DOI: 10.1002/cjoc.201300366

Regioselective Synthesis of 2,6-Dimethyl-3,5-bis[(3-aryl-5-trifluoromethyl)-isoxazol-4-carbonyl]-pyridine Derivatives

Yindi Yang,[a] Min Zhang,*,[a] Yiwen Zhu,[a] Li Zhang,[a] Qiqiang Xie,[a]
Liping Song,*,[a,b] and Hongmei Deng[c]

[a] *School of Science, Shanghai University, Shanghai 200444, China*
[b] *Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China*
[c] *Laboratory for Microstructures, Shanghai University, Shanghai 200444, China*

Ethyl 4,4,4-trifluoro-3-oxo-butyrate reacted with 2,6-dimethyl-3,5-diacetyl-pyridine **1** in the presence of $NaOC_2H_5$ at 0 ℃ to give 2,6-dimethyl-3,5-bis(4,4,4-trifluoro-1,3-oxo-butyl)-pyridine (**2a**) in good yield. Cyclization reaction of **2a** and aryl imidoyl chlorides **5a**—**5i**, obtained from chlorination of aryl oximes with *N*-chlorosuccimide, afforded 2,6-dimethyl-3,5-bis[(3-aryl-5-trifluoromethyl)-isoxazol-4-carbonyl]-pyridine derivatives **6a**—**6i**.

Keywords cyclization reaction, trifluoromethyl-1,3-diketones, aryl imidoyl chlorides, regioselective, 3,5-bis(5-trifluoromethyl-isoxazol)-pyridine derivatives

Introduction

Pyridine derivatives are useful pharmaceutical intermediates. For example, some benzoxepin [4,3-*b*] pyridine derivatives have been reported having important pharmacology properties, such as antitumor, analgesic, antimicrobial activities.[1-4] Fluorinated organic compounds, in particular, trifluoromethylated compounds, have received considerable attention due to their unique biological properties,[5-7] and been used as excellent building blocks for the construction of more complex CF_3-containing heterocyclic compounds.[8-12] The isoxazole ring system is an major class of five-membered nitrogen heterocycle and an important core component in natural products, which is particularly interesting since it is readily transformed into various biodynamic agents, including those with antithrombotic, PAF antagonist, and hypolipidemic properties.[13-16]

Therefore, tremendous synthetic approaches for the construction of the 5-trifluoromethyl isoxazole framework have been actively reported, for example, cyclization reaction between trifluoromethyl-1,3-dione with imidoyl chlorides,[17,18] or with hydroxylamine.[19] However, to date, few reports have appeared on the simultaneous construction of bis-5-trifluoromethyl-isoxazole ring systems in one molecule. Herein, we wish to report a new synthesized pyridine derivatives bearing bis-5-trifluoromethyl isoxazole ring system via cycloaddition reaction of trifluoromethyl-1,3-dione with aryl imidoyl chlorides.

Experimental

^{1}H NMR spectra were recorded at 500 MHz with tetramethylsilane as internal reference. ^{13}C NMR spectra were recorded at 125 MHz with deuterated chloroform as internal reference. ^{19}F NMR spectra were recorded at 470 MHz with $CFCl_3$ as internal reference. Deuterated chloroform was the solvent in all cases. Mass spectra were obtained by using Waters Micromass GCT. Elemental analysis data were obtained by using Vario ELIII Analyzer. X-ray crystal structure data were collected by using BRUKER APEX-Ⅱ CCD.

Melting points were determined in open capillary tubes and are uncorrected. Flash chromatography was performed on silica gel (200—300 mesh) with ethyl acetate/petroleum ether as the eluent.

General procedure for the preparation of 2,6-dimethyl-3,5-bis[(5-trifluoromethyl)-isoxazol-4-carbonyl]-pyridines (one-pot, two-step procedure)

N-Chlorosuccimide (1.9 mmol) was added to a solution of **4a**—**4i** (1.8 mmol) in DMF (15 mL). The resultant mixture was stirred at 60 ℃ for 1 h, then cooled to room temperature. The compound **2a** (0.9 mmol) and $KHCO_3$ (2.2 mmol) were added to the above solution at room temperature. The mixture was continuously stirred at r.t. and the reaction was monitored by TLC. Until the completion of the reaction, the mixture was extracted with ethyl acetate and water three times, the oil lay was dried over $MgSO_4$ and evaporated under vacuum. The

* E-mail: mzhang@shu.edu.cn (M. Zhang); lpsong@shu.edu.cn (L. P. Song)
Received April 29, 2013; accepted June 20, 2013; published online July 5, 2013.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cjoc.201300366 or from the author.

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crude residue was purified by flash column chromatography on silica gel to afford the pure product **6a**—**6i**.

2,6-Dimethyl-3,5-bis[3-(4-nitro-phenyl)-5-trifluoromethyl-isoxazol-4-carbonyl]-pyridine (**6a**): Yellow solid, m.p. 194.2—195.6 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.23 (d, J=8.5 Hz, 4H), 7.65 (d, J=8.5 Hz, 4H), 7.64 (s, 1H), 2.81 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 185.4, 164.3, 160.1, 157.6 (q, $^2J_{C\text{-}F}$=43.0 Hz), 149.5, 140.9, 131.8, 129.3, 128.6, 124.5, 119.0, 116.2 (q, $^1J_{C\text{-}F}$=275.0 Hz), 25.4; ^{19}F NMR (470 MHz, $CDCl_3$) δ: –62.3 (s, 6F); IR (KBr) v: 3085, 2861, 1676, 1526, 852, 692 cm^{-1}; MS (EI, 70 eV) m/z (%): 675 (M^+, 14), 658 (23), 606 (100), 235 (22), 76 (23). Anal. calcd for $C_{29}H_{15}F_6N_5O_8$: C 51.57, H 2.24, N 10.37; found C 51.60, H 2.41, N 10.27.

2,6-Dimethyl-3,5-bis[3-(4-cyano-phenyl)-5-trifluoromethyl-isoxazol-4-carbonyl]-pyridine (**6b**): White solid, m.p. 165.7—167.2 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.69 (d, J=8.5 Hz, 4H), 7.58 (d, J=8.5 Hz, 4H), 7.58 (s, 1H), 2.81 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 185.5, 164.2, 160.3, 157.5 (q, $^2J_{C\text{-}F}$=43.0 Hz), 140.8, 133.1, 130.1, 128.9, 128.6, 119.0, 117.5, 117.2 (q, $^1J_{C\text{-}F}$=271.0 Hz), 115.4, 25.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ: –62.3 (s, 6F); IR (KBr) v: 3105, 2988, 2235, 1675, 1168, 879 cm^{-1}; MS (EI, 70 eV) m/z (%): 635 (M^+, 6), 620 (29), 566 (100), 265 (28), 215 (40), 128 (31), 102 (30). Anal. calcd for $C_{31}H_{15}F_6N_5O_4$: C 58.59, H 2.38, N 11.02; found C 58.42, H 2.69, N 10.72.

2,6-Dimethyl-3,5-bis[3-(4-bromo-phenyl)-5-trifluoromethyl-isoxazol-4-carbonyl]-pyridine (**6c**): Yellow solid, m.p. 183.7—185.2 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.47 (s, 1H), 7.46 (d, J=8.5 Hz, 4H), 7.20 (d, J=8.5 Hz, 4H), 2.83 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 185.8, 164.4, 160.5, 157.2 (q, $^2J_{C\text{-}F}$=43.0 Hz), 141.6, 132.9, 129.3, 128.1, 126.4, 124.7, 118.8, 117.3 (q, $^1J_{C\text{-}F}$=270.0 Hz), 25.4; ^{19}F NMR (470 MHz, $CDCl_3$) δ: –62.7 (s, 6F); IR (KBr) v: 3053, 1682, 1313, 1165, 880 cm^{-1}; MS (EI, 70 eV) m/z (%): 743 (M^+, 19), 674 (100), 320 (38), 275 (61), 155 (43), 102 (37), 75 (30). Anal. calcd for $C_{29}H_{15}Br_2F_6N_3O_4$: C 46.86, H 2.03, N 5.65; found C 46.87, H 2.03, N 5.57.

2,6-Dimethyl-3,5-bis[3-(4-chloro-phenyl)-5-trifluoromethyl-isoxazol-4-carbonyl]-pyridine (**6d**): Yellow solid, m.p. 179.9—181.5 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.47 (s, 1H), 7.29 (d, J=8.5 Hz, 4H), 7.27 (d, J=8.5 Hz, 4H), 2.83 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 185.8, 164.3, 160.4, 157.2 (q, $^2J_{C\text{-}F}$=43.0 Hz), 141.6, 136.0, 129.8, 129.2, 128.1, 124.2, 118.9, 117.3 (q, $^1J_{C\text{-}F}$=271.0 Hz), 25.4; ^{19}F NMR (470 MHz, $CDCl_3$) δ: –62.7 (s, 6F); IR (KBr) v: 3055, 1681, 1313, 1165, 881 cm^{-1}; MS (EI, 70 eV) m/z (%): 653 (M^+, 16), 584 (100), 274 (38), 224 (41), 111 (39), 75 (19). Anal. calcd for $C_{29}H_{15}Cl_2F_6N_3O_4$: C 53.23, H 2.31, N 6.42; found C 53.27, H 2.41, N 6.46.

2,6-Dimethyl-3,5-bis[3-(4-fluoro-phenyl)-5-trifluoromethyl-isoxazol-4-carbonyl]-pyridine (**6e**): Yellow solid, m.p. 160—161 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.46 (s, 1H), 7.37—7.34 (m, 4H), 7.04—7.00 (m, 4H), 2.83 (s, 6H); ^{13}C NMR (125 HMz, $CDCl_3$) δ: 185.9, 165.5, 164.2, 163.5, 160.4, 157.2 (q, $^2J_{C\text{-}F}$=43.0 Hz), 141.6, 130.2, 130.1, 128.2, 122.0, 121.9, 118.9, 117.3 (q, $^1J_{C\text{-}F}$=271.0 Hz), 116.9, 116.8, 25.4; ^{19}F NMR (470 MHz, $CDCl_3$) δ: –62.7 (s, 6F), –107.2 (m, 2F); IR (KBr) v: 3054, 2998, 1689, 1321, 1211, 1156, 885 cm^{-1}; MS (EI, 70 eV) m/z (%): 621 (M^+, 20), 552 (100), 293 (23), 258 (44), 161 (23), 95 (34). Anal. calcd for $C_{29}H_{15}F_8N_3O_4$: C 56.05, H 2.43, N 6.76; found C 56.04, H 2.44, N 6.73.

2,6-Dimethyl-3,5-bis[3-(4-methyl-phenyl)-5-trifluoromethyl-isoxazol-4-carbonyl]-pyridine (**6f**): Yellow solid, m.p. 195—197 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.38 (s, 1H), 7.16 (d, J=8 Hz, 4H), 7.07 (d, J=8 Hz, 4H), 2.82 (s, 6H), 2.28 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 186.1, 164.0, 161.0, 157.1 (q, $^2J_{C\text{-}F}$=43.0 Hz), 142.0, 141.9, 130.1, 127.7, 122.8, 119.1, 117.4 (q, $^1J_{C\text{-}F}$=271.0), 25.3, 21.4; ^{19}F NMR (470 MHz, $CDCl_3$) δ: –62.8 (s, 6F); IR (KBr) v: 3031, 3006, 2968, 2925, 1676, 1320, 1204, 1140, 881, 748 cm^{-1}; MS (EI, 70 eV) m/z (%): 613 (M^+, 78), 544 (80), 254 (48), 204 (48), 91 (100). Anal. calcd for $C_{31}H_{21}F_6N_3O_4$: C 60.69, H 3.45, N 6.85; found C 60.83, H 3.67, N 6.71.

2,6-Dimethyl-3,5-bis[3-(4-methoxy-phenyl)-5-trifluoromethyl-isoxazol-4-carbonyl]-pyridine (**6g**): White solid, m.p. 155.8—157.5 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.45 (s, 1H), 7.23 (d, J=8.5 Hz, 4H), 6.78 (d, J=8.5 Hz, 4H), 3.75 (s, 6H), 2.84 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 186.3, 164.1, 161.9, 160.7, 156.9 (q, $^2J_{C\text{-}F}$=43.0 Hz), 142.2, 129.4, 127.9, 118.9, 117.8, 117.4 (q, $^1J_{C\text{-}F}$=271.0 Hz), 114.9, 55.4, 25.4; ^{19}F NMR (470 MHz, $CDCl_3$) δ: –62.8 (s, 6F); IR (KBr) v: 3013, 2941, 1678, 1263, 1176, 883, 840 cm^{-1}; MS (EI, 70 eV) m/z (%): 645 (M^+, 100), 305 (26), 270 (33), 133 (28), 77 (27). Anal. calcd for $C_{31}H_{21}F_6N_3O_6$: C 57.68, H 3.28, N 6.51; found C 57.59, H 3.56, N 6.52.

2,6-Dimethyl-3,5-bis[3-(5-bromo-pyridin-2-yl)-5-trifluoromethyl-isoxazol-4-carbonyl]-pyridine (**6h**): Yellow solid, m.p. 155—156 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.21—8.20 (m, 2H), 7.91—7.86 (m, 4H), 7.54 (s, 1H), 2.95 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 185.1, 163.1, 160.2, 156.3 (q, $^2J_{C\text{-}F}$=43.0 Hz), 150.5, 143.6, 141.2, 140.3, 128.6, 123.2, 123.1, 119.3, 117.4 (q, $^1J_{C\text{-}F}$=270.0 Hz), 24.9; ^{19}F NMR (470 MHz, $CDCl_3$) δ: –63.1 (s, 6F); IR (KBr) v: 3082, 1676, 1316, 1157, 843 cm^{-1}; MS (EI, 70 eV) m/z (%): 745 (M^+, 5), 676 (100), 158 (78), 156 (78), 76 (34). Anal. calcd for $C_{27}H_{13}Br_2F_6N_5O_4$: C 43.52, H 1.76, N 9.40; found C 43.54, H 1.83, N 9.38.

2,6-Dimethyl-3,5-bis[3-(6-bromo-pyridin-3-yl)-5-trifluoromethyl-isoxazol-4-carbonyl]-pyridine (**6i**): Yellow solid, m.p. 151.6—153.2 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.43 (d, J=3.0 Hz, 2H), 7.72 (dd, J_1=3.0 Hz, J_2=8.0 Hz, 2H), 7.67 (s, 1H), 7.57 (d, J=8.0 Hz, 2H), 2.80 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 185.3, 164.2, 158.7, 157.6 (q, $^2J_{C\text{-}F}$=43.0), 148.9, 145.5, 140.7, 137.7, 128.9, 128.6, 121.6, 118.7, 117.2 (q, $^1J_{C\text{-}F}$=271.0 Hz), 25.4; ^{19}F NMR (470 MHz, $CDCl_3$) δ: –62.2 (s, 6F); IR (KBr) v: 3084, 3054, 1676, 1311, 1144, 882 cm^{-1};

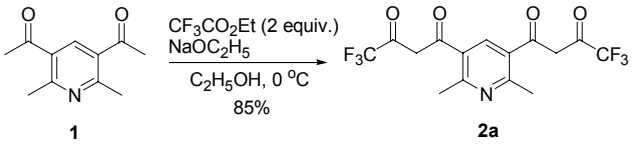
MS (EI, 70 eV) *m/z* (%): 745 (M^+, 7), 730 (100), 676 (43), 608 (51), 319 (34), 271 (50), 158 (60), 103 (84), 76 (61). Anal. calcd for $C_{27}H_{13}Br_2F_6N_5O_4$: C 43.52, H 1.76, N 9.40; found C 43.65, H 1.81, N 9.49.

Results and Discussion

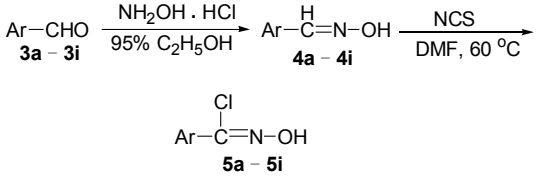
The synthetic route for preparation of 2,6-dimethyl-3,5-bis(4,4,4-trifluoro-1,3-oxo-butyl)-pyridine (**2a**) was illustrated in Scheme 1. 2 equiv. of ethyl 4,4,4-trifluoro-3-oxo-butyrate was added dropwise to a stirring solution of 2,6-dimethyl-3,5-diacetyl-pyridine (**1**) in the presence of $NaOC_2H_5$ in EtOH at 0 ℃. After the completion of the reaction (monitored by TLC), the solvent was then evaporated and the residue was purified by flash column chromatography on silica gel to afford the pure product **2a**.

Aryl imidoyl chlorides **5** were readily synthesized by chlorination of the corresponding aryl oximes, obtained from the acidic catalytic dehydration of aromatic aldehydes **3a**—**3i** and hydroxylamine, with NCS in high yields according to the reported methods (Scheme 2).[20-24]

Scheme 1



Scheme 2



Ar=*p*-$NO_2C_6H_4$, *p*-NCC_6H_4, *p*-BrC_6H_4, *p*-ClC_6H_4, 5-bromo-pyridin-2-yl, 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$, 4-FC_6H_4, 6-bromo-pyridin-3-yl

We initiated our investigation with the cyclization of **2** and **5** in the presence of base (Scheme 3). We firstly attempted the reaction of **5a** and **2a** in DMF in the presence of a little bit excess of Et_3N at ambient temperature. However, the desired product was not detected (Table 1, Entry 1). When the reaction was performed in the presence of NaOH as base (Table 1, Entry 2), only a trace of desired product was detected by TLC analysis. It was found that the reaction in $KHCO_3$ as base gave the desired product **6a** in 30.2% yield (Table 1, Entry 3). We next examined the same reaction in THF or 95% EtOH in the presence of the $KHCO_3$ to afford a little bit lower yields (Table 1, Entries 4, 5). The reaction proceeded smoothly at ambient temperature, whereas the reaction at low temperature decreased the yields (Table 1, Entry 6). However, the reaction at elevated temperature resulted in the complicated products, TLC analysis showed that only a trace of desired product was detected, and a large amounts of unidentified by-products were formed (Table 1, Entry 7).

Table 1 Optimization of reaction conditions for the cycloaddition reaction of **5a** and **2a**

Entry	Base	*T*/℃	Solvent	Yield[a]/%
1	Et_3N	25	DMF	—[b,d]
2	NaOH	25	DMF	trace[d]
3	$KHCO_3$	25	DMF	30.2[c]
4	$KHCO_3$	25	THF	27.5[c]
5	$KHCO_3$	25	95% EtOH	29.3[c]
6	$KHCO_3$	5	DMF	23.0[c]
7	$KHCO_3$	60	DMF	trace[d]

[a] Isolated yield. [b] No product was detected. [c] Reaction conditions: **5a**—**5i** (2 mmol) and **2a** (1 mmol), 6 h. [d] Reaction conditions: **5a**—**5i** (2 mmol) and **2a** (1 mmol), 12 h.

After briefly screening the reaction conditions, we next investigated the possibility of the above-reaction in one-pot, two-step manner. It was found that the cyclization reaction could be performed by one-pot, two-step reaction in DMF without further purification of the reaction intermediates aryl imidoyl chlorides **5**. The desired products **6a**—**6i** could be readily obtained by one-pot procedure from the corresponding compounds **4a**—**4i** without obviously loss of the products yields (Scheme 3).

With the suitable reaction conditions in hand, the scope and limitation of this cyclization reaction was explored to establish the generality of the process using one-pot, two-step reaction. The corresponding pyridine derivatives bearing bis-5-trifluoromethyl isoxazole ring **6a**—**6i** were obtained. The reaction facilitated the various aryl imidoyl chlorides bearing either electron-withdrawing groups such as fluoro, chloro, cyano and nitro (Table 3, Entries 1—4, 8) or electron-donating groups such as alkyl and alkoxyl (Table 3, Entries 6, 7). For other aromatic analogues bearing heteroaryl groups (*ie*: pyridin-2-yl, pyridine-3-yl), we also obtained the corresponding products (Table 3, Entries 5, 9).

It was noteworthy that we have made great efforts to improve the yields of this reaction by screening of various inorganic and tertiary amine bases, solvent, reaction temperatures and by varying of molecular ratio of the starting materials, unfortunately, all attempts were failed. The fairly low yields of products were attributed to the formation of nitrile oxide dimers as major byproducts under the present reaction conditions[25] and a sterically demanding of the desired products. XRD analysis showed that the product **6d** adopted a torsional configuration (Figure 1).

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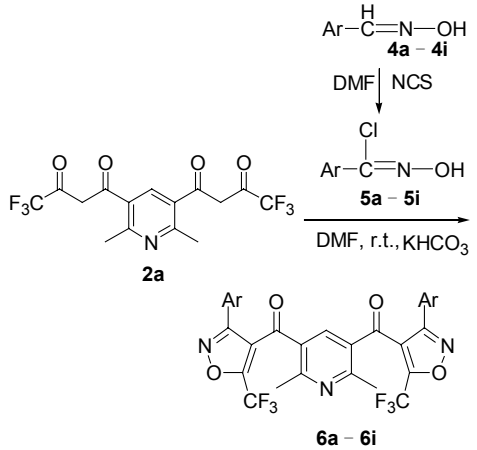
Scheme 3



Ar=*p*-$NO_2C_6H_4$, *p*-NCC_6H_4, *p*-BrC_6H_4, *p*-ClC_6H_4, 5-bromo-pyridin-2-yl, 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$, 4-FC_6H_4, 6-bromo-pyridin-3-yl

Table 2 Synthesis of pyridine derivatives **6a**—**6i**

Entry	Ar	Product	Yield[a]/%
1	*p*-$NO_2C_6H_4$	**6a**	30.2
2	*p*-NCC_6H_4	**6b**	34.5
3	*p*-BrC_6H_4	**6c**	33.3
4	*p*-ClC_6H_4	**6d**	29.5
5	4-FC_6H_4	**6e**	29.2
6	4-$CH_3C_6H_4$	**6f**	31.7
7	4-$CH_3OC_6H_4$	**6g**	20.0
8	5-Bromo-pyridin-2-yl	**6h**	35.5
9	6-Bromo-pyridin-3-yl	**6i**	33.7

[a] Isolated yield.

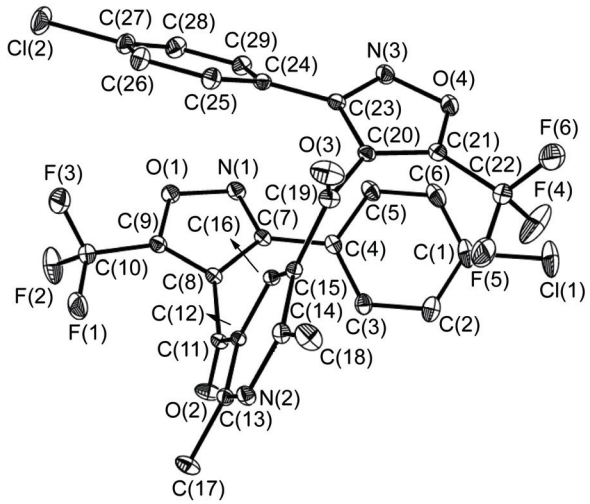


Figure 1 X-ray crystal structure of **6d**.

It should be note that the reaction was the regioselective one, giving the 5-CF_3 isoxazole ring exclusively, the regioisomer (3-CF_3 isoxazole ring) of the products **6** was not obtained. The mechanism for formation of isoxazole ring was in close consistent with the literature reports as the cyclization proceeds through a stepwise reaction mechanism involving nucleophilic addition of **2** to nitrile oxides generated *in situ* form **5**.[26]

Conclusions

In conclusion, we have synthesized a series of new pyridine derivatives **6** bearing bis-5-trifluoromethyl-isoxazole ring systems with high regioselectivity, which are potentially important and widely applicable for the syntheses of pharmaceuticals and agrochemicals. The simultaneous construction of bis-5-trifluoromethyl-isoxazole ring systems in one molecule is a practical way to more complex molecules.

Acknowledgement

The authors thank the National Natural Science Foundation of China (NNSFC) (Nos. 21072128, 21272153), the Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry for financial support.

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(Pan, B.; Qin, X.)

