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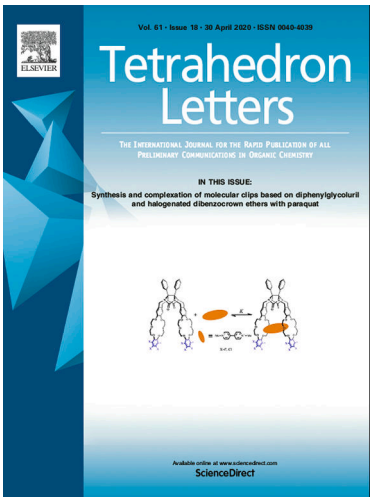

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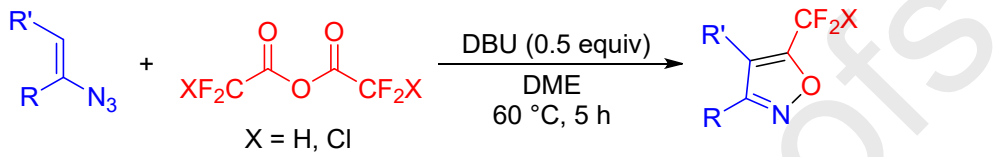
Jiawei Lin,[a] Wei Wu,[b,*] and Zhiqiang Weng[b,*]



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A general method for the synthesis of 5-difluoromethyl isoxazoles

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ABSTRACT

An efficient reaction of vinyl azides with difluoroacetic anhydride or chlorodifluoroacetic anhydride has been developed. It involved sequential difluoroacetylation of vinyl azides, followed by deprotonation, cyclization, and dinitrogen elimination, providing a convenient synthesis of both 5-difluoromethyl and 5-chlorodifluoromethyl isoxazoles at yields up to 89%.

The incorporation of fluorinated substituents into organic molecules can have a profound influence on their metabolic stabilities and pharmacokinetic properties.[1-4] Among organofluorine molecules, difluoromethylated compounds, particularly difluoromethylated heterocyclic frameworks, play a unique and significant role in agricultural and medicinal chemistry.[5-13] It is known that the difluoromethyl ($-CF_2H$) functionality behaves as isosteric and isopolar to the hydroxy (–OH) group and can act as a hydrogen donor through hydrogen bonding.[14,15] As a consequence, the exploration of efficient methods for the synthesis of difluoromethylated heterocyclic compounds has received much attention.

Among these heterocyclic products, isoxazole nuclei are ubiquitous scaffolds that play a central role in many therapeutic compounds, which possess excellent biological properties such as antinociceptive, antimicrobial, antibiotic, anti-inflammatory, and anticancer activities.[16-19] Some representative examples of bioactive molecules containing isoxazole motif with various pharmacological properties are shown in Figure 1.

Introduction of fluorinated substituents into isoxazole derivatives may lead to drastically change in their physico-chemical and biological properties. For example, BMS-960, a trifluoromethyl isoxazole-based compound, is a potent and selective $S1P_1$ receptor agonist.[20] Because of the important pharmaceutical activities and other applications, immense attention has been paid to the synthesis of fluoroalkyl isoxazole molecules. Classically, these compounds were prepared through the 1,3-dipolar cycloaddition and addition of hydroxylamine to conjugated ynone or β-diketone derivatives.[21-26] Both of these procedures, although widely applied, suffered from their individual limitations, such as the requirement of using specific reagents, narrow substrate scopes, multistep reaction processes, and generation of undesirable regioisomers.

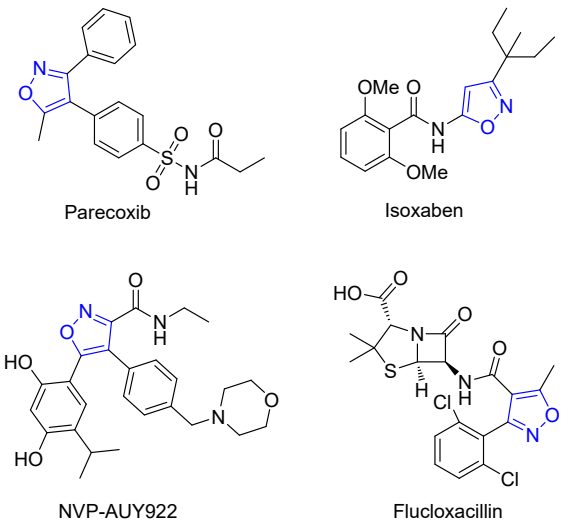
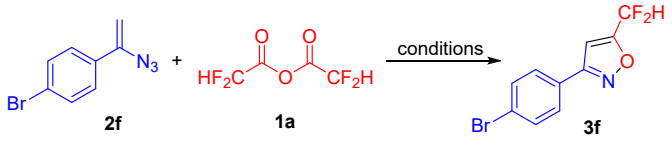


Figure 1. Some examples of bioactive isoxazole derivatives.

In connection with our recent research on the synthesis of fluorinated heterocyclic compounds, we became interested in using relatively low cost and readily available perfluorocarboxylic anhydrides as fluorinating sources.[27-30] Recently, we developed a new method for the synthesis of 5-(trifluoromethyl)isoxazoles through denitrogenative cyclization of vinyl azides with trifluoroacetic anhydride.[31] Encouraged by these results, we planned to develop a new synthesis strategy that

pe... the biological interest.

Table 1
Optimization of the reaction conditions[a]

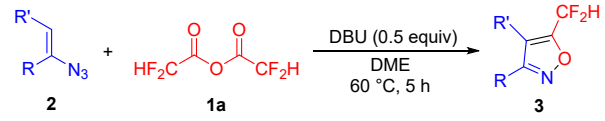


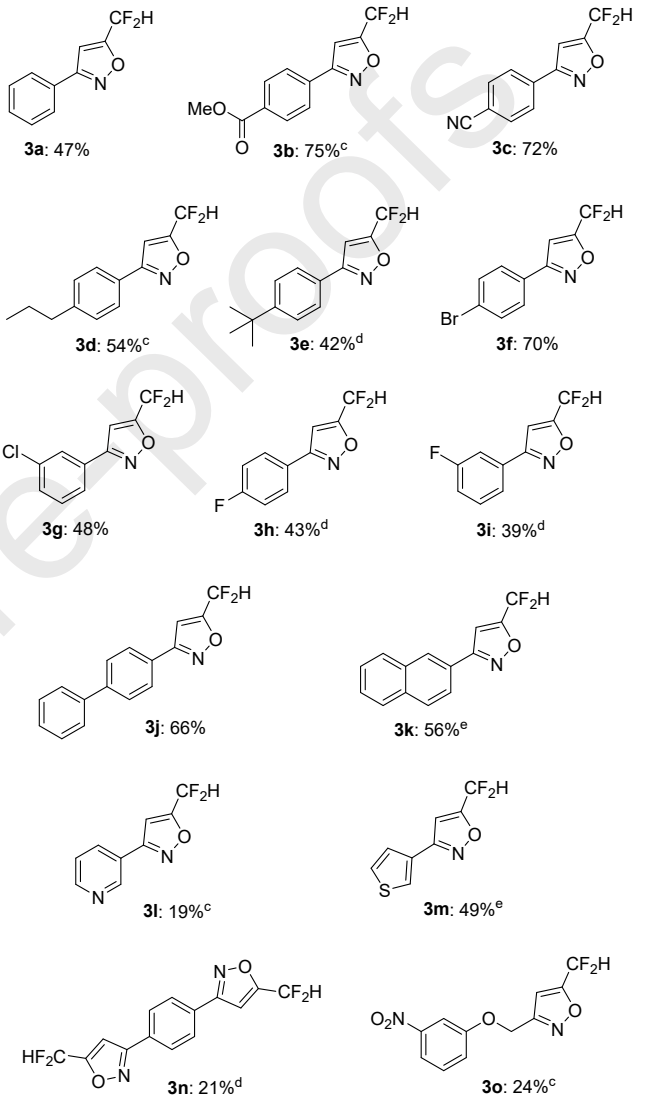
Entry	1a (equiv)	Base (equiv)	Solvent	Temp (°C)	Time (h)	Yield (%) [b]
1	(2)	NEt_3 (0.5)	dioxane	60	5	46
2	(4)	NEt_3 (0.5)	dioxane	60	5	63
3	(5)	NEt_3 (0.5)	dioxane	60	5	68
4	(5)	DBU (0.5)	dioxane	60	5	72
5	(5)	DABCO (0.5)	dioxane	60	5	60
6	(5)	Na_2CO_3 (0.5)	dioxane	60	5	65
7	(5)	K_2CO_3 (0.5)	dioxane	60	5	58
8	(5)	NaOH (0.5)	dioxane	60	5	54
9	(5)	KOH (0.5)	dioxane	60	5	49
10	(5)	DBU (0.5)	DME	60	5	74
11	(5)	DBU (0.5)	DMF	60	5	41
12	(5)	DBU (0.5)	MeCN	60	5	27
13	(5)	DBU (0.5)	DME	50	5	30
14	(5)	DBU (0.5)	DME	80	5	58
15	(5)	DBU (0.5)	DME	60	10	73
16	(5)	DBU (1)	DME	60	5	64

[a] Reaction conditions: **1a** (0.50 mmol), **2f** (0.10 mmol), solvent (0.5 mL), under N_2 atmosphere, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DABCO = 1,4-diazabicyclo[2.2.2]octane, DME = dimethoxyethane, DMF = *N*,*N*-dimethylformamide.
[b] The yield was determined by ^{19}F NMR spectroscopy with $PhOCF_3$ as internal standard.

To assess preliminary parameters for the denitrogenative cyclization of vinyl azides, we conducted a series of test experiments in which 1-(1-azidovinyl)-4-bromobenzene (**2f**) was reacted with difluoroacetic anhydride (**1a**) under different reaction conditions (Table 1). Initially, we studied the model reaction following our recently established denitrogenative cyclization of vinyl azides with trifluoroacetic anhydride.[31] The desired difluoromethylated isoxazole product **3f** was obtained in 46% yield when using 2 equiv of **1a** and 0.5 equiv of NEt_3 at 60 °C in dioxane (Entry 1). Encouraged by these preliminary results, we sought to improve the reaction with the goal of developing a general method for the synthesis of difluoromethylated isoxazole. Increasing the anhydride amount to 4 equiv, the yield of **3f** increased to 63%, and with 5 equiv it reached up to 68% (Entries 2 and 3). The reaction in different bases such as DBU, DABCO, Na_2CO_3, K_2CO_3, NaOH, and KOH was also screened; among these bases (Entries 3−9), the best yield of **3f** was obtained with DBU as the base (Entry 4). A variety of solvents such as dioxane, DME, DMF, and MeCN (Entries 4, 10−12) have been tested for this reaction. No solvents were found to be effective like DME, which gave 74% difluoromethylated product **3f** (Entry 13). Decreasing the reaction temperature to 50 °C or increasing temperature to 80 °C, extended reaction time (10 h), and increasing the amount of DBU (1 equiv), the yield of **3f** was reduced (Entries 13−16).

Table 2. Scope of the reaction of vinyl azides with difluoroacetic anhydride [a,b]





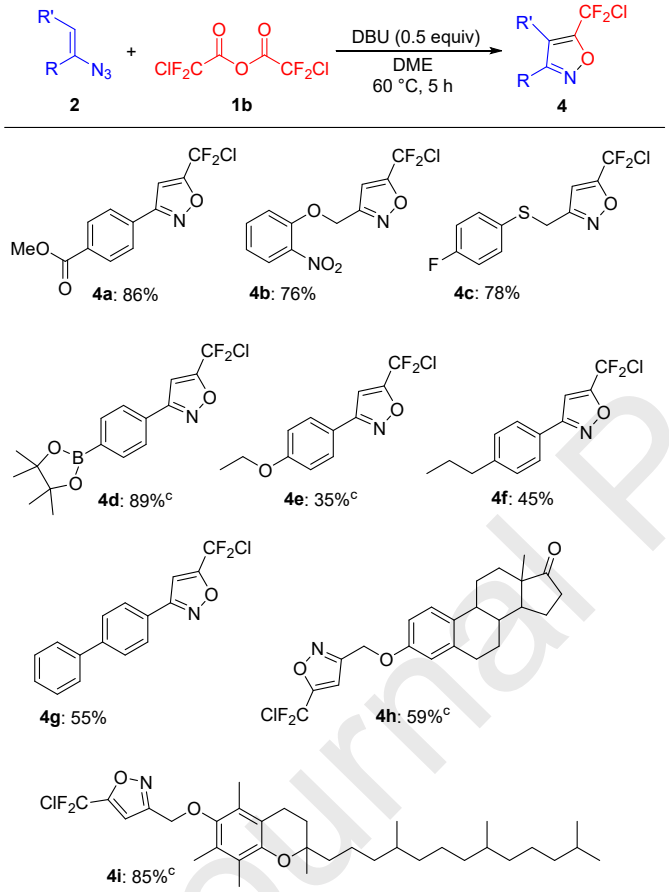
[a] Reaction conditions: **1a** (1.50 mmol, 5 equiv), **2** (0.30 mmol), DBU (0.15 mmol, 0.5 equiv), DME (1.5 mL), under N_2 atmosphere.
[b] Isolated yields.
[c] NEt_3 and dioxane was used instead of DBU and DME.
[d] NEt_3 was used instead of DBU.
[e] Dioxane was used instead of DME.

Having the optimized conditions in hand, the scope of the reaction of vinyl azides **2** with difluoroacetic anhydride (**1a**) was explored (Table 2). The unsubstituted α-phenyl vinyl azide **2a** reacted smoothly with **1a** and resulted in the corresponding 5-(difluoromethyl)-3-phenylisoxazole **3a** in 47% yield. α-Aryl vinyl azides having electron-withdrawing (ester, nitrile) delivered the corresponding derivatives of 5-difluoromethyl isoxazoles (**3b**

and E

propyl, and *t*-butyl gave moderate yields of the corresponding derivatives (**3d** and **3e**). It is noteworthy to mention that the halo substituents such as Br (**3f**), Cl (**3g**), and F(**3h** and **3i**) remained intact after the reaction, available for further functionalizations. The polycyclic aromatic vinyl azides were also well tolerated, furnishing the 5-difluoromethyl isoxazoles (**3j** and **3k**) in moderate yields. α-Heteoaryl vinyl azides could also be tolerated to give the difluoromethylated products **3l** and **3m** in 19% and 49% yield, respectively. Next, an bis-(vinyl azides) derivative was also reacted, and the desired bis-difluoroethylated product **3n** were obtained in 21% yield. Interestingly, when a α-alkyl vinyl azide was employed, the desired 5-difluoromethyl isoxazole **3o** was obtained in 24% yield.

Table 3. Scope of the reaction of vinyl azides with chlorodifluoroacetic anhydride [a,b]



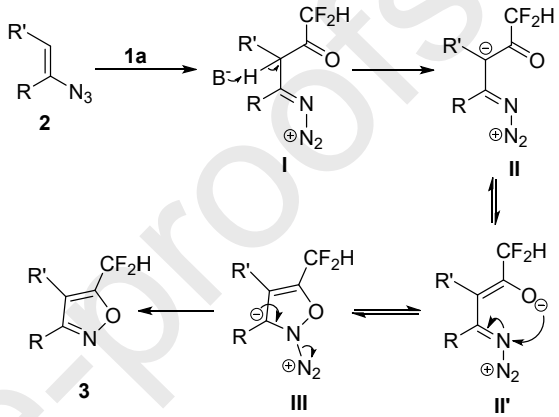
[a] Reaction conditions: **1b** (1.50 mmol, 5 equiv), **2** (0.30 mmol), DBU (0.15 mmol, 0.5 equiv), DME (1.5 mL), under N_2 atmosphere.

[b] Isolated yields.

[c] NEt_3 and dioxane was used instead of DBU and DME.

After establishing this denitrogenative cyclization for the synthesis of 5-difluoromethyl isoxazoles, we extended our study to access chlorodifluoromethylated isoxazoles (Table 3). Thus, the vinyl azides **2** was treated with chlorodifluoroacetic anhydride (**4**) under the above optimized cyclization reaction conditions, and we were pleased to find that the reaction afforded the corresponding chlorodifluoromethylated isoxazoles **4a**–**4g** in moderate to good yields. Moreover, the reaction scope was further studied by employing various vinyl azides containing derivatives as substrates with **1b** to furnish the desired chlorodifluoromethylated isoxazoles **4h** and **4i** in 59% and 85% yields, respectively.

On the basis of literature precedence[32,33] and our previous work,[31] a plausible reaction mechanism is proposed in Scheme 1. Initially, difluoroacetylation of vinyl azides with difluoroacetic anhydride would form intermediate **I**, which underwent deprotonation with a base to generate intermediate **II**. Upon isomerization of **II** to an alkoxyl anion **II′**, followed by a 5-endo cyclization could produce the intermediate **III**. Finally, the intermediate **III** underwent a dinitrogen elimination, affording the isoxazole product **3**.



Scheme 1. Proposed mechanism.

In conclusion, we have developed a facile and general method for the synthesis of 5-difluoromethyl and 5-chlorodifluoromethyl isoxazoles from reaction of vinyl azides with difluoroacetic anhydride or chlorodifluoroacetic anhydride. The newly developed protocol constitutes sequential difluoroacetylation of vinyl azides, followed by deprotonation, cyclization, and dinitrogen elimination. The reactions are operationally simple under mild conditions, compatible with a range of functional groups. Moreover, the method is applicable to molecules containing complex architectures.

Acknowledgments

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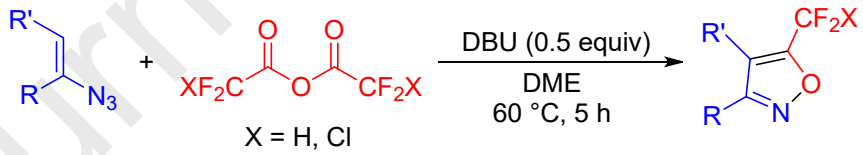

Highlights:

- A method for synthesis of 5-(chloro)difluoromethyl isoxazoles was developed.
- Various 5-(chloro)difluoromethyl isoxazoles were isolated in moderate to excellent yields.
- A variety of functional groups were tolerated.

Declaration of interests

☑ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: