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Synthesis of fluorinated triazole and isoxazole derivatives by electrochemical fluorination

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ABSTRACT

Partially fluorinated triazole derivatives were synthesized through anodic fluorination of alkynes having arylthio group and following Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) with benzyl azide. The other route toward the fluorinated triazoles, namely the anodic fluorination of triazole derivatives once prepared by advanced CuAAC of the alkyne and azide above was also investigated. It was shown that these two routes are mutually complementary methodology for the synthesis of new mono- and difluoromethyltriazole derivatives. Furthermore, Cu(I)-catalyzed isoxazole synthesis from fluorinated alkynes and imidoyl chloride was demonstrated.

1. Introduction

Organofluorine compounds are highly useful in various fields such as pharmaceutical chemistry and material science due to their unique chemical, physical, and biological properties.[1] Since almost all organofluorine compounds are not naturally occurring, they must be synthesized according to appropriate molecular design. Recent development of synthetic technique of organofluorine compounds is very noticeable. Among them, the anodic partial fluorination proceeds through electrochemical oxidation of organic compounds and following fluorination with fluoride ion used as a supporting electrolyte. This electrochemical method does not require any hazardous reagents, it is therefore regarded as a green method.[2] We have demonstrated the synthesis of partially fluorinated compounds having various functional groups for bioactive applications and synthetic building blocks so far.[3] Previously, we reported the first electrochemical synthesis of a series of fluorinated terminal alkynes,[4] which are potentially applicable as synthetic building blocks in organic synthesis. One promising reaction using terminal alkyne is Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC). This so-called click chemistry can produce a 1,4-disubstituted triazole derivative in excellent yield without byproduct under mild conditions.[5] For example, Jørgensen and his co-workers reported the synthesis of fluorinated triazoles by CuAAC of propargyl fluoride and azide derivative.[6] Recently, Médebielle and his co-workers reported the synthesis and antiviral properties of difluoromethylbenzoxazole pyrimidine thioether derivatives as non-nucleoside HIV-1 reverse transcriptase inhibitors.[7] In consideration to these facts, the combination of anodic fluorination and CuAAC is of interest to develop versatile organofluorine compounds having a triazole moiety. Our goal in this study is to prepare a variety of fluorinated triazole derivatives from terminal alkyne having arylthio group and benzyl azide through two pathways, i.e., anodic fluorination of alkynes, followed by CuAAC (Route A) and anodic fluorination of triazoles once prepared by CuAAC (Route B) as shown in Scheme 1. In addition, another kind of click chemistry, the Cu(I)-catalyzed isoxazole synthesis[8] was also investigated using fluorinated alkynes (Route C).

2. Results and discussion

According to Scheme 1, Route A, the electrochemical partial fluorination of alkyne derivative **1** was carried out under optimized conditions with a passage of constant current between Pt anode and Pt cathode (Table 1).[4] The fluorination of the starting materials takes place through the anodic oxidation at the arylthio group, followed by deprotonation and subsequent fluorination at its α-position. In general, sulfides having an electron-withdrawing group undergo selective anodic fluorination with good efficiencies due to the stabilization of once fluorinated products.[9] We reported previously that an acetylene moiety attached to the α-carbon can act as an electron-withdrawing group such as esters and nitriles evidenced by electrochemical measurements.[4] In the case of

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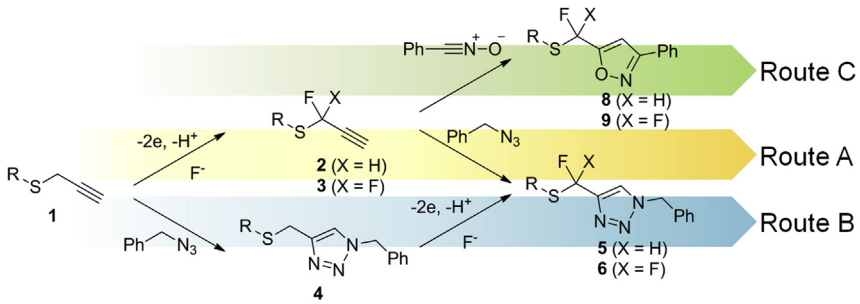
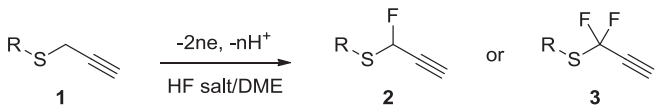
0040-4020/

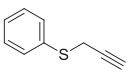
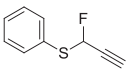
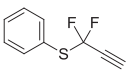
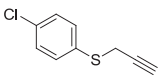
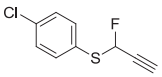
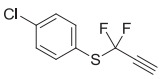
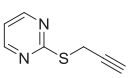
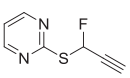
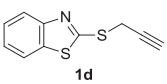
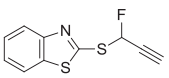
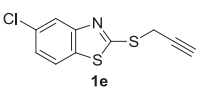
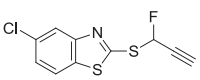
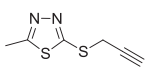
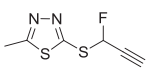
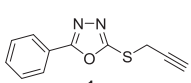
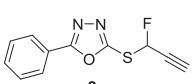


Scheme 1. Routes toward triazoles and isoxazoles with fluoromethylsulfenyl group.

fluorination of **1a** and **1b**, mono-fluorinated products (**2a** and **2b**) and di-fluorinated products (**3a** and **3b**) were obtained selectively depending on the supporting HF salt used and electricity. The free triethylamine contained in Et_3N-3HF effectively acted as a base at the deprotonation step for difluorination even though the sacrificial oxidation of triethylamine itself also occurred. Other mono-fluorinated products (**2c**–**2g**) were also successfully obtained under optimal conditions including the choice of supporting HF salts. These fluorinated alkynes were readily available for CuAAC. As indicated in our previous study, mono-fluorinated products **2a** and

Table 1
Electrochemical fluorination of alkyne derivative **1**



Entry	Alkyne 1	Supporting salt	Electricity (F/mol)	Product	Yield (%)[a]
1	 **1a**	Et_3N-5HF	4.0	 **2a**	77[b,c]
2		Et_3N-3HF	8.0	 **3a**	70[c]
3	 **1b**	Et_3N-5HF	4.0	 **2b**	35
4		Et_3N-3HF	8.0	 **3b**	66[c]
5	 **1c**	Et_3N-3HF	12.0	 **2c**	55[d]
6	 **1d**	Et_4NF-3HF	10.0	 **2d**	20[d]
7	 **1e**	Et_3N-3HF	12.0	 **2e**	30[d]
8	 **1f**	Et_4NF-4HF	7.0	 **2f**	38
9	 **1g**	Et_4NF-4HF	8.0	 **2g**	42

[a] Isolated yield.
[b] Determined by ^{19}F NMR.
[c] Ref. 4a.
[d] Ref. 4b.

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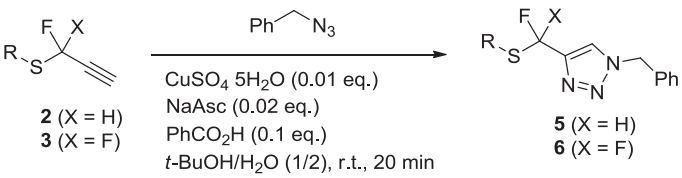
2b were relatively unstable to be easily transformed to fluoroallenes under basic conditions; therefore, they were used for further reactions immediately after purification.

The CuAAC of the obtained mono-fluorinated alkynes (**2a**–**2g**) and di-fluorinated alkynes (**3a** and **3b**) was carried out with benzyl azide in the presence of $CuSO_4$, sodium ascorbate and benzoic acid in *t*-BuOH/H_2O (1/2) according to the conditions reported (Table 2).[10] The CuAAC of di-fluorinated substrates **3a** and **3b** afforded the corresponding 1,4-disubstituted triazole products **6a** and **6b** in high yields (Entries 2 and 4). Among the mono-fluorinated substrates, the CuAAC of **2a**–**2c** and benzyl azide did not proceed at all accompanying the formation of unidentified defluorinated products owing to the instability of **2a** and **2b**. Although **2c** seemed to be stable due to the electron-withdrawing 2-pyrimidyl group, the desired product was not formed. On the other hand, substrates **2d**–**2g** were successfully transformed to desired products **5d**–**5g** in good to excellent yields, respectively. In contrast to **2a** and **2c**, the heterocyclic groups of **2d**–**2g** are electron-withdrawing to suppress the defluorination, therefore CuAAC seemed to proceed smoothly without defluorination. Thus, the two-step reactions containing electrochemical fluorination and the following CuAAC (Scheme 1, Route A) gave partially fluorinated triazole derivatives.

Table 2
CuAAC of fluorinated alkyne **2** and **3**



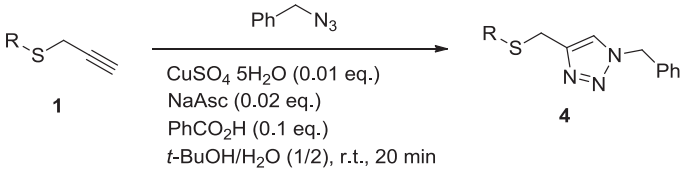
Entry	Fluorinated alkyne	Product	Yield (%)[a]
1	**2a**	**5a**	0[b]
2	**3a**	**6a**	80
3	**2b**	**5b**	0[b]
4	**3b**	**6b**	90
5	**2c**	**5c**	0[b]
6	**2d**	**5d**	80
7	**2e**	**5e**	98
8	**2f**	**5f**	71
9	**2g**	**5g**	96

[a] Isolated yield.
[b] Unidentified defluorinated products were mostly formed.

The Route B shown in Scheme 1 contains the CuAAC of substrate **1** and benzyl azide to form 1,4-disubsituted triazoles **4**, and subsequent anodic fluorination of **4**. As expected, the CuAAC of **1a**–**1g** with benzyl azide successfully afforded the corresponding triazoles **4a**–**4g** in good yields under optimized conditions (Table 3).

The second step of Route B, the anodic fluorination of triazoles **4**, was performed in a similar manner to the fluorination step in Route A. The triazole moiety seems to work as a weak electron-withdrawing group similarly to alkyne moiety, which is advantageous for the anodic fluorination of the substrates. In order to estimate the oxidation behavior of substrate **4**, density functional theory (DFT) calculation for **4a** was carried out.[11] The highest occupied molecular orbital (HOMO) of **4a** was located mainly on the phenylthio moiety, not on the benzyl moiety, indicating the exclusive oxidation at the phenylthio moiety. Consequently the following deprotonation and fluorination can take place at the α-position of the phenylthio group. We then investigated the anodic fluorination of triazoles **4** under the same conditions with that of **1**

Table 3
CuAAC of alkyne **1**



Entry	Alkyne	Product	Yield (%)[a]
1	**1a**	**4a**	85
2	**1b**	**4b**	82
3	**1c**	**4c**	97
4	**1d**	**4d**	94
5	**1e**	**4e**	53
6	**1f**	**4f**	89
7	**1g**	**4g**	99

[a] Isolated yield.

for comparison (Table 4). The anodic fluorination of **4a** and **4b** did not yield any fluorinated products after a passage of 4 F/mol of charge in the presence of Et_3N-5HF. Instead, a byproduct, aldehyde **7** was obtained in moderate yield (Entries 1 and 3). Interestingly, when Et_3N-3HF was used as fluorine source and supporting salt, (Entries 2 and 4), di-fluorinated products **6a** and **6b** were obtained as a main product However, aldehyde **7** was also detected even under these conditions. Other substrates (**4c**–**4g**) were treated under optimized conditions for the case of mono-fluorination of the corresponding alkynes as shown in Table 1, and resulted in producing mono-fluorinated products **5c**–**5g**, together with the formation of aldehyde **7**. Although the CuAAC of **2c** and benzyl azide did not give the corresponding **5c** at all in Route A (Table 2, Entry 5), the anodic fluorination of **4c** afforded mono-fluorinated triazole **5c** in moderate yield in Route B (Table 4, Entry 5).

Finally, the fluorinated alkynes (**2** and **3**) were utilized for another click chemistry, namely the Cu(I)-catalyzed cyclization with a nitrile oxide derived from an imidoyl chloride[8] to produce isoxazoles **8** and **9** as shown in Route C, Scheme 1. As summarized in Table 5, each fluorinated alkyne successfully gave the isoxazole derivatives in moderate yields except for the case of Entry 1, in which undesired defluorination of substrate **2a** mainly occurred owing to the instability of **2a**. In Entry 4, the alkyne having the pyrimidylthio group (**2c**) underwent the cyclization in 35% yield different from the case of CuAAC.

3. Conclusion

We have synthesized various fluorinated compounds by combining the CuAAC and electrochemical fluorination. Through Route A, the partially fluorinated alkynes underwent the CuAAC with benzyl azide to give the fluorinated triazole products. In Route B, anodic fluorination of the triazole substrates was successfully demonstrated to give the desired products; however the considerable amount of the byproduct was also detected. We found that the partially fluorinated triazole derivatives could be obtained from alkynes and benzyl azide by appropriate choice of the Routes. The partially fluorinated alkynes also reacted with imidoyl chloride in the presence of Cu(I) as a catalyst to afford the corresponding partially fluorinated isoxazoles.

4. Experimental

4.1. General

^1H, ^{13}C, and ^{19}F NMR spectra were recorded on JEOL JNM EX-270 (^1H: 270 MHz, ^{13}C: 67.8 MHz, ^{19}F: 254 MHz) spectrometer in $CDCl_3$.

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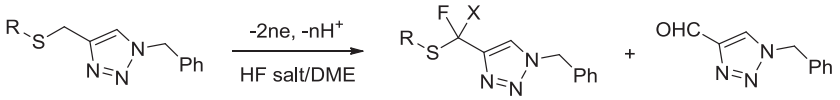
Table 4
Electrochemical fluorination of 1,2,3-triazole derivative **4**

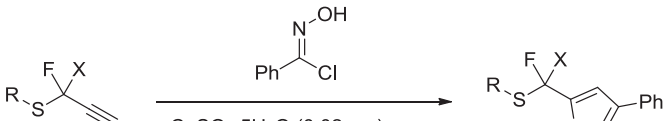


4 **5** (X = H) **6** (X = F) **7**

Entry	Substrate	Supporting salt	Electricity (F/mol)	Yield of 5 (%)[a]	Yield of 6 (%)[a]	Yield of 7 (%)[b]	Total yield (%)
1	**4a**	Et_3N-5HF	4.0	—	—	47[c]	47
2	**4a**	Et_3N-3HF	8.0	—	35	24	59
3	**4b**	Et_3N-5HF	4.0	—	—	48[c]	48
4	**4b**	Et_3N-3HF	8.0	—	53[c]	17	70
5	**4c**	Et_3N-3HF	12.0	61[c]	—	13	74
6	**4d**	Et_4NF-3HF	10.0	22	—	51	73
7	**4e**	Et_3N-3HF	12.0	64[c]	—	18	82
8	**4f**	Et_4NF-4HF	7.0	55[c]	—	32	87
9	**4g**	Et_4NF-4HF	8.0	30	—	52	82

[a] Determined by ^{19}F NMR.
[b] Determined by ^{1}H NMR.
[c] Isolated yield.

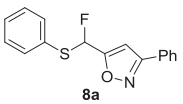
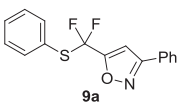
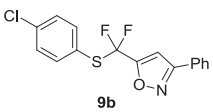
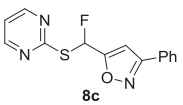
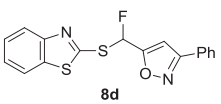
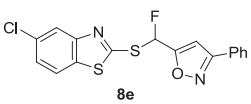
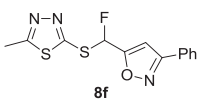
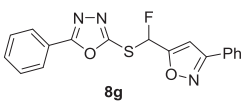
Table 5
Cu(I)-Catalyzed synthesis of 3,5-substituted isoxazole **8** and **9**



2 (X = H)
3 (X = F)

$CuSO_4$ 5H_2O (0.02 eq.)
NaAsc (0.1 eq.)
$KHCO_3$ (4.3 eq.)
t-BuOH/H_2O (1/1), r.t., 15 h

8 (X = H)
9 (X = F)

Entry	Substrate	Product	Yield (%)[a]
1	**2a**	 **8a**	0[b]
2	**3a**	 **9a**	35
3	**3b**	 **9b**	40
4	**2c**	 **8c**	35
5	**2d**	 **8d**	38
6	**2e**	 **8e**	56
7	**2f**	 **8f**	35
8	**2g**	 **8g**	72

[a] Isolated yield.
[b] Unidentified defluorinated product was mostly detected.

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The chemical shifts for ^{1}H, ^{13}C, and ^{19}F NMR spectra were given in δ (ppm) from internal TMS, $CDCl_3$, and monofluorobenzene (−36.5 ppm), respectively. EI mass spectra were recorded on Shimadzu GC−MS-QP5050A mass spectrometer. Cyclic voltammetry measurements were carried out using ALS 600A Electrochemical Analyzer. The preparative electrolysis was performed using Metronix Corp. constant current power supply model 5944 monitored with coulomb/ampere hour meter HF-201. High resolution mass spectra (HRMS) were recorded on JEOL The MStaion JMS-700. Melting point was determined using Yanako Micro Melting Point Apparatus MP-500P. Molecular orbital were obtained using Gaussian 03W calculated by DFT B3LYP/6-31G+(2d,p)//B3LYP/6-31G(d).[11]

4.2. Materials

All chemicals were obtained commercially and were used without further purification. Dry solvents were used as received. Alkynes **1a**−**1g** were synthesized according to the literature.[4] The known compounds **1a**−**1e** were characterized by comparison with spectral data in the literature.[4]

*4.2.1. 2-Methyl-5-(prop-2-yn-1-ylthio)-1,3,4-thiadiazole (**1f**).* Dark brown oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 4.04 (d, J=2.7 Hz, 2H), 2.75 (s, 3H), 2.34 (t, J=2.7 Hz, 1H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 165.4, 162.9, 77.6, 72.5, 21.0. HRMS(EI): m/z [M^+] calcd for $C_6H_6N_2S_2$: 169.9972; Found: 169.9977.

*4.2.2. 2-Phenyl-5-(prop-2-yn-1-ylthio)-1,3,4-oxadiazole (**1g**).* White solid. Mp=45.4−46.4 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 8.03−8.00 (m, 2H), 7.57−7.46 (m, 3H), 4.07 (d, J=2.7 Hz, 2H), 2.35 (t, J=2.7, 1H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 166.1, 162.4, 131.7, 129.0, 126.6, 123.3, 76.5, 72.9. HRMS(EI): m/z [M^+] calcd for $C_{11}H_8N_2OS$: 216.0357; Found: 216.0359.

4.3. Typical procedure for anodic fluorination

Anodic oxidation of **1a** (1.0 mmol) was carried out in an undivided cell equipped with a platinum plate anode (2×2 cm^2) and a platinum cathode (2×2 cm^2) in a solution of dimethoxyethane (DME) (10 ml) containing 1 M HF salt at room temperature. A constant current (5.0 mA/cm^2) was passed until the starting material **1a** was mostly consumed (monitored by TLC). After the electrolysis, the electrolytic solution was passed through a short column filled with silica gel using EtOAc as an eluent to remove the HF salt. The fluorinated product was further purified by column chromatography over silica gel using a mixed solution of EtOAc and hexane as an eluent. Fluorinated products, **2a**−**2e**, **3a**, **3b** were identified by comparison with ^{19}F NMR and MS spectral data of their authentic samples.

*4.3.1. 2-((1-Fluoroprop-2-yn-1-yl)thio)-5-methyl-1,3,4-thiadiazole (**2f**).* Pale yellow oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 6.79 (dd, J=52.7, 2.2 Hz, 1H), 3.10 (dd, J=4.9, 2.2 Hz, 1H), 2.81 (s, 3H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 168.4, 158.8 (d, J=3.4 Hz), 85.2 (d, J=222.5 Hz), 81.3 (d, J=7.8 Hz), 74.8 (d, J=29.6 Hz), 15.8. ^{19}F NMR (254 MHz, $CDCl_3$): δ −66.0 (dd, J=53.6, 5.6 Hz). HRMS(EI): m/z [M^+] calcd for $C_6H_5FN_2S_2$: 187.9878; Found: 187.9879.

*4.3.2. 2-((1-Fluoroprop-2-yn-1-yl)thio)-5-phenyl-1,3,4-oxadiazole (**2g**).* Pale yellow oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 8.05−8.03 (m, 2H), 7.57−7.49 (m, 3H), 6.90 (dd, J=52.7, 1.9 Hz, 1H), 3.14 (dd, J=4.6, 1.9 Hz, 1H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 167.0, 159.0, 132.2, 129.2, 126.9, 123.1, 84.4 (d, J=225.2 Hz), 81.75 (d, J=7.8 Hz), 74.52 (d, J=29.0 Hz). ^{19}F NMR (254 MHz, $CDCl_3$): δ −65.6 (dd, J=51.8, 5.6 Hz). HRMS(EI): m/z [M^+] calcd for $C_{11}H_7FN_2OS$: 234.0263; Found: 234.0259.

4.4. Typical procedure for CuAAC

To a stirred solution of alkyne **1a** (0.5 mmol) and benzyl azide (1.1 equiv) in t-BuOH/H_2O (1/2, 3.0 ml) was added $CuSO_4 \cdot 5H_2O$ (0.01 equiv), sodium ascorbate (0.02 equiv) and benzoic acid (0.1 equiv), and the reaction mixture was stirred for 20 min at room temperature. Dichloromethane (10 ml) was added to the mixture and the organic phase was washed with water and brine. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The product triazole was further purified by column chromatography over silica gel using a mixed solution of EtOAc and hexane as an eluent.

*4.4.1. 1-Benzyl-4-((phenylthio)methyl)-1H-1,2,3-triazole (**4a**).* White solid. Mp=74.8−75.8 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.36−7.16 (m, 11H), 5.45 (s, 2H), 4.20 (s, 2H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 144.7, 135.0, 134.4, 129.3, 128.6, 128.5, 128.2, 127.4, 126.1, 121.9, 53.5, 28.5. HRMS(FAB): m/z [M+H^+] calcd for $C_{16}H_{16}N_3S$: 282.1065; Found: 282.1074.

*4.4.2. 1-Benzyl-4-(((4-chlorophenyl)thio)methyl)-1H-1,2,3-triazole (**4b**).* White solid. Mp=93.6−95.0 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.38−7.33 (m, 3H), 7.22−7.15 (m, 7H), 5.45 (s, 2H), 4.17 (s, 2H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 144.3, 134.3, 133.4, 132.0, 130.8, 128.6, 128.6, 128.2, 127.4, 121.8, 53.5, 28.6. HRMS(EI): m/z [M^+] calcd for $C_{16}H_{14}ClN_3S$: 315.0597; Found: 315.0596.

*4.4.3. 2-(((1-Benzyl-1H-1,2,3-triazol-4-yl)methyl)thio)pyrimidine (**4c**).* Pale yellow oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 8.50 (d, J=4.6 Hz, 2H), 7.45 (s, 1H), 7.36−7.34 (m, 3H), 7.24−7.21 (m, 2H), 6.97 (t, J=4.9 Hz, 1H), 5.48 (s, 2H), 4.48 (s, 2H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 170.6, 156.7, 144.3, 134.2, 128.3, 127.9, 127.3, 122.1, 116.3, 53.3, 25.0. HRMS(EI): m/z [M^+] calcd for $C_{14}H_{13}N_5S$: 283.0892; Found: 283.0890.

*4.4.4. 2-(((1-Benzyl-1H-1,2,3-triazol-4-yl)methyl)thio)benzo[d]thiazole (**4d**).* White solid. Mp=104.0−105.0 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.83 (d, J=7.6 Hz, 1H), 7.75 (d, J=7.8 Hz, 1H), 7.53 (s, 1H), 7.42−7.39 (m, 1H), 7.33−7.31 (m, 4H), 7.22−7.18 (m, 2H), 5.47 (s, 2H), 4.66 (s, 2H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 165.4, 152.6, 143.7, 135.1, 134.2, 128.7, 128.3, 127.6, 125.8, 124.1, 122.7, 121.1, 120.8, 53.7, 27.5. HRMS(EI): m/z [M^+] calcd for $C_{17}H_{14}N_4S_2$: 338.0660; Found: 338.0650.

*4.4.5. 2-(((1-Benzyl-1H-1,2,3-triazol-4-yl)methyl)thio)-5-chlorobenzo[d]thiazole (**4e**).* White solid. Mp=139.8−140.9 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.78 (d, J=1.9 Hz, 1H), 7.64 (d, J=8.4 Hz, 1H), 7.51 (s, 1H), 7.35−7.20 (m, 6H), 5.48 (s, 2H), 4.65 (s, 2H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 167.9, 153.6, 143.8, 134.3, 133.6, 132.0, 129.0, 128.7, 127.9, 124.6, 123.0, 121.6, 121.2, 54.1, 27.7. HRMS(EI): m/z [M^+] calcd for $C_{17}H_{13}ClN_4S_2$: 372.0270; Found: 372.0280.

*4.4.6. 2-(((1-Benzyl-1H-1,2,3-triazol-4-yl)methyl)thio)-5-methyl-1,3,4-thiadiazole (**4f**).* Pale brown solid. Mp=80.7−81.5 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.60 (s, 1H), 7.37−7.34 (m, 3H), 7.25−7.23 (m, 2H), 5.48 (s, 2H), 4.59 (s, 2H), 2.71 (s, 3H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 164.9, 163.9, 142.9, 134.1, 128.4, 128.0, 127.3, 122.8, 53.4, 27.6, 15.1. HRMS(EI): m/z [M^+] calcd for $C_{13}H_{13}N_5S_2$: 303.0612; Found: 303.0606.

*4.4.7. 2-(((1-Benzyl-1H-1,2,3-triazol-4-yl)methyl)thio)-5-phenyl-1,3,4-oxadiazole (**4g**).* White solid. Mp=106.0−108.9 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 8.00−7.96 (m, 2H), 7.70 (s, 1H), 7.52−7.47 (m,

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3H), 7.36–7.33 (m, 3H), 7.26–7.23 (m, 2H), 5.49 (s, 2H), 4.58 (s, 2H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 165.6, 163.4, 142.9, 134.2, 131.4, 128.7, 128.3, 127.6, 126.2, 123.0, 53.8, 26.7. HRMS(EI): *m/z* [M^+] calcd for $C_{18}H_{15}N_5OS$: 349.0997; Found: 349.0993.

4.5. Synthesis of fluorinated triazoles

The second step in Route A and Route B was performed by CuAAC and anodic fluorination, respectively.

*4.5.1. 2-(((1-Benzyl-1H-1,2,3-triazol-4-yl)fluoromethyl)thio)pyrimidine (**5c**).* ^{1}H NMR (270 MHz, $CDCl_3$): δ 8.62 (d, *J*=4.9 Hz, 2H), 7.95 (dd, *J*=51.6, 0.5 Hz, 1H), 7.68 (s, 1H), 7.42–7.38 (m, 3H), 7.33–7.27 (m, 2H), 7.11 (t, *J*=4.9 Hz, 1H), 5.57 (s, 2H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 185.1, 157.8, 129.4, 129.3, 129.0, 128.4, 128.3, 122.3 (d, *J*=1.6 Hz), 118.0, 90.4 (d, *J*=214.7 Hz), 54.5. ^{19}F NMR (254 MHz, $CDCl_3$): δ −70.5 (d, *J*=51.8 Hz). HRMS(EI): *m/z* [M^+] calcd for $C_{14}H_{12}FN_5S$: 301.0797; Found: 301.0795.

*4.5.2. 2-(((1-Benzyl-1H-1,2,3-triazol-4-yl)fluoromethyl)thio)benzo[d]thiazole (**5d**).* White solid. Mp=117.2–120.8 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 8.00–7.97 (m, 1H), 7.83–7.81 (m, 1H), 7.77 (d, *J*=52.9 Hz, 1H), 7.66 (s, 1H), 7.51–7.45 (m, 1H), 7.41–7.26 (m, 6H), 5.56 (s, 2H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 152.8, 143.5, 143.1, 135.9, 133.8, 129.3, 129.1, 128.2, 126.4, 125.1, 122.5, 122.4 (d, *J*=2.2 Hz), 121.2, 91.8 (d, *J*=220.8 Hz), 54.5. ^{19}F NMR (254 MHz, $CDCl_3$): δ −66.7 (d, *J*=53.6 Hz). HRMS(EI): *m/z* [M^+] calcd for $C_{17}H_{13}FN_4S_2$: 356.0566; Found: 356.0569.

*4.5.3. 2-(((1-Benzyl-1H-1,2,3-triazol-4-yl)fluoromethyl)thio)-5-chlorobenzo[d]thiazole (**5e**).* Pale brown solid. Mp=110.0–111.2 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.96–7.28 (m, 10H), 5.57 (s, 2H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 153.6, 134.0, 133.7, 132.5, 129.3, 129.1, 128.6, 128.3, 126.4, 125.6, 122.4, 122.4, 121.8, 91.6 (d, *J*=221.4 Hz), 54.6. ^{19}F NMR (254 MHz, $CDCl_3$): δ −67.0 (d, *J*=51.8 Hz). HRMS(EI): *m/z* [M^+] calcd for $C_{17}H_{12}ClFN_4S_2$: 390.0176; Found: 390.0186.

*4.5.4. 2-(((1-Benzyl-1H-1,2,3-triazol-4-yl)fluoromethyl)thio)-5-methyl-1,3,4-thiadiazole (**5f**).* Pale yellow solid. Mp=107.8–108.3 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.70 (s, 1H), 7.54–7.27 (m, 6H), 5.56 (s, 2H), 2.76 (s, 3H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 167.6, 160.0, 142.8 (d, *J*=26.2 Hz), 133.8, 129.2, 129.0, 128.2, 122.5 (d, *J*=1.6 Hz), 91.9 (d, *J*=222.4 Hz), 54.5, 15.7. ^{19}F NMR (254 MHz, $CDCl_3$): δ −66.8 (d, *J*=53.6 Hz). HRMS(EI): *m/z* [M^+] calcd for $C_{13}H_{12}FN_5S_2$: 321.0518; Found: 321.0510.

*4.5.5. 2-(((1-Benzyl-1H-1,2,3-triazol-4-yl)fluoromethyl)thio)-5-phenyl-1,3,4-oxadiazole (**5g**).* Pale yellow solid. Mp=87.9–88.9 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 8.02–7.99 (m, 2H), 7.79 (s, 1H), 7.70–7.46 (m, 4H), 7.38–7.28 (m, 5H), 5.57 (s, 2H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 166.5, 163.4, 142.9, 133.7, 132.0, 129.1, 129.0, 128.9, 128.1, 126.7, 123.0, 122.7 (d, *J*=1.7 Hz), 90.9 (d, *J*=224.7 Hz), 54.4. ^{19}F NMR (254 MHz, $CDCl_3$): δ −66.4 (d, *J*=51.8 Hz). HRMS(EI): *m/z* [M^+] calcd for $C_{18}H_{15}FN_5OS$: 368.0981; Found: 368.0989.

*4.5.6. 1-Benzyl-4-(difluoro(phenylthio)methyl)-1H-1,2,3-triazole (**6a**).* White solid. Mp=96.7–97.2 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.61–7.59 (m, 2H), 7.51 (s, 1H), 7.41–7.38 (m, 3H), 7.35–7.21 (m, 5H), 5.53 (s, 2H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 143.9 (t, *J*=31.3 Hz), 136.5, 133.7, 130.0, 129.2, 129.0, 128.1, 126.3 (t, *J*=1.7 Hz), 122.4 (t, *J*=2.2 Hz), 54.3. ^{19}F NMR (254 MHz, $CDCl_3$): δ 8.2 (s). HRMS(EI): *m/z* [M^+] calcd for $C_{16}H_{13}F_2N_3S$: 317.0798; Found: 317.0798.

*4.5.7. 1-Benzyl-4-(((4-chlorophenyl)thio)difluoromethyl)-1H-1,2,3-triazole (**6b**).* Pale yellow solid. Mp=95.1–97.7 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.58 (s, 1H), 7.52–7.48 (m, 2H), 7.40–7.38 (m, 3H), 7.30–7.13 (m, 4H), 5.52 (s, 2H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 143.6 (t, *J*=31.5 Hz), 137.7, 136.7, 134.3, 133.6, 129.2, 129.0, 128.1, 124.7 (t, *J*=1.6 Hz), 122.4 (t, *J*=2.2 Hz), 54.3. ^{19}F NMR (254 MHz, $CDCl_3$): δ 8.2 (s). HRMS(EI): *m/z* [M^+] calcd for $C_{16}H_{12}ClF_2N_3S$: 351.0409; Found: 351.0404.

*4.5.8. 1-Benzyl-1H-1,2,3-triazole-4-carbaldehyde (**7**).* This compound was identified by comparison with ^{1}H NMR spectral data of its authentic sample.[12]

4.6. Typical procedure for isoxazole synthesis

To a stirred solution of alkyne **2c** (0.5 mmol) and imidoyl chloride[8] (1.1 equiv) in *t*-BuOH/H_2O (1/1, 3.0 ml) was added $CuSO_4 \cdot 5H_2O$ (0.02 equiv), sodium ascorbate (0.1 equiv) and $KHCO_3$ (4.3 equiv), and the reaction mixture was stirred for 15 h at room temperature. Dichloromethane (10 ml) was added to the mixture and the organic phase was washed with water and brine. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The product isoxazole was further purified by column chromatography over silica gel using a mixed solution of EtOAc and hexane as an eluent.

*4.6.1. 5-(Fluoro(pyrimidin-2-ylthio)methyl)-3-phenylisoxazole (**8c**).* ^{1}H NMR (270 MHz, $CDCl_3$): δ 8.64 (d, *J*=4.9 Hz, 2H), 7.98 (dd, *J*=50.0, 0.8 Hz, 1H), 7.84–7.80 (m, 2H), 7.48–7.46 (m, 3H), 7.15 (t, *J*=4.9 Hz, 1H), 6.86 (s, 1H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 167.52 (d, *J*=2.8 Hz), 165.86 (d, *J*=29.6 Hz), 162.5 (d, *J*=1.7 Hz), 157.9, 157.4, 130.3, 128.9, 126.8, 118.3, 101.9 (d, *J*=1.7 Hz), 88.8 (d, *J*=218.6 Hz). ^{19}F NMR (254 MHz, $CDCl_3$): δ −77.5 (d, *J*=50.0 Hz). HRMS(EI): *m/z* [M^+] calcd for $C_{14}H_{10}FN_3OS$: 287.0529; Found: 287.0521.

*4.6.2. 5-((Benzo[d]thiazol-2-ylthio)fluoromethyl)-3-phenylisoxazole (**8d**).* Pale yellow solid. Mp=88.3–90.2 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 8.03–7.75 (m, 5H), 7.53–7.37 (m, 5H), 6.86 (s, 1H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 165.1 (d, *J*=27.3 Hz), 162.6, 159.8, 152.6, 136.0, 131.7, 130.2, 129.3, 128.4, 127.9, 125.8, 122.4, 120.1, 102.2 (d, *J*=175.7 Hz), 91.8 (d, *J*=162.3 Hz). ^{19}F NMR (254 MHz, $CDCl_3$): δ −74.0 (d, *J*=51.8 Hz). HRMS(EI): *m/z* [M^+] calcd for $C_{17}H_{11}FN_2OS_2$: 342.0297; Found: 342.0298.

*4.6.3. 5-(((5-Chlorobenzo[d]thiazol-2-yl)thio)fluoromethyl)-3-phenylisoxazole (**8e**).* White solid. Mp=106.5–107.5 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 8.00–7.73 (m, 4H), 7.50–7.36 (m, 5H), 6.87 (s, 1H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 165.2, 164.7, 162.4 (d, *J*=37.4 Hz), 153.4, 134.1, 132.8, 130.6, 129.1, 127.9, 126.9, 125.9, 122.5, 120.8, 102.3 (d, *J*=1.1 Hz), 89.9 (d, *J*=225.8 Hz). ^{19}F NMR (254 MHz, $CDCl_3$): δ −74.5 (d, *J*=49.8 Hz). HRMS(EI): *m/z* [M^+] calcd for $C_{17}H_{10}ClFN_2OS_2$: 375.9907; Found: 375.9917.

*4.6.4. 5-(Fluoro((5-methyl-1,3,4-thiadiazol-2-yl)thio)methyl)-3-phenylisoxazole (**8f**).* Yellow solid. Mp=45.0–45.6 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.82–7.41 (m, 6H), 6.82 (s, 1H), 2.80 (s, 3H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 168.2, 164.7 (d, *J*=29.0 Hz), 162.6, 158.5, 130.6, 129.0, 127.9, 126.9, 102.4, 90.2 (d, *J*=226.9 Hz), 15.8. ^{19}F NMR (254 MHz, $CDCl_3$): δ −74.7 (d, *J*=49.8 Hz). HRMS(EI): *m/z* [M^+] calcd for $C_{13}H_{10}FN_3OS_2$: 307.0249; Found: 307.0243.

*4.6.5. 2-((Fluoro(3-phenylisoxazol-5-yl)methyl)thio)-5-phenyl-1,3,4-oxadiazole (**8g**).* Brown paste. ^{1}H NMR (270 MHz, $CDCl_3$): δ 8.02–8.00 (m, 2H), 7.80–7.77 (m, 2H), 7.70–7.45 (m, 7H), 6.88 (s, 1H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 167.0, 164.4 (d, *J*=7.8 Hz), 162.6 (d, *J*=1.2 Hz), 158.9, 131.7, 130.2, 128.3, 127.9, 127.6, 126.1, 125.6, 122.8, 102.5 (d, *J*=174.5 Hz), 90.7 (d, *J*=230.3 Hz). ^{19}F NMR (254 MHz,

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$CDCl_3$): δ −74.6 (d, *J*=49.8 Hz). HRMS(EI): *m/z* [M^+] calcd for $C_{18}H_{12}FN_3O_2S$: 353.0634; Found: 353.0642.

*4.6.6. 5-(Difluoro(phenylthio)methyl)-3-phenylisoxazole (**9a**).* White solid. Mp=65.7–67.1 °C. ^1H NMR (270 MHz, $CDCl_3$): δ 7.77–7.73 (m, 2H), 7.62–7.59 (m, 2H), 7.47–7.34 (m, 6H), 6.69 (s, 1H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 164.1 (t, *J*=35.1 Hz), 162.3, 136.8, 130.7, 130.6, 129.3, 129.0, 127.8, 126.8, 125.1 (t, *J*=2.2 Hz), 121.5, 102.5 (t, *J*=1.7 Hz). ^{19}F NMR (254 MHz, $CDCl_3$): δ 3.8 (s). HRMS(EI): *m/z* [M^+] calcd for $C_{16}H_{11}F_2N_4OS$: 303.0529; Found: 303.0531.

*4.6.7. 5-(((4-Chlorophenyl)thio)difluoromethyl)-3-phenylisoxazole (**9b**).* Pale yellow solid. Mp=73.5–75.7 °C. ^1H NMR (270 MHz, $CDCl_3$): δ 7.78–7.75 (m, 2H), 7.56–7.34 (m, 7H), 6.73 (s, 1H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 163.9 (t, *J*=35.1 Hz), 162.4 (t, *J*=1.1 Hz), 138.0, 137.5, 130.7, 129.6, 128.6, 127.7, 126.9, 123.4 (t, *J*=2.2 Hz), 121.2, 102.6. ^{19}F NMR (254 MHz, $CDCl_3$): δ 3.9 (s). HRMS(EI): *m/z* [M^+] calcd for $C_{16}H_{10}ClF_2N_4OS$: 337.0140; Found: 337.0144.

References and notes

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