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Electrophilic monofluoromethylation of *O*-, *S*-, and *N*-nucleophiles with chlorofluoromethane

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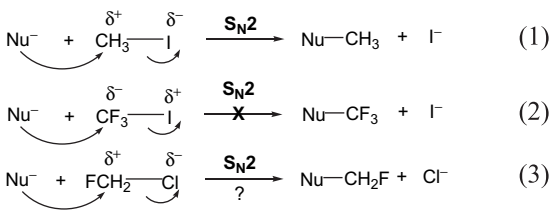
Abstract—CH_2ClF has been found to be a useful electrophilic monofluoromethylating agent for a variety of *O*-, *S*-, and *N*-nucleophiles. The reaction is not sensitive to the radical scavenger such as nitrobenzene, which strongly supports an S_N2 mechanism rather than an SET mechanism. Although most of these products (fluoromethyl ethers, sulfides, and amines) can be isolated with good purity, some of these compounds do intend to decompose (via defluorination) during storage. The electrophilic monofluoromethylation of carbon-nucleophiles was attempted with CH_2ClF, CH_2FI, or FCH_2OTs as monofluoromethylating agents, but with no success.

1. Introduction

Electrophilic fluoroalkylation reactions, which are usually different from regular electrophilic alkylations in hydrocarbon chemistry, represent one of the unique aspects of organofluorine chemistry.[1] For instance, while the bimolecular nucleophilic substitution (S_N2) reaction between a nucleophile (Nu^-, such as a thiophenoxide) and methyl iodide can proceed very readily (Scheme 1, Eq. 1), the similar S_N2 type of reaction between a nucleophile and trifluoromethyl iodide has been proven to be unsuccessful (Scheme 1, Eq. 2).[2] This is mainly due to the fact that, in sharp contrast to normal alkyl halides, for perfluoroalkyl halides (R_fX) the electronegativities of perfluoroalkyl groups (R_f) are higher than those of halogen atoms (X) and thus nucleophiles attack at halogen instead of the halogen-substituted carbon.[3] To overcome this problem, several novel electrophilic trifluoromethylating agents such as (trifluoromethyl)-aryliodonium salts and (trifluoromethyl)chalcogen salts have been developed by Yagulpol'skii et al.,[4] Umemoto et al.,[1] and others.[5,6] On the other hand, the electrophilic difluoromethylation (the direct transfer of a 'CF_2H^+' building block into a nucleophile) has been a long-standing challenge, and indeed, the currently known methods for introducing a difluoromethyl moiety to oxygen-, sulfur-, phosphorus-, and nitrogen-nucleophiles are mainly based on de facto electrophilic difluoromethylations with difluorocarbene reagents.[2,3] Recently, Prakash et al. reported the first *real* electrophilic difluoromethylation chemistry with *S*-(difluoromethyl)diarylsulfonium tetrafluoroborate reagent, which is able to incorporate an electrophilic CF_2H group into certain nucleophiles such as sulfonic acids, tertiary amines, imidazole derivatives, and phosphines.[7]



Scheme 1.

Compared with electrophilic trifluoroalkylation and difluoromethylation (both de facto and *real* ones), much less has been known about electrophilic monofluoromethylation (the electrophilic transfer of 'CH_2F^+' building block). In 1953, Olah and Pavlath reported the first example of electrophilic monofluoromethylation—the acid-catalyzed monofluoromethylation of benzene with fluoromethanol (FCH_2OH).[8] However, during the following 32 years, the electrophilic monofluoromethylation was almost neglected.[9] Since 1985, several examples of electrophilic monofluoromethylation of oxygen-, sulfur-, nitrogen-, and carbon-nucleophiles have been reported, by use of CH_2FI,[10] CH_2FBr,[11] CH_2FCl,[11e,12] or CH_2FOSO_2R (R=CF_3, CH_3, tolyl)[11d,13] as monofluoromethylating agents. However, most of these electrophilic monofluoromethylations are [^{18}F]-labeled fluoromethylation, and it has been pointed

Keywords: Fluorine; Electrophilic; Monofluoromethylation; S_N2 reaction.
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out that the yields of some reactions were not reproducible due to the unstable nature of the monofluoromethylated products.[10d]

Intrigued by the biological importance of incorporating monofluoromethyl group into organic molecules, recently we reported the first *nucleophilic* monofluoromethylation using $PhSO_2CH_2F$ reagent.[14] Thereafter, *nucleophilic* monofluoromethylation has been studied by several different research groups.[15] We have been interested in the *electrophilic* monofluoromethylation using inexpensive and readily available chlorofluoromethane (CH_2ClF, **1**), with the following aims: (1) to explore the substrate scope of electrophilic monofluoromethylation reactions; (2) to ascertain the reaction mechanism (S_N2 or SET, see Scheme 1, Eq. 3); (3) to determine the stability of the monofluoromethylated products. In this article, we wish to report our results in these studies.

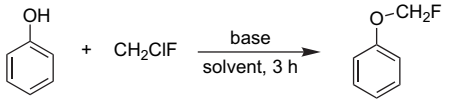
2. Results and discussion

2.1. With oxygen-nucleophiles

In the preliminary studies, we chose phenol **2a** as a model compound to optimize the reaction conditions (Table 1). The typical experimental procedure is as follows: compound **2a** (2 mmol) and the base were stirred in a pressure tube for 15 min, then the chlorofluoromethane (**1**) was bubbled into the solution for a period of 15 min (ca. 15 mmol) at the room temperature. The tube was then sealed and the reaction mixture was heated to the desired temperature for additional 3 h. When K_2CO_3 was used as a base, the reaction was unsuccessful and no desired product **3a** was detected by the ^{19}F NMR spectroscopy (Table 1, entry 1). By using KOH as a base in CH_3CN, we only obtained the product **3a** in <10% yield (Table 1, entries 2 and 3). When DMF was used as a solvent, the product yield was increased to 53% (Table 1, entry 4). It was found that NaH in DMF gave better results (with 74% yield) at room temperature (Table 1, entry 5). The best yield (86%) was obtained when the reaction temperature was raised to 80 °C (see Table 1, entry 7). Furthermore, we found that other polar non-protic solvents such as DMSO and NMP were also suitable for the reaction (Table 1, entries 9 and 10).

To ascertain the mechanism of this electrophilic monofluoromethylation with CH_2ClF, we added a radical scavenger (1.0 equiv of nitrobenzene) in the reaction mixture and found that the radical scavenger did not show inhibition effect of the monofluoromethylation reaction (Table 1, compare entries 11 and 5). This observation strongly indicates that the current electrophilic monofluoromethylation proceeded via a nucleophilic substitution (very possibly through

Table 1. Screening the reaction conditions

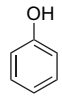
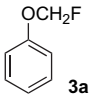
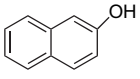
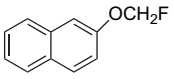
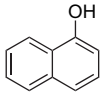
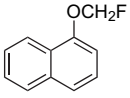
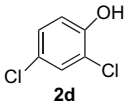
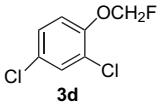
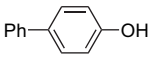
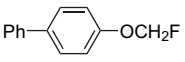
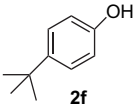
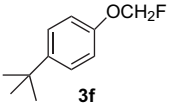
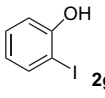
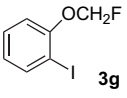
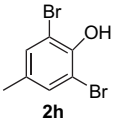
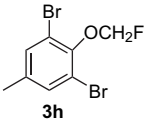
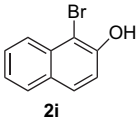
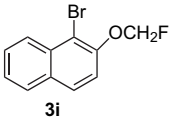
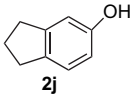
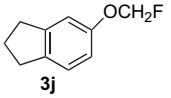
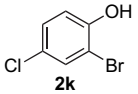
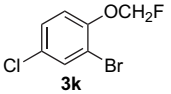


2a **1** **3a**

Entry	Base	Base/**2a**	Solvent	*T* (°C)	Yield[a] (%)
1	K_2CO_3	1.1:1	Ether	rt	n.r
2	KOH[b]	2.0:1	CH_3CN	rt	<10
3	KOH[b]	4.0:1	CH_3CN	rt	<10
4	KOH[b]	2.0:1	DMF	rt	53
5	NaH	1.1:1	DMF	rt	74
6	KOH	2.0:1	DMF	80	64
7	NaH	1.1:1	DMF	80	86
8	NaH	1.1:1	THF	80	22
9	NaH	1.1:1	DMSO	80	83
10	NaH	1.1:1	NMP	80	84
11[c]	NaH	1.1:1	DMF	rt	78

[a] Determined by ^{19}F NMR spectroscopy.
[b] KOH (30 wt % in H_2O).
[c] Nitrobenzene of 1.0 equiv was added.

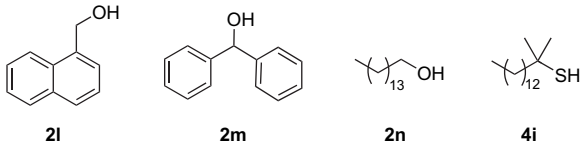
Table 2. Electrophilic monofluoromethylation of phenyl derivatives **2** with CH_2ClF

Entry	Substrate	Product	Yield[a] (%)
1	 **2a**	 **3a**	86[b]
2	 **2b**	 **3b**	90
3	 **2c**	 **3c**	93
4	 **2d**	 **3d**	86
5	 **2e**	 **3e**	95
6	 **2f**	 **3f**	87
7	 **2g**	 **3g**	88
8	 **2h**	 **3h**	92
9	 **2i**	 **3i**	87
10	 **2j**	 **3j**	91
11	 **2k**	 **3k**	92

[a] Isolated yield.
[b] Determined by ^{19}F NMR spectroscopy.

S_N2) mechanism, rather than halophilic or single electron transfer (SET) mechanism.[16]

By using the optimized reaction condition, we studied the scope of the electrophilic monofluoromethylation reactions with oxygen-nucleophiles. The results are summarized in Table 2. A variety of structurally diverse phenol derivatives **2a**–**2k** were smoothly monofluoromethylated by CH_2ClF in the presence of NaH in DMF solvent to give the corresponding products **3a**–**3k** in excellent yields (86–95%). The reaction was compatible with bromo- and iodo-substituted phenols (Table 2, entries 7–9, and 11) to give products **3g**–**3i**, **3k**, which are possible for further elaboration through transition metal-catalyzed cross-coupling reactions. In addition, we used the naphthalen-1-ylmethanol (Fig. 1, **2l**) and diphenylmethanol (Fig. 1, **2m**) as the *O*-nucleophile in the reaction, and it was found that the yields determined by ^{19}F NMR spectroscopy were 73% (for the reaction with **2l**, ^{19}F NMR δ −152.6 (t, J=56.8 Hz)) and 96% (for the reaction with **2m**, ^{19}F NMR δ −152.7 (t, J=56.4 Hz)), respectively. However, we were not able to isolate these two monofluoromethylated ether products through silica gel chromatography due to the instability of these two products (defluorination was observed). Furthermore, aliphatic alcohol **2n** was also found to be able to react with CH_2ClF under similar reaction condition, but with lower yield (22%, monitored by ^{19}F NMR).



2l **2m** **2n** **4i**

Figure 1. Compounds **2l**–**2n** and **4i**.

2.2. With sulfur-nucleophiles

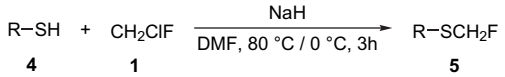
We further examined the electrophilic monofluoromethylation reaction with sulfur-nucleophiles. The results are summarized in Table 3. It was found that under similar reaction condition (CH_2ClF/NaH/DMF, 80 °C, 3 h), thiophenol and its derivatives showed high reactivity toward monofluoromethylation with CH_2ClF, and corresponding monofluoromethylated sulfide products were obtained in high yields (72–80%, Table 3, entries 1–4). Interestingly, phenylmethanethiol (**4e**), 1-*tert*-butyl-1,2,3,4-tetrazole-5-thiol (**4f**), 1-phenyl-1,2,3,4-tetrazole-5-thiol (**4g**), and 2-benzothiazolethiol (**4h**) were all able to be efficiently monofluoromethylated by CH_2ClF in 64–86% yield (Table 3, entries 5–8). However, we found that the simple aliphatic thiol **4i** (see Fig. 1) did not show reactivity toward CH_2ClF under similar reaction condition.

It is noteworthy that the stability of products **5a** and **5c** was quite low. For example, we found that when the liquid compound **5c** was stored in a refrigerator for 15 days, it polymerized to give a white solid material.

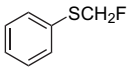
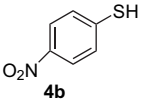
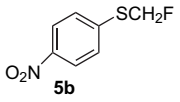
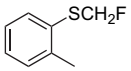
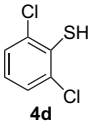
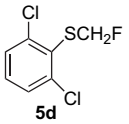
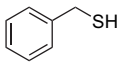
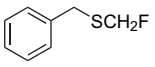
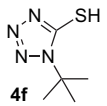
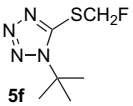
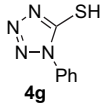
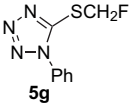
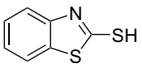
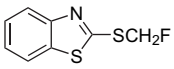
2.3. With nitrogen-nucleophiles

It is well-recognized that monofluoromethylated amines bearing an α-H ($RNHCH_2F$) are thermally unstable, they have high tendency to undergo dehydrofluorination reactions.[17] The electrophilic monofluoromethylation of tertiary amines with CH_2ClF (to give fluoromethylated ammonium salts) with low yields has been reported.[12] However, we were not aware of any reports on the electrophilic monofluoromethylation of secondary amines to give fluoromethylated tertiary amines. As shown in Table 4, a variety of structurally diverse *N*-heterocyclic compounds **6a**–**6i** were readily monofluoromethylated to give the corresponding *N*-CH_2F-containing products **7a**–**7i**. We found that products **7f**–**7i** were difficult to isolate due to their tendency of decomposition (during purification) and/or their high volatility.

Table 3. Electrophilic monofluoromethylation of thiols **4** with CH_2ClF



4 **1** **5**

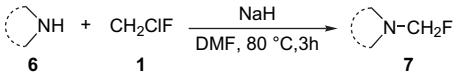
Entry	Substrate	Product	Yield[a] (%)
1	 **4a**	 **5a**	72
2	 **4b**	 **5b**	75
3	 **4c**	 **5c**	74
4	 **4d**	 **5d**	80
5	 **4e**	 **5e**	70
6[b]	 **4f**	 **5f**	86
7[b]	 **4g**	 **5g**	64
8[b]	 **4h**	 **5h**	82

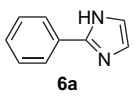
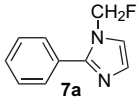
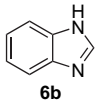
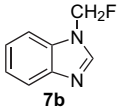
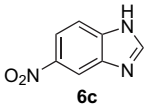
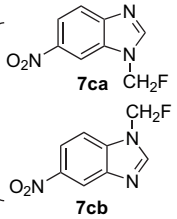
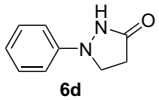
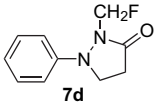
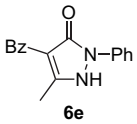
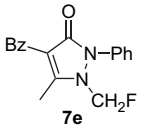
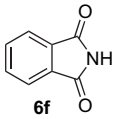
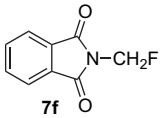
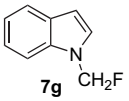
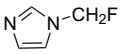
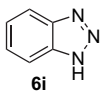
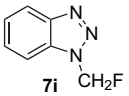
[a] Isolated yield.
[b] Chlorofluoromethane was bubbled into the solution at 0°C, then the mixture was warmed to room temperature gradually and stirred overnight.

2.4. With carbon-nucleophiles

Electrophilic monofluoromethylation with carbon-nucleophiles (C–C bond formation) could be a very useful reaction for the synthesis of many fluoromethylated bioactive compounds. Although there are several successful examples of electrophilic monofluoromethylation of certain carbon-nucleophiles with CH_2ClF,[12b] CH_2BrF,[11c] CH_2FI,[9] and FCH_2OH,[8] these reports did not show the scope and

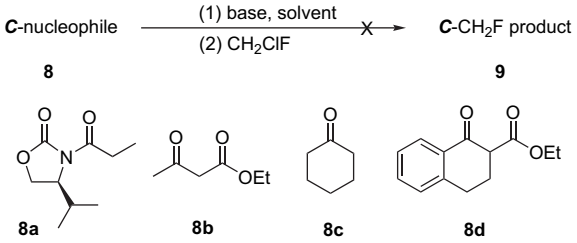
Table 4. Electrophilic monofluoromethylation of nitrogen-nucleophiles **6** with CH_2ClF



Entry	Substrate	Product	Yield[a] (%)
1	 **6a**	 **7a**	71
2	 **6b**	 **7b**	84
3[b]	 **6c**	 **7ca** **7cb**	71
4[b]	 **6d**	 **7d**	50
5[b]	 **6e**	 **7e**	71
6	 **6f**	 **7f**	23[c]
7	 **6g**	 **7g**	80[c]
8	 **6h**	 **7h**	28[c]
9	 **6i**	 **7i**	46[c]

[a] Isolated yield.
[b] Stirred overnight.
[c] Determined by ^{19}F NMR spectroscopy.

generality of the C-monofluoromethylation reaction. Based on our above-mentioned study of *O*-, *S*-, and *N*-monofluoromethylation with CH_2ClF, we attempted to apply the similar reaction condition to the carbon-nucleophiles. As shown in Scheme 2, we used several carbon pro-nucleophiles **8a**–**8d** as model compounds to test the C-monofluoromethylation with CH_2ClF. It was found that upon treatment of LDA in THF at −78 °C, compounds **8a**–**8c** (corresponding carbanions) could not undergo electrophilic monofluoromethylation with CH_2ClF. We also tried to use CH_2FI (to replace CH_2ClF) as monofluoromethylating agent to react with **8a** and **8b**, but in both cases no *C*-fluoromethylated products were observed. Fluoromethyl tosylate (FCH_2OTs) was also used as monofluoromethylating agent to react with **8a**, and no success was achieved. Under similar reaction condition as those for Tables 2–4, the C-monofluoromethylation was also found to be unsuccessful with compound **8d**.



Scheme 2.

3. Conclusion

In summary, we have shown that CH_2ClF can be used as a useful electrophilic monofluoromethylating agent for a variety of *O*-, *S*-, and *N*-nucleophiles. The reaction is not sensitive to the radical scavenger such as nitrobenzene, which strongly supports an S_N2 mechanism rather than an SET mechanism. Although most of these products (fluoromethyl ethers, sulfides, and amines) can be isolated with good purity, some of these compounds do intend to decompose (via defluorination) during storage. The electrophilic monofluoromethylation of carbon-nucleophiles was attempted with CH_2ClF, CH_2FI, or FCH_2OTs as monofluoromethylating agents, but in all cases the reaction did not occur. More efficient electrophilic monofluoromethylating agent for C-fluoromethylation is thus highly desired, and further efforts aiming at this goal are currently underway in our laboratory.

4. Experiment sections

4.1. General information

All solvents and reagents were purchased from commercial sources and used as received. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on a 500, 400, or 300 MHz NMR spectrometer. ^1H NMR chemical shifts were determined relative to internal $(CH_3)_4Si$ (TMS) at δ 0.0 or to the signal of a residual protonated solvent: $CDCl_3$ δ 7.26. ^{13}C NMR chemical shifts were determined relative to internal TMS at δ 0.0. ^{19}F NMR chemical shifts were determined relative to $CFCl_3$ at δ 0.0. Mass spectra were obtained on a mass spectrometer. High-resolution mass data were recorded on a high-resolution mass spectrometer in the EI, ESI, or MALDI mode.

4.2. General procedure

Naphthalen-2-ol **2b** (288 mg, 2 mmol), DMF (4 mL), and NaH (60 wt %, 88 mg, ca. 2.2 mmol) were stirred in a pressure tube at room temperature for 15 min, then the chlorofluoromethane (**1**) was bubbled into the solution for a period of 15 min (ca. 15 mmol). The tube was then sealed and the reaction mixture was heated to 80 °C for additional 3 h. Then to the mixture was added H_2O (8 mL) and extracted with ethyl acetate (25 mL×3), the combined organic

phase was washed with brine and dried over $MgSO_4$. After the removal of solvents under vacuum, the crude product was further purified by silica gel column chromatography to give the product **3b** as a white solid. Yield: 90% (316 mg).

4.2.1. 2-(Fluoromethoxy)naphthalene (3b).[10d] White solid. ^{1}H NMR: δ 7.79 (t, J=8.7 Hz, 3H), 7.38–7.50 (m, 3H), 7.24–7.27 (m, 1H), 5.83 (d, J=54.6 Hz, 2H). ^{19}F NMR: δ −148.8 (t, J=54.1 Hz, 1F).

4.2.2. 1-(Fluoromethoxy)naphthalene (3c). Colorless liquid. IR (film): 3057, 2925, 1597, 1510, 1392, 1260, 1237, 1126, 979, 771 cm^{-1}. ^{1}H NMR: δ 8.19–8.22 (m, 1H), 7.78–7.81 (m, 1H), 7.56 (d, J=8.1 Hz, 1H), 7.46–7.51 (m, 2H), 7.37 (t, J=7.8 Hz, 1H), 7.14 (d, J=7.2 Hz, 1H), 5.86 (d, J=54.3 Hz, 2H). ^{19}F NMR: δ –148.1 (t, J=53.9 Hz, 1F). ^{13}C NMR: δ 152.8, 134.6, 127.6, 126.7, 125.9, 125.8, 125.7, 123.3, 121.8, 109.2, 101.1 (d, J=217.8 Hz). MS (EI, m/z, %): 176 (M^+, 62.43), 115 (100.00). Anal. Calcd for $C_{11}H_9FO$: C, 74.99; H, 5.15. Found: C, 74.98; H, 5.24.

4.2.3. 2,4-Dichloro-1-(fluoromethoxy)benzene (3d).[18] White solid. ^{1}H NMR: δ 7.42 (s, 1H), 7.23 (d, J=8.7 Hz, 1H), 7.14 (d, J=8.7 Hz, 1H), 5.71 (d, J=54.0 Hz, 2H). ^{19}F NMR: δ −150.0 (t, J=54.1 Hz, 1F).

4.2.4. 4-Phenyl-1-(fluoromethoxy)benzene (3e). White solid. Mp: 72–73 °C. IR (film): 3034, 1610, 1522, 1486, 1296, 1240, 1095, 950, 836, 758 cm^{-1}. ^{1}H NMR: δ 7.56 (d, J=8.1 Hz, 4H), 7.43 (t, J=7.2 Hz, 2H), 7.33 (t, J=7.2 Hz, 1H), 7.16 (d, J=8.7 Hz, 2H), 5.75 (d, J=54.6 Hz, 2H). ^{19}F NMR: δ −148.9 (t, J=53.9 Hz, 1F). ^{13}C NMR: δ 156.3, 140.4, 136.7, 128.8, 128.4, 127.1, 126.9, 117.0, 100.8 (d, J= 217.4 Hz). MS (EI, m/z, %): 202 (M^+, 100.00). Anal. Calcd for $C_{13}H_{11}FO$: C, 77.21; H, 5.48. Found: C, 77.31; H, 5.52.

4.2.5. 1-*tert*-Butyl-4-(fluoromethoxy)benzene (3f). Colorless liquid. IR (film): 2965, 1612, 1515, 1365, 1299, 1232, 1187, 1091, 979, 834 cm^{-1}. ^{1}H NMR: δ 7.33 (d, J=8.7 Hz, 2H), 7.01 (d, J=8.7 Hz, 2H), 5.67 (d, J=54.9 Hz, 2H), 1.30 (s, 9H). ^{19}F NMR: δ −147.9 (t, J=52.7 Hz, 1F). ^{13}C NMR: δ 154.6, 146.3, 126.3, 116.2, 101.0 (d, J=216.7 Hz), 34.2, 31.4. MS (EI, m/z, %): 182 (M^+, 18.05), 167 (100.00). HRMS (EI) calcd for $C_{11}H_{15}FO$: 182.1107. Found: 182.1115.

4.2.6. 1-(Fluoromethoxy)-2-iodobenzene (3g). Colorless liquid. IR (film): 2927, 1585, 1473, 1231, 1089, 1021, 984, 752 cm^{-1}. ^{1}H NMR: δ 7.79 (d, J=7.8 Hz, 1H), 7.31 (t, J=8.1 Hz, 1H), 7.10 (d, J=8.1 Hz, 1H), 6.84 (t, J=7.5 Hz, 1H), 5.71 (d, J=54.3 Hz, 2H). ^{19}F NMR: δ −149.1 (t, J= 54.7 Hz, 1F). ^{13}C NMR: δ 155.9, 139.7, 129.7, 125.3, 116.0, 101.1 (d, J=219.8 Hz), 87.2. MS (EI, m/z, %): 252 (M^+, 100.00). Anal. Calcd for C_7H_6FIO: C, 33.36; H, 2.40. Found: C, 33.45; H, 2.31.

4.2.7. 1,3-Dibromo-2-(fluoromethoxy)-5-methylbenzene (3h). Colorless liquid. IR (film): 2989, 1590, 1488, 1457, 1410, 1244, 1080, 1049, 1000, 741 cm^{-1}. ^{1}H NMR: δ 7.35 (s, 2H), 5.67(d, J=54.0 Hz, 2H), 2.28 (s, 3H). ^{19}F NMR: δ −149.0 (t, J=53.0 Hz, 1F). ^{13}C NMR: δ 148.6, 137.9, 133.3, 117.4, 103.9 (d, J=224.3 Hz), 20.2. MS (EI, m/z, %): 298 (M^+, 100.00). Anal. Calcd for $C_8H_7Br_2FO$: C, 32.25; H, 2.37. Found: C, 32.53; H, 2.37.

4.2.8. 1-Bromo-2-(fluoromethoxy)naphthalene (3i). White solid. Mp: 71–72 °C. IR (film): 3015, 1596, 1504, 1284, 1229, 1147, 1112, 972, 958, 802 cm^{-1}. ^{1}H NMR: δ 8.25 (d, J=8.4 Hz, 1H), 7.81 (d, J=8.7 Hz, 2H), 7.60 (t, J=8.4 Hz, 1H), 7.39–7.49 (m, 2H), 5.83 (d, J=54.6 Hz, 2H). ^{19}F NMR: δ −148.5 (t, J=52.5 Hz, 1F). ^{13}C NMR: δ 151.4, 132.9, 131.3, 129.2, 128.1, 127.9, 126.8, 125.6, 117.7, 111.6, 101.8 (d, J=220.1 Hz). MS (EI, m/z, %): 254 (M^+, 100.00). Anal. Calcd for $C_{11}H_8B_rFO$: C, 51.79; H, 3.16. Found: C, 51.72; H, 3.21.

4.2.9. 5-(Fluoromethoxy)-2,3-dihydro-1*H*-indene (3j). Colorless liquid. IR (film): 2930, 1611, 1492, 1286, 1241, 1168, 1144, 1101, 975, 816 cm^{-1}. ^{1}H NMR: δ 7.14 (d, J=7.8 Hz, 1H), 6.96 (s, 1H), 6.85 (d, J=8.1 Hz, 1H), 5.67 (d, J=54.9 Hz, 2H), 2.83–2.91 (m, 4H), 2.03–2.13 (m, 2H). ^{19}F NMR: δ −147.9 (t, J=54.7 Hz, 1F). ^{13}C NMR: δ 155.7, 146.0, 139.3, 124.9, 114.8, 113.0, 101.3 (d, J=216.4 Hz), 33.1, 32.1, 25.8. MS (EI, m/z, %): 166 (M^+, 49.20), 117 (100.00). HRMS (EI) calcd for $C_{10}H_{11}FO$: 166.0794. Found: 166.0788.

4.2.10. 2-Bromo-4-chloro-1-(fluoromethoxy)benzene (3k). White solid. Mp: 59–60 °C. IR (film): 3079, 1573, 1477, 1295, 1235, 1094, 967, 869, 808 cm^{-1}. ^{1}H NMR: δ 7.58 (s, 1H), 7.27 (d, J=8.7 Hz, 1H), 7.11 (d, J=8.7 Hz, 1H), 5.71 (d, J=54.0 Hz, 2H). ^{19}F NMR: δ −150.1 (t, J=53.0 Hz, 1F). ^{13}C NMR: δ 152.3, 133.1, 129.5, 128.7, 118.1, 113.8, 101.1 (d, J=220.8 Hz). MS (EI, m/z, %): 238 (M^+, 46.62), 63 (100.00). HRMS (EI) calcd for $C_7H_5BrClFO$: 237.9196. Found: 237.9203.

4.2.11. (Fluoromethyl)(phenyl)sulfane (5a).[19] Colorless liquid. ^{1}H NMR: δ 7.47–7.50 (m, 2H), 7.28–7.36 (m, 3H), 5.70 (d, J=53.1 Hz, 2H). ^{19}F NMR: δ −182.0 (t, J= 52.4 Hz, 1F).

4.2.12. (Fluoromethyl)(4-nitrophenyl)sulfane (5b).[20] Yellow solid. ^{1}H NMR: δ 8.19 (d, J=8.7 Hz, 2H), 7.57 (m, J=8.7 Hz, 2H), 5.85 (d, J=52.2 Hz, 2H). ^{19}F NMR: δ −185.2 (t, J=53.9 Hz, 1F).

4.2.13. (Fluoromethyl)(*o*-tolyl)sulfane (5c). Colorless liquid. ^{1}H NMR: δ 7.56–7.58 (m, 1H), 7.23–7.25 (m, 3H), 5.74 (d, J=52.8 Hz, 2H), 2.44 (s, 3H). ^{19}F NMR: δ −182.7 (t, J=52.2 Hz, 1F). It is an unstable compound.

4.2.14. (2,6-Dichlorophenyl)(fluoromethyl)sulfane (5d). Colorless liquid. IR (film): 2945, 1568, 1556, 1427, 1404, 1321, 1189, 976, 779 cm^{-1}. ^{1}H NMR: δ 7.44 (d, J= 8.1 Hz, 2H), 7.27 (d, J=8.1 Hz, 1H), 5.70 (d, J=52.2 Hz, 2H). ^{19}F NMR: δ −185.8 (t, J=52.2 Hz, 1F). ^{13}C NMR: δ 141.3, 131.0, 130.3, 128.9, 88.2 (d, J=218.9 Hz). MS (EI, m/z, %): 210 (M^+, 100). Anal. Calcd for $C_7H_5Cl_2FS$: C, 39.83; H, 2.39. Found: C, 40.00; H, 2.32.

4.2.15. Benzyl(fluoromethyl)sulfane (5e).[21] Colorless liquid. ^{1}H NMR: δ 7.34–7.36 (m, 5H), 5.38 (d, J=52.8 Hz, 2H). ^{19}F NMR: δ −189.2 (t, J=51.6 Hz, 1F).

4.2.16. 1-*tert*-Butyl-5-(fluoromethylthio)-1*H*-tetrazole (5f). White solid. Mp: 54–55 °C. IR (film): 2982, 1476, 1399, 1373, 1336, 1289, 1227, 1139, 1104, 985, 720,

591 cm^{-1}. ^1H NMR: δ 6.25 (d, J=49.8 Hz, 2H), 1.75 (s, 9H). ^{19}F NMR: δ −187.9 (t, J=50.0 Hz, 1F). ^{13}C NMR: δ 149.6, 84.4 (d, J=225.4 Hz), 61.7, 29.1. MS (EI, *m/z*, %): 190 (M^+, 1), 57 (100). Anal. Calcd for $C_6H_{11}FN_2S$: C, 37.88; H, 5.83; N, 29.45. Found: C, 38.06; H, 5.49; N, 29.79.

4.2.17. 5-(Fluoromethylthio)-1-phenyl-1*H*-tetrazole (5g). White solid. Mp: 86–87 °C. IR (film): 2969, 1597, 1591, 1502, 1425, 1396, 1244, 1002, 982, 765, 719, 697, 689, 555 cm^{-1}. ^1H NMR: δ 7.53–7.61 (m, 5H), 6.22 (d, J=50.1 Hz, 2H). ^{19}F NMR: δ −188.4 (t, J=49.8 Hz, 1F). ^{13}C NMR: δ 151.4, 133.1, 130.7, 130.0, 124.2, 83.9 (d, J=226.8 Hz). MS (EI, *m/z*, %): 211 ([M+H]$^+$, 1), 46 (100). Anal. Calcd for $C_8H_7FN_4S$: C, 45.70; H, 3.36; N, 26.65. Found: C, 45.81; H, 3.38; N, 26.32.

4.2.18. 2-(Fluoromethylthio)benzo[*d*]thiazole (5h). White solid. Mp: 59–60 °C. IR (film): 2930, 1467, 1455, 1431, 1411, 1322, 1311, 1005, 972, 766, 754,718, 674 cm^{-1}. ^1H NMR δ 7.80–7.98 (m, 2H), 7.33–7.50 (m, 2H), 6.16 (d, J=50.7 Hz, 2H). ^{19}F NMR δ −186.7 (t, J=51.1 Hz, 1F). ^{13}C NMR δ 62.4, 152.9, 135.8, 126.4, 125.0, 122.4, 121.2, 84.8 (d, J=222.2 Hz). MS (EI, *m/z*, %): 199 (M^+, 42), 135 (100). Anal. Calcd for $C_8H_6FNS_2$: C, 48.22; H, 3.03; N, 7.03. Found: C, 48.36; H, 3.03; N, 7.04.

4.2.19. 1-(Fluoromethyl)-2-phenyl-1*H*-imidazole (7a). Yellow liquid. IR (film): 3394, 1506, 1483, 1468, 1394, 1284, 984, 776, 700 cm^{-1}. ^1H NMR: δ 7.70–7.73 (m, 2H), 7.47–7.51 (m, 3H), 7.18–7.20 (m, 2H), 5.88 (d, J= 52.8 Hz, 2H). ^{19}F NMR: δ −157.9 (t, J=54.1 Hz, 1F). ^{13}C NMR: δ 149.1, 129.6, 129.2, 128.8, 121.6, 83.3 (d, J=198.2 Hz). MS (EI, *m/z*, %): 176 (M^+, 100). HRMS (EI): calcd for $C_{10}H_9FN_2$: 176.0750. Found: 176.0754.

4.2.20. 1-(Fluoromethyl)-1*H*-benzo[*d*]imidazole (7b). Yellow solid. Mp: 70–71 °C. IR (film): 3086, 1616, 1501, 1460, 1371, 1268, 1219, 987, 973 cm^{-1}. ^1H NMR: δ 8.02 (s, 1H), 7.83–7.85 (m, 1H), 7.50–7.53 (m, 1H), 7.33–7.41 (m, 2H), 6.14 (d, J=53.4 Hz, 2H). ^{19}F NMR: δ −163.7 (t, J=54.1 Hz, 1F). ^{13}C NMR: δ 144.0, 143.1, 133.2, 124.3, 123.5, 120.8, 109.5, 81.7 (d, J=199.5 Hz). MS (EI, *m/z*, %): 150 (M^+, 100). Anal. Calcd for $C_8H_7FN_2$: C, 63.99; H, 4.70; N, 18.66. Found: C, 63.97; H, 4.77; N, 18.47.

4.2.21. 1-(Fluoromethyl)-6-nitro-1*H*-benzo[*d*]imidazole (7ca) and 1-(fluoromethyl)-5-nitro-1*H*-benzo[*d*]imidazole (7cb). Yellow solid. IR (film): 3101, 1620, 1525, 1500, 1344, 986, 767 cm^{-1}. ^1H NMR: δ 8.76 (s, 1H), 8.52 (s, 1H), 8.32–8.37 (m, 2H), 8.29 (s, 1H), 8.24 (s, 1H), 7.94 (d, J=8.7 Hz, 1H), 7.64 (d, J=8.7 Hz, 1H), 6.26 (d, J=52.5 Hz, 2H), 6.24 (d, J=52.8 Hz, 2H). ^{19}F NMR: δ −165.0 (t, J=52.5 Hz, 1F), −165.5 (t, J=52.4 Hz, 1F). ^{13}C NMR: δ 147.3, 146.1, 143.7, 121.2, 120.0, 119.4, 117.5, 108.3 (d, J=238.0 Hz). MS (EI, *m/z*, %): 195 (M^+, 100.00). Anal. Calcd for $C_8H_6FN_3O_2$: C, 49.24; H, 3.10; N, 21.53. Found: C, 49.46; H, 3.04; N, 21.48.

4.2.22. 2-(Fluoromethyl)-1-phenylpyrazolidin-3-one (7d). Yellow liquid. IR (film): 3030, 1649, 1600, 1502, 1370, 1000, 751 cm^{-1}. ^1H NMR: δ 7.22−7.28 (m, 2H), 6.95–6.98 (m, 2H), 6.80–6.86 (m, 1H), 5.84 (d, J= 51.3 Hz, 2H), 3.80 (t, J=9.6 Hz, 2H), 2.96 (t, J=9.6 Hz, 2H). ^{19}F NMR: δ −155.8 (t, J=51.9 Hz, 1F). ^{13}C NMR: δ 159.4, 148.6, 129.0, 119.2, 133.3, 98.3 (d, J=221.4 Hz), 50.7, 30.5. MS (EI, *m/z*, %): 194 (M^+, 35.64), 77 (100.00). Anal. Calcd for $C_{10}H_{11}FN_2O$: C, 61.85; H, 5.71; N, 14.42. Found: C, 61.77; H, 5.78; N, 14.25.

4.2.23. 4-Benzoyl-1-(fluoromethyl)-5-methyl-2-phenyl-1,2-dihydropyrazol-3-one (7e). White solid. Mp: 85−86 °C. IR (film): 3053, 1636, 1549, 1508, 1468, 1396, 992, 906 cm^{-1}. ^1H NMR: δ 7.81 (d, J=8.1 Hz, 2H), 7.69 (d, J=8.7 Hz, 2H), 7.58 (t, J=7.4 Hz, 1H), 7.44–7.51 (m, 4H), 7.37 (t, J=7.2 Hz, 1H), 5.44 (d, J=52.5 Hz, 2H), 2.26 (s, 3H). ^{19}F NMR: δ −149.9 (t, J=52.5 Hz, 1F). ^{13}C NMR: δ 190.4, 150.2, 138.8, 137.3, 132.8, 129.2, 128.5, 128.0, 123.7, 108.0, 104.0 (d, J=228.9 Hz), 15.0. MS (EI, *m/z*, %): 310 (M^+, 58.58), 77(100.00). Anal. Calcd for $C_{18}H_{15}FN_2O_2$: C, 69.67; H, 4.87; N, 9.03. Found: C, 69.68; H, 4.88; N, 8.91.

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