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

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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-

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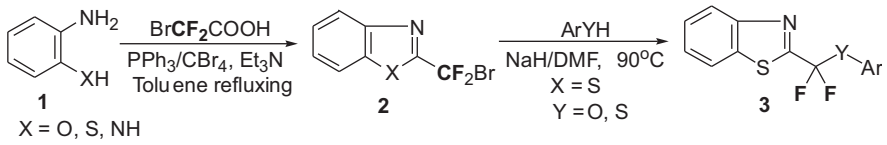
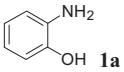
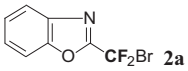
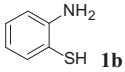
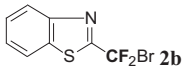
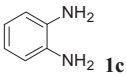
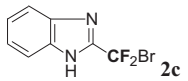
doi:10.1016/j.jfluchem.2011.08.008



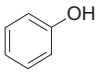
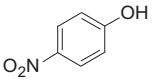
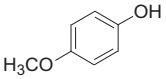
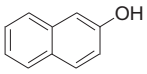
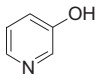
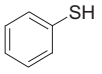
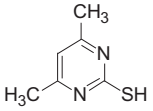
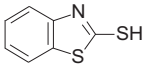
Scheme 1. Preparation of 2-bromodifluoromethyl benzo-1,3-diazoles and its application in the synthesis of *gem*-difluoromethylene linked aryl ethers.

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.

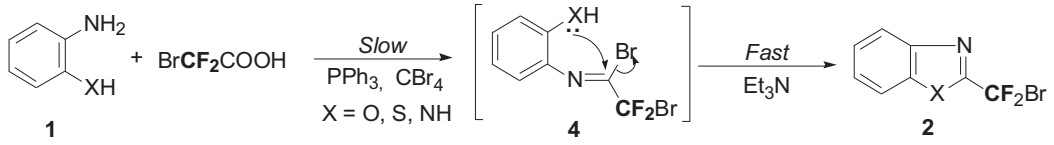
Table 2
The reaction of 2-bromodifluoromethyl benzothiazole **2b** with phenolates.

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.