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O-Difluoromethylation of 1,3-diones with *S*-difluoromethyl sulfonium salt†

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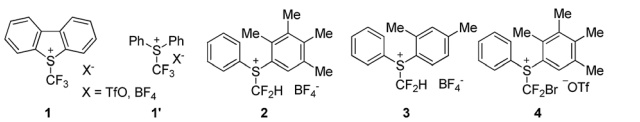
The *O*-difluoromethylation of 1,3-diones with *S*-difluoromethyl sulfonium salt is described. The sulfonium salt was previously believed to be a direct difluoromethylation reagent, but our mechanistic investigation reveals that the *O*-difluoromethylation reaction proceeds not only *via* the direct transfer of the CF_2H group, but also *via* a difluorocarbene process. This work represents the first protocol for mild *O*-difluoromethylation of acyclic 1,3-diones.

The difluoromethyl moiety (CF_2H) is a valuable functionality in medicinal chemistry since it is isosteric and isopolar to a hydroxy (OH) and thiol (SH) unit, and can also act as a lipophilic hydrogen donor. Consequently, determined efforts have been directed towards the development of efficient difluoromethylation approaches and the exploration of direct difluoromethylation agents.[1] Given that *S*-(trifluoromethyl)sulfonium salts including Umemoto's reagent[2] (**1**, Scheme 1) and *S*-(trifluoromethyl)diphenylsulfonium salts[3] (**1′**) are powerful electrophilic trifluoromethylation agents, it was believed that *S*-(difluoromethyl)diarylsulfonium salts should be efficient and direct difluoromethylation agents. It turned out that sulfonium salt **2** can't be used for the construction of C–CF_2H bond even though various non-carbon nucleophiles are applicable for difluoromethylation, demonstrating its narrow applicability.[4] On the basis of its ability for difluoromethylation, Prakash *et al.* regarded this salt as an electrophilic reagent which can directly incorporate CF_2H moiety into organic molecules.[4] However, we found that *O*-difluoromethylation of 1,3-diones with sulfonium salt **3** proceeded not only by the direct transfer of "CF_2H" group, but also *via* a difluorocarbene process.

The *O*-difluoromethylation reaction is an attractive strategy for the construction of HCF_2O-functionality, which is a valuable pharmacophore in medicinal chemistry and drug discovery.[5] But the strategy has been largely limited to the conversion of phenols and alcohols. Recently, Shibata[6] and Weng[7] independently reported the *O*-difluoromethylation of 1,3-diones. They disclosed that *S*-bromodifluoromethyl sulfonium salt (**4**)[6] and ethyl chlorodifluoroacetate[7] were efficient reagents for this reaction. However, the conversion is only applicable to cyclic substrates, not suitable for acyclic substrates. Besides, harsh reaction conditions such as low temperature or strong basic conditions are required in this transformation. We found that *O*-difluoromethylation of both cyclic and acyclic 1,3-diones with salt **3** proceeded smoothly at room temperature. Compared to Shibata's case, in which the sulfonium salt **4** was simply a difluorocarbene precursor, sulfonium salt **3** acts both as the direct difluoromethylation agent and as the difluorocarbene precursor. The preliminary results are described herein.

The synthesis of the known salt **2** requires the use of 1,2,3,4-tetramethylbenzene, an electron-rich arene which is convenient for the synthetic process due to its high reactivity. But its high cost prompted us to search for a more suitable alternative. Fortunately, we found that the inexpensive 1,3-dimethylbenzene is also reactive even though it is a less-electron-rich arene, and therefore sulfonium salt **3** was easily obtained (See ESI†).

O-Difluoromethylation of 1,3-cyclohexanedione with salt **3** in CH_2Cl_2 or EA (ethyl acetate) at room temperature could occur to give the expected product even in the absence of base albeit in low yield (entries 1 and 2, Table 1). THF was not a suitable solvent because salt **3** can lead to the polymerization of THF



Scheme 1 Electrophilic fluoroalkylation agents.

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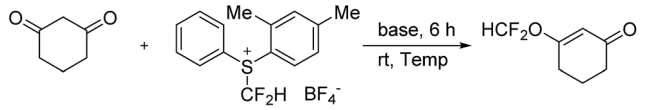
Table 1 Optimization of the reaction conditions[a]

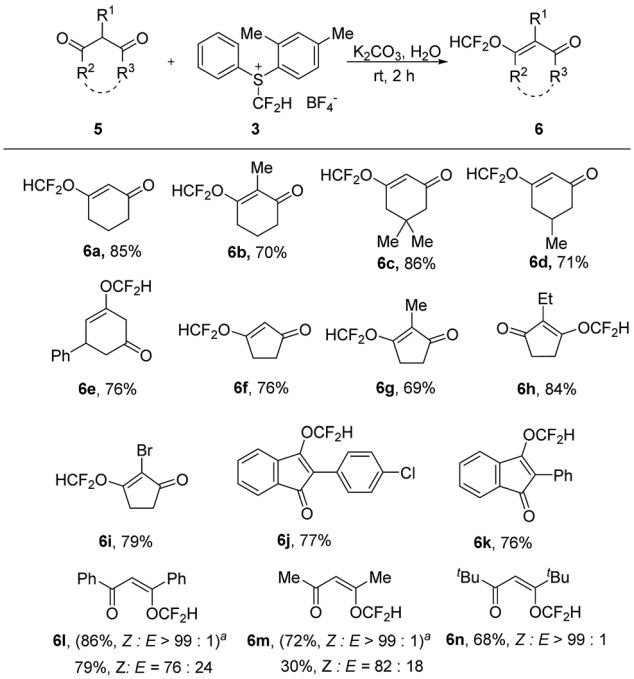


Entry	Solvent	5a : 3 : base	Base	Yield[b] (%)
1	DCM	1.0 : 1.0	—	9
2	EA	1.0 : 1.0	—	18
3	THF	1.0 : 1.0	—	Trace
4	CH_3CN	1.0 : 1.0	—	4
5	DMF	1.0 : 1.0	—	ND
6	DMSO	1.0 : 1.0	—	ND
7	EA	1.0 : 1.0 : 1.0	Na_2CO_3	61
8	EA	1.0 : 1.0 : 1.0	$NaHCO_3$	52
9	EA	1.0 : 1.0 : 1.0	K_2CO_3	44
10	EA	1.0 : 1.0 : 1.0	$KHCO_3$	14
11	EA	1.0 : 1.0 : 1.0	Et_3N	15
12	EA	1.0 : 1.0 : 1.0	DBU	20
13	DCM	1.0 : 1.0 : 1.0	Na_2CO_3	70
14	DCM	1.0 : 1.0 : 1.0	$NaHCO_3$	48
15	DCM	1.0 : 1.0 : 1.0	K_2CO_3	73
16	DCM	1.0 : 1.0 : 1.0	$KHCO_3$	44
17	DCM	1.0 : 1.0 : 1.0	Et_3N	19
18	DCM	1.0 : 1.0 : 1.0	DBU	38
19	DCM	1.0 : 1.5 : 1.5	K_2CO_3	94
20	DCM	1.0 : 2.0 : 2.0	K_2CO_3	93
21[c]	DCM	1.0 : 1.5 : 1.5	K_2CO_3	42
22[c,d]	DCM	1.0 : 1.5 : 1.5	K_2CO_3	90

[a] Reaction conditions: **5a** (0.1 mmol), **3** and base in solvent (1.5 mL); ND = not detected. [b] The reaction was stirred for 4 h. [c] The reaction system was stirred for 2 h. [d] 1.5 equiv. of H_2O was added.

(entry 3), implying the strong electrophilicity of salt **3**. Both DMF and DMSO would also react with salt **3**, hindering the desired difluoromethylation reaction (entries 5 and 6). The yield was increased significantly by conducting the reaction in EA in the presence of base (entry 7). A brief survey of inorganic bases (entries 7–10) and organic base (entries 11 and 12) revealed that only moderate yield could be obtained in EA (entry 7). The use of DCM (dichloromethane) (entries 13–18) instead of EA led to a slightly rise in the yield. Potassium carbonate (K_2CO_3) seemed to be a nice base, and the corresponding reaction gave the desired product in good yield (73%) (entry 15). Increasing the loading of sulfonium salt **3** and base further increases the yield (entries 19 and 20). 6 h of reaction time can guarantee the full conversion of salt **3**. Shortening the reaction time to 2 h led to a lower yield of the product (entry 21). Interestingly, the addition of water would speed up the reaction (entry 22), which should be due to the better solubility of K_2CO_3 in the reaction system.

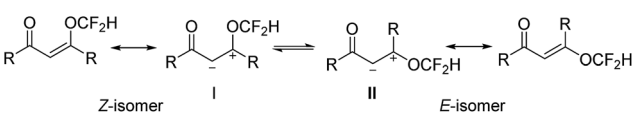
With the optimized reaction conditions in hand, we then explored the substrate scope for the *O*-difluoromethylation of 1,3-diones with sulfonium salt **3** (Scheme 2). The reaction is not only applicable to 1,3-cyclohexanediones (**6a–6e**), but also applicable to 1,3-cyclopentanediones (**6f–6k**). The good yields obtained for the conversion of substrates containing 2-position



Scheme 2 Substrate scope for *O*-difluoromethylation of 1,3-diones. Isolated yields. [a] The yields and the diastereoselectivity in parentheses were determined by ^{19}F NMR before purification.

substituents (**6b, 6g–6k**) suggests that the transformation is not quite sensitive to steric effects. Investigation of the electronic effects of 2-position substituents revealed that neither electron-donating (**6b, 6g–6h**) nor electron-withdrawing group (**6i–6k**) would clearly affect the transformation. Although *O*-difluoromethylation of 1,3-diones has been reported, the *O*-difluoromethylation of acyclic 1,3-diones remains a significant challenge. Our protocol can be well applied to the conversion of acyclic 1,3-diones (**6l–6n**). Low isolated yield of **6m** was mainly due to its high volatility. The stereoselectivity is an issue worthy of attention. Before the reaction was quenched, only *Z*-isomer was observed by ^{19}F NMR spectroscopy (**6l–6m**). However, *E*-isomer appeared after purification by flash column chromatography. The *Z*-configuration of **6l** was determined by NOE spectroscopy (See ESI†). Interestingly, both *Z*- and *E*-isomers would interconvert slowly in $CDCl_3$. In the case of **6n** the bulky ^{t}Bu group prevents its isomerization. Therefore, only *Z*-isomer was obtained before and after separation.

The *Z*/*E* interconversion between **6l** and **6m** may proceed *via* resonance structures **I** and **II** (Scheme 3). On one side of the C=C bond in *Z* isomer, there is an electron-withdrawing group (carbonyl group), and two electron-donating groups on the other side. As a result, the electron density would concentrate



Scheme 3 Interconversion between *Z* and *E* isomer.

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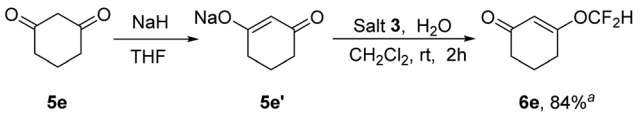
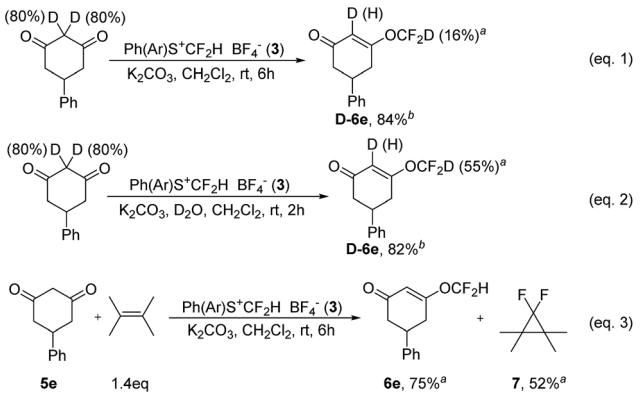


Scheme 4 Direct difluoromethylation of the enolate **5e′**. [a] Determined by ^{19}F NMR.

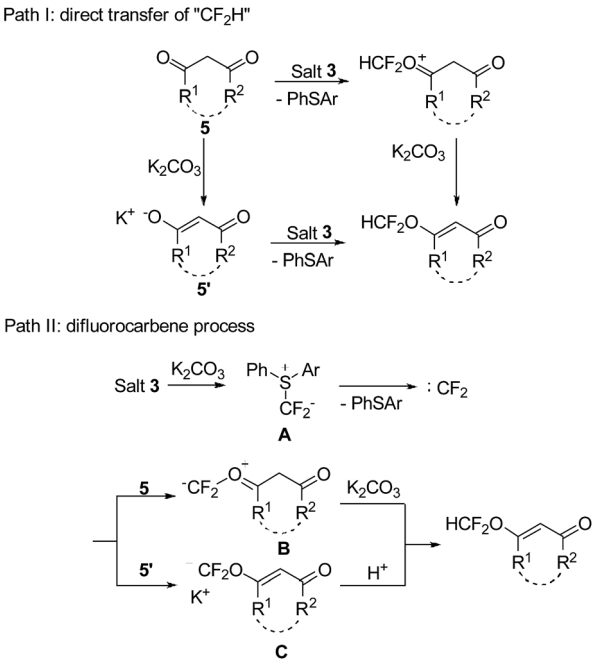
on the carbon adjacent to the carbonyl group, meaning that resonance structure **I** makes non-negligible contribution to the weighted composite structure of *Z*-isomer. The rotation around the C^{-}–C^{+} bond in structure **I** may readily occur to produce structure **II**, which is a reasonable resonance structure of *E*-isomer. The reverse process explains the conversion of *E*-isomer into *Z*-isomer. But in the case of **6n**, the *E*-configuration would be completely suppressed because of the strong steric interaction between ^{t}BuCO and ^{t}Bu groups.

Obviously, K_2CO_3 acts as a base in this difluoromethylation reaction. But how it works is an interesting issue. Based on the observation that salt **3** can lead to the polymerization of THF (entry 3, Table 1) and realize the difluoromethylation without using base (entries 1 and 2, Table 1), it is reasonable to conceive that the electrophilic ability of salt **3** is very strong and the direct transfer of the "CF_2H" group can occur, meaning that K_2CO_3 is a base for the deprotonation of the substrates. Indeed, the difluoromethylation of the enolate **5e′** gave the desired product in 84% yield (Scheme 4). However, we also found that K_2CO_3 can lead to complete decomposition of salt **3**, indicating that K_2CO_3 might be able to deprotonate salt **3** to generate the sulfur ylide. Therefore, we speculate that *O*-difluoromethylation may also proceed *via* the generation of sulfur ylide and then difluorocarbene.

In order to get more information on the difluorocarbene process, more experimental data were collected. Difluoromethylation of the deuterated **5e** (80% deuterated) in the absence of water (under the reaction conditions shown in entry 19 of Table 1) gave the product with 16% deuterated at the CF_2D group (eqn (1), Scheme 5), and the presence of D_2O afforded the product with 55% deuterated at this group (eqn (2)), suggesting that CF_2–H bond in salt **3** might be broken during the process. If



Scheme 5 Evidence to support the difluorocarbene process. [a] Determined by ^{19}F NMR; [b] isolated yield.



Scheme 6 Proposed reaction mechanism.

the cleavage of this bond takes place, sulfur ylide should be produced, followed by the generation of difluorocarbene. The addition of tetramethylethylene ($Me_2C{=}CMe_2$) into the difluoromethylation reaction system without water furnished *gem*-difluorocyclopropane **7**, further providing solid evidence for the difluorocarbene process.

On the basis of the above results, we propose that the *O*-difluoromethylation reaction may proceed *via* two different pathways, as shown in Scheme 6. Since the electrophilic ability of salt **3** is strong, direct transfer of CF_2H group to substrate **5** or **5′** would be likely to occur (path I). Another path is the difluorocarbene process (path II). Deprotonation of salt **3** gives ylide **A**, the further dissociation of which produces difluorocarbene. Difluorocarbene is a moderately electrophilic species, and would be readily trapped by **5** or **5′** to afford **B** or **C** respectively. Deprotonation of **B** or protonation of **C** furnishes the final product.

Conclusions

In summary, we have described the *O*-difluoromethylation of 1,3-diones with *S*-(difluoromethyl)sulfonium salt to give the desired products in high yields. This work represents the first protocol for mild *O*-difluoromethylation of acyclic 1,3-diones. Mechanistic investigation reveals that the reaction proceeds not only *via* the direct transfer of CF_2H group, but also *via* a difluorocarbene process. This unique reactivity of the sulfonium salt implies that it may find applications in other research areas.

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