Journal of Fluorine Chemistry 131 (2010) 426–432

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Synthesis of bromodifluoromethyl substituted pyrazoles and isoxazoles

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ARTICLE INFO

Article history:
Received 3 November 2009
Received in revised form 7 December 2009
Accepted 15 December 2009
Available online 23 December 2009

Keywords:
Bromodifluoromethyl
Pyrazoles
Isoxazoles
Regioselectivity
Synthesis

ABSTRACT

Bromodifluoromethyl substituted β-diketone **3a–3d**, prepared from corresponding ketones and ethyl bromodifluoroactate in the presence of sodium methoxide, reacted with aryl hydrazine derivatives affording bromodifluoromethyl substituted pyrazoles in high regioselectivity. The reaction of **3a–3d** with hydroxylamine hydrochloride gave dihydroisoxazoles, which afforded bromodifluoromethyl substituted isoxazoles through dehydration by PPA or concentrated sulfuric acid.

1. Introduction

There is an increasing interest in the synthesis of fluorinated heterocyclic compounds in view of the potential biological properties of such molecules [1–6]. The change is mainly due to the high electronegativity of fluorine, the strong carbon–fluorine bond, and increased lipid solubility. Fluorinated five-membered heterocycles has been shown to be effective anti-tumor agents, anti-malarials, enzyme inhibitors or precursor to antibiotics [7]. Fluorinated pyrazoles and isoxazoles are of particular interest to the biochemical scientists because they exhibit various bioactivities [2,8–10]. Many examples have been reported on the synthesis of trifluoromethyl substituted pyrazoles and isoxazoles, and such compounds have found their applications in medicine and agriculture [11]. However there are limited examples on the synthesis of halodifluoromethyl substituted heterocyles, especially pyrazoles and isoxazoles [11,12]. Prabhakaran et al. [11] and Talley et al. [13] described the synthesis of bromodifluoromethyl and chlorodifluoromethyl substituted pyrazoles from corresponding β-diketones and hydrazine derivatives respectively, however, both in low yields. Halodifluoromethyl pyrazoles or isoxazoles may have potential biological activities [12,14]. They also would be very useful starting materials to build new difluoromethylated pyrazoles or isoxazoles by the displacement of bromine [15–21]. In this paper, we would like to report the reaction of bromodifluoromethyl substituted β-diketones **3** and aryl hydrazine derivatives **4** or hydroxylamine hydrochloride to give the corresponding bromodifluoromethyl substituted pyrazoles in high regioselectivity or dihydroisoxazoles, which were dehydrated by PPA or concentrated sulfuric acid to give isoxazoles.

2. Results and discussion

4-Bromo-4,4-difluoro-1-arylbutane-1,3-diones (**3**) were obtained from ketones **1** and ethyl bromodifluoroacetate **2** in the presence of sodium methoxide in ethyl ether in 67–85% yields (Scheme 1). The results are listed in Table 1. The results showed that the reaction gave lower conversion of ketone **1** in absolute methanol or anhydrous tetrahedydrofuran (Table 1, entries 2 and 3).

The condensation of 4-bromo-4,4-difluoro-1-phenylbutane-1,3-diones (**3aa**) with phenylhydrazine (**4aa**) was investigated. The reaction proceeded smoothly in anhydrous ethanol to give a mixture of **5aa**, **6aa**, **7aa**, **8aa** (Scheme 2, Table 1, entries 1–4). The ratio of **5aa**/**6aa** was nearly equal to **7aa**/**8aa**. In the presence of different acids as catalyst, the content of **7aa** and **8aa** ranged from 18% to 25%. However, **7aa** and **8aa** decreased below 5% when the reaction was carried out without any acid catalyst. It was found that **7aa** and **8aa** was formed from the further reaction of **5aa** and **6aa** respectively, which could be illustrated by the increasing content of **7aa** and **8aa** with longer reaction time. The results showed that in refluxing ethanol containing concentrated sulfuric acid the reaction afford a better product ratio of **5aa**/**6aa**, which

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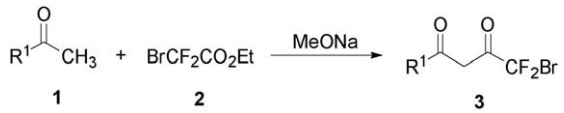
0022-1139/$ – see front matter © 2010 Published by Elsevier B.V.
doi:10.1016/j.jfluchem.2009.12.017



Scheme 1.

Table 1
Data of the preparation of β-diketone **3**.

Entry	R^1	Time (h)	Solvent	Conversion of **1**[a]	Products	Yields[b] (%)
1	Ph	48	Et_2O	83	**3a**	83
2	Ph	48	CH_3OH	29	**3a**	–
3	Ph	48	THF	26	**3a**	–
4	4-MePh	30	Et_2O	60	**3b**	67
5	4-MeOPh	40	Et_2O	70	**3c**	80
6	2-Thienyl	18	Et_2O	87	**3d**	85

[a] Based on GC.
[b] Isolated yield and based on converted aryl ketone **1**.

was similar to the reaction of trifluoromethyl substituted β-diketones with phenylhydrazine [22].

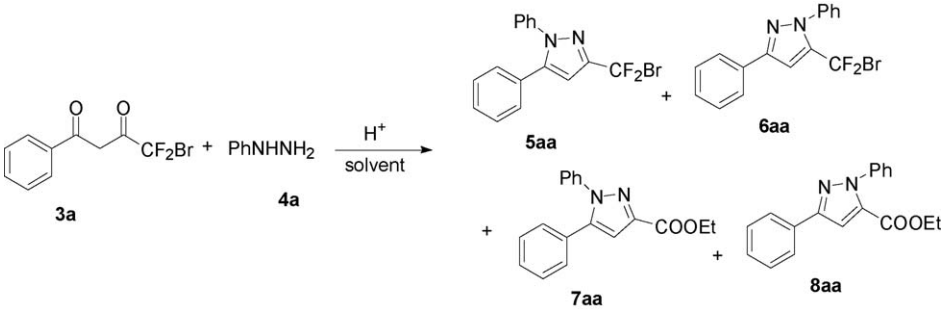
To avoid the formation of **7aa** and **8aa** and to obtain high regioselectivity, the reaction was carried out in aprotic polar solvent DMSO and DMF. As illustrated in Table 2, in DMSO or DMF containing AcOH as catalyst, the reaction of **3aa** and **4aa** proceeded smoothly to afford isomer **5aa** as the main product with a trace of **6aa** (Scheme 2 and Table 2, entries 5 and 6). However, a mixture of **5aa** and **6aa** in a ratio of 88:12 ratios was obtained in DMF in the presence of 35% HCl (Scheme 2 and Table 1, entry 8). When DMF containing concentrated sulfuric acid was used as the solvent, high regioselectivity and higher yield of **5aa** was achieved (Table 1, entry 7).

The reaction of **3** and **4a–d** was carried out using DMF as the solvent in the presence of concentrated sulfuric acid to give isomer **5** as the main product in moderate yields (Scheme 3). The results were summarized in Table 3. The regioselectivity of the reaction varied from 94:6 to >99:1, which was obtained by analysis of ^{19}F NMR of the crude reaction mixture. The product could be purified by column chromatography eluted by a mixture of ethyl acetate and petroleum ether or by recrystallization.

The reaction of **3** and excess hydroxylamine hydrochloride was carried out for 3–6 h in ethanol or DMF to afford dihydroisoxazoles **9** in isolated yields of 70–86% (Scheme 4 and Table 4). The compound **9** was dehydrated in PPA at 150–160 °C or refluxed in butanol containing catalytic concentrated sulfuric acid to give bromodifluoromethyl substituted isoxazoles **10** (Scheme 4).

The structures of **5aa** and its regioisomer **6aa** were deduced from their NMR spectrums. The ^1H NMR signal of the pyrazole 4-H of **5aa** appeared at higher field (δ 6.72 ppm, 1H, s) than that of its regioisomer **6aa** (δ 7.06 ppm, 1H, s). The ^{19}F NMR signal of **5aa** was also at upfield (δ −43.6 ppm for **5aa** and δ −40.3 ppm for **6aa**). The results were in close agreement with the trifluoromethyl substituted pyrazoles [7]. Further support for the structure of **5aa** and **6aa** was provided by the ^{13}C NMR spectrum. For **5aa**, the signals of pyrazole 3-C (adjacent to CF_2Br) appeared as a triplet at δ 150.1 ($^2J_{C-F}$ = 29.2 Hz) due to the coupling of the 3-C and fluorine. For **6aa**, the corresponding pyrazole 5-C (adjacent to CF_2Br) showed a signal as a triplet at δ 140.8 ($^2J_{C-F}$ = 30.6 Hz), in lower field than that of **5aa**.

The dihydropyrazoles were easily identified by NMR spectroscopy. For example, the ^1H NMR spectrum of **9a** displayed the dihydropyrazole 4-CH_2 protons as an AB system (doublets at δ_A 3.79 and δ_B 3.55, with the germinal coupling constant ^2J = 17.8 Hz). In ^{13}C NMR, dihydropyrazole 3-C, 4-C and 5-C displayed signals at δ 157.8, δ 43.3 and δ 107.4 (t, $^2J_{C-F}$ = 27.4 Hz), respectively. Had the CF_2Br group in dihydroisoxazole been present at position-3, the signal at ~δ 107.4 would be appeared as a singlet instead of a triplet. Finally, the ^{19}F NMR showed a typical AB system (doublets at δ_A −62.53 and δ_B −63.65, with the germinal coupling constant $^2J_{F-F}$ = 166.4 Hz). For **11a**, obtained form the dehydration of **9a**, the signal of the isoxazole

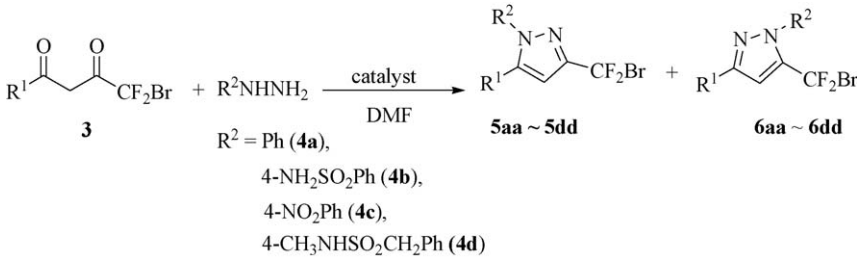


Scheme 2.

Table 2
Reaction of β-diketone **3a** with phenyl hydrazine **4a**.

Entry	Catalyst	Solvent	Temperature	Time (h)	Ratio of **5aa**/**6aa**[a]	Content of **7a** and **8a** (%)[b]	Yields (%)[c]
1	AcOH	EtOH	Reflux	3	82:18	20	57
2	HCl	EtOH	Reflux	3	60:40	25	73
3	–	EtOH	Reflux	3	64:36	<5	85
4	H_2SO_4	EtOH	Reflux	3	82:18	18	81
5	AcOH	DMSO	100 °C	3	>99:1	–	63
6	AcOH	DMF	100 °C	2	>99:1	–	61
7	H_2SO_4	DMF	100 °C	3	>99:1	–	86
8	HCl	DMF	100 °C	6	88:12	–	53

[a] Crude reaction mixture ratios based on ^{19}F NMR.
[b] Crude reaction mixture ratios based on ^1H NMR.
[c] Isolated yield of **5aa** or a mixture.



Scheme 3.

Table 3
Data of the reaction of **3** with nucleophilic reagents **4**.

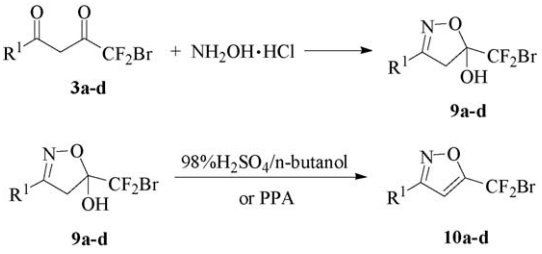
Entry	3	R^1	4[a]	R^2	Time (h)	Product	Yield (%)	Ratio of 5/6[b]
1	**3a**	Ph	**4a**	Ph	6	**5aa**	86	>99:1
2	**3a**	Ph	**4b**	4-NH_2SO_2Ph	2	**5ab**	84	>99:1
3	**3a**	Ph	**4c**	4-NO_2Ph	7	**5ac**	68	>99:1
4	**3a**	Ph	**4d**	4-$MeNH_2SO_2CH_2Ph$	4	**5ad**	70	>99:1
5	**3b**	4-MePh	**4a**	Ph	3	**5ba**	69	99:1
6	**3b**	4-MePh	**4b**	4-NH_2SO_2Ph	3	**5bb**	84	>99:1
7	**3b**	4-MePh	**4c**	4-NO_2Ph	4	**5bc**	79	95:5
8	**3c**	4-MeOPh	**4a**	Ph	2	**5ca**	81	>99:1
9	**3c**	4-MeOPh	**4b**	4-NH_2SO_2Ph	2	**5cb**	76	>99:1
10	**3c**	4-MeOPh	**4c**	4-NO_2Ph	4	**5cc**	86	96:4
11	**3c**	4-MeOPh	**4d**	4-$MeNH_2SO_2CH_2Ph$	4	**5cd**	78	>99:1
12	**3d**	2-Thienyl	**4a**	Ph	3	**5da**	75	94:6
13	**3d**	2-Thienyl	**4b**	4-NH_2SO_2Ph	2	**5db**	83	96:4
14	**3d**	2-Thienyl	**4d**	4-$MeNH_2SO_2CH_2Ph$	3	**5dd**	81	>99:1

[a] **4b** and **4d** was used as their hydrochloride.
[b] Crude reaction mixture ratios based on ^{19}F NMR.

Table 4
Reactions of β-diketones **3** with hydroxylamine hydrochloride.

Entry	β-Diketone	Solvent	Reaction time (h)	Yield of **9** (%)[a]	Yield of **10** (%)[a,b]
1	**3a**	EtOH	4	86	78
2	**3a**	DMF	10	78	–
3	**3b**	EtOH	3	82	71
4	**3c**	EtOH	4	82	80
5	**3d**	EtOH	5	84	81

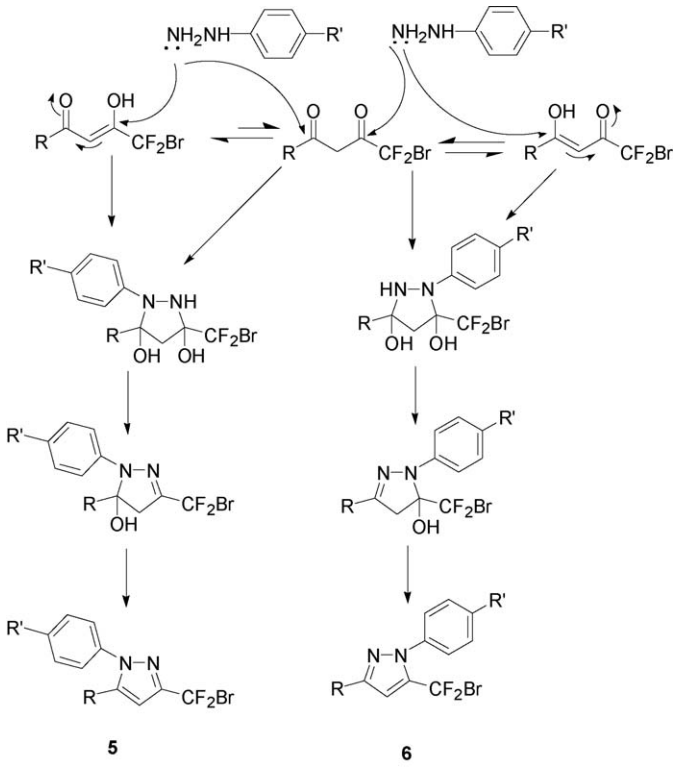
[a] Isolated yield.
[b] Dehydrated by PPA.



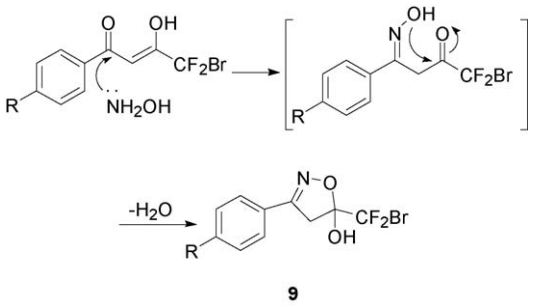
Scheme 4.

4-CH proton appeared at δ 6.92 (s, 1H) and the 5-C at 164.8 (t, J = 35.3 Hz).

Similar to trifluoromethyl substituted aryl β-diketones [23,24], **3** was supposed to exist in enol form and the direction of enolization is largely towards COAr. It is therefore likely that the reaction of **3** and **4** proceeds via conjugate addition of the terminal nitrogen of the hydrazine derivatives into the two enols (Scheme 5). Subsequent cyclization affords the isomeric dihydroxytertrahydropyrazoles. One molecule of water is then eliminated to give the hydroxydihydropyrazoles. Further elimination of water yields the aromatic pyrazoles **5** and **6**. The ratio of the two regioisomers mainly depends on the proportion of the



Scheme 5.



Scheme 6.

two enols at equilibrium, which was affected by solvent, acid and temperature.

In the reaction of **3** and hydroxylamine hydrochloride, the nucleophilic attack of NH_2 of hydroxylamine takes place on the carbonyl carbon attached to the aryl group (i.e. COAr) of the diketones (Scheme 6), which was in conformity with the reaction of trifluoromethyl substituted diketones and hydroxylamine hydrochloride [25].

In summary, we reported a convenient synthesis of bromodifluoromethyl substituted pyrazole and isoxazole derivatives in high regioselectivity using bromodifluoromethyl substituted β-diketones **3** and aryl hydrazine derivatives **4** or hydroxylamine hydrochloride.

3. Experimental

IR spectra were measured on a Nicolet Magna IR-550 spectrometer. High-resolution mass spectra were carried out on a Finnigan GC-MS-4021 spectrometer. NMR spectra were recorded in $CDCl_3$ solution at 20 °C on a Bruker AC-500 spectrometer operating at 500 MHz (^{1}H), 125.8 MHz (^{13}C) and 470.5 MHz (^{19}F). Chemical shifts (δ) are given in ppm relative to TMS for ^{1}H and ^{13}C, and relative to $CFCl_3$ for ^{19}F. Column chromatography was performed by using silica gel H, particle size 20–30 μm. Melting points are uncorrected.

3.1. General procedure for the preparation of bromodifluoromethyl β-diketones 3

To the suspension of sodium methoxide (prepared from sodium (6.9 g, 0.3 mol) and methanol) in ethyl ether (80 mL) was added the mixture of ethyl bromodifluoromethyl acetate (40.0 g, 0.2 mol), methyl ketone **1** (24 g, 0.2 mol) and ethyl ether (120 mL) in 1 h. After stirring for 24–48 h at room temperature, the reaction mixture was acidified to pH 2–3 with 1N HCl. The organic layer was separated and washed with water and dried with anhydrous sodium sulfate. After removal of ethyl ether, the residue was distillated under vacuum to give bromodifluoromethyl β-diketone **3**.

3.1.1. 4-Bromo-4,4-difluoro-1-phenylbutane-1,3-dione (3a)

B.p. 120–122 °C/5 mmHg. IR (film, υ_{max}, cm^{-1}): 3120, 3064, 1604, 1571, 1491, 1255, 1187, 1152, 1110, 1094, 1066, 1001, 873, 759, 700, 685. ^{1}H NMR ($CDCl_3$) δ: (enol) 14.9 (broad, 1H), 7.96–7.50 (m, 5H), 6.52 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: (enol, major) 184.7, 183.1 (t, J = 27.4 Hz), 134.5, 133.2, 129.6, 128.1, 114.1 (t, J = 313.9 Hz), 93.1 (*E*), 90.5 (*Z*); (ketone, minor) 185.4, 182.2 (t, J = 34.7 Hz), 134.1, 133.9, 129.5,128.0, 117.6 (t, J = 277.5 Hz), 51.7 (t, J = 6.8 Hz). ^{19}F NMR ($CDCl_3$) δ: (enol) −63.00 (s, 2F). HRMS (EI): $C_{10}H_7BrF_2O_2$ calcd: 275.9597; found: 275.9591. Only enol was observed in ^{1}H NMR and ^{19}F NMR for the much lower concentration than in ^{13}C NMR.

3.1.2. 4-Bromo-4,4-difluoro-1-p-tolylbutane-1,3-dione (3b)

B.p. 135–137 °C/10 mmHg. ^{1}H NMR ($CDCl_3$) δ: 15.0 (s, 1H), 7.85 (d, 2H, J = 8.16 Hz), 7.31 (d, 2H, J = 8.16 Hz), 6.48 (s, 1H), 2.44 (s, 3H) [11].

3.1.3. 4-Bromo-4,4-difluoro-1-(4-methoxyphenyl)butane-1,3-dione (3c)

Pale yellow oil. B.p. 146–148 °C/5 mmHg. IR (film, υ_{max}, cm^{-1}): 3121, 1590, 1507, 1459, 1269, 1182, 1145, 1101, 1067. ^{1}H NMR ($CDCl_3$) δ: (enol) 15.5 (broad, 1H), 7.95–7.91 (m, 2H), 6.99–6.92 (m, 2H), 6.43 (s, 1H), 3.89 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: (enol) 184.9, 181.9 (t, J = 27.2 Hz), 165.1, 130.5, 125.7, 115.0, 114.4 (t, J = 313.4 Hz), 89.5, 56.3. ^{19}F NMR ($CDCl_3$) δ: −62.41 (s, 2F). HRMS (EI): $C_{11}H_9BrF_2O_3$ calcd: 305.9706; found: 305.9723.

3.1.4. 4-Bromo-4,4-difluoro-1-(thiophen-2-yl)butane-1,3-dione (3d)

B.p. 117.0–119.0 °C/1.5 mmHg. IR (film, υ_{max}, cm^{-1}): 3110, 1592, 1520, 1412, 1258, 1215, 1148, 1101, 1063, 944, 869, 724. ^{1}H NMR ($CDCl_3$) δ: (enol, major) 14.9 (broad, 1H), 7.83 (dd, 1H, J_1 = 3.90 Hz, J_2 = 1.10 Hz), 7.74 (dd, 1H, J_1 = 5.00 Hz, J_2 = 1.10 Hz), 7.20 (dd, 1H, J_1 = 5.00 Hz, J_2 = 3.90 Hz), 6.44 (s, 0.12H, *E*), 6.37 (s, 0.88H, *Z*); (ketone, minor) 7.80 (1H, dd, J_1 = 3.90 Hz, J_2 = 1.10 Hz), 7.70 (1H, dd, J_1 = 4.90 Hz, J_2 = 1.10 Hz), 7.18 (1H, dd, J_1 = 4.90 Hz, J_2 = 3.90 Hz), 3.72 (2H, s). ^{13}C NMR ($CDCl_3$) δ: (enol, major) 181.3, 178.5 (t, J = 27.7 Hz), 139.2, 135.4, 133.1, 129.5, 113.9 (t, J = 311.3 Hz), 94.0 (*E*), 91.0 (*Z*); (ketone, minor) 182.8, 186.2 (t, J = 37.3 Hz), 140.5, 135.0, 132.7, 129.3, 117.8 (t, J = 268.8 Hz), 51.7. ^{19}F NMR ($CDCl_3$) δ: (enol, major) −62.11 (s, 2F); (ketone, minor) −84.58 (s, 2F). HRMS (EI): $C_8H_5BrF_2O_2S$ calcd: 281.9162; found: 281.9153.

3.2. General procedure for the preparation of bromodifluoromethyl pyrazoles

The mixture of bromodifluoromethyl β-diketone **3** (2 mmol), solvent (10 mL), acid (0.05 mL), hydrazine derivative (2 mmol) was stirred at room temperature for 2–5 h and then heated to 120 °C. After stirring for 2–6 h at this temperature, the reaction mixture was treated with water (10 mL) and extracted with ethyl acetate of 30 mL × 3. After dried with sodium sulfate and removal of the solvent, the residue was purified by recrystallization or column chromatography eluted with a mixture of ethyl acetate and petroleum oil.

3.2.1. 3-(Bromodifluoromethyl)-1,5-diphenyl-1H-pyrazole (5aa)

Pale yellow oil (column). ^{1}H NMR ($CDCl_3$) δ: 7.35–7.32 (m, 8H), 7.23–7.21 (m, 2H), 6.73 (s, 1H). ^{19}F NMR ($CDCl_3$) δ: −43.4 (s, 2F).

3.2.2. A mixture of 3-(bromodifluoromethyl)-1,5-diphenyl-1H-pyrazole (5aa) and 5-(bromodifluoromethyl)-1,3-diphenyl-1H-pyrazole (6aa)

Yellow oil (column). IR (film, υ_{max}, cm^{-1}): 3133, 3058, 1595, 1500, 1272, 1207, 1115, 1087, 1073, 992. ^{1}H NMR ($CDCl_3$) δ: (**5aa**) 7.86–7.21 (m, 10H), 6.72 (s, 1H); (**6aa**) 7.86–7.21 (m, 10H), 7.06 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: (**5aa**) 150.1 (t, J = 29.2 Hz), 145.3, 139.9, 130.1, 129.8, 129.6, 129.4, 129.3, 127.5, 126.2, 115.1 (t, J = 301.9 Hz), 105.5; (**6aa**) 151.8, 140.8 (t, J = 30.6 Hz), 140.0, 132.4, 129.8, 129.6, 129.4, 129.3, 129.1, 126.5, 111.6 (t, J = 301.9 Hz), 105.5. ^{19}F NMR ($CDCl_3$) δ: (**5aa**) −43.6 (s, 2F); (**6aa**) −40.3 (s, 2F). HRMS (EI): $C_{16}H_{11}N_2F_2Br$ cacld: 348.0074; found: 348.0078.

3.2.3. 1,5-Diphenyl-1H-pyrazole-3-carboxylic acid ethyl ester (7aa) [26,27]

White powder with mp 66.0–67.0 °C (column). ^{1}H NMR ($CDCl_3$) δ: 7.35–7.21 (m, 10H), 7.05 (s, 1H), 4.46 (q, 2H, J = 7.10 Hz), 1.39 (t, 3H, J = 7.10 Hz). MS (EI): 292 (M^+, 59.33), 247 (M^+-OC_2H_5, 45.73),

220 (100), 219 (M^+-$COOC_2H_5$, 70.32), 180 (18.87), 117 (14.14), 104 (16.05), 77 (Ph, 22.39).

*3.2.4. 2,5-Diphenyl-2H-pyrazole-3-carboxylic acid ethyl ester (**8aa**) [27]*

White powder with mp 71.5–71.9 °C (column). ^{1}H NMR ($CDCl_3$) δ: 7.89–7.33 (m, 10H), 7.33 (s, 1H), 4.27 (q, 2H, J = 7.10 Hz), 1.27 (t, 3H, J = 7.10 Hz). MS (EI): 292 (M^+, 100), 264 (8.65), 263 (M^+-C_2H_5, 11.8), 247 (M^+-OC_2H_5, 12.9), 219 (M^+-$COOC_2H_5$, 17.9), 117 (5.83), 116 (7.38), 77 (Ph, 7.86).

*3.2.5. 4-(3-(Bromodifluoromethyl)-5-phenyl-1H-pyrazol-1-yl) benzenesulfonamide (**5ab**)*

Yellow solid with mp 151.1–152.1 °C (column). IR (film, υ_{max}, cm^{-1}): 3342, 3266, 3141, 3080, 1598, 1506, 1322, 1206, 1160. ^{1}H NMR ($CDCl_3$) δ: 7.92 (d, 2H, J = 8.52 Hz), 7.49 (d, 2H, J = 8.52 Hz), 7.43–7.37 (m, 3H), 7.26–7.24 (m, 2H), 6.76 (s, 1H), 4.84 (s, 2H). ^{13}C NMR ($CDCl_3$) δ: 151.0 (t, J = 29.2 Hz), 145.8, 143.1, 142.1, 130.3, 129.7, 129.5, 129.3, 128.2, 126.2, 114.6 (t, J = 301.9 Hz), 106.6. ^{19}F NMR ($CDCl_3$) δ: −44.2 (s, 2F). HRMS (EI): $C_{16}H_{12}BrF_2N_3O_2S$ cacld: 426.9802; found: 426.9816.

*3.2.6. 3-(Bromodifluoromethyl)-1-(4-nitrophenyl)-5-phenyl-1H-pyrazole (**5ac**)*

Pale yellow oil (column). IR (film, υ_{max}, cm^{-1}): 3121, 3085, 1596, 1524, 1346, 1270, 1206, 1110, 1087, 991, 971, 857. ^{1}H NMR ($CDCl_3$) δ: 8.22 (d, 2H, J = 9.06 Hz), 7.52 (d, 2H, J = 9.06 Hz), 7.44–7.38 (m, 3H), 7.25–7.24 (m, 2H), 6.77 (s, 1H). ^{19}F NMR ($CDCl_3$) δ: −44.5 (s, 2F). ^{13}C NMR ($CDCl_3$) δ: 151.4 (t, J = 29.7 Hz), 147.5, 145.9, 144.6, 130.4, 129.8, 129.5, 126.6, 126.1, 125.3, 114.6 (t, J = 299.4 Hz), 106.9. HRMS (EI): $C_{16}H_{10}N_3O_2F_2Br$ cacld: 392.9924; found: 392.9922.

*3.2.7. C-[4-(3-Bromodifluoromethyl-5-phenylpyrazol-1-yl)-phenyl]-N-methyl-methanesulfonamide (**5ad**)*

White powder with mp 116.8–117.8 °C (column). IR (KBr, υ_{max}, cm^{-1}): 3210, 1610, 1520, 1313, 1266, 1199, 1157, 1124, 1086, 1069, 991, 864, 706, 665. ^{1}H NMR ($CDCl_3$) δ: 7.41–7.22 (m, 9H), 6.74 (s, 1H), 4.26 (s, 2H), 4.05 (q, 1H, J = 5.00 Hz, NH), 2.68 (q, 3H, J = 5.00 Hz). ^{13}C NMR ($CDCl_3$) δ: 150.4 (t, J = 29.1 Hz), 145.4, 140.2, 132.0, 130.3 129.9, 129.7, 129.5, 129.4, 126.4, 114.8 (t, J = 299.2 Hz), 105.8, 57.9, 30.6. ^{19}F NMR ($CDCl_3$) δ: −43.9 (s, 2F). HRMS (EI): $C_{18}H_{16}N_3O_2F_2S$ cacld: 455.0115; found: 455.0119.

*3.2.8. 3-(Bromodifluoromethyl)-1-phenyl-5-p-tolyl-1H-pyrazole (**5ba**)*

Colorless oil (column). IR (film, υ_{max}, cm^{-1}): 3123, 3068, 1605, 1509, 1270, 1209, 1105, 1086, 1063. ^{1}H NMR ($CDCl_3$) δ: 7.35–7.31 (m, 5H), 7.13–7.09 (m, 4H), 6.70 (s, 1H), 2.35 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 150.9 (t, J = 29.2 Hz), 144.3, 139.2, 131.0, 129.7, 129.5, 129.2, 129.1, 127.5, 126.2, 115.2 (t, J = 301.9 Hz), 105.3, 21.5. ^{19}F NMR ($CDCl_3$) δ: −43.4 (s, 2F). HRMS (EI): $C_{17}H_{13}BrF_2N_2$, calcd: 362.0285; found: 362.0286.

*3.2.9. 4-(3-(Bromodifluoromethyl)-5-p-tolyl-1H-pyrazol-1-yl) benzenesulfonamide (**5bb**) [11]*

Yellow crystal with mp 176.0–177.0 °C (from PE:EA = 1:2).

IR (KBr, υ_{max}, cm^{-1}): 3358, 3277, 3141, 3105, 2921, 1720, 1600, 1500, 1455, 1327. ^{1}H NMR ($CDCl_3$) δ: 7.90 (d, 2H, J = 8.65 Hz), 7.50 (d, 2H, J = 8.65 Hz), 7.18 (d, 2H, J = 8.03 Hz), 7.13 (d, 2H, J = 8.03 Hz), 6.73 (s, 1H), 4.82 (s, 2H), 2.39 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 150.3 (t, J = 29.3 Hz), 145.2, 142.6, 141.2, 139.8, 129.8, 128.7, 127.5, 125.7, 125.5, 114.2 (t, J = 301.9 Hz), 105.6, 21.3. ^{19}F NMR ($CDCl_3$) δ: −44.15 (s, 2F). HRMS (EI): $C_{17}H_{14}BrF_2N_3O_2S_2$, calcd: 440.9958; found: 440.9958.

*3.2.10. 3-(Bromodifluoromethyl)-1-(4-nitrophenyl)-5-p-tolyl-1H-pyrazole (**5bc**)*

Colorless oil (column). IR (film, υ_{max}, cm^{-1}): 3120, 3095, 1600, 1526, 1356, 1269, 1203, 1109, 1085, 992, 978. ^{1}H NMR ($CDCl_3$) δ: 8.23 (d, 2H, J = 9.01 Hz), 7.53 (d, 2H, J = 9.01 Hz), 7.19 (d, 2H, J = 8.03 Hz), 7.14 (d, 2H, J = 8.03 Hz), 6.73 (s, 1H), 2.39 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 151.9 (t, J = 29.20 Hz), 146.1, 143.0, 141.1, 139.4, 130.1, 128.4, 127.3, 125.9, 125.7, 114.3 (t, J = 295.4 Hz), 105.4, 22.3. ^{19}F NMR ($CDCl_3$) δ: −44.4 (s, 2F). HRMS (EI): $C_{17}H_{12}BrF_2N_3O_2$ cacld: 407.0119; found: 407.0120.

*3.2.11. 3-(Bromodifluoromethyl)-5-(4-methoxyphenyl)-1-phenyl-1H-pyrazole (**5ca**)*

Yellow oil (column). IR (film, υ_{max}, cm^{-1}): 3134, 3067, 1613, 1595, 1577, 1552, 1499, 1253, 1206, 1177, 1086, 1032, 991, 862, 836. ^{1}H NMR ($CDCl_3$) δ: 7.38–7.31(m, 5H), 7.14 (d, 2H, J = 8.8 Hz), 6.84 (d, 2H, J = 8.8 Hz), 6.67 (s, 1H), 3.80 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 160.7, 150.0 (t, J = 29.1 Hz), 145.1, 140.0, 130.8, 129.7, 128.9, 126.2, 122.2, 115.2 (t, J = 295.4 Hz), 114.8, 104.9, 55.9. ^{19}F NMR ($CDCl_3$) δ: −44.4 (s, 2F). HRMS (EI): $C_{17}H_{13}N_2OF_2Br$ cacld: 378.0179; found: 378.0201.

*3.2.12. 4-(3-(Bromodifluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide (**5cb**)*

White solid with mp 181.9–182.3 °C (from ethanol). IR (KBr, υ_{max}, cm^{-1}): 3372, 3271, 2937, 2840, 1612, 1498, 1439, 1337, 1161 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.92 (d, 2H, J = 8.68 Hz), 7.50 (d, 2H, J = 8.68 Hz), 7.15 (d, 2H, J = 8.74 Hz), 6.90 (d, 2H, J = 8.74 Hz), 6.70 (s, 1H), 4.87 (s, 2H), 3.84 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 161.2, 150.9 (t, J = 29.2 Hz), 145.7, 143.2, 142.0, 130.9, 128.1, 126.2, 121.5, 115.2, 114.7 (t, J = 301.9 Hz), 106.0, 56.0. ^{19}F NMR ($CDCl_3$) δ: −44.15 (s, 2F). HRMS (EI): $C_{17}H_{14}BrF_2N_3O_3S$ cacld: 456.9907; found: 456.9909.

*3.2.13. 3-(Bromodifluoromethyl)-5-(4-methoxyphenyl)-1-(4-nitrophenyl)-1H-pyrazole (**5cc**)*

Yellow solid with mp 122.3–122.7 °C (column). IR (KBr, υ_{max}, cm^{-1}): 3075, 1610, 1342, 1292, 1249, 1201, 1178, 1098, 1064, 1027, 991, 967, 859, 838. ^{1}H NMR ($CDCl_3$) δ: 8.21 (2H, d, J = 8.98 Hz), 7.53 (2H, d, J = 8.98 Hz), 7.15 (2H, d, J = 8.69 Hz), 6.91 (2H, d, J = 8.69 Hz), 6.68 (s, 1H), 3.84 (s, 3H). ^{19}F NMR ($CDCl_3$) δ: −44.4 (s, 2F). ^{13}C NMR ($CDCl_3$) δ: 161.3, 151.3 (t, J = 29.6 Hz), 147.4, 145.8, 144.7, 130.9, 126.0, 125.2, 121.5, 115.0, 114.6 (t, J = 299.4 Hz), 106.4, 56.0. HRMS (EI): $C_{17}H_{12}N_3O_3F_2Br$ cacld: 423.0030; found: 423.0022.

*3.2.14. C-{4-[3-Bromodifluoromethyl-5-(4-methoxy-phenyl)-pyrazol-1-yl]-phenyl}-N-methyl-methanesulfonamide (**5cd**)*

White powder with mp 138.0–140.0 °C (column).

IR (KBr, υ_{max}, cm^{-1}): 3234, 1611, 1502, 1319, 1273, 1253, 1234, 1205, 1179, 1122, 1082, 991, 797, 722. ^{1}H NMR ($CDCl_3$) δ: 7.33 (d, 2H, J = 8.40 Hz), 7.27 (d, 2H, J = 8.40 Hz), 7.07 (d, 2H, J = 8.80 Hz), 6.77 (d, 2H, J = 8.80 Hz), 6.60 (s, 1H), 4.22 (q, 1H, J = 4.90 Hz), 4.17 (s, 2H), 3.74 (s, 3H), 2.60 (d, 3H, J = 4.90 Hz). ^{13}C NMR ($CDCl_3$) δ: 160.9, 150.3 (t, J = 27.9 Hz), 145.3, 140.3, 132.0, 130.8, 130.2, 126.4, 121.9, 114.9, 112.5 (t, J = 279.6 Hz), 105.4, 58.0, 56.0, 30.5. ^{19}F NMR ($CDCl_3$) δ: −43.8 (s, 2F). HRMS (EI): $C_{19}H_{18}N_3O_3F_2BrS$ cacld: 485.0220; found: 485.0221

*3.2.15. 3-(Bromodifluoromethyl)-1-phenyl-5-(thiophen-2-yl)-1H-pyrazole (**5da**)*

Yellow solid with mp 74.2–75.0 °C (column). IR (KBr, υ_{max}, cm^{-1}): 3069, 1592, 1497, 1466, 1209, 1120, 989. ^{1}H NMR ($CDCl_3$) δ: 7.38–7.40 (m, 5H), 7.32 (1H, dd, J_1 = 5.01 Hz, J_2 = 1.11 Hz), 6.94 (1H, dd, J_1 = 5.01 Hz, J_2 = 3.70 Hz), 6.86 (1H, dd, J_1 = 3.71H, J_2 = 1.11 Hz), 6.71 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 150.9 (t, J = 29.2 Hz), 138.9, 129.2,

128.1, 127.6, 127.4, 126.9, 126.4, 125.7, 124.9, 114.1 (t, J = 301.9 Hz), 104.5. ^{19}F NMR ($CDCl_3$) δ: −43.7 (s, 2F). HRMS (EI): $C_{14}H_9BrF_2N_2S$ cacld: 353.9638; found: 353.9641.

*3.2.16. 4-(3-(Bromodifluoromethyl)-5-(thiophen-3-yl)-1H-pyrazol-1-yl)benzenesulfonamide (**5db**)*

White solid with mp 196.8–197.0 °C (from PE:EA = 3:1). IR (KBr, υ_{max}, cm^{-1}): 3353, 3218, 3099, 2922, 1559, 1345, 1163, 1092. ^{1}H NMR ($CDCl_3$) δ: 7.97 (d, 2H, J = 8.59 Hz), 7.59 (d, 2H, J = 8.59 Hz), 7.41 (d, 1H, J = 5.06 Hz), 7.03 (1H, dd, J_1 = 5.06 Hz, J_2 = 3.71 Hz), 6.92 (d, 1H, J = 3.71 Hz), 6.80 (s, 1H), 4.86 (s, 2H). ^{19}F NMR ($CDCl_3$) δ: −44.39 (s, 2F). ^{13}C NMR ($CDCl_3$) δ: 156.7 (t, J = 29.2 Hz), 151.2, 142.2, 141.9, 138.6, 128.9, 128.3, 127.9, 127.6, 126.2, 114.2 (t, J = 301.9 Hz), 106.2. HRMS (EI): $C_{14}H_{10}BrF_2N_3O_2S_2$ calcd: 432.9366; found: 432.9369.

*3.2.17. C-{4-[3-(Bromodifluoromethyl)-5-thiophen-3-yl-pyrazol-1-yl]-phenyl}-N-methyl-methanesulfonamide (**5dd**)*

Pale yellow powder with mp 164.8–165.1 °C (from ethanol). IR (KBr, υ_{max}, cm^{-1}): 3279, 3147, 1611, 1550, 1567, 1411, 1382, 1326, 1123, 1091, 992, 933, 864, 793, 700. ^{1}H NMR ($CDCl_3$) δ: 7.49–6.36 (m, 4H), 7.36 (dd, 1H, J_1 = 5.10 Hz, J_2 = 1.10 Hz), 6.99 (dd, 1H, J_1 = 5.10 Hz, J_2 = 3.60 Hz), 6.91 (dd, 1H, J_1 = 3.60 Hz, J_2 = 1.10 Hz), 6.79 (1H, s), 4.28 (2H, s), 4.12 (1H, q, J = 4.30 Hz, NH), 2.72 (3H, d, J = 4.30 Hz). ^{13}C NMR ($CDCl_3$) δ: 150.3 (t, J = 29.6 Hz), 139.9, 139.3, 132.1, 131.2, 130.0, 129.1, 128.5, 128.3, 127.2, 114.6 (t, J = 299.3 Hz), 105.8, 58.0, 30.5. ^{19}F NMR ($CDCl_3$) δ: −44.1 (2F, s). HRMS (EI): $C_{16}H_{14}N_3O_2F_2S_2Br$ cacld: 460.9679; found: 460.9696.

3.3. General procedure for the preparation of bromodifluoromethyl dihydroisoxazoles

The mixture of bromodifluoromethyl β-diketone **3** (2 mmol), ethanol (10 mL), hydroxylamine hydrochloride (8 mmol) was refluxed for 2–10 h. The reaction mixture was treated with water (10 mL) and extracted with ethyl acetate of 30 mL × 3. After dried with sodium sulfate and removal of the solvent, the residue was purified by recrystallization to give **9**.

*3.3.1. 5-(Bromodifluoromethyl)-3-phenyl-4,5-dihydroisoxazol-5-ol (**9a**)*

White solid with mp 125.0–125.3 °C (from 30 to 60 petroleum ether). IR (KBr, υ_{max}, cm^{-1}): 3180 (broad), 3042, 1636, 1610, 1574, 1448, 127.9, 1242, 1210, 1142, 1063, 1013, 927, 850. ^{1}H NMR ($CDCl_3$) δ: 7.69–7.43 (m, 5H), 3.79 (d, 1H, J = 17.87 Hz), 3.62 (br, 1H), 3.55 (dt, 1H, J_{H-H} = 17.87 Hz, J_{H-F} = 1.48 Hz). ^{19}F NMR ($CDCl_3$) δ: −62.53 (d, 1F, J = 166.4 Hz), −63.65 (d, 1F, J = 166.4 Hz). ^{13}C NMR ($CDCl_3$) δ: 157.8, 131.8, 129.7, 128.7, 127.6, 121.4 (t, J = 312.8 Hz), 107.4 (t, J = 27.4 Hz), 43.3. HRMS (EI): $C_{10}H_8NO_2F_2Br$, cacld: 290.9706; found: 290.9710.

*3.3.2. 5-(Bromodifluoromethyl)-3-p-tolyl-4,5-dihydroisoxazol-5-ol (**9b**)*

White solid with mp 121.2–121.7 °C (from PE:EA = 50:1). IR (KBr, υ_{max}, cm^{-1}): 3182 (broad), 3041, 1634, 1610, 1584, 1458, 127.9, 1242, 1142, 1063, 927. ^{1}H NMR ($CDCl_3$) δ: 7.54 (d, 2H, J = 7.95 Hz), 7.22 (d, 2H, J = 7.95 Hz), 3.82 (d, 1H, J = 17.40 Hz), 3.54 (d, 1H, J = 17.40 Hz), 2.50 (s, 1H), 2.39 (s, 3H). ^{19}F NMR ($CDCl_3$) δ: −62.9 (d, J = 165.7 Hz), −63.7 (d, J = 165.7 Hz). ^{13}C NMR ($CDCl_3$) δ: 161.8, 158.2, 129.5, 122.6 (t, J = 310.8 Hz), 121.5, 115.3, 108.2 (t, J = 26.4 Hz), 56.4, 20.3. HRMS (EI): $C_{11}H_{10}BrF_2NO_2$ cacld: 304.9982; found: 304.9984.

*3.3.3. 5-(Bromodifluoromethyl)-3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-ol (**9c**)*

White solid with mp 110.9–111.1 °C (from PE:EA = 50:1). IR (KBr, υ_{max}, cm^{-1}): 3173 (broad), 1608, 1517, 1309, 1258, 1180, 1146, 1109, 1070, 1044, 1018, 944, 914, 850, 829. ^{1}H NMR (DMSO) δ: 7.72 (d, 2H, J = 8.55 Hz), 7.11 (d, 2H, J = 8.55 Hz), 3.90 (d, 1H, J = 18.60 Hz), 3.83 (s, 3H), 3.58–3.47 (m, 1H). ^{19}F NMR ($CDCl_3$) δ: −63.63 (d, J = 168.0 Hz), −64.62 (d, J = 168.0 Hz). ^{13}C NMR ($CDCl_3$) δ: 162.3, 158.0, 129.6, 122.1 (t, J = 310.8 Hz), 121.2, 115.5, 108.0 (t, J = 26.4 Hz), 56.4, 43.6. HRMS (EI): $C_{11}H_{10}BrF_2NO_3$ cacld: 320.9812; found: 320.9830.

*3.3.4. 5-(Bromodifluoromethyl)-3-(thiophen-2-yl)-4,5-dihydroisoxazol-5-ol (**9d**)*

White solid with mp 149.1–149.5 °C (from PE:EA = 50:1). IR (KBr, υ_{max}, cm^{-1}): 3209 (broad), 3098, 2904, 2689, 1599, 1457. ^{1}H NMR ($CDCl_3$) δ: 7.48 (dd, 1H, J_1 = 5.10 Hz, J_2 = 1.10 Hz), 7.27 (dd, 1H, J_1 = 3.70 Hz, J_2 = 1.10 Hz), 7.10 (dd, 1H, J_1 = 5.10 Hz, J_2 = 3.70 Hz), 3.89 (d, 1H, J = 17.66 Hz), 3.56 (s, 1H), 3.54 (dt, 1H, J_1 = 17.66 Hz, J_2 = 1.36 Hz). ^{19}F NMR ($CDCl_3$) δ: −62.9 (d, J = 166.6 Hz), −63.7 (d, J = 166.6 Hz). ^{13}C NMR ($CDCl_3$) δ: 153.4, 130.7, 130.5, 130.3, 128.3, 121.2 (t, J = 312.6 Hz), 107.3 (t, J = 27.4 Hz), 44.0. HRMS (EI): $C_8H_6BrF_2NO_2S$ cacld: 296.9271; found: 296.9264.

3.4. General procedure for the preparation of bromodifluoromethyl isoxazoles

The mixture of **9** (5 mmol) and PPA (3.0 g) was heated at 150 °C for 30 min and then cooled to room temperature. After treated with crushed ice (15 g), the reaction mixture was neutralized with 25% aqueous ammonia to pH 7 and then extracted with trichloromethane of 20 mL × 3. After dried with sodium sulfate and removal of the solvent, the residue was purified by column chromatography eluted with a mixture of ethyl acetate and petroleum oil to give **10**.

*3.4.1. 5-(Bromodifluoromethyl)-3-phenylisoxazole (**10a**)*

Pale yellow oil. IR (film, υ_{max}, cm^{-1}): 3137, 3067, 1610, 1580, 1442, 1403, 1288, 1210, 1104, 994, 862. ^{1}H NMR ($CDCl_3$) δ: 7.83–7.50 (m, 5H), 6.92 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 164.8 (t, J = 33.2 Hz), 163.2, 131.5, 129.8, 128.1, 127.6, 109.9 (t, J = 299.9 Hz), 102.2. ^{19}F NMR ($CDCl_3$) δ: −48.90 (s, 2F). HRMS (EI): $C_{10}H_6BrF_2NO$ cacld: 272.9601; found: 272.9620.

*3.4.2. 5-(Bromodifluoromethyl)-3-p-tolylisoxazole (**10b**)*

Pale yellow oil. IR (film, υ_{max}, cm^{-1}): 3138, 3012, 2937, 2834, 1610, 1523, 1461, 1431, 1248. ^{1}H NMR ($CDCl_3$) δ: 7.69 (d, 2H, J = 8.10 Hz), 7.29 (d, 2H, J = 8.10 Hz), 6.87 (s, 1H), 2.42 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 171.4, 162.9 (t, J = 33.3 Hz), 141.9, 130.5, 126.6, 124.7, 113.1 (t, J = 300.7 Hz), 100.4, 20.4. ^{19}F NMR ($CDCl_3$) δ: −48.8 (s, 2F). HRMS (EI): $C_{11}H_8BrF_2NO$ cacld: 286.9757; found: 286.9759.

*3.4.3. 5-(Bromodifluoromethyl)-3-(4-methoxyphenyl)isoxazole (**10c**)*

Pale yellow oil. IR (film, υ_{max}, cm^{-1}): 3135, 3006, 2936, 2839, 1612, 1529, 1460, 1431, 1258. ^{1}HNMR ($CDCl_3$): 7.73 (d, 2H, J = 8.75 Hz), 7.00 (d, 2H, J = 8.75 Hz), 6.86 (s, 1H), 3.86 (s, 3H). ^{19}F NMR ($CDCl_3$) δ: −49.04 (s, 2F). ^{13}C NMR ($CDCl_3$) δ: 164.5 (t, J = 33.2 Hz), 162.8, 162.3, 129.0, 120.5, 115.2, 109.9 (t, J = 299.9 Hz), 102.0, 56.1. HRMS (EI): $C_{11}H_8BrF_2NO_2$ cacld: 302.9706; found: 302.9708.

*3.4.4. 5-(Bromodifluoromethyl)-3-(thiophen-2-yl)isoxazole (**10d**)*

Pale yellow oil. IR (KBr, υ_{max}, cm^{-1}): 3150, 2976, 2875, 1608, 1564, 1106. ^{1}H NMR ($CDCl_3$) δ: 7.53–7.48 (m, 2H), 7.16 (dd, 1H, J_1 = 5.10 Hz, J_2 = 3.60 Hz), 6.84 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 164.1 (t, J = 33.6 Hz), 157.7, 128.9, 128.8, 128.5, 127.9, 109.0 (t, J = 300.1 Hz), 101.5. ^{19}F NMR ($CDCl_3$) δ: −49.12 (s, 2F). HRMS (EI): $C_8H_4BrF_2NOS$ cacld: 278.9165; found: 278.9165.

Acknowledgment

We thank the National Natural Science Foundation of China (Grant No. 20672034) for financial support.

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