Synthesis L.-L. Zhang et al. Paper

Efficient Synthesis of 5-Trifluoromethylthio-1,2,3-Triazoles: One-Pot Multicomponent Reaction from Elemental Sulfur and $TMSCF_3$

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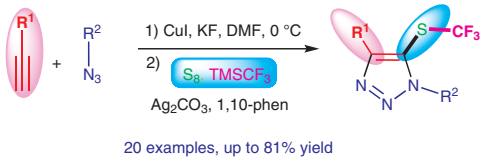


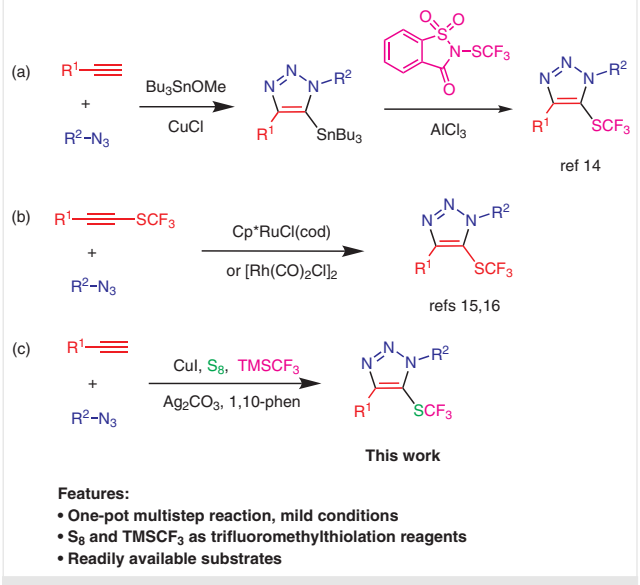
Received: 15.08.2019
Accepted after revision: 29.09.2019
Published online: 21.10.2019
DOI: 10.1055/s-0039-1690716; Art ID: ss-2019-h0451-op

Abstract A sequential multistep reaction toward 5-trifluoromethylthio-1,2,3-triazoles has been established, starting from alkynes, organoazides, S_8, and (trifluoromethyl)trimethylsilane ($TMSCF_3$). This reaction features mild conditions, easy operation, and readily available substrates.

Key words copper iodide, sulfur, triazole, (trifluoromethyl)trimethylsilane, multicomponent reaction

The trifluoromethylthio group (SCF_3) has been used as a structural motif in drug design due to its unique properties, such as high lipophilicity (Hansch lipophilicity parameter π = 1.44) and electron-withdrawing properties.[1] This group also enhances drugs' cell-membrane permeability, metabolic stability, bioavailability, and pharmacokinetics.[2] In addition, the 1,2,3-triazole core shows high solubility, good metabolic stability, strong hydrogen bonds, and dipole-dipole interactions.[3] The triazole moiety is also an ideal spacer or linker used in conjugating with biomacromolecules[4] or linking multitarget drugs.[5] Furthermore, 1,2,3-triazole derivatives exhibit extensive biological activities, such as anticancer, anti-HIV, antituberculosis, antifungus, antibacteria, antivirus, and anti-inflammation.[6]

The Huisgen 1,3-dipolar cycloaddition of azides and internal alkynes (AAC) is the most straightforward and atom-economical approach for synthesizing 1,2,3-triazloes. Nevertheless, this method has some disadvantages, such as low regioselectivities, high reaction temperatures, and long reaction times.[7] In 2002, Sharpless[8] and Meldal[9] reported copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reactions to regioselectively synthesize 1,4-di-substituted 1,2,3-triazoles. Synthetic methods for various fully substituted 1,2,3-triazoles have been reported in recent years. Xu's group[10] developed a three-component click reaction of azides, alkynes, and aryl halides by using Cu/Pd transmetalation relay catalysis. Song's group reported an iridium-catalyzed[11] cycloaddition of azides to ynamides and a regiodivergent rhodium(I)-catalyzed[12] azide-thioalkyne cycloaddition (RhAAC) to form 5-amido-1,2,3-triazoles and either 4- or 5-sulfonyl-1,2,3-triazoles, respectively. Recently, the methods for synthesizing fully substituted 5-thio-1,2,3-triazoles have been widely studied, such as the cycloaddition of thioalkynes to azides under IrAAC[13] or RuAAC[14] reaction reactions, and the electrophilic sulfenylation of Cu(I) triazolides using benzene thiosulfonate under CuAAC[10b,15] reactions.



Scheme 1 Strategies for constructing 5-trifluoromethylthio-1,2,3-triazoles

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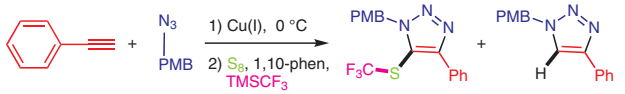
Trifluoromethylthio-1,2,3-triazoles combine the advantages of the SCF_3 group and the 1,2,3-triazole core, possessing enhanced bioactivity and bioavailability.[2,16] Few synthetic methods for this type of compound have been described. Recently, Xu's group[17] reported a two-step method (Scheme 1a). Bench-stable 5-stannyltriazoles, obtained via a copper-catalyzed click reaction, serve as powerful nucleophilic reagents to react with a specific electrophilic trifluoromethylthiolation reagent, generating the 5-triflormethylthiotriazoles. Ruthenium(II)-[18] and rhodium(I)-catalyzed[19] azide-alkyne cycloaddition reactions between azides and alkynyltrifluoromethyl sulfides afforded 5-trifluoromethylthio-1,2,3-triazoles (Scheme 1b). These methods, however, involve an indirect two-step strategy (Scheme 1a) or noble-metal catalysts and commercially unavailable starting materials (Scheme 1b). In continuation of our studies on the synthesis of functionalized 1,2,3-triazoles,[20] we herein report a one-pot multicomponent reaction to synthesize 5-trifluoromethylthio-1,2,3-triazoles from elemental sulfur and $TMSCF_3$ (Scheme 1c).

We have reported a multistep reaction for synthesis of various thiotriazoles from sulfur powder.[21] Under similar reaction conditions, phenylacetylene and 4-methoxybenzyl azide ($PMBN_3$) were chosen as model substrates to conduct the reaction and the desired trifluoromethylthiotriazole **1a** was formed in 41% yield, and the protonated triazole **4** was

Table 1 Optimization of the Reaction Conditions[a]

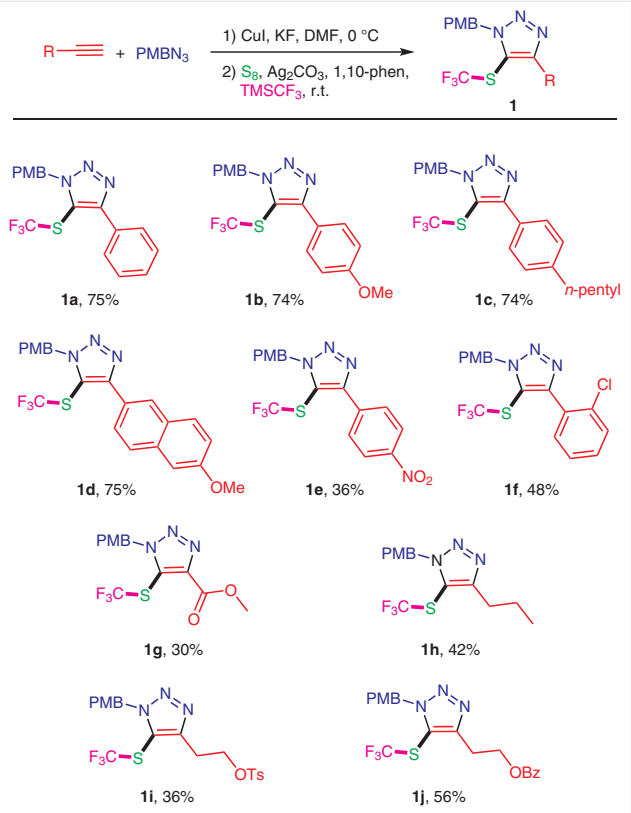


1a **4**, side product

Entry	Additive (mol equiv)	Cu(I)	Silver salt	Ligand	Solvent	Yield (%)[b] of **1a**
1	K_2CO_3 (2.0)	CuI	Ag_2CO_3[c]	1,10-phen	DMF	41
2	Et_3N (2.0)	CuI	Ag_2CO_3[c]	1,10-phen	DMF	28
3	NaOH (2.0)	CuI	Ag_2CO_3[c]	1,10-phen	DMF	34
4	KOH (2.0)	CuI	Ag_2CO_3[c]	1,10-phen	DMF	trace
5	18-crown-6 (2.0)	CuI	Ag_2CO_3[c]	1,10-phen	DMF	0
6	KF (2.0)	CuI	Ag_2CO_3[c]	1,10-phen	DMF	48
7	KF (1.0)	CuI	Ag_2CO_3[c]	1,10-phen	DMF	62
8	KF (1.0)	CuI	Ag_2CO_3[d]	1,10-phen	DMF	36
9	**KF (1.0)**	**CuI**	**Ag_2CO_3**	**1,10-phen**	**DMF**	**75**
10	KF (1.0)	CuI	–	1,10-phen	DMF	23
11	KF (1.0)	CuI	$AgNO_3$	1,10-phen	DMF	38
12	KF (1.0)	CuI	AgOAc	1,10-phen	DMF	25
13	KF (1.0)	CuI	AgOTf	1,10-phen	DMF	27
14	KF (1.0)	CuI	Ag_2CO_3	–	DMF	19
15	KF (1.0)	CuI	Ag_2CO_3	PPh_3	DMF	18
16	KF (1.0)	CuI	Ag_2CO_3	bpy	DMF	26
17	KF (1.0)	CuI	Ag_2CO_3	DMEDA	DMF	32
18	KF (1.0)	CuSCN	Ag_2CO_3	1,10-phen	DMF	0
19	KF (1.0)	CuCN	Ag_2CO_3	1,10-phen	DMF	–
20	KF (1.0)	CuOTf	Ag_2CO_3	1,10-phen	DMF	30
21	KF (1.0)	CuI[e]	Ag_2CO_3	1,10-phen	DMF	13
22	KF (1.0)	CuI	Ag_2CO_3	1,10-phen	toluene	0
23	KF (1.0)	CuI	Ag_2CO_3	1,10-phen	MeCN	trace
24	KF (1.0)	CuI	Ag_2CO_3	1,10-phen	THF	–

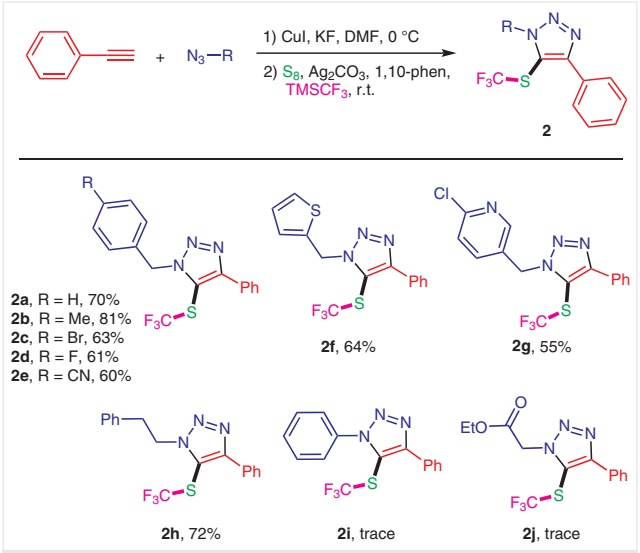
[a] Reaction conditions: 1) phenylacetylene (35 μL, 0.31 mmol), $PMBN_3$ (49 mg, 0.30 mmol), Cu(I) (0.39 mmol), additive, solvent (2 mL), 0 °C, 3 h. 2) S_8 (29 mg, 0.90 mmol), silver salt (332 mg, 1.20 mmol), 1,10-phen (13 mg, 0.07 mmol), $TMSCF_3$ (0.18 mL, 1.20 mmol), rt, 12 h.
[b] Isolated yields.
[c] Ag_2CO_3 (166 mg, 0.60 mmol).
[d] Ag_2CO_3 (17 mg, 0.06 mmol).
[e] CuI (11 mg, 0.06 mmol).

also detected in 44% yield (Table 1, entry 1). To improve the yield of **1a**, the effect of additive bases was first examined. Results indicated that Et_3N, NaOH, KOH, and 18-crown-6 were all less efficient than K_2CO_3 (entries 2–5). KF led to a good yield and the addition of Ag_2CO_3 improved the yield to 75% (entries 6–10). Other silver salts led to much lower yields (entries 11–13). Various ligands were also examined (entries 8, 14–17), and 1,10-phenanthroline (1,10-phen) was found to be the most effective. Displacement of CuI with CuSCN, CuCN, and CuOTf led to failures and a much lower yield, respectively (entries 18–20). Catalytic amount of CuI gave protonated triazole **4** in 73% yield, while the desired product **1a** in only 13% yield (entry 21). Dramatic effects of solvents on the performance were observed, as the desired product was not generated in a solution of other solvents like toluene, acetonitrile, and tetrahydrofuran (entries 22–24). Thus, the conversion conditions were optimized as 1 equivalent $PMBN_3$, 1.05 equivalents phenylacetylene, 1.3 equivalents CuI, 1.0 equivalents KF in DMF at 0 °C for 3 h in step 1; and 3 equivalents S_8, 4 equivalents Ag_2CO_3, 22 mol% 1,10-phen, and 4 equivalents $TMSCF_3$ at room temperature for 12 hours in step 2.



Scheme 2 Substrate effect of alkynes. *Reagents and conditions*: 1) alkyne (0.31 mmol), $PMBN_3$ (49 mg, 0.30 mmol), CuI (75 mg, 0.39 mmol), KF (18 mg, 0.30 mmol), DMF (2 mL), 0 °C, 3 h; 2) S_8 (29 mg, 0.90 mmol), Ag_2CO_3 (332 mg, 1.20 mmol), 1,10-phen (13 mg, 0.07 mmol), $TMSCF_3$ (0.18 mL, 1.20 mmol), rt, 12 h. Isolated yields are shown. For **1f**, step 2 of the reaction was carried out at 50 °C for 24 h.

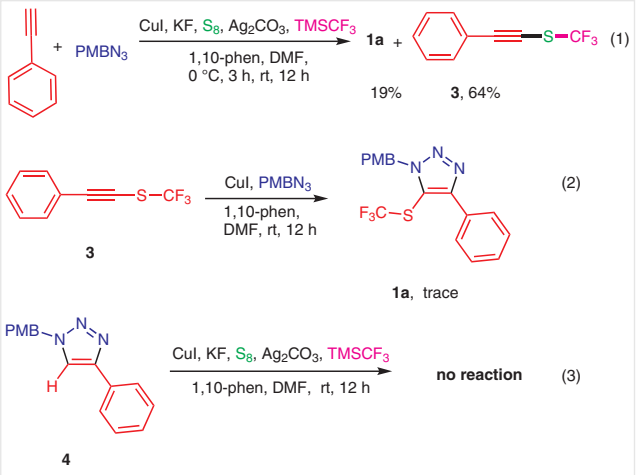
Under the optimized reaction conditions, the scope with respect to terminal alkynes was examined (Scheme 2). Electron-donating groups (methoxyl and alkyl groups) on aryl alkynes favored this multicomponent reaction to form products **1a–d** in quite good yields. Electron-withdrawing groups led to lower yields (**1e–g**). Alkylalkynes afforded the desired products in moderate yields (**1h–j**). The next set of tests examined the influence of azides (Scheme 3). Under the standard one-pot reaction conditions, both benzyl azide and 4-methylbenzyl azide were transformed into the corresponding 5-trifluoromethylthio ethers **2a** and **2b** in quite good yields. Electron-withdrawing groups decreased the yields (**2c–e**). The heterocyclic azides were also suitable substrates (**2f**, **2g**). 2-Phenethyl azide produced the expected product **2h** in 72% yield. Phenyl azide and azidoacetate could not support this transformation under the reaction conditions (**2i**, **2j**).



Scheme 3 Substrate effect of azides. *Reagents and conditions*: 1) phenylacetylene (35 µL, 0.31 mmol), azide (0.30 mmol), CuI (75 mg, 0.39 mmol), KF (18 mg, 0.30 mmol), DMF (2 mL), 0 °C, 3 h; 2): S_8 (29 mg, 0.90 mmol), Ag_2CO_3 (332 mg, 1.20 mmol), 1,10-phen (13 mg, 0.07 mmol), $TMSCF_3$ (0.18 mL, 1.20 mmol), rt, 12 h. Isolated yields are shown. For **2f**, step 2 of the reaction was carried out at 50 °C for 24 h.

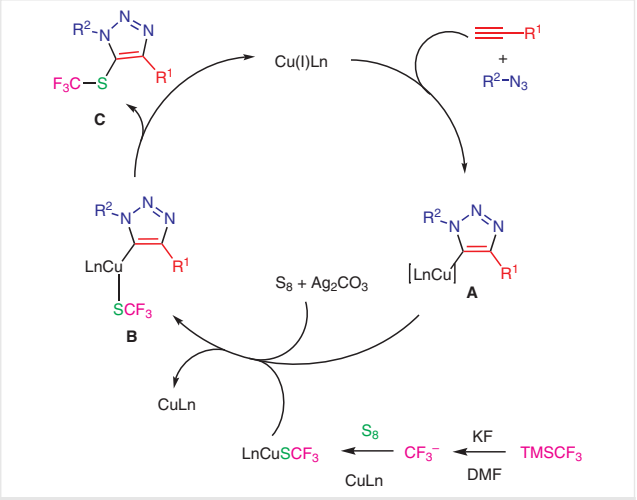
In addition, all reagents like phenylacetylene, $PMBN_3$, CuI, KF, 1,10-phen, $TMSCF_3$, S_8, and Ag_2CO_3 were mixed together to run this multicomponent reaction. The main product was 1-phenyl-2-[(trifluoromethyl)thio]acetylene **3** in 64% yield and the expected trifluoromethyl thioether **1a** was formed in only 19% yield (Scheme 4, Eq 1). Cycloaddition of **3** with $PMBN_3$ in the presence of CuI and 1,10-phen was conducted, and only a trace amount of **1a** was generated (Scheme 4, Eq 2). These results suggested that **3** was not the key intermediate for the expected thiotriazole product **1a** and the copper(I) triazolide should be essentially formed in the first stage of the multistep reaction. Furthermore, protonated triazole **4** was unreactive under the standard

conditions (Scheme 2, Eq 3), suggesting that C–H trifluoromethylthiolation of **4** could not take place in the conditions to afford the target compound **1a**.



Scheme 4 Control experiments. *Reagents and conditions*: phenylacetylene (35 µL, 0.31 mmol), $PMBN_3$ (49 mg, 0.30 mmol), CuI (75 mg, 0.39 mmol), KF (18 mg, 0.30 mmol), S_8 (29 mg, 0.90 mmol), Ag_2CO_3 (332 mg, 1.20 mmol), 1,10-phen (13 mg, 0.07 mmol), $TMSCF_3$ (0.18 mL, 1.20 mmol), DMF (2 mL). Isolated yields are shown (see also Supporting Information).

On the basis of these preliminary results, we propose the reaction mechanism described in Scheme 5. In the presence of KF, CuI, and 1,10-phen, CF_3SiMe_3 and S_8 gets converted into $[(phen)Cu(SCF_3)]_2$,[22] which would react with copper(I) triazolide **A** to form the key intermediate **B**. Reductive elimination of **B** produces the 5-trifluoromethylthiotriazole **C**.[21]



Scheme 5 Proposed mechanism

In conclusion, we have developed a new method for the synthesis of 5-trifluoromethylthio-1,2,3-triazoles via a one-pot multistep reaction from sulfur powder and $TMSCF_3$. All starting materials are readily available, including S_8, $TMSCF_3$, alkynes, and azides.

All reagents and starting materials were of analytical grade, and obtained from commercial sources and used without further purification. All solvents were dried by standard methods. All reactions were conducted under argon in oven-dried glassware. Reactions were monitored by TLC on silica gel plates. Column chromatography was performed on silica gel (300–400 mesh) to purify the products. ^1H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded on a NMR spectrometer at 400 MHz, 101 MHz and 376 MHz, respectively. ^1H and ^{13}C NMR spectra are referenced to $SiMe_4$ or the residual solvent peak. $CDCl_3$ was used as the NMR solvent. All products were further characterized by HRMS (high-resolution mass spectra).

1-(4-Methoxybenzyl)-4-phenyl-5-[(trifluoromethyl)thio]-1*H*-1,2,3-triazole (1a); Typical Procedure

To a solution of $PMBN_3$ (49 mg, 0.30 mmol) in DMF (2 mL) were added CuI (75 mg, 0.39 mmol), KF (18 mg, 0.30 mmol), and phenylacetylene (35 µL, 0.31 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 3 h until the triazole was completely formed. Then, to the solution were added sulfur powder (29 mg, 0.90 mmol), Ag_2CO_3 (332 mg, 1.20 mmol), 1,10-phen (13 mg, 0.07 mol), and $TMSCF_3$ (0.18 mL, 1.2 mmol). The reaction mixture was stirred at rt for 12 h. The solid was filtered and washed with CH_2Cl_2 (30 mL). The organic filtrate was washed with H_2O (2 × 25 mL). The organic layer was dried (anhyd $MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (EtOAc/PE 2:8) to afford **1a** as a pale yellow solid; yield: 80 mg (75%); mp 50–52 °C; R_f = 0.55 (EtOAc/PE 2:8).

^1H NMR (400 MHz, $CDCl_3$): δ = 8.04 (dd, J = 8.1, 1.6 Hz, 2 H), 7.50–7.38 (m, 3 H), 7.31 (d, J = 8.7 Hz, 2 H), 6.88 (d, J = 8.7 Hz, 2 H), 5.67 (s, 2 H), 3.79 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.89, 152.90, 129.59, 129.31, 129.25, 128.65, 127.66 (q, $J_{F,C}$ = 313.1 Hz), 127.45, 126.20, 114.50 (q, $J_{F,C}$ = 2.5 Hz), 114.33, 55.33, 52.30.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –41.54 (s, 3 F).

HRMS (ESI): m/z calcd for $[C_{17}H_{14}F_3N_3OS + H]^+$: 366.0882; found: 366.0877.

1-(4-Methoxybenzyl)-4-(4-methoxyphenyl)-5-[(trifluoromethyl)thio]-1*H*-1,2,3-triazole (1b)

Eluent: EtOAc/PE (1:9); yield: 88 mg (74%); pale yellow solid; mp 73–74 °C; R_f = 0.42 (EtOAc/PE 2:8).

^1H NMR (400 MHz, $CDCl_3$): δ = 8.04–7.96 (m, 2 H), 7.34–7.27 (m, 2 H), 7.02–6.95 (m, 2 H), 6.90–6.84 (m, 2 H), 5.64 (s, 2 H), 3.84 (s, 3 H), 3.78 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.45, 159.87, 152.76, 129.54, 128.79, 127.71 (q, $J_{F,C}$ = 313.3 Hz), 126.30, 121.82, 114.31, 114.08, 113.59 (q, $J_{F,C}$ = 2.5 Hz), 55.30, 55.28, 52.22.

HRMS (ESI): m/z calcd for $[C_{18}H_{16}F_3N_3O_2S + H]^+$: 396.0988; found: 396.0982.

1-(4-Methoxybenzyl)-4-(4-pentyphenyl)-5-[(trifluoromethyl)thio]-1*H*-1,2,3-triazole (1c)

Eluent: EtOAc/PE (1:9); yield: 97 mg (74%); colorless oil; R_f = 0.60 (EtOAc/PE 2:8).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.2 Hz, 2 H), 7.33–7.24 (m, 4 H), 6.87 (d, *J* = 8.7 Hz, 2 H), 5.66 (s, 2 H), 3.79 (s, 3 H), 2.64 (t, *J* = 7.7 Hz, 2 H), 1.72–1.59 (m, 2 H), 1.34 (dt, *J* = 7.5, 3.7 Hz, 4 H), 0.94–0.83 (m, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.87, 153.00, 144.37, 129.53, 128.70, 127.30, 127.71 (q, $J_{F,C}$ = 313.2 Hz), 126.60, 126.30, 114.31, 114.05 (q, $J_{F,C}$ = 2.6 Hz), 55.30, 52.23, 35.77, 31.48, 30.91, 22.53, 14.01.

HRMS (ESI): *m*/*z* calcd for $[C_{22}H_{24}F_3N_3OS + H]^+$: 436.1665; found: 436.1656.

4-[2-(6-Methoxynaphthyl)]-1-(4-methoxybenzyl)-5-[(trifluoromethyl)thio]-1*H*-1,2,3-triazole (1d)

Eluent: EtOAc/PE (1:9); yield: 100 mg (75%); pale yellow solid; mp 88–90 °C; R_f = 0.48 (EtOAc/PE 2:8).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (s, 1 H), 8.14 (dd, *J* = 8.6, 1.8 Hz, 1 H), 7.81 (d, *J* = 8.7 Hz, 2 H), 7.34 (d, *J* = 8.7 Hz, 2 H), 7.21–7.14 (m, 2 H), 6.93–6.86 (m, 2 H), 5.69 (s, 2 H), 3.94 (s, 3 H), 3.79 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.90, 158.50, 153.04, 134.87, 130.15, 129.57, 128.65, 127.71 (q, $J_{F,C}$ = 313.4 Hz), 127.14, 126.92, 126.27, 125.22, 124.48, 119.36, 114.34, 114.24 (q, $J_{F,C}$ = 2.7 Hz), 105.69, 55.37, 55.32, 52.30.

HRMS (ESI): *m*/*z* calcd for $[C_{22}H_{18}F_3N_3O_2S + H]^+$: 446.1145; found: 446.1141.

1-(4-Methoxybenzyl)-4-(4-nitrophenyl)-5-[(trifluoromethyl)thio]-1*H*-1,2,3-triazole (1e)

Eluent: EtOAc/PE (1:9); yield: 44 mg (36%); pale yellow solid; mp 65–67 °C; R_f = 0.44 (EtOAc/PE 2:8).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.39–8.24 (m, 4 H), 7.41–7.29 (m, 2 H), 6.93–6.86 (m, 2 H), 5.69 (s, 2 H), 3.80 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.08, 150.39, 148.12, 135.44, 129.70, 128.04, 127.46 (q, $J_{F,C}$ = 313.4 Hz), 125.70, 123.94, 116.08 (q, $J_{F,C}$ = 2.5 Hz), 114.44, 55.33, 52.57.

HRMS (ESI): *m*/*z* calcd for $[C_{17}H_{13}F_3N_4O_3S + Na]^+$: 433.0553; found: 433.0568.

4-(2-Chlorophenyl)-1-(4-methoxybenzyl)-5-[(trifluoromethyl)thio]-1*H*-1,2,3-triazole (1f)

Step 2 was conducted at 50 °C for 24 h; eluent: EtOAc/PE (1:9); yield: 58 mg (48%); pale yellow oil; R_f = 0.54 (EtOAc/PE 2:8).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52–7.47 (m, 1 H), 7.46–7.33 (m, 3 H), 7.33–7.27 (m, 2 H), 6.93–6.87 (m, 2 H), 5.68 (s, 2 H), 3.80 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.91, 152.64, 133.85, 132.06, 130.78, 129.80, 129.42, 128.52, 127.53 (q, $J_{F,C}$ = 312.6 Hz), 126.77, 126.13, 117.97 (q, $J_{F,C}$ = 2.7 Hz), 114.38, 55.31, 52.56.

HRMS (ESI): *m*/*z* calcd for $[C_{17}H_{13}ClF_3N_3OS + H]^+$: 400.0493; found: 400.0504.

Methyl 1-(4-Methoxybenzyl)-5-[(trifluoromethyl)thio]-1*H*-1,2,3-triazole-4-carboxylate (1g)

Eluent: EtOAc/PE (2:8); yield: 31 mg (30%); pale yellow oil; R_f = 0.30 (EtOAc/PE 2:8).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.24 (m, 2 H), 6.92–6.81 (m, 2 H), 5.66 (s, 2 H), 3.98 (s, 3 H), 3.79 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.10, 159.86, 144.15, 129.64, 127.28 (q, $J_{F,C}$ = 312.6 Hz), 125.42, 122.63 (q, $J_{F,C}$ = 2.9 Hz), 114.43, 55.32, 52.58, 52.54.

HRMS (ESI): *m*/*z* calcd for $[C_{13}H_{12}F_3N_3O_3S + H]^+$: 348.0624; found: 348.0610.

1-(4-Methoxybenzyl)-4-propyl-5-[(trifluoromethyl)thio]-1*H*-1,2,3-triazole (1h)

Eluent: EtOAc/PE (1:9); yield: 43 mg (42%); white solid; mp 52–54 °C; R_f = 0.57 (EtOAc/PE 2:8).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.23 (m, 2 H), 6.86 (d, *J* = 8.7 Hz, 2 H), 5.57 (s, 2 H), 3.79 (s, 3 H), 2.78–2.67 (m, 2 H), 1.77 (dq, *J* = 14.9, 7.4 Hz, 2 H), 0.97 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.78, 155.93, 129.47, 127.62 (q, $J_{F,C}$ = 312.2 Hz), 126.38, 115.48 (q, $J_{F,C}$ = 2.8 Hz), 114.24, 55.30, 52.17, 27.09, 22.08, 13.88.

HRMS (ESI): *m*/*z* calcd for $[C_{14}H_{16}F_3N_3OS + H]^+$: 332.1039; found: 332.1023.

1-(4-Methoxybenzyl)-2-{5-[trifluoromethyl)thio]-1*H*-1,2,3-triazol-4-yl}ethyl 4-Methylbenzene-1-sulfonate (1i)

Eluent: EtOAc/PE (25:75); yield: 52 mg (36%); colorless oil; R_f = 0.45 (EtOAc/PE 25:75).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 8.3 Hz, 2 H), 7.31–7.22 (m, 4 H), 6.90–6.83 (m, 2 H), 5.55 (s, 2 H), 4.37 (t, *J* = 7.1 Hz, 2 H), 3.79 (s, 3 H), 3.13 (t, *J* = 7.1 Hz, 2 H), 2.43 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.94, 150.51, 144.88, 132.77, 129.84, 129.55, 127.91, 127.46 (q, $J_{F,C}$ = 312.3 Hz), 125.95, 117.08 (q, $J_{F,C}$ = 2.5 Hz), 114.34, 67.69, 55.32, 52.37, 25.28, 21.62.

HRMS (ESI): *m*/*z* calcd for $[C_{20}H_{20}F_3N_3O_4S_2 + H]^+$: 488.0920; found: 488.0914.

1-(4-Methoxybenzyl)-2-{5-[trifluoromethyl)thio]-1*H*-1,2,3-triazol-4-yl}ethyl Benzoate (1j)

Eluent: EtOAc/PE (2:8); yield: 73 mg (56%); white solid; mp 74–76 °C; R_f = 0.39 (EtOAc/PE 2:8).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96–7.88 (m, 2 H), 7.58–7.50 (m, 1 H), 7.42–7.36 (m, 2 H), 7.25–7.20 (m, 2 H), 6.88–6.81 (m, 2 H), 5.59 (s, 2 H), 4.68 (t, *J* = 6.9 Hz, 2 H), 3.78 (s, 3 H), 3.27 (t, *J* = 6.9 Hz, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.28, 159.85, 152.07, 132.93, 130.00, 129.57, 129.38, 128.30, 127.54 (q, $J_{F,C}$ = 312.2 Hz), 126.17, 116.77 (q, $J_{F,C}$ = 2.7 Hz), 114.31, 62.77, 55.29, 52.37, 25.05.

HRMS (ESI): *m*/*z* calcd for $[C_{20}H_{18}F_3N_3O_3S + H]^+$: 438.1094; found: 438.1083.

1-Benzyl-4-phenyl-5-[(trifluoromethyl)thio]-1*H*-1,2,3-triazole (2a)[19]

Eluent: EtOAc/PE (1:9); yield: 70 mg (70%); colorless oil; R_f = 0.71 (EtOAc/PE 2:8).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15–7.97 (m, 2 H), 7.51–7.42 (m, 3 H), 7.41–7.30 (m, 5 H), 5.74 (s, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 152.92, 134.17, 129.35, 129.21, 129.00, 128.72, 128.66, 127.92, 127.65 (q, $J_{F,C}$ = 314.3 Hz), 127.45, 114.78 (q, $J_{F,C}$ = 2.7 Hz), 52.69.

HRMS (ESI): *m*/*z* calcd for $[C_{16}H_{12}F_3N_3S + H]^+$: 336.0777; found: 336.0785.

1-(4-Methylbenzyl)-4-phenyl-5-[(trifluoromethyl)thio]-1*H*-1,2,3-triazole (2b)[19]

Eluent: EtOAc/PE (1:9); yield: 85 mg (81%); pale yellow oil; R_f = 0.47 (EtOAc/PE 1:9).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12–8.03 (m, 2 H), 7.50–7.42 (m, 3 H), 7.25–7.15 (m, 4 H), 5.70 (s, 2 H), 2.34 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 152.89, 138.65, 131.19, 129.64, 129.31, 129.26, 128.64, 127.96, 127.67 (q, $J_{F,C}$ = 313.2 Hz), 127.46, 114.65 (q, $J_{F,C}$ = 2.5 Hz), 52.52, 21.14.

HRMS (ESI): *m*/*z* calcd for $[C_{17}H_{14}F_3N_3S + H]^+$: 350.0933; found: 350.0943.

1-(4-Bromobenzyl)-4-phenyl-5-[(trifluoromethyl)thio]-1*H*-1,2,3-triazole (2c)

Eluent: EtOAc/PE (1:9); yield: 78 mg (63%); pale yellow solid; mp 90–92 °C; R_f = 0.68 (EtOAc/PE 2:8).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (dt, *J* = 8.0, 1.4 Hz, 2 H), 7.54–7.40 (m, 5 H), 7.22 (d, *J* = 8.4 Hz, 2 H), 5.68 (s, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.02, 133.08, 132.20, 129.67, 129.46, 129.04, 128.70, 127.57 (q, $J_{F,C}$ = 313.3 Hz), 127.45, 122.97, 114.76 (q, $J_{F,C}$ = 2.6 Hz), 51.99.

HRMS (ESI): *m*/*z* calcd for $[C_{16}H_{11}BrF_3N_3S + H]^+$: 413.9882; found: 413.9888.

1-(4-Fluorobenzyl)-4-phenyl-5-[(trifluoromethyl)thio]-1*H*-1,2,3-triazole (2d)

Eluent: EtOAc/PE (1:9); yield: 71 mg (61%); pale yellow solid; mp 81–82 °C; R_f = 0.37 (EtOAc/PE 1:9).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11–8.00 (m, 2 H), 7.51–7.39 (m, 3 H), 7.39–7.32 (m, 2 H), 7.10–7.02 (m, 2 H), 5.70 (s, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.86 (d, $J_{F,C}$ = 248.2 Hz), 152.98, 129.99 (d, $J_{F,C}$ = 8.3 Hz), 129.90, 129.43, 129.08, 128.70, 127.59 (q, $J_{F,C}$ = 313.3 Hz), 127.44, 116.02 (d, $J_{F,C}$ = 21.9 Hz), 114.65 (q, $J_{F,C}$ = 2.5 Hz), 51.95.

HRMS (ESI): *m*/*z* calcd for $[C_{16}H_{11}F_4N_3S + H]^+$: 354.0683; found: 354.0691.

1-(4-Cyanobenzyl)-4-phenyl-5-[(trifluoromethyl)thio]-1*H*-1,2,3-triazole (2e)

Eluent: EtOAc/PE (2:8); yield: 65 mg (60%); pale yellow oil; R_f = 0.33 (EtOAc/PE 2:8).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09–8.02 (m, 2 H), 7.70–7.65 (m, 2 H), 7.51–7.40 (m, 5 H), 5.78 (s, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.14, 139.07, 132.83, 129.63, 128.82, 128.76, 128.53, 127.47 (q, $J_{F,C}$ = 313.5 Hz), 127.44, 118.08, 115.01 (q, $J_{F,C}$ = 2.6 Hz), 112.92, 51.88.

HRMS (ESI): *m*/*z* calcd for $[C_{17}H_{11}F_3N_4S + H]^+$: 361.0729; found: 361.0737.

4-Phenyl-1-[(thiophen-2-yl)methyl]-5-[(trifluoromethyl)thio]-1*H*-1,2,3-triazole (2f)

Step 2 was conducted at 50 °C for 24 h; eluent: EtOAc/PE (1:9); yield: 65 mg (64%); white solid; mp 65–67 °C; R_f = 0.42 (EtOAc/PE 1:9).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09–8.02 (m, 2 H), 7.51–7.40 (m, 3 H), 7.31 (dd, *J* = 5.1, 1.2 Hz, 1 H), 7.18 (dd, *J* = 3.6, 1.1 Hz, 1 H), 6.99 (dd, *J* = 5.2, 3.5 Hz, 1 H), 5.90 (d, *J* = 0.8 Hz, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 152.84, 135.76, 129.42, 129.11, 128.69, 128.28, 127.64 (q, $J_{F,C}$ = 313.2 Hz), 127.47, 127.19, 127.06, 114.39 (q, $J_{F,C}$ = 2.3 Hz), 47.21.

HRMS (ESI): *m*/*z* calcd for $[C_{14}H_{10}F_3N_3S_2 + H]^+$: 342.0341; found: 342.0349.

1-{[5-(2-Chloropyridyl)]methyl}-4-phenyl-5-[(trifluoromethyl)-thio]-1*H*-1,2,3-triazole (2g)

Eluent: EtOAc/PE (1:9); yield: 61 mg (55%); pale yellow oil; R_f = 0.56 (EtOAc/PE 2:8).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.48 (d, *J* = 2.5 Hz, 1 H), 8.08–7.99 (m, 2 H), 7.68 (dd, *J* = 8.3, 2.6 Hz, 1 H), 7.52–7.43 (m, 3 H), 7.35 (d, *J* = 8.2 Hz, 1 H), 5.72 (s, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.19, 152.27, 149.30, 138.68, 129.64, 128.77, 128.76, 128.71, 127.46 (q, $J_{F,C}$ = 313.3 Hz), 127.46, 124.78, 114.82 (q, $J_{F,C}$ = 2.6 Hz), 49.26.

HRMS (ESI): *m*/*z* calcd for $[C_{15}H_{10}ClF_3N_4S + H]^+$: 371.0340; found: 371.0352.

4-Phenyl-1-(2-phenethyl)-5-[(trifluoromethyl)thio]-1*H*-1,2,3-triazole (2h)[19]

Eluent: EtOAc/PE (1:9); yield: 75 mg (72%); pale yellow oil; R_f = 0.70 (EtOAc/PE 2:8).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09–7.94 (m, 2 H), 7.51–7.40 (m, 3 H), 7.29 (dddd, *J* = 12.4, 7.5, 4.6, 2.2 Hz, 3 H), 7.17–7.09 (m, 2 H), 4.80–4.71 (m, 2 H), 3.35–3.27 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 152.30, 136.62, 129.33, 129.26, 128.84, 128.74, 128.66, 127.63 (q, $J_{F,C}$ = 313.0 Hz), 127.53, 127.27, 115.33 (q, $J_{F,C}$ = 2.4 Hz), 49.89, 36.60.

HRMS (ESI): *m*/*z* calcd for $[C_{17}H_{14}F_3N_3S + H]^+$: 350.0933; found: 350.0938.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690716.

References

(1) Shao, X.-X.; Xu, C.-F.; Lu, L.; Shen, Q.-L. *Acc. Chem. Res.* **2015**, *48*, 1227.

(2) (a) Leroux, F.; Jeschke, P.; Schlosser, M. *Chem. Rev.* **2005**, *105*, 827. (b) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214. (c) Xu, X.-H.; Matsuzaki, K.; Shibata, N. *Chem. Rev.* **2015**, *115*, 731.

(3) (a) Ferreira, S. B.; Sodero, A. C.; Cardoso, M. F.; Lima, E. S.; Kaiser, C. R.; Silva, F. P.; Ferreira, V. F. *J. Med. Chem.* **2010**, *53*, 2364. (b) Lauria, A.; Delisi, R.; Mingoia, F.; Terenzi, A.; Martorana, A.; Barone, G.; Almerico, A. M. *Eur. J. Org. Chem.* **2014**, 3289.

(4) Liebert, T.; Hänsch, C.; Heinze, T. *Macromol. Rapid Commun.* **2006**, *27*, 208.

(5) (a) Devender, N.; Gunjan, S.; Chhabra, S.; Singh, K.; Pasam, V. R.; Shukla, S. K.; Sharma, A.; Jaiswal, S.; Singh, S. K.; Kumar, Y.; Lal, J.; Trivedi, A. K.; Tripathi, R.; Tripathi, R. P. *Eur. J. Med. Chem.*

2016, *109*, 187. (b) Boechat, N.; Ferreira, M. L. G.; Pinheiro, L. C. S.; Jesus, A. M. L.; Leite, M. M. M.; Junior, C. C. S.; Aguiar, A. C. C.; Andrade, I. M.; Krettli, A. U. *Chem. Biol. Drug Des.* **2014**, *84*, 325.
(6) (a) Agalave, S. G.; Maujan, S. R.; Pore, V. S. *Chem. Asian J.* **2011**, *6*, 2696. (b) Dheer, D.; Singh, V.; Shankar, R. *Bioorg. Chem.* **2017**, *71*, 30.
(7) (a) Huisgen, R. *Angew. Chem. Int. Ed.* **1963**, *2*, 565. (b) Huisgen, R. *Angew. Chem. Int. Ed.* **1963**, *2*, 633.
(8) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596.
(9) Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057.
(10) (a) Wei, F.; Li, H.-Y.; Song, C.-L.; Ma, Y.-D.; Zhou, L.; Tung, C.-H.; Xu, Z.-H. *Org. Lett.* **2015**, *17*, 2860. (b) Wei, F.; Wang, W.-G.; Ma, Y.-D.; Tung, C.-H.; Xu, Z.-H. *Chem. Commun.* **2016**, *52*, 14188.
(11) Song, W.-Z.; Zheng, N. *Org. Lett.* **2017**, *19*, 6200.
(12) Song, W.-Z.; Zheng, N.; Li, M.; Dong, K.; Li, J.-H.; Ullah, K.; Zheng, Y.-B. *Org. Lett.* **2018**, *20*, 6705.
(13) (a) Ding, S.; Jia, G.; Sun, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 1877. (b) Luo, Q.; Jia, G.; Sun, J.; Lin, Z. *J. Org. Chem.* **2014**, *79*, 11970.
(14) Destito, P.; Couceiro, J. R.; Faustino, H.; López, F.; Mascarenas, J. L. *Angew. Chem. Int. Ed.* **2017**, *56*, 10766.
(15) (a) Wang, W.; Lin, Y.; Ma, Y.; Tung, C.-H.; Xu, Z. *Org. Lett.* **2018**, *20*, 2956. (b) Wang, W.; Peng, X.; Wei, F.; Tung, C.-H.; Xu, Z. *Angew. Chem. Int. Ed.* **2016**, *55*, 649.
(16) Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529.
(17) Wei, F.; Zhou, T.; Ma, Y.-D.; Tung, C.-H.; Xu, Z.-H. *Org. Lett.* **2017**, *19*, 2098.
(18) Shen, Q.; Han, E.-J.; Huang, Y.-G.; Chen, Q.-Y.; Guo, Y. *Synthesis* **2015**, *47*, 3936.
(19) Song, W.-Z.; Zheng, N.; Li, M.; He, J.-N.; Li, J.-H.; Dong, K.; Ullah, K.; Zheng, Y.-B. *Adv. Synth. Catal.* **2019**, *361*, 469.
(20) (a) Wu, G.-L.; Wu, Q.-P. *ChemistrySelect* **2018**, *3*, 5212. (b) Wu, G.-L.; Wu, Q.-P. *Adv. Synth. Catal.* **2018**, *360*, 1949. (c) Wu, G.-L.; Wu, Q.-P. *Synthesis* **2018**, *50*, 2768.
(21) Zhang, L.-L.; Li, Y.-T.; Gao, T.; Guo, S.-S.; Yang, B.; Meng, Z.-H.; Dai, Q.-P.; Xu, Z.-B.; Wu, Q.-P. *Synthesis* **2019**, in press; DOI: 10.1055/s-0039-1690618.
(22) Weng, Z.; He, W.; Chen, C.; Lee, R.; Tan, D.; Lai, Z.; Kong, D.; Yuan, Y.; Huang, K.-W. *Angew. Chem. Int. Ed.* **2013**, *52*, 1548.