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Copper-Promoted Sandmeyer Trifluoromethylation Reaction

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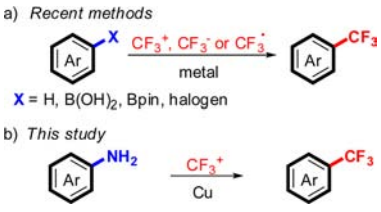
Supporting Information

ABSTRACT: A copper-promoted trifluoromethylation reaction of aromatic amines is described. This transformation proceeds smoothly under mild conditions and exhibits good tolerance of many synthetically relevant functional groups. It provides an alternative approach for the synthesis of trifluoromethylated arenes and heteroarenes. It also constitutes a new example of the Sandmeyer reaction.

Trifluoromethylated arenes ($ArCF_3$) have been recognized as important structural motifs in many bioactive compounds.[1] The CF_3 group can enhance the metabolic stability, lipophilicity, and bioavailability of the parent molecule. Considerable interest has been paid to the development of methods for the synthesis of $ArCF_3$.[2] Earlier methods such as the conversion of toluene and benzoic acid derivatives to $ArCF_3$ usually suffer from harsh reaction conditions and limited functional group tolerance.[3] To overcome these problems, recent research has been directed to transition-metal-promoted trifluoromethylation reactions that usually employ aryl halides,[4] boronic acid derivatives,[5] and even arenes[6] as substrates (Scheme 1a). For further improvement of the flexibility and selectivity of the trifluoromethylation process, it remains important to explore the conversion of other functional groups to CF_3.

Scheme 1. Aromatic Trifluoromethylation



In this context, we explored the conversion of $ArNH_2$ to $ArCF_3$ because aromatic amines are cheap and readily available substrates. We were surprised to find that when Umemoto's reagent is used as the trifluoromethylation agent, $ArCF_3$ can be easily synthesized under Sandmeyer reaction conditions (Scheme 1b). It is significant that this Sandmeyer-type trifluoromethylation reaction enjoys operational simplicity with a good functional group tolerance. Thus, the new reaction provides a useful alternative method for the synthesis of trifluoromethylated arenes as well as heteroarenes. Moreover, although the Sandmeyer reaction[7] has been used for the conversion of $ArNH_2$ amine group into numerous functional groups such as halogen, hydrogen, hydroxyl, cyano, azido, and boronate groups,[8−13] our study adds an unprecedented yet synthetically important example to this century-old transformation.

We began the study by examining the reaction between 4-phenoxyaniline (**1a**) and Umemoto's reagent (**2a**) in the presence of different metals and alkyl nitrites (Table 1). It was interesting to find that when Cu powder was used as the promoter, the desired product **3a** was obtained in 30% yield in CH_3CN at room temperature under air (entry 1). We then

Table 1. Optimization of the Reaction Conditions[a]

entry	metal	RONO	solvent	T (°C)	yield (%)[b]
1	Cu	*t*-BuONO	CH_3CN	23	30
2	Zn	*t*-BuONO	CH_3CN	23	trace
3	Mn	*t*-BuONO	CH_3CN	23	trace
4	Fe	*t*-BuONO	CH_3CN	23	trace
5	Mg	*t*-BuONO	CH_3CN	23	trace
6	Ni	*t*-BuONO	CH_3CN	23	trace
7	Cu	*n*-BuONO	CH_3CN	23	46
8	Cu	*i*-BuONO	CH_3CN	23	48
9	Cu	*i*-AmONO	CH_3CN	23	51
10	Cu	*n*-AmONO	CH_3CN	23	49
11	Cu	*i*-AmONO	PhCN	23	19
12	Cu	*i*-AmONO	$PhCF_3$	23	0
13	Cu	*i*-AmONO	DCE	23	0
14	Cu	*i*-AmONO	DMAc	23	trace
15	Cu	*i*-AmONO	CH_3CN	50	28
16	Cu	*i*-AmONO	CH_3CN	0 to 15	62
17	**Cu**	***i*-AmONO**	**CH_3CN**	**0 to 15**	**74**[c]
18	Cu	*i*-AmONO	CH_3CN	0 to 15	68[c,d]
19	none	*i*-AmONO	CH_3CN	0 to 15	0

[a]Reaction conditions: **1a** (0.2 mmol, 1 equiv), **2a** (0.3 mmol, 1.5 equiv), metal (0.6 mmol, 3 equiv), and RONO (0.6 mmol, 3 equiv) in the solvent (1.0 mL) for 8 h under an air atmosphere, unless otherwise noted. [b]GC yields with biphenyl as an internal standard added after the reaction. [c]Under an Ar atmosphere. [d]The reaction was performed with **2b** instead of **2a**.

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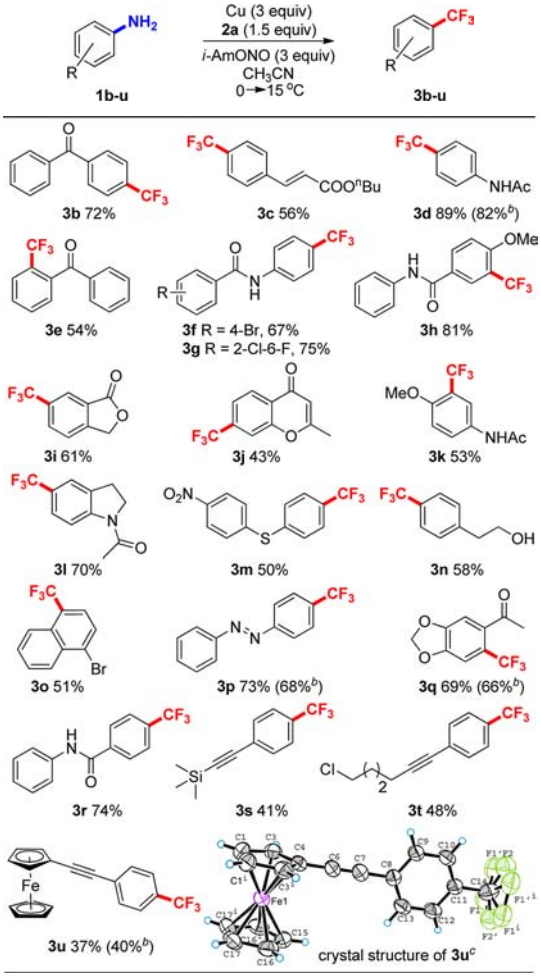
examined whether or not Cu could be replaced by an even cheaper metal such as Zn, Mn, Fe, Mg, or Ni (entries 2−6). Unfortunately, only trace amounts of the desired product were detected. Next, we tested different alkyl nitrites (entries 7−10). The use of isoamyl nitrite (*i*-AmONO) increased the yield of **3a** to 51% (entry 9). Furthermore, the reaction efficiency was found to be affected by the solvent system (entries 11−14). CH_3CN was the optimal medium for the reaction, whereas in $PhCF_3$, 1,2-dichloroethane (DCE), and *N*,*N*-dimethylacetamide (DMAc) we observed a considerable amount of deamination/protonation product [see the Supporting Information (SI)]. In regard to the influence of temperature on the reaction, it was found that the yield of **3a** increased to 62% at 0 to 15 °C (entry 16), whereas a low yield of 28% was obtained when the reaction was conducted at 50 °C (entry 15). Finally, by changing the reaction atmosphere from air to argon, we further increased the yield of **3a** to 74% (entry 17). When the triflate salt **2b** was used instead of **2a**, the reaction also proceeded smoothly with a yield of 68% (entry 18). It is important to mention that no product was detected when no metal promoter was employed (entry 19).

With the optimized conditions in hand, we investigated the scope of the new reaction with diverse aryl amines (Table 2). It was found that a variety of aryl amines can be successfully trifluoromethylated to the desired product in modest to good yields. The reaction can tolerate well electron-donating groups such as ether (**3k**, **3q**), thioether (**3m**), and amide (**3d**, **3f**, **3g**, **3l**) as well as electron-withdrawing groups such as ketone (**3b**, **3e**, **3j**, **3q**), nitro (**3m**), ester (**3i**), and azo (**3p**). Unsaturated C═C double bonds (**3c**) and C≡C triple bonds (**3s**, **3t**, **3u**) are also compatible with the process. It is interesting to note that the present reaction can even tolerate an unprotected OH group (**3n**). In some recent studies, Umemoto's reagent was shown to be capable of trifluoromethylating the ortho C−H bond of some functional groups (e.g., amide) under Pd or Cu catalysis.[6] Under the present conditions, all of the C−H bonds are compatible with the trifluoromethylation process (**3d**, **3f**−**h**, **3k**, **3r**). Furthermore, aryl halide (**3f**, **3g**, **3o**) as well as alkyl halide (**3t**) groups were also found to be compatible with the new transformation. The above features indicate that the present method is complementary to the previous transition-metal-catalyzed trifluoromethylation processes.[14] These features also make additional functionalization reactions possible at the ortho C−H bonds or halogenated positions.

In regard to the trifluoromethylation of heteroaromatic amines, our tests showed that six- or five-membered ring heterocycles (including pyridines and pyrazoles) can be converted to the corresponding trifluoromethylated products in modest yields (Table 3). These transformations can tolerate electron-donating groups such as amide (**5b**) as well as sterically hindered substrates (**5c**). It should be noted that the C−H bonds of the heterocycle were not affected by the present trifluoromethylation process. Thus, the present method enables site-selective trifluoromethylation of heteroaromatic amines.

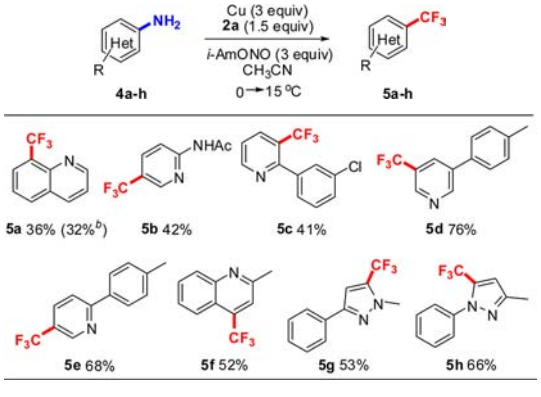
To understand the mechanism of the copper-promoted Sandmeyer trifluoromethylation reaction, we examined the trifluoromethylation of 2-(allyloxy)aniline (**6a**).[4k,15] Interestingly, we obtained only the cyclized product **7a** in 68% yield, whereas the acyclic product **8** was not detected in the GC−MS or ^{19}F NMR analysis (Scheme 2). This observation indicated that the reaction should proceed with the intermediacy of an aryl radical, which is presumably generated from the aryldiazonium intermediate. It is worth noting that the above cyclization/trifluoromethylation sequence also provides an interesting new approach for the synthesis of CF_3-substituted heterocycles. Indeed, similar reactions of **6b**−**d** gave trifluoromethylated 2,3-dihydrobenzofuran, chroman, and indoline derivatives in modest isolated yields.

Table 2. Substrate Scope for Aryl Amines[a]



[a]The reactions were carried out for 8 h on a 0.2 mmol scale. Isolated yields are shown. See the SI for more details. [b]Shown in parentheses are the isolated yields for reactions performed on a 1.0 mmol scale. [c]The X-ray crystal structure of **3u** is shown with the thermal ellipsoids set at 35% probability.

Table 3. Substrate Scope for Heteroaromatic Amines[a]



[a]The reactions were carried out for 8 h on a 0.2 mmol scale. Isolated yields are shown. [b]Shown in parentheses is the isolated yield for a reaction performed on a 1.0 mmol scale.

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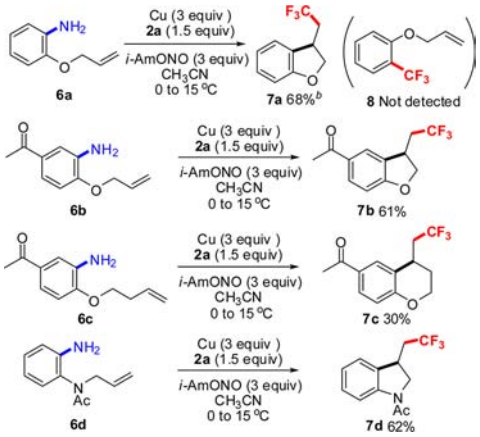
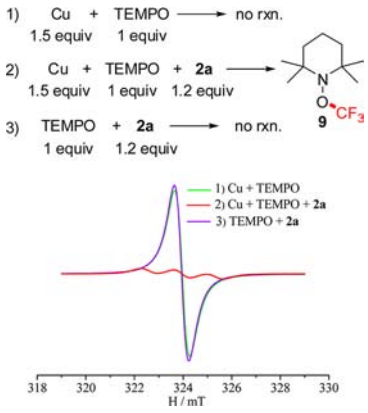
Scheme 2. Formation of CF_3-Substituted Heterocycles[a]



[a]The reactions were carried out for 8 h on a 0.2 mmol scale. Isolated yields are shown. [b]Yield determined by ^{19}F NMR spectroscopy with 1,3,5-trifluorobenzene as an internal standard.

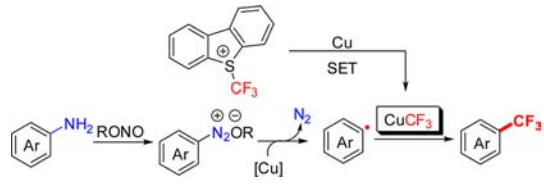
Scheme 3. Trapping of CF_3 Radical by TEMPO



Furthermore, we tested the reaction of Umemoto's reagent with 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) under the promotion of copper (Scheme 3). When either copper or Umemoto's reagent was not added, the solution of TEMPO exhibited a characteristic electron spin resonance (ESR) spectrum. On the other hand, when both Umemoto's reagent and copper were added, the ESR signal of TEMPO decreased significantly, presumably due to the formation of **9** (whose identity was also confirmed by GC–MS analysis). Thus, the above experiment implies the generation of CF_3 radical when Umemoto's reagent is treated with copper powder. In addition, we examined the reaction of Umemoto's reagent with copper (see the SI). This reaction generated a product with an ^{19}F NMR chemical shift of −34.72 ppm, matching that previously reported for $CuCF_3$.[4b,i]

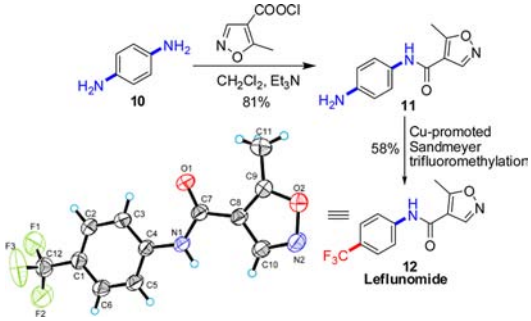
On the basis of the above experimental observations (i.e., the intermediacy of an aryl radical and the generation of CF_3Cu), we propose that the Cu-promoted Sandmeyer trifluoromethylation reaction may proceed through the mechanism shown in Scheme 4. First, copper-mediated single electron transfer (SET) in Umemoto's reagent generates the CF_3 radical, which then reacts with copper to produce CF_3Cu. Second, CF_3Cu reacts with the aryl radical generated from the aryldiazonium ion (produced in situ from the aryl amine and alkyl nitrite) to afford the desired product.[16]

Scheme 4. Proposed Mechanism



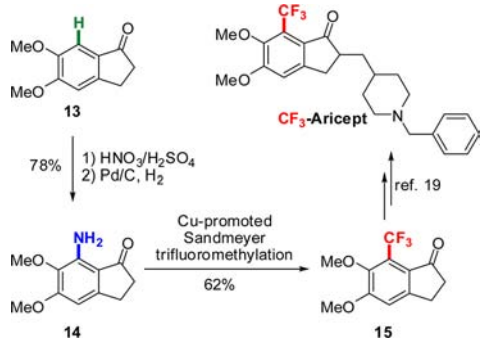
To test the synthetic utility of the copper-promoted Sandmeyer trifluoromethylation reaction, we examined a new route for the preparation of leflunomide (**12**), a disease-modifying antirheumatic drug that can be used to treat moderate to severe rheumatoid arthritis and psoriatic arthritis.[17] As shown in Scheme 5, 1,4-benzenediamine (**10**) was easily acylated to afford **11** in 81% yield. With the new reaction described in the present study, **11** can be converted to **12** in 58% yield (Scheme 5).

Scheme 5. New Synthesis of Leflunomide



Moreover, site-selective C–H trifluoromethylation remains an important challenge for the synthesis of CF_3-containing compounds.[6,18] While aromatic nitration is a traditional transformation, it remains synthetically useful for the functionalization of aromatic C–H bonds. Because the nitro group can be readily reduced to an amino group, the copper-promoted Sandmeyer trifluoromethylation reaction provides an effective new approach for the conversion of an aromatic C–H bond to a C–CF_3 bond. This approach is expected to be useful for the rapid generation of trifluoromethylated derivatives of biologically active molecules. As shown in Scheme 6, we can selectively introduce an NO_2 group onto 5,6-dimethoxy-1-indanone (**13**) and then reduce the intermediate to **14** through catalytic hydrogenation. Using the new reaction developed in the present

Scheme 6. C–H Trifluoromethylation of Bioactive Compounds



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study, we can easily convert **14** to **15** in 62% yield. Notably, compound **15** is a trifluoromethylated derivative of an Alzheimer's drug (Aricept) precursor[19] that was previously made by Nagib and MacMillan[6e] through photoredox catalysis.

In summary, we have developed a copper-promoted Sandmeyer trifluoromethylation reaction for the conversion of aromatic amines to trifluoromethylated arenes and heteroarenes. This new reaction is operationally simple and can be conducted under very mild conditions. A variety of synthetically important functional groups are well-tolerated. Thus, we expect that the new reaction can be used for the rapid generation of trifluoromethylated derivatives of biologically active molecules. To reduce the cost of the reaction further, our next challenge will be the search for less expensive trifluoromethylating agents for the Sandmeyer process.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data. 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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