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A Route to α-Fluoroalkyl Sulfides from α-Fluorodiaroylmethanes

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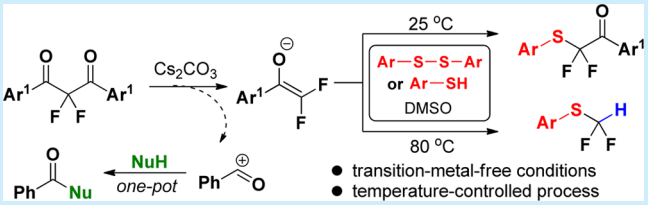
Supporting Information

ABSTRACT: α,α-Difluorodiaroylmethane can be used as a nucleophilic difluoromethylation reagent for generating α-thioaryl-α,α-difluoroacetophenones (Ar^1COCF_2SAr) and difluoromethylthiolated arenes ($ArSCF_2H$) under transition-metal-free conditions. The reaction selectivity is mainly dependent on temperature. The method has also been extended to the synthesis of α-thioaryl-α-monofluoroacetophenones using α-monofluorodibenzoylmethane. Moreover, the benzoyl cation derived from α,α-difluorodibenzoylmethane can react with nucleophiles to afford the desired products in a one-pot process.



Recently, the selective introduction of a difluoro(arylthio)-methyl group ($ArSCF_2$) into organic molecules has been found to be attractive, since compounds containing such a moiety have potential biological applications,[1] such as anti-HIV-1 reverse transcriptase inhibitors and agrochemical intermediates. Moreover, the concurrence of the $ArSCF_2$ group and carbonyl group is especially beneficial because the carbonyl group is of great importance in organic chemistry and can be transformed into versatile functional groups. Several reports have mentioned the synthesis of this kind of compounds. $S_{RN}1$ reactions between arylthiolates and halodifluoromethyl compounds[1b] or halogen exchange reactions with the *gem*-α,α-dichloroalkylsulfenyl carbonyl compounds have been applied to construct these compounds.[2] Prakash's group has developed the $TMSCF_2SPh$ as a nucleophilic (phenylthio)difluoro-methylating reagent to introduce $ArSCF_2$ moieties to ketones.[3]

However, these strategies suffer from limitations, such as harsh reaction conditions, use of toxic or hazardous reagents, and limited substrate scopes. Meanwhile, spurred by the work of Colby's group, which used **1** to generate an α,α-difluoroenolate intermediate for aldol reactions,[4] we find that the stable and easy-to-handle α,α-difluorodiaroylmethane **2** prepared from diaroylmethane and Selecfluor in water can also generate the same intermediate under basic conditions.[5] Therefore, we envision that the Ar^1COCF_2SAr would be prepared by the treatment of α,α-difluorodibenzoylmethane with diaryl disulfides or aryl thiols (Figure 1). Along this line, we disclose a mild approach for the generation of Ar^1COCF_2SAr with harmless and safe α,α-difluorodiaroyl-methane.

On the other hand, α-thioaryl-α, α-difluoroacetophenones (Ar^1COCF_2SAr) have great potential to be transformed into difluoromethylthiolated arenes ($ArSCF_2H$) via the Haller–Bauer reactions.[6] $ArSCF_2H$ is of particular interest, since the CF_2H moiety not only can act as a hydrogen donor through hydrogen bonding but also can be isosteric and isopolar to a carbinol (CH_2OH) unit,[7] which may result in pronounced biological as well as physical and chemical effects.[1c−f]

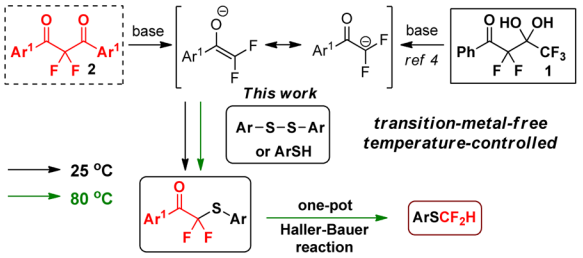


Figure 1. Strategies for the preparation of Ar^1COCF_2SAr and $ArSCF_2H$.

Methodologies for electrophilic[8] (and, to a lesser extent, radical[9]) difluoromethylation of aryl thiolates have been studied comprehensively, but there is only one example, developed by Goossen using nucleophilic difluoromethylating reagents, in which stoichiometric copper is required.[10] Thus, the further exploration of transition-metal-free methods for the synthesis of $ArSCF_2H$ using nucleophilic CF_2H sources is still desirable. Herein, we have disclosed the first example of a one-pot formation of $ArSCF_2H$ using α,α-difluorodibenzoylmethane as a nucleophilic CF_2H source via a base-induced C−C cleavage reaction under transition-metal-free conditions (Figure 1).

Initially, we started the investigation by selecting the reaction of α,α-difluorodibenzoylmethane **2a** with di-*p*-tolyl disulfide **3a** as the model reaction. During the screening of reaction conditions (Table S1, Supporting Information), we found both 2,2-difluoro-1-phenyl-2-(*p*-tolylthio)ethanone **4a** and (difluoro-methyl)(*p*-tolyl)sulfane **5a** could be afforded with high selectivity by controlling the temperature. With the optimized conditions in hand, a series of diaryl disulfides were applied to establish the scope and generality of this protocol (Scheme 1).

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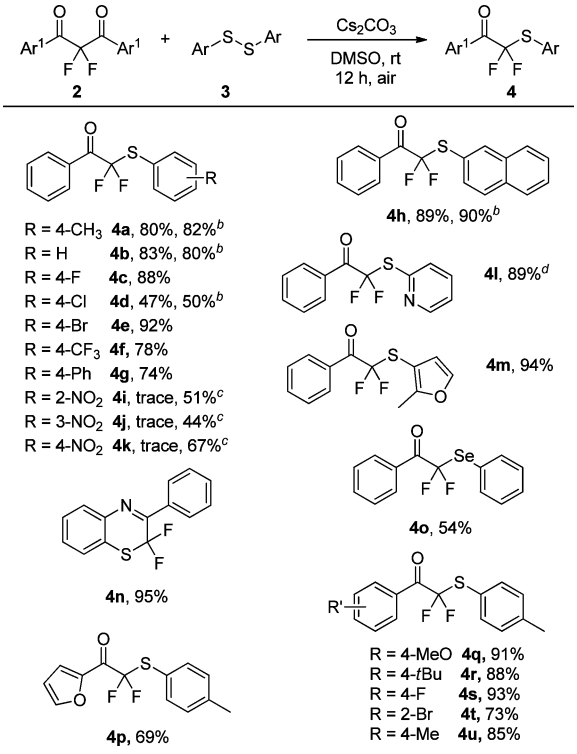
Scheme 1. Synthesis of 4 from 2 and 3[a]



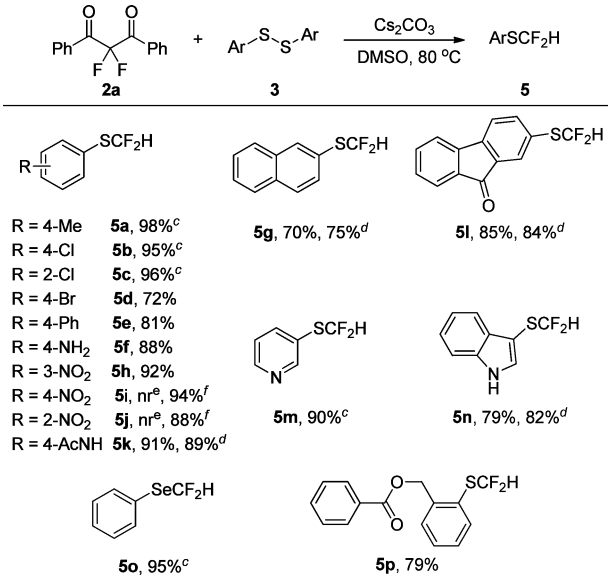
[a]Isolated yields of **4**. [b]The corresponding thiols instead of disulfides were used. [c]Reaction conditions: *α,α*-difluorodibenzoylmethane **2** 0.250 mmol, diaryl disulfide **3** 0.250 mmol, Cs_2CO_3 0.750 mmol, toluene 1 mL, 110 °C, 12 h, air. [d]The amount of Cs_2CO_3 is 1.0 equiv.

Most diaryl disulfides which have electron-donating and -withdrawing groups could react with **2a** to give the corresponding adducts in moderate to excellent yields (**4a**–**4h**). However, the diaryl disulfides bearing a nitro group showed low activities in this reaction due to its strong electron-withdrawing ability (**4i**–**4k**). To further improve the poor yields of **4i**–**4k**, the reactions were performed in water-insoluble solvent, in which the hydrolysis of **3i**–**3k** might be inhibited even under heating conditions.[11]

Not surprisingly, the moderate yields of **4i**–**4k** were provided in toluene under reflux conditions. Diheteroaryl disulfides were also applied in the reaction successfully with satisfactory results (**4l**, **4m**). It was worth noting that only 1.0 equiv of Cs_2CO_3 was required when 2,2′-dithiodipyridine was treated with **1a** for the basic nature of pyridine (**4l**). An intramolecular cyclocondensation was derived from the treatment of 2,2′-diaminodiphenyl disulfide with **1a** through the subsequent Schiff base reaction to provide a cycloproduct (**4n**). In addition, the 1,2-diphenyldiselane could also provide the desired product under identical conditions (**4o**). The corresponding thiols instead of disulfides were also applied in the reaction with satisfactory yields (**4a**, **4b**, **4d**, **4h**). However, the dialkyl disulfides failed to undergo this reaction. In order to study the scope of **2**, we used aryl substituted *α,α*-difluorodiaroylmethane to react with **3a**, affording the desired products in good yields as well (**4p**–**4u**).

Likewise, we used the optimized reaction conditions to explore the substrate scope of this new strategy for the preparation of difluoromethylthiolated arenes (Scheme 2). Both electron-rich and -deficient diaryl disulfides provided the corresponding products in good to excellent yields (**5a**–**5l**).

Scheme 2. Synthesis of 5 from 2a and 3[a,b]

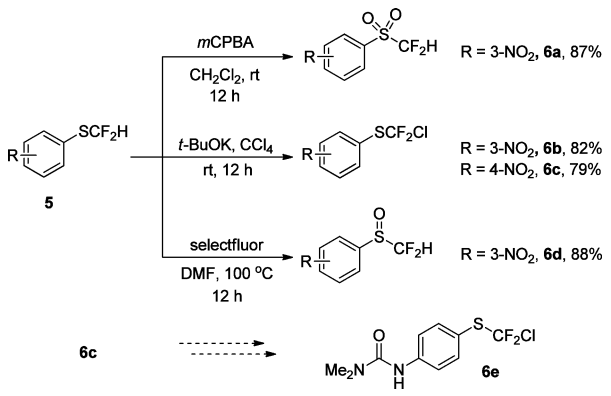


[a]Method A: **2** 0.250 mmol, **3** 0.150 mmol, Cs_2CO_3 0.750 mmol, DMSO 1 mL, 80 °C, 12 h, air. [b]Isolated yields of **5**. [c]The yield was determined by GC-MS, and only ^{19}F NMR spectroscopy was available. [d]The corresponding thiols instead of disulfides were used. [e]No reaction. [f]Method B: [step **I**] **2** 0.250 mmol, **3** 0.150 mmol, Cs_2CO_3 0.750 mmol, toluene 110 °C, 12 h, air; [step **II**] KOH 1.25 mmol, H_2O 2.75 mmol, 100 °C, 7 h.

This reaction was also applicable to heteroarene disulfides (**5m**, **5n**) and diphenyldiselenide (**5o**). However, no reaction took place using a disulfide containing a nitro group in the 2 or 4 position of the benzene ring, so another useful strategy was explored to prepare **5i** and **5j** through one-pot, two-step reactions (method B). In some cases, the resulting difluoromethylthiolated arenes are volatile (**5a**–**5c**, **5m**, **5o**), which are only characterized by ^{19}F NMR spectroscopy and MS. The use of thiols in place of disulfides proved to be also feasible in the transformation (**5g**, **5k**, **5l**, **5n**). Remarkably, a disubstituted product **5p** was formed when (2-mercaptophenyl)methanol was employed, indicating the oxo(phenyl)methylium might be also utilized by adding a nucleophile.

Furthermore, the versatile synthetic utility of the difluoromethylarylsulfanes was studied (Scheme 3). We prepared **6a** by simple oxidation of **5h** with *m*-chloroperbenzoic acid, which

Scheme 3. Transformations of Difluoromethylthiolated Arenes



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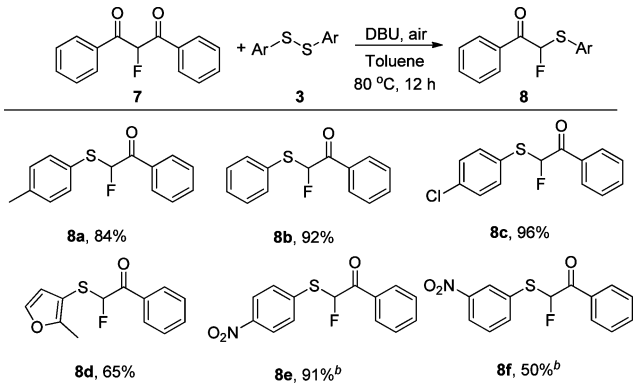
proved to have strong herbicidal activities.[12] The method for the synthesis of **6b** and **6c** was also found, and **6c** was a crucial intermidiate for the formation of **6e** which was a selective herbicide for rice.[13] In addition, a selective oxidation of **5h** was disclosed using selectfluor as the oxidizing reagent to generate **6d** as the only product.

α-Thioaryl-α-monofluoroketones, a potentially important block for a variety of biologically and synthetically interested SCF_2H-containing compounds,[14] were generally prepared by the fluorination of sulfides under extremely strict conditions with special fluorination reagents.[15] Delightedly, our developed protocol was also efficient for the construction of α-thioaryl-α-monofluoroketones with α-monofluorodibenzoyl-methane using DBU or DABCO as the base in toluene (Scheme 4).

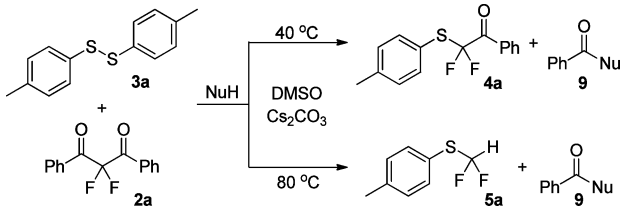
Scheme 4. Reactions of 7 with 3 To Give α-Thioaryl-α-monofluoroketones 8[a]



[a]Isolated yields of **8**. [b]DABCO instead of DBU was used.

Nevertheless, the synthesis of **4** and **5** from **2** must undergo debenzoylation, which resulted in very poor atom economy since the reaction generated 1 or 2 equiv of an aromatic acid. Therefore, encouraged by the result of **5p**, initial attempts were made to eliminate the issue (Table 1). The results indicated the benzoyl cation derived from **2a** can react with different nucleophiles to afford the desired products **9** in a one-pot process with high yields. In most cases, no obvious influence was found on the yields of **4a** or **5a** using nucleophiles in the transformations. However, a slight lower yield of **4a** was noted when morpholine was added in the reaction of **2a** and **3a** at 40 °C (entry 2).

Table 1. Transformations of 2a, 3a, and Nucleophiles



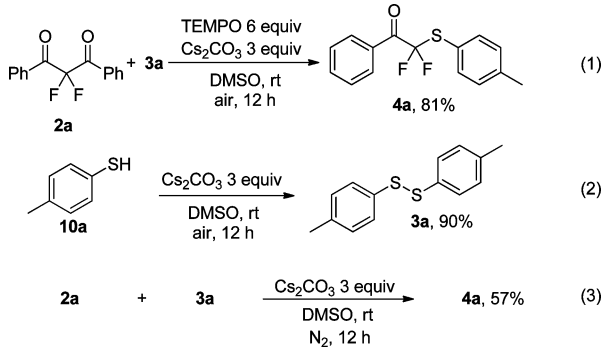
entry	NuH	yield (**4a**/**9**, %)[a,b]	yield (**5a**/**9**, %)[b,c]
1	NH_3	75/80 (**9a**)	98[d]/87 (**9a**)
2	morpholine	64/91 (**9b**)	97[d]/93 (**9b**)
3	benzyl alcohol	79/86 (**9c**)	99[d]/95 (**9c**)
4	H_2O[e]	81	99[d]
5	none[f]	59	trace[d]

[a]Conditions: **2a** 0.250 mmol, **3a** 0.250 mmol, NuH 0.300 mmol (NH_3 0.750 mmol), Cs_2CO_3 0.500 mmol, DMSO 1 mL, 40 °C, 12 h, air. [b]Isolated yields. [c]Conditions: **2a** 0.250 mmol, **3a** 0.150 mmol, NuH 0.600 mmol (NH_3 1.50 mmol), Cs_2CO_3 0.750 mmol, DMSO 1 mL, 80 °C, 12 h, air. [d]The yield was determined by GC-MS. [e]3 equiv of H_2O were added in dry DMSO. [f]Dry DMSO.

The method may be a potential route to utilize the aroyl cation which used to be a waste during the reaction. Meanwhile, the formation of corresponding acetophenone derivatives **9** in the reaction can demonstrate the existence of decarbonylation processes in the reaction. A small amount of water proves to be beneficial for the reaction (entries 4 vs 5), because water can promote the process of decarbonylation to form aromatic carboxylates (much higher polarity than products) under basic conditions, which can facilitate the workup procedure.

To further probe the mechanism, several control experiments were designed and investigated (Scheme 5). Under the assumption that this reaction involved a free radical pathway, we chose TEMPO as the radical scavenger to trap the radical generated in this reaction. The reaction proceeds smoothly to give the corresponding product **4a** without significantly affecting the efficiency, indicating that the free radical pathway is not involved in this transformation (eq 1). It has been reported that thiols can be oxidized to disulfide medicated by DMSO.[16] We hypothesize that a possible dimerization pathway of benzenethiol formed after the attack of diaryl disulfide by α,α-difluoroenolates was operative to regenerate disulfide in DMSO, since 0.5 equiv of diaryl disulfide is enough to undergo this reaction.

Scheme 5. Mechanistic Studies and Control Experiments



Thus, we treated benzenethiol with standard reaction conditions, which showed that benzenethiol could be oxidized to disulfide **3a** in DMSO (eq 2). The reaction is inhibited in a N_2 atmosphere, indicating that air may promote the oxidation of diaryl disulfide and benzenethiolate (eq 3).[17] Based on these results, we proposed a plausible mechanism for this reaction shown in Figure 2. Initially, the α,α-difluorodibenzoylmethane **2a** is attacked by Cs_2CO_3 to form α,α-difluoroenolate intermediate **11**, which reacts with disulfide **3** subsequently to generate product **4** and benzenethiolate **12**. The product **4** is finally transformed into difluoromethylthiolated arene **5** through the base-induced Haller–Bauer reaction while the benzenethiolate **12** is oxidized to a disulfide and merged into the reaction cycle.

In summary, we have developed a transition-metal-free protocol to afford the α-thioaryl-α,α-difluoroacetophenones and difluoromethylthiolated arenes from α,α-difluorodibenzoyl-methane. The broad scope of diaryl disulfides and further

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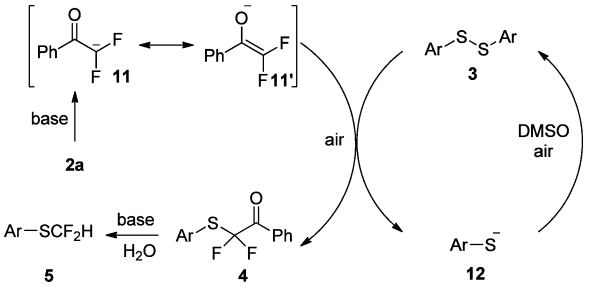

Figure 2. A proposed mechanism for the synthesis of **4** and **5** from *α*,*α*-difluoro-dibenzoylmethane **2a**.

applications of these products are demonstrated. The seclectivity between *α*-thioaryl-*α*,*α*-difluoroacetophenones and difluoromethylthiolated arenes can be controlled by temperature. This method has been successfully extended for the synthesis of *α*-thioaryl-*α*-monofluoroacetophenones using *α*-monofluorobenzoylmethane. In addition, nucleophiles can react with the benzoyl cation in the protocol with high yields without inhibiting the fluoridations. Further investigations to apply *α*-fluorodibenzoylmethane for other processes are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03654.

Experimental details; copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra of all products (PDF)

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Notes

The authors declare no competing financial interest.

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