Difluorocarbene-Based [4 + 1] Cycloaddition Strategy for Synthesizing Derivatives of 5-Fluorinated Thiazoles and Oxazoles

Kohei Fuchibe,*[1] Yuki Morota,[1] Takaya Miura,[1] and Junji Ichikawa*[1]
[1] *Division of Chemistry, Faculty of Pure and Applied Sciences, University of Tsukuba, Tsukuba, Ibaraki 305–8571, Japan.*

E-mail: kfuchibe@chem.tsukuba.ac.jp, junji@chem.tsukuba.ac.jp

When treated with difluorocarbene, which was generated from $FSO_2CF_2CO_2SiMe_3$ with a 1,8-bis(dimethylamino)naphthalene catalyst, *N*-(thioacyl)amidines underwent [4 + 1] cycloaddition to afford the corresponding amino-substituted 5,5-difluorothiazolines. Both dehydrofluorination and a Hofmann elimination/S_N2'-type reaction sequence enabled the aromatization of the obtained products, affording 5-fluorothiazoles. The [4 + 1] cycloaddition strategy was also applied to *N*-acylamidines, affording the corresponding 5-fluorooxazole derivatives.

Keywords: Difluorocarbene, Fluorine, Heterocycles

Thiazoles and oxazoles are found in the core structures of various beneficial compounds. For example, firefly luciferin[1] and aztreonam[2] possess the thiazole ring and act as luminescent compounds and antibiotics, respectively (Figure 1). Retosiban is an oxytocin receptor antagonist that exhibits the oxazole substructure.[3]

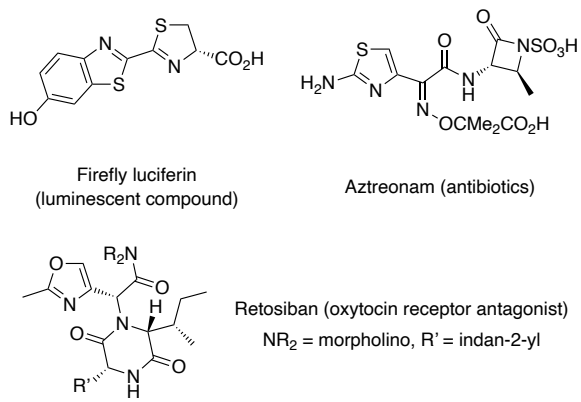
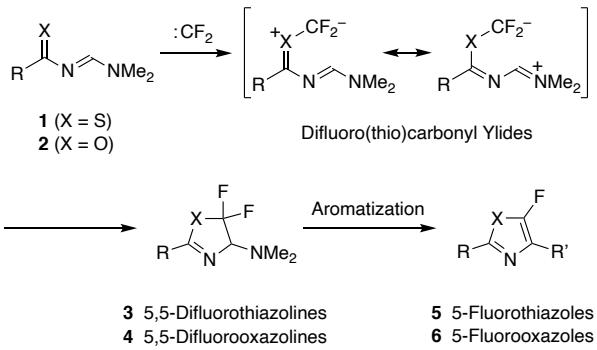


Figure 1. Beneficial thiazole derivatives and oxazole derivatives.

Fluorine is frequently introduced into organic molecules to improve or change their biological activities and spectra.[4] Thus, the synthesis of fluorinated thiazoles and oxazoles may aid in the development of innovative and high-performance medicines and agrochemicals. However, the direct introduction of a fluorine atom onto such heterocyclic rings is problematic due to low yields and a lack of regioselectivity.[5,6]

We established an organocatalyzed process for difluorocarbene generation and its applications,[7] some of which undergo three-membered thiirane ring formation ([2 + 1] cycloaddition) using difluorothiocarbonyl ylide intermediates.[8] To overcome the drawbacks of fluorine introduction into five-membered thiazole and oxazole rings, we adopted a [4 + 1] cycloaddition strategy using π-extended (thio)carbonyl ylides (Scheme 1).[9,10] Thus, on treatment with difluorocarbene, *N*-(thio)acylamidines **1** (X = S) and **2** (X = O) would form difluoro(thio)carbonyl ylides.[11] Nucleophilic five-membered ring closure of the ylide intermediates (5-*endo-trig* cyclization) may yield 5,5-difluorothiazolines **3** and 5,5-difluorooxazolines **4**,[12] whose aromatization would form 5-fluorothiazoles **5** and 5-fluorooxazoles **6**. Notably, the pendant NMe_2 group may aid the five-membered ring formation by resonance (5-*exo-trig* cyclization) and serve as a functional group to allow aromatization.[13]

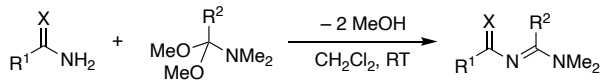


Scheme 1. [4 + 1] Cycloaddition strategy to afford 5-fluorothiazole and 5-fluorooxazole derivatives.

The required precursors were prepared according to the literature (Table 1).[14] Commercially available thioamides or amides were condensed with dimethyl acetals of *N*,*N*-dimethylformamide (Entries 1–4 and 8) or *N*,*N*-dimethylacetamide (Entries 5–7). The required *N*-(thioacyl)amidines **1** and *N*-acylamidines **2** were afforded in 69%–quantitative yields.[15]

Using **1e** as the model substrate, the reaction conditions were tuned (Table 2). A diluted solution of **1e** (0.05 M) was treated with 2 equivalents of trimethylsilyl 2,2-difluoro-2-(fluorosulfonyl)acetate (TFDA)[16] in the presence of a 1,8-bis(dimethylamino)naphthalene (proton sponge) catalyst (5 mol%).[7b] The expected adduct **3e** was afforded in all the studied common solvents such as hexane (74% yield determined by ^{19}F NMR analysis, Entry 1) and toluene (86% yield, Entry 2). However, the reaction showed poor reproducibility when conducted in toluene. The product gradually decreased in CCl_4 (Entry 3) and 1,2-dichloroethane (Entry 4), whereas **3e** was produced slowly but in good yields in nitromethane (Entry 5). Finally, tetrahydrofuran was selected as a solvent because it afforded 5,5-difluorothiazoline **3e** by treating the **1e** solution (0.2 M, Entry 8) with 1.05 equivalents of TFDA.[17]

Table 1. Preparation of *N*-(thioacyl)amidines and *N*-acylamidines



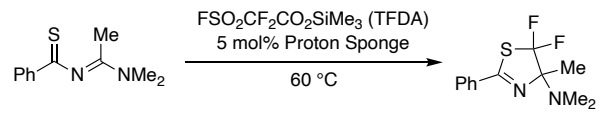
(X = S, O) 1.1 equiv **1** (X = S) **2** (X = O)

Entry	X	R^1	R^2	*t* (h)	Yield (%) [a]
1	S	Ph	H	3	**1a** 75
2	S	C_6H_4*p*-Cl	H	3	**1b** 96
3	S	C_6H_4*p*-CF_3	H	16	**1c** 84
4	S	C_6H_4*p*-Me	H	6	**1d** 85
5	S	Ph	Me	1	**1e** quant
6	S	C_6H_4*p*-Cl	Me	19	**1f** 69
7	S	C_6H_4*p*-Me	Me	15	**1g** 69
8	O	C_6H_4*p*-OMe	H	23	**2a** quant

[a] Isolated yield.

Several (thioacyl)amidines **1** yielded the corresponding difluorothiazolines **3** under optimized conditions (Table 3). Benzthioamide-derived **1a** reacted with in situ-generated difluorocarbene to form **3a** in a 90% yield (Entry 1). Chlorinated, trifluoromethylated, and methylated difluorothiazolines **3b**–**d** were afforded in 72%–87% yields via the reactions of electron-deficient and -rich substrates **1b**–**d**, respectively (Entries 2–4). The obtained products **3** were separated via Kügelrohr distillation. Moreover, **3e**–**g** with a methyl group on the ring (R^2) were synthesized from **1e**–**g**, respectively, in 86–96% yields

Table 2. Optimization of reaction conditions



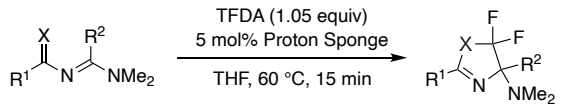
1e **3e**

Entry	Solvent	*c* (M) [a]	TFDA (equiv)	*t* (min)	Yield (%) [b,c]
1	Hexane	0.05	2.0	30	74
2	Toluene [d]	0.05	2.0	30	86 [e]
3	CCl_4	0.05	2.0	5	58
4	DCE	0.05	2.0	15	61
5	$MeNO_2$	0.05	2.0	30	84
6	THF	0.05	2.0	15	quant
7	THF	0.2	2.0	15	63
8	THF	0.2	1.05	15	quant

[a] Concentration of **1e**. [b] ^{19}F NMR yield based on an internal standard $(CF_3)_2C$*p*-Tol_2. [c] Substrate **1e** was consumed in all of the entries. [d] Reflux. [e] Poorly reproduced. Proton sponge = 1,8-Bis(dimethylamino)naphthalene. DCE = 1,2-Dichloroethane.

(Entries 5–7). The oxygen analog **2a** afforded the corresponding 5,5-difluorooxazoline **4a** in a 63% yield (determined by ^{19}F NMR analysis, Entry 8).

Table 3. Synthesis of 5,5-difluorothiazolines and 5,5-difluorooxazolines

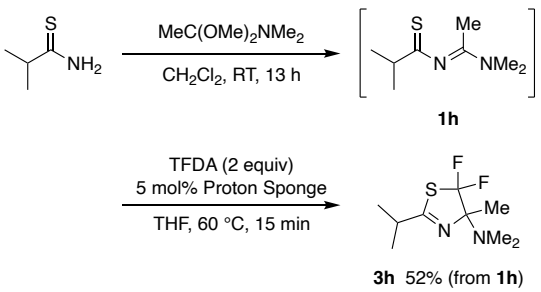


1 or **2** (0.2 M) **3** or **4**

Entry	**1** or **2**	R^1	R^2	Yield (%) [a,b]
1	**1a**	Ph	H	**3a** 90
2	**1b**	C_6H_4*p*-Cl	H	**3b** 87
3	**1c**	C_6H_4*p*-CF_3	H	**3c** 75
4	**1d**	C_6H_4*p*-CH_3	H	**3d** 72 (82)
5	**1e**	Ph	Me	**3e** 96
6	**1f**	C_6H_4*p*-Cl	Me	**3f** 86
7	**1g**	C_6H_4*p*-Me	Me	**3g** 86
8	**2a**	C_6H_4*p*-OMe	H	**4a** (63)

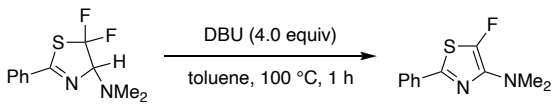
[a] Isolated yield [^{19}F NMR yield based on an internal standard $(CF_3)_2C$*p*-Tol_2 is shown in parentheses]. [b] The product was isolated via Kügelrohr distillation [115–120 °C (bath temp.)/0.8 mmHg].

Furthermore, *N*-(thioacyl)amidines derived from aliphatic thioamides were less stable than those derived from aromatic thioamides. Thus, in situ-generated isopropyl precursor **1h** was treated with difluorocarbene to afford the corresponding isopropyl-substituted 5,5-difluorothiazoline **3h** in a 52% yield (determined by ^{19}F NMR analysis, eq 1).



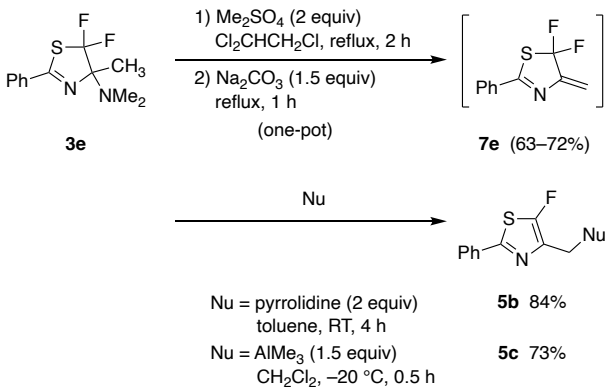
The resulting products **3** thus obtained were then converted to 5-fluorothiazoles **5**. First, **3a** was treated with 4 equivalents of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene at 100 °C. Dehydrofluorination afforded the aromatized **5a** in an 80% yield (determined by ^{19}F NMR analysis, Scheme 2).[18]

The quaternization of the dimethylamino group facilitated the synthesis of aromatized 5-fluorothiazoles **5**, where elimination followed by the S_N2'-type reaction with nucleophiles produced the additional C–N or C–C bond (Scheme 3).[19] When treated with dimethyl sulfate, **3e** with a methyl group on the carbon α to the dimethylamino group yielded the trimethylammonium salt (not shown), whose



Scheme 2. Aromatization of 5,5-difluorothiazolines via dehydrofluorination (^{19}F NMR yield based on an internal standard $PhCF_3$).

Hofmann elimination produced 4-methylidene-5,5-difluorothiazoline **7e**. The obtained exo-methylene moiety of **7e** was reactive toward nucleophiles such as pyrrolidine and trimethylaluminium, affording 2,4-disubstituted 5-fluorothiazole products **5b** (with pyrrolidine) and **5c** (with $AlMe_3$) in 84% and 73% yields, respectively.



Scheme 3. Aromatization of 5,5-difluorothiazolines via a Hofmann elimination/S_N2'-type reaction sequence (Isolated yield).

In conclusion, convenient access to 5-fluorothiazole and 5-fluorooxazole derivatives was devised using a difluorocarbene-based [4 + 1] cycloaddition strategy. Treating *N*-(thioacyl)amidines or *N*-acylamidines with difluorocarbene generated from $FSO_2CF_2CO_2SiMe_3$ with a proton sponge catalyst allowed cycloaddition to yield the corresponding 5,5-difluorothiazolines and 5,5-difluorooxazolines with an amino group. Both dehydrofluorination and a Hofmann elimination/S_N2'-type reaction sequence successfully afforded the corresponding aromatized 5-fluorothiazoles.

Supporting Information is available on http://dx.doi.org/10.1246/cl.******.

References and Notes

1 E. H. White, F. McCapra, G. F. Field, W. D. McElroy, *J. Am. Chem. Soc.* **1961**, *83*, 2402.

2 R. B. Sykes, D. P. Bonner, K. Bush, N. H. Georgopapadakou, J. S. Wells, *J. Antimicr. Chemoth.* **1981**, *8 (Suppl. E)*, 1.

3 J. Liddle, M. J. Allen, A. D. Borthwick, D. P. Brooks, D. E. Davies, R. M. Edwards, A. M. Exall, C. Hamlett, W. R. Irving, A. M. Mason, G. P. McCafferty, F. Nerozzi, S. Peace, J. Philp, D. Pollard, M. A. Pullen, S. S. Shabbir, S. L. Sollis, T. D. Westfall, P. M. Woollard, C. Wu, D. M. B. Hickey, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 90.

4 a) B. E. Smart, *J. Fluorine Chem.* **2001**, *109*, 3. b) K. Uneyama, in *Organofluorine Chemistry*, Blackwell Publishing, Oxford, **2006**, pp. 206–222. c) W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359. d) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432.

5 For fluorination of thiazole and oxazole derivatives, see: a) J. M. Hatfield, C. K. Eidell, C. E. Stephens, *Tetrahedron Lett.* **2013**, *54*, 1025. b) S. M. Riyadh, H. Ishii, T. Fuchigami, *Tetrahedron* **2002**, *58*, 9273.

6 For the syntheses of fluorinated thiazole and oxazole derivatives by methods other than direct fluorination, see: [Fluorothiazole derivarives] a) V. V. Saloutina, *Russ. J. Org. Chem.* **2000**, *36*, 887. b) T. I. Filyakova, M. I. Kodess, P. A. Slepukhin, A. Y. Zapevalov, *Russ. J. Org. Chem.* **2009**, *45*, 1700. [Fluorooxazole derivatives] c) V. M. Koshelev, T. D. Truskanova, V. F. Cherstkov, D. V. Romanov, N. V. Vasili'ev, *Russ. Chem. Bull.* **2005**, *54*, 1675. d) L. V. Saloutina, A. Y. Zapevalov, V. I. Saloutin, P. A. Slepukhin, M. I. Kodess, O. N. Chupakhin, *J. Fluorine Chem.* **2009**, *130*, 853. e) A. Bigot, J. Blythe, C. Pandya, T. Wagner, O. Loiseleur, *Org. Lett.* **2011**, *13*, 192.

7 a) K. Fuchibe, Y. Koseki, H. Sasagawa, J. Ichikawa, *Chem. Lett.* **2011**, *40*, 1189. b) K. Fuchibe, R. Takayama, T. Yokoyama, J. Ichikawa, *Chem. Eur. J.* **2017**, *23*, 2831. c) R. Takayama, K. Fuchibe, J. Ichikawa, *ARKIVOC* **2018**, 72. d) K. Fuchibe, R. Takayama, T. Aono, J. Hu, T. Hidano, H. Sasagawa, M. Fujiwara, S. Miyazaki, R. Nadano, J. Ichikawa, *Synthesis* **2018**, *50*, 514.

8 a) R. Takayama, A. Yamada, K. Fuchibe, J. Ichikawa, *Org. Lett.* **2017**, *19*, 5050. b) K. Fuchibe, A. Yamada, K. Hachinohe, K. Matsumoto, J. Ichikawa, *Bull. Chem. Soc. Jpn.* **2021**, *94*, 2451. See also: c) K. Fuchibe, I. Mukohara, A. Yamada, D. Miyazaki, R. Takayama, J. Ichikawa, *Org. Lett.* **2022**, *24*, 169.

9 For our previous 5-membered ring construction via [4 + 1] cycloaddition using a copper(I) difluorocarbene complex, see: K. Fuchibe, T. Aono, J. Hu, J. Ichikawa, *Org. Lett.* **2016**, *18*, 4502.

10 Difluorocarbene-based [4 + 1] cycloaddition for constructing fluorinated heterocyclic systems has been quite limited. For two such examples, see: a) Z. V. Safronova, L. A. Simonyan, Y. V. Zeifman, N. P. Gambaryan, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1979**, *28*, 1688. b) A. F. Khlebnikov, M. S. Novikov, S. A. Dolgikh, J. Magull, *ARKIVOC* **2008**, *2008*, 94.

11 a) K. Fuchibe, Y. Koseki, T. Aono, H. Sasagawa, J. Ichikawa, *J. Fluorine Chem.* **2012**, *133*, 52. b) K. Fuchibe, M. Bando, R. Takayama, J. Ichikawa, *J. Fluorine Chem.* **2015**, *171*, 133.

12 Difluoromethylene compounds are of interest as pharmaceuticals and agrochemicals and thus their syntheses have been studied. For reviews containing difluoromethylene compounds, see: a) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*, 8315. b) W. Zhang, Y. Wang, *Tetrahedron Lett.* **2018**, *59*, 1301.

13 During the preparation of this manuscript, Lin and Wan reported the synthesis of 2,2-difluoro-2,3-dihydrofuranes by the reaction of enaminones with difluorocarbene, where the amino group was not utilized. J. Ying, T. Liu, Y. Liu, J.-P. Wan, *Org. Lett.* **2022**, *24*, 2404.

14 Y.-i. Lin, S. A. Lang, S. R. Petty, *J. Org. Chem.* **1980**, *45*, 3750.

15 All the precursors were obtained as single diastereomeric isomers, whose alkene geometry were not determined.

16 W. R. Dolbier Jr., F. Tian, J.-X. Duan, A.-R. Li, S. Ait-Mohand, O. Bautista, S. Buathong, J. Marshall Baker, J. Crawford, P. Anselme, X. H. Cai, A. Modzelewska, H. Koroniak, M. A. Battiste, Q.-Y. Chen, *J. Fluorine Chem.* **2004**, *125*, 459.

17 For the details in the optimization, see Supporting Information.

18 The amino-substituted fluorothiazoles were less stable during their purification.

19 For a review on the S_N2'-type reactions of allylic fluorides, see: J.-D. Hamel, J.-F. Paquin, *Chem. Commun.* **2018**, *54*, 10224.

Graphical Abstract

Textual Information

A brief abstract	On treatment with difluorocarbene, generated from $FSO_2CF_2CO_2SiMe_3$ with a 1,8-bis(dimethylamino)naphthalene catalyst, *N*-(thioacyl)amidines successfully underwent [4 + 1] cycloaddition to afford the corresponding amino-substituted 5,5-difluorothiazolines. Both dehydrofluorination and a Hofmann elimination/S_N2'-type reaction sequence, facilitated aromatization of the products to provide 5-fluorothiazoles. The [4 + 1] cycloaddition strategy was also applied to *N*-acylamidines to afford the corresponding 5-fluorooxazole derivatives.
Titl	Difluorocarbene-Based [4 + 1] Cycloaddition Strategy for Synthesizing Derivatives of 5-Fluorinated Thiazoles and Oxazoles
Authors' Names	Kohei Fuchibe,* Yuki Morota, Takaya Miura, and Junji Ichikawa*

Graphical Information