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A highly efficient TBAF-promoted intramolecular cyclization of *gem*-dibromoolefins for the synthesis of 2-bromobenzofurans(thiophenes)†

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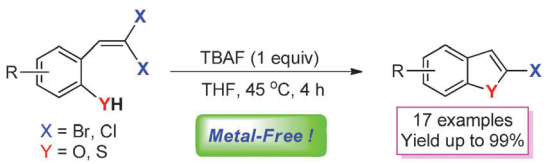
A highly efficient tetra-(*n*-butyl)ammonium fluoride (TBAF)-promoted intramolecular cyclization of *gem*-dibromoolefins has been developed for the synthesis of 2-bromobenzofused heterocycles. The reaction provides a convenient approach to 2-bromobenzofurans(thiophenes) from the corresponding readily available *gem*-dibromovinyl substrates without a metal.

Halogenated organic compounds have been widely used as important building blocks in organic synthesis, materials science, and the chemical industry in view of their activity and ease of derivatization.[1] In particular, halogenated heterocycles are of important value mainly due to their cross-coupling reactions of carbon–halide bonds with various nucleophiles for the formation of heteroaromatic derivatives of interest in biology, pharmacology, optics, and electronics fields.[2] The synthesis of halogenated heterocycles is accomplished normally by the direct electrophilic halogenation of heterocycles in the presence of a Lewis acid catalyst. However, apart from the method involving hazardous, toxic, and corrosive electrophilic halogen sources and catalysts which further limit their applications in large-scale transformations for environmental reasons, the conventional electrophilic halogenation reactions typically provide 3-halogenated substrates for benzofused five-membered heterocycles, such as benzofurans, benzothiophenes, and indoles. Therefore, development of an environmentally benign method with high selectivity for the preparation of 2-halogenated benzofused heterocycles from the readily available starting materials is highly desirable.

The versatility of *gem*-dihaloolefins, owing to higher reactivity and easy accessibility from inexpensive aldehydes, has been exploited,[3] notably, as a key unit for the synthesis of various heterocycles such as indoles,[4] benzothiophenes,[5] benzofurans,[4i,5b,6] isocoumarins,[7] and other heterocycles[8] through transition-metal-catalyzed tandem Ullman-type or Suzuki–Miyaura coupling/amination, Suzuki, Sonogashira, Heck, or C–H activation. Most recently, Lautens and co-workers elegantly utilized CuI-catalyzed intramolecular cross-coupling reactions of 2-(*gem*-dibromovinyl)-phenols(thiophenols) for the preparation of 2-bromobenzofurans-(thiophenes), and $Pd(OAc)_2$/P(*t*-Bu)$_3$-catalyzed intramolecular cross-coupling reactions of 2-(*gem*-dibromovinyl)anilines for the synthesis of 2-bromoindoles.[5b,9] It expanded the scope of the versatility of *gem*-dihaloolefins and provided a new and practical straightforward route to 2-halogenated benzofused heterocycles, which are significant synthetic intermediates that can be used for carbon–carbon and carbon–heteroatom bond formation *via* transition-metal-catalyzed cross-coupling reactions.

Herein, we wish to report a tetra-(*n*-butyl)ammonium fluoride (TBAF)-promoted intramolecular cyclization of *gem*-dibromoolefins for the synthesis of 2-bromobenzofused heterocycles. The reactions generated 2-bromobenzofurans and 2-bromobenzothiophenes from the corresponding readily available *gem*-dibromovinyl substrates in high efficiency and excellent selectivity under metal-free reaction conditions, which can overcome the drawbacks of their expensive, poisonous, and air-sensitive properties.[10] In addition, this mild, operationally simple methodology can also be readily extended to synthesis of 2-chlorobenzofuran (Scheme 1).

In our attempt to prepare 2-(bromoethynyl)phenol from 2-(*gem*-dibromovinyl)phenol according to the elimination reaction utilizing TBAF·3H_2O reported in the literature,[11] 2-bromobenzofuran was obtained but no 2-(bromoethynyl)-phenol was detected during our investigation. When a reaction of 2-(*gem*-dibromovinyl)phenol was carried out in the presence of TBAF·3H_2O (1.0 equiv.) in THF at 45 °C for 4 h, to our delight, 2-bromobenzofuran was obtained in 98% isolated yield. This result aroused our great interest, because it not only developed an alternative halogenation route to 2-bromobenzofurans, but also could be expanded to the synthesis of 2-bromobenzothiophenes. The biggest advantages of the reaction are avoiding corrosive and irritant halogen sources used in the reaction, as well as resolving the regio-selectivity of the general electrophilic halogenation reactions, which in some cases



Scheme 1

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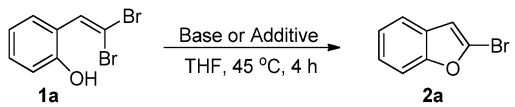
generate a mixture of mono- and multi-halogenated products that are difficult to separate.

To establish the feasibility of our approach to 2-bromobenzofurans and 2-bromobenzothiophenes, a model conversion of 2-(*gem*-dibromovinyl)phenol (**1a**) into the corresponding 2-bromobenzofuran (**2a**) promoted by a variety of organic and inorganic bases or additives under metal-free reaction conditions was explored. As listed in Table 1, a base is essential for the model reaction and TBAF is the best one among the examined bases. Either the commercially available solid TBAF·3H_2O or TBAF solution in THF (commercially available as a 1.0 M solution in THF, also containing approximately 5% water) was an effective promoter in the model reaction. It also indicated that the presence of water in TBAF had little effect on the reaction (Table 1, entries 1 and 2). When other organic or inorganic bases, such as K_3PO_4, K_2CO_3, ^{t}BuOLi, Et_3N, or pyridine, were used instead of TBAF in the xmodel reaction, no desired product **2a** was isolated (Table 1, entries 3–7). However, the analogues of TBAF, tetra-(*n*-butyl)-ammonium chloride (TBAC), tetra-(*n*-butyl)ammonium bromide (TBAB), tetra-(*n*-butyl)ammonium iodide (TBAI), tetra-(*n*-butyl)-ammonium hydroxide (TBAH), and tetra-(*n*-butyl)ammonium acetate (TBA·OAc) were ineffective promoters in the reaction (Table 1, entries 8–12). It is reasonable to speculate that a fluoride anion is an efficacious basic activator for the intramolecular cyclization of **1a** because TBAF is a good candidate for a fluoride anion source. However, neither KF nor CsF as a fluoride anion source promoted the model reaction very well and over 85% of the starting material **1a** was recovered (Table 1, entries 13 and 14). With the combination of TBAC–CsF, TBAB–CsF, TBAI–CsF, TBA·OH–CsF, and TBA·OAc–CsF in 1 : 1 molar ratios, 33–89% yields of desired product **2a** were obtained (Table 1, entries 15–19). It appears that both a soluble cation and an F anion are important. With respect to the TBAF loading, 1 equiv. of TBAF was found to be optimal. When less than 1 equiv. of TBAF was used, the reaction did not proceed to completion. No significant improvement of product yield was observed with more than 1 equiv. of TBAF, which could enhance the reaction (Table 1, entries 20–22). By changing different TBAF–CsF molar ratios, such as TBAF–CsF (0.3 : 1 equiv.), TBAF–CsF (0.5 : 1 equiv.) and TBAF–CsF (1 : 1 equiv.), 50, 65 and 99% yields of **2a** were isolated, respectively (Table 1, entries 23–25). Thus, a stoichiometric amount of TBAF is necessary in the reaction.

Table 1 The effect of a base or an additive on the intramolecular cyclization of 2-(*gem*-dibromovinyl)phenol (**1a**)[a]



1a **2a**

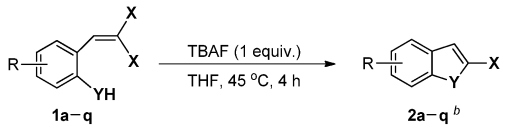
Entry	Base or additive	Yield[b] (%)
1	tetra-Butylammonium fluoride (TBAF)·3H_2O (1 equiv.)	98
2	TBAF·THF (1 equiv.)	99
3	K_3PO_4 (1 equiv.)	N.R.
4	K_2CO_3 (1 equiv.)	N.R.
5	^{t}BuOLi (1 equiv.)	N.R.
6	Et_3N (1 equiv.)	N.R.
7	Pyridine (1 equiv.)	N.R.
8	tetra-Butylammonium chloride (TBAC) (1 equiv.)	Trace
9	tetra-Butylammonium bromide (TBAB) (1 equiv.)	Trace
10	tetra-Butylammonium iodide (TBAI) (1 equiv.)	Trace
11	tetra-Butylammonium hydroxide (TBAH) (1 equiv.)	Trace
12	tetra-Butylammonium acetate (TBA·OAc) (1 equiv.)	Trace
13	KF (1 equiv.)	8
14	CsF (1 equiv.)	12
15	TBAC–CsF (1 : 1 equiv.)	89
16	TBAB–CsF (1 : 1 equiv.)	82
17	TBAI–CsF (1 : 1 equiv.)	65
18	TBA·OH–CsF (1 : 1 equiv.)	46
19	TBA·OAc–CsF (1 : 1 equiv.)	33
20	TBAF (0.75 equiv.)	78
21	TBAF (0.5 equiv.)	58
22	TBAF (2.0 equiv.)	99[c]
23	TBAF–CsF (0.3 : 1 equiv.)	50
24	TBAF–CsF (0.5 : 1 equiv.)	65
25	TBAF–CsF (1 : 1 equiv.)	99

[a] Reaction conditions: 2-(*gem*-dibromovinyl)phenol (**1a**, 1.0 mmol), a base or an additive (amount indicated in parentheses), THF (2.0 mL) at 45 °C for 4 h. [b] Isolated yield. [c] At room temperature for 4 h.

The choice of solvent was also important and different solvents were examined for the intramolecular cyclization of 2-(*gem*-dibromovinyl)phenol (**1a**). The results indicated that the cyclization of **1a** in a polar aprotic solvent was generally better than that in a non-polar aprotic solvent. However, the intramolecular cyclization reaction did not occur in polar protic solvents such as H_2O, C_2H_5OH and *n*-C_4H_9OH. Because of the good solubility of TBAF in THF, THF was chosen as the reaction medium for the cyclization reaction (see ESI† for details). During the course of our further optimization of the reaction conditions, the reaction was completed in 4 h at 45 °C.

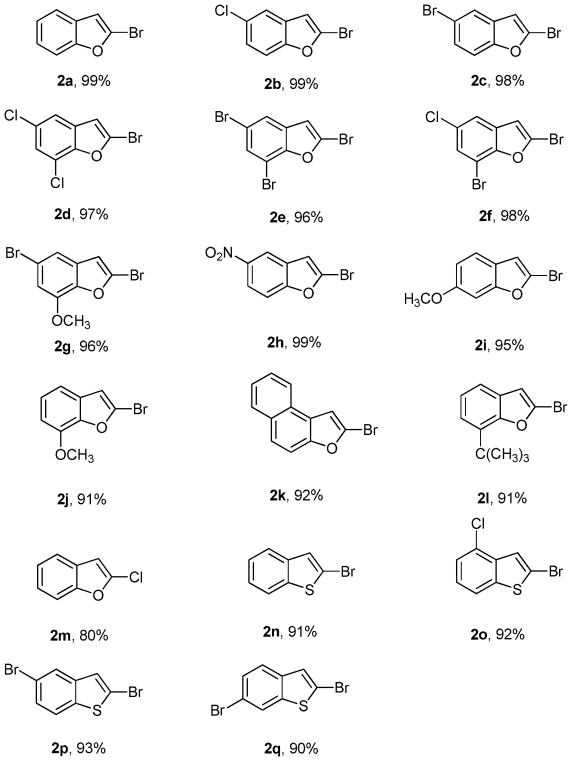
Having established our approach for the preparation of **2a**, we decided to investigate the reaction scope under the optimized reaction conditions, which involved 1.0 equiv. of TBAF in THF at 45 °C for 4 h. A variety of 2-(*gem*-dibromovinyl)phenols bearing substituents on the benzene rings were examined and the results are summarized in Table 2. As shown in Table 2, a variety of functional groups, including electron-donating and electron-withdrawing ones, were tolerated under the present mild reaction conditions, and provided the desired cyclization products in nearly quantitative yields. Halogen substituents, either Cl or Br, as well as either mono-halogen or di-halogens on the benzene rings underwent the clean conversions and afforded very high yields of the corresponding di- or multi-halogenated benzofurans **2b–g** (Table 2), which are the potentially versatile building blocks in organic synthesis and can provide the opportunities for further transformation through transition metal-catalyzed cross-coupling reactions with various nucleophiles. 2-(*gem*-Dibromovinyl)-phenol with a strong electron-withdrawing functionality, such as NO_2, on the phenol gave a superior product (**2h**) yield to that of **2i** and **2j**, with a strong electron-donating group, such as OCH_3 on the phenols (Table 2). Meanwhile, a little *ortho*-position effect has been observed in the reaction (**2i** *vs.* **2j**). Under the recommended reaction conditions, 1-(*gem*-dibromovinyl)-2-naphthalenol also underwent the intramolecular cyclization well to generate the corresponding product **2k** in 92% yield. It is important to note that even the sterically hindered substituted 2-(*gem*-dibromovinyl)phenol (**1l**) also gave the corresponding product **2l** in 91% isolated yield. Notably, 2-(*gem*-dichlorovinyl)-phenol (**1m**) also could proceed the intramolecular cyclization to generate the corresponding 2-chlorobenzofuran (**2m**) in good yield under the present reaction conditions.

Table 2 Synthesis of 2-bromo(chloro)benzofurans(thiophenes) through TBAF-promoted intramolecular cyclization of **1**[a]



1a–q X = Br, Cl; Y = O, S

2a–q [b]



[a] Reaction conditions: **1** (1.0 mmol), TBAF (1.0 mmol), THF (2.0 mL) at 45 °C for 4 h. [b] Isolated yields.

To demonstrate the general applicability of the reaction system for synthesis of 2-halogenated benzofurans, we would like to extend this methodology to synthesize 2-bromobenzothiophenes and 2-bromoindoles. As anticipated, the intramolecular cyclizations of 2-(*gem*-dibromovinyl)thiophenol (**1n**) and substituted 2-(*gem*-dibromovinyl)thiophenols, such as **1o**, **1p** and **1q**, proceeded very well to give the corresponding products, with 2-bromobenzothiophene (**2n**), **2o**, **2p** and **2q**, in 90–93% yields under the present reaction conditions (Table 2). It was obvious that the electronic and steric effect of substituted groups on benzene rings had little impact on the yields of the products. It also provides an alternative route to 2-bromobenzothiophenes using commercially available materials in a simple metal-free protocol. However, the present reaction conditions were not suitable for the synthesis of 2-bromoindoles from the corresponding 2-(*gem*-dibromovinyl)aniline, 2-(*gem*-dibromovinyl)-*N*-acetylaniline, 2-(*gem*-dibromovinyl)-*N*-trifluoroacetylaniline and 2-(*gem*-dibromovinyl)-*N*-Boc-aniline.

The prepared 2-bromobenzofuran (**2a**) was then reacted with phenylboronic acid and phenylacetylene to generate the corresponding cross-coupling products in high yields under the Suzuki and Sonogashira reaction conditions,[4d,6] respectively (see ESI† for details).

In conclusion, we have developed a highly efficient TBAF-promoted intramolecular cyclization of *gem*-dibromoolefins for the synthesis of 2-bromobenzofused heterocycles. The reactions generated 2-bromobenzofurans and 2-bromobenzothiophenes from the corresponding readily available *gem*-dibromovinyl substrates in nearly quantitative yields. In addition, this mild, operationally simple methodology can also be readily extended to synthesis of 2-chlorobenzofuran. The present method has advantages of availability of reagents, broad substrate scope, operational simplicity, mild reaction conditions, high regioselectivity, excellent yields of the products, and metal-free reaction conditions. The detailed mechanistic study and further investigation on metal-free reactions is currently underway.

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