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Graphical Abstract





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Difluoromethylation of Alcohols with TMSCF₂Br in Water: A New Insight into the Generation and Reactions of Difluorocarbene in a Two-Phase System

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ABSTRACT

Although many difluorocarbene-involved reactions can be performed in the presence of water, the reaction of difluorocarbene using water as the only reaction medium is rare. By using TMSCF₂Br as a unique difluorocarbene reagent and KHF₂ as a mild activator, the difluoromethylation of liquid alcohols in water only is described. This research not only developed an environmentally benign process for the synthesis of difluorocarbene in an oil-water two-phase system.

1. Introduction

Difluorocarbene is an important intermediate that has been widely used in the synthesis of difluoromethyl (thio)ethers, gemdifluorocyclopropa(e)nes, and gem-difluoroalkenes (including tetrafluoroethene) [1,2]. More recently, it has also found applications in difluoromethylation of carbon acids [3], ¹⁸Flabeled trifluoromethylation [4], metal-mediated fluoroalkylation and fluorocarbon homologation [5] [6], and difluoromethylenative coupling reactions [7], among others [8]. Due to the combined inductive effect of fluorine (destabilization effect) and π -donation from the fluorine to the carbon (stabilization effect), difluorocarbene in its singlet ground state is a moderately electrophilic species and reacts much more easily with the electron-rich substrates than the electron-poor ones [1c]. In this context, structurally diverse difluorocarbene precursors that allow its efficient generation and further reaction under varying conditions have been developed [1a,2]. It is interesting to note that in heteroatom-difluoromethylation with various difluorocarbene precursors, an alkaline base is usually needed to activate both the pronucleophiles and the difluorocarbene precursor. Correspondingly, either a miscible or biphasic aqueous-organic solvent system is preferred to dissolve the reactants [1a,1e,2a-g]. However, although many difluorocarbeneinvolved reactions, including some [2+1] cycloadditions with alkenes, have been achieved in the presence of water [1,2,9,10], there have been no report on the reaction of difluorocarbene with organic compounds in water as the sole solvent [11].

In 2017, by using TMSCF_2Br , a general and versatile difluorocarbene source first introduced by us [2h,12], we achieved the difluoromethylation of alcohols under the activation of mild activators such as KHF_2 in a mixed solvent system of

dichloromethane/water at room temperature (Scheme 1a) [1a], which not only addressed the synthetic problem of difluoromethylation of alcohols with difluorocarbene under strongly basic conditions, but also showed that the reaction of alcohols with difluorocarbene can proceed readily in a manner different from phenols. Since our last publication of this method, it has found application in the preparation of alkyl difluoromethyl ethers of potential biological interest [13]. In view of the high reactivity of neutral alcohols towards difluorocarbene and the mildness of the conditions for the generation of difluorocarbene from TMSCF₂Br, we were curious about the reaction of alcohols with TMSCF₂Br in water only, in other words, in the absence of organic solvent. In organic synthesis, water is not only a green reaction medium, but also can impressively accelerate many reactions [14]. Herein, we present our results on difluoromethylation of alcohols with difluorocarbene generated from TMSCF₂Br under more environmentally benign conditions (Scheme 1b). This research also provides new insights into the generation and reaction of difluorocarbene in a two-phase system. We showed that in a two-phase system, the transfer of an activated difluorocarbene precursor from the interfacial region to the organic phase region, which has been a challenging process even under phase-transfer catalysis [1d,9,15], can be a feasible process when TMSCF₂Br is used as a unique reagent in the absence of any catalyst, since TMSCF₂Br can form a lipophilic pentacoordinate intermediate in the interfacial region.

a) Previous work; difluorocarbene reaction in aqueous-organic solvent system

$$\begin{array}{cccc} R^{1} & OH \\ R^{2} \uparrow & & \\ R^{3} \end{array} & + & \begin{array}{c} F \\ TMS \end{array} \xrightarrow{F} Br & \begin{array}{c} KHF_{2} \\ \hline CH_{2}CI_{2}, H_{2}O, rt \end{array} & \begin{array}{c} R^{1} \\ R^{2} \uparrow \\ R^{3} \end{array} \xrightarrow{CF_{2}H} \end{array}$$

b) This work: difluorocarbene reaction in water only

$$\begin{array}{c} R_{2}^{1} OH \\ R_{R}^{2} R^{3} \end{array} + \begin{array}{c} F \\ TMS \end{array} \begin{array}{c} F \\ Br \end{array} \xrightarrow{KHF_{2}, H_{2}O} \\ organ \end{array} \begin{array}{c} R_{1}^{1} O \\ R_{R}^{2} T \\ R^{3} \end{array} \xrightarrow{CF_{2}H}$$

Scheme 1. Difluoromethylation of alcohols with TMSCF₂Br.

2. Results and discussion

2.1. Optimization of reaction conditions

At the onset of our investigation, we chose alcohol **1a** as a model substrate to survey the influence of organic solvent on the reaction (Table 1; and Table S-2 in Electronic supporting information, ESI). In our previous report, the reaction between alcohols and TMSCF₂Br (2) was performed in a mixed solvent system of CH₂Cl₂/water (1:1, v/v) under the activation of KHF₂. By using the reported optimal reactant ratio, we first investigated the difluoromethylation of **1a** in water (0.6 L per mol of alcohol) in the presence of varying volume of CH₂Cl₂. To reflect the kinetic profile, the reaction was usually quenched before the full consumption of the starting materials and detected by ¹⁹F NMR analysis. As shown in Table 1, the reaction was sensitive to the volume of CH₂Cl₂. Decreasing the volume of CH₂Cl₂ significantly accelerated the reaction, which probably arose from the increase of the concentration of both reactants 1a and TMSCF₂Br (Table 1, entries 1-3). Considering that both alcohol 1a and TMSCF₂Br are liquid and of low solubility in water at ambient temperature, we performed the reaction in water only. Surprisingly, the reaction proceeded much faster than in the mixed solvent system (Table 1, entries 4 and 5). The difluoromethyl ether 3a was produced in 97% ¹⁹F NMR yield in half an hour (Table 1, entry 5). Encouraged by this finding, we further investigated the influence of the amount of water. When more water was used, a nearly complete consumption of TMSCF₂Br gave much lower yields of **3a** (Table 1, entries 6-8), and the addition of a second portion of reagents further improved the yield (Table 1, entry 9). When less water (0.3 L per mol of alcohol) was used, a 61% consumption of TMSCF₂Br led to the formation of 3a in 82% yield, showing an enhanced conversion of TMSCF₂Br to **3a** (Table 1, entry 10); however, the reaction was retarded to some extent due to the insufficient dissolution of KHF₂ in water (39.2 g/100 mL, 20 °C). This phenomenon is different from the extensively studied "on-water" reaction, where the reaction occurs in the oil-water interface and is not influenced by the amount of water [14]. In our current reaction, if the difluoromethylation of 1a mainly occurs in the interfacial region, although much more water could dilute the activator KHF₂, and thus result in a lower concentration of pentacoordinate silicate intermediate generated at the oil-water interface, the conversion of TMSCF₂Br to 3a should not decrease, because the concentrations of 1a and TMSCF2Br do not change. The observed decrease of the utilization of TMSCF₂Br as the increase of the amount of water indicates that the difluoromethylation mainly occurs in the organic phase, as the transfer rate of the pentacoordinate silicate intermediate can be influenced by its concentration in the interfacial region. Moreover, control experiments showed that TMSCF₂Br was consumed at the similar rate no matter in the presence or absence of 1a (Table 1, entries 10 and 12), suggesting that a controlled release of difluorocarbene from TMSCF₂Br and an efficient capture of difluorocarbene by enhancing the concentration of alcohol would be helpful for improving the difluoromethylation.

TM Screen or reaction conditions for the uniteromethylation of alcohor 1a with $TMSCF_2Br$ (2).



Entry	CH ₂ Cl ₂ (mL)	H ₂ O (mL)	Time (min)	3a , Yield (%) ^{<i>a</i>}	2 , Conv. (%) ^{<i>a</i>}
1	0.5	0.3	60	28	32
2	0.3	0.3	60	44	40
3	0.1	0.3	60	60	51
4	0	0.3	10	45	32
5	0	0.3	30	97	85
6	0	0.6	60	82	98
7	0	1.2	60	67	>99
8	0	2.4	60	42	98
9^b	0	2.4	60+60	67	95
10	0	0.15	60	82	61
11^c	0	0.3	70	-	92
12^c	0.3	0.3	60	-	36

^{*a*} The yield of **3a** and total conversion of **2** were determined by ¹⁹F NMR analysis of the reaction mixture using PhOCF₃ as an internal standard. ^{*b*} A second portion of TMSCF₂Br (1.0 mmol) and KHF₂ (2.0 mmol) were added after 60 min.

^c The reaction was conducted in the absence of alcohol **1a**.

2.2. Scope and limitation

We examined the substrate scope of the reaction between alcohols and TMSCF₂Br in water only. As shown in Table 2, primary, secondary, and tertiary cohols that are liquid at ambient temperature readily underwent the reaction to give difluoromethyl ethers in moderate to excellent yields. For primary alcohols (1a-1k), the reaction was conducted by using 2.0 equiv of TMSCF₂Br and 4.0 equiv of KHF₂ in water (0.6 mL per mmol of alcohol). The reaction typically completed in 2 h. For secondary alcohols (11-1s), 3.0 equiv of TMSCF₂Br and 6.0 equiv of KHF2 were needed due to the steric hindrance of alcohols towards difluorocarbene, and prolonged reaction time (6 h) was required to achieve high yields. When a tertiary alcohol (1t) was subject to the reaction, the use of more amount of TMSCF₂Br (4.0 equiv) and KHF₂ (8.0 equiv) was necessary to ensure the efficient conversion of alcohol 1t into difluoromethyl ether 3t, and the reaction completed in 12 h. Compared to our previous report [2a], the reaction in water could afford the difluoromethyl ethers in comparable or higher yields (Table 2, 3g, 3h, 3p, and 3r-t).

In the cases of solid alcohols, the difluoromethylation at ambient temperature was found to be of very low efficiency. For example, reaction of hexadecan-1-ol (1x) gave the difluoromethyl ether 3x in only 24% yield, despite complete consumption of TMSCF₂Br. It was found that heating, which allows melting the alcohols to liquid, is a viable way to improve the reaction. For alcohols with moderate melting points (**1u-1aa**) (for details, see SI), performing the reaction at a temperature slightly higher than the melting points of these alcohols afforded the corresponding difluoromethyl ethers in good yields (**3u-3aa**).

As a complementary and an alternative approach, the reaction of solid alcohols can also proceed in water at ambient temperature with the addition of a minimum volume of CH_2Cl_2 to dissolve the alcohols (Table 3). Thus, adding CH_2Cl_2 (0.2 L per mol of alcohol) into the reaction mixture of alcohols with varying melting points, TMSCF₂Br and KHF₂ in water (0.6 mL per mmol of alcohol) resulted in the production of difluoromethyl ether **3** in of $C_{\Pi_2 C_{I_2}}$ per mor or acconor).

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Scope of alcohols *a,b*.



^{*a*} For primary alcohols, 2.0 equiv of **2** and 4.0 equiv of KHF₂ were used, and the reaction was typically complete within 2 h; for secondary alcohols, 3.0 equiv of 2 and 6.0 equiv of KHF2 were used, and the reaction was typically complete within 6 h.

Yields determined by ¹⁹F NMR analysis using PhOCF₃ as an internal standard were given in the parentheses. Reported yields [2a] for the reaction conducted in CH₂Cl₂/water (0.3 mL/0.3 mL) were given in the square brackets.

^e KOAc was used instead of KHF₂. ^d The final yields were determined at 12 h. ^e Conditions: **2** (4.0 equiv), KHF₂ (8.0 equiv), 12 h.



Figure 1. Unsuccessful examples.

minimum amount of dichloromethane^a.



....e of

^a Yields determined by ¹⁹F NMR analysis using PhOCF₃ as an internal standard were given in the parentheses. Reported yields [2a] for the reaction conducted in CH2Cl2/water (0.3 mL/0.3 mL) were given in the square brackets

Conditions: 2 (4.0 equiv), KHF₂ (8.0 equiv), 12 h.

The reaction of triol lac or sugar derivative lad with TMSCF₂Br/KHF₂ in water afforded trace amount of difluoromethylation product (Figure 1), indicating the limitation of the current protocol when applying it to some water-soluble alcohols. However, ethanol, which is also miscible with water, smoothly underwent the difluoromethylation, with C₂H₅OCF₂H being detected in about 30% yield, despite its volatility. TMSCF₂Br-water extraction tests of alcohols 1a, 1ac, 1ad and ethanol in the absence of KHF₂ showed that almost no alcohol 1ac or 1ad was extracted by TMSCF₂Br, while 95% of alcohol 1a and about 1% of ethanol entered the organic phase (for details, see section 3 in ESI). Obviously, the extraction of the alcohol by TMSCF₂Br is necessary for the difluoromethylation, providing an evidence to support that difluoromethylation of alcohols mainly occurs in the organic phase.

To demonstrate the practicability of current protocol, we conducted the difluoromethylation of alcohol 1a on 10-mmol scale in water only. After the completion of the reaction, a direct ¹H NMR analysis of the organic phase showed that difluoromethyl ether 3a was formed with a purity of almost 90%. After workup, the isolated yield of crude 3a was 85% (Scheme 2).



Scheme 2. Large scale synthesis without purification.

2.3. Proposed mechanism

Based on our results and discussion, and taking into account the previous mechanistic studies on reaction of carbenes with hydroxyl groups [1d,2c,16], a plausible mechanism for the difluoromethylation of alcohols with difluorocarbene in water is proposed (Scheme 3). In the two-phase system consisting of TMSCF₂Br with an alcohol and an aqueous solution of KHF₂, TMSCF₂Br was activated by KHF₂ to form a pentacoordinate silicate intermediate at the oil-water interface, which then enters the organic phase under the driving force of its lipophilicity (Scheme 3, Eq. 1). In the organic phase, BrCF₂K is released from the pentacoordinate silicate intermediate (Scheme 3, Eq. 2), and then splits into KBr and the singlet difluorocarbene (Scheme 3, Eq. 3). The latter species interacts with two alcohol molecules to form a five-membered complex with oxonium character [16c], which eventually undergoes double proton transfer to deliver the difluoromethyl ether and regenerate one alcohol molecule (Scheme 3, Eq. 4). The complex is probably formed through the interaction of the central carbon's vacant p-orbital with the oxygen's lone pair of the first alcohol molecule and the hydrogen

molecule [16a]. At the oil-water interface, $BrCF_2K$ released from the pentacoordinate silicate intermediate readily undergoes protonation (Scheme 3, Eqs. 5 and 6), which constitutes the major side reaction of $TMSCF_2Br$ when KHF_2 is used as the activator.

The feasibility of generating difluorocarbene from $TMSCF_2Br$ in the organic phase of a biphasic system is further supported by the *gem*-difluorocyclopropanation of an electron-rich alkene, 1,1-diphenylethene (for detail, see section 4 in ESI).

Activation of TMSCF₂Br

Difluoromethylation of alcohols

KBr (aq.)

:CF

$$2\text{ROH (org.)} + :CF_2 (\text{org.}) \xrightarrow{F_2C^{-}-H} \xrightarrow{F_2C^{-}-H} \text{ROCF}_2\text{H (org.)} + \text{ROH (org.) (4)}$$

Competitive side reactions

 $[Me_{3}Si(CF_{2}Br)F]^{-}K^{+} (int.) \longrightarrow BrCF_{2}^{-}K^{+} (int.) + Me_{3}SiF (int.) (5)$ $BrCF_{2}^{-}K^{+} (int.) + 2HF (int.) \longrightarrow BrCF_{7}H (int.) + KHF_{2} (int.) (6)$

Scheme 3. Proposed mechanism for difluoromethylation of alcohols with difluorocarbene in water.

2.4. A comparison with the difluoromethylation of phenols

We compared the difluoromethylation of phenol 4 using water as the only solvent to that in CH₂Cl₂/water (Scheme 4). As previously reported [2g], the basic activator KOH is necessary, which promotes the generation of difluorocarbene and subsequent reaction with phenol (via phenolate anion). Using the reported optimal reactant ratio, the reaction in water (without organic solvent) afforded product 5 in moderate yield, although TMSCF₂Br was consumed completely. In contrast, the reaction in CH₂Cl₂/water was much more efficient, where a 60% conversion of TMSCF₂Br led to the formation of 5 in 86% yield (similar to previous report). The relative low efficiency of the reaction in water may be attributed to the fast consumption of difluorocarbene by KOH at the oil-water interface (for the proposed mechanism, see section 5 in ESI). A dilution of TMSCF₂Br with CH₂Cl₂ would slow down the formation of difluorocarbene; however, the utilization of difluorocarbene would be enhanced due to the relative enrichment of the phenolate anion and pentacoordinate silicate into the organic phase, which would reduce the contact between difluorocarbene and KOH correspondingly.



3. Conclusion

In summary, we have shown that the difluoromethylation of primary, secondary, and tertiary alcohols by using TMSCF₂Br as the difluorocarbene reagent and KHF₂ as a mild activator can proceed in water only. Although no organic solvent is used, the liquid alcohol and TMSCF₂Br constitute the organic phase. On the one hand, for primary and secondary alcohols, compared with the reaction in a combined solvent system of CH₂Cl₂/water, the reaction in water only proceeded faster due to the enhanced concentration of the reactants in the organic phase. On the other hand, less water can improve the conversion of TMSCF₂Br to difluoromethyl ethers, although the reaction can be retarded when the dissolution of KHF₂ is not sufficient. In the case of solid alcohols, dissolving the alcohols with a minimum amount of organic solvent such as CH2Cl2 is necessary. Importantly, by probing the influence of the amount of water on the difluoromethylation of alcohols with TMSCF₂Br, we have identified a new mechanism for the generation and reaction of difluorocarbene in a biphasic oil-water system, which is revealing for the design of new difluorocarbene reagents and the development of new difluorocarbene reactions.

4. Experimental section

The typical procedures for the difluoromethylation of primary alcohols (liquid) are as follows: Into a 10-mL plastic tube containing 2-phenylethanol (**1a**) (61 mg, 0.5 mmol) and KHF₂ (156 mg, 2.0 mmol) was added water (0.3 mL). After stirring for a while to dissolve KHF₂, TMSCF₂Br (**2**) (156 μ L, 1.0 mmol) was added. The reaction mixture was vigorously stirred at room temperature for 2 h, and then diluted with CH₂Cl₂ (2.0 mL) for the determination of the ¹⁹F NMR yield. For characterization of the product, the above reaction mixture was further treated with water (2.0 mL) and extracted with CH₂Cl₂ (3 × 2.0 mL). The organic layers were combined and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (heptane/CH₂Cl₂, 5:1, v/v) to afford the desired product **3a** in 77% yield (66 mg).

The procedures for the difluoromethylation of other alcohols, the characterization data of isolated compounds, and the 1 H, 19 F, and 13 C NMR spectra are presented in ESI.

Declaration of competing interest

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2020.xxxxxx.

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Tetrahedron

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Graphical Abstract

TMSCF₂Br, KHF₂, H₂C R^3 organic blvent up to 98% yield

6 (20

Graphical Abstract



Highlights

- 1. TMSCF₂Br is a unique difluorocarbene reagent.
- 2. Difluoromethylation of alcohols can proceed in water only.
- 3. Providing new insights into the generation and reaction of difluorocarbene.

Johnalbreit