Synthetic Methods

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Copper-Promoted Sandmeyer Difluoromethylthiolation of Aryl and Heteroaryl Diazonium Salts**

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Abstract: *An efficient copper-promoted difluoromethylthiolation of aryl and heteroaryl diazonium salts is described. The reaction is conducted under mild reaction conditions and various functional groups were compatible. In addition, reactions of heteroaryl diazonium salts such as pyridyl, quinolinyl, benzothiazolyl, thiophenyl, carbazolyl, and pyrazolyl diazonium salts occurred smoothly to afford the medicinally important difluoromethylthiolated heteroarenes. Furthermore, a more practical one-pot direct diazotization and difluoromethylthiolation protocol was developed, and it converts the aniline derivatives into difluoromethylthiolated arenes. The utility of the method is demonstrated by difluoromethylthiolation of a number of natural products and drug molecules.*

Organofluorine compounds, which generally serve as potent active ingredients in drugs and crop protecting agents, are of great interest in the field of pharmaceuticals and agrichemicals.[1] Fluorine and trifluoromethyl groups represent two prominent, well-developed structural motifs which effectively enhance the drug's pharmacokinetics, metabolic stability, and binding selectivity, whereas the effects of other fluoroalkyl groups, such as difluoromethyl and difluoromethylthio groups, are less recognized. However, interests in these fluoroalkyl groups are increasing rapidly.[2] More specifically, the difluoromethylthiolated arenes and heteroarenes ($ArSCF_2H$) represent promising structural units which might bring desirable changes to the physical and biological properties of drug molecules since the difluoromethylthio group is generally considered a highly lipophilic hydrogen-bonding donor.[3] Therefore, the development of new and efficient methods for the formation of difluoromethylthiolated arenes and heteroarenes is of great current interest.

The most well-known strategy for the formation of difluoromethylthiolated arenes and heteroarenes is based on the nucleophilic reaction of aryl thiolates with difluorocarbene with subsequent protonation. Toward this end, several different difluorocarbene precursors such as HCF_2Cl (F22), $BrCF_2P(O)(OEt)_2$, $ClCF_2CO_2Na$, $TMSCF_2Br$, HCF_2OTf, and $PhS(O)(NTs)CF_2H$ have been developed.[4] In addition, three reports for difluoromethylation of aryl thiolates by either an electrophilic or radical substitution pathway have been independently reported by the groups of Prakash, Hu, and Baran.[5] Nevertheless, the methods mentioned above typically require strong basic conditions to deprotonate the thiol and are incompatible with many base-sensitive functional groups. In addition, these methods require the preformation of the aryl thiols and the formation of structurally complicated aryl thiols is an intricate task. Thus, a new strategy which can form difluoromethylthiolated arenes and heteroarenes under mild reaction conditions is highly desirable.

The Sandmeyer reaction[6] represents one of the fundamental functional-group transformations routinely practiced in research laboratories and applied in industry to efficiently convert the NH_2 group of $ArNH_2$ into a variety of functional groups such as halogen (F, Cl, Br, I), hydroxy, cyano, and boryl groups.[7] More recently Sandmeyer-type trifluoromethylation[8] and trifluoromethylthiolation[9] of aryl diazonium salts have also been developed. Although it is still elusive, the mechanism of the Sandmeyer reaction was generally believed to be initiated with a single-electron transfer (SET) from CuX to the diazonium group to form a diazo radical and $Cu^{II}X$. The diazo radical then releases a molecule of nitrogen to form an aryl radical, which reacts with $Cu^{II}X$ to from the final ArX product.

Inspired by the mechanism of the Sandmeyer reaction and the recent advances in this field, we envisioned that if a $CuSCF_2H$ species could be generated in situ, a similar Sandmeyer-type difluoromethylthiolation reaction could be developed. Thus, an alternative strategy for the formation of aryl and heteroaryl difluoromethylthiolation could be created and would allow incorporation of the difluoromethylthio group at a later stage of the synthesis of drug candidates (Figure 1).

Herein, we report the preparation and characterization of the thermally stable N-heterocyclic carbene (NHC) ligated

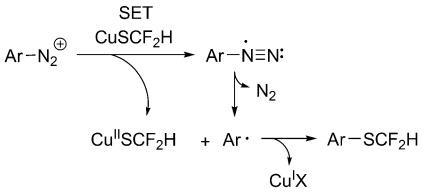

Figure 1. Proposed Sandmeyer difluoromethylthiolation of diazonium salts.

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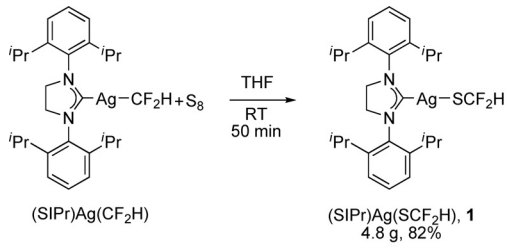
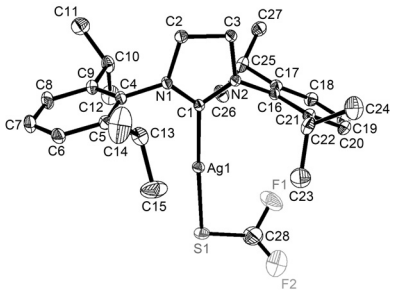
difluoromethylthiolated silver complex [(SIPr)Ag(SCF_2H)] [**1**; SIPr = 1,3-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene].[10] In the presence of one equivalent of [Cu(CH_3CN)$_4$]PF_6/bpy, the reaction of **1** with a variety of aryl and heteroaryl diazonium salts occurred smoothly to generate difluoromethylthiolated arenes and heteroarenes in good to excellent yields under mild reaction conditions. Furthermore, a one-pot sequence for diazotization/difluoromethylthiolation of aniline derivatives was developed. The broad range of substrates, mild reaction conditions, and operational simplicity make the method very attractive as the method of choice for the formation of difluoromethylthiolated arenes and heteroarenes.

[(SIPr)Ag(SCF_2H)] (**1**) could be easily synthesized from the reaction of [(SIPr)Ag(CF_2H)], a complex previously discovered in our own laboratory,[11] with sulfur in THF for 50 minutes at ambient temperature.[12] The reaction can be readily scaled up to 4.8 grams and **1** was isolated as a white solid in 82% yield. The complex **1** was fully characterized by ^1H, ^{13}C, and ^{19}F NMR spectroscopy and elemental analysis.

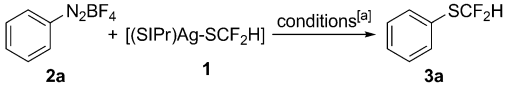




The structure of **1** was further unambiguously confirmed by X-ray analysis of its single crystals (see the Supporting Information for details).[16] The compound **1** is not sensitive to either moisture, light, or air. No detectable decomposition was observed after more than one week storage on the shelf at ambient temperature. The compound **1** is stable in solvents such as MeCN, CH_2Cl_2, 1,4-dioxane, THF, DMF, and $CHCl_3$ at room temperature for at least 12 hours as determined by ^{19}F NMR spectroscopy.

With **1** in hand, we initially chose the reaction of phenyl diazonium tetrafluoroborate (**2a**) with **1** as a model reaction to identify reaction conditions for the conversion of aryl diazonium salts into difluoromethylthiolated arenes. Considering that the halogen anion may involve in the Sandmeyer reaction, we tried the reaction using [Cu(CH_3CN)$_4$]PF_6 as the catalyst and the product **3a** was observed in 27% yield after 24 hours at 50 °C (Table 1, entry 1). Interestingly, unlike the classic Sandmeyer reaction, addition of the dinitrogen ligand

Table 1: Optimization of the copper-catalyzed difluoromethylthiolation of a phenyl diazonium salt.[a]

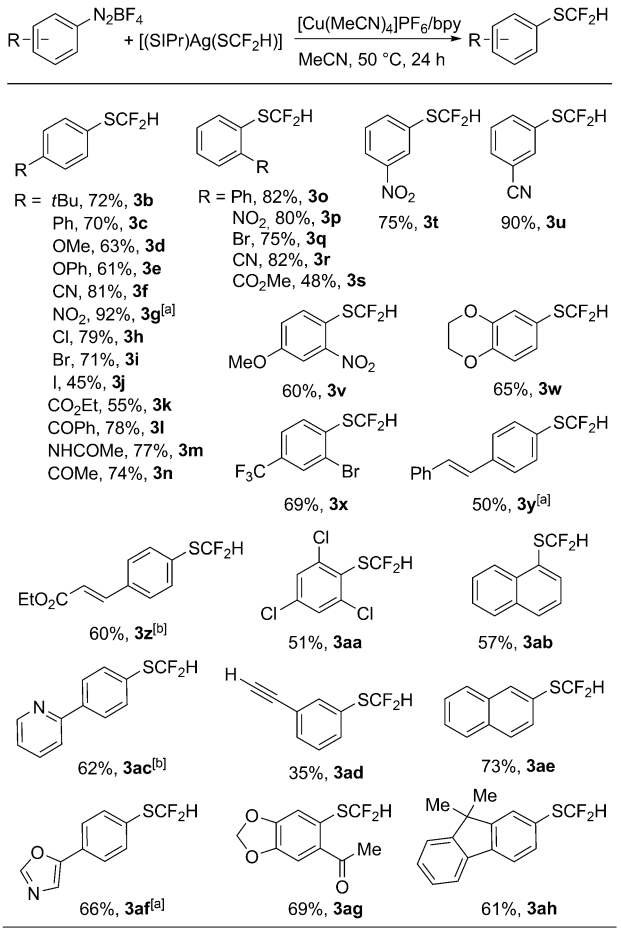


	CuX	Ligand	Solvent	Yield [%][b]
1	Cu(CH_3CN)$_4$$PF_6$	–	CH_3CN	27
2	Cu(CH_3CN)$_4$$PF_6$	2,2′-bipyridine	CH_3CN	65
3	CuI	2,2′-bipyridine	CH_3CN	62
4	CuCl	2,2′-bipyridine	CH_3CN	43
5	CuSCN	2,2′-bipyridine	CH_3CN	43
6	CuCN	2,2′-bipyridine	CH_3CN	32
7	Cu(CH_3CN)$_4$$PF_6$	2,2′-bipyridine	DMF	< 5
8	Cu(CH_3CN)$_4$$PF_6$	2,2′-bipyridine	THF	< 5
9	Cu(CH_3CN)$_4$$PF_6$	2,2′-bipyridine	CH_2Cl_2	10
10	Cu(CH_3CN)$_4$$PF_6$	2,2′-bipyridine	toluene	< 5
11	Cu(CH_3CN)$_4$$PF_6$	1,10-phenanthroline	CH_3CN	43
12	Cu(CH_3CN)$_4$$PF_6$	bathophenanthroline	CH_3CN	50
13	Cu(CH_3CN)$_4$$PF_6$	4,4′-dimethyl-2,2′-bipyridyl	CH_3CN	47
14	Cu(CH_3CN)$_4$$PF_6$	5,5′-dimethyl-2,2′-bipyridyl	CH_3CN	55
15	Cu(CH_3CN)$_4$$PF_6$	4,4′-dimethoxy-2,2′-bipyridyl	CH_3CN	52
16	Cu(CH_3CN)$_4$$PF_6$	4,4′-di-*tert*-butyl-2,2′-bipyridyl	CH_3CN	48
17	Cu(CH_3CN)$_4$$PF_6$	2,2′-bipyridine	CH_3CN	72[c]
18	Cu(CH_3CN)$_4$$PF_6$	2,2′-bipyridine	CH_3CN	76[d]
19	Cu(CH_3CN)$_4$$PF_6$	2,2′-bipyridine	CH_3CN	79[e]

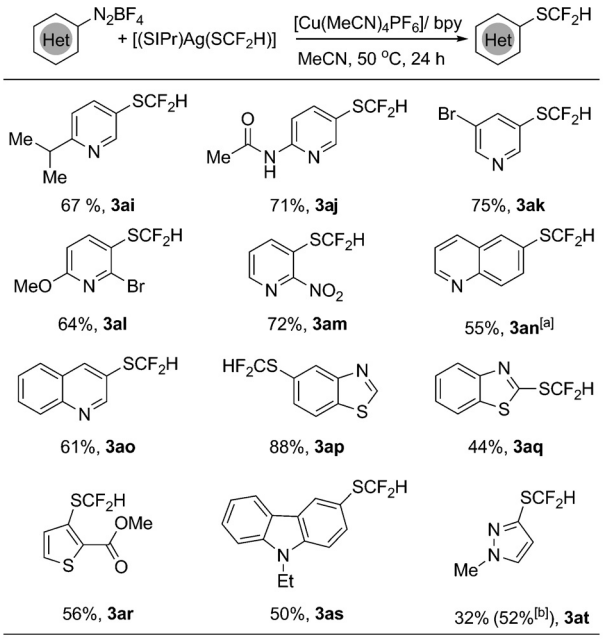
[a] Reaction conditions: phenyl diazonium salt (0.05 mmol), **1** (0.05 mmol), CuX (40 mol%), ligand (40 mol%) in different solvent (1.0 mL) at 50 °C for 24 h. [b] Yields were determined by ^{19}F NMR analysis of the crude reaction mixture with trifluorotoluene as an internal standard. [c] [Cu(CH_3CN)$_4$]PF_6 (80 mol%) and bpy (80 mol%) were used as the catalyst. [d] [Cu(CH_3CN)$_4$]PF_6 (100 mol%) and bpy (100 mol%) were used as the catalyst. [e] [Cu(CH_3CN)$_4$]PF_6 (100 mol%) and bpy (100 mol%) as the catalyst and 1.2 equiv of **2a** were used. DMF = *N*,*N*-dimethylformamide.

2,2′-bipyridine (bpy) significantly increased the yield of the reaction to 65% (entry 2). Switching the copper salt from [Cu($MeCN$)$_4$]PF_6 to CuI resulted in a slightly lower yield, and reactions with other copper salts such as CuCl, CuSCN, and CuCN occurred in much lower yields (entries 3–6). Using CH_3CN as the solvent is important for the conversion of the reaction since reactions conducted in other solvents, such as DMF, THF, CH_2Cl_2, and toluene, generated the desired difluoromethylthiolated product in less than 10% yield (entries 7–10). Other dinitrogen ligands such as 1,10-phenanthroline, bathophenanthroline, 4,4′-dimethyl-2,2′-bipyridine, 5,5′-dimethyl-2,2′-bipyridine, 4,4′-dimethoxy-2,2′-bipyridine, and 4,4′-di-*tert*-butyl-2,2′-bipyridine were tested, but reactions under these conditions formed less than 55% of the difluoromethylthiolated benzene (entries 11–16). Finally, the yields of the desired products were improved to 72% and 76% when 0.8 and 1.0 equivalentsof [Cu(CH_3CN)$_4$]PF_6/bpy, respectively, were used as the catalyst (entries 17 and 18). The yield was further increased to 79% when 1.2 equivalents of the phenyl diazonium salt were used (entry 19).

A variety of aryl diazonium salts were subjected to the reaction conditions used in entry 19, Table 1, and the reactions occurred smoothly to give the corresponding difluoromethylthiolated arenes in good to excellent yields, as



Scheme 1. Scope of the copper-promoted difluoromethylthiolation of aryldiazonium salt. Reaction conditions: aryl diazonium salt (0.6 mmol), **1** (0.5 mmol), $[Cu(CH_3CN)_4]PF_6$ (1.0 equiv), and bpy (1.0 equiv) in CH_3CN (10.0 mL) at 50 °C for 24 h. Yield is that of the isolated product. [a] Reaction was conducted in 2.0 mL of CH_3CN.

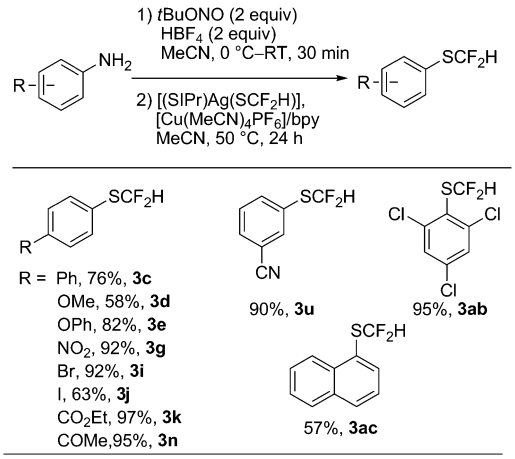


Scheme 2. Difluoromethylthiolation of heteroaryl diazonium salts. Reaction conditions: heteroaryl diazonium salt (0.6 mmol), **1** (0.5 mmol), $[Cu(CH_3CN)_4]PF_6$ (1.0 equiv), and bpy (1.0 equiv) in CH_3CN (2.0 mL) at 50 °C for 24 h. Yield is that of the isolated product. [a] Reaction was conducted in 10.0 mL of CH_3CN. [b] Yield was determined by ^{19}F NMR spectroscopy using trifluorotoluene as the internal standard.

summarized in Scheme 1. In general, both electron-rich and electron-poor aryl diazonium salts reacted in high yields. Sterically hindered *ortho*-substituted diaryl diazonium salts also underwent efficient difluoromethylthiolation to give the *ortho*-substituted difluoromethylthioether in high yields (**3o–s**, **3v**, **3aa**, and **3ag**). A variety of functional groups such as ester, amide, enolizable ketone, alkene, alkyne, cyano, nitro, chloro, bromo, iodo, and heteroaryl pyridyl and oxazolyl functional groups were compatible with the reaction conditions (**3f–n**, **3p–v**, **3x–z**, **3ac–ad**, **3af–ag**). Notably, aryl diazonium salts with a halogen group such as chloride, bromide, and iodide all reacted under the standard reaction conditions to give the corresponding products in 79, 71, and 45 % yield, respectively (**3h–j**). These products are of interest since they could be further functionalized through well-known cross-coupling reactions.[13]

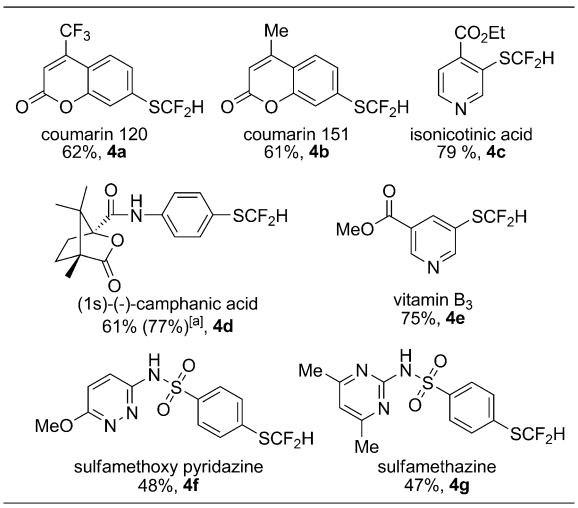
Fluoroalkylated heteroarenes are valuable synthons for medicinally important compounds or crop-protecting agents and there is an urgent need for new efficient methods to access these compounds.[2] Encouraged by the general and excellent protocol for the formation of difluoromethylthioethers, we tried to extend this method to heteroaryl diazonium salts. As illustrated in Scheme 2, we found that this new protocol also allowed the efficient conversion of heteroaryl diazonium salts into difluoromethylthiolated heteroarenes in good to excellent yields. More specifically, difluoromethylthiolation of six-atom pyridyl or quinoliny diazonium salts occurred in 55–75 % yields (**3ai–ao**). Reactions of five-atom heteroaryl diazonium salts such as diazonium salts of benzothiazole, thiophene, carbazole, and pyrazole were less efficient but acceptable yields of the desired products were obtained (**3ap–at**). It is worth mentioning that these difluoromethylthiolated heteroarenes are not easily accessible by the conventional methods.

In general, aryl diazonium salts are not commercially available and are usually prepared by the reaction of anilines with a source of nitrite before use.[7] Thus, if difluoromethylthiolated arenes could be directly accessed from readily available aniline derivatives through diazotization and difluoromethylthiolation, a more practical and attractive one-pot protocol that circumvents the isolation of the diazonium salts could be developed. Indeed, it was found that treatment of a mixture of aniline derivatives and HBF_4 in CH_3CN with *t*BuONO[14] at 0 °C for 30 minutes formed the aryl diazonium salts. After evaporation of the solvent and volatiles, the residue was directly treated with the copper catalyst and **1** in CH_3CN at 50 °C and after 24 hours generated the desired difluoromethylthiolated arenes in good to excellent yields (Scheme 3). Again, many functional groups were compatible with this one-pot protocol.



Scheme 3. One-pot diazotization/difluoromethylthiolation of aniline derivatives. Reaction conditions: aniline derivative (1.0 mmol), HBF_4 (2.0 mmol), *t*BuONO (2.0 mmol), MeCN (1.0 mL) at 0 °C–room temperature for 30 min; **1** (0.5 mmol), $[Cu(CH_3CN)_4]PF_6$ (1.0 equiv), and bpy (1.0 equiv) in CH_3CN (2.0 mL) at 50 °C for 24 hours. Yield is that of the isolated product.

Late-stage modification of natural compounds or drug candidates is a valuable strategy for medicinal chemists attempting to fine-tune the activity of the leading compounds. We selected several natural compounds and drug molecules to illustrate the advantage of the current difluoromethylthiolation protocol. Amino derivatives of biologically active molecules such as coumarin 120/151, isonicotinic acid, (1s)-(+)-camphoric acid, vitamin B_3, and drug molecules sulfamethoxy pyridazine and sulfamethazine[15] are all compatible with copper-mediated difluoromethylthiolation conditions (Scheme 4). These results demonstrate the utility of the copper-mediated reaction for late-stage difluoromethylthiolation to access compounds which are not easily accessible by conventional methods.



Scheme 4. Difluoromethylthiolation of diazonium salts of natural compounds or drug molecules. Yield is that of the isolated product. Conditions for **4a–c** and **4e–g**: aryl diazonium salt (0.6 mmol), compound **1** (0.5 mmol), $[Cu(CH_3CN)_4]PF_6$ (1.0 equiv), bpy (1.0 equiv) in CH_3CN (10.0 mL) at 50 °C for 24 h; for **4d**: aniline derivative (1.0 mmol), HBF_4 (2.0 mmol), *t*BuONO (2.0 mmol), MeCN (1.0 mL), 0 °C to room temperature, 30 min; compound **1** (0.5 mmol), $[Cu(CH_3CN)_4]PF_6$ (1.0 equiv), bpy (1.0 equiv) in CH_3CN (2.0 mL) at 50 °C for 24 h. [a] Yield was determined by ^{19}F NMR spectroscopy using trifluorotoluene as the internal standard.

In summary, we have demonstrated the first copper-mediated Sandmeyer-type difluoromethylthiolation of aryl and heteroaryl diazonium salts.[17] The reactions were conducted under mild reaction conditions and a variety of functional groups were compatible. The advantage of this method was further demonstrated by application in a number of biologically active molecules. Thus, the current method provides an alternative and attractive strategy for the formation of the difluoromethylthiolated arenes and heteroarenes. Mechanistic studies and synthetic applications of these transformations are ongoing in our laboratory.

Keywords: copper · diazo compounds · fluorine · heterocycles · synthetic methods

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[16] CCDC 1052050 (**1**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[17] During the review process, Goossen and co-workers reported a method for the synthesis of difluoromethyl thioethers from difluoromethyltrimethylsilane and organothiocyanates: B. Bayarmagnai, C. Matheis, K. Jouvin, L. J. Goossen, *Angew. Chem. Int. Ed.* **2015**, DOI: 10.1002/anie.201500899; *Angew. Chem.* **2015**, DOI: 10.1002/anie.201500899.

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