Accepted Manuscript

Title: Synthesis of trifluoromethyl-/cyclopropyl-substituted 2-isoxazolines by DBU-promoted domino reaction

Author: Xiao-Dong Liu Hai-Yan Ma Chun-Hui Xing Long Lu

PII: S1001-8417(17)30109-2
DOI: http://dx.doi.org/doi:10.1016/j.cclet.2017.03.031
Reference: CCLET 4026

To appear in: *Chinese Chemical Letters*

Received date: 6-1-2017
Revised date: 20-3-2017
Accepted date: 22-3-2017

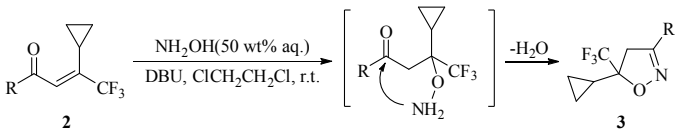
Please cite this article as: X.-D. Liu, H.-Y. Ma, C.-H. Xing, L. Lu, Synthesis of trifluoromethyl-/cyclopropyl-substituted 2-isoxazolines by DBU-promoted domino reaction, *Chinese Chemical Letters* (2017), http://dx.doi.org/10.1016/j.cclet.2017.03.031

Graphical Abstract

Synthesis of trifluoromethyl-/cyclopropyl-substituted 2-isoxazolines by DBU-promoted domino reaction

Xiao-Dong Liu[a], Hai-Yan Ma[a,*], Chun-Hui Xing[b,*], Long Lu[b]

[a] *School of Chemistry and Molecular Engineering, East China University of Science and Technology, Shanghai 200237, China*
[b] *Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China*



Trifluoromethyl and cyclopropyl substituted 2-isoxazolines were synthesized *via* a DBU-promoted domino reaction of *β*-trifluoromethyl-/*β*-cyclopropyl-substituted enones with hydroxylamine. A wide range of 3-substituted 5-cyclopropyl-5-trifluoromethyl-2-isoxazolines were obtained in good to excellent yields under mild reaction conditions.

* Corresponding authors.
E-mail addresses: haiyanma@ecust.edu.cn; xingch@sioc.ac.cn

Original article

Synthesis of trifluoromethyl-/cyclopropyl-substituted 2-isoxazolines by DBU-promoted domino reaction

Xiao-Dong Liu[a], Hai-Yan Ma[a,*], Chun-Hui Xing[b, *], Long Lu[b]

[a] *School of Chemistry and Molecular Engineering, East China University of Science and Technology, Shanghai 200237, China*
[b] *Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China*

ARTICLE INFO

Article history:
Received 8 January 2017
Received in revised form 14 March 2017
Accepted 16 March 2017
Available online

Keywords:
Isoxazoline
Enone
Michael addition
Cyclization
Domino reaction

ABSTRACT

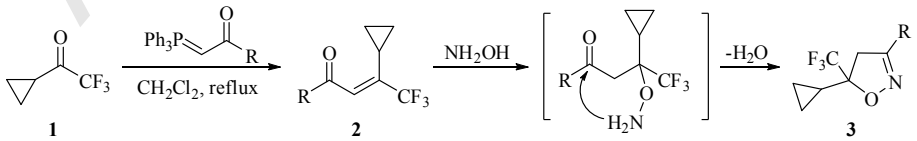
Trifluoromethyl and cyclopropyl substituted 2-isoxazolines were synthesized *via* a DBU-promoted domino reaction of *β*-trifluoromethyl-/*β*-cyclopropyl-substituted enones with hydroxylamine. The domino reaction consists of a Michael addition and the followed cyclization. A wide range of 3-substituted 5-cyclopropyl-5-trifluoromethyl-2-isoxazolines were obtained in good to excellent yields under mild reaction conditions. The method could also apply to other trifluoromethyl-substituted enones.

1. Introduction

2-Isoxazolines are important heterocycle structures in agricultural and medicinal chemistry [1]. Their derivatives exhibit multiple bioactivities such as anti-inflammation, anti-thrombus, and antibacterial activity [2]. Therefore, the synthesis of 2-isoxazolines has attracted more attentions [3-5]. Construction of these compounds generally involves 1, 3-dipolar cycloaddition of nitrile oxides with alkenes or intramolecular cyclization of oxime derivatives [4,5]. Recently, 5-trifluoromethyl-2-isoxazolines were emerged as a class of antiparasitic compounds and drew certain interests [6]. For preparation of these fluorinated 2-isoxazolines, a more efficient method was developed through the domino reaction of Michael addition/cyclization of trifluoromethyl-substituted enone and hydroxylamine [7].

As is well-known, organofluorine chemicals are vital to pharmaceutical, agrochemical and material sciences. The employment of fluorine or fluorine-containing substituents especially the trifluoromethyl group into organic molecules, might lead to the enhancement of their bioactivities [8, 9]. On the other hand, cyclopropanes are also crucial synthons in organic synthesis and significant structural units in many natural products [10]. We are recently focusing on exploring the applications of cyclopropyl trifluoromethyl ketone (**1**) in constructing complex compounds. As a novel fluorinated building blocks, **1** combines trifluoromethyl group with cyclopropyl unit. Both important functional groups would be installed into various molecules through the transformation of the synthon **1**.

We have already investigated bisindolylation reaction of **1** catalyzed by trifluoromethanesulfonic acid [11]. As the continuing study, we prepared trifluoromethyl-/cyclopropyl-substituted enone **2** from **1**, and explored the domino reaction of Michael addition/cyclization of **2** with hydroxylamine (Scheme 1). It provides an efficient method for the syntheses of 5-cyclopropyl-5-trifluoromethyl-2-isoxazoline derivatives **3** with broad substrate generality. Herein, we report the results.



Scheme 1. General route for the syntheses of 5-cyclopropyl-5-trifluoromethyl-2-isoxazolines.

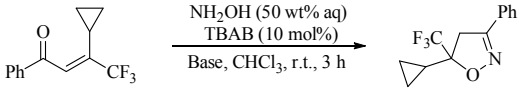
2. Results and discussion

* Corresponding authors.
E-mail addresses: haiyanma@ecust.edu.cn; xingch@sioc.ac.cn

The initial study began with the examination of the reaction of trifluoromethyl and cyclopropyl substituted enone **2a** with hydroxylamine. No reaction took place in the absence of base at room temperature. Carbonates were tested at first and could not trigger the reaction (Table 1, entries 1~3). Neither could other weaker inorganic bases (Table 1, entries 9, 10). With the aid of TBAB (tetrabutylammonium bromide), NaOH, KOH and CsOH may promote **2a** to react with hydroxylamine, and afford the desired 2-isoxazoline product **3a** in 27%, 51% and 87% yields, respectively, after being stirred at room temperature for 3 h (Table 1, entries 5~7). A few organic bases were examined as well. The reaction did not happen with Et_3N as base (Table 1, entry 12). Low yield was detected in the existence of TMG (tetramethylguanidine) (Table 1, entry 11). To our pleased, DBU displayed excellent activation ability, and 99% yield of 2-isoxazoline was obtained (Table 1, entry 13).

Table 1

Screening of bases for the reaction of **2a** with NH_2OH [a]



2a **3a**

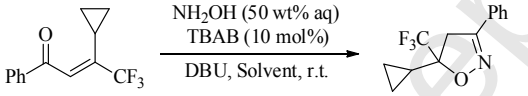
Entry	Base	Yield (%)[b]
1	Na_2CO_3	n.r.
2	K_2CO_3	n.r.
3	Cs_2CO_3	n.r.
4	LiOH	n.r.
5	NaOH	27
6	KOH	51
7	CsOH	87
8	K_3PO_4	5
9	LiOAc	n.r.
10	NaOAc	n.r.
11	TMG	11
12	Et_3N	n.r.
13	DBU	99

[a] Reaction conditions: **2a** (0.1 mmol), NH_2OH (50 wt% aq., 0.3 mmol), TBAB (0.01 mmol, 10 mol%), and base (0.3 mmol) in $CHCl_3$ (1 mL), stirred at room temperature in a Schlenk tube for 3 h.
[b] Yields were determined by ^{19}F NMR using 1-fluoronaphehalene as an internal standard.

Then, a brief screening of solvents was performed with DBU as base. The results listed in Table 2 showed that the reaction proceeded smoothly in all kinds of solvents. 1, 2-Dichloroethane was chosen as the optimal solvent since the highest yield was obtained in it (Table 2, entry 2). Actually, phase transfer catalyst TBAB had few effects on this DBU-promoted reaction. The reaction still worked well and gave the comparable yield without it (Table 2, entry 3).

Table 2

Screening of solvents for the reaction of **2a** with NH_2OH [a]



2a **3a**

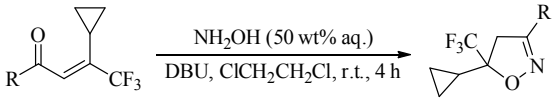
Entry	Solvent	Time (h)	Yield (%)[b]
1	CH_2Cl_2	2	81
2	$ClCH_2CH_2Cl$	2	88
3[c]	$ClCH_2CH_2Cl$	2	84
4	$CHCl_3$	2	40
5	CH_3CN	4	78
6	THF	4	47
7	1,4-Dioxane	4	31
8	MeOH	4	72
9	EtOH	4	77
10	DMSO	4	49
11	DMF	4	66
12	Toluene	4	65

[a] Reaction conditions: **2a** (0.1 mmol), NH_2OH (50 wt% aq., 0.15 mmol), TBAB (0.01 mmol, 10 mol%), and base (0.2 mmol) in solvent (1 mL), stirred at room temperature in a Schlenk tube.
[b] Yields were determined by ^{19}F NMR using 1-fluoronaphehalene as an internal standard.
[c] The reaction was performed without TBAB.

With the optimal conditions established, the scope of substrates enones **2** was then explored. As listed in Table 3, a wide range of substituents including electron-donating and electron-withdrawing groups on the aromatic ring of trifluoromethyl substituted enones **2** are tolerated, and good to excellent yields of the corresponding tirfluoromethyl and cyclopropyl substituted 2-

isoxazoline **3** were obtained (Table 3, **3a-3l**). In addition, tirfluoromethyl-substituted heteroaryl enones **2m** was applied to this reaction, nearly quantitative yield of 3-(thiophen-2-yl)-5-(trifluoromethyl)-4,5-dihydroisoxazole was isolated (Table 3, **3m**). Besides, alkyl-substituted enones also reacted with hydroxylamine smoothly and afforded the corresponding products in satisfied yields (Table 3, **3n** & **3o**).

Table 3
Scope of *β*-cyclopropyl-/*β*-trifluoromethyl-substituted enones **2** for the domino reaction with NH_2OH. [a,]

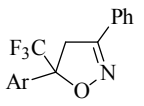


2 **3**

Entry	**2**	R	Product	Yield (%)[b]
1	**2a**	C_6H_5	**3a**	82
2	**2b**	4-$MeOC_6H_5$	**3b**	95
3	**2c**	2-MeC_6H_5	**3c**	88
4	**2d**	3-MeC_6H_5	**3d**	88
5	**2e**	4-MeC_6H_5	**3e**	95
6	**2f**	4-FC_6H_5	**3f**	94
7	**2g**	4-ClC_6H_5	**3g**	95
8	**2h**	4-BrC_6H_5	**3h**	87
9	**2i**	4-$CF_3C_6H_5$	**3i**	89
10	**2j**	4-CNC_6H_5	**3j**	82
11	**2k**	4-$NO_2C_6H_5$	**3k**	80
12	**2l**	2-Naphthyl	**3l**	80
13	**2m**	Thiophen-2-yl	**3m**	94
14	**2n**	*n*-Butyl	**3n**	85
15	**2o**	$C_6H_5CH_2CH_2$	**3o**	80

[a] Reaction conditions: **2** (1.0 mmol), NH_2OH (50 wt% aq., 1.5 mmol), and DBU (2.0 mmol) in $ClCH_2CH_2Cl$ (10 mL), stirred at room temperature in a Schlenk tube for 4 h.
[b] Isolated yield.

Furthermore, under the same conditions, the method was applied to other enones derived from aryl or heteroaryl trifluoromethyl ketones and the corresponding products were isolated in moderate to excellent yields (Fig. 1, **3p-3v**).



3

	Ar	Yield (%)
3p	C_6H_5	95
3q	4-$MeOC_6H_5$	94
3r	4-FC_6H_5	92
3s	4-ClC_6H_5	87
3t	4-BrC_6H_5	88
3u	Thiophen-2-yl	96
3v	Pyridin-2-yl	50

Fig. 1. The products and yields of reactions between enones derivatives under the same conditions.

3. Conclusion

In summary, we have demonstrated a DBU-mediated Michael addition/cyclization domino reaction of trifluoromethyl and cyclopropyl substituted enones with hydroxylamine. The mild conditions and convenient manipulation made this protocol a practical method to synthesis various 5-cyclopropyl-5-trifluoromethyl-2-isoxazoline derivatives efficiently. This method may also apply to other enones derived from aryl or heteroaryl trifluoromethyl ketones.

4. Experimental

^1H NMR and ^{19}F NMR spectra were obtained with an Agilent AM-400 instrument with TMS as the internal standard and $CFCl_3$ as the external standard, respectively. ^{13}C NMR spectra were recorded on an Agilent AM-400 or AM-500 instrument with TMS as the internal standard. Chemical shifts (δ) are reported in ppm, and coupling constants (J) are in Hertz (Hz). FT-IR spectra were obtained with a Nicolet AV-360 spectrophotometer. Mass spectra were obtained on an Agilent 5973 Network or a Waters Micromass GCT Premier instrument. All melting points were determined on a Büchi B-545 melting point apparatus and are uncorrected. All commercially available reagents were purchased from commercial sources and used directly. All reactions were monitored by TLC, ^{19}F NMR or ^1H NMR. Flash column chromatograph was carried out using 300-400 mesh silica gel at medium pressure.

General procedure for the syntheses of cyclopropyl-/trifluoromethyl-substituted 2-isoxazolines: Enone **2** (1.0 mmol, 1.0 equiv.), NH_2OH (50 wt% aq., 1.5 mmol, 1.5 equiv.), DBU (2.0 mmol, 2.0 equiv.) and DCE (10 mL) were added to a Schlenk tube

equipped with a stir bar. The reaction mixture was stirred at room temperature for appropriate time. The completion of the reaction was monitored by ^{19}F NMR. When the reaction was completed, DCE was evaporated and the residue was purified by column chromatography on silica gel to afford 2-isoxazoline **3** as the desired product.

Spectral data of representative products were listed below. Others and general method for the preparation of enones **2** are provided in Supporting information .

5-Cyclopropyl-3-phenyl-5-(trifluoromethyl)-4,5-dihydroisoxazole (**3a**): White solid. Mp: 72-73 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67-7.60 (m, 2H), 7.48-7.38 (m, 3H), 3.67 (d, 1H, J = 17.2 Hz), 3.35 (d, 1H, J = 17.3 Hz), 1.36-1.29 (m, 1H), 0.88-0.81 (m, 1H), 0.68-0.60 (m, 1H), 0.59-0.51 (m, 1H), 0.47-0.41 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -80.61 (s, 3F). ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.32, 130.70, 128.84, 128.33, 126.77, 125.04 (q, J = 284.3 Hz), 85.81 (q, J = 29.1 Hz), 41.86, 13.27 (d, J = 0.9 Hz), 1.74, -0.48. IR (KBr, cm^{-1}): 3095, 3017, 2961, 2942, 1604, 1572, 1497, 1447, 1438, 1366, 1328, 1221, 1189, 1163, 1154, 1140, 1032, 983, 920, 779. MS (EI): *m/z* (%) 255 (M^+, 54.50), 69 (100), 77, 186, 41, 119, 51, 91. HRMS (EI): Mass calculated for $C_{13}H_{12}NOF_3$: 255.0871; Found: 255.0867.

5-Cyclopropyl-3-(4-methoxyphenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (**3b**): White solid. Mp: 73-75 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, 2H, J = 8.7 Hz), 6.93 (d, 2H, J = 8.8 Hz), 3.85 (s, 3H), 3.64 (d, 1H, J = 17.2 Hz), 3.32 (d, 1H, J = 17.4 Hz), 1.39-1.26 (m, 1H), 0.90-0.79 (m, 1H), 0.69-0.59 (m, 1H), 0.59-0.50 (m, 1H), 0.49-0.38 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -80.59 (s, 3F). ^{13}C NMR (101 MHz, $CDCl_3$): δ 161.45, 155.81, 128.32, 125.06 (q, J = 284.2 Hz), 120.75, 114.20, 85.42 (q, J = 29.1 Hz), 55.38, 42.10, 13.24 (d, J = 1.1 Hz), 1.74, -0.50. IR (KBr, cm^{-1}): 3097, 3017, 2962, 2937, 2909, 2840, 1610, 1520, 1438, 1421, 1365, 1327, 1256, 1186, 1162, 1141, 1127, 1034, 985, 919, 832. MS (EI): *m/z* (%) 285 (M^+, 82.08), 69 (100), 149, 147, 135, 133, 77, 41. HRMS (EI): Mass calculated for $C_{14}H_{14}NO_2F_3$: 285.0977; Found: 285.0975.

5-Cyclopropyl-3-(*o*-tolyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (**3c**): White solid. Mp: 51-52 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.22 (m, 4H), 3.71 (d, 1H, J = 17.3 Hz), 3.42 (d, 1H, J = 17.3 Hz), 2.54 (s, 3H), 1.38-1.29 (m, 1H), 0.91-0.83 (m, 1H), 0.69-0.62 (m, 1H), 0.60-0.53 (m, 1H), 0.50-0.43 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -80.57 (s, 3F). ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.22, 138.20, 131.71, 129.90, 128.78, 127.33, 125.88, 125.08 (q, J = 284.4 Hz), 84.56 (q, J = 29.1 Hz), 44.39, 22.89, 13.21, 1.80, -0.49. IR (KBr, cm^{-1}): 3102, 3075, 3023, 2971, 2936, 1603, 1593, 1560, 1495, 1460, 1441, 1386, 1348, 1326, 1287, 1189, 1166, 1125, 1038, 899, 866, 828, 759. MS (EI): *m/z* (%) 269 (M^+, 32.85), 200 (100), 69, 130, 91, 65, 41, 132. HRMS (EI): Mass calculated for $C_{14}H_{14}NOF_3$: 269.1027; Found: 269.1032.

5-Cyclopropyl-3-(4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (**3f**): Yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73-7.52 (m, 2H), 7.11 (t, 2H, J = 8.7 Hz), 3.64 (d, 1H, J = 17.3 Hz), 3.34 (d, 1H, J = 17.3 Hz), 1.37-1.29 (m, 1H), 0.88-0.80 (m, 1H), 0.68-0.61 (m, 1H), 0.59-0.52 (m, 1H), 0.47-0.40 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -80.66 (s, 3F), -108.73--108.83 (m, 1F). ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.02 (d, J = 251.8 Hz), 155.39 (d, J = 0.8 Hz), 128.76 (d, J = 8.6 Hz), 124.95 (q, J = 284.3 Hz), 124.51 (d, J = 3.4 Hz), 115.99 (d, J = 22.1 Hz), 85.90 (q, J = 29.2 Hz), 41.85 (d, J = 0.6 Hz), 13.17 (d, J = 1.3 Hz), 1.72, -0.52. IR (KBr, cm^{-1}): 3095, 3020, 1604, 1516, 1437, 1414, 1362, 1325, 1204, 1237, 1204, 1165, 1127, 1040, 917, 836. MS (EI): *m/z* (%) 273 (M^+, 0.83), 69 (100), 41, 300, 231, 76, 67, 89, 162. HRMS (EI): Mass calculated for $C_{13}H_{11}NOF_4$: 273.0777; Found: 273.0781.

5-Cyclopropyl-3-(thiophen-2-yl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (**3m**): White solid. Mp: 62-64 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (dd, 1H, J = 5.1, 1.1 Hz), 7.22 (dd, 1H, J = 3.6, 1.0 Hz), 7.08 (dd, 1H, J = 5.1, 3.7 Hz), 3.67 (d, 1H, J = 17.1 Hz), 3.36 (d, 1H, J = 17.1 Hz), 1.36-1.28 (m, 1H), 0.89-0.79 (m, 1H), 0.70-0.60 (m, 1H), 0.60-0.51 (m, 1H), 0.49-0.40 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -80.55 (s, 3F). ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.04, 130.50, 129.03, 129.01, 127.40, 124.90 (q, J = 284.2 Hz), 85.98 (q, J = 29.3 Hz), 42.57, 13.20, 1.78 (s), -0.44. IR (KBr, cm^{-1}): 3108, 3027, 2922, 2852, 1598, 1438, 1366, 1325, 1161, 1179, 1145, 1120, 1039, 897, 727. MS (EI): *m/z* (%) 261 (M^+, 56.77), 69 (100), 125, 123, 109, 70, 192, 97. HRMS (EI): Mass calculated for $C_{11}H_{10}NOF_3S$: 261.0435; Found: 261.0439.

3-Butyl-5-cyclopropyl-5-(trifluoromethyl)-4,5-dihydroisoxazole (**3n**): Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.22 (d, 1H, J = 17.6 Hz), 2.91 (dd, 1H, J = 17.6, 0.7 Hz), 2.32 (t, 2H, J = 7.6 Hz), 1.58-1.47 (m, 2H), 1.42-1.29 (m, 2H), 1.26-1.14 (m, 1H), 0.93 (t, 3H, J = 7.3 Hz), 0.81-0.71 (m, 1H), 0.62-0.54 (m, 1H), 0.54-0.45 (m, 1H), 0.40-0.33 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -80.83 (s, 3F). ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.83, 125.12 (q, J = 284.3 Hz), 84.37 (q, J = 29.1 Hz), 43.88, 28.29, 26.86, 22.12, 13.63, 13.12, 1.66, -0.68. IR (KBr, cm^{-1}): 3095, 3019, 2961, 2935, 2875, 1635, 1469, 1435, 1327, 1163, 1124, 1035, 1009. MS (EI): *m/z* (%) 235 (M^+, 1.06), 193 (100), 69, 57, 166, 67, 98, 110, 206. HRMS (EI): Mass calculated for $C_{11}H_{16}NOF_3S$: 235.1184; Found: 235.1191.

3-Phenyl-5-(pyridin-2-yl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (**3v**): White solid. Mp: 97-99 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65 (dd, 1H, J = 4.8, 0.6 Hz), 7.88 (d, 1H, J = 7.9 Hz), 7.81 (td, 1H, J = 7.8, 1.7 Hz), 7.74-7.66 (m, 2H), 7.49-7.39 (m, 3H), 7.35 (ddd, 1H, J = 7.4, 4.8, 1.1 Hz), 4.47 (d, 1H, J = 17.8 Hz), 4.00 (d, J = 17.8 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -78.78 (s, 3F). ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.77, 154.11, 148.95, 137.02, 130.82, 128.84, 128.09, 126.96, 124.32, 124.01 (q, J = 284.4 Hz), 122.96, 88.82 (q, J = 29.7 Hz), 41.87. IR (KBr, cm^{-1}): 3070, 2978, 1589, 1574, 1473, 1438, 1361, 1308, 1289, 1170, 1091, 1005, 986, 889, 759. MS (EI): *m/z* (%) 292 (M^+, 7.03), 223 (100), 261, 262, 78, 106, 193, 79, 51. HRMS (EI): Mass calculated for $C_{15}H_{11}N_2OF_3$: 292.0823; Found: 292.0818.

Acknowledgment

Supports from the National Natural Science Foundation of China (Nos. 21272257, 21274041 and 21474028) are gratefully acknowledged.

References

[1] A. Padwa, W.H. Pearson, Synthetic Applications Of 1, 3-Dipolar Cycloaddition Chemistry Toward Heterocycles And Natural Products, Wiley, New York, 2002.

[2] (a) Y. Al-Abed, D. Dabideen, B. Aljabari, et al., ISO-1 binding to the tautomerase active site of MIF inhibits its pro-inflammatory activity and increases survival in severe sepsis, J. Biol. Chem. 280 (2005) 36541-36544;
(b) M.C. Pirrung, L.N. Tumey, C.R.H. Raetz, et al., Inhibition of the antibacterial target UDP-(3-*O*-acyl)-*N*-acetylglucosamine deacetylase (LpxC): Isoxazoline Zinc amidase inhibitors bearing diverse metal binding groups, J. Med. Chem. 45 (2002) 4359-4370;
(c) J.B. Lubetsky, A. Dios, J. Han, et al., The tautomerase active site of macrophage migration inhibitory factor is a potential target for discovery of novel anti-inflammatory agents, J. Biol. Chem. 277 (2002) 24976-24982;
(d) M.L. Quan, C.D. Ellis, A.Y. Liauw, et al., Design and synthesis of isoxazoline derivatives as factor Xa inhibitors. 2, J. Med. Chem. 42 (1999) 2760-2773.

[3] H. Kawai, Y. Sugita, E. Tokunaga, et al., Diastereoselective additive trifluoromethylation/halogenation of isoxazole triflones: Synthesis of all-carbon-functionalized trifluoromethyl isoxazoline triflones, ChemistryOpen 3 (2014) 14-18.

[4] (a) M. Gucma, W.M. Gołębiewski, 1,3-Dipolar cycloaddition reaction of nitrile oxides revisited-Unusual side products characterized by 2D NMR, J. Heterocyclic Chem. 51 (2014) 572-578;
(b) H. Suga, Y. Adachi, K. Fujimoto, et al., Asymmetric 1,3-dipolar cycloaddition reactions of nitrile oxides catalyzed by chiral binaphthyldiimine-Ni(II) complexes, J. Org. Chem. 74 (2009) 1099-1113;
(c) Y. Brinkmann, R.J. Madhushaw, R. Jazzar, G. Bernardinellib, E. P. Kündig, Chiral ruthenium Lewis acid-catalyzed nitrile oxide cycloadditions, Tetrahedron 63 (2007) 8413-8419;
(d) A. Ros, E. Alvarez, H. Dietrich, R. Fernández, J.M. Lassaletta, A practical synthesis of enantiopure 4,5-dihydroisoxazole-5-carboxylic acids, Synlett (2005) 2899-2904;
(e) M.P. Sibi, K. Itoh, C.P. Jasperse, Chiral Lewis acid catalysis in nitrile oxide cycloadditions, J. Am. Chem. Soc. 126 (2004) 5366-5367;
(f) C.D. Davies, S.P. Marsden, E.S.E. Stokes, Enhanced asymmetric induction in cycloadditions to bridgehead-chiral vinyl dioxazaborocines, Tetrahedron Lett. 41 (2000) 4229-4233.

[5] (a) Q. Wei, J.R. Chen, X.Q. Hu, et al., Photocatalytic radical trifluoromethylation/cyclization cascade: synthesis of CF_3-containing pyrazolines and isoxazolines, Org. Lett. 17 (2015) 4464-4467;
(b) H. Kawai, S. Okusu, E. Tokunaga, N. Shibata, Enantioselective synthesis of 5-trifluoromethyl-2-isoxazolines and their *N*-oxides by [Hydroxy(tosyloxy)iodo]benzene-mediated oxidative N-O coupling, Eur. J. Org. Chem. (2013) 6506-6509;
(c) Y.T. He, L.H. Li, Y.F. Yang, et al., Copper-catalyzed synthesis of trifluoromethyl-substituted isoxazolines, Chem. Commun. 49 (2013) 5687-5689;
(d) R. Aggarwal, A. Bansal, A. Mittal, Synthesis and antimicrobial activity of 3-(2-thienyl)-4-arylazo-5-hydroxy-5-trifluoromethyl-D2-isoxazolines and 3-(2-thienyl)-4-arylazo-5-trifluoromethylisoxazoles, J. Fluorine Chem. 145 (2013) 95-101;
(e) A.L. Norman, M.D. Mosher, Enantioselectivity in the synthesis of 3,5-disubstituted Δ^2-isoxazolines, Tetrahedron Lett. 49 (2008) 4153-4155;
(f) V. Kumar, R. Aggarwal, S.P. Singh, The reaction of hydroxylamine with aryl trifluoromethyl-b-diketones: Synthesis of 5-hydroxy-5-trifluoromethyl-Δ^2-isoxazolines and their dehydration to 5-trifluoromethylisoxazoles, J. Fluorine Chem. 127 (2006) 880-888;
(g) M. Zielinska-Błajet, R. Kowalczyk, J. Skarżewski, Ring-closure reactions through intramolecular substitution of thiophenoxide by oxygen and nitrogen nucleophiles: simple stereospecific synthesis of 4,5-dihydroisoxazoles and 4,5-dihydropyrazoles, Tetrahedron 61 (2005) 5235-5240;
(h) J. Diab, A. Laurent, I.L. Dréan, Synthesis of isomeric trifluoromethyl pyrazoles and isoxazoles, J. Fluorine Chem. 84 (1997) 145-147.

[6] Y. Ozoe, M. Asahi, F. Ozoe, K. Nakahira, T. Mita, The antiparasitic isoxazoline A1443 is a potent blocker of insect ligand-gated chloride channels, Biochem. Biophys. Res. Commun. 391 (2010) 744-749.

[7] (a) H. Kawai, N. Shibata, Asymmetric synthesis of agrochemically attractive trifluoromethylated dihydroazoles and related compounds under organocatalysis, Chem. Rec. 14 (2014) 1024-1040;
(b) K. Matoba, H. Kawai, T. Furukawa, et al., Enantioselective synthesis of trifluoromethyl-substituted 2-isoxazolines: Asymmetric hydroxylamine/enone cascade reaction, Angew. Chem. Int. Ed. 49 (2010) 5762-5766;
(c) A. Pohjakallio, P.M. Pihko, Enantioselective synthesis of 2-isoxazolines by a one-flask conjugate addition/oxime-transfer process, Chem. Eur. J. 15 (2009) 3960-3964.

[8] (a) P. Kirsch, Modern fluoroorganic chemistry: Synthesis, reactivity, applications, Second Edition; Wiley-VCH GmbH & Co: KGaA 2013;
(b) K. Uneyama, Organofluorine chemistry, Wiley-Blackwell: Oxford 2006;
(c) R. Filler, Y. Kobayashi, L.M. Yagupolskii, Organofluorine compounds in medicinal chemistry and biomedical applications, Elsevier, Amsterdam, 1993.

[9] (a) V.M. Muzalevskiy, A.V. Shastin, E.S. Balenkova, G. Haufe, V.G. Nenajdenko, Synthesis of trifluoromethyl pyrroles and their benzo analogues, Synthesis (2009) 3905-3929;

(b) A.W. Erian, Recent trends in the chemistry of fluorinated five and six-membered heterocycles, J. Heterocyclic Chem. 38 (2001) 793-808;
(c) J.T. Welch, Advances in the preparation of biologically active organofluorine compounds, Tetrahedron 43 (1987) 3123-3197.
[10] (a) A. Reichelt, S.F. Martin, Synthesis and properties of cyclopropane-derived peptidomimetics, Acc. Chem. Res. 39 (2006) 433-442;
(b) H. Lebel, J.F. Marcoux, C. Molinaro, A.B. Charette, Stereoselective cyclopropanation reactions, Chem. Rev. 103 (2003) 977-1050;
(c) W.A. Donaldson, Synthesis of cyclopropane containing natural products, Tetrahedron 57 (2001) 8589-8627.
[11] Y. Wang, Y. Yuan, C.H. Xing, L. Lu, Trifluoromethanesulfonic acid-catalyzed solvent-free bisindolylation of trifluoromethyl ketones, Tetrahedron Lett. 55 (2014) 1045-1048.