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Organocatalytic, difluorocarbene-based *S*-difluoromethylation of thiocarbonyl compounds

Kohei Fuchibe, Masaki Bando, Ryo Takayama, Junji Ichikawa *

Division of Chemistry, Faculty of Pure and Applied Sciences, University of Tsukuba, Tsukuba 305-8571, Japan

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ABSTRACT

Upon treatment with trimethylsilyl 2,2-difluoro-2-fluorosulfonylacetate (TFDA) and a catalytic amount of *N*,*N*,*N*′,*N*′-tetramethyl-1,8-diaminonaphthalene, secondary thioamides and thiocarbamates undergo selective difluoromethylation on the sulfur atom to give *S*-difluoromethyl thioimidates and thioiminocarbonates in good yields, respectively. This is the first report on the synthesis of acyclic difluoromethyl thioimidates and thioiminocarbonates. The key for *S*-difluoromethylation is the organocatalytic generation of difluorocarbene ($:CF_2$) under mild conditions, which prevents decomposition of the substrates. This process provides an efficient approach to pharmaceuticals and agrochemicals bearing a difluoromethylsulfanyl group, starting from widely available thiocarbonyl compounds.

1. Introduction

In recent years, the difluoromethyl group (CHF_2 group) has been of considerable interest especially for developing pharmaceuticals and agrochemicals [1]. The difluoromethyl group has a hydrogen atom that behaves as a non-nucleophilic proton donor for hydrogen bonding [2], which leads to unique properties as a bioisostere of the hydroxy group (Fig. 1) [3]. In addition, introduction of fluoroalkyl groups, including the difluoromethyl group, often lowers Hildebrand's δ values and improves the lipophilicity of the original molecule [4,5]. Due to these advantages, the difluoromethyl group is now widely employed as a highly versatile substituent [6].

Accordingly, synthetic methods for difluoromethylated compounds have been developed in the past few years [7]. Concerning the synthesis of difluoromethylated arenes, for example, the conversion of a formyl group to a difluoromethyl group has often been conducted using diethylaminosulfur trifluoride (DAST) [8] and related reagents [9,10]. Direct [11] and several-step [12] installations of the difluoromethyl unit onto an aromatic skeleton have been also recently reported.

Difluorocarbene ($:CF_2$) [13] is most commonly used to introduce difluoromethyl groups onto a heteroatom center [7a,14–16]. Typically, phenols are treated with chlorodifluoromethane in the presence of strong bases such as potassium hydroxide. The phenoxides are difluoromethylated with difluorocarbene, which is generated in situ via α-elimination, to give difluoromethyl aryl ethers in moderate to good yields. Although difluorocarbene generation via α-elimination has been improved with modified protocols including nucleophilic attack on carbonyl groups [17], phosphoryl groups [18], or sulfonyl groups [17c,19], there remain limitations such as harsh reaction conditions [20].

Recently, we reported on the organocatalyzed generation of difluorocarbene under mild conditions (Scheme 1) [21]. When trimethylsilyl 2,2-difluoro-2-fluorosulfonylacetate (TFDA) [22] was treated with a catalytic amount of *N*-heterocyclic carbene (NHC) [23] at 80–100 °C, decomposition of TFDA smoothly proceeded under nearly neutral conditions to generate difluorocarbene. Ketones and secondary amides underwent selective difluoromethylation on the carbonyl oxygens with the electrophilic carbene thus generated, which afforded difluoromethyl vinyl ethers [21a] and difluoromethyl imidates [21b] in high yields, respectively. By combining this organocatalytic *O*-difluoromethylation and DDQ dehydrogenation, the syntheses of difluoromethyl aryl ethers and difluoromethoxyquinolines were accomplished in a one-pot operation.

In this report, we describe a difluorocarbene-based synthesis of difluoromethylsulfanylated compounds (difluoromethyl sulfides) starting from thiocarbonyl compounds. The difluoromethylsulfanyl group is encountered in a variety of bioactive compounds. For example, flomoxef, which is an oxacephem antibiotic, is successfully used for therapeutic purposes (Fig. 2) [24]. 2-Difluoromethylsulfanyl-4,6-bis(isopropylamino)-1,3,5-triazine (SSH-108) exhibits herbicidal activity [25]. In spite of their utility, the methods for difluoromethylation of sulfur functional groups have been mostly

* Corresponding author. Tel.: +81 298534237; fax: +81 298534237.
E-mail address: junji@chem.tsukuba.ac.jp (J. Ichikawa).

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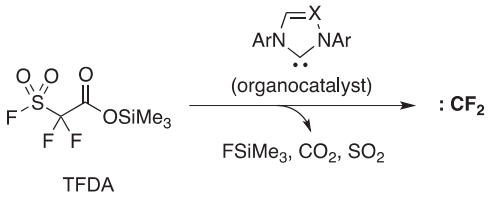
0022-1139/

Fig. 1. Difluoromethyl group as bioisotere of hydroxy group.



Scheme 1. Organocatalytic generation of difluorocarbene.

limited to those of aromatic thiols [15c–e,16,18,19b]. To broaden the scope of difluoromethylsulfanylated compounds, the methods for introduction of the difluoromethyl group to sulfur functionalities other than thiols are highly desirable.

We thus focused our attention on the use of thiocarbonyl compounds as substrates for difluoromethylation because they are readily accessible from appropriate starting materials. However, thiocarbonyl compounds are generally unstable toward hydrolysis; thus, in particular, there have been no reports on difluoromethylation of acyclic thiocarbonyl compounds [26]. We expected that our organocatalyzed generation of difluorocarbene, conducted under mild conditions, would allow an efficient *S*-difluoromethylation of thiocarbonyl compounds without decomposition of these substrates.

2. Results and discussion

2.1. Optimization of the catalyst and synthesis of 2-difluoromethylsulfanylpyridine *2a*

To make the best use of difluorocarbene for difluoromethylation, the rate of the difluorocarbene generation needs to be controlled to prevent undesired dimerization, which leads to loss of difluorocarbene. Therefore, optimization of the catalyst was performed by using 2-thiopyridone **1a** as the model substrate (Table 1). Dimesitylimidazolidene **4** and diphenyltriazolidene **5**, which were effective in our previous *O*-difluoromethylation, were first examined [21]. In each case, **2a** was obtained in 61% yield (Entries 1 and 2), which was confirmed using the reported spectroscopic data of **2a** [27]. It must be emphasized that the *N*-difluoromethylated product **3** was not observed. Whereas triphenylphosphine afforded **2a** only in 28% yield (Entry 3), trialkylamines and pyridine derivatives gave **2a** in 49–69% yields (Entries 4–10). Finally, aniline derivatives were more effective, and *N*,*N*,*N*′,*N*′-tetramethyl-1,8-diaminonaphthalene **6** gave the highest yield of **2a** (78%) at 50 °C in 10 min (Entries 11 and 12).

2.2. Synthesis of S-difluoromethyl thioimidates

As described above, difluoromethylation of acyclic thiocarbonyl compounds with difluorocarbene has not been reported yet. The optimized catalytic system was successfully applied to the synthesis of difluoromethylsulfanylated compounds with a linear structure (Table 2) [28]. The required thioamides **1b–g** were prepared through the reported thionation reaction of carboxamides with 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide (Lawesson's reagent) [29].

Thioamide **1b**, which was derived from cyclohexanecarboxamide, underwent the expected difluoromethylation at 80 °C in 10 min to give *S*-difluoromethyl thioimidate **2b** in quantitative yield

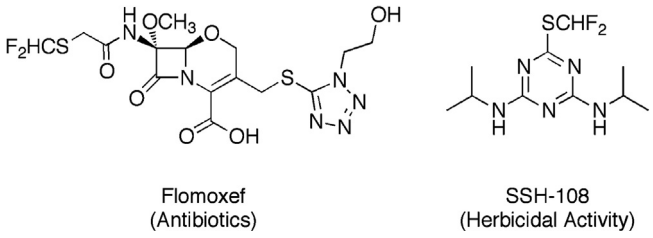
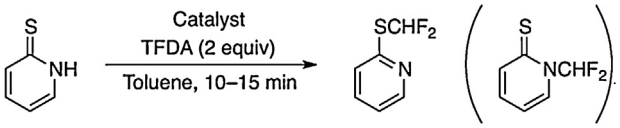


Fig. 2. Useful difluoromethylsulfanylated compounds.

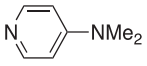
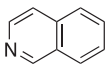
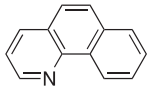
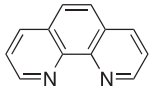
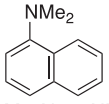
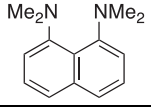
with a 79:21 diastereomeric ratio (Entry 1). Not only cyclohexanethiocarboxamide but also thioacetamides bearing a phenyl (**1c**) or a *p*-chlorophenyl (**1d**) group on the nitrogen atom afforded the corresponding products **2c**,**d** in 70% and 75% yields, respectively (Entries 2 and 3, 80 °C). Thioamides derived from aromatic carboxamides also underwent *S*-difluoromethylation. Thioamides **1e–g** afforded the expected thioimidates **2e–g** in 51–85% yields (Entries 4–6, 80 °C).

It was revealed that aliphatic thioamides were more reactive than aromatic thioamides when the reactions were conducted at 50 °C. Namely, electron-donating alkyl thioamides **1b–d** afforded

Table 1
Optimization of the catalyst.



1a **2a** **3** not detected

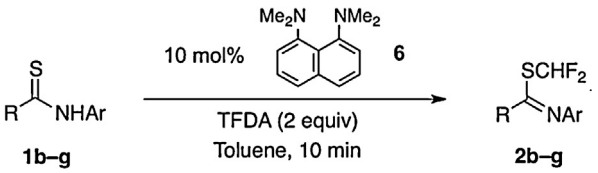
Entry	Catalyst (mol%)		Temp. [°C]	Yield [%][a,b]
1	**4** (5), Na_2CO_3 (20)		80	61
2	**5** (5), Na_2CO_3 (20)		80	61
3	PPh_3 (10)		80	28
4	NEt_3 (20)		80	49
5	DABCO (20)		80	65
6	Pyridine (20)		80	62
7		(10)	80	58
8		(10)	80	63
9		(20)	80	69
10		(10)	80	65
11		(10)	80	68
12		**6** (10)	50	78

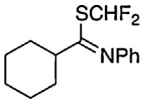
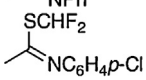
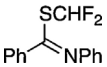
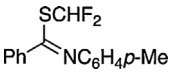
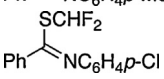
DABCO = 1,4-Diazabicyclo[2.2.2]octane. Mes = 2,4,6-trimethylphenyl.

[a] Determined by ^{19}F NMR spectroscopy using $(CF_3)_2C(C_6H_4p\text{-}Me)_2$ as the internal standard.

[b] TFDA was consumed in all entries.

Table 2
Catalytic synthesis of *S*-difluoromethyl thioimidates.



Entry	Thioamide			Thioimidate		Yield [%] (dr)[a]	
	R	Ar				80 °C	50 °C
1	*c*-C_6H_{11}	Ph	**1b**		**2b**	Quant (79/21)	71 (81/19)
2	Me	Ph	**1c**		**2c**	70 (77/23)	47 (74/26)
3	Me	C_6H_4*p*-Cl	**1d**		**2d**	75 (77/23)	47[b] (100/0)
4	Ph	Ph	**1e**		**2e**	85 (48/52)	27 (50/50)
5	Ph	C_6H_4*p*-Me	**1f**		**2f**	51 (60/40)	12 (64/36)
6	Ph	C_6H_4*p*-Cl	**1g**		**2g**	76 (63/37)	40[b] (65/35)

[a] The geometries of **2** were not determined.
[b] Determined by ^{19}F NMR spectroscopy using $(CF_3)_2C(C_6H_4p\text{-}Me)_2$ as the internal standard.

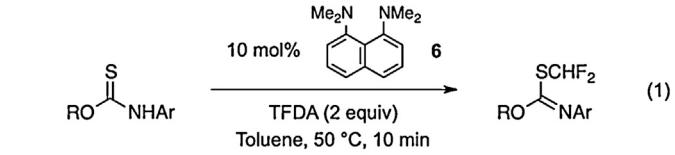
2b–d in 47–71% yields at 50 °C (Entries 1–3), whereas the less electron-donating aryl thioamides **1e–g** afforded **2e–g** only in 12–40% yields (Entries 4–6, 50 °C). This is probably due to the fact that the electron-deficient difluorocarbene favors the electron-rich aliphatic thioamides.

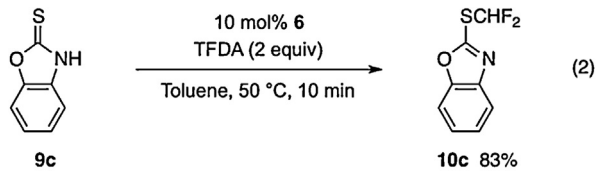
As mentioned above, the products were obtained as diastereomeric mixtures. Comparisons between the spectral data of the products and those in the literature revealed that they were *S*-difluoromethylated products. Namely, all the products exhibited ^{13}C NMR signals at 158–172 ppm and IR absorption signals at 1618–1645 cm^{-1} (Fig. 3). The reported thioimidate **7** exhibits its ^{13}C NMR signal at 170 ppm (C=N) and an IR absorption signal at 1630 cm^{-1} (C=N stretching) [30]. Thioamide **8** exhibits its ^{13}C NMR signal at 203 ppm (*C*=S) and an IR absorption signal at 1247 cm^{-1} (C=S stretching) [31]. These data suggested that the products had a C=N double bond and therefore were *S*-difluoromethylated compounds.

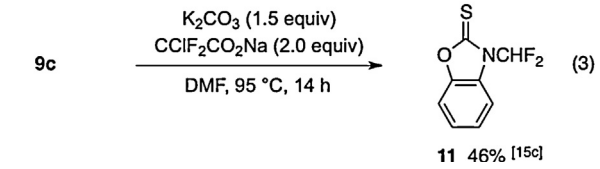
2.3. Synthesis of S-difluoromethyl thioiminocarbonates

Thiocarbamates were more reactive than thioamides in the *S*-difluoromethylation. The required thiocarbamates **9a**,**b** were readily prepared from isothiocyanates and alkoxides [32].

Methyl thiocarbamate **9a** was subjected to the organocatalyzed difluoromethylation (Eq. (1)). The reaction proceeded smoothly even at 50 °C in 10 min, and the expected *S*-difluoromethyl thioiminocarbonate **10a** was obtained in 93% yield [33]. Thiocarbamate **9b** also afforded the corresponding thioiminocarbonate **10b** in 97% yield [33]. *S*-Difluoromethylation of the cyclic thiocarbamate **9c** proceeded in a similar manner to give difluoromethylsulfanylated benzoxazole **10c** in 83% yield (Eq. (2)). Interestingly, Greaney and coworkers reported that the *N*-difluoromethylation of **9c** proceeded with difluorocarbene, which was generated from sodium chlorodifluoroacetate in the presence of potassium carbonate, in DMF at 95 °C for 14 h to afford benzoxazol-2-thione **11** in 46% yield (Eq. (3), vide infra) [15c].







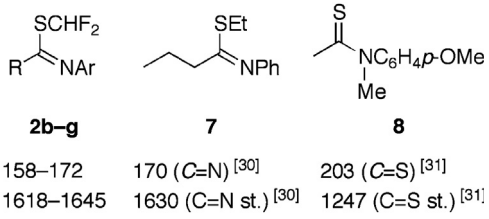
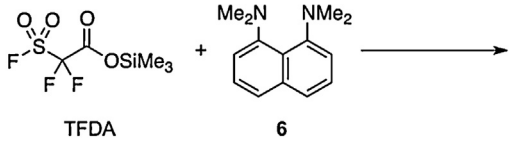


Fig. 3. Selected spectral data of products and reported compounds.

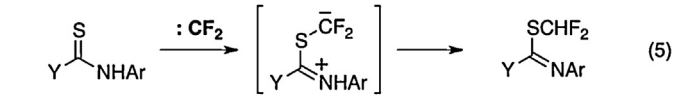
2.4. Reaction mechanism

The abovementioned *S*-difluoromethylation of thiocarbonyl compounds can be rationalized by the mechanism shown below. TFDA undergoes decomposition caused by diaminonaphthalene **6** to generate difluorocarbene (Eq. (4)) [22]. The formed silylated diaminonaphthalene [**6**–$SiMe_3$]$^+$ undergoes desilylation in the presence of the released fluoride ion to regenerate free diamine **6** (not shown) [34]. The difluorocarbene thus generated was attacked by the electron-rich sulfur atom of the substrates **1**/**9** (Eq. (5)). Subsequently, intra- and/or intermolecular proton shift gave the products **2**/**10**.



TFDA 6

$$F^- + SO_2 + :CF_2 + CO_2 + [6\text{–}SiMe_3]^+ \quad (4)$$



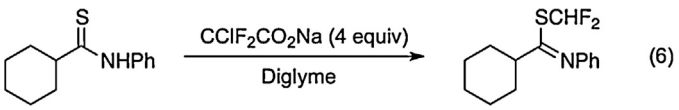
(5)

1 Y = alkyl, aryl
9 Y = alkoxy, aryloxy

2 Y = alkyl, aryl
10 Y = alkoxy, aryloxy

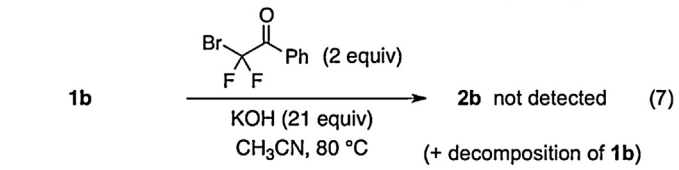
2.5. Comparison with the reported methods for the generation of difluorocarbene

To demonstrate the advantage of the organocatalyzed generation of difluorocarbene, in addition to its sulfur-selectivity, *S*-difluoromethylation of thioamides using previously reported methods for the generation of difluorocarbene was also performed. As mentioned above, thioamide **1b** undergoes *S*-difluoromethylation with TFDA in the presence of diaminonaphthalene **6** to give thioimidate **2b** in quantitative yield at 80 °C (Table 2, Entry 1). On the other hand, treatment of **1b** with sodium chlorodifluoroacetate at 80 °C did not give **2b** (Eq. (6)), which was due to the fact that its pyrolysis required harsh conditions (higher temperatures). Thioimidate **2b** was actually formed from **1b** on treatment with sodium chlorodifluoroacetate in 98% yield, only when the reaction was performed at 160 °C. Difluorocarbene generated under alkaline conditions also did not afford **2b** (Eq. (7)). Treatment of **1b** with bromodifluoroacetophenone, which is analogous to the reported chlorodifluoroacetophenone [17a], in the presence of a large excess amount of potassium hydroxide resulted in the partial decomposition of **1b** without formation of **2b**.



(6)

1b **2b** not detected (80 °C), 98% (160 °C)



1b **2b** not detected (+ decomposition of **1b**) (7)

Based on their study, Yagupol'skii and coworkers reported that difluoromethylation of sulfanyltetrazoles with difluorocarbene, generated from chlorodifluoromethane in the presence of potassium hydroxide, proceeded kinetically on the sulfur atom and thermodynamically on the nitrogen atom [35]. Mild reaction temperature (50 °C in Eq. (2) vs. 95 °C in Eq. (3)) and short reaction time (10 min vs. 14 h) provide a rationale for the high sulfur selectivity observed in our organocatalyzed system [36].

Thus, the generation of difluorocarbene under organocatalysis is particularly suitable for *S*-difluoromethylation of thioamides because of its mild reaction conditions.

3. Conclusion

Organocatalytic generation of difluorocarbene has allowed efficient *S*-difluoromethylation of thiocarbonyl compounds. Treatment of secondary thioamides with TFDA in the presence of tetramethyldiaminonaphthalene **6** at 80 °C afforded *S*-difluoromethyl thioimidates in good to excellent yields. Difluoromethylation of secondary thiocarbamates proceeded in a similar manner at 50 °C to afford *S*-difluoromethyl thioiminocarbonates in excellent yields. The starting thiocarbonyl compounds were readily prepared from carboxamides or isothiocyanates. Decomposition of these substrates was not substantially observed under the mild reaction conditions represented by the organocatalysis. The mild conditions also allowed high sulfur selectivity, leading to the formation of the difluoromethylsulfanylated products in high yields.

4. Experimental

4.1. General information

IR spectra were recorded on Horiba FT-300S spectrometer. NMR spectra were recorded on a Bruker Avance 500 spectrometer in $CDCl_3$ at 500 MHz (^{1}H NMR), at 126 MHz (^{13}C NMR), and at 470 MHz (^{19}F NMR). Chemical shift values were given in ppm relative to internal Me_4Si (for ^{1}H NMR: δ = 0.00), $CDCl_3$ (for ^{13}C NMR: δ = 77.0), and C_6F_6 (for ^{19}F NMR: δ = 0.0). Mass spectra were taken with JMS-T100GCV spectrometer (EI, 70 eV). Elemental analyses were performed with a YANAKO MT-3 CHN Corder apparatus. TFDA was prepared from the corresponding acid, which was purchased from Sigma–Aldrich Co. LLC, by the reported procedure [22]. ^{19}F NMR analysis suggested that the prepared TFDA contained a small amount of the starting acid and that its purity was higher than 98% (mol/mol). *N*,*N*,*N*′,*N*′-Tetramethyl-1,8-diaminonaphthalene **6** was purchased from Sigma–Aldrich Co. LLC and used as received.

4.2. Preparation of thioamides and thiocarbamates

2-Thiopyridone **1a** and benzoxazole **9c** were purchased from Sigma–Aldrich Co. LLC. Thioamides **1b**–**g** and thiocarbamates **9a**,**b** were prepared by the reported procedures, using commercially available 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide (Lawesson's reagent) for **1b**–**g** [29] and commercially available isothiocyanates for **9a**,**b** [32].

4.2.1. *N*-(*p*-Methylphenyl)benzenecarbothioamide (**1f**)

Preparation of thioamide **1f** is described as a typical procedure.

To a THF solution (50 mL) of Lawesson's reagent (432 mg, 1.07 mmol) was added a solution of *N*-(*p*-methylphenyl)benzenecarboxamide (461 mg, 2.18 mmol) at room temperature. The reaction mixture was stirred and heated to 50 °C for 2.5 h. After cooling the resulting mixture to room temperature, the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 2:1) to give thioamide **1f** (481 mg, 97% yield).

*4.2.2. O-Methyl N-phenylthiocarbamate (**9a**)*

Preparation of thiocarbamate **9a** is described as a typical procedure.

To a methanol solution (3 mL) of phenyl isothiocyanate (0.60 mL, 5.0 mmol) was added a methanol solution (1 mol/L, 10 mL) of sodium methoxide (10 mmol). The reaction mixture was stirred for 30 min at room temperature. Concentrated hydrochloric acid was then added to adjust the pH of the crude mixture to 4–5. The resulting white precipitate was filtered with suction and washed with methanol. The filtrate was concentrated under reduced pressure to give thiocarbamate **9a** (556 mg, 67% yield).

4.3. Synthesis of difluoromethylsulfanylated compounds

4.3.1. Synthesis of S-difluoromethyl thioimidates

Synthesis of *S*-difluoromethyl imidate **2b** is described as a typical procedure.

To a toluene solution (1.0 mL) of tetramethyldiaminonaphthalene **6** (4.1 mg, 0.019 mmol) was added thioamide **1b** (42 mg, 0.19 mmol) at room temperature. The reaction mixture was stirred and heated to 80 °C, and TFDA (80 μL, 0.40 mmol) was added. After the resulting mixture was stirred for 10 min and cooled to room temperature, the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 10:1) to give thioimidate **2b** (53 mg, quant).

4.3.2. Synthesis of S-difluoromethyl thioiminocarbonates

Synthesis of *S*-difluoromethyl thioiminocarbonate **10b** is described as a typical procedure.

To a toluene solution (1.0 mL) of tetramethyldiaminonaphthalene **6** (4.3 mg, 0.020 mmol) was added thiocarbamate **9b** (46 mg, 0.21 mmol) at room temperature. The reaction mixture was stirred and TFDA (80 μL, 0.40 mmol) was added. The reaction mixture was heated to 50 °C, and stirred for 10 min. After cooling the resulting mixture to room temperature, the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 10:1) to give thioiminocarbonate **10b** (56 mg, 97% yield).

4.4. Spectral data of products

*4.4.1. S-Difluoromethyl N-phenylcyclohexanecarbothioimidate (**2b**)*

The product **2b** was obtained as an inseparable diastereomeric mixture. Spectral data of the major isomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.99–1.09 (m, 3H), 1.35 (td, J = 12.0, 12.0 Hz, 2H), 1.53 (d, J = 12.0 Hz, 1H), 1.65 (t, J = 12.0 Hz, 4H), 2.59 (t, J = 12.0 Hz, 1H), 6.66 (d, J = 7.4 Hz, 2H), 7.06 (t, J = 7.4 Hz, 1H), 7.28 (t, J = 7.4 Hz, 2H), 7.49 (t, J = 55.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 24.9, 29.4, 30.4, 43.0, 119.2, 120.7 (t, J = 269 Hz), 123.6, 129.1, 148.6, 171.6; ^{19}F NMR (470 MHz, $CDCl_3$): δ 61.3 (d, J = 56 Hz); IR (neat): $\tilde{\nu}$ 2931, 1628, 1596, 1448, 970 cm^{-1}; HRMS: m/z calcd. for $C_{14}H_{17}F_2NS$ ($[M]^+$): 269.1050; found: 269.1050. Characteristic ^{1}H and ^{19}F NMR signals of the minor isomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.93 (t, J = 55.2 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ 69.1 (d, J = 55 Hz).

*4.4.2. S-Difluoromethyl N-phenylethanethioimidate (**2c**)*

The product **2c** was obtained as an inseparable diastereomeric mixture. Spectral data of the major isomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.06 (s, 3H), 6.76 (d, J = 8.1 Hz, 2H), 7.11 (t, J = 8.1 Hz, 1H), 7.33 (t, J = 8.1 Hz, 2H), 7.68 (t, J = 55.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.7, 119.8, 120.2 (t, J = 270 Hz), 124.2, 129.1, 148.8, 162.1; ^{19}F NMR (470 MHz, $CDCl_3$): δ 60.9 (d, J = 55 Hz); IR (neat): $\tilde{\nu}$ 2870, 1645, 1487, 1138, 1068 cm^{-1}; HRMS: m/z calcd. for $C_9H_9F_2NS$ ($[M]^+$): 201.0424; found: 201.0421. A characteristic ^{19}F NMR signal of the minor isomer: ^{19}F NMR (470 MHz, $CDCl_3$): δ 69.9 (d, J = 56 Hz).

*4.4.3. S-Difluoromethyl N-(p-chlorophenyl)ethanethioimidate (**2d**)*

The product **2d** was obtained as an inseparable diastereomeric mixture. Spectral data of the major isomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.06 (s, 3H), 6.70 (d, J = 8.6 Hz, 2H), 7.29 (d, J = 8.6 Hz, 2H), 7.64 (t, J = 55.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.7, 120.0 (t, J = 270 Hz), 121.2, 129.2, 129.3, 147.2, 163.2; ^{19}F NMR (470 MHz, $CDCl_3$): δ 60.9 (d, J = 55 Hz); IR (neat): $\tilde{\nu}$ 2951, 1645, 1161, 1049, 694 cm^{-1}; HRMS: m/z calcd. for $C_9H_8ClF_2NOS$ ($[M]^+$): 235.0034; found: 235.0033. Characteristic ^{1}H and ^{19}F NMR signals of the minor isomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14 (t, J = 55.6 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ 70.0 (d, J = 56 Hz).

*4.4.4. S-Difluoromethyl N-phenylbenzenecarbothioimidate (**2e**)*

The product **2e** was obtained as an inseparable diastereomeric mixture. Spectral data of the mixture (50:50): ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.72 (t, J = 56.3 Hz, 1H × 0.50), 6.73 (d, J = 7.6 Hz, 2H × 0.50), 6.97 (d, J = 7.8 Hz, 2H × 0.50), 7.04 (t, J = 7.4 Hz, 1H × 0.50), 7.21 (t, J = 7.4 Hz, 2H × 0.50), 7.25–7.32 (m, 5H × 0.50), 7.38 (d, J = 7.2 Hz, 1H × 0.50), 7.47 (t, J = 7.4 Hz, 2H × 0.50), 7.57–7.72 (m, 3H × 0.50), 7.75 (t, J = 55.0 Hz, 1H × 0.50), 7.87 (d, J = 7.4 Hz, 2H × 0.50); ^{13}C NMR (126 MHz, $CDCl_3$): δ 119.5, 120.3 (t, J = 265 Hz), 120.4 (t, J = 270 Hz), 120.9, 121.1, 124.0, 125.3, 128.0, 128.5, 128.8, 129.0, 129.1, 130.5, 131.5, 133.5, 136.6, 148.2, 148.9, 157.9, 162.6; ^{19}F NMR (470 MHz, $CDCl_3$): δ 60.5 (d, J = 55 Hz), 69.6 (d, J = 56 Hz); IR (neat): $\tilde{\nu}$ 3062, 1618, 1593, 1049, 762, 690 cm^{-1}; HRMS: m/z calcd. for $C_{14}H_{11}F_2NS$ ($[M]^+$): 263.0580; found: 263.0578. The GC peaks of the isomers were not isolated from each other on GC-HRMS analysis.

*4.4.5. S-Difluoromethyl N-(p-methylphenyl)benzenecarbothioimidate (**2f**)*

The product **2f** was obtained as an inseparable diastereomeric mixture. Spectral data of the mixture (63:37): ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.23 (s, 3H × 0.37), 2.37 (s, 3H × 0.63), 6.59 (d, J = 8.0 Hz, 2H × 0.37), 6.68 (t, J = 56.3 Hz, 1H × 0.63), 6.85 (d, J = 8.2 Hz, 2H × 0.63), 6.96 (d, J = 8.2 Hz, 2H × 0.37), 7.21–7.26 (m, 2H), 7.29 (t, J = 7.4 Hz, 1H × 0.63), 7.35 (d, J = 7.4 Hz, 1H × 0.37), 7.53–7.56 (m, 2H), 7.71 (t, J = 55.4 Hz, 1H × 0.37), 7.82 (d, J = 7.4 Hz, 2H × 0.63); ^{13}C NMR (126 MHz, $CDCl_3$): δ 20.9, 21.1, 119.5, 120.4 (t, J = 274 Hz), 120.4 (t, J = 270 Hz), 121.1, 128.2, 128.5, 129.0, 129.3, 129.5, 129.7, 130.4, 131.4, 133.6, 135.2, 136.6, 138.6, 145.5, 146.2, 157.5, 161.9; ^{19}F NMR (470 MHz, $CDCl_3$): δ 60.5 (d, J = 55 Hz), 69.5 (d, J = 56 Hz); IR (neat): $\tilde{\nu}$ 2924, 1618, 1506, 1072, 769 cm^{-1}; HRMS: m/z calcd. for $C_{15}H_{13}F_2NS$ ($[M]^+$): 277.0737; found: 277.0732. The GC peaks of the isomers were not isolated from each other on GC-HRMS analysis.

*4.4.6. S-Difluoromethyl N-(p-chlorophenyl)benzenecarbothioimidate (**2g**)*

The product **2g** was obtained as an inseparable diastereomeric mixture. Spectral data of the mixture (55:45): ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.56–6.61 (m, 2H × 0.5), 6.65 (t, J = 56.3 Hz, 1H × 0.5), 6.81–6.88 (m, 2H × 0.5), 7.05–7.10 (m, 2H × 0.5), 7.13–7.19 (m, 2H × 0.5), 7.22–7.28 (m, 2H × 0.5), 7.30–7.37 (m, 3H × 0.5), 7.47–7.56 (m, 4H × 0.5), 7.73–7.81 (m, 2H × 0.5); ^{13}C NMR (126 MHz, $CDCl_3$): δ 120.1 (t, J = 271 Hz), 120.3 (t, J = 275 Hz), 121.0, 122.5, 128.0, 128.5, 128.7, 128.8, 129.0, 129.2, 130.5, 130.7, 131.7, 133.1, 136.4, 138.6, 146.7, 147.2, 158.8, 163.7; ^{19}F NMR (470 MHz, $CDCl_3$): δ 60.5 (d, J = 55 Hz), 69.5 (d, J = 56 Hz); IR (neat): $\tilde{\nu}$ 2927, 1620, 1483, 1076, 698 cm^{-1}; HRMS: m/z calcd. for $C_{14}H_{10}ClF_2NS$ ($[M]^+$): 297.0191; found: 297.0188. The GC peaks of the isomers were not isolated from each other on GC-HRMS analysis.

*4.4.7. S-Difluoromethyl O-methyl N-phenylthioiminocarbonate (**10a**)*

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.04 (s, 3H), 6.85 (dd, J = 7.0, 1.0 Hz, 2H), 7.13 (tt, J = 7.0, 1.0 Hz, 1H), 7.32 (t, J = 7.0 Hz, 2H), 7.37 (t, J = 56.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 56.9, 119.0 (t, J = 274 Hz), 121.2, 124.6, 129.2, 145.7, 152.6; ^{19}F NMR (470 MHz, $CDCl_3$): δ 68.7 (d, J = 57 Hz); IR (neat): $\tilde{\nu}$ 2951, 1645, 1161, 1049, 694 cm^{-1}; HRMS: m/z calcd. for $C_9H_9F_2NOS$ ([M]$^+$): 217.0373; found: 217.0371.

*4.4.8. S-Difluoromethyl O-isopropyl N-p-(methoxyphenyl)thioiminocarbonate (**10b**)*

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.40 (d, J = 6.2 Hz, 6H), 3.78 (s, 3H), 5.36 (sept, J = 6.2 Hz, 1H), 6.78 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 7.32 (t, J = 57.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.6, 55.4, 73.7, 114.4, 119.4 (t, J = 277 Hz), 122.2, 139.2, 151.4, 156.7; ^{19}F NMR (470 MHz, $CDCl_3$): δ 66.6 (d, J = 57 Hz); IR (neat): $\tilde{\nu}$ 2983, 1639, 1504, 1033, 769 cm^{-1}; HRMS: m/z calcd. for $C_{12}H_{15}F_2NO_2S$ ([M]$^+$): 275.0792; found: 275.0790.

*4.4.9. 2-(Difluoromethylsulfanyl)benzoxazole (**10c**)*

Spectroscopic data of ^{1}H and ^{19}F NMR were in agreement with those in the literature [11a].

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