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# Trifluoromethylthiocopper — stability and reaction chemistry

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## Abstract

Trifluoromethylthiocopper, a useful reagent for the introduction of the $SCF_3$ group, decomposes in the presence of oxygen and a solvent or a support material. The decomposition results in the formation of $Cu_2S$ and $(CF_3)_2S_2$.

## Introduction

The trifluoromethylthio group is becoming one of the most popular substituents in the design of biologically active molecules [1]. Of the methods available for the synthesis of trifluoromethylthio compounds, the use of $CuSCF_3$ in nucleophilic substitution reactions is one of the most promising. We recently reported a new and facile synthesis for this reagent and its use in the form of $CuSCF_3$–alumina [2], although the instability of the reagent and the need to use it in large excess in reaction with aryl halides were major drawbacks. In the light of this we have carried out a detailed investigation on the stability and decomposition chemistry of $CuSCF_3$ which enables us to arrive at the best condition for its use as a source of $CF_3S^-$.

## Results and discussion

In our attempt to optimize the rate and efficiency of the model reaction of 2-bromonitrobenzene with $CuSCF_3$, we discovered an unexpected solvent dependency. At 90 °C, no reaction occurred in pyridine and hexamethylphosphoramide — solvents that are normally considered to be effective for copper(I) reactions [3] — whereas in *N,N*-dimethyl acetamide, dimethyl sulphoxide and dimethyl formamide, the reaction proceeded at a reasonable rate. The measured enthalpy of activation for the reactions in the three effective solvents varied over a wide range (Table 1).

In an attempt to understand these observations, the stability of $CuSCF_3$ in different solvents was studied by variable-temperature $^{19}F$ NMR spectroscopy

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TABLE 1

Values of $\Delta H^{\dagger}$ for a range of solvents[a]

| Solvent | $\Delta H^{\dagger}$ (kJ mol$^{-1}$) |
|---|---|
| DMSO | 56.5 |
| DMF | 76.4 |
| DMAc | 93.9 |

[a]Insufficient data were obtained for pyridine and HMPA, hence no $\Delta H^{\dagger}$ values could be calculated.

TABLE 2

Solvent effects on the stability of the $CuSCF_3$ species

| Solvent | Chemical shift ($\delta$) at 30 °C (ppm) | Temp. (°C)[a] | $CuSCF_3$/DS[b] |
|---|---|---|---|
| MeCN | −25.3 | 90 | 1:0 |
| Py | −16.7 | 60 | 0:1 |
| DMF | −25.4 | 90 | 1:0 |
| DMSO | −23.6 | 90 | 1:0 |
| HMPA | −21.7 | 90 | 0:1 |
| DMAc | −25.5 | 90 | 1:0 |

[a]The samples were allowed 10 min to equilibrate at the set temperature before $^{19}F$ NMR spectra were run. $^{19}F$ NMR spectra were run at 30 °C, 60 °C and 90 °C, respectively.
[b]DS = decomposition species. The ratio stated is the ratio of the integral of the $CuSCF_3$ signal to the integral of the decomposition species signal.

TABLE 3

Substrate effects on the stability of the $CuSCF_3$ species

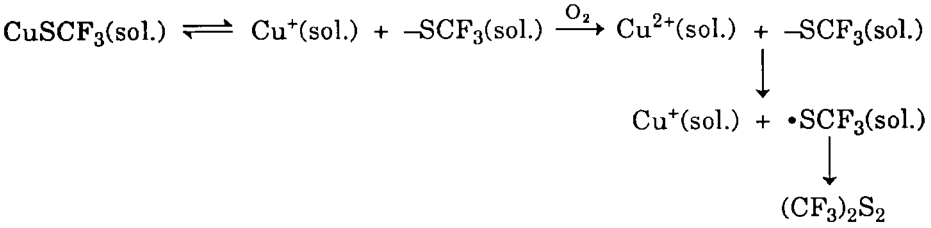
| Substrate | Temp. (°C)[a] | $CuSCF_3$/DS[b] |
|---|---|---|
| fluorobenzene | 90 | 1:4 |
| chlorobenzene | 90 | 2:1 |
| bromobenzene | 90 | 8:1 |
| iodobenzene | 90 | 1:0 |

[a]The samples were allowed 10 min to equilibrate at the set temperature before $^{19}F$ NMR spectra were run. $^{19}F$ NMR spectra were run at 30 °C, 60 °C and 90 °C, respectively.
[b]DS = decomposition species. The ratio stated is the ratio of the integral of the $CuSCF_3$ signal to the integral of the decomposition species signal.

(Table 2). In DMAc ($\delta = -25.5$ ppm), DMSO ($\delta = -23.6$ ppm) and DMF ($\delta = -25.4$ ppm), a single sharp resonance corresponding to $CuSCF_3$ was observed at temperatures up to 90 °C, whereas in pyridine ($\delta = -16.7$ ppm at 60 °C) and HMPA ($\delta = -21.7$ ppm at 90 °C) this resonance was replaced by a broad line at *c.* −180 ppm corresponding to HF. Further to this, we have found that the stability of $CuSCF_3$ is also dependent on the substrate, so that for monohalobenzenes, PhX, the stabilization of the copper salt follows the order $X = 1 > Br > Cl > F$ (Table 3). It seems that highly polarizable solvents and the more polarizable halogens can stabilize $CuSCF_3$. HMPA and pyridine are known to be good ligands for $Cu^+$, which may suggest that the first step in the decomposition is the dissociation of $CuSCF_3$ to $Cu^+$ and $SCF_3^-$.

In an attempt to further investigate the mechanism of decomposition of $CuSCF_3$, the compound was heated at 150 °C in DMAc for 1 h. This gave a solid precipitate which was isolated and characterized as containing $Cu_2S$ by fast-atom-bombardment mass spectrometry. Distillation of the residual liquid gave DMAc only. Further investigation of this reaction system revealed a gaseous product which was isolated and characterized by mass spectrometry and $^{19}F$ NMR spectroscopy as $(CF_3)_2S_2$. Total exclusion of $O_2$ from the reaction system completely inhibited the decomposition of the $CuSCF_3$ [4], whereas addition of $Cu^{II}$ (in the form of $CuCl_2$) had a marked catalytic effect on the decomposition (causing complete and rapid breakdown even at room temperature).

In the light of the above observations we propose the following mechanism for the decomposition of $CuSCF_3$:



The original reaction system of $CuSCF_3$ in DMAc at 150 °C was then monitored by ESR spectroscopy. This showed a build-up in the concentration of $Cu^{2+}$ ions with time, consistent with the proposed aerial oxidation of $Cu^+$. It was also possible, via spin-trapping (using DMPO) [5], to follow the build-up and subsequent loss of radicals believed to be $CF_3S\cdot$ (Fig. 1).

Attempts to prove the identity of this radical by photolysis of authentic $(CF_3)_2S_2$ in the presence of DMAc and the spin-trap DMPO were frustrated by complex spectra that could be due to the formation of other radicals, notably $CF_3\cdot$ and oxygen-centred radicals. It is possible to rationalize the formation of HF (observed by $^{19}F$ NMR spectroscopy) by the decomposition of trifluoromethyl-containing oxygen-centred radicals to $F\cdot$, which then scavenges a hydrogen atom from the solvent. Alternatively, the HF may arise from the hydrolysis of $(CF_3)_2S_2$ brought about by water in the solvent which we observed in the presence of $Cu^I$ (but not $Cu^{II}$).

At very high concentrations of spin-trap it was possible to see a spectrum identical to that observed from the decomposed $CuSCF_3$ (Fig. 2). We believe that the difficulty in generating $CF_3S\cdot$ from $(CF_3)_2S_2$ is due to the weak C–S bond [6].

The use of $CuSCF_3$ as a reagent clearly requires care, and oxygen must be excluded if a competitive decomposition of the reagent is to be avoided. It is also important to note that the decomposition requires the presence

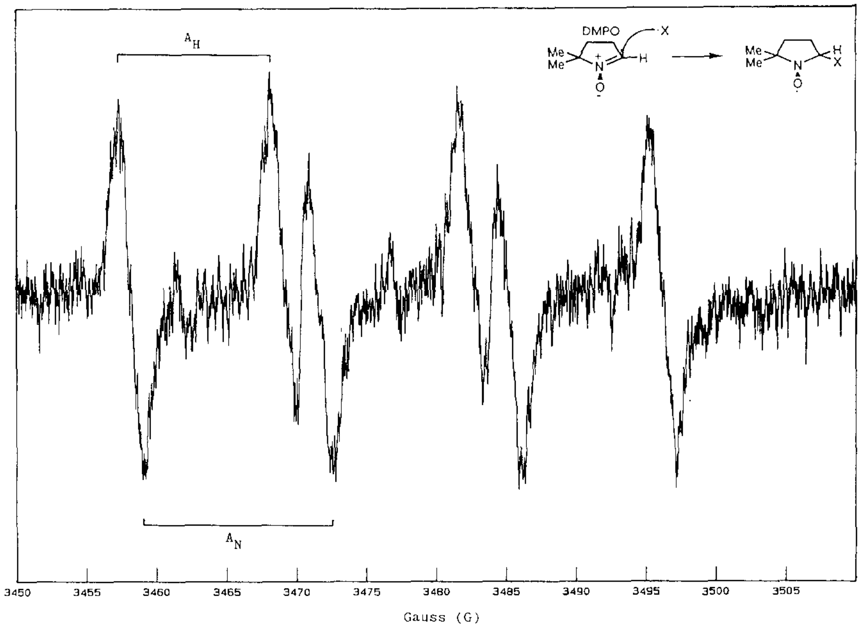


Fig. 1. ESR spectrum of solution of $CuSCF_3$, DMPO and DMAc, after heating at 50 °C for 5 min. The spectrum indicates the presence of a sulphur-centred radical, possibly $SCF_3\cdot$ ($A_H = 10.8$ G; $A_N = 13.5$ G).

of a solvent (no decomposition of $CuSCF_3$ alone occurs on heating in air) and that the identity of the solvent has an effect on the rate of decomposition. The nature of the substrate can also influence the rate of decomposition.

It is perhaps now easier to understand the susceptibility of supported $CuSCF_3$ to decomposition [2], since the alumina support can be regarded as a 'solid solvent'. Indeed, oxygen is again required for the decomposition of $CuSCF_3$–alumina (as monitored by variable-temperature IR spectroscopy – see Fig. 3) and a re-investigation of the value of this material for the incorporation of $SCF_3$ groups may be justified.

## Experimental

### *Instrumental*

Variable-temperature $^{19}F$ NMR spectra were obtained using a Bruker WP80 NMR spectrometer (80 Hz) with $CFCl_3$ as an internal reference for $^{19}F$ and TMS for $^{1}H$ measurements.

Gas–liquid chromatograms were obtained on a Philips PU450 instrument equipped with a Hewlett-Packard 3396A integrator. The column employed was 10% OV101 silicone on Chromasorb. Dinitrogen carrier gas and dioxygen/air flame ionization detection was used throughout.

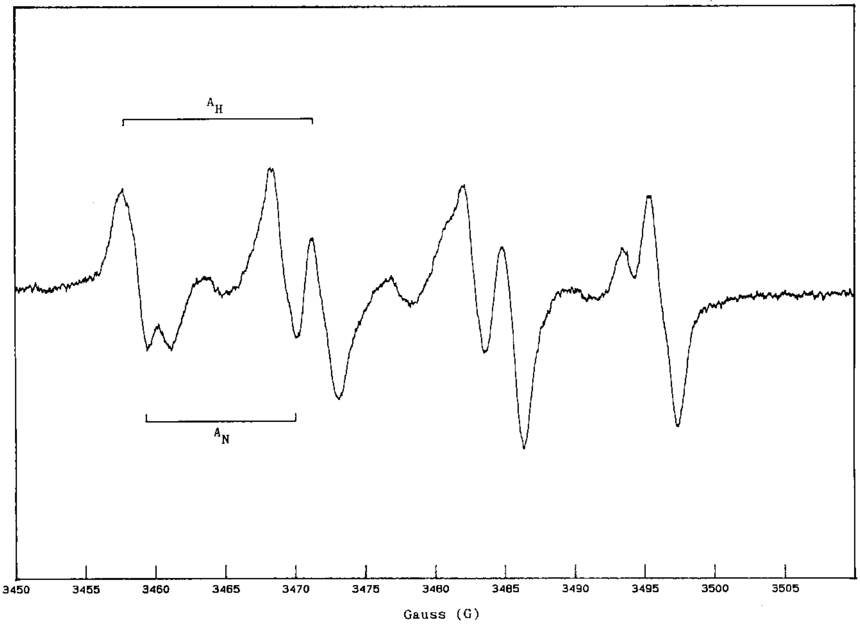


Fig. 2. ESR spectrum of a solution of $(CF_3)_2S_2$, DMPO and DMAc. The spectrum indicates the presence of an oxygen-centred radical, possibly $CF_3O_2\cdot$, and a sulphur-centred radical, possibly $SCF_3\cdot$ ($A_H = 10.7$ G; $A_N = 13.5$ G).

ESR spectra were obtained using an ESP 300 spectrometer (9.77 GHz). Due to the nature of the solvent (dipolar aprotic) employed, flat cells were used throughout.

Infrared spectra were obtained using the environmental Drift chamber 19779 equipped with a 20130 PID controller supplied by Specac. Variable-temperature IR spectra were run in air and under a dinitrogen atmosphere. The spectra were run on a Perkin-Elmer 1720 FT instrument.

Positive and negative ion fast-atom bombardment mass spectra were obtained using a caesium ion gun (27 keV). Mass spectra were obtained by electron impact on a VG Autospec mass spectrometer. GC–MS data were obtained using a Hewlett-Packard 5890 series II spectrometer. All reagents were taken from commercial sources, except those whose synthesis are referenced.

*General procedures*

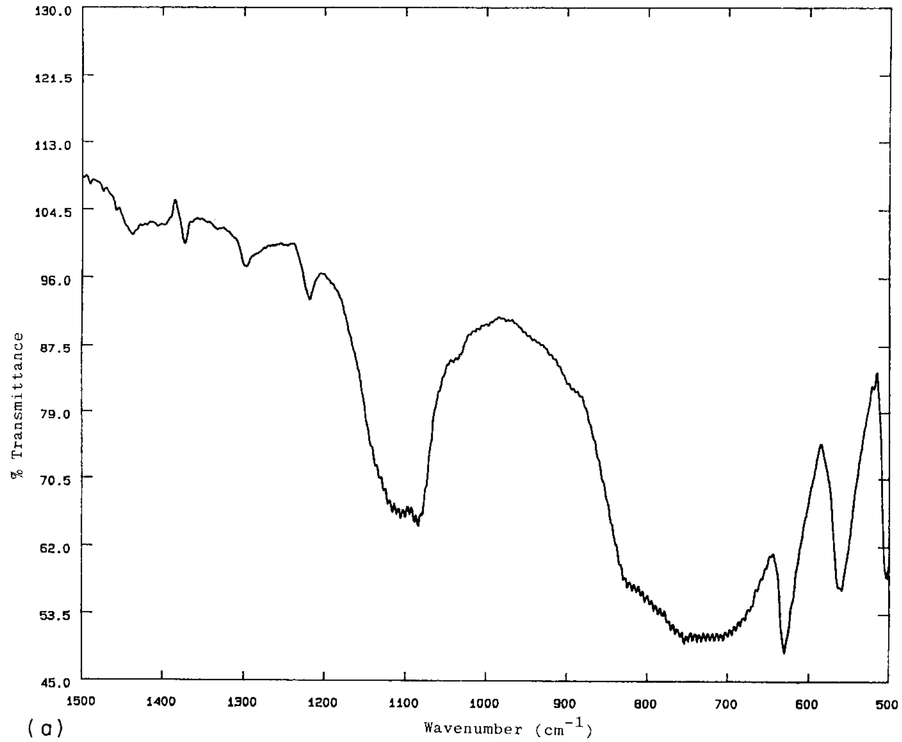
All work-ups were carried out in the same manner. The sample was first quenched, by addition to cold water, and then this solution was extracted with ether. Further quantities of water were added to the ether layer, before it was separated and dried over anhydrous magnesium sulphate. After filtration, the ether was removed on a rotary evaporator. A sample, diluted by ether, was then injected into the GLC equipment.

*Solvent-dependency reactions*

*(1)* N,N-*Dimethyl acetamide*

Trifluoromethylthiocopper(I) (0.69 g, 4.2 mmol), 2-bromonitrobenzene (0.40 g, 2 mmol) and DMAc (20 ml) were placed in a 25 ml, two-necked, round-bottom flask. A condenser was attached and the flask placed in a preheated oil bath at 90 °C. The flask was left stirring (magnetic flea) and samples were removed periodically for up to 3 h. Each sample was worked-up and analyzed as described in General procedures above. The presence of two peaks was confirmed by GLC and identified by GC–MS as (i) 2-nitrophenyltrifluoromethyl sulphide; MS: $M^+$ 223: 154 (100); 98 (75); 69 (65); 106 (50); 78 (34); 45 (32); 223 (29); 39 (28). $^{19}F$ NMR $\delta$: −43.0 ppm. $^1H$ NMR $\delta$: multiplets at 8.1, 7.8 and 7.6 ppm; and (ii) 2-bromonitrobenzene (starting material). The percentage yield of (i) increased and (ii) decreased with time. The above reaction was repeated at temperatures of 110 °C and 130 °C. From the data obtained it was possible to calculate a rate constant for each temperature, and using the Arrhenius equation, $k=Ae^{-E_a/RT}$, an activation energy and subsequently a $\Delta H^\dagger$ value for the reaction in DMAc.

The following reactions (2)–(5) were carried out in the same manner: (2) dimethyl sulphoxide – $\Delta H^\dagger$ value calculated; (3) dimethylformamide



(a)

Fig. 3.

(*continued*)

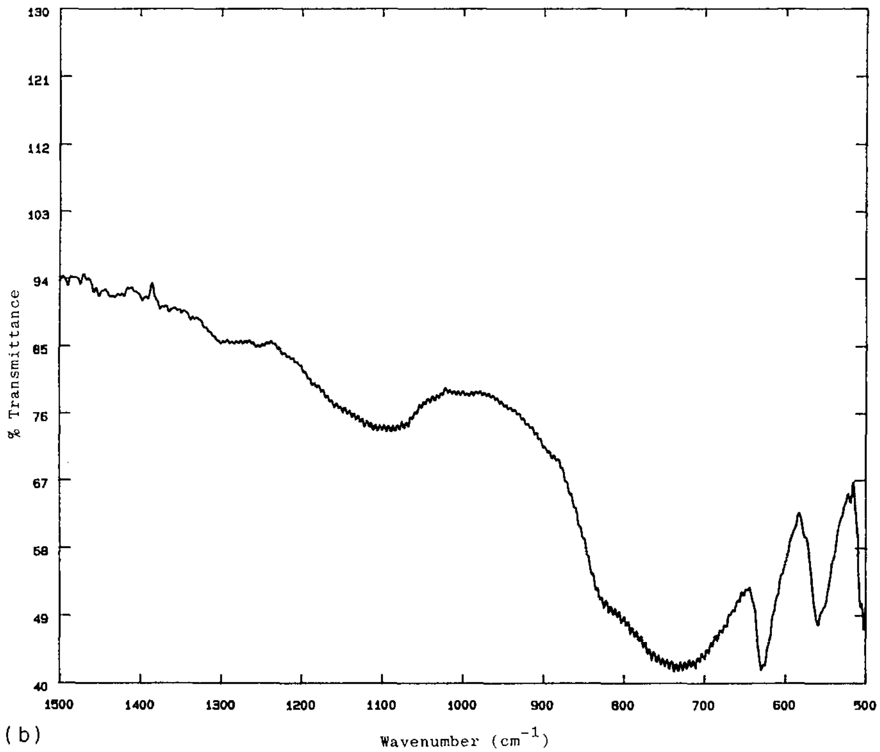


Fig. 3. IR spectra of supported $CuSCF_3$ in air, (a) before heating — C–F stretch occurring at 1100 cm$^{-1}$ — and (b) after heating to 130 °C for 30 min. In the latter case, the C–F stretch has almost completely disappeared.

— $\Delta H^{\dagger}$ value calculated; (4) pyridine — insufficient data obtained, no $\Delta H^{\dagger}$ value calculated; and (5) hexamethylphosphoramide — insufficient data obtained, no $\Delta H^{\dagger}$ value calculated.

*Solvent-variable temperature study*

*(1)* N,N-*Dimethyl acetamide*

A solution of trifluoromethylthiocopper(I) (0.33 g, 0.2 mmol) in DMAc (1 ml) was studied using $^{19}F$ NMR variable-temperature spectroscopy. Spectra were run at 30 °C, 60 °C and 90 °C, respectively. Experiments (2)–(5) above were repeated in the same manner but with a change of solvent, i.e. (2) DMSO, (3) DMF (4) Py and (5) HMPA. The appearance of a broad signal at $-179$ ppm indicated the decomposition of $CuSCF_3$. The ratio of the integral of the $CuSCF_3$ signal to the integral of the signal $-179$ ppm gave an indication of the amount of decomposition that had occurred.

*Substrate-variable temperature study*

*(1) 2-Fluoronitrobenzene*

A solution of trifluoromethylthiocopper(I) (0.33 g, 0.2 mmol) and 2-fluoronitrobenzene (7 mg, 0.05 mmol) in DMAc (1 ml) was studied using

$^{19}$F NMR variable-temperature spectroscopy. Spectra were run at 30 °C, 60 °C and 90 °C, respectively. Experiments (2)–(4) above were repeated in a similar manner, except with variation of the substrate employed, i.e. (2) 2-chloronitrobenzene (7.9 mg, 0.05 mmol), (3) 2-bromonitrobenzene (0.01 g, 0.05 mmol) and (4) 2-iodonitrobenzene (0.13 g, 0.05 mmol).

### *Decomposition reactions*

#### *(1a) Isolation of decomposition products*

Trifluoromethylthiocopper(I) (0.69 g, 4.2 mmol) in DMAc (20 ml) was placed in a 50 ml, two-necked round-bottom flask. One neck was stoppered, the other attached to a condenser. The flask was then placed in a preheated oil bath at 150 °C and left stirring (magnetic flea). After 1 h, the reaction was terminated. As the resulting solution consisted of a liquid with a black precipitate, it was necessary to carry out a vacuum distillation. The isolated liquid was analyzed by IR spectroscopy and the solid by FAB–MS.

#### *(1b) Isolation of gaseous product*

Experiment (1a) was repeated but this time the experiment was run in a Schlenck tube attached to a vacuum. The closed reaction system, containing air, was heated at 150 °C for 0.5 h before being opened to the vacuum. Due to the resulting bumping of the reaction mixture, two liquid nitrogen traps were set up in series. The gaseous product was trapped in the second trap and analyzed by mass spectrometry.

#### *(2) Argon atmosphere*

The decomposition reaction was carried out as described in (1b) above except that the vacuum was replaced by an argon line. The air was displaced from the reaction system before heating. After 1 h, the reaction mixture was analysed by $^{19}$F NMR spectroscopy when no decomposition was observed.

#### *(3) Argon atmosphere and catalyst*

The decomposition reaction was carried out as described in (2) above except for the addition of copper(II) chloride (2.7 mg, 0.02 mmol). After heating, the reaction mixture was analyzed by $^{19}$F NMR spectroscopy showing that complete decomposition had occurred.

### *ESR spectroscopy reactions*

#### *(1) $Cu^{2+}$ ions*

A solution of trifluoromethylthiocopper(I) (33 mg, 0.2 mmol) in DMAc (1 ml) was used. The solution was analyzed before, during and after decomposition.

#### *(2) Spin-trapping experiments*

A solution of trifluoromethylthiocopper(I) (33 mg, 0.3 mmol) in DMAc (1 ml) and the addition of 0.5 ml of a solution of DMPO (50 mg, 0.4 mmol) in DMAc (3 ml) were used. The solution was analyzed before, during and after decomposition.

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