Journal of Fluorine Chemistry 133 (2012) 167–170

Contents lists available at SciVerse ScienceDirect

Journal of Fluorine Chemistry

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

# A facile preparation of 2-bromodifluoromethyl benzo-1,3-diazoles and its application in the synthesis of *gem*-difluoromethylene linked aryl ether compounds

Haizhen Jiang [a], Shijie Yuan [a], Yeshan Cai [a], Wen Wan [a], Shizheng Zhu [b,*], Jian Hao [a,b,**]

[a] *Department of Chemistry, Shanghai University, Shanghai 200444, China*
[b] *Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China*

ARTICLE INFO

*Article history:*
Received 25 June 2011
Received in revised form 5 August 2011
Accepted 14 August 2011
Available online 22 August 2011

*Keywords:*
2-Bromodifluoromethyl benzo-1,3-diazolines
Building block
*gem*-Difluoromethylene
Aryl ether

This paper is dedicated to Professor Wei-Yuan Huang on the occasion of his 90th birthday.

ABSTRACT

A facile preparation of 2-bromodifluoromethyl benzo-1,3-diazoles as novel $CF_2Br$-containing heterocyclic building blocks has been developed through a one-pot process of reaction of 2-OH, 2-SH, or 2-$NH_2$ substituted aniline with bromodifluoroacetic acid in the presence of 3 molar equivalents of $CBr_4$ and $Ph_3P$ in refluxing toluene. 2-Bromodifluoromethyl benzo-1,3-thiazole (**2b**) was successfully utilized in the preparation of *gem*-difluoromethylene linked aryl ether compounds through the reaction with phenolates or thiophenolate in DMF in good yields.

## 1. Introduction

*gem*-Difluoromethylene linked aryl ether compounds have attracted substantial attention due to their wide range of applications in pharmaceuticals, agrochemicals and electronic materials, such as enzyme inhibitors, anti-HIV agents, potassium channel activators, and smectic phase liquid crystals [1]. The most common methods used for the synthesis of *gem*-difluoromethylene aryl ether compounds are the approaches *via* the $CF_2$-containing building block [2]. It has been of great interest to develop and effectively use the $CF_2Br$-containing heterocyclic building blocks for the construction of *gem*-difluoromethylene linked heterocyclic-containing aryl ethers. However, till present, only few papers about synthesis and applications of $CF_2Br$-containing heterocyclic building blocks have been reported [3]. Herein, we present the results on a facile synthesis of 2-$CF_2Br$-containing benzo-1,3-diazolic building blocks **2** *via* a one-pot reaction of 2-OH, 2-SH or 2-$NH_2$ substituted aniline with bromodifluoroacetic acid in the presence of 3 molar equivalents of $CBr_4$ and $Ph_3P$ in refluxing toluene, which involves the formation of $CF_2Br$-containing imidoyl bromide intermediate and subsequent intramolecular ring-closure reaction. In addition, 2-$CF_2Br$-containing benzo-1,3-thiazolic building block **2b** was successfully applied to the synthesis of *gem*-difluoromethylene linked benzo-1,3-thiazole-containing aryl ethers **3** through the reaction with phenolates or thiophenolate in a suspension of sodium hydride in DMF *via* a process of $S_{RN}1$ (Scheme 1).

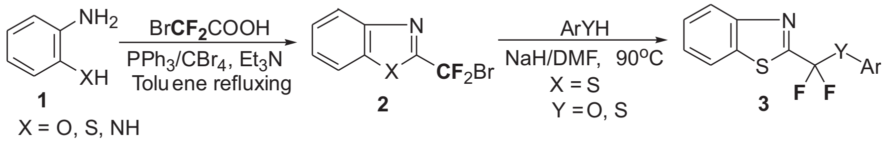
## 2. Results and discussion

$CF_2Br$-containing building blocks have been widely used to introduce a $CF_2$ unit into organic molecules *via* Reformatsky reaction, aldol reaction, cross-coupling reaction or radical addition reaction, *etc.* [4] on the basis of high reactivity of the C–Br bond in $CF_2Br$ group, which could easily be attacked by an electrophile or a radical. However, such high reactivity of C–Br bond makes the way of synthesis of $CF_2Br$-containing building blocks greatly differ from those for $CF_3$ and $CF_2H$-containing building blocks. The development of the synthetic method of $CF_2Br$-containing building blocks, especially for $CF_2Br$-containing heterocyclic building blocks, still encountered great challenges. The first example of synthesis of 2-

---

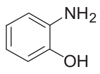
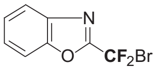
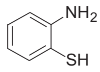
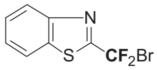
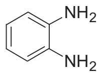
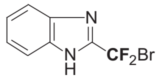
* Corresponding author at: Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China. Tel.: +86 21 54925185.
** Corresponding author at: Department of Chemistry, Shanghai University, Shanghai 200444, China. Tel.: +86 21 66133380; fax: +86 21 66133380.
*E-mail addresses:* zhusz@mail.sioc.ac.cn (S. Zhu), jhao@staff.shu.edu.cn (J. Hao).

0022-1139/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2011.08.008



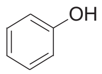
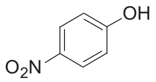
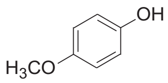
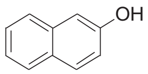
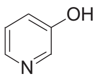
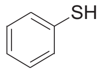
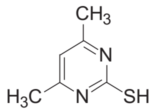
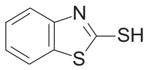
**Scheme 1.** Preparation of 2-bromodifluoromethyl benzo-1,3-diazoles and its application in the synthesis of *gem*-difluoromethylene linked aryl ethers.

**Table 1**
Synthesis of 2-bromodifluoromethyl benzo-1,3-diazoles.

| Entry | Reactant | Product | Reaction time (h) | Yield (%)[a] |
|---|---|---|---|---|
| 1 |  **1a** |  **2a** | 8 | 85 |
| 2 |  **1b** |  **2b** | 24 | 65 |
| 3 |  **1c** |  **2c** | 10 | 15[b] |

[a] Isolated yield.
[b] 1:2 molar ratio of bromodifluoro acetic acid to $PPh_3/CBr_4$.

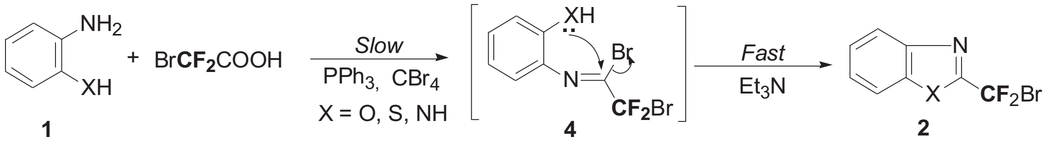
**Table 2**
The reaction of 2-bromodifluoromethyl benzothiazole **2b** with phenolates.

| Entry | ArYH | Product | Reaction time (h) | Conversion of **2b** (%)[a] | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 |  | **3bd** | 22 | 85 | 65 |
| 2 |  | **3be** | 22 | 80 | 73 |
| 3 |  | **3bf** | 20 | 83 | 64 |
| 4 |  | **3bg** | 24 | 90 | 78 |
| 5 |  | **3bh** | 20 | 88 | 75 |
| 6 |  | **3bi** | 20 | 83 | 62 |
| 7 |  | **3bj** | 36 | – | – |
| 8 |  | **3bk** | 36 | – | – |

[a] The conversions of **2b** were determined by $^{19}F$ NMR analysis.
[b] Isolated yield.

bromodifluoromethyl benzo-1,3-oxazole was reported to be through a bromination of $CF_2H$ group on the benzo-1,3-oxazole ring in the presence of excess amount of NBS. However, the bromination of $CF_2H$ group through such radical process suffered from either low yield or long reaction time [5]. Thus, our attention was drawn back to modify the original Uneyama's preparation of fluorinated imidoyl halids. It was demonstrated that the reaction of 2-OH substituted aniline with bromodifluoroacetic acid in the presence of 3 molar equivalents of $CBr_4$ and $Ph_3P$ in refluxing toluene initially led to the formation of bromodifluoromethyl substituted imidoyl bromide *in situ*, which further underwent intramolecular ring-closure reaction to form the desired 2-bromodifluoromethyl benzo-1,3-oxazole product **2a** effectively [6]. This synthetic method is also suitable for other substrates, such as 2-SH or 2-$NH_2$ substituted aniline as listed Table 1.

This one-pot reaction involves a slow formation of imidoyl bromide intermediate (**4**) in the first step. Upon the formation of **4**, the subsequent intramolecular ring-closure reaction occurred *via* nucleophilic substitution of bromide by neighboring XH group under the promotion of $Et_3N$ (Scheme 2). 2-OH Substituted aniline **1a** provided the desired product in better yield with shorter reaction time (entry 1, Table 1) in comparison with 2-SH aniline **1b** (entry 2, Table 1) as a substrate due to the electron-releasing characteristic of hydroxyl group which enriches the electron density of neighboring amino group to accelerate the formation of intermediate **4a** in the rate-determining step. However, 2-$NH_2$ substituted aniline provided a much lower yield under the same reaction conditions. The reaction could occur only when the amounts of carbon tetrabromide and triphenylphosphine were decreased from 3 to 2 molar equivalents and the desired 2-bromodifluoromethyl benzo-1,3-imidazole (**2c**) was obtained in 15% yield. The reason could possibly be the existence of the further reaction of unprotected NH group of **2c** with the excess amount of $PPh_3$ and $CBr_4$ [7].



**Scheme 2.** Mechanism of formation of 2-bromodifluoromethyl benzo-1,3-diazoles.

$CF_2Br$-containing heterocyclic building blocks have been successfully applied to the reactions with aldehydes [4] for the preparation of biologically reactive *gem*-difluoromethylene linked compounds. It was found that the molecules that have difluoromethylene group as a tether connecting benzo-1,3-oxazole-contaning compounds could significantly increase the anti-HIV activity [8]. Considering potential biological activities of benzothiazole derivatives, 2-bromodifluoromethyl-benzo-1,3-thiazolic building block (**2b**) was selected for the further synthesis of biologically interesting *gem*-difluoromethylene linked benzo-1,3-thiazole-contaning aryl ethers. This reaction was carried out in DMF through the displacement of bromide from 2-bromodifluoromethyl-benzothiazole by phenolates generated *in situ* from phenols in a suspension of sodium hydride. The raw material **2b** could not be consumed completely when equimolar amount of the phenolate was added to the solution of 2-bromodifluoromethyl benzo-1,3-thiazole in DMF. The residual of reactant **2b** could still be detected by $^{19}F$ NMR analysis of the reaction mixture even though the reaction time was prolonged, or the reaction temperature was raised. The conversion of the reactant **2b** could be improved if the amount of the phenolate was increased, however, it caused difficulties in purification. After screening of the reaction conditions, an optimal yield of **3bd** was obtained when the reaction was carried out in DMF at 90 °C for 22 h with an molar ratio of **1b**:phenolate = 1:1.1. Under the optimized reaction condition, various phenolates were employed to investigate the generality of this substitution reaction, the results are shown in the Table 2. Substituted phenolates could provide higher yields of the desired compounds (Table 2). The eletronic natures of these phenolates did not significantly influence the yields of products. The reaction of **2b** with benzenethiolate could also form the desired compound **3bi** in 62% yield (entry 6, Table 2). However, the heterocyclic thiolates examined did not work in this reaction (entries 7 and 8, Table 2). The reaction of $CF_2Br$-contaning heterocycle building block and phenolates or thiolate was considered undergoing an $S_{RN}1$ rather than a typical $S_N2$ mechanism due to the influence of the fluorine atoms in $CF_2Br$ group [9].

## 3. Conclusion

2-Bromodifluoromethyl benzo-1,3-diazoles as novel $CF_2Br$-containing heterocyclic building blocks were successfully prepared through a facile one-pot reaction of 2-OH, or 2-SH, or 2-$NH_2$ substituted aniline with bromodifluoroacetic acid in the presence of 3 molar equivalents of $CBr_4$ and $Ph_3P$ *via* the initial formation of imidoyl bromide intermediate (**4**) followed by intramolecular ring-closure reaction. 2-Bromodifluoromethyl-benzo-1,3-thiazole (**2b**) was successfully utilized in the preparation of biologically interesting *gem*-difluoromethylene linked aryl ether compounds. The reaction of 2-bromodifluoromethyl-benzo-1,3-thiazole **(2b)** with substituted phenolates or thiophenolate, which were generated *in situ* from substituted phenols or thiophenol in suspension of sodium hydride in DMF, is considered to undergo a $S_{RN}1$ process.

## 4. Experimental

### 4.1. General

Reactions were generally carried out under nitrogen atmosphere in an appropriate round bottom flask with magnetic stirring. Thin layer chromatography (TLC) was performed on a silica gel. $^1H$, $^{13}C$ and $^{19}F$ NMR spectra were recorded on a 500 MHz spectrometer. Chemical shifts for $^1H$ NMR spectra are reported in ppm downfield from TMS, chemical shifts for $^{13}C$ NMR spectra are reported in ppm relative to internal chloroform ($\delta$ 77.2 ppm for $^{13}C$), and chemical shifts for $^{19}F$ NMR spectra are reported in ppm downfield from internal fluorotrichloromethane ($CFCl_3$). Coupling constants ($J$) are given in Hertz (Hz). The terms m, s, d, t, q refer to multiplet, singlet, doublet, triplet, quartlet; br refers to a broad signal. Infrared spectra (IR) were recorded on a FT-IR spectrometer, absorbance frequencies are given at maximum of intensity in $cm^{-1}$. Mass spectra were obtained using ESI. High resolution mass spectra were obtained using EI at 70 eV.

### 4.2. General procedure for preparation of 2-bromodifluoromethyl benzo-1,3-diazoles (2)

A 200-ml three-necked flask equipped with a condenser was charged with $Ph_3P$ (2.20 g, 8.4 mmol), $Et_3N$ (0.85 g, 8.4 mmol), $CBr_4$ (16.8 g, 8.4 mmol), and bromodifluoro acetic acid (2.8 mmol) in toluene (10.0 ml) at 0 °C under nitrogen atmosphere. After the solution was stirred for about 10 min (ice water bath), 2-amino phenol (3.3 mmol) dissolved in toluene (5.0 ml) was added dropwise. The mixture was refluxed under stirring for 6–24 h. Solvent was evaporated under reduced pressure, and the residue was diluted with petroleum ether (60–90 °C) and filtered. The residual solid of $Ph_3PO$ and $Et_3N{\cdot}HCl$ was washed with petroleum ether 3 times. The filtrate was concentrated; the residue was then purified by column chromatography to obtain the product **2**.

#### 4.2.1. 2-Bromodifluoromethyl-benzooxazole (2a)

**2a** was obtained as a yellow oil in 85% yield by flash column chromatography on silica gel; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.81–7.83 (m, 1H, Ar*H*), 7.58–7.61 (m, 1H, Ar*H*), 7.41–7.50 (m, 2H, Ar*H*); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 155.7 (t, $^2J_{C\text{-}F}$ = 32.5 Hz), 150.6, 139.6, 127.8, 126.0, 121.9, 111.6, 108.9 (t, $^1J_{C\text{-}F}$ = 300.6 Hz); $^{19}F$ NMR (470 MHz, $CDCl_3$): $\delta$ −51.4 (s, 2F); IR ($cm^{-1}$): $\nu$ 3069, 1620, 1490, 1245, 1066, 760, 681; HRMS calcd for ($M^+$) $C_8H_4BrF_2NO$: 246.9444, found 246.9441.

#### 4.2.2. 2-Bromodifluoromethyl-benzothiazole (2b)

**2b** was obtained as a yellow oil in 65% yield by flash column chromatography on silica gel; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 8.11 (d, $J$ = 8.5 Hz, 1H, Ar*H*), 7.86 (d, $J$ = 7.5 Hz, 1H, Ar*H*), 7.52 (m, 1H, Ar*H*), 7.45 (m, 1H, Ar*H*); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 162.0 (t, $^2J_{C\text{-}F}$ = 30.0 Hz), 151.8, 135.1, 127.4, 127.3, 124.7, 122.9, 113.5 (t, $^1J_{C\text{-}F}$ = 301.3 Hz); $^{19}F$ NMR (470 MHz, $CDCl_3$): $\delta$ −43.16 (s, 2F); IR ($cm^{-1}$): $\nu$ 3067, 1618, 1510, 1249, 1031, 761, 686; HRMS calcd for ($M^+$) $C_8H_4BrF_2NS$: 262.9216, found 262.9213.

#### 4.2.3. 2-Bromodifluoromethyl-benzoimidazole (2c)

**2c** was obtained as a yellow solid in 15% yield by flash column chromatography on silica gel; mp 206.8–207.6 °C; Lit. [10] mp 206.0–208.8 °C; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 10.4 (s, 1H, NH), 7.88 (d, $J$ = 8.0 Hz, 1H, Ar*H*), 7.55 (d, $J$ = 7.5 Hz, 1H, Ar*H*), 7.41 (m, 2H, Ar*H*); $^{19}F$ NMR (470 MHz, $CDCl_3$): $\delta$ −51.17 (s, 2F); IR ($cm^{-1}$): $\nu$ 3412, 3053, 1591, 1447, 1241, 1081, 764, 684.

### 4.3. General procedure for preparation of compounds 3

A 25 ml three-necked, round-bottom flask was charged with NaH (2 mmol, 60%) and 10 ml of dry DMF under nitrogen atmosphere. To the stirred suspension was added phenol (1.1 mmol). Hydrogen gas was evolved and the flask became warm. After stirring for 30 min, a clear solution was obtained. 2-Bromodifluoromethyl benzothiazole (1 mmol) in 5 ml DMF was added dropwise. Then the solution was allowed to stir at 80 °C for 22–36 h. The mixture was poured into 5 ml of ice water, then extracted 3 times with 10 ml portions of ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated by rotary evaporation at reduced pressure. The residue was then purified by column chromatography (2:1 petroleum ether:ethyl acetate) on basic aluminum oxide to obtain the product **3**.

### *4.3.1. 2-Difluorophenoxymethyl-benzothiazole (**3bd**)*

**3bd** was obtained as a white solid in 65% yield by flash column chromatography; mp 39.5–41.1 °C; $^{1}$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.19 (d, $J$ = 8.5 Hz, 1H, Ar$H$), 7.91 (dd, $J$ = 10.0, 2.5 Hz, 1H, Ar$H$), 7.54 (td, $J$ = 7.0, 1.0 Hz, 1H, Ar$H$), 7.49–7.45 (m, 1H, Ar$H$), 7.38–7.33 (m, 4H, Ar$H$), 7.24 (tt, $J$ = 6.5, 2.0 Hz, 1H, Ar$H$); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 160.2 (t, $^{2}J_{C\text{-}F}$ = 40.0 Hz), 152.5, 149.8, 135.3, 129.7, 127.1, 127.0, 126.5, 124.9, 122.2, 122.1, 118.3 (t, $^{1}J_{C\text{-}F}$ = 261.3 Hz); $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ −63.03 (s, 2F); IR (cm$^{-1}$): $\nu$ 3067, 1592, 1490, 1295, 1193, 1066, 999, 760, 689; HRMS calcd for (M$^{+}$) $C_{14}H_9F_2NOS$: 277.0373, found 277.0372.

### *4.3.2. 2-Difluoro-(4-nitro)-phenoxymethyl-benzothiazole (**3be**)*

**3be** was obtained as a white solid in 73% yield by flash column chromatography; mp 158.4–160.2 °C; $^{1}$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.28 (dt, $J$ = 9.0, 3.0 Hz, 2H, Ar$H$), 8.20 (d, $J$ = 8.0 Hz, 1H, Ar$H$), 7.99 (d, $J$ = 7.5 Hz, 1H, Ar$H$), 7.61 (td, $J$ = 7.5, 1.0 Hz, 1H, Ar$H$), 7.55 (td, $J$ = 8.0, 1.0 Hz, 1H, Ar$H$), 7.49 (d, $J$ = 9.0 Hz, 2H, Ar$H$); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 158.7 (t, $^{2}J_{C\text{-}F}$ = 37.5 Hz), 154.6, 152.4, 145.6, 135.2, 127.5, 127.4, 125.7, 125.0, 122.2, 122.0, 118.5 (t, $^{1}J_{C\text{-}F}$ = 263.8 Hz); $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ −63.57 (s, 2F); IR (cm$^{-1}$): $\nu$ 3084, 1615, 1594, 1517, 1343, 1272, 1154, 997, 764; HRMS calcd for (M$^{+}$) $C_{14}H_8F_2N_2O_3S$: 322.0224, found 322.0220.

### *4.3.3. 2-Difluoro-(4-methoxy)-phenoxymethyl-benzothiazole (**3bf**)*

**3bf** was obtained as a white solid in 64% yield by flash column chromatography; mp 79.1–81.3 °C; $^{1}$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.20 (d, $J$ = 8.5 Hz, 1H, Ar$H$), 7.92 (d, $J$ = 8.0 Hz, 1H, Ar$H$), 7.55 (dd, $J$ = 7.0, 7.0 Hz, 1H, Ar$H$), 7.48 (dd, $J$ = 7.5, 7.5 Hz, 1H, Ar$H$), 7.26 (d, $J$ = 9.0 Hz, 2H, Ar$H$), 6.87 (dd, $J$ = 7.5, 2.0 Hz, 2H, Ar$H$), 3.76 (s, 3H, -OC$H_3$); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 160.2 (t, $^{2}J_{C\text{-}F}$ = 38.8 Hz), 157.9, 152.4, 143.1, 135.3, 127.1, 127.0, 124.9, 123.5, 122.1, 118.3 (t, $^{1}J_{C\text{-}F}$ = 261.3 Hz), 114.6, 55.6; $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ −63.42 (s, 2F); IR (cm$^{-1}$): $\nu$ 3074, 2970, 1503, 1298, 1176, 1058, 998, 762; HRMS calcd for (M$^{+}$) $C_{15}H_{11}F_2NO_2S$: 307.0479, found 307.0481.

### *4.3.4. 2-Difluoro-(2-naphthyl)-oxymethyl-benzothiazole (**3bg**)*

**3bg** was obtained as a white solid in 78% yield by flash column chromatography; mp 89.7–91.3 °C; $^{1}$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.24 (d, $J$ = 8.0 Hz, 1H, Ar$H$), 7.97 (d, $J$ = 7.5 Hz, 1H, Ar$H$), 7.86 (dd, $J$ = 16.0, 14.5 Hz, 4H, Ar$H$), 7.60 (td, $J$ = 7.0, 1.0 Hz, 1H, Ar$H$), 7.54–7.48 (m, 4H, Ar$H$); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 160.1 (t, $^{2}J_{C\text{-}F}$ = 40.0 Hz), 152.5, 147.4, 135.3, 133.8, 131.7, 129.8, 127.9, 127.8, 127.1, 127.0, 126.9, 126.2, 125.0, 122.1, 121.5, 119.3, 118.5 (t, $^{1}J_{C\text{-}F}$ = 261.3 Hz); $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ −62.97 (s, 2F); IR (cm$^{-1}$): $\nu$ 3061, 1598, 1511, 1295, 1180, 1050, 997, 760, 732; HRMS calcd for (M$^{+}$) $C_{18}H_{11}F_2NOS$: 327.0529, found 327.0525.

### *4.3.5. 2-Difluoro-(3-pyridyl)-oxymethyl-benzothiazole (**3bh**)*

**3bh** was obtained as a pale-yellow solid in 75% yield by flash column chromatography; mp 43.7–44.6 °C; $^{1}$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.63 (d, $J$ = 2.5 Hz, 1H, Ar$H$), 8.48 (dd, $J$ = 5.0, 1.0 Hz, 1H, Ar$H$), 8.14 (d, $J$ = 8.0 Hz, 1H, Ar$H$), 7.91 (d, $J$ = 7.5 Hz, 1H, Ar$H$), 7.65–7.63 (m, 1H, Ar$H$), 7.53 (td, $J$ = 7.0, 1.0 Hz, 1H, Ar$H$), 7.46 (td, $J$ = 8.0, 1.0 Hz, 1H, Ar$H$), 7.30–7.28 (m, 1H, Ar$H$); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 158.9 (t, $^{2}J_{C\text{-}F}$ = 37.5 Hz), 152.2, 147.6, 146.5, 143.9, 135.0, 129.4, 127.1, 127.0, 124.8, 124.1, 122.0, 118.3 (t, $^{1}J_{C\text{-}F}$ = 263.75 Hz); $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ −63.28 (s, 2F); IR (cm$^{-1}$): $\nu$ 3064, 2360, 1522, 1297, 1158, 1074, 1000, 763, 704; HRMS calcd for (M$^{+}$) $C_{13}H_8F_2N_2OS$: 278.0325, found 278.0329.

### *4.3.6. 2-Difluorophenylsulfanylmethyl-benzothiazole (**3bi**)*

**3bi** was obtained as a white solid in 62% yield by flash column chromatography; mp 93.5–94.0 °C; $^{1}$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.20 (d, $J$ = 8.0 Hz, 1H, Ar$H$), 7.93 (d, $J$ = 8.0 Hz, 1H, Ar$H$), 7.71 (d, $J$ = 7.0 Hz, 2H, Ar$H$), 7.57 (t, $J$ = 8.0 Hz, 1H, Ar$H$), 7.51–7.44 (m, 2H, Ar$H$), 7.39 (t, $J$ = 7.5 Hz, 2H, Ar$H$); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 162.6 (t, $^{2}J_{C\text{-}F}$ = 33.8 Hz), 152.4, 137.0, 135.4, 130.6, 129.3, 127.1, 126.9, 125.6 (t, $^{1}J_{C\text{-}F}$ = 125.0 Hz), 124.8, 122.0; $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ −66.73 (s, 2F); IR (cm$^{-1}$): $\nu$ 3059, 1510, 1244, 1057, 1019, 885, 689; HRMS calcd for (M$^{+}$) $C_{14}H_9F_2NS_2$: 293.0144, found 293.0141.

## Acknowledgements

This work was financially supported by the National Natural Science Foundation of China (Nos. 21072127 and 21032006) and the Science Foundation of Shanghai Municipal Commission of Sciences and Technology (10JC1405600).

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jfluchem.2011.08.008.

## References

[1] (a) J.P. Bégué, D. Bonnet-Delpon, Bioorganic and Medicinal Chemistry of Fluorine, Wiley-VCH, Weinheim, 2008;
(b) P. Kirsch, Modern Fluoroorganic Chemistry: Synthesis Reactivity, Applications, Wiley-VCH, Weinheim, 2004;
(c) K. Müller, C. Faeh, F. Diederich, Science 317 (2007) 1881–1886;
(d) N. Chauret, D. Guay, C. Li, S. Day, J. Silva, M. Blouin, Y. Ducharme, J.A. Yergey, D.A. Nicoll-Griffith, Bioorg. Med. Chem. Lett. 12 (2002) 2149–2152;
(e) T. Ohmine, T. Katsube, Y. Tsuzaki, M. Kazui, N. Kobayashi, T. Komai, M. Hagihara, T. Nishigaki, A. Iwamoto, T. Kimura, H. Kashiwase, M. Yamashita, Bioorg. Med. Chem. Lett. 12 (2002) 739–742;
(f) L.M. Yagupol'skii, K.I. Petko, Y.V. Tarasova, Zh. Org. Farm Khim. 2 (2004) 11–17;
(g) T. Tasaka, S. Takenaka, K. Kabu, Y. Morita, H. Okamoto, Ferroelectronics 276 (2002) 83–87.
[2] M.J. Tozer, T.F. Herpin, Tetrahedron 52 (1996) 8619–8683.
[3] (a) W.R. Dolbier, C.R. Burkholder, M. Medebielle, J. Flourine Chem. 95 (1999) 127–130;
(b) J.T. Zhu, H.B. Xie, Z.X. Chen, S. Li, Y.M. Wu, Chem. Commun. (2009) 2338–2340;
(c) S. Li, Y.F. Yuan, J.T. Zhu, H.B. Xie, Z.X. Chen, Y.M. Wu, Adv. Synth. Catal. 352 (2010) 1582–1586.
[4] (a) R.E. Banks, B.E. Smart, J.C. Tatlow (Eds.), Organofluorine Chemistry: Principles and Commercial Applications, Plenum Press, New York, 1994;
(b) K. Sato, M. Omote, A. Ando, I. Kumadaki, J. Fluorine Chem. 125 (2004) 509–515.
[5] F.L. Ge, Z.X. Wang, W. Wan, W.C. Lu, J. Hao, Tetrahedron Lett. 48 (2007) 3251–3254.
[6] H.Z. Jiang, S.J. Yuan, W. Wan, K. Yang, H.M. Deng, J. Hao, Eur. J. Org. Chem. 9 (2010) 4227–4236.
[7] R. Appel, R. Kleinstiick, Chem. Ber. 107 (1974) 5–12.
[8] C.R. Burkholder, W.R. Dolbier, M. Medebielle, J. Fluorine Chem. 109 (2001) 39–48.
[9] R.A. Rossi, A.B. Pierini, S.M. Palacios, in: D.D. Tanner (Ed.), Advances in Free-Radical Chemistry, vol. 1, JAI Press, Greenwich, CT, USA, 1990, pp. 193–252.
[10] Q.F. Wang, Y.Y. Mao, S.Z. Zhu, C.M. Hu, J. Fluorine Chem. 95 (1999) 141–143.