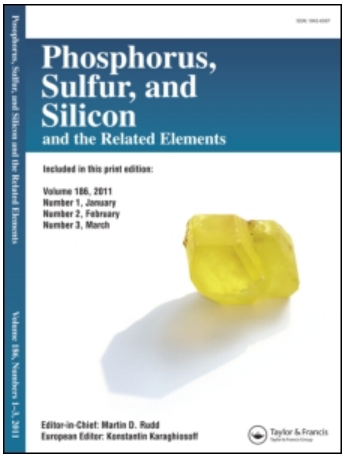

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TRIFLUOROMETHYLTHIOLATION OF N,O-BIS-(TRIMETHYLSILYL)ACETAMIDE

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The treatment of N,O-bis-(trimethylsilyl)acetamide with trifluoromethyl-sulfenyl chloride furnishes N-mono- and di-trifluoromethylthiolated acetamides.

Keywords: mon- and bis-thiolated products; NMR and mass spectra; silylacetamide; trifluoromethylthiolation

INTRODUCTION

Since organic compounds containing fluoroine and fluorine containing functional groups, such as the trifluoromethyl and trifluoromethylthio moieties exhibit unique biological properties[1] such as high electronegativities,[2] stability under acidic environment,[3] lipophilicity,[4a] and ready in vivo absorption and facile transportation,[1j,4] considerable interest has manifested in the development of methodologies for the incorporation of these functional groups into organic compounds.[5] However, the direct introduction of these groups into organic compounds, particularly into the bioactive heterocyclic compounds, entails low regiospecificity and the use of hazardous reagents.[6] Commonly used procedures include: (1) the radical addition of perfluoroiodides to olefins,[7] (2) the Ullman-type reaction of fluorinated-aromatics,[8] (3) cationic perfluoroalkylation with fluoroalkyl-phenyliodinium sulfones,[9] (4) organocadmium and -zinc complexes[10] and trifluoromethylthiocopper.[11] Sonication has found only a limited application in selective perfluoroalkylation of organic molecules.[12] The regio- and stereospecific

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introduction of the said groups profoundly affects the physico-chemical and biological properties of the parent precursors.[1g,13] Of specific concern so far has been the preparation of fluoro- and trifluoromethyl synthons, since they are known to affect the behavior and mechanism of action of the enzymes.[14]

Silyl enol ethers have attracted considerable attention as a versatile group of synthetic intermediates.[15] The selectivity and stereocontrol exhibited by these compounds is due to steric effects and/or electronic effects.[16] The steric effect of the silyl group is primarily due to its bulk, which is greater than that of the t-butyl group.[17] The reaction of silyl enol ethers with alkyl and arylsulfenyl chlorides constitutes a facile procedure for the preparation of α-sulfenylated carbonyl intermediates.[17] In view of the observation that the trifluoromethylthio group facilitates in vivo absorption of compounds containing this moiety,[4b] its convenient transportation in the biological matrices[1j] and that it profoundly enhances the precursors biological activity,[18a] we have been interested in the chemistry of this functional group.[19] The incorporation of this group into organic compounds involves the use of highly hazardous reagents.[20] We recently have developed a novel procedure to accomplish this goal[21a] and have described the x-ray crystallographic structure determination of this reagent, namely $CuSCF_3$.[21b] This reagent can not be used to prepare α-trifluoromethylthiolated carbonyl compounds. This article describes trifluoromethylthiolation of silyl enol ethers and the spectral characterization of the reaction products.

RESULTS AND DISCUSSION

Silyl enol ethers are known to react with electrophiles such as bromine[22a] and the Simmons-Smith reagent.[22b] Cyclopropanation of silyl enol ethers furnishes synthetically useful intermediates.[22c] Ene-silyloxy compounds readily react with carbonyl compounds and acetals in the presence of tin (IV) chloride[23a] and lanthanide triflates.[23b] Lewis acid and fluorides catalyze the reaction of C,O,O-tris-(trimethylsilyl)ketene with aldehydes to form the respective alkenoic acids.[24] Allylic alkylation of enol silyl ethers[25] has been described. Lewis acid catalyzed α-thiolation of enol silyl ethers using 2,2′-diethylthiopropane has been described.[26] Direct fluorination of silyl enol ethers gave mono- and difluorinated carbonyl compounds both mono- and difluorinated carbonyl compounds as well as mono- and silyl enol ethers.[27]

The search for a safe, stable, and effective trifluoromethylthiolating agent led us to N-trifluoromethylthiophthalimide and

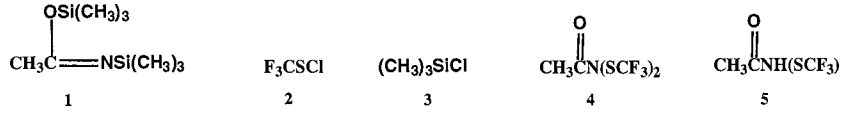

FIGURE 1 Reaction of N,O-bis-(trimethylsilyl)acetamide with F_3CSCI.

α-trifluoromethylthiolated carbonyl compounds in reasonably good yields (~80%).[28] In continuation of our interest in the chemistry of the trifluoromethylthio group,[19] the reaction of N,O-bis-(trimethylsilyl)-acetamide (**1**), which is a versatile silylating reagent, with trifluoromethylsulfenyl chloride (**2**) was examined and found to be straightforward. In addition to trimethylsilyl chloride, N-(trifluormethylthio)- and N,N-bis-(trifluormethylthio)acetamides were characterized (Figure 1) The mechanism of the formation of the three compounds has been rationalized in Figure 2. Trimethylsilyl chloride (**3**) can arise from the free radical reaction of the trimethylsilyl radical with chlorine radical, the latter split off from trifluoromethylsulfenyl chloride (**2**) (Figure 2). The formation and reactions of the silyl radicals have been discussed.[29] It is interesting to note that the trifluoromethylthiyl radical gets attached to nitrogen only. The initally formed intermediate (**6**), as shown

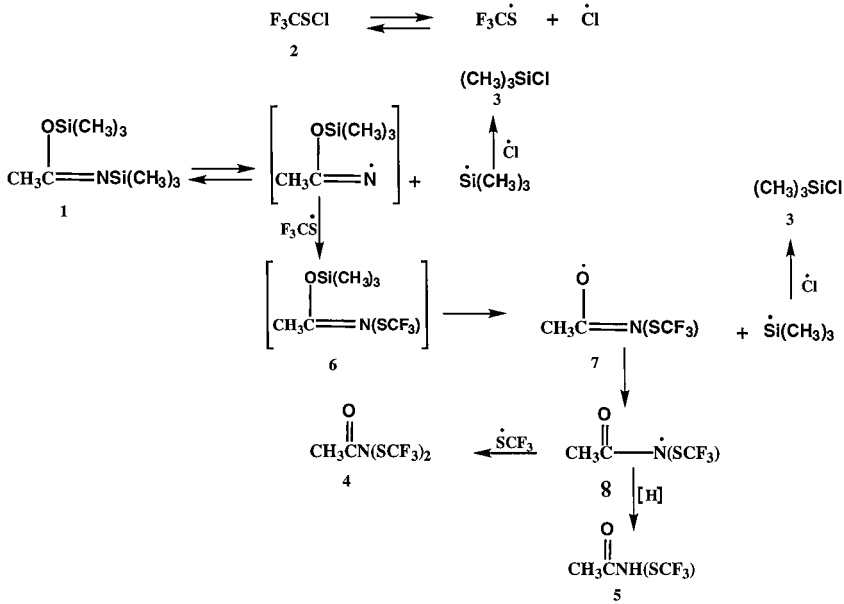

FIGURE 2 Mechanism of formation of products from N,O-bis-(trimethylsilyl)acetamide.

TABLE I Mass Spectral Fragmentation of Compounds Derived from N,O-Bis-(trimethylsilyl)acetamide

Mass spectral fragmentation of bis-(N,N-trifluoromethythio)acetamide (**4**):
$M^+ = 259$ (100); 240 (M-F); 240 (M-HF); 158 ($CH_3CONSCF_3$); 142 (CH_3CNSCF_3); 140 (C_2HNSCF_3); 103 (C_2HNS_2); 83 ($CHSF_2$) and 63 (CSF).
Mass spectral fragmentation of N-(trifluoromethythio)acetamide (**5**):
$M^+ = 159$ (100%); 140 (M-F); 103 (C_2HNS_2); 83 ($CHSF_2$); 63 (CSF) and 58 (M-SCF_3).

in Figure 2, leads to the intermediate **8**, which then either abstracts a hydrogen to form compound **5** or reacts with another thiyl radical to give N-(trifluormethylthio)- and N,N-bis-(trifluormethylthio)acetamides respectively. The mass spectral breakdown of silyl ethers has been discussed.[30] 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$(CH_3)_3$]. Table I gives the mass spectral breakdown behavior of these compounds. The proposed structures were further confirmed by their ^{1}H- and ^{13}C-NMR data Table II.

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: 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

TABLE II ^{1}H- and ^{13}C-NMR Data

^{1}H-NMR of bis (N,N-(trifluoromethythio)acetamide (**4**):
22.8 (s, 3H)
^{13}C-NMR of bis-N,N-(trifluoromethythio)acetamide (**4**):
22.8 $\underline{C}H_3$, 141.42 (S$\underline{C}F_3$) and 172.8 [$\underline{C}$(O)$NSCF_3$]
^{1}H-NMR of N-(trifluoromethythio)acetamide (**5**):
22.3 (s, 3H) and 8.72 (broad singlet, 1H).
^{13}C-NMR of N-(trifluoromethythio)acetamide (**5**):
22.8 $\underline{C}H_3$, 127.26 (S$\underline{C}F_3$) and 171.1 [$\underline{C}$(O)$NSCF_3$].

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 × 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 external reference for ^{19}F was CCl_3F. The chemical shifts are given as ppm.

Reaction of N,O-Bis-(trimethylsilyl)acetamide (**1**) with trifluoromethylsulfenyl chloride (**2**): Stoichiometric amounts of N,O-bis-(trimethylsilyl) acetamide (**1**, 2.03 g, 0.0l mmol) with trifluoromethylsulfenyl chloride (**2**, 1.36 g, 0.01 mmol) were mixed at −80°C in dry freshly distilled acetonitrile and allowed to react for 3 h at this temperature with stirring. Then the reaction mixture was stirred over night at room temperature. After the solvent was removed under reduced pressure, the residue was subjected to vacuum distillation. The GC-MS analysis of the vacuum distillate showed it to primarily consist of: (1) trimethylsilyl chloride (3, $M^+ = 108$, 2.75%); (2) N,N-bis(trifluoromethylthio)acetamide (**4**, $M^+ = 259$, 90.4%); and (3) N-(trifluoromethylthio)acetamide (**5**, $M^+ = 159$, 6.0%) (Figure 1). Attempts to separate compounds **4** and **5** via vacuum distillation resulted in partial decomposition.

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