Heteroatom Chemistry
Volume 3, Number 2, 1992

Preparations and Reactions of Trifluoromethylthiocopper

Shekar Munavalli[1]

Geo-Centers, Inc., Ft. Washington, MD 20744

David I. Rossman, Dennis K. Rohrbaugh, C. Parker Ferguson, and Fu-Lian Hsu

US Army Chemical Research, Development and Engineering Center, Aberdeen Proving Ground, MD 21010

Received 12 August 1991.

ABSTRACT

Trifluoromethylthiocopper, a versatile reagent for the introduction of the trifluoromethylthio group into organic compounds, has been prepared in a crystalline form. The thiyl radicals, generated in situ from this precursor, cause the cleavage of the S—S bond of di- and trisulfides to give unsymmetrical di- and trisulfides. Unsymmetrical n-butyl trifluoromethyl disulfide is formed by the cleaveage of the C—S bond of n-butyl sulfide.

INTRODUCTION

Biological properties associated with trifluoromethyl and trifluoromethylthio groups have been well documented [1a–b]. This has rekindled interest in the preparation and use of trifluoromethyl- and triflurometylthiometallo-derivatives as potential precursors for the introduction of these functional groups into organic compounds [2a–c]. Burton and coworkers have developed elegant methods for the synthesis of trifluoromethylcadmium, -copper, and -zinc reagents [2d]. Prakash and Olah have described a convenient reagent, trimethyl trifluoromethyl silane, for the introduction of the trifluoromethyl functionality into compounds containing carbonyl groups [2e]. The reaction of [(trimethylsilyl)methyl]-magnesium chloride with $LiCuBr_2$ was used for the *in situ* generation of [(trimethylsilyl)methyl]copper and its "ate" derivatives, which were in turn used for the synthesis of a wide array of olefinic synthons [2f]. Until recently [2c], trifluoromethylthiocopper (**1**) was prepared *in situ* by heating a mixture of trifluoromethylthiomercury and copper powder [1b, 2b]. In connection with our on-going projects, large quantities of **1** were required. After several unsuccessful attempts to prepare **1** according to the published procedure [2c], a new method has been developed in our laboratory [3a].

Recently we have been interested in the chemistry of the S—S and C—S bonds [3b–d]. Reactions of organolithium and Grignard reagents with disulfides usually result in the scission of the S—S bond and the formation of sulfides [4]. As a logical extension of our recent interest [3], the reaction of **1** with di- and trisulfides has now been examined and found to furnish unsymmetrical di- and trisulfides. Interestingly, n-butyl trifluoromethyl disulfide was obtained in small amounts from the cleavage of the C—S bond of n-butyl sulfide. This communication describes the preparation and reaction of **1** with mono-, di-, and trisulfides.

Table 1 lists the products which have been identified. The characterization of the mixed di- and trisulfides clearly indicates that the thiyl radicals generated *in situ* from **1** cause the scission of the C—S and

---

[1] To whom correspondence should be addressed.

1042-7163/92/$3.50 + .25

TABLE 1 $F_3CSCu + RSSR \longrightarrow F_3CSSR^a$

Reaction No.	*R*	*CSF_2*	*CS_2*	*CF_3SSR*	*CF_3SSSR*	*RSC(O)SR*
1	C_6H_5			73.8%		
2	C_2H_5		1.2%	9.0%		21.0%
3	n-C_3H_7	0.4%		13.5%		0.3%
4	i-C_3H_7			2.1%		
5	n-C_4H_9	0.9%		29.5%		
6	i-C_4H_9			4.8%		
7	s-C_4H_9			6.8%		
8	t-C_4H_9	1.2%	1.5%	1.6%		
9[b]	t-C_4H_9				17.2%[b]	
10[c]	n-C_4H_9	6.9%		0.2%		

[a] The yields are calculated from the GC/MS data and are not optimized. Starting materials constituted the rest of the products.
[b] Reaction with trisulfide.
[c] Reaction with sulfide.

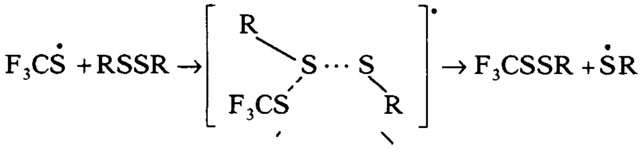
S—S bonds. From a mechanistic point of view, two possible pathways: a) a stepwise free radical process (Scheme 1) and b) a synchronous attack (Scheme 2), can be envisaged. The stepwise free radical process takes into account the susceptibility of the weak S—S bond of the disulfides to a radical attack [4a]. The addition product formed in Step 2 as an intermediate readily dissociates as shown in Steps 3 and 3' to give the mixed disulfides identified by their mass spectra. However, products corresponding to Steps 5 and 6 are not observed. The second pathway incorporates a synchronous attack on sulfur to give an intermediate radical, which then collapses to yield the mixed disulfide. Haszeldine and coworkers have proposed a similar synchronous attack to explain the formation of methyl trifluoromethyl sulfide [4b–c]. Dithioalkyl difluoromethane and carbon disulfide have been detected as by-products in the reactions of **1** [5a]. The trifluoromethylthiyl radical has been generated from its mercury precursor and its spectrum has been recorded [5b]. Also, a stepwise free radical process has been proposed for the substitution reaction of this thiyl radical with alkanes [5c]. The participation of $F_3CS\cdot$ radical in the reaction between CS_2 and IF_5 at 60–200°C [6a] and that between F_3CI and sulfur at 310°C [6b] has been postulated. A similar suggestion has also been made to rationalize the products formed during the reaction betwee $F_3C\cdot$ radicals and sulfur vapor [6c]. Evidence has been presented for the free radical nature of the reaction between disulfides and Grignard reagents [6d]. The formation of CS_2 has been attributed to the involvement of free radicals [6c]. At least twenty different substrates have been reacted with trifluormethylthiocopper in our laboratory. In almost all the cases, bis(trifluoromethyl di- and trisulfides have been indentified by their mass spectra. If the mechanism were a stepwise free radical process, then mixed mono- and trisulfides (Steps 5 and 6) should have been formed. Since no mixed mono- and trisulfides were detected by GC-MS, we are inclined to be in favor of the free radical catalyzed synchronous process (Scheme 2).

$$\begin{array}{lcll}
F_3CSCu & \longrightarrow & F_3C\dot{S} + \dot{C}u & 1 \\
F_3C\dot{S} + RSSR & \longrightarrow & F_3CS\;S(R)SR]^{\bullet} & 2 \\
F_3CSS(R)SR]^{\bullet} & \longrightarrow & F_3CSR + \dot{S}R & 3 \\
F_3C\dot{S} + \dot{S}R & \longrightarrow & F_3CSSR & 3' \\
[F_3CSS(R)SR]^{\bullet} & \longrightarrow & F_3CSR + \dot{S}SR & 4 \\
F_3C\dot{S} + \dot{S}SR & \longrightarrow & F_3CSSSR & 5 \\
F_3C\dot{S} + \dot{R} & \longrightarrow & F_3CSR & 6 \\
\dot{R} + \dot{S}R & \longrightarrow & RSR & 7 \\
2\dot{S}R & \longrightarrow & RSSR & 8 \\
2\dot{R} & \longrightarrow & R\text{-}R & 9
\end{array}$$

Scheme 1

EXPERIMENTAL

Warning! Because of the high toxicity associated with bis(trifluoromethyl) disulfide, extreme care should be exercised in working with these compounds. The Mass spectra were recorded on a Finnigan Model 5100 GC/MS equipped with a silica 25 m × 0.31 mm (i.d.) SE-54 capillary column (J & W Scientific, Rancho Cordova, CA). Routine GC separations were accomplished with a Hewlett Packard 5890A gas chromatograph equipped with a 30 m × 0.53 mm (i.d.) column (J & W Scientific, Folsom CA). The solvents were dried and freshly distilled prior to use. Reactions were carried out in a flame-dried, argon purged three-neck flask equipped with a magnetic



Scheme 2

stirrer, gas inlet tube, and a reflux condenser attached to a dry ice/acetone cooled trap. The temperature of the coolant circulating through the condenser was kept at −20°C. The reaction of **1** with phenyl disulfide is described in detail. The remaining reactions were carried out in a similar manner. Table 1 describes the reaction and products that have been identified. The mas spectral data of the compounds thus identifed are included as Supplementary Data. A copy may be obtained from the authors upon request.

Trifluoromethylthiocopper

Freshly distilled dry acetonitrile (50 mL) and freshly activated copper powder (7.6 g, 0.13 gm-atoms) were placed in a flame-dried, argon gas purged 100 mL three neck flask equipped with gas inlet tube, reflux condenser attached to a dry ice/acetone cooled condenser with argon gas/vacuum inlet. After cooling of the reaction flask to −78°C, the system was evacuated to 90 mm and bis(trifluoromethyl) disulfide (16 g, 0.08 moles) was sparged into the stirred flask. After

TABLE 2 Mass Spectral Fragmentation of the Mixed Disulfides Formed by the Scission of the C—S and S—S Bonds with CF_3SCu

Reaction No.	*R*	*Mass Spectral Fragmentation*
1[a]	C_6H_5	**M^+ = 210;** 141 (100%, M-CF_3), 109(M-SCF_3); 101(SCF_3); 82(CF_2); 77(C_6H_5); 69(CF_3) and 45(CSH).
2	C_2H_5	**M^+ = 162;** (100%); 147(M-CH_3); 143(M-F); 134(M-C_2H_4); 114(134-HF); 101(SCF_3); 93(M-CF_3); 82(CSF_2) 69(CF_3); 64(S-S); 61(SC_2H_5); 50(CF_2) and 45(CSH).
3	n-C_3H_7	**M+ =176;** 157(M-F); 147(M-C_2H_5); 133(M-C_3H_7); 114(133-F); 101(SCF_3); 82(CSF_2); 78($SSCH_2$); 75(SC_3H_7); 69(100%, CF_3); 64(S-S); 59(SC_2H_3) and 45(CSH)
4	i-C_3H_7	**M^+ = 176;** 157(M-F); 133(M-C_3H_7); 114(133-F); 101(SCF_3); 82(CSF_2); 78($SSCH_2$); 75(SC_3H_7); 69(100%, CF_3); 64(S-S); 59(SC_2H_3) and 45(CSH).
5	n-C_4H_9	**M^+ = 190;** 171(M-F); 161(M-C_2H_5); 147(M-C_3H_7); 133(M-C_4H_9); 82(CSF_2); 78($SSCH_2$); 69(CF_3); 64(S-S) 57(100%, C_4H_9) and 45(CSH).
6	i-C_4H_9	**M^+ = 190;** 147(M-C_3H_7); 133(M-C_4H_9); 101(SCF_3); 89(M-SCF_3); 82(CSF_2); 69(CF_3); 64(S-S); 57(100%, C_4H_9) and 45(CSH).
7	s-C_4H_9	**M^+ = 190;** 161(M-C_2H_5); 133(M-C_4H_9); 101(SCF_3); 89(SC_4H_9); 73(89-CH_4); 69(CF_3); 64(S-S); 57(100%, C_4H_9) and 45(CSH).
8	t-C_4H_9	**M^+ 190;** 175(M-CH_3); 133(M-C_4H_9); 101(SCF_3); 89(SC_4H_9); 82(CSF_2); 69(CF_3); 64(S-S); 57(100%, C_4H_9) and 45(CSH).
9[b]	t-C_4H_9[b]	**M^+ = 222;** 133(M-C_4H_9); 121 (M-SCF_3); 96(S-S-S); 74(SC3H6); 64(S-S); 57(100%, C_4H_9) and 45(CSH).
10[c]	n-C_4H_9	**M^+ = 190;** 79($SSCH_3$); 69(CF_3); 57(100%, C_4H_9); 47(SCH_3) and 45(CSH)

[a]Refers to the reaction number cited in Table 1.
[b]Reaction with trisulfide.
[c]Reaction with sulfide.

having been stirred at −78°C for 1/2, hr the reaction mixture was allowed to warm to ambient temperature and then heated at 55–60°C for 14–16 hr. During the course of the reaction, the copper metal dissolved to give a clear solution. Under an argon atmosphere, the reaction solution was concentrated under reduced pressure and the concentrate cooled overnight (refrigerator) to give 12 g. of a white solid. Overnight drying under vacuum gave a product which was shown to be a 1 : 1 trifluoromethylthiocopper : acetonitrile adduct (GC/MS), m.p. 184–186°C (decomp.) Stored over P_2O_5 at ambient temperature, the material is stable for several months without significant decomposition (a year old sample was used in the reaction described in Table 1). MS: 102(F_3CSH); 82(CSF_2); 69(CF_3); 63(FCS); 44(CS); 33(SH) and 42(CH_3CNH); 41(CH_3CN); 40(CH_2CN); 39(CHCN); 38(CCN). The peak, m/e = 42, is due to the protonation of CH_3CN and is usually observed if the concentration of CH_3CN is relatively high [6e].

Phenyl Trifluoromethyl Disulfide

A mixture of trifluoromethylthiocopper (1.03 g, 5 mmol.) and phenyl disulfide (1.09 g, 5 mmol.) in 2 mL of dry acetonitrile was stirred at 80–85°C for six hours. The flash distillate of the reaction mixture consisted of 74% phenyl trifluoromethyl disulfide, and 26% starting disulfide.

REFERENCES

[1] (a) R. Filler, Y. Kobayashi, (Eds) *Biomedicinal Aspects of Fluorine Chemistry*, Kodasha/Elsevier, New York, 1982; (b) W. C. Randall, P. S. Anderson, E. L. Cresson, C. A. Hunt, T. F. Lyon, K. E. Rittle, D. C. Reny, J. P. Springer, J. M. Hirsfield, K. Hoogsteen, M. Williams, E. A. Risley, J. A. Totaro, *J. Med. Chem. 22*, 1979, 1222 (and references cited therein).

[2] (a) J. A. Morrison, *Adv. Inorg. Chem. Radiochem., 27*, 1983, 293; (b) F. H. Mann, D. D. Coffman, E. L. Muetterties, *J. Am. Chem. Soc., 81*, 1959, 3575; (c) N. Y. Kondratenko, A. A. Kolomeystev, V. I. Popov, L. M. Yagupolskii, *Synthesis*, 1985, 667; (d) D. J. Burton, D. M. Wiemars, *J. Am Chem. Soc., 107*, 1985, 5014; (e) G. K. S. Prakash, R. Krisnamurti, G. Olah, *J. Am. Chem. Soc., 111*, 1989, 393; (f) H. Kleijn, P. Vermeer, *J. Org. Chem., 50*, 1985, 5143.

[3] (a) S. Munavalli and D. I. Rossman (Patent pending). (b) S. Munavalli, D. I. Rossman, D. K. Rohrbaugh, C. P. Ferguson, 201st. National Meeting American Chemical Society, Atlanta, Apr. 14–19, 1991, Abst. #53 and 54; (c) S. Munavalli, D. I. Rossman, D. K. Rohrbaugh, C. P. Ferguson, H. D. Banks, Fourth Chemical Congress of North America, Aug. 25–30, 1991, Abst. #251; (d) S. Munavalli, D. I. Rossman, D. K. Rohrbaugh, C. P. Ferguson, L. J. Szafraniec, Fourth Cemical Congress of North America, Aug. 25–30, 1991, #253.

[4] (a) W. A. Pryor, *Mechanism of Sulfur Reactions*, McGraw-Hill Book Company, New York, 1962, pp. 42; (b) R. N. Haszeldine, B. Higgenbottom, R. B. Rigby, A. E. Tipping, *J. Chem. Soc. Perkins Trans. 1*, 1972, 155; (c) R. N. Haszeldine, R. B. Rigby, *J. Chem. Soc. Perkins Trans. 1*, 1972, 159, 2180; (d) T. Nguyen, M. Rubinstein, C. Wakselman, J. Org. Chem., 40, 1981, 1938; (e) J. L. Kice, *Acc. Chem. Res., 1*, 1968, 58.

[5] (a) S. Munavalli, D. I. Rossman, D. K. Rohrbaugh, C. P. Ferguson, 201st National Meeting American Chemical Society, Atlanta, Apr. 14–19, 1991, Abst #167; (b) P. S. H. Bolman, I. Safarik, D. A. Stiles, W. J. R. Tyerman, O. P. Strause, *Can. J. Chem., 48*, 1970, 3872; (c) J. F. Harris, *J. Org. Chem., 31*, 1966, 936.

[6] (a) R. N. Haszeldine and J. M. Kidd, *J. Chem. Soc.*, 1953, 3219. (b) G. R. A. Brandt, H. J. Emeleus and R. N. Haszeldine, *J. Chem. Soc.*, 1952, 2198. (c) T. Yasumura and R. J. Lagow, *Inorg. Chem., 17*, 1978, 3108. (d) A. W. P. Jarvie and D. Skelton, *J. Organometal. Chem., 30*, 1971, 145. (e) National Bureau of Standards Library Compilation (1984), Finnigan Corporation, San Jose, CA 95134.