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THE INTRODUCTION OF SCF_3 INTO AROMATIC SUBSTRATES USING CuSCF3 AND ALUMINA-SUPPORTED $CuSCF_3$

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SUMMARY

Trifluoromethylthiocopper(I) has been readily prepared from the silver analogue, using a metathetical reaction with copper(I) bromide. Homogeneous $CuSCF_3$ and the supported reagent $CuSCF_3$–alumina have been compared in their reactivity towards aryl iodides, in order to form trifluoromethylaryl sulphides in good yields.

INTRODUCTION

There is a growing interest in the preparation and biological activity of molecules containing the trifluoromethylthio group[1]. The exploitation of trifluoromethylthio compounds is hindered by the difficulty in their synthesis. The methods that are currently available involve harsh conditions and toxic materials[2], or are not applicable to a wide range of substrates[3]. Trifluoromethylthio-copper(I) is a more promising source of the SCF_3 group and is reported to react well with iodoaromatics, but is difficult to prepare.

The reaction of silver monofluoride with carbon disulphide at high pressure followed by methathesis with copper(I) bromide[4], that of mercury difluoride with

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carbon disulphide followed by a redox reaction with copper metal[5] and that of copper metal with bis(trifluoromethyl) disulphide[6] have all been used to prepare the desired salt, but all involve either forcing conditions or highly toxic materials.

Our interest in using copper(I) salts in the form of supported reagents[7] as well as our interest in new methods of preparing fluorinated molecules[8], led us to investigate the preparation and use of the trifluoromethylthiocopper(I) salt further.

RESULTS AND DISCUSSION

We have found that the precursor salt trifluoromethylthiosilver(I) can be easily prepared in the laboratory by the reaction of silver monofluoride with carbon disulphide in dipolar aprotic solvents such as acetonitrile or N-methylpyrrolidone (NMP). Acetonitrile was the preferred solvent due to its easy removal by rotary evaporation. This is a marked improvement on the previously reported methods, since standard laboratory glassware can be employed. The copper salt can then be obtained by the methathetical reaction of the trifluoromethylthiosilver(I) with copper(I) bromide. In this way the trifluoromethylthiocopper(I) product can be consistently prepared in a yield of greater than 95% with respect to the silver fluoride used.

Analysis of the $CuSCF_3$ by positive ion FAB-MS showed only copper ions; no silver remained in the isolated product. The negative ion spectrum showed peaks at 145, 126 and 107 m/z respectively, corresponding to $CuSCF_2$, CuSCF and CuSC fragments. The ^{19}F NMR of the salt was found to be very solvent dependent: -18.7 ppm in pyridine to -28.7 ppm in sulpholane (relative to $CFCl_3$).

The trifluoromethylthiocopper(I) salt prepared in this way underwent reaction with iodoaromatics as previously reported[4-6], (see Table). We found that these reactions were very difficult to work up and resulted in poor isolated yields. In the light of this we decided to look at supported reagent versions of the salt. These were easily prepared by the addition of the high surface area material to a solution of trifluoromethylthiocopper(I) in acetonitrile, and then removing the solvent slowly under reduced pressure. For alumina and silica, a loading of 1 mmol of $CuSCF_3$ to 1 g of support material was employed, for charcoal 3.3 mmolg^{-1}. The reactions of various supported reagent versions of the $CuSCF_3$ salt were investigated using 2-iodonitrobenzene as the model substrate. From the results it is clear that alumina is the best support material for these reactions (see Table). The alumina supported reagent was found to undergo reaction with other iodoaromatics and activated bromoaromatics (see Table) and to result in much higher isolated product yields.

The major advantage of the system was in the ease of purification of the product. The reaction mixture was simply poured onto a silica column and the reaction solvent (t-BuPh) was removed by eluting the column with petroleum ether (40 - 60). The product was then washed off the column using diethyl ether and isolated by the removal of all solvent under reduced pressure.

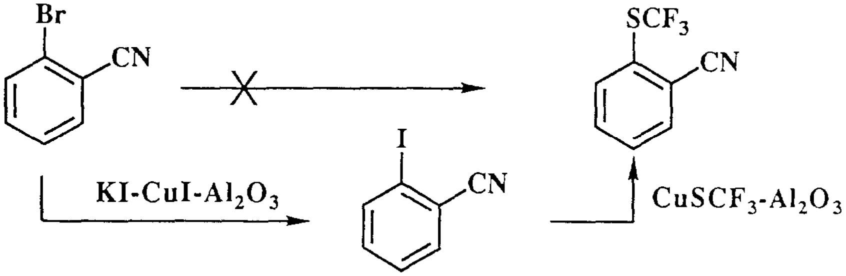
TABLE

The formation of trifluoromethylaryl sulphides

Reagent	Substrate	t/h	Yield of $ArSCF_3$ % (isolated)
$CuSCF_3$[a]	2-Iodonitrobenzene	2	100 (53)
$CuSCF_3$[a]	4-Iodonitrobenzene	18	100 (45)
$CuSCF_3$[a]	Iodobenzene	8	85 (60)
$CuSCF_3$[a]	2-Iodotoluene	10	78 (54)
Charcoal-$CuSCF_3$[b]	2-Iodonitrobenzene	8	40
Silica-$CuSCF_3$[b]	2-Iodonitrobenzene	24	0
Alumina-$CuSCF_3$[b]	2-Iodonitrobenzene	2	100
Alumina-$CuSCF_3$[b]	Iodobenzene	12	98 (65)
Alumina-$CuSCF_3$[b]	4-Iodonitrobenzene	8	81 (70)
Alumina-$CuSCF_3$[b]	2-Iodotoluene	18	68 (65)
Alumina-$CuSCF_3$[b]	4-Iodoanisole	12	91 (83)
Alumina-$CuSCF_3$[b]	2-bromonitrobenzene	5	100 (95)
Alumina-$CuSCF_3$[b]	2-bromobenzonitrile	15	0
Alumina-KI-CuI[b] Alumina-$CuSCF_3$	2-bromobenzonitrile	15[c]	83 (64)

[a] Homogeneous reactions in NMP at 150°C. [b] Supported reagent reactions in ^{t}BuPh at 150°C. [c] 2-bromobenzonitrile, iodinated with an Alumina-KI-CuI reagent 7h; then Alumina-$CuSCF_3$ added. Yield after a further 8h.

We were able to extend the substrates to include the activated bromoaromatic 1-bromo-2-nitrobenzene. In the case of unreactive bromo-substrates such as 2-bromobenzonitrile, we have discovered that it is possible to achieve production in situ Thus the initial addition of the iodinating supported reagent, KI-CuI-alumina[9], followed by $CuSCF_3-Al_2O_3$ resulted in the conversion of bromobenzonitrile to trifluoromethyl (2-cyanophenyl) sulphide in good yield.



An important factor to note is that the supported reagent $CuSCF_3-Al_2O_3$, unlike the parent salt, was found to decompose with time and therefore should be used immediately after preparation. The fate of the trifluoromethylthiocopper(I) on the support surface is presently under investigation and may be linked to the requirement of a five fold excess of the reagent in the reactions above.

In conclusion, we have shown that trifluoromethylthiocopper(I) can be easily prepared using standard laboratory glassware. The reagent can be used to convert iodoaromatics in dipolar aprotic solvents to trifluoromethylthio aromatics or it can be converted to and used as a supported reagent $CuSCF_3$-alumina. The latter material enables reaction to be carried out in a non-polar solvent and results in higher isolated yields.

EXPERIMENTAL

Positive and negative ion fast atom bombardment mass spectra were obtained with a ZAB-E instrument (VG Ltd., Manchester, UK) fitted with a saddle/field FAB gun (Ion Tech, Teddington, UK) Xenon was used as the bombarding atom with a beam energy of approximately ~ 8 keV. A stainless steel probe tip was used. All spectra were peak averaged from a minimum of 10 scans using an 11/250 data system. Mass spectra were obtained by electron impact on a Kratos MS-3074 with a Hewlett Packard 26299 data station. Proton and fluorine NMR spectra were obtained using a Bruker WP80SY (80MHz) NMR spectrometer using TMS as internal reference for the ^1H and $CFCl_3$ as internal reference for the ^{19}F

measurement. ^{13}C NMR spectra were obtained using a JEOL FX90Q NMR spectrometer using TMS as an internal reference. The chemical shifts are expressed in ppm with respect to the reference and the signal characterised by s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). A Phillips PU4500 with a Hewlett Packard 3396A integrator were used for GLC analysis using 10% OV101 on chromasorb.

Preparation of Trifluoromethylthiocopper(I)

Silver fluoride (15 g, 0.12 mol), carbon disulphide (15 ml) and acetonitrile (100 ml) were placed in a 3-neck 250 ml flask fitted with overhead stirrer and condenser. The mixture was stirred for 14 h at 80°C (oil bath). After this time the condenser's position was altered in order to distill off any remaining carbon disulphide. Copper(I) bromide (5.69 g, 0.04 mol) was then added and the mixture left stirring for a further 1h. The black precipitate formed was filtered off and washed 3x with 25 ml of acetonitrile. The filtrates were combined and the acetonitrile was removed under reduced pressure, to yield a white/grey solid (6.6 g, 98%). [^{19}F NMR showed this to be mainly $CuSCF_3$ with slight contamination from HF_2^- species.

Reactions of the Salt

4-Iodoanisole

(0.47 g, 2 mmol) trifluoromethylthiocopper(I), (1.55 g, 10 mmol) 4-iodoanisole and NMP (10) ml) were placed in a 25 ml round bottom flask and heated at 150°C for 18 h. The resultant black solution was allowed to cool. Water was then added and the organic products extracted into diethylether twice. The ether extracts were combined and washed with 3 further aliquots of water. The ether was removed on a rotary evaporator to yield 0.21 g of product (45%). MS : M^+ 208: 139(100) 208(60) 96(19) 69(18) 124(12) 45(5) 77(4) 189(3). [^{19}F NMR : -44.4 ppm. ^1H NMR: 7.1 ppm (dd 58.6 and 8.8 Hz) and 3.7 ppm. $^{13}C\{^1H\}$ NMR: 161.9 (C-O), 138.2 (C-H), 129.6 (q, CF_3, 307.6 Hz). 115.0 (C-H) and 55.3 (CH_3) ppm. The C-CF_3 coupling was not obvious.

2-Iodonitrobenzene reaction was carried out as above, but employing a 2x mole excess of trifluoromethylthiocopper(I). MS : M^+ 223: 154(100) 98(77) 69(65) 106(49) 78(35) 45(32) 223(29) 39(28). ^{19}F NMR: -43.0 ppm. ^1H NMR: multiplets at 8.2, 7.6 and 7.4 ppm.

Iodobenzene reaction was carried out in the same manner as 4-iodoanisole. MS : M^+ 178: 109(100) 178(80) 65(25) 51(12) 39(10) 159(5) 82(3). ^{19}F NMR : -41.7 ppm.

Iodotoluene reaction was carried out as above. MS : M$^+$ 192: 192(100) 123(99) 69(50) 44(49) 79(34) 91(31) 51(22). ^{19}F NMR : -42.1 ppm.

Preparation of $CuSCF_3-Al_2O_3$ (1 mmolg^{-1})

Trifluoromethylthiocopper(I) (10 mmol) was dissolved in acetonitrile (50 ml) and alumina (BDH neutral, 10g) was added. The solvent was then slowly removed on a rotary evaporator to produce a free flowing powder. The silica supported reagent was produced in the same way, but the charcoal reagent was 3.3 mmolg^{-1}.

Reactions of Supported Trifluoromethylthiocopper(I)

2-Iodonitrobenzene

$CuSCF_3-Al_2O_3$ (11.9 g, 10 mmol $CuSCF_3$), 2-iodonitrobenzene (1.24 g, 5 mmol) and t-butylbenzene (50 ml) were placed in a 3 neck round bottomed flask fitted with an overhead stirrer and condenser. The mixture was stirred at 150°C for 2 h. The reaction mixture was allowed to cool and the solid filtered off and washed with 2 x 25 ml ether. The filtrates were added together and the ether removed under reduced pressure. The resultant liquid was poured down a silica column (Kieselgel 70 - 230 mesh) using pet. ether (40 - 60) as the eluent. After all the t-butylbenzene had been removed the column was washed with diethylether to remove the product. The ether was then removed under reduced pressure to yield the desired product. Analysis was carried out as above.

Other substrates

The same method was employed for the other substrates mentioned in the text (not bromobenzonitrile, see below); except that a 5x excess (with respect to substrate) of $CuSCF_3$ was added. Analysis was by g.l.c. and ^{19}F NMR (presented above).

2-Bromobenzonitrile

Preparation of the $KI-CuI-Al_2O_3$ supported reagent was carried out by dissolving copper iodide (1.71 g, 9 mmol) in acetonitrile (200 ml) and potassium iodide (3.48 g, 21 mmol) in water (10 ml). The two solutions were mixed together with alumina (BDH neutral, 30 g) and the solvents slowly removed under reduced pressure. The resulting pale brown powder was washed 4x with acetone to yield a lime green free flowing powder, which was dried at room temperature under vacuum for 3 h. 2-Bromobenzonitrile (2 mmol), $KI-CuI-Al_2O_3$ (11.73 g, 10 mmol of I^-) and 30 ml of t-butylbenzene were placed in a 100 ml round bottomed flask with condenser and overhead stirrer attached. The mixture was stirred together for 8 h at 150°C after which time the $CuSCF_3$ supported reagent was added and the reaction continued for 7 more hours. The work up procedure was as above. ^{19}F showed a peak at -42.6 ppm.

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