ChemComm

Trifluoromethylthiodediazoniation: a simple, efficient route to trifluoromethyl aryl sulfides

Dave J. Adams, Andrew Goddard, James H. Clark* and Duncan J. Macquarrie

Clean Technology Centre, Chemistry Department, University of York, Heslington, York, UK YO10 5DD.
E-mail: jhc1@york.ac.uk

Received (in Liverpool, UK) 15th February 2000, Accepted 28th April 2000

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 SCF_3 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 CF_3SiMe_3 and Bu_4NF.[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 ($CuSCF_3$) being used for the formation of trifluoromethyl aryl sulfides *via* reaction with iodobenzenes at high temperature[5] 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 $CuSCF_3$.

Addition of a solution of 2-nitrobenzenediazonium tetrafluoroborate **1a**[6] to an acetonitrile solution of $CuSCF_3$ at 50 °C[7] leads to rapid evolution of gas with concurrent formation of a deep yellow colour[8] ^1H NMR, ^{19}F 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 system[9] 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 similarily (Table 1). Halo, nitro and cyano groups 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]

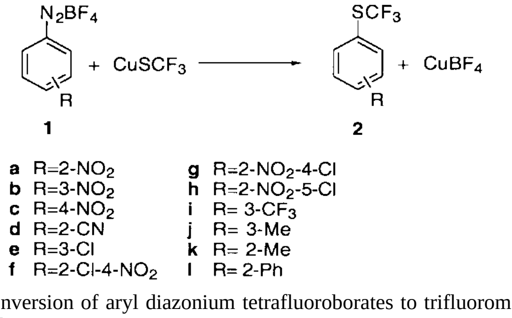

Fig. 1 Conversion of aryl diazonium tetrafluoroborates to trifluoromethyl aryl sulfides.

Table 1 Yields of $ArSCF_3$ 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.

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 $CuSCF_3$ 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 similarily.

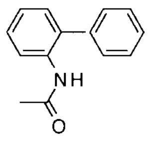

Fig. 2 Product from the reaction of 2-diazobiphenyl tetrafluoroborate with $CuSCF_3$.

In an effort to avoid the isolation of the diazonium intermediate, we investigated other diazotisation methods. Because $CuSCF_3$ reacts with acids to give $HSCF_3$, 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 decribed 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 $CuSCF_3$ in acetonitrile at 50 °C, the solution

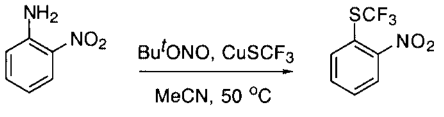

Fig. 3 One-pot synthesis of trifluoromethyl aryl sulfides from anilines.

DOI: 10.1039/b002560g

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.

We gratefully acknowledge the support of the EPSRC (ROPA grant), the EPSRC/RAEng (Clean Technology Fellowship to J. H. C.) and the Royal Society (University Research Fellowship to D. J. M.). We would also like to thank Alec Taylor for helpful discussions.

Notes and references

1 R. Filler, in *Organofluorine Chemical and their Industrial Applications*, ed. R. E. Banks, Ellis Horwood Ltd, Chichester, 1979; B. E. Smart, in *Organofluorine Chemistry. Principles and Commercial Applications*, ed. R. E. Banks, B. E. Smart and C. Tatlow, Plenum Press, New York, 1994; R. M. DeMarinis and W. M. Bryan, *J. Org. Chem.*, 1977, **42**, 2024.

2 M. A. McClinton and D. A. McClinton, *Tetrahedron*, 1992, **37**, 6555; J. F. Harris, *J. Org. Chem.*, 1967, **32**, 2063; J. H. Clark, D. Wails and T. W. Bastock, *Aromatic Fluorination*, CRC Press, New York, 1997.

3 T. Billard and B. R. Langlois, *Tetrahedron Lett.*, 1996, **37**, 6865; T. Billard, S. Large and B. R. Langlois, *Tetrahedron Lett.*, 1997, **38**, 65.

4 A. F. Hegarty, in *The Chemistry of the Diazonium and Diazo Groups*, ed. S. Patai, J. Wiley and Sons, Bristol, 1978.

5 L. M. Yagupolskii, N. V. Kondratenko and V. P. Sabur, *Synthesis*, 1975, 721; D. C. Remy, K. E. Rittle, C. A. Hunt and M. B. Freedman, *J. Org. Chem.*, 1976, **41**, 1644.

6 Diazonium salts were prepared *via* the method described in A. Roe, *Org. React.*, 1949, **5**, 193.

7 J. H. Clark, C. W. Jones, A. P. Kybett, M. A. McClinton, J. M. Miller, D. Bishop and R. J. Blade, *J. Fluorine Chem.*, 1990, **48**, 249.

8 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_F(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 $C_7H_4SF_3NO_2$ *m*/*z* 222.991485; Found *m*/*z* 222.991794; ν_{max}/cm^{-1} 1570s (C–NO_2), 1345s (C–NO_2), 1103s (C–F), 777m (C–S).

9 H. Ku and J. R. Barrio, *J. Org. Chem.*, 1981, **46**, 5239.

10 H. H. Hodgson and A. P. Mahaderon, *J. Chem. Soc.*, 1947, 173.

11 O. Schere, *Angew. Chem.*, 1939, **52**, 457.

12 W. E. Hanby and W. A Waters, *J. Chem. Soc.*, 1939, 1792.

13 L. Friedman and J. F. Chelbowski, *J. Org. Chem.*, 1968, **33**, 1636.

14 M. P. Doyle, B. Siegfried and J. F Dellona, *J. Org. Chem.*, 1977, **42**, 2426.

15 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.

Typeset and printed by Black Bear Press Limited, Cambridge, England