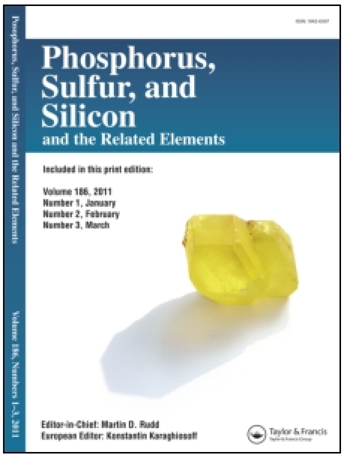

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Reaction of 1,3-Dithiane with Trifluoromethylthiocopper

S. Munavalli[a]; D. K. Rohrbaugh[b]; D. I. Rossman[b]; H. D. Durst[b]
[a] Science Applications International Corporation, Gunpowder Branch, Aberdeen Proving Ground, Maryland, USA [b] U.S. Army, Edgewood Chemical Biological Center, Aberdeen Proving Ground, Maryland, USA

To cite this Article Munavalli, S. , Rohrbaugh, D. K. , Rossman, D. I. and Durst, H. D.(2006) 'Reaction of 1,3-Dithiane with Trifluoromethylthiocopper', Phosphorus, Sulfur, and Silicon and the Related Elements, 181: 1, 105 — 112

To link to this Article: DOI: 10.1080/104265090969027

URL: http://dx.doi.org/10.1080/104265090969027

Phosphorus, Sulfur, and Silicon, 181:105–112, 2006
Copyright © Taylor & Francis LLC
ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426509096902

Reaction of 1,3-Dithiane with Trifluoromethylthiocopper

S. Munavalli
Science Applications International Corporation, Gunpowder Branch,
Aberdeen Proving Ground, Maryland, USA

D. K. Rohrbaugh
D. I. Rossman
H. D. Durst
U.S. Army, Edgewood Chemical Biological Center,
Aberdeen Proving Ground, Maryland, USA

The 1,3-dithiane ring undergoes cleavage even under mild neutral reaction conditions when heated in the presence of trifluoromethylthiocopper. The free-radical nature of the reaction was confirmed by the characterization of bis-(trifluoromethyl)disulfide as one of the products.

Keywords 1,3-dithialane; 1,3-dithiane; free-radical reactions; ring cleavage products; trifluoromethylthiocopper

Since the 1970s 1, 3-dithiane (**1**) has been employed extensively as a building block in the preparation of a vast array of organic intermediates and synthons required for the total synthesis of several scores of interesting organic compounds. The synthetic utility and usefulness of 1,3-dithiane (**1**) rest squarely on the facile introduction of functional groups and the removal of the masking moiety, namely the 1,3-propanedithiol fragment after the accomplishment of the successful synthesis. The pioneering work of Corey and Seebach[1] has demonstrated the synthetic utility and versatility of the dithiane synthons. The chemistry of dithiane and dithialanes has been reviewed.[2] An excellent report on the synthetic applications of the anions derived from 1,3-dithiane has been published.[2c] In this context, it is worth mentioning that the dithiane ring system has been modified to 1,3-oxathiane and its synthetic applications have been described.[3]

Received December 16, 2004; in final form January 11, 2005.

Address correspondence to S. Munavalli, Geo-Centers, Inc., P.O. Box 68, Gunpowder Branch, Aberdeen Proving Ground, Maryland 21010, USA. E-mail: shekar.munavalli@us.army.mil

The presence of fluorine, trifluoromethyl and trifluoromethylthio groups contributes significantly towards the enhancement of the biological potency and effectiveness of active compounds.[4,5] This observation has created considerable interest in the development of methodologies best suited to introduce and incorporate these functional groups into the molecular architecture of biologically active compounds. In continuation of our interest in the chemistry of the trifluoromethylthio group,[6] attempts were made to synthesize new potential transfer agents, in particular, 2-(trifluoromethylthio)-1, 3-dithialane and -dithiane. This expectation was based on the use of N-trifluoromethylthiophthalimide) in α-trifluoromethylthiolation of carbonyl compounds.[7] These sulfur stabilized trifluoromethylthiolating agents were considered to be of particular interest and use as synthetic intermediates and thiolating agents. The reaction of 1,3-dithiane (**1**) with trifluoromethylthiocopper (**2**) was examined. The GC-MS analysis of the reaction mixture enabled the characterization of six out of nine compounds present in the reaction product. Thus the structures of compounds **3** through **8** have now been deduced by the examination of their mass spectral fragmentation behavior. This communication describes the probable mechanism of the formation and the structure elucidation of the various compounds resulting from the reaction of 1,3-dithiane (**1**) with trifluoromethylthiocopper (**2**).

RESULTS AND DISCUSSION

The treatment of 2,2-diaryl-1,3-dithialanes and -1,3-dithianes with n-BuLi has been observed to induce the cleavage of the dithiane ring.[8] This facile fission of the ring and the formation of the products have been attributed to the attack on sulfur by the alkyl anion, followed by hydrogen abstraction. Anion-induced gas phase deprotonation has been described to result in the cleavage of the dithiane ring and to form 1-allylthiomethylthiyl anion intermediate.[9]

The stability of the carbanions of the dithiane have been examined in detail[10a] and the concept of back-donation of electrons into the vacant d-orbitals has been advanced to account for their observed stability.[10b] Simple ab initio calculations on the α-thio carbanions have shown the involvement and participation of the induced polarization.[11a] Later calculations have indicated significant contribution of the d-orbitals to the reactivity of the α-thio carbanions.[11b] Reaction of 2-lithio-2-trimethylsilyl-, 2-lithio-2-trimethylstannyl-, and 2-lithio-2-trimethylgermanyl-1,3-dithianes with acylchloride has been reported to furnish, in addition to 2-acyl-1,3-dithianes, the thiane ring cleavage products, namely bis-1,3-dithia-acylpropane.[12] The reaction of

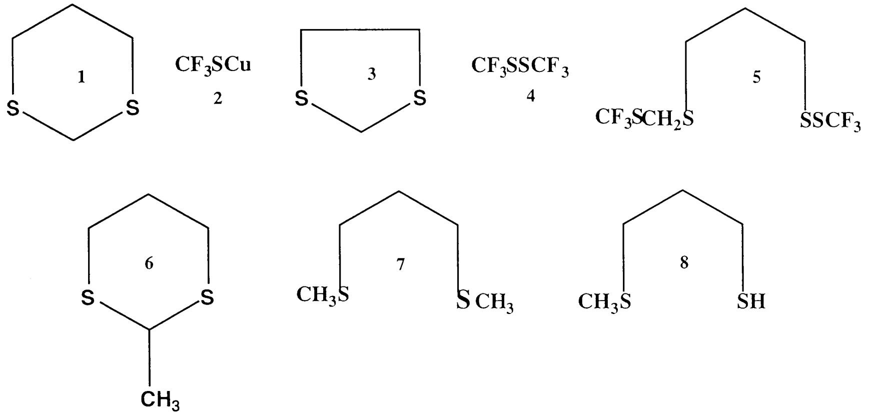

FIGURE 1 Compounds from the reaction of 1,3-dithiane and CF_3SCu.

2-alkyl-2-lithio-1,3-dithiane with bis-(methyl)disulfide has been stated to yield 2-alkyl-2-methylthio-1,3-dithiane.[13]

The loss of CH_3, SH, CH_2S, CH_3S, and C_3H_7S moieties from the molecular ion was seen in the mass spectral breakdown of 1,3-dithiane. The expulsion of these entities involves a variety of cleavages and hydrogen migrations. A detailed examination of the mass spectral breakdown of 1,3-dithiane using labelled substrates has appeared.[14a] FAB and CI-induced as well as collision-induced dissociation of dithiane fragmentation also has been investigated.[14b] The mass spectral fragmentation of 1,3-dithialane and its derivatives has been discussed.[15] The sulfur-stabilized anions serve as masked nucleophilic acylating agents.[16]

The GC-MS analysis of the product of the reaction of 1,3-dithiane (**1**) with trifluoromethylthiocopper (**2**) indicated the presence of the following compounds (cf. Figure 1): (1) 1,3-dithiane (**1**); (2) 1,3-dithiolane (**3**); (3) bis-(tri-fluoromethyl)disulfide (**4**); (4) 1-(trifluoromethylthio)-3-(trifluoromethylthio-methyl)-1,3-propanedithiol (5); (5) 2-methyl-1,3-dithiane: (**6**); bis-(1,3-dimethyl)-1,3-propanedithiol (**7**); and (6) l-methyl-1,3-propanedithiol (**8**). The presence of 1,3-dithialane (**3**) was somewhat surprising in that its origin could not be immediately traced. Its presence can be attributed to two sources: (1) it could either have been formed from **1** during the GC-MS analysis in the mass spectrometer, (**2**) or it could have arisen during the course of the reaction itself. To see if it accompanied the reaction substrate, namely **1**, as an impurity, **1** was subjected to GC-MS analysis. This analysis showed that **3** was present to the extent of 0.2%. But the fact that its concentration in the reaction mixture was 0.5% would favor the latter contention. The origin and formation of

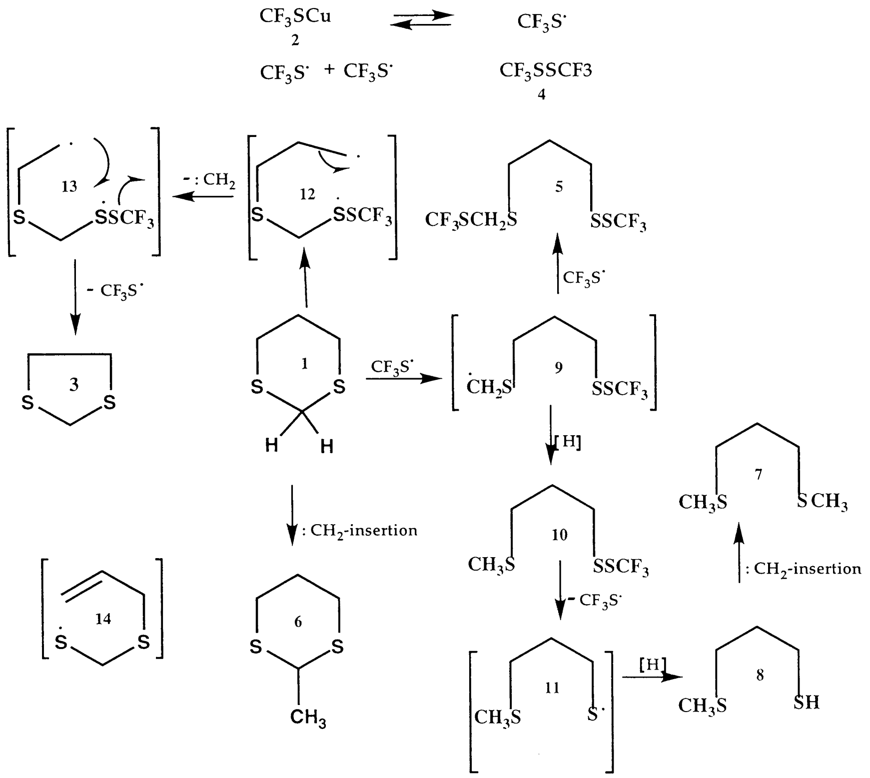

FIGURE 2 Probable mechanism of the compounds cited in the narrative.

bis-(trifluoromethyl)disulfide (**4**) have been previously explained.[6d] Figure 2 attempts to provide a rational explanation for the formation of compounds **3–8**. The attack on S of 1,3-dithiane (**1**) by $CF_3S^{\cdot}$ formed from trifluoromethylthiocopper (**2**), followed by the cleavage of the S_1—C_2 bond results in the intermediate **9**, which further can react with $CF_3S^{\cdot}$ to yield compound **5**. It is worth mentioning here that this compound was identified to be present in the products of the reaction

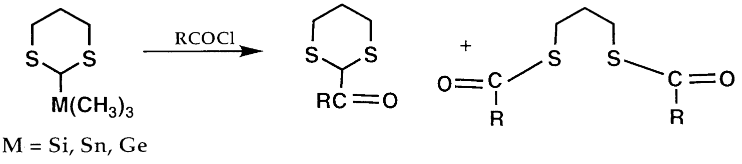

FIGURE 3 Products from the acylation of 2-M(CH3)3-1,3-dithiane (cf. Ref. 15).

of trifluoromethylsulfenyl chloride (CF_3SCI) with **1**. If, on the other hand, the S_1—C_6 gets cleaved after the attack by the $CF_3S^{\cdot}$ radical, then that would give rise to intermediate **12**, which can fragment off a methylene (carbene) moiety to generate the diradical intermediate **13**, which simply then goes on to form 1,3-dithialane (**3**). The intermediate **9** can simply abstract hydrogen to yield compound **10**. The latter then can fragment off the $CF_3S^{\cdot}$ radical to give intermediate **11**, which, in turn, abstracts hydrogen to furnish 1-methyl-1,3-propanedithiol (**8**). It remains to explain the genesis 2-methyl-1,3-dithiane (**6**) and bis-(1,3-dimethyl)-1,3-propanedithiol (**7**). The origin of **6** can be ascribed to the methylene (carbene) insertion between the C_2—H bond of 1,3-dithiane (**1**), while the formation of 7 requires the methylene insertion to occur between S—H bond of **8**. There are precedents supporting the suggested CH_2-insertion.[18] The suggested attack on the sulfur atom of 1,3-dithiane (**1**) has precedent (Figure 3).[8] It is worth noting that the presence of the sulfur anion analog of intermediate **14** has been invoked to rationalize the gas-phase cleavage reaction of 1,3-dithiane (**1**).[9b] Table I describes the mass spectral fragmentation of the compounds mentioned in the text.

EXPERIMENTAL

Mass spectra were obtained using a Finnigan TSQ-7000 GC/MS/MS equipped with a 30 m × 0.25 mm. i.d. DB-5 capillary column (J and W Scientific, Folsom, CA) or a Finnigan 5100 GC/MS equipped with a 15 m × 0.25 mm. i.d. Rtx-5. capillary column (Restek, Bellefonte, PA). The conditions on 5100 were the following oven temperature was 60–270°C

TABLE I Mass Spectral Fragmentation of Compounds Cited in the Narrative

Mass Spectral Fragmentation of 1-(trifluoromethylthiomethyl)-3-trifluoromethylthio-1,3-propanedithiol (**5**): $M^+ = 322$; 207 (322-CF_3SCH_2); 147 (CF_3SCH_2S): 135 ($CH_2F_3S_2$), 133 (CF_3SS); 107 ($C_3H_7S_2$, 100%); 106 ($C_3H_6S_2$); 82 (CSF_2); 78 (CH_2S_2); 73 (C_3H_5S); 69 (CF_3); 64 (SS); and 47 (SCH_3). Incidentally, this assignment is supported by comparison of the mass spectrum of the compound obtained by the treatment of **1** with trfluoromethanesulfenyl chloride at −78°C.

Mass Spectral Fragmentation of 2-methyl-1,3-dithiane (**6**): ($M^+ = 134$ (100%); 106 (M—C_2H_2); 90 (106-CH_4); 78 (CH_2S_2); 73 (C_3H_4S); 61 (C_2H_5S); 47 (SCH_3); and 45 (CSH).

Mass Spectral Fragmentation of bis-1,3-dimethyl-1,3-propamedithiol (7): $M^+ = 136$ (100%); 120 (M—CH_4); 119 ($C_4H_7S_2$); 106 (M—C_2H_6); 90 ($C_4H_{10}S$); 87 (C_4H_7S); 73 (87-CH_2); 61 (C_2H_5S); and 45 (CSH).

Mass Spectral Fragmentation of 3-methylthiopropanethiol (**8**): M^+ 122 (100%); 106 (M—CH_4); 94 (M—C_2H_4); 73 (C_3H_5S); 64 (SS); and 45 (CSH).

at 10°C/min injection temperature was 210°C, interface temperature was 230°C, electron energy, was 70 eV, emission current was 500 μA, and scan time was 1 s. The conditions on the TSQ-7000 were the followings oven temperature was 60–270°C at 15°C/min, injection temperature was 220°C, interface temprature was 250°C, source temprature was 150°C, electron energy was 70 eV (El) or 200 eV (Cl), the emission current was 400 μA (El) or 300 μA (Cl), and scan time was 0.7 s. Data was obtained in both the electron ionization mode (range 45–450 da) and chemical ionization mode (mass range 60–450 da) Ultrahig-purity methane was used as the Cl agent gas with a source pressure of 0.5 Torr (5100) or 4 Torr (TSQ-7100). Routine GC analyses were accomplished with a Hewlett-Packard 5890A gas chromatograph equipped with a J and W Scientific 30 m × 0.53 mm i.d. DB-5 column (J and W Scientific). We have previously described the preparation, the use of, and the X-ray crystal structure of trifluoromethylthiocopper.[17]

Reaction of 1,3-Dithiane (1) with Trifluoromethylthiocopper (2)[19]

Stoichiometric amounts of 1,3-dithiane (**1**) and trifluoromethylthiocopper (**2**) in dry toluene were reacted at 100–10°C for 14 h. After the reaction mixture cooled to room temperature, it was treated with a saturated solution of ammonium chloride and extracted with methylene chloride; the organic layer separated, washed with a saturated solution of sodium chloride, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The GC-MS analysis of the residue indicated it to consist of (**1**) bis-(trifluoromethyl)disulfide (**4**, 2.3%: $M^+ = 202$; (2) 1,3-dithiane (1, 50.7%, $M^+ = 120$, starting material); (3) 1-(trifluoromethyl)-thio-3-(trifluoromethylthiomethyl)-1,3-propanedithiol (**5**, 0.4% M^+ not seen)'(3.) 2-methyl-1,3-dithiane: (**6**, 0.5% $M^+ = 134$); (4) bis-(1,3-dimethyl)-1,3-propanedithiol (**7**, 45.7%, $M^+ = 136$); (5) 1-methyl-1,3-propanedithiol (**8**, 0.1%, $M^+ = 122$); and (6) 1,3-dithiolane (**3**, 0.5%, $M^+ = 106$). Three more minor compounds occurring in trace amounts could not be identified as they underwent extensive degradation in the mass spectrometer before their M^+ ions got recorded. The mass spectral fragmentation of bis-trifluoroemethyl) disulfde (**4**), 1,3-dithiane (**1**), and 1,3-dithialane (**3**) has already been descibed.[6e,14,15]

REFERENCES

[1] D. Seebach and E. J. Corey, *J. Org. Chem.*, **40,** 231 (1975) and refs. cited therein.

[2] (a) B. T. Grobel and D. Seebach, *Synthesis*, 357 (1977); (b) L. Field, *Synthesis*, 101 (1972); (c) A. Katritzky and C. W. Rees, Eds. *Comprehensive Heterocyclic Chemistry*,

Vol. 3 (Pergamon Press, New York, 1984), pp. 943, (d) P. C. Bulman Page, M. B. van Niel, and P. C. Prodger, *Tetrahedron*, **45,** 7643 (1989); (e) L. F. Tietze, B. Weiga, and C. Wulff, *Synthesis*, 69 (2000).

[3] (a) K. Fuji, M. Ueda, K. Sumi, and E. Fujita, *J. Org. Chem.* **50,** 662 (1985); (b) K. Fuji, M. Ueda, K. Sumi, K. Kajiwara, E. Fujita, T. Iwashi and T. Miura, *J. Org. Chem.*, **50,** 657 (1985).

[4] (a) S. Munavalli, D. I. Rossman, J. W. King, L. L. Szafraniec, W. T. Beaudry, and C. P. Ferguson, In Proc. ERDEC Scientific Conf. on Chemical Defense, 1993, (b) S. Munavalli, D. I. Rossman, D. K. Rohrbaugh, C. P. Ferguson, and L. C. Buettner, *J. Fluorine Chem.*, **65,** 15 (1993).

[5] (a) R. Filler and Y. Kobayashi, Eds., Biomedicinal Aspects of Fluorine Chemistry, (Kodash/Elsevier, New York, 1982); (b) W. C. Randall, P. S. Anderson, E. A. Cresson, C. A. Hunt, T. F. Lyon, K. Hoogsteen, M. Williams, E. A. Risley, and J. A. Totaro, *J. Med. Chem.*, **22,** 1222 (1979) and references cited therein; (c) E. A. Nodiff, S. Lipschutz, and M. Gordon, *J. Org. Chem.*, **25,** 60 (1960); (d) J. -P. Belgue and D. Bonnet-Delpon, *Tetrahedron*, **47,** 3207 (1991); D. J. Burton and Z. -Y. Yang, *Tetrahedron*, **48,** 189 (1992); (f) G. A. McClinton, *Tetrahedron*, **48,** 6555 (1992).

[6] (a) S. Munavalli, D. I. Rossman, A. J. Muller, H. S. Aaron, C. P. Ferguson, J. W. King, D. K. Rohrbaugh, and L. C. Buettner, American Chemical Society 10th Winter Fluorine Conference, St. Petersburg, FL, 1991, Abstract No. 38; (b) S. Munavalli, D. I. Rossman, D. K. Rohrbaugh, C. P. Ferguson, and L. J. Szafraniec, *J. Fluorine Chem.*, **59,** 91 (1992); (c) S. Munavalli, D. I. Rossman, D. K. Rohrbaugh, and H. D. Durst, *J. Organometal. Chem.*, **587,** 160 (1999); (d) S. Munavalli, A. Hassner, D. I. Rossman, S. Singh, D. K. Rohrbaugh, and C. P. Ferguson, *J. Fluorine Chem.*, **73,** 7 (1995); (e) S. Munavalli, D. I. Rossman, D. K. Rohrbaugh, C. P. Ferguson, and H. D. Durst, *J. Fluorine Chem.*, **76,** 7 (1996); (f) S. Munavalli, D. K. Rohrbaugh, D. I. Rossman, and H. D. Durst, *J. Flourine Chem.*, **89,** 189 (1998) and refernces cited there in; (g) S. Munavalli, G. W. Wagner, A. Bashir-Hashemi, D. K. Rohrbaugh, and H. D. Durst, *Synthetic Comm.*, **27,** 2847 (1997); (h) S. Munavalli, D. K. Rohrbaugh, D. I. Rossman, W. G. Wagner, and H. D. Durst, *Phosphorous, Sulfur, and Silicon*, **177,** 1021 (2002); (i) S. Munavalli, D. K. Rohrbaugh, D. I. Rossman, W. G. Wagner, and H. D. Durst, *Phosphorus, Sulfur, and Silicon*, **177,** 1073 (2002); (j) S. Munavalli, D. K. Rohrbaugh, D. I. Rossman, H. D. Durst, and A. Dondoni, *Phosphorus, Sulfur, and Silicon*, **177,** 2465 (2002); (k) S. Munavalli, D. K. Rohrbaugh, D. I. Rossman, W. G. Wagner, and H. D. Durst, *Phosphorus, Sulfur, and Silicon*, **107,** 1073 (2003); (1). S. Munavalli, D. K. Rohrbaugh, H. D. Durst, and D. I. Rossman, in Recent Developments in Organometallic Chemistry, Vol. 5, Research Signpost (Trivandrum) (2003), p. 15; (m) S. Munavalli, D. K. Rohrbaugh, W. G. Wagner, H. D. Durst, and F. R. Longo, *Phosphorus, Sulfur, and Silicon*, **179,** 1635 (2004); (n) S. Munavalli, D. K. Rohrbaugh, D. I. Rossman, F. J. Berg, and H. D. Durst, *Phosphorus, Sulfur, and Silicon*, **179,** 1645 (2004); S. Munavalli, D. K. Rohrbaugh, and H. D. Durst, *Phosphorus, Sulfur, and Silicon*, **179,** 1657 (2004).

[7] S. Munavalli, D. K. Rohrbaugh, D. I. Rossman, F. J. Berg, G. W. Wagner, and H. D. Durst, *Synthetic Comm.*, **30,** 2847 (2000).

[8] H. Ikehira, S. Tanimoto, and T. Oida, *J. Chem. Soc., Perkin Trans.*, **1,** 1223 (1984).

[9] (a) N. M. M. Nibbering, S. Ingemann, and L. J. de Koning in Supplement S, The Chemistry of Sulfur Containing Functional Groups, S. Patai and Z. Rappoport Eds., (Wiley and Sons, New York, 1993), p. 310; (b) J. E. Bartness, R. L. Hayes, H. N. Khatri, R. N. Misra, and S. R. Wilson, *J. Am. Chem. Soc.*, **103,** 4746 (1991).

[10] (a) J. H. Bowie and P. Y. White, *Org. Mass Spectrom.,* **6,** 317 (1972); (b) M. Dedieu, Y. L. Pascal, P. Dizabo, and J. J. Basselier, *Org. Mass Spectrom.*, **12,** 153 (1977);

(c) C. J. Shaw and V. V. Kane, *Org. Mass Spectrom.*, **15,** 502 (1980); (d) J. H. Bowie, P. Y. White, and T. Blumethal, *Org. Mass Spectrom.*, **22,** 5417 (1987); (e) A. Sturaro and P. Traldi, *Org. Mass Spectrom.*, **21,** 335 (1986).

[11] (a) R. H. Shapiro, T. E. McEntee, and D. L. Coffen, *Tetrahedron*, **24,** 2809 (1968); (b) D. L. Coffen, K. C. Bank, and P. E. Garrett, *J. Org, Chem.*, **34,** 605 (1969).

[12] E. J. Corey and D. Seebach, *Angew. Chem. Int. Ed.*, **4,** 1075 (1965).

[13] (a) J. -M. Lehn and G. Wipff, *J. Am. Chem. Soc.*, **98,** 7498 (1976), (b) A. Krief, *Tetrahedron*, **36,** 2531 (1980).

[14] (a) A. Streitwieser and S. P. Ewing, *J. Am. Chem. Soc.*, **97,** 190 (1975); (b) S. Wofe, S. Stowlow, and L. A. LaJohn, *Tetrahedron Lett.*, **24,** 4071 (1983) and references cited therein.

[15] (a) F. A. Carey and A. S. Court, *J. Org. Chem.*, **37,** 1926 (1972); (b) D. Seebach, B.-T. Grobel, A. K. Beck, M. Braun, and K.-H. Geiss, *Angew. Chem. Int. Ed.*, **11,** 443 (1972); (c) P. Jutzi and O. Lorey, *Phosphorus and Sulfur*, 203 (1979); (d) B. Lindgren, P. Stjernlof, and L. Trogen, *Acta Chrm. Scand. (B)*, **41,** 180 (1987); (e) S. R. Wilson, P. Caldera, and M. A. Jester, *J. Org. Chem.*, **47,** 3319 (1982); (f) W. W. Wood, in Organicsulfur Chemistry, P. Page, Ed. (Academic Press, New York, 1995), pp. 133.

[16] R. A. Elison, W. D. Waesner, and C. C. Williams, *J. Org. Chem.*, **37,** 2767 (1992).

[17] (a) S. Munavalli, D. I. Rossman, D. K. Roghrbaugh, C. P. Ferguson, and F.-L. Hsu, *Heteroatom Chem.*, **3,** 189 (1992); (b) S. Munavalli, D. I. Rossman, D. K. Roghrbaugh, C. P. Ferguson, and A. L. Rheingold, Proc. Edgewood Research Development and Engineering Center, Annual Conference D. A. Berg (ed.), Edgewood, MD (1994); (c) A. L. Rheingold, S. Munavalli, D. I. Rossman, D. K. Rohrbaugh, and C. P. Ferguson, *Inorg. Chem.*, **33,** 1723 (1994).

[18] D. K. Rohrbaugh, H. D. Durst, F. R. Longo, and S. Munavalli, *Phosphorus, Sulfur, and Silicon*, **180,** 2179 (2005).

[19] S. Munavalli, D. K. Rohrbaugh, D. I. Rossman, and H. D. Durst, Reaction of Trifluoromethylthiocopper with 1,3-Dithiane. Presented at the 211th National Meeting, American Chemical Society, New Orleans (1996).