 139.3, 134.0 (q, $^2J_{F\text{-}C}$ = 39.3 Hz), 131.9, 129.4, 129.2, 128.9, 128.8, 126.0, 125.8, 119.9 (q, $^1J_{F\text{-}C}$ = 269.5 Hz), 106.2 (q, $^3J_{F\text{-}C}$ = 1.9 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ −57.6 (s, 3F); IR (KBr): 3061, 1687, 1444, 1148, 691 cm^{-1}; HRMS (APCI-TOF, m/z): [M + H]$^+$ Calcd for $C_{16}H_{12}F_3N_2$, 289,0947; found, 289,0940.

3-(Naphthalen-2-yl)-1-phenyl-5-(trifluoromethyl)-1H-pyrazole (***2b***). 284.2 mg, 84% yield, yellow oil; eluting with petroleum ether/ethyl acetate = 20:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27−8.30 (m, 1H), 7.97 (dd, J = 8.5, 1.5 Hz, 1H), 7.84 (d, J = 8.5 Hz, 2H), 7.78−7.80 (m, 1H), 7.55 (d, J = 7.0 Hz, 2H), 7.40−7.47 (m, 5H), 7.17 (s, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 151.7, 139.3, 134.0 (q, $^2J_{F\text{-}C}$ = 39.3 Hz), 133.6, 133.6, 129.4, 129.2, 128.6, 128.4, 127.9, 126.5, 126.4, 125.8, 124.9, 123.8, 119.9 (q, $^1J_{F\text{-}C}$ = 269.5 Hz), 106.4 (q, $^3J_{F\text{-}C}$ = 2.3 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ −57.4 (s, 3F); IR (KBr): 3056, 1599, 1492, 1144, 762 cm^{-1}; HRMS (APCI-TOF, m/z): [M + H]$^+$ Calcd for $C_{20}H_{13}F_3N_2$ + H, 339.1104; found, 339.1099.

1-Phenyl-3-(p-tolyl)-5-(trifluoromethyl)-1H-pyrazole (***2c***). 260.0 mg, 86% yield, yellow solid, mp: 71−72 °C; eluting with petroleum ether/ethyl acetate = 20:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, J = 8.0 Hz, 2H), 7.61−7.64 (m, 2H), 7.52−7.58 (m, 3H), 7.30 (d, J = 8.0 Hz, 2H), 7.14 (s, 1H), 2.45 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 151.8, 139.4, 138.7, 134.0 (q, $^2J_{F\text{-}C}$ = 39.1 Hz), 129.6, 129.3,

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J. Org. Chem. 2021, 86, 2810−2819

129.2, 129.1, 125.9, 125.8, 119.9 (q, $^{1}J_{F\text{-}C}$ = 269.5 Hz), 106.0 (q, $^{3}J_{F\text{-}C}$ = 2.0 Hz), 21.4; ^{19}F NMR (471 MHz, $CDCl_3$) δ −57.5 (s, 3F); IR (KBr): 3059, 1596, 1444, 1138, 779 cm^{-1}; HRMS (APCI-TOF, *m*/*z*): [M + H]$^+$ Calcd for $C_{17}H_{14}F_3N_2$, 303.1104; found, 303.1099.

3-(4-(tert-Butyl)phenyl)-1-phenyl-5-(trifluoromethyl)-1H-pyrazole (**2d**). 278.9 mg, 81% yield, brown oil; eluting with petroleum ether/ethyl acetate = 20:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.44−7.56 (m, 7H), 7.08 (s, 1H), 1.35 (s, 9H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 151.9, 151.8, 139.4, 133.8 (q, $^{2}J_{F\text{-}C}$ = 38.8 Hz), 129.3, 129.2, 129.1, 125.9, 125.7, 119.9 (q, $^{1}J_{F\text{-}C}$ = 267.4 Hz), 106.1, 34.8, 31.4; ^{19}F NMR (471 MHz, $CDCl_3$) δ −57.5 (s, 3F); IR (KBr): 3060, 2958, 1595, 1492, 1143, 757 cm^{-1}; HRMS (APCI-TOF, *m*/*z*): [M + H]$^+$ Calcd for $C_{20}H_{20}F_3N_2$, 345.1573; found, 345.1568.

3-(4-Methoxyphenyl)-1-phenyl-5-(trifluoromethyl)-1H-pyrazole (**2e**). 273.7 mg, 86% yield, yellow solid; eluting with petroleum ether/ethyl acetate = 10:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85−7.88 (m, 2H), 7.60−7.63 (m, 2H), 7.50−7.56 (m, 3H), 7.09 (s, 1H), 7.00−7.04 (m, 2H), 3.86 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 160.2, 151.5, 139.3, 133.8 (q, $^{2}J_{F\text{-}C}$ = 38.9 Hz), 129.2, 129.1, 127.2, 125.7, 124.5, 119.9 (q, $^{1}J_{F\text{-}C}$ = 267.5 Hz), 114.3, 105.7, 55.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.5 (s, 3F); IR (KBr): 3059, 2923, 1596, 1444, 1138, 779 cm^{-1}; HRMS (APCI-TOF, *m*/*z*): [M + H]$^+$ Calcd for $C_{17}H_{14}F_3N_2O$, 319.1053; found, 319.1052.

3-(3-Methoxyphenyl)-1-phenyl-5-(trifluoromethyl)-1H-pyrazole (**2f**). 257.8 mg, 81% yield, brown solid, mp: 80−81 °C; eluting with petroleum ether/ethyl acetate = 20:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62−7.65 (m, 2H), 7.50−7.57 (m, 5H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.17 (s, 1H), 6.98−7.01 (m, 1H), 3.89 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 160.1, 151.6, 139.2, 133.8 (q, $^{2}J_{F\text{-}C}$ = 39.0 Hz), 133.1, 129.9, 129.3, 129.1, 125.8, 119.9 (q, $^{1}J_{F\text{-}C}$ = 267.6 Hz), 118.4, 114.7, 111.0, 106.3, 55.2 (d, $J_{F\text{-}C}$ = 6.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.5 (s, 3F); IR (KBr): 3074, 2937, 1609, 1442, 1135, 830 cm^{-1}; HRMS (APCI-TOF, *m*/*z*): [M + H]$^+$ Calcd for $C_{17}H_{14}F_3N_2O$, 319.1053; found, 319.1045.

3-(4-Fluorophenyl)-1-phenyl-5-(trifluoromethyl)-1H-pyrazole (**2g**). 269.5 mg, 88% yield, yellow solid, mp: 80−81 °C; eluting with petroleum ether/ethyl acetate = 20:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78−7.83 (m, 2H), 7.51−7.56 (m, 2H), 7.43−7.49 (m, 3H), 7.06−7.12 (m, 2H), 7.02 (s, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 163.2 (d, $^{1}J_{F\text{-}C}$ = 248.5 Hz), 150.8, 139.3, 134.0 (q, $^{2}J_{F\text{-}C}$ = 39.2 Hz), 129.5, 129.2, 128.1 (d, $^{4}J_{F\text{-}C}$ = 3.0 Hz), 127.7 (d, $^{3}J_{F\text{-}C}$ = 8.3 Hz), 125.8, 119.9 (q, $^{1}J_{F\text{-}C}$ = 269.8 Hz), 115.9 (d, $^{2}J_{F\text{-}C}$ = 21.5 Hz), 106.0 (q, $^{3}J_{F\text{-}C}$ = 2.4 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ −57.6 (s, 3F), −112.9 to −112.8 (m, 1F); IR (KBr): 3068, 1603, 1447, 1148, 826 cm^{-1}; HRMS (APCI-TOF, *m*/*z*): [M + H]$^+$ Calcd for $C_{16}H_{11}F_4N_2$, 307.0853; found, 307.0847.

3-(2-Fluorophenyl)-1-phenyl-5-(trifluoromethyl)-1H-pyrazole (**2h**). 229.7 mg, 75% yield, yellow solid, mp: 81−82 °C; eluting with petroleum ether/ethyl acetate = 20:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05−8.09 (m, 1H), 7.54−7.55 (m, 2H), 7.44−7.50 (m, 3H), 7.26−7.33 (m, 2H), 7.12−7.21 (m, 2H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 160.4 (d, $^{1}J_{F\text{-}C}$ = 250.4 Hz), 146.5, 139.3, 133.7 (q, $^{2}J_{F\text{-}C}$ = 37.8 Hz), 130.1 (d, $^{3}J_{F\text{-}C}$ = 8.3 Hz), 129.5, 129.2, 128.6 (d, $^{4}J_{F\text{-}C}$ = 3.4 Hz), 125.8, 124.5 (d, $^{4}J_{F\text{-}C}$ = 3.3 Hz), 119.9 (q, $^{1}J_{F\text{-}C}$ = 269.6 Hz), 119.8 (d, $^{3}J_{F\text{-}C}$ = 11.7 Hz) 116.3 (d, $^{2}J_{F\text{-}C}$ = 22.2 Hz), 109.5 (d, $^{3}J_{F\text{-}C}$ = 9.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.5 (s, 3F), −115.9 to −115.8 (m, 1F); IR (KBr): 3062, 1589, 1446, 1117, 755 cm^{-1}; HRMS (APCI-TOF, *m*/*z*): [M + H]$^+$ Calcd for $C_{16}H_{11}F_4N_2$, 307.0853; found, 307.0847.

3-(2,4-Difluorophenyl)-1-phenyl-5-(trifluoromethyl)-1H-pyrazole (**2i**). 223.7 mg, 69% yield, yellow solid, mp: 82−83 °C; eluting with petroleum ether/ethyl acetate = 15:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (q, *J* = 8.0 Hz, 1H), 7.53−7.59 (m, 5H), 7.26 (d, *J* = 2.8 Hz, 1H), 6.93−7.00 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 163.1 (dd, $J_{F\text{-}C}$ = 249.2, 11.9 Hz), 160.4 (dd, $J_{F\text{-}C}$ = 251.0, 11.7 Hz), 145.7, 139.1, 133.8 (q, $^{2}J_{F\text{-}C}$ = 38.9 Hz), 129.6, 129.3, 125.8, 119.8 (q, $^{1}J_{F\text{-}C}$ = 267.6 Hz), 116.2 (dd, $J_{F\text{-}C}$ = 11.9, 4.0 Hz), 112.0 (dd, $J_{F\text{-}C}$ = 21.4, 3.6 Hz), 109.1 (dq, $J_{F\text{-}C}$ = 11.0, 2.3 Hz), 104.5 (t, $J_{F\text{-}C}$ = 25.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.6 (s, 3F), −109.3 to −109.2 (m, 1F), −111.9 to −111.8 (m, 1F); IR (KBr): 3059, 1596, 1444, 1138, 779 cm^{-1}; HRMS (APCI-TOF, *m*/*z*): [M + H]$^+$ Calcd for $C_{16}H_{20}F_5N_2$, 325.0759; found, 325.0754.

3-(4-Chlorophenyl)-1-phenyl-5-(trifluoromethyl)-1H-pyrazole (**2j**). 251.2 mg, 78% yield, yellow solid, mp: 70−72 °C; eluting with petroleum ether/ethyl acetate = 15:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.4 Hz, 2H), 7.48−7.54 (m, 5H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.11 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 151.0, 137.7, 135.5, 134.8, 134.2 (q, *J* = 39.5 Hz), 130.2, 129.5, 129.2, 127.2, 127.0, 119.7 (q, *J* = 269.3 Hz), 106.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.6 (s, 3F); IR (KBr): 3061, 1589, 1446, 1117, 755 cm^{-1}; HRMS (APCI-TOF, *m*/*z*): [M + H]$^+$ Calcd for $C_{16}H_{11}ClF_3N_2$, 323.0557; found, 323.0551.

3-(2-Chlorophenyl)-1-phenyl-5-(trifluoromethyl)-1H-pyrazole (**2k**). 264.6 mg, 82% yield, yellow solid, mp: 80−81 °C; eluting with petroleum ether/ethyl acetate = 15:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87−7.90 (m, 1H), 7.46−7.58 (m, 6H), 7.36 (s, 1H), 7.29−7.33 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 149.4, 139.2, 133.2 (q, $^{2}J_{F\text{-}C}$ = 38.9 Hz), 132.5, 130.8, 130.8, 130.6, 129.8, 129.5, 129.3, 127.2, 125.8, 119.9 (q, $^{1}J_{F\text{-}C}$ = 267.5 Hz), 110.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.5 (s, 3F); IR (KBr): 3060, 1590, 1434, 1116, 761 cm^{-1}; HRMS (APCI-TOF, *m*/*z*): [M + H]$^+$ Calcd for $C_{16}H_{11}ClF_3N_2$, 323.0557; found, 323.0553.

3-(4-Bromophenyl)-1-phenyl-5-(trifluoromethyl)-1H-pyrazole (**2l**). 260.7 mg, 71% yield, red solid, mp: 70−71 °C; eluting with petroleum ether/ethyl acetate = 15:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.4 Hz, 2H), 7.57−7.60 (m, 4H), 7.50−7.54 (m, 3H), 7.09 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 150.6, 139.1, 134.0 (q, $^{2}J_{F\text{-}C}$ = 39.1 Hz), 132.0, 130.8, 129.4, 129.2, 127.4, 125.7, 122.8, 119.7 (q, $^{1}J_{F\text{-}C}$ = 267.6 Hz), 106.1 (q, $^{3}J_{F\text{-}C}$ = 2.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.5 (s, 3F); IR (KBr): 3065, 1589, 1440, 1147, 820 cm^{-1}; HRMS (APCI-TOF, *m*/*z*): [M + H]$^+$ Calcd for $C_{16}H_{11}BrF_3N_2$, 367.0052; found, 367.0049.

3-(4-Iodophenyl)-1-phenyl-5-(trifluoromethyl)-1H-pyrazole (**2m**). 310.6 mg, 75% yield, brown solid, mp: 80−81 °C; eluting with petroleum ether/ethyl acetate = 20:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.48−7.55 (m,5H), 7.07 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 150.7, 139.2, 134.2 (q, $^{2}J_{F\text{-}C}$ = 39.2 Hz), 131.4, 129.5, 129.3, 127.6, 125.8, 119.7 (q, $^{1}J_{F\text{-}C}$ = 267.8 Hz), 106.1, 94.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.6 (s, 3F); IR (KBr): 3061, 1588, 1442, 1145, 813 cm^{-1}; HRMS (APCI-TOF, *m*/*z*): [M + H]$^+$ Calcd for $C_{16}H_{11}F_3IN_2$, 414.9914; found, 414.9906.

1-Phenyl-5-(trifluoromethyl)-3-(4-(trifluoromethyl)phenyl)-1H-pyrazole (**2n**). 277.9 mg, 78% yield, yellow solid, mp: 70−71 °C; eluting with petroleum ether/ethyl acetate = 10:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 8.0 Hz, 2H), 7.53−7.61 (m, 5H), 7.19 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 150.3, 139.2, 135.3, 134.4 (q, $^{2}J_{F\text{-}C}$ = 39.3 Hz), 130.3 (q, $^{2}J_{F\text{-}C}$ = 32.4 Hz), 129.7, 129.3, 126.2, 125.9 (q, $^{3}J_{F\text{-}C}$ = 3.8 Hz), 125.8, 124.3 (q, $^{1}J_{F\text{-}C}$ = 270.3 Hz), 119.8 (q, $^{1}J_{F\text{-}C}$ = 267.6 Hz), 106.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.8 (s, 3F), −62.7 (s, 3F); IR (KBr): 3061, 1588, 1445, 1145, 813 cm^{-1}; HRMS (APCI-TOF, *m*/*z*): [M + H]$^+$ Calcd for $C_{17}H_{11}F_6N_2$, 357.0821; found, 357.0815.

4-(1-Phenyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)benzonitrile (**2o**). 209.9 mg, 67% yield, brown solid, mp: 105−106 °C; eluting with petroleum ether/ethyl acetate = 8:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.50−7.56 (m, 5H), 7.16 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 149.7, 138.9, 136.1, 134.5 (q, $^{2}J_{F\text{-}C}$ = 39.3 Hz), 132.7, 129.8, 129.3, 126.3, 125.7, 119.6 (q, $^{1}J_{F\text{-}C}$ = 267.7 Hz), 118.8, 112.1, 106.6 (q, $^{3}J_{F\text{-}C}$ = 2.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.7 (s, 3F); IR (KBr): 3065, 2223, 1598, 1442, 1113, 825 cm^{-1}; HRMS (APCI-TOF, *m*/*z*): [M + H]$^+$ Calcd for $C_{17}H_{11}F_3N_3$, 314.0900; found, 314.0893.

3-(1-Phenyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)benzonitrile (**2p**). 260.0 mg, 83% yield, light yellow solid, mp: 158−159 °C; eluting with petroleum ether/ethyl acetate = 8:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 8.07 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.51−7.55 (m, 5H), 7.13 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 149.4, 138.9, 134.5 (q, $^{2}J_{F\text{-}C}$ = 39.5 Hz), 133.1, 132.0,

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J. Org. Chem. 2021, 86, 2810−2819

130.0, 129.8, 129.7, 129.4, 129.3, 125.7, 119.6 (q, $^1J_{F-C}$ = 267.5 Hz), 118.6, 113.2, 106.6 (q, $^3J_{F-C}$ = 1.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.7 (s, 3F); IR (KBr): 3058, 1534, 1424, 1082, 690 cm^{-1}; HRMS (APCI-TOF, m/z): [M + H]$^+$ Calcd for $C_{17}H_{11}F_3N_3$, 314.0900; found, 314.0892.

*1,4-Bis(1-phenyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)benzene (**2q**).* 423.7 mg, 85% yield, yellow solid, mp: 170−171 °C; eluting with petroleum ether/ethyl acetate = 20:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 4H), 7.51−7.61 (m, 10H), 7.18 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 151.3, 139.3, 134.2 (q, $^2J_{F-C}$ = 39.0 Hz), 132.1, 129.5, 129.3, 126.4, 125.9, 119.9 (q, $^1J_{F-C}$ = 267.5 Hz), 106.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.6 (s, 6F); IR (KBr): 3063, 1594, 1434, 1143, 758 cm^{-1}; HRMS (APCI-TOF, m/z): [M + H]$^+$ Calcd for $C_{26}H_{17}F_6N_4$, 499.1352; found, 499.1346.

*(S)-1-Phenyl-3-(4-(prop-1-en-2-yl)cyclohex-1-en-1-yl)-5-(trifluoromethyl)-1H-pyrazole (**2r**).* 289.2 mg, 87% yield, brown oil; eluting with petroleum ether/ethyl acetate = 20:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.57 (m, 5H), 6.92 (s, 1H), 6.48 (t, J = 2.8 Hz, 1H), 4.84 (s, 2H), 2.76−2.82 (m, 1H), 2.49−2.59 (m, 1H), 2.29−2.45 (m, 2H), 2.17−2.24 (m, 1H), 2.01−2.05 (m, 1H), 1.84 (s, 3H), 1.62−1.72 (m, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 153.1, 149.4, 139.4, 133.2 (q, $^2J_{F-C}$ = 38.7 Hz), 129.3, 129.0, 129.0, 125.8, 125.7, 119.9 (q, $^1J_{F-C}$ = 267.5 Hz), 109.0, 105.1 (q, $^3J_{F-C}$ = 1.4 Hz), 40.8, 31.0, 27.4, 26.2, 20.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.5 (s, 3F); IR (KBr): 3073, 2941, 1715, 1462, 1152, 700 cm^{-1}; HRMS (APCI-TOF, m/z): [M + H]$^+$ Calcd for $C_{19}H_{20}F_3N_2$, 333.1573; found, 333.1567.

*1-Phenyl-3-(thiophen-2-yl)-5-(trifluoromethyl)-1H-pyrazole (**2s**).* 247.2 mg, 84% yield, brown solid, mp: 70−71 °C; eluting with petroleum ether/ethyl acetate = 20:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.58 (m, 5H), 7.45 (d, J = 3.6 Hz, 1H), 7.32 (d, J = 5.2 Hz, 1H), 7.11 (t, J = 4.4 Hz, 1H), 7.03 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 147.1, 139.0, 134.7, 133.9 (q, $^2J_{F-C}$ = 39.3 Hz), 129.5, 129.2, 127.7, 125.8, 125.8, 125.0, 119.8 (q, $^1J_{F-C}$ = 267.8 Hz), 106.1 (q, $^3J_{F-C}$ = 1.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.6 (s, 3F); IR (KBr): 3079, 1590, 1487, 1144, 699 cm^{-1}; HRMS (APCI-TOF, m/z): [M + H]$^+$ Calcd for $C_{14}H_{10}F_3N_2S$, 295.0511; found, 295.0507.

*3-(Furan-2-yl)-1-phenyl-5-(trifluoromethyl)-1H-pyrazole (**2t**).* 217.0 mg, 78% yield, yellow oil; eluting with petroleum ether/ethyl acetate = 20:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.54 (m, 6H), 7.04 (s, 1H), 6.80 (t, J = 2.0 Hz, 1H), 6.50 (d, J = 1.2 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 147.1, 144.2, 142.6, 138.9, 133.7 (q, $^2J_{F-C}$ = 39.4 Hz), 129.5, 129.1, 125.8, 119.6 (q, $^1J_{F-C}$ = 267.6 Hz), 111.5, 107.2, 105.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.8 (s, 3F); IR (KBr): 3061, 1703, 1474, 1148, 758 cm^{-1}; HRMS (APCI-TOF, m/z): [M + H]$^+$ Calcd for $C_{14}H_{10}F_3N_2O$, 279.0740; found, 279.0736.

*Ethyl 1-Phenyl-5-(trifluoromethyl)-1H-pyrazole-3-carboxylate (**2u**).* 255.8 mg, 90% yield, yellow oil; eluting with petroleum ether/ethyl acetate = 10:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.54 (m, 5H), 7.33 (s, 1H), 4.44 (q, J = 7.2 Hz, 2H), 1.41 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.2, 144.0, 138.5, 134.2 (q, $^2J_{F-C}$ = 39.7 Hz), 130.1, 129.2, 126.0, 119.0 (q, $^1J_{F-C}$ = 267.7 Hz), 111.2, 61.6, 14.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −58.0 (s, 3F); IR (KBr): 3071, 2975, 1733, 1484, 1234, 769 cm^{-1}; HRMS (APCI-TOF, m/z): [M + H]$^+$ Calcd for $C_{13}H_{12}F_3N_2O_2$, 285.0845; found, 285.0841.

*1-(4-Fluorophenyl)-3-phenyl-5-(trifluoromethyl)-1H-pyrazole (**2v**).* 257.3 mg, 84% yield, brown solid, mp: 78−79 °C; eluting with petroleum ether/ethyl acetate = 20:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83−7.85 (m, 2H), 7.50−7.54 (m, 2H), 7.41−7.45 (m, 2H), 7.35−7.39 (m, 1H), 7.16−7.20 (m, 2H), 7.09 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.8 (d, $^1J_{F-C}$ = 248.2 Hz), 151.9, 135.3 (d, $^4J_{F-C}$ = 3.4 Hz), 134.1 (q, $^2J_{F-C}$ = 39.0 Hz), 131.7, 129.0, 128.9, 127.9 (d, $^3J_{F-C}$ = 8.7 Hz), 126.0, 119.8 (q, $^1J_{F-C}$ = 267.5 Hz), 116.2 (d, $^2J_{F-C}$ = 23.0 Hz), 106.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.7 (s, 3F), −111.3 (s, 1F); IR (KBr): 3063, 1512, 1438, 1123, 837 cm^{-1}; HRMS (APCI-TOF, m/z): [M + H]$^+$ Calcd for $C_{16}H_{11}F_4N_2$, 307.0853; found, 307.0848.

*1-(4-Chlorophenyl)-3-phenyl-5-(trifluoromethyl)-1H-pyrazole (**2w**).* 258.2 mg, 80% yield, brown oil; eluting with petroleum ether/ethyl acetate = 15:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82−7.85 (m, 2H), 7.34−7.51 (m, 7H), 7.10 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 152.7, 137.8, 135.4, 134.0 (q, $^2J_{F-C}$ = 39.0 Hz), 131.6, 129.5, 129.0, 127.0, 126.0, 119.8 (q, $^1J_{F-C}$ = 267.5 Hz), 106.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.6 (s, 3F); IR (KBr): 3063, 1502, 1443, 1289, 1145, 830 cm^{-1}; HRMS (APCI-TOF, m/z): [M + H]$^+$ Calcd for $C_{16}H_{11}ClF_3N_2$, 323.0557; found, 323.0552.

*4-(3-Phenyl-5-(trifluoromethyl)-1H-pyrazol-1-yl)benzonitrile (**2x**).* 175.4 mg, 56% yield, white solid, mp: 78−79 °C; eluting with petroleum ether/ethyl acetate = 10:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85−7.87 (m, 2H), 7.81 (d, J = 8.4 Hz, 2H), 7.73 (d, J = 8.4 Hz, 2H), 7.39−7.48 (m, 3H), 7.18 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 152.8, 142.6, 133.9 (q, $^2J_{F-C}$ = 39.4 Hz), 133.3, 131.2, 129.3, 129.0, 126.0, 125.7 (q, $^3J_{F-C}$ = 1.7 Hz), 119.8 (q, $^1J_{F-C}$ = 267.6 Hz), 117.9, 112.9, 107.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.2 (s, 3F); IR (KBr): 3163, 1589, 1450, 1229, 1113, 759 cm^{-1}; HRMS (APCI-TOF, m/z): [M + H]$^+$ Calcd for $C_{17}H_{11}F_3N_3$, 314.0899; found, 314.0894.

*3-(tert-Butyl)-1-phenyl-5-(trifluoromethyl)-1H-pyrazole (**2y**).* 214.6 mg, 80% yield, yellow oil; eluting with petroleum ether/ethyl acetate = 30:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.45 (m, 5H), 6.67 (s, 1H), 1.35 (s, 9H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.6, 138.0, 134.9, 132.8 (q, $^2J_{F-C}$ = 38.6 Hz), 129.4, 127.0, 119.8 (q, $^1J_{F-C}$ = 267.4 Hz), 106.2, 32.4, 30.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.3 (s, 3F); IR (KBr): 3057, 2961, 1497, 1241, 1131, 829 cm^{-1}; HRMS (APCI-TOF, m/z): [M + H]$^+$ Calcd for $C_{14}H_{16}F_3N_2$, 269.1260; found, 269.1252.

*3-Cyclohexyl-1-phenyl-5-(trifluoromethyl)-1H-pyrazole (**2z**).* 176.6 mg, 60% yield, yellow oil; eluting with petroleum ether/ethyl acetate = 30:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.49 (m, 5H), 6.61 (s, 1H), 2.70−2.77 (m, 1H), 2.02−2.07 (m, 2H), 1.70−1.85 (m, 3H), 1.28−1.52 (m, 5H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.5, 139.5, 132.7 (q, $^2J_{F-C}$ = 38.6 Hz), 129.1, 129.0, 125.7, 120.1 (q, $^1J_{F-C}$ = 267.3 Hz), 106.2, 37.5, 33.1, 26.3, 26.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.4 (s, 3F); IR (KBr): 3064, 2928, 1462, 1289, 1145, 771 cm^{-1}; HRMS (APCI-TOF, m/z): [M + H]$^+$ Calcd for $C_{16}H_{18}F_3N_2$, 295.1417; found, 295.1413.

*Phenyl-3-propyl-5-(trifluoromethyl)-1H-pyrazole (**2aa**).* 122.1 mg, 48% yield, yellow oil; eluting with petroleum ether/ethyl acetate = 30:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.48 (m, 5H), 6.61 (s, 1H), 2.68 (t, J = 7.6 Hz, 2H), 2.68 (m, 2H), 2.68 (t, J = 7.6 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 153.7, 139.4, 133.0 (q, $^2J_{F-C}$ = 38.8 Hz), 129.2, 129.1, 125.8, 120.0 (q, $^1J_{F-C}$ = 267.2 Hz), 107.8, 30.1, 22.8, 14.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.5 (s, 3F); IR (KBr): 3061, 2953, 1476, 1288, 1132, 759 cm^{-1}; HRMS (APCI, m/z): [M + H]$^+$ Calcd for $C_{13}H_{14}F_3N_2$, 255.1104; found, 255.1099.

Gram-Scale Synthesis of 2u. An oven-dried clean round-bottom flask was charged with a magnetic stirring bar, hydrazonyl chloride **1u** (2.266 g, 10 mmol) diluted in xylene (50 mL), 2-bromo-3,3,3-trifluoropropene (BTP) (3.499 g, 20 mmol), and DABCO (3.365 g, 30 mmol), and the mixture was vigorously stirred at 90 °C for 24 h. Then the mixture was stopped stirring, water was added (60 mL), and the mixture was extracted with EtOAc (60 mL × 3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Further purification by flash column chromatography on silica gel (eluting with petroleum ether/ethyl acetate = 10:1) provided the product **2u** in 87% isolated yield (2.471 g).

Ethyl 1-phenyl-5-(trifluoromethyl)-1*H*-pyrazole-3-carboxylate (**2u**) (284.2 mg, 1 mmol) was diluted in anhydrous CH_2Cl_2 (10 mL), and DIBAL (2 mL, 1.5 M in toluene, 3 mmol) was added dropwise to the solution at 0 °C under N_2. The reaction mixture was stirred at room temperature for 6 h, and then the solution was cooled to 0 °C, after which MeOH (10 mL) was added dropwise. The solvent was evaporated under reduced pressure, and the solid was subsequently extracted with EtOAc (20 mL × 3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Further purification by flash column chromatography on silica gel (eluting with petroleum ether/ethyl acetate = 6:1) provided the product **4** in 85% isolated yield.

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J. Org. Chem. 2021, 86, 2810−2819

(1-Phenyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)methanol (**4**). 205.7 mg, 85% yield, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.49 (m, 5H), 6.81 (s, 1H), 4.75 (s, 2H), 2.48 (brs, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 152.6, 139.0, 133.7 (q, $^2J_{F-C}$ = 39.2 Hz), 129.5, 129.3, 125.8, 119.7 (q, $^1J_{F-C}$ = 267.4 Hz), 107.5, 58.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.7 (s, 3F); IR (KBr): 3391, 3065, 2934, 1498, 1136, 765 cm^{-1}; HRMS (APCI, *m*/*z*): $[M + H]^+$ Calcd for $C_{11}H_{10}F_3N_2O$, 243.0740; found, 243.073.

PBr_3 (405 mg, 1.5 mmol) was added to a solution of alcohol **4** (242.2 mg, 1 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The mixture was stirred at room temperature for 12 h, cooled to 0 °C, quenched with ice water, and then diluted with CH_2Cl_2 (50 mL). The organic layer was dried and evaporated. Further purification by flash column chromatography on silica gel (eluting with petroleum ether/ethyl acetate = 30:1) provided the product **5** in 75% isolated yield.

3-(Bromomethyl)-1-phenyl-5-(trifluoromethyl)-1H-pyrazole (**5**).[3d] 228.8 mg, 75% yield, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 5H), 6.91 (s, 1H), 4.54 (s, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 149.5, 138.9, 134.0 (q, *J* = 39.5 Hz), 129.7, 129.3, 125.7, 119.6 (q, *J* = 269.3 Hz), 109.0, 23.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.7 (s, 3F); IR (KBr): 3063, 2953, 1485, 1133, 686 cm^{-1}.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02765.

Copies of ^{1}H, ^{13}C NMR, and ^{19}F NMR spectra data for the new reactant **1r** and all the products **2**, **4**, and **5** (PDF)

Accession Codes

CCDC 2034673 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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