Silver-Mediated Trifluoromethylation of Aryldiazonium Salts: Conversion of Amino Group into Trifluoromethyl Group

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Supporting Information

ABSTRACT: A novel strategy for aromatic trifluoromethylation by converting aromatic amino group into CF₃ group is reported herein. This method, which can be considered as trifluoromethylation variation of the classic Sandmeyer reaction, uses readily available aromatic amines as starting materials and is performed under mild conditions.

Tri fluoromethylated arenes have become increasingly prevalent in numerous fields, ranging from pharmaceuticals, agrochemicals, to functional materials. However, CF₃-containing compounds are absent in nature, which accounts for the vital importance of developing general and practical methods to introduce a CF₃ group onto aromatic structures. In recent years, the scientific community has witnessed a rapid development of methods for trifluoromethylation of arenes. The traditional means for introducing a CF₃ group onto an aromatic ring relies on a Swarts-type reaction, pioneered by Swarts in 1892. The Swarts-type reaction involves exhaustive chlorination at the benzylic position, followed by chlorine/flourine exchange with HF under harsh conditions (Scheme 1a). Although relatively practical for large-scale industrial production of CF₃-containing aromatic building blocks and intermediates, this process is not appropriate for late-stage introduction of a CF₃ group onto an aromatic structure, which is becoming increasingly important in drug development. To tackle such a problem, methodologies for the direct trifluoromethylation of arenes have been developed. A commonly applied approach is the conversion of halogen substituents into CF₃ groups through transition-metal-mediated or -catalyzed reactions (Scheme 1b). Since the first discovery by McLoughlin and Thrower in 1969, CuCF₃ reagents have been extensively studied and widely used in the stoichiometric trifluoromethylation of aryl halides. More recently, Cu- or Pd-catalyzed trifluoromethylation has attracted great attention from the synthetic community. Accordingly, significant progress in this field has been achieved. Closely related methods, the Cu-catalyzed or -mediated conversion of a boron group into a CF₃ group, have also been developed (Scheme 1c). In addition to the transition-metal-catalyzed or -promoted methods, a distinct approach to introducing a CF₃ group is the facile trifluoromethylation of an aromatic C–H bond through a radical process (Scheme 1, d,e).

Aromatic amines are commonly used chemicals and easily available. The aromatic amino group serves as a versatile motif, which can be converted into various functional groups. These transformations mostly proceed through arene diazonium salts, which are important intermediates in organic chemistry. Since their first discovery in 1858, several named reactions related to arene diazonium salts have been established as classic methods for functional group transformations. Undoubtedly, the most prominent one is the Sandmeyer reaction, which can replace aromatic amino groups with halides or pseudohalides. Another important reaction is the Balz–Schiemann reaction, which can convert an amino group into a fluoro group. These classic

Scheme 1. Methods for Aryl Trifluoromethylation Categorized by the Groups Being Converted

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transformations are not only routinely practised in research laboratories but also widely applied in industry.

Based on the oxidizing properties of aryl diazonium salts and the strong σ-donor nature of the trifluoromethyl group in the [AgCF₃] complex and also inspired by Ritter’s recent reports on reductive elimination from bimetallic high-valent silver complex to form Cₛ₋ₐ-F bonds, we proposed that oxidative addition of diazonium salt A would be favored at an electron-rich silver center to afford intermediate B (Scheme 2).

Scheme 2. Proposed Strategy for Trifluoromethylation of Aromatic Amines

Subsequently, intermediate B undergoes reductive elimination to form a Cₛ₋ₐ-F₃ bond and a AgCl precipitate. According to this hypothesis, we envisioned that conversion of aromatic amines into the corresponding trifluoromethyl arenes (trifluoromethylation variant of the classic Sandmeyer reaction) would be feasible.

Initially, we imitated the classic Sandmeyer reaction conditions by slowly adding a solution of [AgCF₃] in MeCN, freshly prepared from AgF and Me₃SiCF₃ (Ruppert−Prakash reagent), into the diazonium chloride (X = Cl) at 0 °C, prepared in MeCN from ethyl 4-aminobenzoate through diazotization with t-BuONO/aq HCl (Table 1). To our delight, the expected trifluoromethylated product 3 was formed in 41% yield based on ¹⁹F NMR analysis (entry 1). It was found that the reaction was favored at low temperature. When the solvent was switched to EtCN (mp = -93 °C) and the addition of [AgCF₃] was carried out at -78 °C, we observed a dramatic increase in the yield (entry 2). It was noted that 3.5 equiv of [AgCF₃] was necessary to maintain the high yield. Further study indicates that the counterions of diazonium salt impose significant affect on the reaction. Br⁻ and CF₃CO₂⁻ afforded similar results as Cl⁻, whereas BF₄⁻ gave diminished yield and t-BuO⁻ gave only a trace amount of the product (entries 3−6). It is noteworthy that using [CuCF₃] as the CF₃ source, freshly prepared from CuCl, CsF, and Me₃SiCF₃ in DMF, the trifluoromethylation also proceeded, albeit with lower yield (entry 7). Finally, other solvents, such as DMF, DCE, MeOH, and EtOH, were all found to give poor results.

With the optimal reaction conditions (Table 1, entry 2), the substrate scope was then surveyed with a series of aromatic amine derivatives (Scheme 3). In general, the aniline derivatives bearing either electron-withdrawing or -donating groups react smoothly to afford the corresponding trifluoromethylation products in moderate to excellent yields. 4-Aminobenzenes is also a suitable substrate for the reaction, affording product. Trifluoromethylation of unprotected alcohol and benzoic acid affords the desired products 15 and 16 in good yields, respectively. Remarkably, oxidation sensitive groups, such as vinyl, alkynyl, Bpin, and TMS groups, also tolerate the reaction conditions (17−22). The anilines bearing ortho-substitutents, including ester and bulky isopropyl groups, also worked well to give 23 and 24, respectively. The diminished yields of 28 and 29 are due to the sublimation of the trifluoromethylated naphthalene products under reduced pressure during purification.

For the substrate bearing pyridine moiety, the reaction gave only a low yield of the product 30, presumably due to the protonation of the pyridine nitrogen. In the case of heteroaromatic amines, such as indoles and benzofurans, the desired products 31−34 could be formed in moderate yields. Besides, various di- and multi-substituted CF₃-bearing arenes could be accessed through this transformation in generally good yields (35−46). Finally, to demonstrate the applicability of this method in more complex molecules, we smoothly converted the amino groups embedded in the estrone and tocopherol framework into the trifluoromethyl groups (47 and 48).

The reaction with ethyl 4-aminobenzoate was also conducted on a gram scale to generate the desired product 3 in comparable yields as the small-scale experiment (eq 1).

Moreover, by employing our previously established metal-free borylation method, we could smoothly convert the two amino groups of benzene-1,4-diamine into Bpin and CF₃ groups successively, with similar Sandmeyer-type reaction for both steps (eq 2). This transformation shows the oxidation sensitive Bpin group tolerates the Sandmeyer-type trifluoromethylation (also see 20 in Scheme 3).

Preliminary mechanistic investigations have been carried out on this reaction. For the Sandmeyer-type transformations, it was proposed that the reaction may involve aryl radical
species. To validate whether aryl radical species are generated in the current trifluoromethylation process, a radical clock probe was introduced by using 2-(but-3-en-1-yl)aniline 52 as the substrate in the reaction (Scheme 4a). The normal trifluoromethylation product 54 was formed in 41% yield (19F NMR), whereas cyclization product 55 could not be detected. The diminished yield of the trifluoromethylation product 54 was due to the decomposition of the substrate and the product under the reaction conditions. These results are not in favor of the possible involvement of aryl radical species. Next, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), a well-known free radical scavenger, was introduced as the additive in the standard reaction (Scheme 4b). The yield of 3 was diminished to 42% and TEMPO-CF₃ 56 was formed in 17% yield when 1.0 equiv of TEMPO was added under standard condition. The yield of 3 was further dropped to 34%, and 73% of TEMPO-CF₃ 56 was observed when 3.5 equiv of TEMPO was added. However, TEMPO-Ar adducts were not observed, as judged by both NMR and GC-MS analysis of the crude product. Nitrobenzene, which has been shown to be the inhibitor of SET steps in free radical aryl C−H trifluoromethylation, has essentially no effect on the reaction. We speculate that the formation of CF₃ radical is due to the background reaction of [AgCF₃] (Scheme 4c). Thus, in the absence of aryl diazonium salt, [AgCF₃] was added to the TEMPO in EtCN. We observed the formation of TEMPO-CF₃ 56 in 18% yield. Moreover, in the trifluoromethylation reaction, we found that most silver remains as Ag(I) salt, rather than Ag(0). Collectively, these results indicate that CF₃ radical is unlikely involved in the trifluoromethylation pathway. An oxidative addition–reductive elimination mechanism involving high-valent silver species, as shown in Scheme 2, may be
involved. However, rigorous investigations are necessary to unambiguously elucidate the detailed mechanism.

In summary, the conversion of an amino group into a CF₃ group is a valuable complement to the previously established trifluoromethylation methods. The reaction proceeds at low temperature and tolerates various functional groups. Moreover, the amino group can be readily protected and deprotected, rendering this method suitable for late-stage introduction of a CF₃ group onto an aromatic structure.

**REFERENCES**