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Sandmeyer Difluoromethylation of (Hetero-)Arenediazonium Salts

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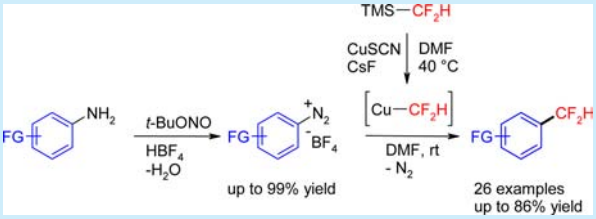
Supporting Information

ABSTRACT: A Sandmeyer-type difluoromethylation process has been developed that allows the straightforward conversion of (hetero-)arenediazonium salts into the corresponding difluoromethyl (hetero-)arenes under mild conditions. The actual difluoromethylating reagent, a difluoromethyl−copper complex, is formed in situ from copper thiocyanate and TMS−CF_2H. The diazonium salts are either preformed or generated in situ from broadly available aromatic amines.



Fluorine-containing residues are central functionalities in pharmaceuticals, agrochemicals, and functional materials.[1] Currently, 30−40% of marketed agrochemicals and about 25% of pharmaceuticals contain fluorine atoms. Whereas perfluoroalkyl chains induce higher lipophilicity and metabolic stability to bioactive substances,[2] the CF_2H group is considered isosteric and isopolar with the hydroxy group.[3] It is weakly acidic and possesses a hydrogen-bond-donating capability comparable to that of OH and NH groups, but the molecule remains more lipophilic. As a result, CF_2H is often a beneficial substitute for such groups in various classes of biologically active compounds. Examples include thiazopyr, fluxapyroxad, deracoxib, eflornithine, pantoprazole, and ZSTK474 (see Figure 1).[1e,4]

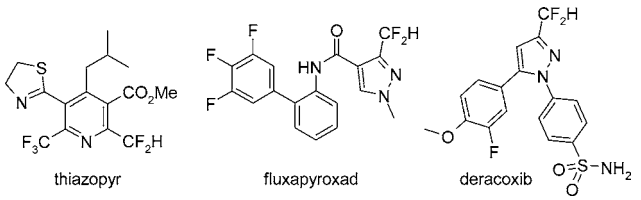


Figure 1. Bioactive molecules containing CF_2H groups.

Traditional approaches to the synthesis of difluoromethyl arenes include the fluorination of benzylic C−H bonds and the deoxo-*gem*-difluoromethylation of aldehydes with SF_4 or aminosulfur trifluorides (e.g., DAST, Deoxofluor).[5] However, these reactions suffer from poor functional group tolerance and harsh reaction conditions.

Methods for the late-stage installation of difluoromethyl groups into functionalized molecules are highly sought-after. However, compared to the tremendous progress made in trifluoromethylation technology,[2a,6] difluoromethylations have met with considerably less success. The advent of easily handled difluoromethylation reagents has sparked new developments in this field. The first type, α-trialkylsilyl difluoroacetate esters, can undergo Cu-catalyzed cross-coupling with aryl iodides, followed by hydrolysis and decarboxylation.[7] The second, difluoromethyl phenyl ketone, can be α-arylated with aryl bromides or chlorides catalyzed by Pd, followed by ketone cleavage with KOH/H_2O.[8] Both these cleavage steps call for rather harsh conditions.

Baran and co-workers disclosed a radical difluoromethylation of heteroaromatic compounds with zinc difluoromethanesulfinate $Zn(SO_2CF_2H)_2$ that proceeds under mild conditions. Unfortunately, the reaction has a limited scope and usually leads to mixtures of regioisomers.[9]

In view of the high level of efficiency reached in the analogous trifluoromethylations, one would have expected that aryl electrophiles could be difluoromethylated with difluoromethyl copper complexes[6e] generated, e.g., from TMS−CF_2H. This difluoromethylating reagent is easily accessible by reducing the Ruppert−Prakash reagent TMS−CF_3 with $NaBH_4$.[10] However, TMS−CF_2H is substantially less reactive than TMS−CF_3 due to the stronger Si−CF_2H bond.[6e,11] Moreover, Cu−CF_2H complexes easily decompose with formation of 1,1,2,2-tetrafluoroethane and *cis*-difluoroethylene.[6g,12]

Despite these difficulties, Hartwig et al. have recently disclosed a nucleophilic difluoromethylation of electron-rich aryl and vinyl iodides with Cu−CF_2H complexes generated from excess TMS−CF_2H and copper iodide.[13] Qing and coworkers have extended this method to electron-poor substrates and heteroarenes, reducing the reaction temperature to room temperature and the amount of TMS−CF_2H to 2.5 equiv by introducing phenanthroline as a ligand and using *t*-BuOK as the base (Scheme 1).[14] Prakash et al. have disclosed a similarly efficient protocol based on copper iodide and *n*-Bu_3SnCF_2H. DFT studies revealed that DMF strongly stabilizes the Cu−CF_2H intermediate.[15]

In the context of our work on late-stage trifluoromethylations,[16] we have recently developed Sandmeyer-type[17] trifluoromethylations[18] and trifluoromethylthiolations.[19] An analogous approach would be highly attractive also for the synthesis of difluoromethyl arenes, because it would be based on easily

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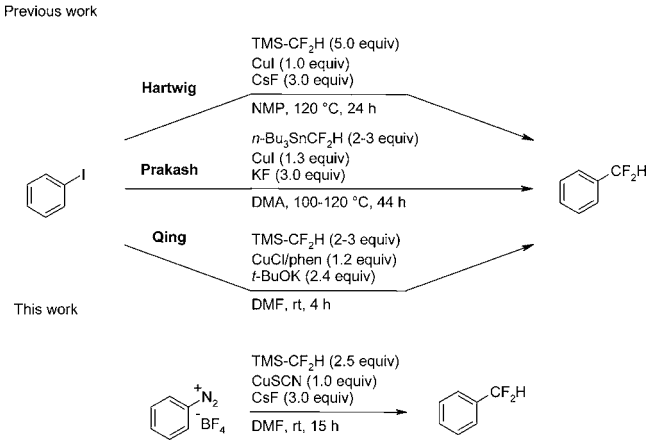
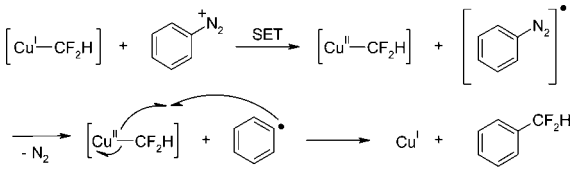
Scheme 1. One-Step Difluoromethylation Strategies



available, inexpensive aryl amines rather than costly aryl iodides (Scheme 1).

However, such a Sandmeyer difluoromethylation may be put into practice only if a suitable Cu−CF_2H complex could efficiently be generated from TMS−CF_2H and sufficiently be stabilized to enter the reaction pathway outlined in Scheme 2.[18a]

Scheme 2. Mechanistic Sketch for a Sandmeyer Difluoromethylation



In order to probe the viability of this approach, we chose the reaction of 4-methoxybenzenediazonium tetrafluoroborate (**1**) with TMS−CF_2H as a model and applied the conditions that had been most efficient in the corresponding trifluoromethylation. However, the desired product was obtained only in very low yield when slowly adding the diazonium salt to a solution of CuSCN, Cs_2CO_3, and TMS−CF_2H in MeCN that had been prestirred for 30 min at room temperature (Table 1, entry 1). Further investigations revealed that, in comparison to Cu−CF_3, the formation of Cu−CF_2H species requires stronger bases, which, however, negatively affect the subsequent Sandmeyer process. With fluoride bases, and CsF in particular, the Cu−CF_2H preformation step became more efficient, so that the overall yield of the process increased (entries 1−3). Changing the reaction solvent to DMF further increased the yields, which is in agreement with the studies by Prakash et al. that this solvent stabilizes Cu−CF_2H species (entries 2, 4, and 5).[15] NMR studies of the mixture of CuSCN, TMS−CF_2H, and CsF in DMF confirmed that, under these conditions, Cu−CF_2H species are formed in high yields.[20]

Among the copper sources tested, copper thiocyanate gave the best results (entry 5). In contrast, copper iodide, which has been used in difluoromethylations of aryl iodides,[13,15] led to unwanted Sandmeyer halogenation (entry 6).

The decisive parameters turned out to be the Cu−CF_2H preformation duration and temperature. In situ NMR studies revealed that this step requires 60 min at 40 °C (entry 9). At

Table 1. Optimization of the Reaction Conditions[a]

entry	Cu-salt	base	solvent	preform. time/temp	yield (%)
1	CuSCN	Cs_2CO_3	MeCN	0.5 h, rt	<10
2	″	CsF	″	″	26
3	″	KF	″	″	<10
4	″	CsF	NMP	″	15
5	″	″	DMF	″	39
6	CuI	″	″	″	28
7	CuSCN	″	″	0.5 h, 80 °C	46
8	″	″	″	0.5 h, 40 °C	58
9	″	″	″	1 h, 40 °C	73
10[b]	″	″	″	″	71
12[b]	–	″	″	″	0
13[b]	CuSCN	–	″	″	0

[a]Reaction conditions: The Cu reagent was preformed by stirring 2.50 mmol of TMS−CF_2H, 0.50 mmol of copper salt, and 1.50 mmol of base in 1 mL of solvent at given temperature and for given time. 0.50 mmol of **1** in 1 mL of solvent was added dropwise at 0 °C and stirred for 12 h at rt. Yields were determined by ^{19}F NMR using trifluoroethanol as an internal standard. [b]1.25 mmol TMS−CF_2H.

lower temperatures or with shorter reaction times, the reaction does not proceed to completion, and at higher temperatures, the Cu−CF_2H species starts to decompose (entries 5, 7, and 8). Accordingly, the highest yield of 73% was obtained when stirring CuSCN, CsF, and TMS−CF_2H for 60 min at 40 °C, then cooling down, adding the diazonium salt, and continuing to stir the reaction mixture overnight at room temperature (entry 9). Following this procedure, the amount of TMS−CF_2H could be reduced to 2.5 equiv without impacting the reaction outcome (entries 9 and 10).

Control experiments revealed that the reaction does not proceed without either copper or base (entries 12 and 13).

Having thus found an efficient protocol for the Sandmeyer difluoromethylation, we next investigated its scope (Scheme 3). Various difluoromethyl arenes were smoothly synthesized from the corresponding arenediazonium tetrafluoroborates. The products were mostly isolated in pure form and fully characterized. Only for some particularly volatile compounds, the yields could only be determined by ^{19}F NMR, and the identity by mass spectroscopy.

Both electron-withdrawing and -donating substrates gave similarly high yields. However, the reaction seems to be sensitive toward steric hindrance, since *ortho*-substituted products (**3**, **5**, **8**, **19**) were formed in somewhat lower yields than their *para*-substituted analogues (**2**, **7**, **18**). Various common functional groups, such as chloro, trifluoromethyl, cyano, nitro, amino, amido, and even bromo substituents, were tolerated, the latter opening up opportunities for further derivatization. Heteroarene diazonium salts including quinolines, carbazole, and indole derivatives were also difluoromethylated in reasonable yields (**23**, **24**, **25**, **27**). Arenediazonium salts bearing carboxylate or iodo substituents were the sole substrates giving unsatisfactory yields. In each case, large amounts of unwanted protodediazotation products were formed. Diazonium salts bearing keto groups (**18**, **19**, **22**) were selectively difluoromethylated at the arene ring. Protodediazotation was the main side reaction; nucleophilic addition of the difluoromethyl group to the carbonyl group was observed only in traces. Remarkably, the latter reaction took place quantitatively for compound **21**, and the difluoromethyl alcohol was isolated in high yield.[11,21]

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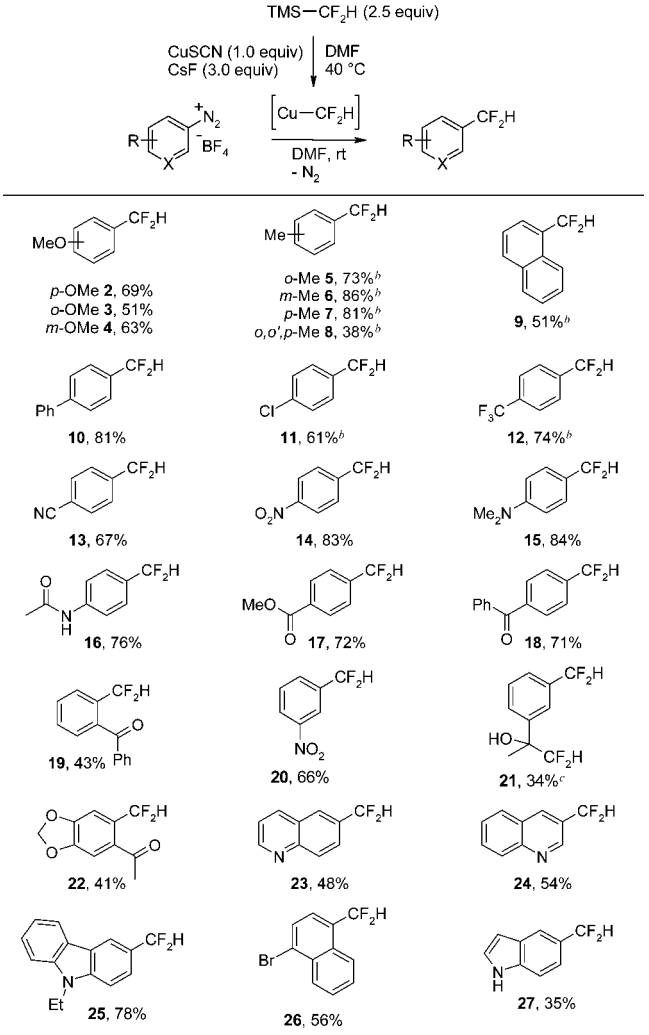
Scheme 3. Scope of the Sandmeyer Difluoromethylation[a]

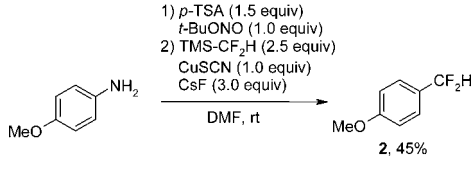


[a]Reaction conditions: The Cu-reagent was preformed by stirring 2.50 mmol of TMS−CF_2H, 1.00 mmol of CuSCN and 3.00 mmol of CsF in 2 mL of DMF at 40 °C for 1 h. 1.00 mmol of Arenediazonium tetrafluoroborate in 2 mL of DMF was added dropwise at 0 °C and stirred for 12 h at rt. Yields of isolated products are given. [b]Yields were determined by ^{19}F NMR using trifluoroethanol as an internal standard. [c]Starting from 3-acetylbenzenediazonium tetrafluoroborate.

We next probed whether the diazonium salts could also be generated from the corresponding anilines directly in the reaction mixture.[18b] Indeed, when 4-methoxyaniline was diazotized in situ with *tert*-butyl nitrite and the resulting solution added to the preformed Cu−CF_2H species, the desired product was obtained in 45% yield based on the aniline (Scheme 4).

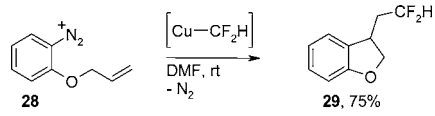
The reaction mechanism was investigated by the addition of radical inhibitors and a radical trapping experiment. When

Scheme 4. One-Pot Diazotization/Difluoromethylation



radical quenchers such as 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) or *p*-benzoquinone are present, the reaction is completely suppressed.[22] Moreover, in the difluoromethylation of 2-(allyloxy)diazonium tetrafluoroborate (**28**), the cyclized product **29** was obtained (Scheme 5). These results, which

Scheme 5. Confirmation of Radical Pathway



confirm that the reaction proceeds via a radical mechanism, are in good agreement with related studies for other Sandmeyer-type reactions and support the mechanistic outline given in Scheme 2.[18a,19,23]

In conclusion, a Sandmeyer-type difluoromethylation of diazonium salts has been developed that opens up an expedient synthetic entry to valuable difluoromethyl arenes and heteroarenes from easily available aromatic amines. The key advantages of the new process are its mild reaction conditions and the fact that the difluoromethylating reagent can be generated in situ from readily available precursors.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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