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Decarboxylative nucleophilic difluoromethylation of aldehydes and imines

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ABSTRACT

The high demand for the biologically active CF_2H-molecules has stimulated significant efforts to develop efficient methods for the installation of CF_2H functionality. We found that phenylsulfonyl difluoroacetate salt ($PhSO_2CF_2CO_2^-$ K^+) could directly undergo decarboxylation under warming conditions to produce active anion ($PhSO_2CF_2^-$) without the need of any base or additive, thus allowing for the subsequent nucleophilic (phenylsulfonyl)difluoromethylation of aldehydes or imines to give $PhSO_2CF_2$-alcohols or -amines, respectively. Interestingly, the removal of $PhSO_2$ group was achieved simply by elevating the reaction temperature for the conversion of aldehydes to afford CF_2H-ketones.

1. Introduction

Difluoromethyl group (CF_2H) is known to be a bioisostere of OH and SH unit and can act as a lipophilic hydrogen bond donor to improve the binding selectivity and cell membrane permeability within the realm of drug design [1]. CF_2H-containing pharmaceuticals and agrochemicals such as Eflornithine, Deracoxib, Dithiopyr and Sulfentrazone have been successively developed. Consequently, significant efforts have been devoted to the exploration of efficient protocols for the incorporation of CF_2H functionality [2]. Two strategies have been well established, direct difluoromethylation [3] and indirect difluoromethylation [4]. Indirect approaches usually involve a two-step procedure including the first incorporation of a CF_2X (X = auxiliary group) moiety and the subsequent removal of the auxiliary group X to obtain CF_2H-products. Direct difluoromethylation is a one-step process and thus is a more straightforward strategy. However, the presence of an auxiliary group may modify the reactivity of difluoromethylation reagents, or lead to the changes in physical state of the reagents for more convenient operations (for instance, a solid reagent may be obtained by incorporating an auxiliary group into a volatile reagent). Therefore, if the auxiliary group can be easily removed, indirect difluoromethylation may still be an attractive strategy.

As phenylsulfonyl group ($PhSO_2$) can modify reactivity of $PhSO_2$-reagents due to its strong electron-withdrawing nature and the group may be easily removed under reductive or basic conditions [5], it has become one of the most widely used auxiliary groups in indirect difluoromethylation protocols. Various $PhSO_2CF_2$-type reagents, such as $PhSO_2CF_2H$ [6,5b], $PhSO_2CF_2Br$ [7], $PhSO_2CF_2SiMe_3$ [8], $PhSO_2CF_2I^{III}$ [9], and [$PhSO_2CF_2S^+$-R_2 TfO^-] [10], have appeared. But these reagents are required to be activated by a base or an initiator [5–9], or suffer from tedious synthetic procedures [10], thus limiting their applicability.

We recently developed an efficient difluorocarbene reagent $Ph_3P^+CF_2CO_2^-$ [11]. Decarboxylation of $Ph_3P^+CF_2CO_2^-$ under warming conditions could directly generate difluorocarbene intermediate via the dissociation of P-CF_2 bond. We speculated that phenylsulfonyl difluoroacetate salt ($PhSO_2CF_2CO_2^-$ M^+) may also directly undergo decarboxylation by warming to produce active anion ($PhSO_2CF_2^-$) without the need of any base or additive, thus allowing for the subsequent nucleophilic reaction. Indeed, nucleophilic (phenylsulfonyl)difluoromethylation of aldehydes or imines with potassium salt ($PhSO_2CF_2CO_2^-$ K^+) was achieved efficiently at 50 °C to afford alcohols or amines, respectively (Scheme 1). Surprisingly, for the reaction of aldehydes, elevating the reaction temperature could remove $PhSO_2$ group to give difluoromethyl

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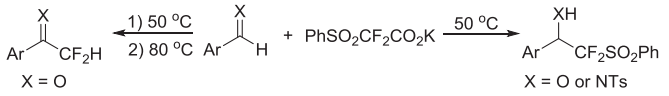


Scheme 1. This work.

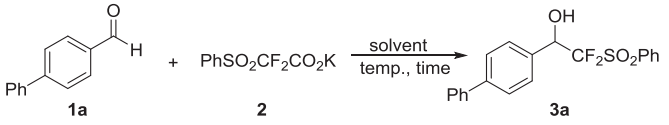
ketones. This is the first example of heat-promoted convenient removal of $PhSO_2$ group from $PhSO_2CF_2$ moiety.

2. Results and discussion

Initial attempts showed that the (phenylsulfonyl)difluoromethylation of aldehyde **1a** with potassium salt **2** ($PhSO_2CF_2CO_2K$) proceeded smoothly in a polar solvent (Table 1, entries 4–6) and acetonitrile seemed to be more suitable (entry 5). Extending the reaction time from 5 h to 7 h increased the yield to 63% (entry 8), and no further increase in the yield was observed with longer reaction time (entry 9 vs. 8). Lowering the reaction temperature decreased the yield dramatically (entry 10 vs. 8). Interestingly, as the reaction temperature was elevated, the yield was decreased (entry 12 vs. 8), and no desired alcohol **3a** was detected by elevating to 80 °C (entry 13). A good yield was obtained by increasing the loading of potassium salt **2** to 1.5 equiv (entry 14), but further increasing the loading did not increase the yield (entry 15).

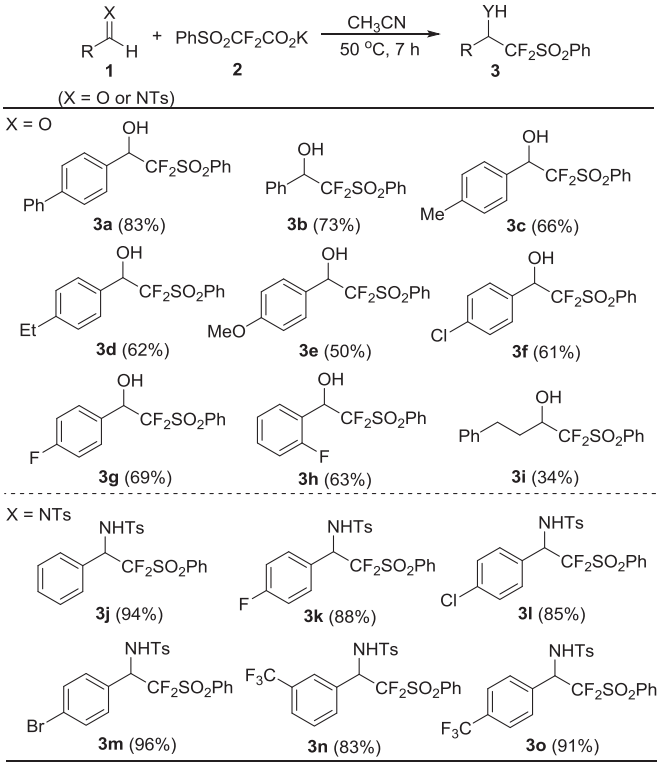
With the optimal reaction conditions in hand (Table 1, entry 14), we then investigated the substrate scope of the nucleophilic (phenylsulfonyl)difluoromethylation of aldehydes and imines (Scheme 2). Various aryl aldehydes were converted into the desired products in moderate to good yields (**3a-3h**). A strong electron-donating group would lead to the decrease in the yield (**3e**), probably because the carbonyl group was deactivated. In contrast to aryl aldehydes, alkyl aldehydes showed lower reactivity and a low yield was obtained (**3i**). The optimal reaction conditions could also be applied to (phenylsulfonyl)difluoromethylation of tosyl-protected imines to afford the corresponding amines in high yields (**3j-3o**).

Table 1
Screening reaction conditions[a].



Entry	ratio[b]	solvent	temp. (°C)	time (h)	yield (%)[c]
1	1:1	CH_2Cl_2	40	5	N.D.
2	1:1	*p*-xylene	40	5	N.D.
3	1:1	THF	40	5	N.D.
4	1:1	DMF	40	5	35
5	1:1	CH_3CN	40	5	51
6	1:1	DMSO	40	5	17
7	1:1	CH_3CN	40	6	55
8	1:1	CH_3CN	40	7	63
9	1:1	CH_3CN	40	10	65
10	1:1	CH_3CN	30	7	18
11	1:1	CH_3CN	50	7	65
12	1:1	CH_3CN	60	7	52
13	1:1	CH_3CN	80	7	N.D.
14	1:1.5	CH_3CN	50	7	79
15	1:2	CH_3CN	50	7	76

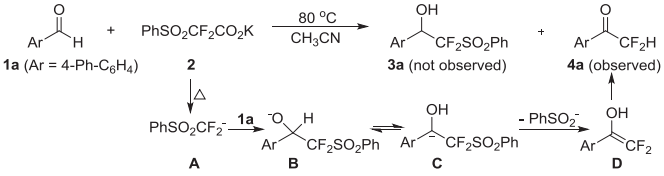
[a] Reaction conditions: aldehyde **1a** (0.2 mmol) and **2** in a solvent (2 mL). N.D. = not detected.
[b] Molar ratio of **1a**:**2**.
[c] The yields were determined by ^{19}F NMR spectroscopy.



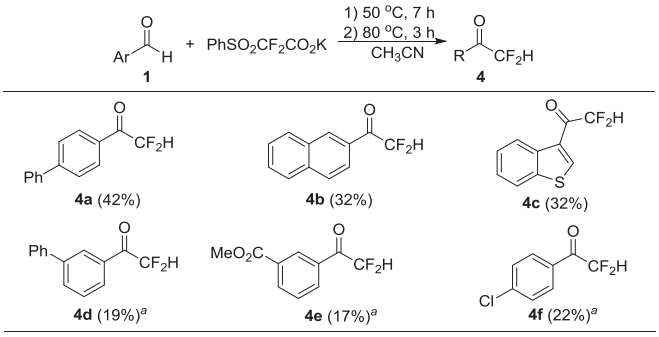
Scheme 2. (Phenylsulfonyl)difluoromethylation of aldehydes and imines. Reaction conditions: substrate **1** (0.5 mmol) and **2** (0.75 mmol) in CH_3CN (5 mL) at 50 °C for 7 h. All yields were isolated yields.

As mentioned above (Table 1, entry 13), elevating the reaction temperature to 80 °C led to the disappearance of alcohol product **3a** (Scheme 3). Surprisingly, a difluoromethyl ketone (**4a**) was observed. This ketone should be formed via a nucleophilic addition process. Decarboxylation of potassium salt **2** under warming conditions generates anion **A**, which would readily attack the aldehyde to produce adduct **B**. An equilibrium is established between intermediates **B** and **C** via 1,2-hydrogen shift. β-Elimination of a sulfonyl group from intermediate **C** furnishes enol **D**, tautomerization of which affords difluoromethyl ketone **4a**.

The attempts to achieve an efficient conversion of aldehyde **1a** into difluoromethyl ketone **4a** were not successful. The optimization of the reaction conditions revealed that the ketone could be obtained in 42% yield by further heating adduct **B** formed from the reaction of aldehyde **1a** with salt **2** at a reaction temperature of 50 °C. The substrate scope was then investigated under these conditions (Scheme 4). Although low yields were obtained for this $PhSO_2$-removal process, this is the first example of heat-promoted removal of $PhSO_2$ group from $PhSO_2CF_2$ moiety. The removal of $PhSO_2$ group was not observed for the reaction of imines.



Scheme 3. The observation of difluoromethyl ketone.



Scheme 4. The conversion of aldehydes into difluoromethyl ketones. Isolated yields. Reaction conditions: substrate **1** (0.5 mmol) and **2** (0.75 mmol) in CH_3CN (5 mL) at 50 °C for 7 h and then 80 °C for 3 h. [a]The yield was determined by ^{19}F NMR spectroscopy.

3. Conclusion

In summary, we have described the decarboxylative difluoromethylation of aldehydes and imines with potassium phenylsulfonyl difluoroacetate ($PhSO_2CF_2CO_2^-$ K^+) simply under warming conditions. Interestingly, elevating the reaction temperature for the conversion of aldehydes led to the direct removal of phenylsulfonyl group to afford difluoromethyl ketones. This work represents the first protocol for heat-promoted removal of $PhSO_2$ group from $PhSO_2CF_2$ moiety. Potassium phenylsulfonyl difluoroacetate may become an efficient difluoromethylation reagent because of its facile synthetic route, ease of handling and the possibility for convenient removal of $PhSO_2$ group.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tet.2018.06.062.

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