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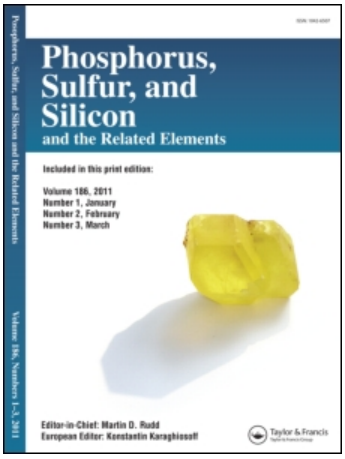

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TRIFLUOROMETHYLTHIOLATION OF TRIMETHYLSILYL ENOL ETHERS

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The treatment of bis-(1,2-trimethylsilyloxy)-1-cyclobutene, 1-(1-trimethylsilyloxy)cyclpentene and 1-(1-trimethylsilyloxy)cyclohexene with trifluoromethylsulfenyl chloride has been found to furnish trifluoromethylthiolated carbonyl derivatives.

Keywords: Trifluoromethylthiolation; trimethylsilyl enol ethers; trifluoromethylthiolated carbonyl derivatives

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INTRODUCTION

Silyl enol ethers have attracted considerable attention as a versatile group of synthetic intermediates.[1] The selectivity and stereocontrol exhibited by these compounds is due to steric effects and/or electronic effects.[2] The steric effect of the silyl group is primarily due to its bulk, which is greater than that of the t-butyl group.[3] The reaction of silyl enol ethers with alkyl and arylsulfenyl chlorides constitutes a facile procedure for the preparation of α-sulfenylated carbonyl intermediates.[3] In view of the observation that the trifluoromethylthio group facilitates in vivo absorption of compounds containing this moiety,[4a] its convenient transportation in the biological matrices[4b] and that it profoundly enhances the precursors biological activity,[5] we have been interested in the chemistry of this functional group.[6] However, the incorporation of this group into organic compounds involves the use of highly hazardous reagents.[7] We have developed a novel procedure to accomplish this goal[8a] and described the x-ray crystallographic structure determination

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of this reagent, namely $CuSCF_3$.[8b] However, this reagent can not be used to prepare α-trifluoromethylthiolated carbonyl compounds. This article describes the trifluoromethylthiolation of silyl enol ethers and the spectral characterization of various products.

RESULTS AND DISCUSSION

Silyl enol ethers are known to react with electrophiles such as bromine[9a] and the Simmons-Smith reagent.[9b] Sequential treatment of silyl enol ethers with silvercarboxylate:iodine (2:1) followed by fluorides has been said to give α-acyloxycarbonyl compounds.[9d] Cyclopropanation of silyl enol ethers yield synthetically useful intermediates.[9e] Ene-silyloxy compounds readily react with carbonyl compounds and acetals in the presence of tin (IV) chloride,[10a] lanthanide triflates,[10b] and titanium (IV) chloride.[10c] Lewis acid[11a] and fluorides catalyze the reaction of C,O,O-tris-(trimethylsilyl)ketene with aldehydes to form the respective alkenoic acids.[11b–c] Allylic alkylation of enol silyl ethers[12] has been described. Electrophilic addition of a sulfur-halide to silyl alkenyl ethers has been described to give interesting α-thioalkylsilylketones.[13] Lewis acid catalyzed α-thiolation of enol silyl ethers using 2,2′-diethylthiopropane has been described.[14] Direct fluorination of silyl enol ethers gave mono- and difluroinated carbonyl compounds as well as mono- and silyl enol ethers.[15]

The search for a safe, stable and effective trifluoromethylthiolating agent led us to N-trifluoromethylthiophthalimide and α-trifluoromethylthiolated carbonyl compounds in reasonably good yields ($\sim$80%).[16] In continuation of our interest in the chemistry of the trifluoromethylthio group,[6] the reaction of bis-(1,2-trimethylsilyloxy)-1-cyclobutene (**1**), 1-(trimethylsilyloxy)-1-cyclopentene (**2**) and 1-(trimethylsilyloxy)-1-cyclohexene (**3**) with trifluoromethylsulfenyl chloride (**4**) has been examined and this communication presents the results.

The formation and reactions of the silyl radicals have been discussed.[17] With compound **1**, in addition to bis-(trifluoromethyl)disulfide (**5**), trimethylsilyl chloride (**6**) and trimethylsilyl fluoride (**7**), bis-(1,2-trimethylsilyloxy)-(3-trifluoromethylthio)-1-cyclobutene (**8**) and 1-(trimethylsilyloxy)-3-(trifluoromethylthio)-2-cyclobutanone (**9**) (Figure 1) were characterized. Figure 2 presents the probable mechanism of formation of **8** and **9**. The origin of compounds **5**, **6**, and **7** has already been discussed.[18] The presence of compounds **5**, **6**, and **7** strongly suggests and supports the involvement of the free radical process described in Figure 2. The allylic radical **10** and the thiyl radical

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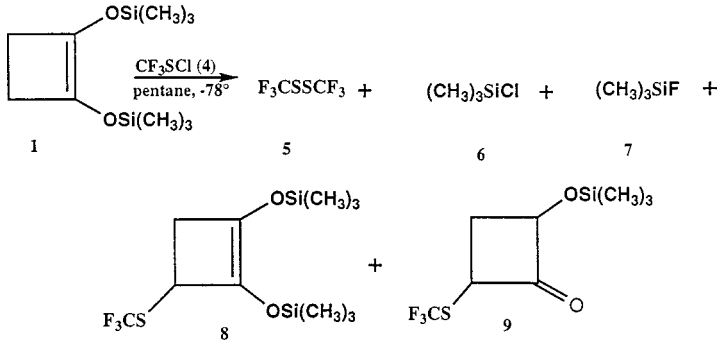

FIGURE 1 Trifluoromethylthiolation of 1,3-bis-(trimethylsilyloxy)-cyclobutene.

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react to give **8**, which via intermediates **11** and **12** leads to compound **9**. There is a precedent for the formation of the cyclobutanone derivative from 1.[19] Table I describes the mass spectral breakdown of **8** and **9**.

The reaction of compound **2** with F_3CSCl (**4**) yields bis-(trifluoromethyl)disulfide (**5**), 2-(trifluoromethylthio)cyclopentanone (**13**), bis-(2,2-trifluoromethylthio)cyclopentanone (**14**), bis-(2,3-trifluoromethylthio)cyclopenatnone (**15**) and bis-(2,5-trifluoromethylthio)-cyclopentanone (**16**) (Figure 3). Figure 4 attempts to rationalize the formation of the above mentioned products. The addition of the thiyl radical to **2** leads to the intermediate **17**, which gives compound **13**.

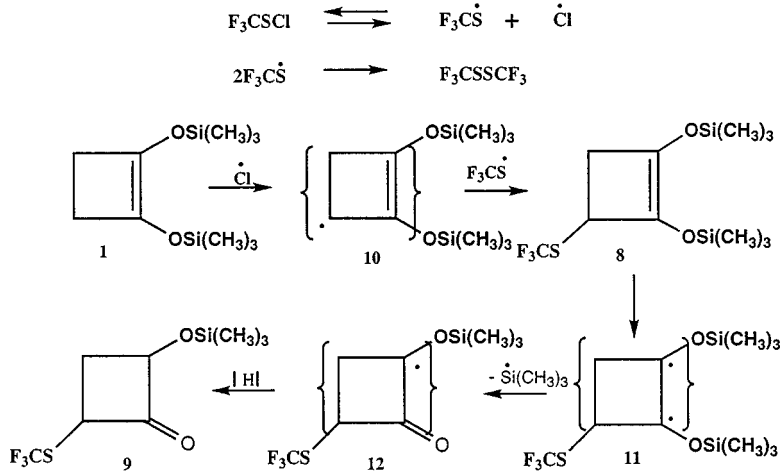

FIGURE 2 Probable mechanism of formation of products derived from 1,3-bis-(trimethylsilyloxy)cyclobutene.

TABLE I Mass Spectral Fragmentation of Compounds Formed from Bis-1,2-(trimethylsilyloxy)cyclobutene (cf. Figure 1)

1. Bis-(1,2-trimethylsilyloxy)-3-(trifluoromethylthio)cyclobutene (**8**): $M^+ = 330$; 261 (M—CF_3); 229 (M—SCF_3); 173 (C_4H_4S, OSi Me_3); 73 (Me_3Si, 100%); 59 (C_2H_3S); 45 (CSH) and 40 (C_3H_4).
2. 2-(trifluoromethylthio)-4-(trimethylsilyloxy)-1-cyclobutanone (**9**): $M^+ = 258$ (not seen under EI, but observed with CI); 243 (M—CH_3 with CI); 189 (M—CF_3); 174 (189—CH_3 or M—Me_3SiH); 161(189-CO); 157 (M—SCF_3); 82 (CSF_2); 73 (Me_3Si, 100%); 69 (CF_3); 56 (C_3H_4O) and 45 (CSH).

Abstraction of hydrogen from **13** results in intermediates **18** and **19**, the former unites with the thiyl radical to form **16**, while the latter similarly leads to **14**. Also, the C_3-hydrogen migrates from the intermediate **19** to C_2 to give intermediate **20**, which subsequently reacts with the thiyl radical to yield compound **15**. Careful vacuum distillation permitted the separation of **13** and **14**. However, **15** and **16** could not be separated and were identified by their GC-MS only. The mass spectral fragmentation of the compounds obtained from **2** is given in Table II. We have recently reported the preparation and mass spectrum of **13**.[16]

However, the reaction of compound **3** with F_3CSCl (**4**) furnishes ten compounds: (1) bis-(trifluoromethyl)disulfide (**5**), (2) trimethylsilyl chloride (**6**), (3) trimethylsilyl fluoride (**7**), (4) 2-(trifluoromethylthio)cyclohexanone (**21**), (5) 3-(trifluoromethylthio)-cyclohexanone (**22**), (6) bis-(2,2-trifluoromethylthio)cyclohexanone (**23**), (7) bis-(2,6-trifluoromethylthio)cyclohexanone (**24**), (8) bis-(2,6-trifluoromethylthio)cyclohexanone (**25**), (9) 2-chloro-6-(trifluoromethylthio)cyclohexanone (**26**) and (10) 2-chloro-6-(trifluoromethylthio)cyclohexanone (**27**) (Figure 5). Figure 6 suggests the probable mechanism of the origin of these compounds. Careful vacuum distillation enabled the separation of **21**, **22**, and **24–25**. The remaining compounds were characterized by their mass spectral fragmentation

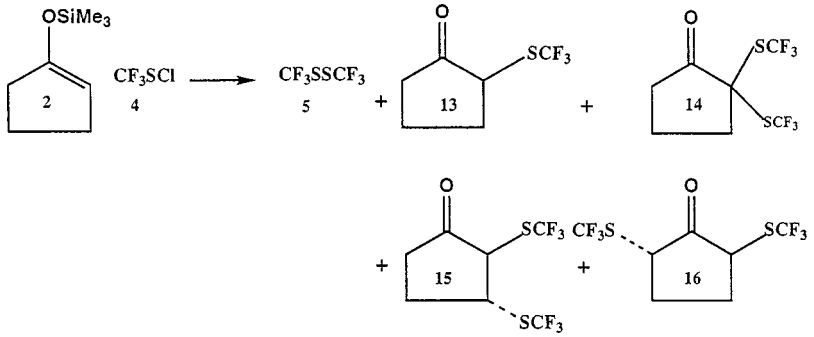

FIGURE 3 Trifluoromethylthiolation of 1-(trimethylsilyloxy)cyclopentene.

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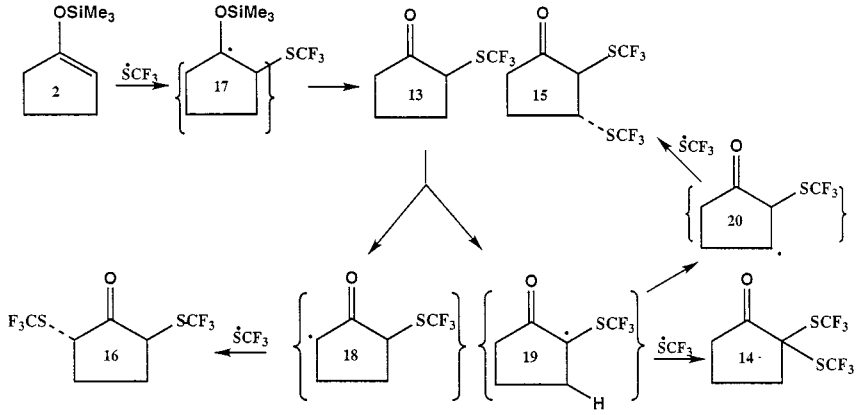

FIGURE 4 Mechanism of Trifluoromethylthiolation of 1-(trimthylsilyloxy)-cyclopentene.

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patterns (Table III). 2-(Trifluoromethylthio)cyclohexanone (**21**) has been previously described.[16]

The mass spectral breakdown of silyl ethers has been discussed.[20] Fragments corresponding to [M—CH_3] and [Si(CH_3)$_3$] (m/e = 73) moieties are commonly seen. Aliphatic silyl ethers show a peak at m/e = 89, which corresponds to [$CH_2OSiH(CH_3)_2$] or [$OSi(CH_3)_3$]. The proposed structures of the major products have been further supported by their ^{13}C-NMR data.

TABLE II Mass Spectral Fragmentation of Compounds Derived from 1-(Trimethylsilyloxy)-1-cyclopentene (cf. Figure 3)

1. 2-(Trifluoromethylthio)cyclopentanone (**13**): $M^+ = 184$ (r.t. = 2.10 min, 86.9%); 156 (M—CO or C_2H_4); 141 (M—C_3H_7); 128 (M—C_3H_4O); 115 (M—CF_3); 101 (SCF_3); 99 (C_4H_3OS); 87 (C_3H_3OS); 83 (M—SCF_3); 69 (CF_3); 59 (C_2H_2S); 55 (C_3H_3O, 100%); 50 (CF_2); 45 (CSH); 42 (C_3H_6); 39 (C_3H_3) and 27 (C_2H_3).
2. Bis-(2,2-trifluoromethylthio)-1-cyclopentanone (**14**): $M^+ = 284$ (not seen, r.t. = 3.47, 1.6%); 215 (M—CF_3); 141 ($C_3H_4SCF_3$); 120 ($FSCF_3$); 102 ($HSCF_3$); 69 (CF_3, 100%); 56 (C_3H_4O); 39 (C_3H_3); 32 (S) and 27 (C_2H_3, 100%).
3. Bis-(2,3-trifluoromethylthio)-1-cyclopentanone (**15**: $M^+ =$ 284 (not seen, r.t. = 3.50 min, 3.9%); 228 [C_2H_2 (SCF_3) 2]; 215 (M—CF_3); 187 (M—CF_3—CO); 183 (M—SCF_3); 159 (M—$C_2H_3SCF_3$); 155 ($C_4H_2F_3OS$); 141 ($C_3H_4SCF_3$); 127 ($C_2H_3SCF_3$); 115 (CH_2SCF_3); 101 (SCF_3); 85 (C_3HOS); 69 (CF_3); 59 (C_2H_3S); 55 (C_3H_3O, 100%); 51 (CHF2); 45 (CSH); 39 (C_3H_3); 32 (S) and 27 (C_2H_3).
4. Bis-(2,5-trifluoromethylthio)-1-cyclopentanone (**16**): $M^+ = 284$ (r.t. = 3.47, 8.5%); 215 (M—CF_3); 187 (M—CF_3—CO); 183 (M—SCF_3); 163 (183-HF); 141 ($C_3H_4SCF_3$); 128 ($C_2H_3SCF_3$, 100%); 115 (CH_2SCF_3); 101 (SCF_3); 85 (C_3HOS); 69 (CF_3); 59 (C_2H_2S); 55 (C_3H_3O, 100%); 51 (CHF_2); 45 (CSH); 39 (C_3H_3); 32 (S) and 27 (C_2H_3).

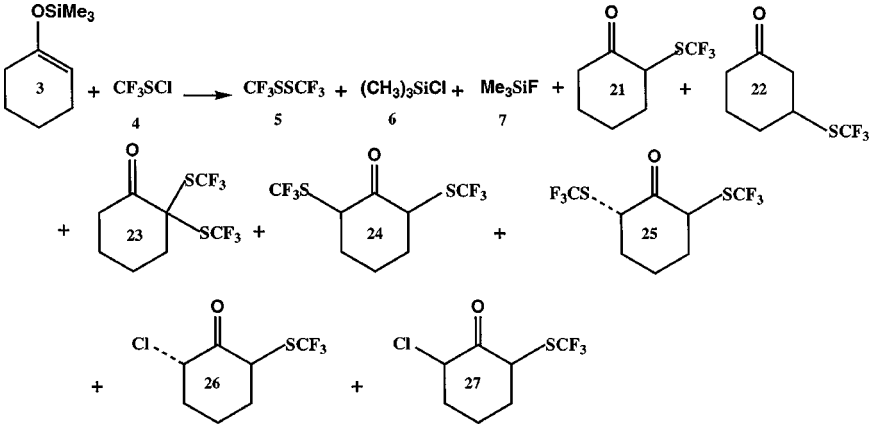

FIGURE 5 Trifluoromethylthiolation of 1-(trimethylsilyloxy)cyclohexene.

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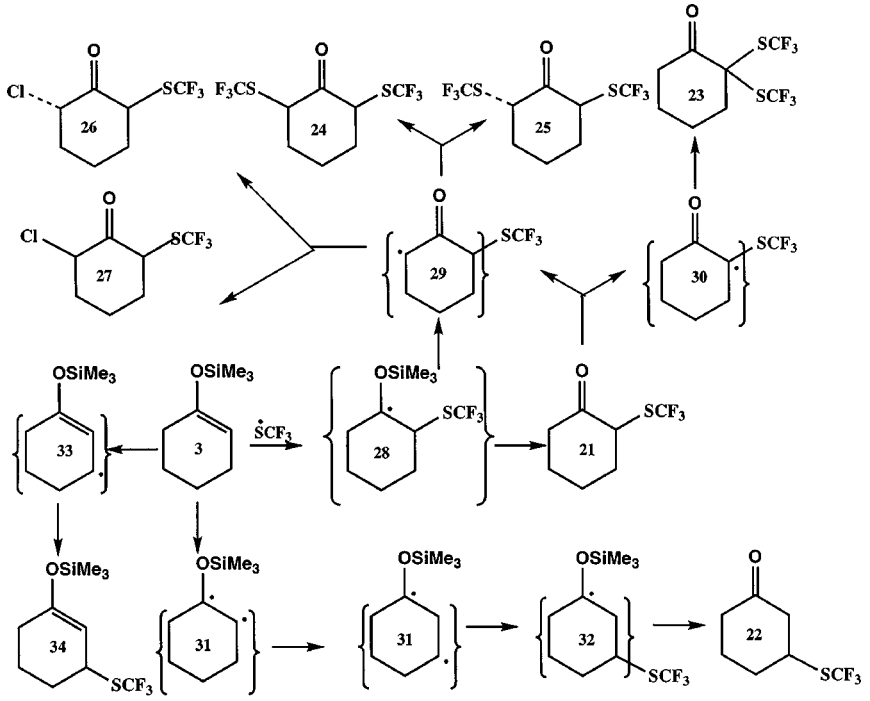

FIGURE 6 Formation of compounds from 1-(trimethylsilyloxy)cyclohexene.

TABLE III Mass Spectral Fragmentation of Compounds from Silyloxycyclohexene (cf. Figure 5)

1. 2-(Trifluoromethylthio)cyclohexanone (**21**)*†: $M^+ = 198$ (r.t. = 3.16 min, 84.9%); 170 (M—CO or —C_2H_4); 154 (M—2H—C_3H_6); 141 ($C_3H_4SCF_3$); 129 (M—CF_3); 128 ($C_2H_3SCF_3$); 101 (SCF_3); 97 (M—SCF_3); 85 (C_4H_5S); 82 (CSF_2); 69 (CF_3, 100%); 67 (C_5H_7); 63 (CSF); 59 (C_2H_3S); 55 (C_3H_3O) and 47 (SCH_3).
2. 3-(Trifluoromethylthio)cyclohexanone (**22**): $M^+ = 198$ (r.t. = 3.06 min, 0.7%); 179 (M—F); 170 (M—CO or C_2H_4); 159 (179-HF); 137 ($C_5H_2F_2S$); 129 (M—CF_3); 101 (SCF_3, 100%); 97 (M—SCF_3); 83 (C_5H_7O); 69 (CF_3) and 60 (C_2H_4S).
3. Bis-(2,2-Trifluoromethylthio)cyclohexanone (**23**): $M^+ = 298$ (r.t. = 5.59 min, 6.25%); 278 (M—HF); 229 (M—CF_3); 201 ($C_4H_4OS.SCF_3$); 197 (M—SCF_3); 177 (197-HF); 141 ($C_3H_4SCF_3$); 128 ($C_2H_3SCF_3$); 115 (CH_2SCF_3); 99 (C_4H_3OS, 100%); 85 (C_4H_5S); 69 (CF_3) and 41 (C_3H_5).
4. Bis-(2,6-Trifluoromethylthio)cyclohexanone (**24**)†: $M^+ = 298$ (r.t. = 5.23 min, 4.9%); 201 (M—CO—CF_3); 169 (M—$C_2H_4SCF_3$); 141 ($C_3H_4SCF_3$); 128 ($C_2H_4SCF_3$); 115 (CH_2SCF_3); 99 (C_4H_3OS); 85 (C_4H_5S); 69 (CF_3, 100%); 67 (C_5H_7) and 47 (SCH_3).
5. Bis-(2,6-Trifluoromethylthio)cyclohexanone (**25**)†: $M^+ = 298$ (r.t. = 4.32 min, 10.6%); 229 (M—CF_3); 201 (298-CF_3—CO); 197 (M—SCF_3); 169(M—$C_2H_4SCF_3$); 141 ($C_3H_4SCF_3$); 128 ($C_2H_3SCF_3$); 115 (CH_2SCF_3); 101 (SCF_3); 99 (C_4H_3OS); 85 (C_4H_5S); 82 (CSF_2); 69 (CF_3, 100%); 67 (C_5H_7); 59 (C_2H_3S); 55 (C_3H_3O) and 47 (SCH_3).
6. 2-Chloro-6-(trifluoromethylthio)cyclohexanone (**26**): $M^+ = 232$ (r.t. = 4.17 min, 0.3%); 213 (M—F, 100%); 177 (M—Cl); 141 ($C_3H_4SCF_3$); 127 ($C_2H_2SCF_3$); 99 (C_4H_3OS); 95 (C_6H_7O); 85 (C_4H_5S); 69 (CF_3) and 67 (C_5H_7, 99%).
7. 2-Chloro-6-(trifluoromethylthio)cyclohexanone (**27**): $M^+ = 232$ (r.t. = 4.08 min, 0.2%); 213 (M—F); 197 (M—Cl, 100%); 179 ($C_4H_9F_2OS$); 147 (M—Cl—CF_2); 131 (M—SCF_3); 111 (147-HCl); 103 (M—$C_2H_4SCF_3$); 101 (SCF_3); 83 (C_4H_5S); 79 (111—S); 69 (CF_3) and 67 (C_5H_7).

*Its preparation using a different procedure and mass spectrum have been reported.[32]

†After vacuum distillation at 26 ~ 28°C/0.001 mm Hg, a fraction containing these three compounds was obtained.

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EXPERIMENTAL

All solvents were dry and freshly distilled prior to use. The general procedure consisted of adding stoichiometric amounts of trifluoromethanesulfenyl chloride (**4**) via the vacuum line at −78°C with stirring and under argon to the solution of the substrate in freshly distilled dry n-pentane (25 ml). The reaction mixture was stirred at −78°C for additional 2 h and then overnight at room temperature. The solvent was removed under reduced pressure and after the initial GC analysis, the residue was subjected to GC-MS analysis. 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: oven temperature 60–270°C at 10°C/min, injection temperature was 210°, interface temperature 230°C, electron energy 70 eV, emission current 500 μA and scan time 1 s. The conditions on the TSQ-7000 were: oven temperature 60–270°C at 15°C/min, injection temperature 220°, interface temperature 250°C, source temperature 150°, electron energy 70 eV (EI) or 200 eV (CI) and emission current 400 μA (EI) or 300 μA (CI) and scan time 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). Ultrahigh purity methane was used as the CI 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 $\times$ 0.53 mm i.d. DB-5 column (J and W Scientific, Folsom, CA). The NMR spectra (^{1}H and ^{13}C) were recorded in $CDCl_3$ with TMS as the internal standard on a Varian VXR-400S spectrometer at 100 MHz and 376 MHz respectively. The chemical shifts are given as ppm.

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Reaction of Bis-(1,2-trimethylsilyloxy)-1-cyclobutene (1) with Trifluoromethylsulfenyl Chloride (4)

A solution of bis-(1,2-trimethylsilyloxy)-1-cyclobutene(**1**, 1.15 g, 5 mmol) in dry pentane was reacted with trifluoromethylsulfenyl chloride (**4**, 0.68 g, 5 mmol) with stirring at −78°C for 3 h under argon. The reaction mixture was allowed to come to room temperature and stirred over night at ambient temperature. The solvent was evaporated under reduced pressure. The gas chromatographic-mass spectrometric analysis of the residue using both EI and CI modes showed it to consist primarily of the following compounds: (a). bis-(trifluoromethyl)disulfide (**5**), (b). trimethylsilyl chloride (**6**), (c). trimethylsilyl fluoride (**7**), (d). bis-(1,2-trimethylsilyloxy)-3-trifluoromethylthio-1-cyclobutene (**8**) and (e) 2-trifluoromethyl-thio-4-trimethylsilyloxy-1-cyclobutanone (**9**) (Figure 1). The formation of **5**, **6**, and **7** and their mass spectral breakdown have been described.[18] Table I gives the mass spectral data of **8** and **9**.

Reaction of 1-(Trimethylsilyloxy)cyclopentene (2) with Trifluoromethylsulfenyl Chloride (4)

Stoichiometric amounts of 1-cyclopentenyloxytrimethylsilane (**2**, 1.56 g, 0.01 mmol) and trifluoromethylsulfenyl chloride (**4**, 1.36 g, 0.01 mmol) were reacted in dry pentane under argon at −78°C with stirring. The stirring was continued for three hours at −78°C and the

reaction mixture was allowed to come to room temperature over night. The GC-MS analysis indicated the presence of four constituents (Figure 3): (a). bis-(trifluoromethyl)disulfide (**5**, $M^+ = 202$, 0.8%), (b). 2-(trifluoromethylthio)cyclopentanone (**13**, $M^+ = 184$, 87.0%), (c). bis-(2,2-trifluoromethylthio)cyclopentanones (**14**, $M^+ = 284$, 11.8%), (d). bis-(2,3-trifluoromethylthio)cyclopentanones (**15)** and (e) bis-(2,5-trifluoromethylthio)cyclopentanones (**16**). The reaction mixture was then subjected to vacuum distillation at 4.5–5.0 mm Hg. The GC-MS-CI analysis of the three fractions showed the presence of two compounds, namely 2-(trifluoromethylthio)cyclopentanone (**13**, major product, 87.0%) and disubstituted-cyclopentanone derivatives (11.8%). However, ^{13}C-NMR of the three fractions indicated the presence of four compounds containing the carbonyl function. The mass spectral breakdown of the vacuum distilled fractions were reexamined using GC-MS-EI and the structures of the disubstituted cyclopentanones have been deduced as (**14–16**). The mass spectral data is described in Table II.

^{13}C-NMR of 2-(trifluoromethylthio)cyclopentanone (**13**): **C**O = 205, S**C**F_3 = 131. (q, J_{CF} = 306 Hz), **C**–SCF_3 = 50.1, (q, J_{CSCF} = 1–2 Hz), C_3 = 32.2 (q, J = 0.7 Hz), C_4 = 20.4, and C_5 = 35.8 ^{13}C-NMR of bis-(2,2-trifluoromethylthio)cyclopentanone (**14**): **C**O = 211.9, S**C**F_3 = 200.2; **C**$(SCF_3)_2$ = 66.1; CH2(next to CO) = 32.9; CH_2[next to **C**$(SCF_3)_2$] = 27.6 and CH_2 = 19.0.

Reaction of 1-(1-Trimethylsilyloxy)cyclohexene (3) with Trifluoromethylsulfenyl Chloride (4)

Stoichiometric amounts of 1-(trimethylsilyloxy)cyclohexene (**3**, 1.70 g, 0.01 mmol) and trifluoromethylsulfenyl chloride (**4**, 1.36 g, 0.01 mmol) were allowed to react with stirring under argon at −78°C. The stirring was continued for 3 h at −78°C and the reaction mixture was allowed to come to room temperature and stirred over night. The GC-MS analysis using both CI and EI techniques indicated the presence of the following compounds: (a) trifluoromethylsulfenyl chloride (**4**), (b) bis-(trifluoromethyl)disulfide (**5**), (c) trimethylsilyl fluoride (**7**), (d) trimethylsilyl chloride (**6**), (e) unknown with no molecular ion peak, (f) 2-(trifluoromethylthio)cyclohexanone (**21**, > 60.0%) (g) 3-(trifluoromethylthio)cyclohexanone (**22**, 0.2%) (h) two isomeric 2-trifluoromethylthio)-6-chloro-cyclohexanones (**26–27**) and (i) three isomeric bis-(trifluoromethylthio)cyclohexanones (**23–25**). The reaction product was then subjected to vacuum distillation at 0.001 mm Hg and three components in 84.9%, 10.3% and 4.8% yields were obtained. The structure of the major compound was deduced as

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1-trifluoromethylthio-2-cyclohexanone (**21**). Its mass spectrum was identical to that of the compound obtained by another route.[16] This assignment was further supported by the ^{13}C-NMR analysis of the reaction product. Three dithiolated cyclohexanones (**23**, **24**, and **25**) were identified by their mass spectral fragmentation patterns. The mass spectral data is given in Table III.

^{13}C-NMR of 1-trifluoromethylthio-2-cyclohexanone (**21**): **C**O = 204.4 ppm, S**C**F$_3$ = 131.3 (q, J_{CF} = 305 Hz), **C**—SCF$_3$ = 54.8 (q, J_{CSCF} = 1 Hz), **C**—CO = 40.9 and the remaining Cs' at 27.3, 24.8 and 24.5 ppm.

^{13}C-NMR of bis-(2,2-trifluoromethylthio)cyclohexanone (**23**): **C**O = 200.2 ppm, S**C**F$_3$ = 130.5 (q, J_{CF} = 306 Hz), **C**—SCF$_3$ = 70.6.

^{13}C-NMR of bis-(2,6-trifluoromethylthio)cyclohexanone (**24**/**25**): **C**O = 199 ppm, S**C**F$_3$ = 131.0 (q, J_{CF} = 306.4 Hz), **C**—SCF$_3$ = 50.6.

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