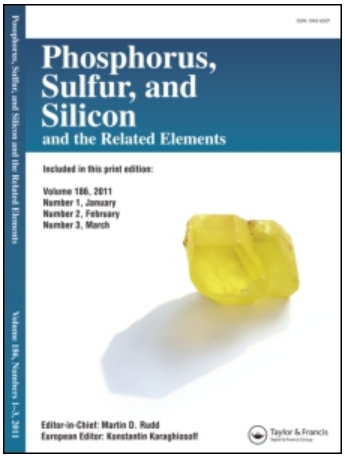

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TRIFLUOROMETHYLTHIOLATION OF MASKED CARBONYL PRECURSORS: REACTION OF TRIFLUOROMETHYLSULFENYL CHLORIDE WITH ENOL ACETATES

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Incorporation of fluorine and fluorine containing groups such as trifluoromethyl and trifluoromethylthio moieties considerably enhances the biological property and potency of the parent products. This communication describes the results of trifluoromethylthiolation of masked carbonyl precursors such as enol acetates, the mechanism of formation and mass spectral characterization of the compounds formed.

Keywords: Enol acetates; GC-MS identification; trifluoromethylthiolation

INTRODUCTION

Owing to the unique biological properties of organic compounds containing fluoroine and fluorine containing functional groups, such as the trifluoromethyl and trifluoromethylthio moieties,[1] their 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 also found application in selective perfluoroalkylation of

organic molecules.[12] The regio- and stereospecific introduction of the said groups profoundly affects the physicochemical and biological properties of the parent precursors.[1g,13] Increasing attention is being evinced in the development of methodology for the stereospecific synthesis of compounds containing these moieties. 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 the enzymes.[14]

The claim[15a] of sulfenylation of active methylene compounds with sulfenamides has been contradicted.[15b] The synthetic utility of α-thioketones has been described.[15b,16] Although the treatment of cyclohexylenamine with trifluoromethyltriflate has been reported to furnish α-trifluoromethylsulfonyl cyclohexanone,[17] α-trifluoromethylthiocarbonyl compounds as such, have not so far been described. For a long time the N-substituted-phthalimides have been employed as tranfer agents of the moiety attached to nitrogen.[18] N-bromosuccinimide is the most popular example of this. Ketones have been reacted with phenyldisulfide in the presence of lithioisopropylcyclohexylamine to give α-thiolated products.[19] N-alkylthio- and -arylthiophthalimides have found application as thiyl transfer agents.[20] N-Fluoropyridinium salts have been shown to effectively fluorinate enamines.[21] N-fluorobenzenesulfonimide has been successfully used to stereospecifically fluorinate enolates.[22] In view of the observation that the trifluoromethylthio group facilitates in vivo absorption of compounds containing this moiety[4b] and its convenient transportation in the biological matrices[1j] and that it profoundly enhances the precursors biological activity,[23a] we have been interested in the chemistry of this functional group.[24] However, the incorporation of this group into organic compounds involves the use of highly hazardous reagents.[25] We have recently developed a novel procedure to accomplish this goal[26a] and have described the x-ray crystallographic structure determination of this reagent, namely $CuSCF_3$.[26b] However, this reagent can not be used to prepare α-trifluoromethylthiolated carbonyl compounds. This article describes the results of the use of trifluoromethylsulfenyl chloride in trifluoromethylthiolating the enol acetates and the mass spectral identification of the compounds formed during the course of this reaction.

RESULTS AND DISCUSSION

Enamines readily react with electrophiles to give mono- and disubstituted products and the involved mechanistic considerations have been amply discussed.[27] Trifluoromethylsulfonate gave

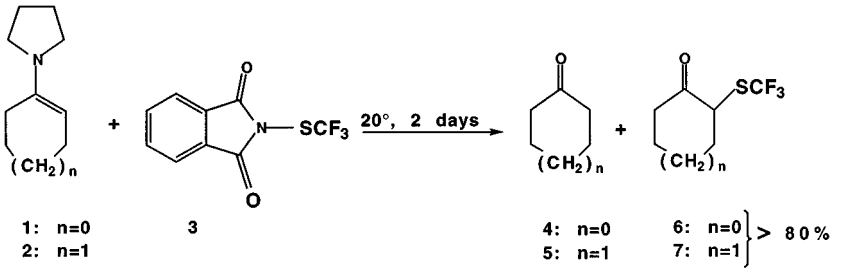

FIGURE 1 Trifluoromethylthiolation of enamines.

α-trifluoromethylsulfonylcyclohexanone with cyclohexenylenamine.[17] The search for a safe, stable and effective trifluoromethylthiolating agent led us to N-trifluoromethylthiophthalimide (**3**, Figure 1) and the α-trifluoromethylthiolated carbonyl compounds were obtained in reasonably good yields ($\sim$80%).[28] Although, enol acetates are easily accessible and readily available and the presence of enhanced reactivity of the carbon-carbon double bond, their use as synthetic intermediates has seen only a limited application; primarily to protect enolizable carbonyl moieties, to trans-esterify other ketones[29a] and phenols in the presence of mercuric acetate[29b] and to transform them into olefins. The arylation of enol acetates yields various products ranging from β-aroyl carbonyls, arylated enol esters and olefins.[30a] Using stoichiometric amounts of arylmercuric acetates and palladium acetate, arylated enol acetates are formed as major products.[30b] Enolacetates have been converted into epoxides[31a] and lithium enolate anions.[31b] The latter have been reported to undergo stereoselective alkylation when treated with alkyl halides.[31b] Enol acetates give mono- and bis-alkylated products on treatment with lithium dialkylcuprates.[31b]

The reaction of enol acetates with F_3CSCl at –80°C usually gives a complex mixture of compounds. Thus, 1-cyclohexen-1-yl acetate (**8**) furnished 10 compounds (**5**, Figure 1 and **10–17**, Figure 2). The mechanism of formation of all but one (**12**) has been discussed in Figure 3. As has been frequently observed,[24] free radical processes are usually associated with the reactions involving F_3CSCl. Deacylation of the substrate gives 1-hydroxy-1-cyclohexene, which then simply rearranges to form cyclohexanone (**5**). If on the other hand, the allylic hydrogen gets abstracted prior to de-acylation to form (**18**), then it yields 2-cyclohexenone (**10**) via the radical intermediate **19**. The same radical intermediate (**18**) serves as a parent to compounds **13**, **14**, and **15** by reacting with the thiyl and chlorine radicals respectively. The addition of the F_3CS and Cl radicals to the carbon-carbon double bond of the enol acetate gives intermediates **20** and **21**, which lose the acyl moiety to form

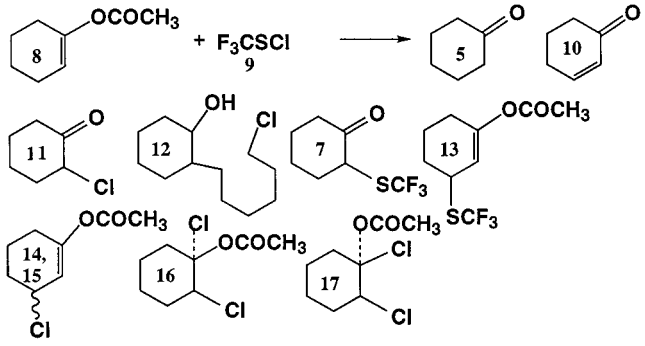

FIGURE 2 Trifluoromethylthiolation of enol acetates.

1-(trifluoromethylthio)- and 1-chloro-2-cyclohexanones (**7** and **11**) respectively. The radical intermediate **21** can further react with Cl radical to yield a pair of stereomers, 1-acetoxy-1,2-dichlorocyclohexanones (**16** and **17**). Figure 3 attempts to rationalize the above observations. In agreement with the report that the mass spectra of stereomeric cyclic acetates are virtually identical,[32,33] the mass spectra of **14** and **15** and **16** and **17** closely resemble each other. The mode of the formation of **12** is under study. The proposed addition to the enol double bond has precedence.[34,35] Table I describes the mass spectral breakdown

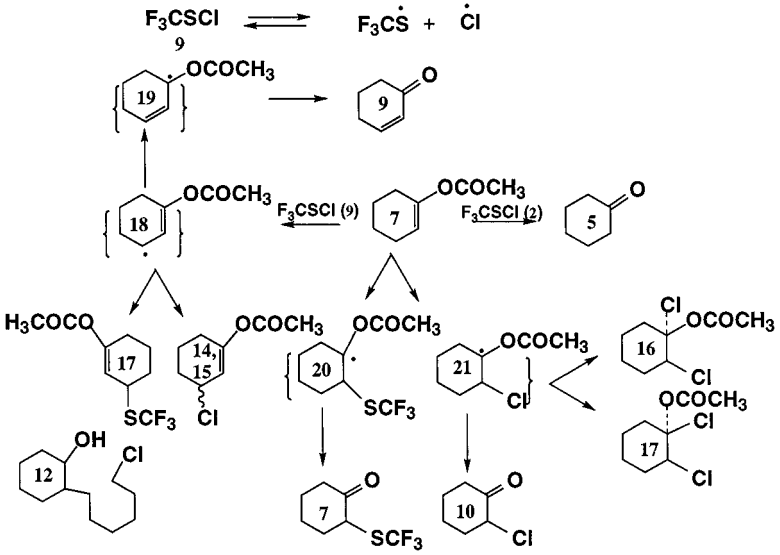

FIGURE 3 Formation of the compounds described in Figure 2.

TABLE I Mass Spectral Fragmentation of the Compounds from 1-Acetoxy-1-cyclohexene[a]

1. Trifluoromthylsulfenyl chloride (**9**, r.t. = 1.41 min, 16.5%): $M^+ = 136$; 117 (M—F); 101 (SCF_3); 82 (CSF_2); 69 (CF_3, 100%); 63 (CSF); and 50 (CF_2).
2. Cyclohexanone (**5**, r.t. = 3.15 min, 3.6%); $M^+ = 98$; 83 (M—CH_3); 78 (M—C_2H_4); 69 (C_5H_9); 55 (C_3H_3O, 100%); 53 (C_4H_5); and 51 (C_4H_3).
3. 2-Cyclohexenone (**10**, r.t. = 3.48 min, 1.0%); $M^+ = 96$; 68 (M—C_2H_4, 100%); 55 (C_3H_3O); and 51 (C_4H_3).
4. 2-Chlorocyclohexanone (**11**, r.t. = 4.71 min, 37.1%); $M^+ = 132$; 97 (M—Cl); 90 (C_4H_7Cl); 88 (C_4H_5Cl); 79 (97-H_2O); 69 (C_4H_5O); 68 (97-C_2H_5); 55 (C_3H_3O, 100%); and 53 (C_4H_5).
5. 2-(1-Chlorohexyl)cyclohexanol (**12**, r.t. = 4.74 min, 1.5%); $M^+ = 218$; 141 ($C_9H_{17}O$); 128 ($C_8H_{16}O$, 100%); 83 (C_6H_{11}); 81 (C_6H_9); 69 (C_5H_9); 55 (C_4H_7); and 53 (C_4H_5).
6. 2-(Trifluoromethylthio)cyclohexanone (**7**, r.t. = 5.02 min, 13.4%); $M^+ = 198$; 170 (M—C_2H_4); 154 (170-O); 128 ($F_3CSC_2H_3$); 101 (SCF_3, 100%); 87 (C_4H_7S); 85 (C_4H_5S); 79 (C_6H_7); 73 (C_3H_5S); 69 CF_3); 67 (C_5H_7); 59 ($OCOCH_3$); 55 (C_3H_3O); and 47 (SCH_3).
7. 1-Acetoxy-3-(Trifluoromethylthio)-1-cyclohexene (**13**, r.t. = 6.14 min, 8.3%); $M^+ = 240$; 198 (M—$COCH_2$, 100%); 178 (198-HF); 150 (178-C_2H_4); 139 (M—SCF_3); 129 ($C_2H_4SCF_3$); 115(CH_2SCF_3); 101 (SCF_3); 97 (139-$COCH_2$); 96 (139-$COCH_3$); 85 (C_4H_5S); 79 (C_6H_7); 69 (CF_3); 67 (C_5H_7); 59 ($OCOCH_3$); 55 (C_4H_7); and 53 (C_4H_5).
8. 1-Acetoxy-3-chloro-1-cyclohexene (**14**, r.t. = 6.27 min, 0.4%); $M^+ = 174$; 139 (M—Cl); 132 (M—$COCH_2$); 131 (M—$COCH_3$); 104 (132-C_3H_4); 97 (C_6H_9O, 100%); 95 (C_6H_7O); 79 (C_6H_7); 69 (C_5H_9); 67 (C_5H_7); and 55 (C_4H_7).
9. 1-Acetoxy-3-chloro-1-cyclohexene (**15**, r.t. = 6.56 min, 16.1%); $M^+ = 174$; 139 (M—Cl); 132 (M—$COCH_2$, 100%); 114 (M—$C_2H_4O_2$); 104 (132-C_2H_4); 97 (C_6H_9O); 79 (C_6H_7); 67 (C_5H_7); and 55 (C_4H_7).
10. 1,2-Dichloro-1-acetoxy-cyclohexane (**16**, r.t. = 7.38 min, 0.7%); $M^+ = 210$ (M—Cl, seen); 150 (M—$C_2H_4O_2$); 132 (175-$COCH_3$); 115 (150-Cl); 97 (C_6H_7O, 100%); 88 (C_4H_5Cl); 70 (C_5H_{10}); 68 (C_5H_8); 55 (C_4H_7); and 53 (C_4H_5).
11. 1,2-Dichloro-1-acetoxy-cyclohexane (**17**, r.t. = 7.74 min, 1.4%); $M^+ = 210$ (M—Cl, seen); 150 (M—$C_2H_4O_2$); 132 (175-$COCH_3$); 115 (150-Cl); 114 (150-HCl); 97 (C_6H_7O, 100%); 88 (C_4H_5Cl); 79 (C_6H_7); 77 (C_6H_5); 68 (C_5H_8); 55 (C_4H_7); and 53 (C_4H_5).

[a]All chlorine containing compounds show ^{37}Cl isotope peaks corresponding to its natural abundance.

behavior of compounds **7–8**, **10**, and **13–17**. The mass spectra of **5** and **10** and 2-chlorocyclohexanone (**11**) have been described respectively.[32]

The reaction of isopropenyl acetate (**22**, Figure 4) with F_3CSCl (**9**) at –80°C is even more complex, in that it furnishes 15 compounds via free radical processes. Figure 5 attempts to rationalize the formation of these compounds. Simple dimerization of the F_3CS radicals

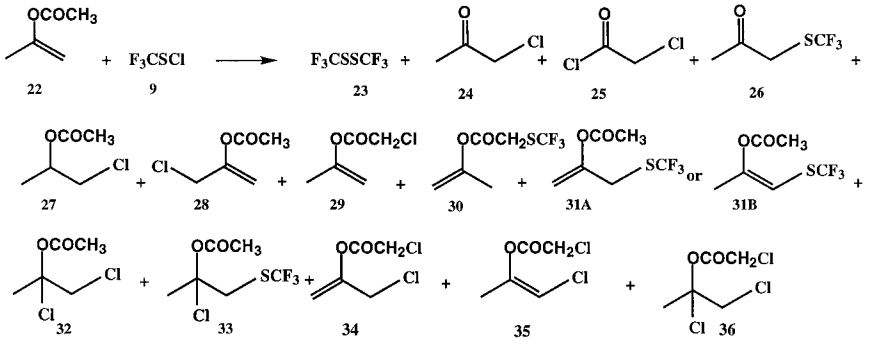

FIGURE 4 Trifluoromethylthiolation of isopropenyl acetate.

results in bis-(trifluoromethyl)disulfide (**23**). It is interesting to note that even the acetoxy entity gets involved in the free radical catalyzed reactions. The addition of Cl radical to **22**, followed by the elimination of the acyl moiety from the radical intermediate gives chloroacetone (**24**). The same radical intermediate can abstract hydrogen to give 1-chloro-2-acetoxypropane (**27**) or can pick up another chlorine radical to form 1,2-dichoro-2-acetoxypropane (**32**). Abstraction of hydrogen from **22** gives rise to resonance stabilized allylic radical, which reacts with Cl and thiyl radicals to give 1-chloro- and 1-(trifluoromethylthio)-2-acetoxy-2-propenes (**28**, **31A**) respectively. Compound **28** itself serves as the source for 2-chloroacetoxy-3-chloro-1-propene (**34**), 1,2-dichloro-2-chloroacetoxypropane (**36**) and chloroacetyl chloride (**25**). The formation of **25** involves the migration of the acyl moiety from oxygen to the adjoining carbon atom, followed by the loss of the CH_2COCH_3 entity. In a similar vein, the genesis of compounds **26**, **33**, and **35** can be explained. Two structures **31A** and **31B** were considered for the component eluting of the GC-MS column at room temperature for 3.04 min (Table II). The presence of the ion at m/e = 115 corresponding to the CH_2SCF_3 fragment in its mass spectrum, permitted the assignment of the correct structure, namely **31A** to this compound. Acetates readily undergo elimination of acetic acid entity and sometimes suffer a loss of the CH_2O moiety. The mass spectra of **22–25** have been described.[32c] The mass spectral breakdown of compounds **24–36** is given in Table II.

Experimental Part

Trifluoromethylsulfenyl chloride and bis-(trifluoromethyl)disulfides are extremely toxic and hazardous and hence utmost care and caution should be exercised in working with them. All solvents were dry

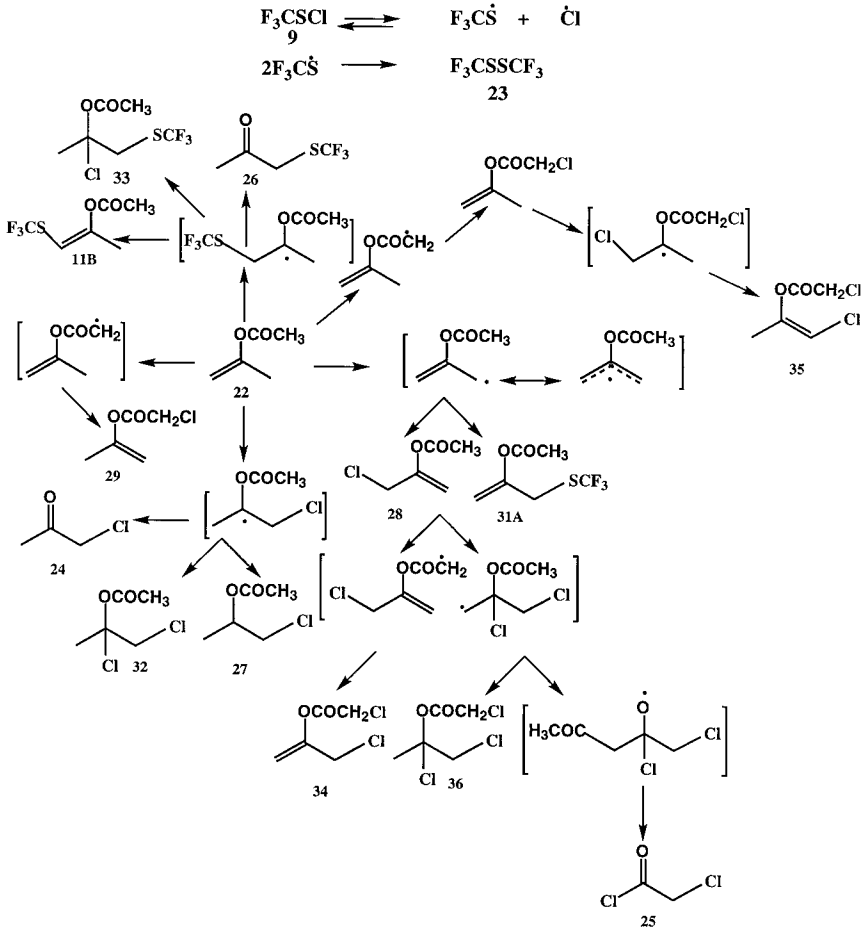

FIGURE 5 Mechanism of the formation of compounds derived from isopropenyl acetate experimental.

and freshly distilled prior to use. The reactions were carried out in a flame-dried, argon gas-purged 10 or 25 ml three-necked flask equipped with a magnetic stirrer, gas inlet-adaptors, and a reflux condenser carrying a dry ice/acetone cooled trap. The temperature of the coolant passing through the condenser was maintained at −20°C. All reactions were carried out by addition of stoichiometric amounts trifluoromethylsulfenyl chloride via the vacuum line to the substrate cooled to −78°C. The reaction mixture was initially analyzed by GC and GC-MS, then the solvent was evaporated under reduced pressure and the residue was

TABLE II Mass Spectral Fragmentation of Compounds Derived from Isopropenyl Acetate

1. Isopropenyl Acetate (**22**, r.t. = 1.80 mim, 1.7%): $M^+ = 100$; 72 (M—CO); 58 (M—$COCH_2$, 100%); 57 (M—$COCH_3$); and 45 (C_2H_5O) [cf. NIST # 1477].
2. Trifluoromethylsulfenyl chloride (**9**) and Bis-(triflurormethyl)disulfide (**23**, r.t. = 1.39 mim, 11.5%): $M^+ = 136$ and 202 and 49 [cf.].
3. 1-Chloroacetone (**24**, r.t. = 1.84 mim, 8.6%): $M^+ = 92$ (100%); 77 (M—CH_3); 57 (M—Cl); and 49 (CH_2Cl) [cf. NIST # 948].
4. Chloroacetyl chloride (**25**, r.t. = 1.94 mim, 0.9%): $M^+ = 112$; 77 (M—Cl, 100%); 63 (COCl); and 49 (CH_2Cl) [cf. NIST # 2451].
5. 1-Trifluoromethylthioacetone (**26**, r.t. = 2.09 mim, 13.2%): $M^+ = 158$ (100%); 115 (M—$COCH_3$ or CH_2SCF_3); 101 (SCF_3); 82 (CSF_2); 73 (C_2HOS); 69 (CF_3); 63 (CH_3OS); 57 (C_3H_5O); 57 (C_3H_5O); and 46 (CH_2S).
6. 1-Chloro-2-acetoxypropane (**27**, r.t. = 2.44 mim, 1.4%): $M^+ = 136$ (not seen); 121 (M—CH_3); 101 (M—Cl, 100%); 77 (M—$OCOCH_3$); 59 ($OCOCH_3$); and 49 (CH_2Cl).
7. 1-Chloro-2-acetoxy-2-propene (**28**, r.t. = 2.44 mim, 1.4%): $M^+ = 134$; 99 (M—Cl, 100%); 92 (M—C_3H_2ClO); 77 ($COCH_2Cl$); 76 (92-O); 63 (C_2H_3ClO); 57 (C_2H_5O); and 49 (CH_2Cl).
8. 1-(2-Chloroacetoxy)propene (**29**, r.t. = 2.85 mim, 1.9%): $M^+ = 134$; 99 (M—Cl, 96%); 92 (M—$OCOCH_2$, 100%); 86 ($C_4H_6O_2$); 76 (92-O); 63 (C_2H_3ClO); 57 (C_2H_5O); and 49 (CH_2Cl).
9. 1-(2-Trifluoromethylthio)propene (**30**, r.t. = 2.98 mim, 6.4%): $M^+ = 200$ (not seen); 158 (M—$COCH_2$); 115 (CH_2SCF_3); 99 (M—SCF_3, 100%); 92 (C_2HClO_2); 77 (C_2H_2ClO); 69 (CF_3); 57 (CH_2COCH_3); and 49 (CH_2Cl).
10. (1-Trifluoromethylthio)-2-acetoxy-2-propene (**31A**, r.t. = 3.04 min, 6.4%): $M^+ = 200$; 158 (M—$COCH_2$, 100%); 138 (158-HF); 115 (CH_2SCF_3); 89 (158-CF_3); and 45 (CSH).
11. 1,2-Dichloro-2-acetoxypropane (**32**, r.t. = 3.75 mim, 16.3%): $M^+ = 170$ (not seen); 135 (M—Cl); 121 (M—CH_2Cl); 110 (C_3H_4Cl, 100%); 93 ($C_2H_2ClO_2$); 75 (110-Cl); 57 (C_3H_5O); and 49 (CH_2Cl).
12. 2-Chloro-2-acetoxy-3-(trifluoromethylthio)propane (**33**, r.t. = 3.88 mim, 1.7%): $M^+ = 236$ (not seen); 201 (M—Cl); 176 (M—$C_2H_4O_2$, 100%); 159 (M—$COCH_3$); 141 (201-$COCH_3$); 115 (CH_2SCF_3); 107 (176-CF_3); 95 (C_2H_4ClS); 75 (C_3H_4Cl); 69 (CF_3); 59 (C_2H_3S); 49 (CH_2Cl); and 45 (CSH).
13. 1-Chloro-2-(chloroacetoxy)-2-propene (**34**, r.t. = 4.85 mim, 1.4%); $M^+ = 168$; 113 (M—Cl); 92 (C_2HClO_2, 100%); 77 ($COCH_2Cl$); 65 (CH_2ClO); and 49 (CH_2Cl).
14. 1-Chloro-2-(chloroacetoxy)-1-propene (**35**, r.t. = 5.07 mim, 1.2%): $M^+ = 168$, not seen); 133 (M—Cl); 119 (M—CH_2Cl); 92 (C_3H_5ClO); 77 ($COCH_2Cl$, 100%); and 49 (CH_2Cl).
15. 1,2-Dichloro-2-(chloroacetoxy)propane (**36**, r.t. = 5.91 mim, 2.5%): $M^+ = 204$ (not seen); 169 (M—Cl); 133 (169-HCl); 111 (M $OCOCH_2Cl$); 93 (C_3H_6ClO); 77 ($COCH_2Cl$ or C_3H_6Cl); 75 (C_3H_4Cl); 63 (COCl); and 49 (CH_2ClO).

vacuum distilled and again analyzed by GC/MS. Mass spectra were obtained on a Finnigan Model 5100 GC/MS equipped with a silica 25 m × 0.31 mm i.d. SE-54 capillary column (J and W Scientific, Rancho Cordova, CA). 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, ^{13}C and ^{19}F) 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 and the chemical shifts are given as ppm.

Reaction of 1-Cyclohexen-1-yl acetate (**8)** trifluoromethylsulfenyl chloride (**9**): To a solution of 1-cyclohexen-1-yl acetate (**8**) in dry pentane (5 ml) was added stoichiometric amounts of trifluoromethylsulfenyl chloride (**9**) via the vacuum line at –80°C under dry nitrogen and the reaction mixture was stirred at –80°C for 2 h, then allowed to come to ambient temperature and stirred over night. Since the reaction mixture was found to consist of several components by gas chromatographic analysis, it was further analyzed using GC-MS and found to contain 10 compounds: (a) trifluoromethylsulfenyl chloride (**9**), (b) cyclohexanone (**5**), (c) 2-cyclohexenone (**10**), (d) 2-chlorocyclohexanone (**11**), (e) 2-(1-chlorohexyl)cyclohexanol (**12**), (f) 2-(trifluoromethylthio)hexanone (**7**), (g) 1-(3-trifluoromethylthio)-1-acetoxycyclohexene (**13**), (h) 3-chloro-1-acetoxycyclohexenes (**14**, **15**), (i) 1,2-dichloro-1-acetoxycyclohexane (**16**) and (j) 1,2-dichloro-1-acetoxycyclohexane (**17**) (Figure 2). The mass spectral break down data is given in Table I.

Reaction of isopropenyl acetate (**22**) trifluoromethylsulfenyl chloride (**9**): To isopropenyl acetate (**22**, 5 ml) was added stoichiometric amounts of trifluoromethylsulfenyl chloride (**9**) via the vacuum line at −80°C under dry nitrogen and the reaction mixture was stirred at −80°C for two hours, then allowed to come to ambient temperature and stirred over night. Since the gas chromatographic analysis showed the reaction product to be a very complex mixture containing over a dozen components, it was further analyzed using GC-MS and found to contain 15 compounds: (a) bis(trifluoromethyl)disulfide (**23**), (b) chloroacetone (**24**), (c) chloroacetyl chloride (**25**), (d) trifluoromethylthioacetone (**26**), (e) 1-choro-2-acetoxypropane (**27**), (f) 1-choro-2-acetoxy-2-propene (**28**), (g) 2-(chloroacetoxy)-1-propene (**29**), (h) 2-(trifluoromethyl-thioacetoxy)-1-propene (**30**), (i) 1-(trifluoromethylthio)-2-acetoxy-2-propene (**31a**), (j) 1,2-dichloro-2-acetoxypropane (**32**), (k) 1-(trifluoromethylthio)-2-acetoxy-2-choropropane (**33**), (l) 1-chloro-2-(chloroacetoxy)-2-propene (**34**), (m) 1-chloro-2-(chloroacetoxy)-1-propene (**35**) and (n) 1,2-dichloro-2-(chloracetoxy)propane (**36**) (Figure 4). The mass spectral fragmentation of these compounds is described in Table II.

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