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One-pot synthesis of 2-trifluoromethyl and 2-difluoromethyl substituted benzo-1,3-diazoles

Fenglian Ge,[a] Zengxue Wang,[a] Wen Wan,[a] Wencong Lu[a] and Jian Hao[a,b,*]

[a]*Department of Chemistry, Shanghai University, 99 Shangda Road, Shanghai 200444, China*
[b]*Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China*

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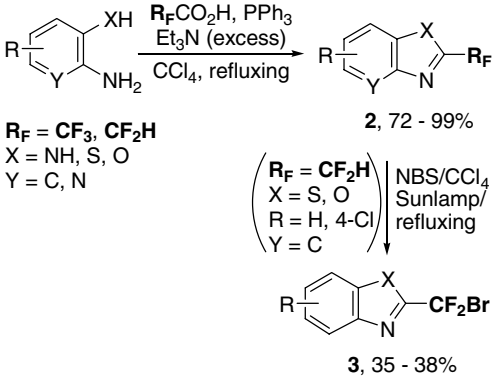
Abstract—2-Trifluoromethyl and 2-difluoromethyl substituted benzimidazole, benzoxazole and benzothiazole derivatives were efficiently prepared through a one-pot reaction of trifluoroacetic acid and difluoroacetic acid, respectively, with commercially available *o*-phenylenediamines, 2-aminophenols, and 2-aminobenzenethiols in good to excellent yields. Subsequential bromination of 2-difluoromethyl groups by photolysis with NBS led to the formation of bromodifluoromethyl benzo-1,3-diazoles which may be utilized to prepare the new generation of *gem*-difluoromethylene linked identical or non-identical twin molecules for drug synthesis.

Benzo-1,3-diazoles are a biologically important class of molecules and are widely used in pharmaceutical production. The studies of structure–activity relationship interestingly reveal that change of the structure of substituent group at C-2 position commonly results the change of its bioactivity. Among those 2-substituted benzo-1,3-diazole derivatives, 2-fluoroalkyl substituted molecules have already received considerable attention due to their potential bioactivities.[1,2] Some known compounds, such as 2-trifluoromethyl and 2-difluoromethyl substituted benzo-1,3-diazole derivatives were reported having the potential anti HIV-1 bioactivities.[3] However, to date, only a few methods have been developed for the synthesis of these important molecules. Most of these procedures are only applicable to the synthesis of certain type of benzo-1,3-diazole molecules. Many new types of 2-fluoroalkyl substituted benzo-1,3-diazole derivatives are still remain uninvestigated due to the lack of a general and mild synthetic approach. This encourage us to develop a general method which can be applied to synthesize a broad range of 2-fluoroalkyl substituted benzo-1,3-diazole derivatives for bioactivity screening.

As one part result from our ongoing research project for the synthesis and pharmaceutical applications of 2-fluoroalkyl substituted benzo-1,3-diazole derivatives, we wish to report a new application of Uneyama's preparation of fluorinated imidoyl chlorides[4] to the efficient synthesis of various 2-trifluoromethyl and 2-difluoromethyl substituted benzo-1,3-diazole derivatives via a rapid and mild one-pot intramolecular cyclization process. Subsequential bromination of 2-difluoromethyl benzo-1,3-diazole products by the photolysis with NBS leads to the formation of bromodifluoromethyl benzo-1,3-diazoles, which provides us an opportunity to access and design a new generation of corresponding *gem*-difluoromethylene linked identical or non-identical twin molecules for drug synthesis (Scheme 1).[5]



Scheme 1. Synthetic route to 2-fluoroalkyl substituted benzo-1,3-diazole derivatives and 2-bromodifluoromethyl benzo-1,3-diazoles.

Keywords: Fluorinated benzo-1,3-diazoles; Fluorinated carboxylic acids; Fluorinated heterocycles; Bromination; Synthesis.
* Corresponding author. Tel./fax: +86 21 6613 3380; e-mail: jhao@mail.shu.edu.cn

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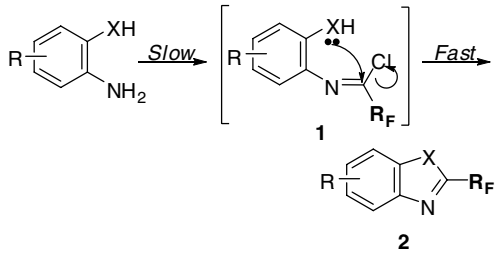
Our initial inspiration came from the electrophilicity of imino group of fluorinated *N*-aryl imidoyl chloride. It was supposed that the intramolecular nucleophilic substitution should occur if there is a nucleophilic substituent (–XH in **1**, Scheme 2) presented at the *ortho* position on benzene ring in *N*-aryl imidoyl chloride intermediate (**1**), and lead to the formation of 2-fluoroalkyl benzo-1,3-diazole derivatives (**2**).



Scheme 2. Postulated mechanism of intramolecular cyclization.

This consideration was experimentally proved when the excess amount of triethylamine was employed in reaction system, and successfully formed 2-trifluoromethyl benzimidazole (**2a**) in our first trial. After that, this method was extended to the synthesis of various 2-fluoroalkyl substituted benzo-1,3-diazole derivatives in good to excellent yields under mild condition (Table 1).

It is assumed that the imidoyl chloride intermediate (**1**) is initially formed under Uneyama's condition. Once **1** is formed, the subsequential intramolecular nucleophilic substitution by neighboring group (–XH) under basic condition rapidly occurred to form the desired product **2** (Scheme 2). Although the substituent group R does

Table 1. Synthesis of 2-fluoroalkyl substituted benzo-1,3-diazole derivatives **2**[a]

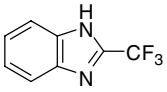
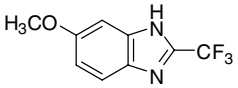
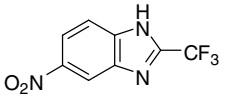
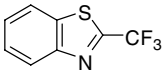
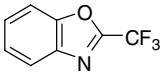
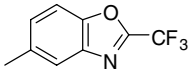
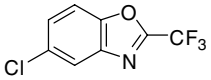
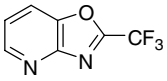
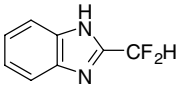
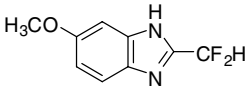
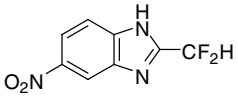
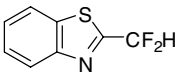
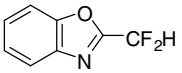
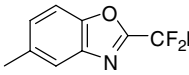
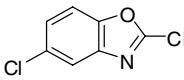
Entry	R_F	X	Y	R	Product **2**	Yield (%)
1	CF_3	NH	C	H	 **2a**	87
2	CF_3	NH	C	4-OCH_3	 **2b**	91
3	CF_3	NH	C	4-NO_2	 **2c**	78
4	CF_3	S	C	H	 **2d**	72
5	CF_3	O	C	H	 **2e**	91
6	CF_3	O	C	4-CH_3	 **2f**	90
7	CF_3	O	C	4-Cl	 **2g**	89
8	CF_3	O	N	H	 **2h**	82
9	CF_2H	NH	C	H	 **2i**	84
10	CF_2H	NH	C	4-OCH_3	 **2j**	89
11	CF_2H	NH	C	4-NO_2	 **2k**	77

Table 1 (*continued*)

Entry	R_F	X	Y	R	Product **2**	Yield (%)
12	CF_2H	S	C	H	 **2l**	85
13	CF_2H	O	C	H	 **2m**	98
14	CF_2H	O	C	$4\text{-}CH_3$	 **2n**	99
15	CF_2H	O	C	4-Cl	 **2o**	92

[a] The yields listed in this table are isolated yields.

not affect the yield of **2** too much, electron-releasing properties of R groups are found to be propitious to this cyclization. The position of R group in benzimidazole products is affirmed by the X-ray crystallographic assignment.

Electron-releasing group, such as methoxyl group, enhances the nucleophilicity of its *para*-amino group to form the imidoyl chloride intermediate (**1**) with priority. The following intramolecular cyclization leads to the formation of **2** with substituent group at 6-position (**2b**, Fig. 1). In contrast, the electron-withdrawing group, such as nitro group, significantly reduces the electron density of *N*-electron lone-pair of its *para*-amino group and diminishes the nucleophilicity of this amino group. Instead, the neighboring amino group participates the reaction to form the corresponding imidoyl chloride intermediate (**1**) with priority. The following intramolecular cyclization leads to the formation of **2** with substituent group at 5-position (**2c**, Fig. 1).[†]

The calculations of total energy and dipole moment of **2b** and **2c** by using the MM+ force field also revealed that **2b** (methoxyl group at 6-position) and **2c** (nitro group at 5-position) are relatively more stable thermodynamically than corresponding compounds with methoxyl group at 5-position and nitro group at 6-position, respectively. No compound with methoxyl group at 5-position or with nitro group at 6-position was detected experimentally.

The reaction of this one-pot synthesis is generally fast and clean. Interestingly, 2-amino-3-hydroxypyridine also yielded 2-(trifluoromethyl)oxazolo[4,5-*b*]pyridine (**2h**, Table 1, entry 8) in 82% yield. This result gives us an information that this approach is possibly applicable to synthesize other interested heterocyclic ring fused 1,3-diazole molecules besides those benz-fused ones.

[†] CCDC 631281 and 631282 contain the Supplementary Crystallographic Data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

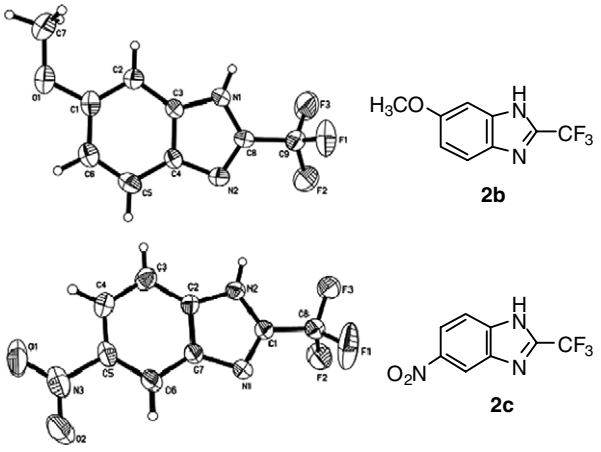
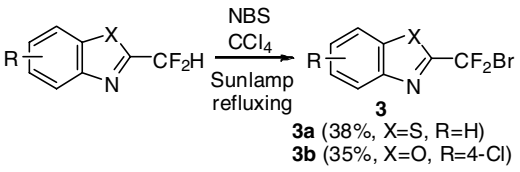


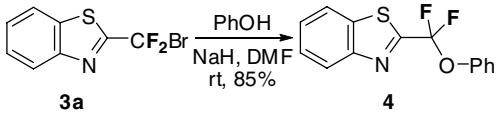
Figure 1. ORTEP diagram of **2b** and **2c**.

Among those products we described here, 2-difluoromethyl substituted benzo-1,3-diazole molecules attracted us much more attention. It is not only because of the potential bioactivities themselves but also the potential application to synthesize the *gem*-difluoromethylene linked identical or non-identical twin molecules which contain the benzo-1,3-diazole moiety. C–H bond activation of difluoromethyl group is a key issue in this assignment. Our previous experience from bromination of other fluorine-containing arenes encouraged us to test the photolytic bromination of 2-difluoromethyl substituted benzo-1,3-diazoles though there is no successful report on the bromination of difluoro-methyl group in benz-fused 1,3-diazole molecules.[3d]

The initial test of bromination of 2-difluoromethyl benzothiazole with NBS under UV irradiation in quartz glass reactor failed to get any products. Fortunately, the bromination of difluoromethyl group finally succeeded while sunlamp was used to replace the UV lamp though the yield was still low. The same condition was also applied to the bromination of 2-difluoromethyl benzoxazole and formed the desired brominated product (Scheme 3).



Scheme 3. Bromination of CF_2H group with sunlamp.



Scheme 4. Reaction of **3a** with sodium phenolate.

It should be pointed out that directly using the commercially available bromodifluoroacetic acid instead of difluoroacetic acid in the synthesis of **2** will also yield the 2-bromodifluoromethyl substituted benzo-1,3-diazole products. However, the cost will be significantly increased because of the higher retail price of bromodifluoroacetic acid. It is worth mentioning that this bromination method is also possibly applicable to other difluoromethyl substituted heterocycles. The optimization and generality of this method is currently under investigation.

The prime results from the reaction of 2-bromodifluoromethyl benzothiazole with phenol in the presence of NaH in DMF successfully yielded the *gem*-difluoromethylene linked product **4** (Scheme 4). Reaction is considered going through a SET mechanism.[3c] The typical S_N2 process of **3a** with nucleophile, such as NaCN in methanol failed to give the desired product.

This SET displacement of bromine atom provides a possibility to synthesize various biologically interested *gem*-difluoromethylene linked new generation of identical and non-identical twin drugs.[5]

In summary, 2-trifluoromethyl and 2-difluoromethyl substituted benzo-1,3-diazole derivatives were successfully prepared through a facile one-pot synthesis from commercially available trifluoroacetic acid and difluoro-acetic acid, respectively, with *o*-phenylenediamines, 2-aminophenols and 2-aminobenzenethiols in good to excellent yields. The bromination of 2-difluoromethyl benzo-1,3-diazoles by photolysis with NBS led to the formation of bromodifluoromethyl benzo-1,3-diazoles. This approach provides us with the possibility to explore and build up various biologically interested *gem*-difluoromethylene linked identical and non-identical twin drug molecules.

Acknowledgments

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