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Difluoromethylation of *N*-arylsulfonyl hydrazones with difluorocarbene leading to difluoromethyl aryl sulfones†

Qu-Tong Zheng,‡[abc] Yun Wei,‡[abc] Jian Zheng,[c] Ya-ya Duan,[c] Gang Zhao,[c] Zong-Bao Wang,[ab] Jin-Hong Lin,*[c] Xing Zheng*[ab] and Ji-Chang Xiao*[abc]

The difluoromethylation of *N*-arylsulfonyl hydrazones with difluorocarbene generated from difluoromethylene phosphobetaine ($Ph_3P^+CF_2CO_2^-$) to give various difluoromethyl aryl sulfones is described.

The past decades have witnessed significant advances in the chemistry of difluorocarbene.[1] As a singlet carbene, difluorocarbene exhibits moderate electrophilicity due to both the electron-withdrawing nature and the electron-donating resonance effect of the fluorine element.[1e] Difluorocarbene has proven to be an important intermediate in organic synthesis and has found widespread application in a variety of organic transformations, such as [2 + 1] cycloaddition,[2] difluoromethylation[1d,3] and trifluoromethylation reactions.[4] Recently, Hu *et al.*,[5] Wang *et al.*,[6] and our group[7] have independently disclosed that difluorocarbene can undergo cross-coupling with diazo compounds to give *gem*-difluoroolefins. These approaches require that the diazo compounds should be stable enough to be prepared and isolated. In order to make these methods more practically useful, it is necessary to investigate the coupling reaction with unstable diazo compounds. Since *N*-tosylhydrazones are stable and have served as efficient precursors of unstable diazo compounds,[8] it is reasonable to speculate that difluorocarbene and *N*-tosylhydrazones should be able to undergo coupling reaction to afford *gem*-difluoroolefins. However, we found that a difluoromethylation reaction instead of the coupling process occurred to furnish difluoromethyl aryl sulfones.

As a frequently used nucleophilic difluoroalkylation agent, difluoromethyl phenyl sulfone ($PhSO_2CF_2H$) has been widely applied to a large number of conversions.[1d,9] This sulfone is able to act not only as a "$PhSO_2CF_2^-$"equivalent[10] and a "CF_2H^-" equivalent,[11] but also as a "CF_2^{2-}" equivalent.[12] It can be reasoned that the modification of the phenyl group may give sulfones with better reactivity. But the modification of the structure remains largely unexplored. Besides, the conventional methods for the preparation of the sulfone require the use of gases HCF_2Cl[13] or volatile reagent F_2CBr_2,[14] or suffer from the tedious synthetic procedures. Herein, we describe the difluoromethylation of *N*-arylsulfonyl hydrazones with difluorocarbene leading to difluoromethyl aryl sulfones. The difluorocarbene precursor, difluoromethylene phosphobetaine ($Ph_3P^+CF_2CO_2^-$, PDFA), which was developed by us recently[7,15] and applied by other groups,[16] was found to be quite efficient for this difluoromethylation process. The reactions were convenient to afford various difluoromethyl aryl sulfones.

Previously, we have shown that low-polarity solvents are favorable for the generation of difluorocarbene from PDFA.[15b] Cyclohexane was then used as the reaction solvent in our initial attempt at the difluoromethylation of *N*-tosylhydrazone **1a**. The conversion in the presence of base at 90 °C was successful to afford the desired product albeit in a low yield (Table 1, entry 1). Polar solvents almost completely suppressed the expected transformation (Table 1, entries 2–3). But highly polar solvents such as CH_3CN and DMF could also afford product **2a** (Table 1, entries 4–5), probably because these solvents may stabilized some reaction intermediates. A brief survey of the bases (Table 1, entries 6–10) revealed that $CsHCO_3$ was the suitable choice (Table 1, entry 9). Decreasing the loading of PDFA and base led to the decrease in the yield (Table 1, entry 11 *vs.* 9). The yield was increased by increasing the loading of PDFA and base (Table 1, entries 12–13 *vs.* 9). Due to the low solubility of $CsHCO_3$ in cyclohexane, $CsHCO_3$ has to be used in a large excess. The use of 8 equiv. of $CsHCO_3$ gave product **2a** in 77% yield (entry 13). The

[a]*Institute of Pharmacy and Pharmacology, University of South China, 28 Western Changsheng Road, Hengyang, Hunan,421001, China. E-mail: zhengxing5018@yahoo.com*

[b]*Hunan Province Cooperative Innovation Center for Molecular Target New Drug Study, 28 Western Changsheng Road, Hengyang, Hunan,421001, China*

[c]*Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China. E-mail: jlin@sioc.ac.cn; jchxiao@sioc.ac.cn; Fax: +86-21-6416-6128; Tel: +86-21-5492-5340*

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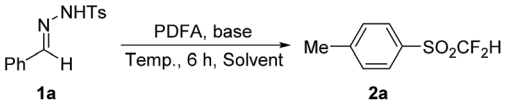
‡ These authors contributed equally to this work.

Table 1 Screening reaction conditions



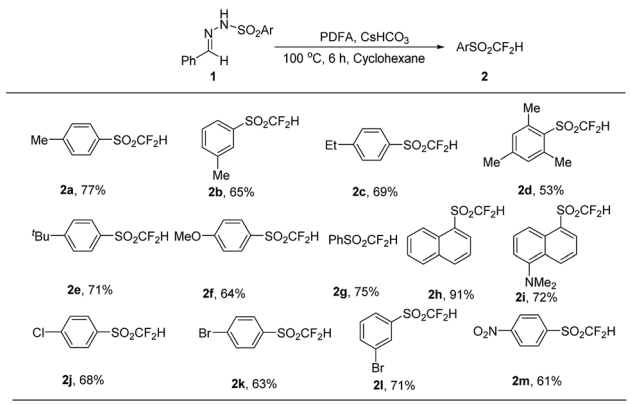
1a 2a

Entry	Temp. (°C)	Base	Ratio[a]	Solvent	Yield[b] (%)
1	90	Cs_2CO_3	1 : 1.5 : 2	Cy[c]	22
2	90	Cs_2CO_3	1 : 1.5 : 2	THF	Trace
3	90	Cs_2CO_3	1 : 1.5 : 2	EA	Trace
4	90	Cs_2CO_3	1 : 1.5 : 2	CH_3CN	9
5	90	Cs_2CO_3	1 : 1.5 : 2	DMF	15
6	90	^tBuOk	1 : 1.5 : 2	Cy	Trace
7	90	Na_2CO_3	1 : 1.5 : 2	Cy	47
8	90	K_2CO_3	1 : 1.5 : 2	Cy	30
9	90	$CsHCO_3$	1 : 1.5 : 2	Cy	60
10	90	$NaHCO_3$	1 : 1.5 : 2	Cy	45
11	90	$CsHCO_3$	1 : 1 : 1	Cy	45
12	90	$CsHCO_3$	1 : 2 : 5	Cy	68
13	90	$CsHCO_3$	1 : 2 : 8	Cy	77
14	70	$CsHCO_3$	1 : 2 : 8	Cy	50
15	100	$CsHCO_3$	1 : 2 : 8	Cy	86
16	130	$CsHCO_3$	1 : 2 : 8	Cy	60
17[d]	100	$CsHCO_3$	1 : 2 : 8	Cy	26
18[e]	100	$CsHCO_3$	1 : 2 : 8	Cy	11

[a] Molar ratio of **1a**: PDFA : base. [b] The yields were determined by ^{19}F NMR. [c] Cy = cyclohexane. [d] $ClCF_2CO_2Na$ was used as the difluorocarbene source instead of PDFA. [e] $BrCF_2CO_2K$ was used as the difluorocarbene source instead of PDFA.

reaction temperature can obviously affect the yield (Table 1, entries 14–16). A high yield was obtained by performing the reaction at 100 °C (Table 1, entry 15). Other difluorocarbene sources such as $ClCF_2CO_2Na$ (entry 17) and $BrCF_2CO_2K$ (entry 18) were also effective for this conversion, but the yields were decreased dramatically.

To explore the scope of this difluoromethylation reaction, the optimized conditions (Table 1, entry 15) were applied to the conversion of a variety of hydrazones with PDFA. As shown in Scheme 1, the reaction proceeded well with various substrates and gave the corresponding difluoromethylation products in moderate to good yields. Irrespective of whether the phenyl ring attached to the sulfonyl group is substituted by an electron-donating (**2a–2i**) or -withdrawing group (**2j–2m**), the transformations occurred smoothly to afford the expected products. The known difluoroalkylation agent, $PhSO_2CF_2H$, was isolated in a good yield (**2g**). Compared with the traditional methods for the synthesis of $PhSO_2CF_2H$ by multi-step procedures,[13,14] this one-step protocol is straightforward and therefore quite attractive. The reaction seems to be moderately sensitive to steric effects, as evidenced by the lower yield obtained for product **2d**. The Br substituent remained intact under these conditions, providing possibilities for further modification of the structures (**2k–2l**).

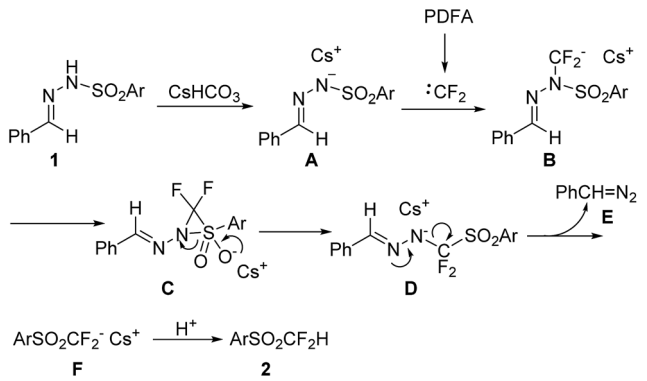


Scheme 1 The substrate scope for difluoromethylation. Isolated yields.

Scheme 2 The determination of the side difluoromethylation product. [a]Isolated yields.

A side difluoromethylation product was always detected by ^{19}F NMR spectrometry (about −102 ppm) in the reaction mixtures. The byproduct for the conversion of substrate **1a** was isolated and its structure was determined (**2a′**, Scheme 2). This byproduct **2a′** should be produced *via* the insertion of difluorocarbene into the N–H bond, which is consistent with our previous observation that PDFA can be used for difluoromethylation of N–H bond.[15b,15d]

On the basis of the above results, we propose that the reaction mechanism shown in Scheme 3 is plausible. Deprotonation of substrate **1** by $CsHCO_3$ produces ionic species **A**, which is trapped by difluorocarbene generated from PDFA[15b,15d] to give intermediate **B**. Intermediate **B** may undergo protonation to afford side product **2a′**, but predominantly undergo intramolecular cyclization to furnish species **C**. Ring-opening of species **C** would readily occur to produce intermediate **D**, which is prone to decomposition to give (diazomethyl)benzene (**E**) and intermediate **F**. (Diazomethyl)benzene is highly reactive and would be transformed into complex products. Protonation of intermediate **F** furnishes the final product. The proton source for the protonation step is the hydrogen in the N–H group in the substrate.



Scheme 3 The proposed reaction mechanism.

Conclusions

In summary, we have described the difluoromethylation of *N*-arylsulfonyl hydrazones with difluorocarbene generated from difluoromethylene phosphobetaine ($Ph_3P^+CF_2CO_2^-$) to give various difluoromethyl aryl sulfones in moderate to good yields. This work represents an efficient and mild protocol for the synthesis of difluoromethyl aryl sulfones and for the modification of the structure of the well-known difluoroalkylation agent, difluoromethyl phenyl sulfone ($PhSO_2CF_2H$).

Acknowledgements

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