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Radical Difluoromethylation of Thiols with (Difluoromethyl)triphenylphosphonium Bromide

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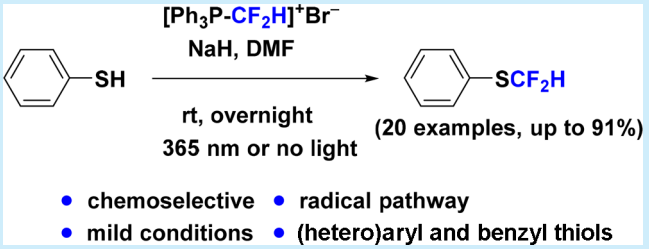
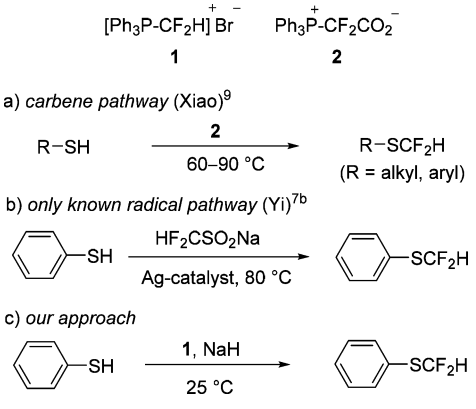
Supporting Information

ABSTRACT: A method for facile difluoromethylation of various thiols using (difluoromethyl)triphenylphosphonium bromide under mild reaction conditions is presented. The transformation proceeds in the absence of any transition metal using a bench-stable and readily accessible phosphonium salt. Deuterium labeling experiments and cyclic voltammetry measurements reveal that the difluoromethylation occurs via a $S_{RN}1$-type mechanism. Substrate scope is broad, and various functional groups are tolerated (OH, NH_2, amide, ester).



The incorporation of tri- and difluoromethyl groups into organic molecules has drawn significant interest over recent years[1] because fluorine-containing compounds are of high importance in various areas such as medicinal chemistry or materials science.[2] Compared to the trifluoromethylation where various reagents such as the Togni reagent,[1b,3] Umemoto reagent,[4] Langlois reagent,[5] Ruppert–Prakash reagent[6] and fluoroalkanesulfinates[7] have been introduced, the difluoromethylation is clearly underexplored.[1e,7b,8] Along these lines, two bench-stable phosphonium salts **1** and **2** have recently been applied to the difluoromethylation (Scheme 1).[1a] These

Scheme 1. Difluoromethylation of Thiols Using Carbene Chemistry (a), Transition-Metal-Catalyzed Process (b), and Our Radical Approach (c)



reactions proceed via the CF_2-carbene that is readily generated from these phosphonium salts, and different functional groups such as aliphatic thiols,[9] alcohols,[10] benzylic halides,[11] or carboxylic acids[9] can be difluoromethylated with such salts or related reagents. Surprisingly, only a few reports on the use of **1** as a C-radical precursor have appeared to date.[12]

Light-initiated $S_{RN}1$-type reactions of aryl thiols have been investigated extensively over the past decades.[13] The aromatic thiolate anion is known to be a very efficient $S_{RN}1$ nucleophile for which mainly halobenzene derivatives have been used as coupling partners.[14] Wakselman and co-workers investigated the halo-difluoromethylation of thiolates with CF_2Br_2 and CF_2Cl_2 and found that these reactions can proceed via carbenes but also via radical intermediates.[15]

Based on these results, we were encouraged to use **1**, which can be prepared easily on a multigram scale from commercially available ethyl bromodifluoroacetate,[12a,16] as a reagent for radical difluoromethylation of thiols under basic conditions (Scheme 1c).

We first investigated solvent effects on the difluoromethylation of thiophenol (**3a**) with phosphonium salt **1** (2 equiv) and KO^{t}Bu (5 equiv) as a base using light initiation (365 nm) (Table 1). Reactions in acetonitrile, THF, DMSO, or dioxane provided the desired compound **4a** in moderate yields (around 30%), and only traces of the target thioether were identified with dichloromethane or toluene as solvent (Table 1, entries 1–6). Yield significantly improved upon switching to DMF (51%, Table 1, entry 7). With the ideal solvent identified, we next screened different bases, and yield further increased to 61% using sodium hydride (Table 1, entry 8). DBU and Cs_2CO_3 provided worse results (Table 1, entries 9 and 10). This observation is a first hint for a $S_{RN}1$-type mechanism because in many $S_{RN}1$ reactions inorganic bases, such as NaH and KO^{t}Bu, are used.[17] The poor reactivity with Cs_2CO_3 can be explained by a known nucleophilic attack of the carbonate to the phosphonium salt, which probably takes place as a side reaction.[18]

We found that the amount of base affects the reaction outcome (Table 1, entries 11–15), and the best result (81% yield) was obtained using 2 equiv of NaH. Decreasing the amount of

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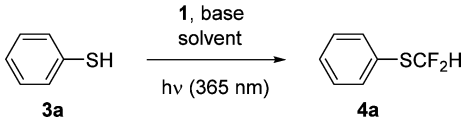
Table 1. Reaction Optimization Using Thiophenol as Substrate[a]



3a 4a

entry	base (equiv)	solvent	1 (equiv)	yield (%)
1	KO^{t}Bu (5)	MeCN	2	33
2	KO^{t}Bu (5)	THF	2	31
3	KO^{t}Bu (5)	DMSO	2	31
4	KO^{t}Bu (5)	dioxane	2	27
5	KO^{t}Bu (5)	toluene	2	traces
6	KO^{t}Bu (5)	CH_2Cl_2	2	traces
7	KO^{t}Bu (5)	DMF	2	51
8	NaH (5)	DMF	2	61
9	Cs_2CO_3 (5)	DMF	2	27
10	DBU (5)	DMF	2	13
11	NaH (1)	DMF	1	3
12	NaH (1)	DMF	2	5
13	NaH (1.5)	DMF	2	18
14	**NaH (2)**	**DMF**	**2**	**81 (70)**[d]
15	NaH (3)	DMF	2	66
16	NaH (2)	DMF	1	13
17	NaH (2)	DMF	1.5	61
18[b]	NaH (2)	DMF	2	78
19[c]	NaH (2)	DMF	2	75
20[b,c]	NaH (2)	DMF	2	73

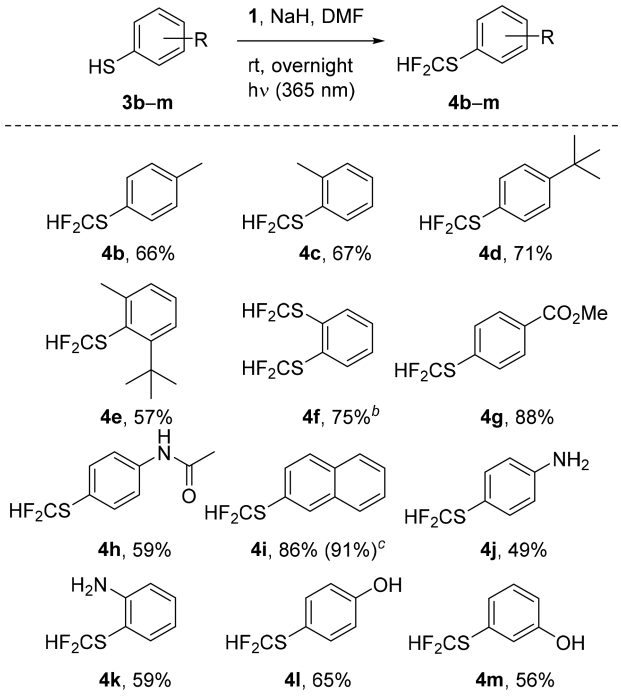
[a]All reactions were carried out with **3a** (0.2 mmol) under irradiation in the given solvent (1 mL) for 16 h. Benzotrifluoride was used as an internal standard to determine the yield by ^{19}F NMR spectroscopy. [b]Reaction was carried out in the dark. [c]Reaction time was decreased to 4 h. [d]Isolated yield.

phosphonium salt **1** to 1.5 and 1 equiv led to worse results (Table 1, entries 11, 16, and 17). A slightly decreased yield was also noted in the absence of light or by shortening of the reaction time (Table 1, entries 17−19).

With optimized conditions in hand (Table 1, entry 14), the scope of the thiol difluoromethylation was studied. Various aryl thiols were tested to explore arene substituent effects (Scheme 2). Compared to the parent thiophenol, electron-donating alkyl groups at the *ortho* or *para* position did not influence the reaction outcome, and the difluoromethylated products **4b−d** were isolated in 66−71% yield. However, with the *ortho*-methyl/*ortho*′-*tert*-butyl congener **3e**, the yield slightly decreased (**4e**). Double difluoromethylation of **3f** yielded **4f** in 75%. High yields were obtained for 2-naphthalenethiol (**3i**) and methyl benzoate **3g** to give **4i** and **4g** in 86 and 88% yields, respectively. Reaction with **3i** was repeated at a larger scale, and the yield of **4i** further improved to 91% (0.19 g prepared). Importantly, in contrast to carbene-mediated difluoromethylations, where free OH and NH groups lead to side reactions (see below), the process introduced herein is highly chemoselective. Hence, thiophenols **3h** and **3j−m** bearing additional amide, amine, or phenol XH moieties underwent SH-difluoromethylation with perfect chemoselectivity. The desired products **4h** and **4j−m** were isolated in moderate to good yields. These results convincingly demonstrate the additional value of the radical-mediated difluoromethylation as compared to the difluoromethyl carbene processes.

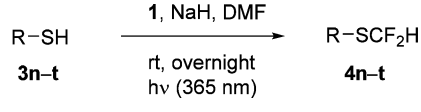
We next tested the difluoromethylation of various heteroaryl thiols, benzylic thiols, and benzeneselenol (Scheme 3). High yields were obtained with pyridine **3n**, pyrimidine **3s**, and

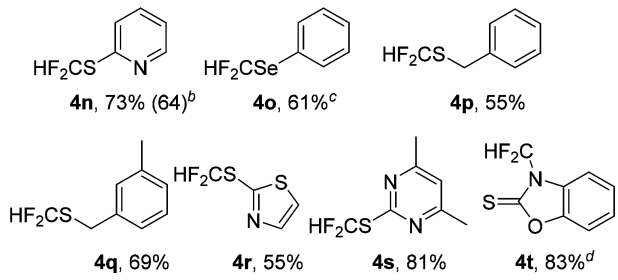
Scheme 2. Scope of Aryl Thiols[a]



[a]All reactions were carried out with thiols **3b−m** (0.2 mmol), NaH (0.4 mmol) and **1** (0.4 mmol) in DMF (1 mL) under irradiation for 16 h. All yields are isolated yields. [b]Reaction was carried out with 0.8 mmol of NaH and 0.8 mmol of **1**. [c]Reaction in parentheses was carried out with thiol **3i** (1 mmol), NaH (2 mmol), and **1** (2 mmol) in DMF (5 mL).

Scheme 3. Difluoromethylation of Heteroaryl and Benzylic Thiols[a]





[a]All reactions were carried out with thiols **3n−t** (0.2 mmol), NaH (0.4 mmol), and **1** (0.4 mmol) in DMF (1 mL) under irradiation for 16 h. [b]Product contains 13% of a side product (based on ^1H NMR), probably difluoromethylation at the nitrogen atom. Yields provided correspond to isolated yields. [c]Benzeneselenol was used instead of thiol. [d]N-Difluoromethylation instead of S-difluoromethylation occurred.

thiazole **3r** (see **4n**, **4s**, and **4p**). Notably, for 2-mercaptopyridine (**3n**), a side product with the same mass as **4n** (probably difluoromethylation at the nitrogen atom) was formed in 13% (see the Supporting Information). Benzylic thiols **3p** and **3q** were transformed successfully to the target thioethers **4p** and **4q**, showing that our method is not restricted to aromatic thiols.

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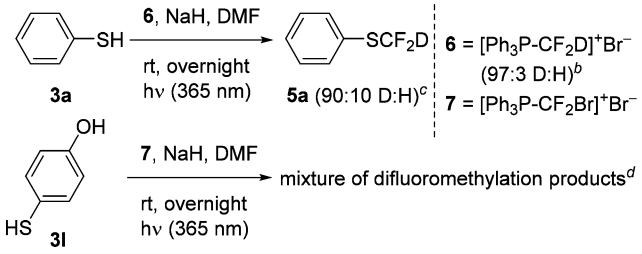
However, aliphatic thiols could not be difluoromethylated under the optimized conditions. Benzeneselenol also engaged in this transformation, and **4o** was isolated in 61% yield. In contrast to other examples where exclusive S-difluoromethylation was achieved, reaction with benzo[*d*]oxazole-2-thiol (**3t**) occurred with complete chemoselectivity at the nitrogen atom to provide oxazolethione **4t** in an excellent yield (83%). The reason for the switch in chemoselectivity is currently not understood.

To confirm our hypothesis that the difluoromethylation proceeds via a radical-type process, we ran additional mechanistic experiments (Scheme 4). Reaction of thiophenol with the

Scheme 4. Mechanistic Studies[a]

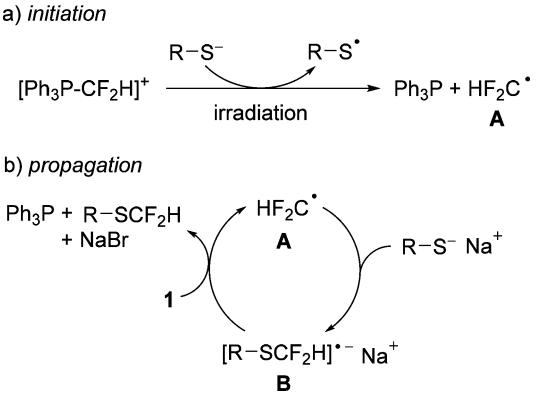


[a]All reactions were carried out with thiol (0.2 mmol), NaH (0.4 mmol), and **6** or **7** (0.4 mmol) in DMF (1 mL) under irradiation for 16 h. [b]D/H ratio of the starting material was 97:3 as analyzed by ^{1}H and ^{19}F NMR spectroscopy. [c]D/H ratio of the isolated product as analyzed by ^{1}H and ^{19}F NMR spectroscopy was 90:10 for 2 equiv of NaH (0.4 mmol) and 95:5 for 1.5 equiv of NaH (0.3 mmol). [d]Yield determined using benzotrifluoride as an internal standard by ^{19}F NMR spectroscopy: S (8%), O (2%), S and O (2%) (see the Supporting Information, section 7).

deuterated phosphonium salt **6** (D/H = 97:3) gave **5a** in 68% yield with 90% deuterium content, which was determined by both ^{1}H and ^{19}F NMR spectroscopy. We assumed that some loss of deuterium content might have been caused after the difluoromethylation by a deprotonation/reprotonation sequence. Indeed, decreasing the amount of base from 2 to 1.5 equiv afforded **6** with 95% D content on the basis of ^{1}H and ^{19}F NMR spectra. Based on these results, it is highly unlikely that reactions proceed via the difluorocarbene as an intermediate. Furthermore, the reaction of **3l** with the typical carbene precursor **7** under standard conditions provided a mixture of products, including the S, O, and double trifluoromethylation product in low overall yield. This result showed that difluorocarbene reacts with **3l** non-chemoselectively, further supporting that the transformation with **1** is radical in nature. Difluorocarbene can be generated from **7** by phenolate or thiolate attack at the Br atom in **7**.

We also measured the reduction potential of **1** by cyclic voltammetry (see the Supporting Information). Salt **1** is reduced at a potential of −1.67 V against the ferrocene/ferrocenium ion pair, and this shows the ability of **1** to act as a weak single electron oxidant. As expected, single electron reduction of **1** is not reversible. For comparison, the oxidation potential of sodium thiophenolate has been previously investigated by Persson and Nygard and lies between −0.4 and −0.5 V (vs SCE) depending on the concentration.[19] However, more important for the radical chain is the electron transfer from radical anion **B** to **A** (Scheme 5). The potential of Ar−S−Ph/Ar−S−Ph$^{\bullet-}$ has been investigated by Saveant et al. and lies between −1.5 and −2.0 V (vs Ag/Ag+) depending on the substituents.[20] Therefore, it is likely that the radical anion **B** acts as a reductant in the chain reaction,

Scheme 5. Proposed Mechanism

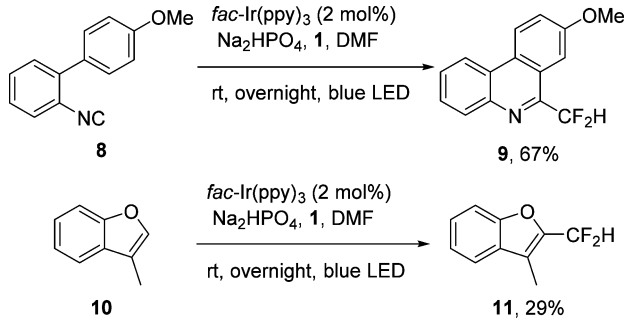


and electron transfer from the thiolate is only important in the initiation step.

Based on these studies, we propose the following mechanism for the difluoromethylation reaction (Scheme 5). Initiation of the chain reaction occurs by electron transfer from the thiolate anion to the phosphonium salt **1** upon irradiation[21] to generate the difluoromethyl radical **A**. Direct electron transfer from the thiolate to the phosphonium salt is also feasible as an initiation step because, albeit less efficiently, the chain is also initiated in the dark. Radical **A** then reacts with the thiolate anion to form the radical anion **B** in a propagation step. Single electron transfer from **B** to the phosphonium salt **1** affords the corresponding difluoromethylation product along with the radical **A**, NaBr, and PPh_3. To our knowledge, this is the first report on an $S_{RN}1$-type reaction using a phosphonium salt.

Finally, we used reagent **1** for the difluoromethylation of both isocyanide **8** and benzofuran **10** to show the versatility of the phosphonium salt in radical transformations (Scheme 6). Note

Scheme 6. Difluoromethylation at Carbon Atoms[a]



[a]All reactions were carried out with **8** or **10** (0.2 mmol), Na_2HPO_4 (0.4 mmol), and **1** (0.4 mmol) in DMF (2 mL).

that the phenanthridine synthesis starting from *ortho*-isocyanobiphenyls has been intensively investigated recently.[1d] In this case, the photoredox catalyst *fac*-Ir(ppy)$_3$ was necessary to mediate the cascade, and the difluoromethylated phenanthridine **9** was obtained in 67% yield. However, with carbene precursor **7** under identical conditions, product **9** was not formed. In addition, benzofuran derivative **10** was successfully difluoromethylated with **1** in moderate yield (see **11**) under these conditions.

In conclusion, we have presented a facile, transition-metal-free method for the difluoromethylation of various thiols under mild conditions. The method shows high functional group tolerance,

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and the phosphonium reagent is readily prepared in large scale. Mechanistic studies reveal that the process is radical in nature. The introduced method is complementary to reported thiol difluoromethylations that proceed via the difluorocarbene intermediate. Clearly, the radical process offers advantages over the carbene routes in terms of functional group tolerance. This letter shows that phosphonium salts can engage in $S_{RN}1$-type reactions, and considering the diverse $S_{RN}1$ chemistry, such salts should have a future as precursors in radical chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02109.

Experimental procedures; characterization data; ^{1}H, ^{13}C, ^{19}F, and ^{31}P spectra; cyclovoltammetry measurements (PDF)

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Notes

The authors declare no competing financial interest.

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