

Trifluoromethylthiodediazoniatio: a simple, efficient route to trifluoromethyl aryl sulfides

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Copper(I) trifluoromethanethiolate reacts with a range of diazonium salts containing electron-withdrawing groups to give the corresponding trifluoromethyl aryl sulfides in high yield; it is also possible to carry out the diazotisation and trifluoromethylthiolation in one pot directly from the anilines.

Incorporation of a SCF₃ group into an aromatic molecule is of interest to the pharmaceutical and agrochemical industries, where the high lipophilicity and high electron-withdrawing ability of the group have important implications.¹ Current industrial methods for the formation of trifluoromethyl aryl sulfides generally involve multi-step processes which requires harsh conditions, restricting the nature of the other substituents on the ring as well as being environmentally damaging.² A simple, direct method for the formation of these compounds is thus highly desirable. One pot methods for preparing trifluoromethyl aryl sulfides have been reported but these are based on preformed thioaryl units (ArSCl and ArSCN) and require excess quantities of both of the expensive reagents CF₃SiMe₃ and Bu₄NF.³ The Sandmeyer reaction is a well known method for the formation of chloro-, bromo- and cyanoarenes *via* reaction of the diazonium salts with copper(I) chloride, bromide or cyanide respectively.⁴ However, despite copper(I) trifluoromethanethiolate (CuSCF₃) being used for the formation of trifluoromethyl aryl sulfides *via* reaction with iodobenzenes at high temperature⁵ there are no reports of its reaction with diazonium salts. We have found that it is possible to form trifluoromethyl aryl sulfides from the corresponding diazonium tetrafluoroborates or directly in one pot from the anilines simply by reacting with CuSCF₃.

Addition of a solution of 2-nitrobenzenediazonium tetrafluoroborate **1a**⁶ to an acetonitrile solution of CuSCF₃ at 50 °C⁷ leads to rapid evolution of gas with concurrent formation of a deep yellow colour⁸ ¹H NMR, ¹⁹F NMR and GC of the solution all show that the major aromatic product is the 2-nitrophenyl trifluoromethylsulfide **2a**. Phenol, biphenyl or azo compounds, which are often observed as byproducts in diazonium reactions, were not formed in this system⁹ although a small amount of nitrobenzene was detected.¹⁰ At room temperature, the reaction is slower, but leads to a very similar product distribution. Other diazonium salts (Fig. 1) containing electron-withdrawing groups react similarly (Table 1). Halo, nitro and cyano groups

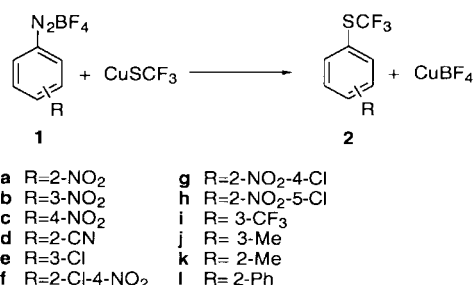


Fig. 1 Conversion of aryl diazonium tetrafluoroborates to trifluoromethyl aryl sulfides.

Table 1 Yields of ArSCF₃ from two-stage dediazoniations

Diazonium salt	Yield of ArSCF ₃ ^a (%)	Diazonium salt	Yield of ArSCF ₃ ^a (%)
1a	89 (83)	1g	60
1b	97	1h	95 (67)
1c	98 (76)	1i	91
1d	95	1j	17
1e	98	1k	7
1f	92	1l	3

^a Yields calculated on the basis of GC area, unoptimised isolated yields in parentheses.

all survived the reaction. Steric factors do not appear to have an important effect: 2-, 3- and 4-nitrobenzenediazonium tetrafluoroborates all reacted immediately under the same conditions to give very similar product yields and impurity profiles, whereas it can be difficult to synthesise *ortho*-substituted derivatives by traditional means.¹¹

Unfortunately, when electron-donating groups are present, the product yields are generally low (Table 1). This is due to a lack of reaction selectivity, thus while 2-diazobiphenyl tetrafluoroborate completely reacts the major product is the amide (Fig. 2). Such reactions have been reported to occur *via* reaction of a diazonium salt with acetonitrile.¹² In benzonitrile, no reaction of this substrate with CuSCF₃ was observed, with the only detected product being 2-hydroxybiphenyl. This was also the major product when the reaction was carried out in acetone. Methylbenzenediazonium tetrafluoroborates reacted similarly.

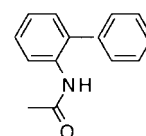


Fig. 2 Product from the reaction of 2-diazobiphenyl tetrafluoroborate with CuSCF₃.

In an effort to avoid the isolation of the diazonium intermediate, we investigated other diazotisation methods. Because CuSCF₃ reacts with acids to give HSCF₃, a non-protic system was required. Although, classically, diazotisation is achieved using sodium nitrite and a mineral acid, alternative methods do exist.¹³ Doyle *et al.* have described the conversion of aryl amines to the corresponding halides in one-pot using *tert*-butyl nitrite and a copper(II) halide.¹⁴ We have found that it is possible to effect a similar one-pot conversion of an aryl amine to a trifluoromethyl aryl sulfide (Fig. 3). Hence, when *tert*-butyl nitrite in acetonitrile was added to a pre-heated solution of 2-nitroaniline and CuSCF₃ in acetonitrile at 50 °C, the solution

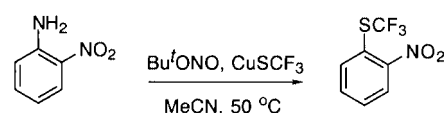


Fig. 3 One-pot synthesis of trifluoromethyl aryl sulfides from anilines.

gradually became black. The formation of 2-nitrotrifluoromethylphenyl sulfide (29%) was detected, along with nitrobenzene (34%) and 2-nitrophenol (2%). It occurred to us that while it is not possible to use a Brønsted acid to improve the reaction, a Lewis acid may be beneficial. Repeating the one-pot reaction of 2-nitroaniline in the presence of BF_3 improved the selectivity to the 2-nitrotrifluoromethylphenyl sulfide to 45%. This method proved to be even more successful with 3-nitroaniline (72%) and 4-nitroaniline (66%), and moderately successful with other activated substrates and aniline itself (Table 2).¹⁵ Substrates containing electron donating groups gave no appreciable yield of the desired trifluoromethyl aryl sulfide.

Table 2 Yields of ArSCF_3 from one-pot reactions of anilines

Aniline	GC yield of ArSCF_3 (%)
Aniline	42
2-Nitroaniline	45
3-Nitroaniline	72
4-Nitroaniline	66
3-Trifluoromethylaniline	46
3-Chloroaniline	18

In conclusion, we have demonstrated a new approach to trifluoromethyl aryl sulfides which is applicable to a wide range of substrates. This has advantages over current methodologies—the yields and product purity are high after a very simple work up procedure; the route is shorter than the traditional multi-step methods; and a wider range of functional groups is accessible owing to the mild conditions utilised. Unfortunately, this methodology is apparently restricted to substrates which are not electron-rich. It is also possible to form trifluoromethyl aryl sulfides in one pot directly from the anilines in a clean, safe and efficient direct route to these important compounds.

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- In a typical reaction, to a solution of CuSCF_3 (0.165 g, 1.0 mmol) in acetonitrile (3 ml) was added **1a** (0.237 g, 1.0 mmol) in acetonitrile (2 ml) at 50 °C with stirring. Rapid evolution of gas was observed and the solution became deep yellow. After stirring for 30 min, the solution was diluted with diethyl ether (200 ml) and filtered through Celite. The solvent was then removed to give **2a** (0.1883 g, 83%). *Selected analytical data*: 2-nitrophenyl trifluoromethyl sulfide **2a** δ_{C} (254 MHz, CD_3CN) -41.3 (s); δ_{H} (270 MHz, CD_3CN) 7.66–7.82 (m), 7.90 (m), 8.12 (m); m/z 223 (M^+); Anal. Calc. for $\text{C}_7\text{H}_4\text{SF}_3\text{NO}_2$ m/z 222.991485; Found m/z 222.991794; $\nu_{\text{max}}/\text{cm}^{-1}$ 1570s (C–NO₂), 1345s (C–NO₂), 1103s (C–F), 777m (C–S).
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- In a typical reaction to a preheated solution of 2-nitroaniline (0.0553 g, 0.4 mmol) and CuSCF_3 (0.0825 g, 0.5 mmol) in acetonitrile at 50 °C is added BF_3 etherate (0.4 mmol BF_3), followed by *tert*-butyl nitrite in acetonitrile. Evolution of a gas was observed and a darkening in the colour of the reaction mixture. Samples for GC, GC–MS and NMR analysis were first added to saturated calcium carbonate solution and then extracted with diethyl ether.