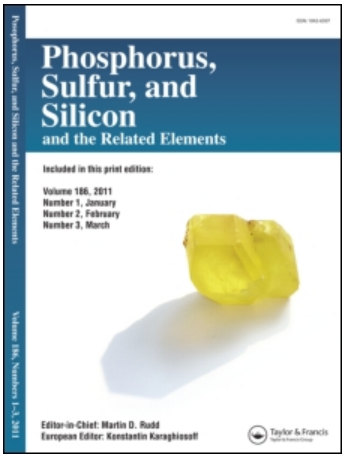

Phosphorus, Sulfur, and Silicon and the Related Elements

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To cite this Article Munavalli, S. , Rohrbaugh, D. K. , Rossman, D. I. , Hsu, F-L. and Durst, H. D.(2001) 'Thiirane Ring Cleavage with Trifluoromethylthiocopper', Phosphorus, Sulfur, and Silicon and the Related Elements, 176: 1, 111 — 118
To link to this Article: DOI: 10.1080/10426500108055107
URL: http://dx.doi.org/10.1080/10426500108055107

Phosphorus, Sulfur and Silicon, 2001, Vol. 176, pp. 111–118

1042-6507/01 $12.00 + .00

THIIRANE RING CLEAVAGE WITH TRIFLUOROMETHYLTHIOCOPPER

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(Received May 8, 2001)

The thiirane ring cleavage of cyclohexene sulfide with trifluoromethylthiocopper furnishes seven compounds. Of these, only one compound does not contain the trifluoromethylthio group. This paper presents the probable mechanism of formation of the compounds and their mass spectral characterization.

Keywords: Free radical cleavage; *thiirane ring*; trifluoromethylthiocopper

INTRODUCTION

Reactions of thiiranes, unlike those of the their oxygen containing counter parts, the oxiranes, have not been studied in detail.[1,2] The chemistry of the thiiranes has been reviewed,[3–9] one review in particular has been devoted to the discussion of thiirenium ion.[9] The most common reaction of the thiiranes is their desulfurization.[5–7] Thioethers undergo facile extrusion of sulfur on pyrolysis.[8,9] Lewis acid catalysts such as tin (IV) chloride, titanium (IV) chloride, aluminum chloride, etc. effect partial cleavage of the thiirane ring followed by polymerization.[5] A brief description of the latest work on the synthesis of the thiiranes can be found elsewhere.[6] During the pyrolysis of the thiiranes, the formation of the sulfur containing compounds has been observed.[8,9] In fact, the pyrolysis of cyclohexene sulfide has been reported to yield, among other compounds, dicyclohexyl sulfide, cyclohexyl phenyl sulfide, dicyclohexyl disulfide, cyclohexanethiol, and cyclohexyl cyclohexenyl sulfide, presumably via sulfur radical species.[10] Desulfurization of the thiiranes

has been shown to be highly stereoselective; in that cis- and trans-thiiranes furnish cis- and trans-alkenes respectively. This process permits stereoselective isomerization of alkenes via their conversion to thiiranes of opposite stereochemistry.[11] Two mechanisms have been proposed to account for the observed stereoselectivity. The treatment of cyclohexene sulfide with ethyl diazoacetate in the presence of copper acetoacetate gives alkene.[12,13] The proposed mechanism for the stereoselective fragmentation involves cheletropic attack by ethoxy carbonylcarbene on the sulfur atom to form the S-ylide intermediate, which then goes on to form the elimination product. Phenoxyaziridines effect desulfurization to form alkenes via the attack on sulfur by nitrogen.[14] However, the thiiranium salt ring opening has been described to yield two isomeric sulfur containing compounds.[15]

The second most common reaction of the thiiranes is the opening of the thiirane ring. It was reported, almost 50 years ago, that the reaction of chlorine with cyclohexene sulfide (**1**) in carbon tetrachloride caused desulfurization.[16] However, a slow addition of chlorine has been shown to give both monomeric and dimeric sulfides containing chlorine respectively.[17,18] The thiiranes in boiling acetic acid resulted in the formation of both mono- and diacetoxy mercaptans.[19] The reaction of cyclohexene sulfide (**1**) with alkylmagnesium bromide, followed by the treatment with acids or UV, has led to the characterization of cyclic compounds such as thiahydrindan and 1-thiadecalin derivatives.[20] In the presence of acids, nitriles react with thiiranes to yield 1,3-thiazolines.[21] An interesting extension of this reaction of the nitrile with the thiiranes is the treatment of trimethylsilyl cyanide and trimethylstannylamines to furnish β-cyanomercaptol and β-aminomercaptol.[22] While the former reaction requires the presence of aluminum chloride, the latter reaction goes by itself. Cyclohexene sulfide (**1**) has been shown to undergo a novel reaction with benzoyl isocyanate[5,7] and N-chlorobenzenesulfonylformimidoyl chloride.[22] Recently, alcoholysis of cyclohexene sulfide has been carried out in the presence of 2,3-dichloro-5,6-dicyano-p-benzoquinone[24] and ceric salts;[1] the latter process has been stated to furnish bis(alkoxy)disulfides involving the thiyl radicals fromed via the single electron transfer (SET) process.

In continuation of our efforts directed at the synthesis of bioactive organofluorine compounds containing the trifluoromethylthio functionality,[25–30] the reaction of trifluoromethylthiocopper (**2**) with cyclohexene sulfide (**1**) has now been investigated. This paper presents the mechanism of the formation and structures of compounds formed during the above-mentioned reaction.

RESULTS AND DISCUSSION

It has been recently reported that trifluoromethylthiocopper (**2**) cleaves the cyclohexene oxide ring (**3**) to furnish various products.[31,32] Various nucleophiles such as water, alcohols, hydroxide ions, alkoxides, carboxylates, oximes, and amines have been reacted with thiiranes. The nucleophiles are known to attack the carbon atoms of the thiiranes to form products resulting from the thiirane ring opening.[5–7] It was considered interesting to see whether the sulfur analog of cyclohexene oxide (**3**), namely cyclohexane episulfide (**1**), would react analogously with trifluoromethylthiocopper (**2**). Although the expectations were met, the formation of unusual products was observed. Seven compounds were detected by GC-MS/MS analysis of the reaction mixture. Their mass spectral fragmentation behavior permitted the characterization of seven compounds formed during the course of the reaction under investigation. As a result, their structures have been deduced (Figure 1).

The reaction of cyclohexane episulfide (**1**) with trifluoromethylthiocopper (**2**) furnishes eight compounds. The structures of seven compounds have been deduced using their mass spectral fragmentation patterns. These compounds are: (1) cyclohexyl (trifluoromethyl) disulfide (**6**); (2) cyclohexyl (trifluoromethyl) sulfide (**10**); (3) bis-(1,2-trifluoromethylthio) cyclohexane (**11**); (4) 2-trifluoromethylthiocyclohexanol (**12A**), (5) Unknown; (6) bis(cyclohexenyl) sulfide (**13**), and (7 and 8) [(trifluoromethylthio)cyclohexyl] cyclohexenyl sulfides (**15A** and **15A**). These two compounds are isomers.

Whatever may be the mechanism of the reaction, ionic or single electron transfer (SET), the sulfur atom of the episulfide entity appears to be certainly associated with and involved in the reaction.[33] Although the precise mechanism has not as yet been described, cyclic sulfides have been stated to dimerize in the presence of Ce (IV) reagents.[34] SET process has been invoked to explain, at least in part, the compounds

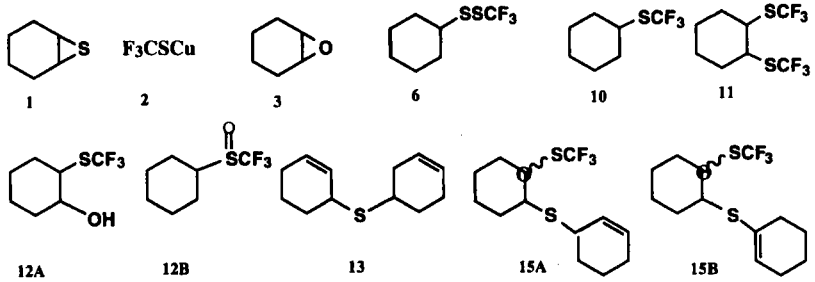

FIGURE 1 Structures of compounds cited in the narrative.

formed during the reaction of the episulfides with Ce (IV) reagents in the presence of alcohols.[1] Active involvement and participation of free radical processes in the thermal and photochemical reactions of cyclohexane episulfide have been implicated and implied.[5,12] After the work described herein was completed and published in part,[7] both ionic and free radical mechanisms have advanced to rationalize the formation of cyclohexenethioketene from the respective "gem-dichlorothiirane."

During the GC-MS identification of the products of the reaction of cyclohexane episulfide (**1**) with trifluoromethylthiocopper (**2**), the first component to come off the column ($M^+ = 200$, r.t. = 4.5 min, 1.4%) corresponds to $C_7H_{11}F_3OS$. Two structures, namely 2-(trifluoromethylthio)-1-cyclohexanol (**12A**) and (cyclohexyl)trifluoromethylsulfoxide (**12B**), were considered for this component. No fragment corresponding to the sulfoxide ion or the loss of oxygen was seen in its mass spectrum. The most intense peak happens to be the ion corresponding to (C_6H_9, m/z = 81). The presence of the ion at m/z = 114 indicated the loss of (OH) from the m/z = 131 ion. These considerations led to structure **12A** for this compound, the genesis of which is schematically described in Figure 2. Its formation can be ascribed to the reaction of the cyclohexylthiyl radical (**9**) with the hydroxyl radical derived from the moisture present in the solvent. The radical intermediate **9** itself arises from the cleavage of the carbon-sulfur bond of cyclohexane episulfide (**1**), followed by the addition of the F_3CS radical and the extrusion of sulfur from the intermediate **8**. An alternate pathway via the radical

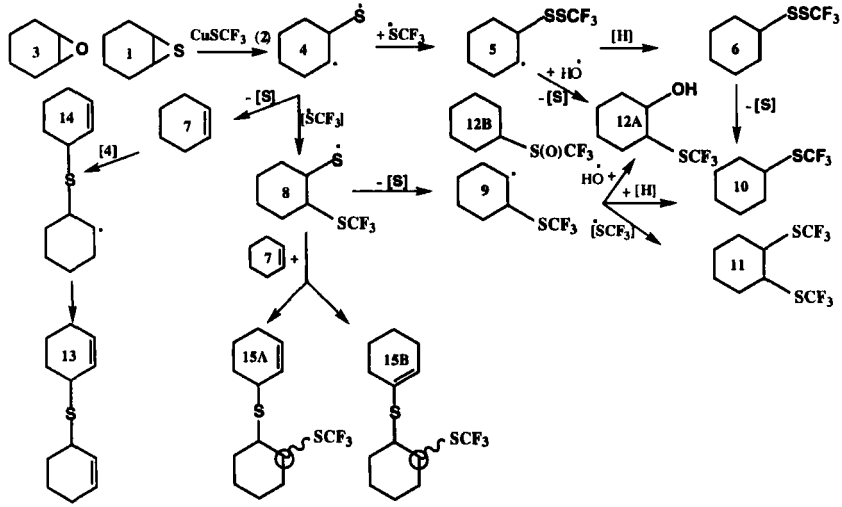

FIGURE 2 Probable mechanism of formation of the products.

intermediate **5** is also possible. The suggested cleavage of the carbon-sulfur bond and extrusion of sulfur have precedents.[1,10,12,13,25–30] The second component to elute has its M^+ = 216 (r.t. = 5.43 min, 1.2%). Its formation can be attributed to cyclohexylthiyl radical (**4**) that reacts with thrifluoromethylthiyl radical (F_3CS) arising from trifluoromethylthiocopper (**2**, F_3CSCu) and subsequent hydrogen abstraction by the resultant radical (**5**), gives compound **6**. Bis-(1,2-trifluoromethylthio)cyclohexane (**11**), the third component to come off (M^+ = 284, r.t. = 7.46 min, 16.8%) is formed from the reaction of 2-(trifluoromethylthio)cyclohexyl radical (**9**) with trifluoromethylthiyl radical formed from CF_3SCu. From the information available in the mass spectrum of the next component (r.t. = 9.06 min, 1.5%), this compound was identified as (trifluoromethylthio)cyclohexane (**10**).

Bis-(2,2′-cyclohexenyl) sulfide (**13**, r.t. = 12.49 min, 6.3%) is the compound eluting in order. This compound has been reported to arise during the free radical reactions of the substrate (**1**).[12,13] Its formation can be rationalized on the basis of the reaction between the radical intermediate **4** and cyclohexene (**7**), which is itself formed from **4** via the extrusion of sulfur; the resultant radical intermediate (**14**) then goes on to lose hydrogen and to furnish compound **13**. Finally, the last two components eluting off the column on the heels of one another have their retention time of 14.03 min and 14.08 min respectively (30.5% and 42.3%). These compounds have the same molecular weight, namely 296. Based on their M^+ ion and their similar mass spectral fragmentation patterns, which are completely identical, two structures **15A** to **15B** were considered for this pair of isomers. The inference that the SCF_3 group is located on the cyclohexyl entity and not the cyclohexenyl moiety is supported by the presence of the ions corresponding to m/z = 183 arising from the loss of the C_6H_9S moiety from the M^+. Also, the presence of the ion $C_6H_{11}SCF_3$ in their mass spectra lends support to structure **15A**. The presence of the ion m/z = 67 (C_5H_7) indicates that this is formed from the cyclohexenyl ion.[35] Thus, the examination of the mass spectral fragmentation behavior (Table I), permitted the elucidation of the structures of the compounds formed during the free radical catalyzed cleavage of cyclohexane episulfide.

Experimental Part

Trifluoromethylthiocopper (**2**) was prepared from bis(trifluoromethyl) disulfide as described by us elsewhere.[36] All solvents were dry and freshly distilled prior to their use. Mass spectra were obtained using a Finnigan TSQ 7000 GC-MS/MS equipped with a 30m × 0.25 mm i.d. DB-5 capillary column (J and W Scientific, Rancho Cordova, CA)

TABLE I Mass Spectral Fragmentation of the Compounds Cited in the Text

Mass Spectral Fragmentation of 2-Trifluoromethylthio-1-cyclohexanol (**12a**): $M^+ = 200$; 131 (M-CF_3); 114 (131-OH); 85 (C_4H_5S); 81 (114-SH, 100%); 70 (114-CS); 69 (CF_3); 67 (C_5H_7); 57 (C_4H_9); 55 (C_4H_7) and 45 (CSH).

Mass Spectral Fragmentation of cyclohexyl (trifluoromethyl) disulfide (**6**): $M^+ = 216$ (not seen); 82 (M-$HSSCF_3$); 81 (C_6H_9, 100%); 79 (C_6H_7); 77 (C_6H_5); 69 (CF_3) and 53 (C_4H_5).

Mass Spectral Fragmentation of Bis-(1,2-trifluoromethylthio) cyclohexane (**11**): $M^+ =$ 284 (not seen); 215 (M-CF_3); 183 (M-SCF_3); 141 ($C_3H_4SCF_3$); 133 ($C_6H_{10}FS$); 115 (H_2CSCF_3); 85 (C_4H_5S); 81 (183-$HSCF_3$ 100%); 69 (CF_3); 53 (C_4H_5) and 45 (CSH).

Mass Spectral Fragmentation of bis-(2,2′-cyclohexenyl) sulfide (**13**): $M^+ = 194$; 113 (M-C_6H_9); 85 (C_4H_5S); 80 (C_6H_8, 100%); 53 (C_4H_5) and 45 (CSH).

Mass Spectral Fragmentation of [(trifluoromethylthio)-cyclohexyl]-2-cyclohexenyl sulfide (**15A**, stereoisomer, r.t. = 14.03 min): $M^+ = 296$; 195 (M-SCF_3); 183 ($C_6H_{11}SCF_3$); 141 ($C_3H_4SCF_3$); 113 (C_6H_9S); 81 (C_6H_9, 100%); 67 (C_5H_7); 59 (C_2H_3S); 53 (C_4H_5) and 45 CSH).

Mass Spectral Fragmentation of [1-(trifluoromethylthio)cyclohexyl]-2-cyclohexenyl sulfide (**15A**, stereoisomer, r.t. = 14.08 min): $M^+ = 296$; 195 (M- SCF_3); 183 ($C_6H_{11}SCF_3$); 141 ($C_3H_4SCF_3$); 113 (C_6H_9S); 81 (C_6H_9, 100%); 67 (C_5H_7); 59 (C_2H_3S); 53 (C_4H_5) and 45 CSH).

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 the 5100 were: oven temperature 60–270°C at 10°C min^{-1}, injection temperature 210°C, interface temperature 230°C, electron energy 70 eV, emission current 500 μA and scan time 1 s. The conditions on TSQ-7000 were: oven temperature 60–270°C at 15°C min^{-1}, injection temperature 220°C, interface temperature 250°C, source temperature 150°C, electron energy 70 (EI) or 200 eV (CI) and emission current 400 (EI) or 300 μA (CI) with a scan time 0.7 s. Data were obtained in both electron ionization mode (range 45–450 da) and chemical ionization mode (mass range 60–450 da). Ultra high purity methane was used as the CI agent gas with a source pressure of 0.5 (5100) or 4 Torr (TSQ-7000). 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, Folsom, CA).

Reaction of cyclohexene sulfide (**1**) with trifluoromethylthiocopper (**2**): A suspension of stoichiometric amounts (usually 1 mmol) of cyclohexene sulfide (**1**) and trifluoromethylthiocopper (**2**) in freshly distilled dry toluene was heated over night at 110–120°C under dry nitrogen, reaction mixture was cooled to room temperature, treated with saturated ammonium chloride, extracted with chloroform, extract washed successively with water and saturated solution of sodium chloride, dried over anhydrous sodium sulfate, and solvent evaporated under reduced pressure. GC-MS analysis of the residue indicated it to consist of at

least seven components. The GC-MS fragmentation behavior permitted the characterization of the following compounds: (1) cyclohexyl (trifluoromethyl) disulfide (**6**); (2) cyclohexyl (trifluoromethyl) sulfide (**10**); (3) bis-(1,2-trifluoromethylthio)cyclohexane (**11**); (4) 2-trifluoromethylthio-1-cyclohexanol (**12A**); (5 and 6) [(trifluoromethylthio)-cyclohexyl]-2-cyclohexenyl sulfides (**15A**, $M^+ = 296$) and (**15A** $M^+ = 296$), these two compounds are stereoisomers and exhibit identical fragmentation behavior; and (i) bis-(2,2′-cyclohexenyl) sulfide (**13**) (Figure 1).

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