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Bromodifluoromethylation of heteroaromatics with sodium bromodifluoromethanesulfinate

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ABSTRACT

The bromodifluoromethylation of heteroaromatics (benzofuran, benzo[*b*]thiophene, and 2*H*-chromen-2-one) with sodium bromodifluoromethanesulfinate ($BrCF_2SO_2Na$) was developed. This reaction proceeded smoothly at room temperature to afford the bromodifluoromethylated products in moderate to high yields.

The growing presence of fluorine in pharmaceuticals and agrochemicals[1] has stimulated renewed interest in methods for the preparation of fluorine-containing compounds.[2] Bromodifluoromethylated compounds are well known as good candidates for the formation of halogen bonding[3] and important intermediates of the preparation of valuable fluorinated compounds.[4] Especially, bromodifluoromethylated aromatics have served as precursors of [^{18}F]trifluoromethylated compounds for positron emission tomography (PET) imaging.[5] Despite the importance of bromodifluoromethylated aromatics, only a few methods are available for the synthesis of these compounds. Normally, these compounds are prepared by bromination of fluorine-containing compounds (Scheme 1a)[6] and transformation from CF_2Br-containing building blocks (Scheme 1b).[7] In 2014, Shiosaki and Inoue reported a bromodifluoromethylation of aromatic Grignard reagents bearing electron-withdrawing groups with CF_2Br_2 (Scheme 1c).[8] However, this reaction involves a difluorocarbene-mediated mechanism. The direct incorporation of bromodifluoromethyl group into aromatic substrates still remains a big challenge.

Recently, impressive progress has been made in the radical trifluoromethyltion with different trifluoromethylating reagents.[9] As a typical radical trifluoromethylating reagent, sodium trifluoromethanesulfinate (CF_3SO_2Na) has attracted a lot of attention for the preparation of trifluoromethylated compounds.[10] Encouraged by these achievements, we anticipated that a similar reagent, sodium bromodifluoromethanesulfinate ($BrCF_2SO_2Na$), might be used as a radical bromodifluoromethylating reagent in the presence of an oxidant. Although $BrCF_2SO_2Na$ has been reported for more than twenty years,[11] its application has been largely unexplored.[12] As part of our continuing research interest in fluoroalkylation of aromatic compounds,[13] herein we describe a direct bromodifluoromethylation of heteroaromatics with $BrCF_2SO_2Na$ in the presence of *tert*-butylhydroperoxide (TBHP) (Scheme 1d). This reaction provided a convenient approach to CF_2Br-containing heteroaromatics.

We initiated our investigation on the reaction of benzofuran **1a** with $BrCF_2SO_2Na$ and TBHP at room temperature (Table 1). The reaction was sensitive to solvent choice. Among the common organic solvents including DCM, CH_3CN, MeOH, acetone, and DMF, CH_3CN was most effective to afford the bromodifluoromethylated product **2a** in 32% yield (entries 1–5). HOAc led to a moderate yield of 54% (entry 6). To our delight, the yield was further improved by using binary solvent mixture (entries 7–10). The highest yield was observed in the mixture of CH_3CN and $CHCl_3$ with a ratio of 1:2 (entry 10). To further improve the reaction yield, different additives, such as CuCl or K_2CO_3, were investigated (entries 11 and 12). However, they had a negligible effect on the reaction. Finally, the reaction temperature was screened, and neither lower (0 °C) nor higher temperature (50 °C) could improve the outcome (entries 13 and 14). Notably, none of the desired products could be detected in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO),

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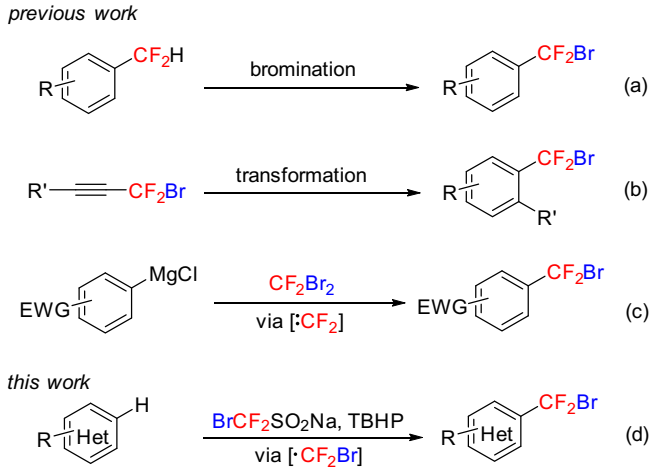
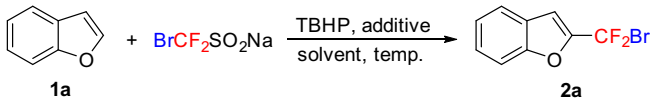


Scheme 1. Different approaches to bromodifluoromethylated aromatics.

which indicated that a radical process was probably involved in this reaction (enrty 15).

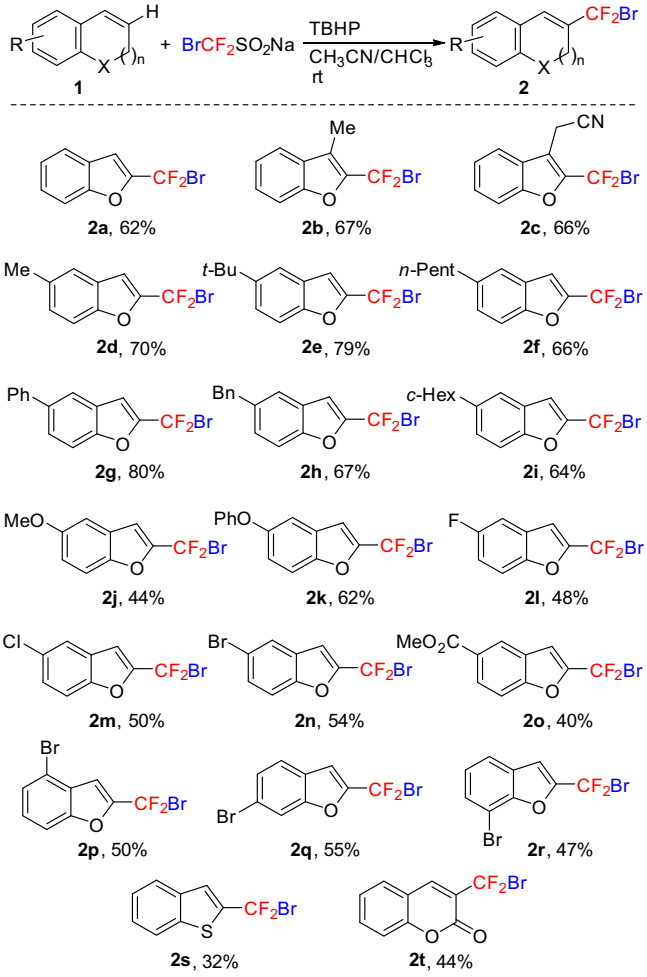
With the optimized reaction conditions in hand (Table 1, entry 10), we next examined the substrate scope of this radical bromodifluoromethylation reaction (Scheme 2). Substrates **1b**–**r** bearing either electron-donating or electron-withdrawing groups at different positions of the benzofuran ring reacted smoothly with $BrCF_2SO_2Na$ to afford the corresponding bromodifluoromethylated products in moderate to high yields. In general, the electron-rich substitutions resulted in slightly higher yields, whereas the electron-poor substitutions gave lower yields. It was noteworthy that chloro- or bromo-containing substrates (**1m**, **1n**, and **1p**–**r**) were compatible with the reaction, thus enabling further transformations via transition-metal-catalyzed cross-coupling reactions. Importantly, this bromodifluoromethylation reaction could also be extended to other heterocycles, such as benzo[*b*]thiophene (**1s**) and 2*H*-chromen-2-one (**1t**), although the desired products were obtained in low yields. In the cases of other substrates,

Table 1
Optimization of reaction conditions[a]



Entry	Additive	Solvent	Temp	Yield[b] (%)
1[c]	—	DCM	Rt	8
2	—	CH_3CN	Rt	32
3	—	MeOH	Rt	3
4	—	Acetone	Rt	11
5	—	DMF	Rt	3
6	—	HOAc	Rt	54
7	—	DCM/MeOH (1:1)	Rt	57
8	—	DCM/CH_3CN (1:1)	Rt	59
9	—	$CH_3CN/CHCl_3$ (1:1)	Rt	62
10	—	$CH_3CN/CHCl_3$ (1:2)	Rt	68
11	CuCl	$CH_3CN/CHCl_3$ (1:2)	Rt	Trace
12	K_2CO_3	$CH_3CN/CHCl_3$ (1:2)	Rt	6
13	—	$CH_3CN/CHCl_3$ (1:2)	0 °C	4
14	—	$CH_3CN/CHCl_3$ (1:2)	50 °C	52
15[c]	—	$CH_3CN/CHCl_3$ (1:2)	Rt	0

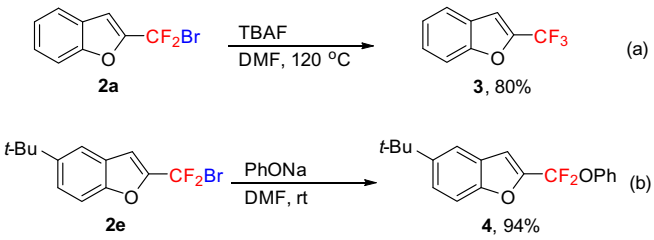
[a] Reactions were carried out using **1a** (0.2 mmol), $BrCF_2SO_2Na$ (0.4 mmol, 2.0 equiv) and additive (0.2 mmol, 1.0 equiv) in solvent (2.0 mL) for 16 h.
[b] Yields were determined by ^{19}F NMR spectroscopy of the crude reaction mixture using benzotrifluoride as an internal standard.
[c] TEMPO (0.4 mmol, 2.0 equiv) was added.



Scheme 2. Direct bromodifluoromethylation of heteroaromatics.

including methoxybenzene, furan, thiophene, and pyridine, low conversion was observed. When 1*H*-indene was subjected to the standard conditions, the reaction became complex. These results showed that both of the phenyl ring and the heteroatom in heteroaromatics were crucial to this reaction.

The characterization and assignment of products **2** was ascertained by comparing the spectral characteristics with the corresponding trifluoromethylated products reported earlier through similar reaction sequences.[10f,14] Furthermore, treatment of **2a** with TBAF gave a known trifluoromethylated product **3**,[13a,15] which further confirms the structure of **2** (Scheme 3a). Additionally, the reaction of **2e** and PhONa in DMF at room temperature afforded (aryloxy)difluoromethylated product **4** in high yield (Scheme 3b). These transformations demonstrated the



Scheme 3. Transformation of bromodifluoromethylated products.

utility of this protocol for the preparation of other fluoroalkylated compounds.

In summary, we have developed an efficient bromodifluoromethylation of benzofurans, benzo[*b*]thiophene, and 2*H*-chromen-2-one with $BrCF_2SO_2Na$. The work represents the first example of using $BrCF_2SO_2Na$ as bromodifluoromethylating reagent. The application of $BrCF_2SO_2Na$ in other bromodifluoromethylation reactions is in progress in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.04.095.

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