by hydrolysis of 8, bromination, and elimination. At this time, CAMEO does not perform the NBS bromination since it is a radical process. However, electrophilic bromination of 11 is predicted by the program to yield 12.

Examples of the Peterson reaction are shown in Scheme III.[53] The process rivals the Wadsworth–Emmons reaction of carbethoxymethylphosphonate anion with carbonyl compounds to form α,β-unsaturated esters.[54] The Wadsworth–Emmons reaction produces low yields of product with readily enolized ketones. However, a 95% yield of 14 from cyclohexanone is reported on using the Peterson reaction.[53]

Scheme IV is part of an olefin inversion[45b] similar to that obtained by using lithium diphenylphosphide.[55] To obtain the reported product, 15 (96%, >99% *Z*), CAMEO performed an S_N2 reaction with inversion and recognized the need for rotation to carry out the synperiplanar elimination of the trimethylsilyloxy anion. 16 and 17 are predicted by the program as possible side products arising from E2 eliminations of the epoxide.

The final sequence, Scheme IV, is composed of selected steps from the recent synthesis of mycorrhizin A (22, R = H).[56] The sequence begins with a cuprate reaction that yields product 18 which then undergoes selective cleavage of the silyl ether in the presence of tetrabutylammonium fluoride. Two oxidation steps, which CAMEO does not handle currently, lead to 20. Electrophilic addition of chlorine yields 21 with no implied stereochemistry according to CAMEO. Chlorine is known to add in both the syn and anti manner to olefins.[4] Next, E2 reactions are predicted by CAMEO to yield both 22 (reported in 73% yield) and the *E* isomer. The program also yields 23 through another possible E2 reaction and two products arising from S_N2 displacement of the chlorines which have not been shown. The last product, 24, is the result of an S_N2' chlorine displacement which by electronic arguments should not be favorable.

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Conclusion

The capabilities of the CAMEO program have been extended to include electrophilic and nucleophilic processes involving organosilicon intermediates. The unique reactivity and directing ability of silyl groups required modification to several parts of the program, including the perception of acidities, electrophiles, nucleophiles, and carbonium ion stabilities. In addition, the stereochemical sophistication of the program has been enhanced to provide correct stereochemistry for products of substitution and β-elimination reactions.

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Reactivity of the Perhaloalkanes CF_2X_2 (X = Cl, Br) with Nucleophiles. 6.[1] Coexistence of Carbene and Radical Processes Initiated by Single-Electron Transfer

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In the condensation of sodium thiophenoxide with CF_2BrCl in DMF at −40 °C, two mechanisms are involved simultaneously. A carbene chain process is postulated for the formation of $C_6H_5SCF_2Br$ and $C_6H_5SCF_2H$. A radical chain process is implicated for the formation of $C_6H_5SCF_2Cl$ and $C_6H_5SCF_2SC_6H_5$. These competitive chain processes could occur after an initial one-electron transfer from the thiophenoxide to CF_2BrCl, giving a caged intimate radical/anion radical pair (RARP).

Recently we showed that perhaloalkanes CF_2BrX (X = Cl, Br) can react by two types of mechanisms when opposed to nucleophiles. In the condensation with phenoxides, thiophenoxides,[2,3] and carbanions,[4] we postulated a chain mechanism involving the difluorocarbene (Scheme I). The fact that hydrogenated byproducts $NuCF_2H$ and bromo derivatives $NuCF_2Br$ were obtained with CF_2BrCl was in favor of this mechanism. Furthermore, the condensation of CF_2Br_2 with potassium 2-allylphenoxide shows evidence for difluorocarbene formation since two CF_2 units are incorporated in the molecule.[1] Other reports are in agreement with the carbene process.[5,6]

Scheme I (Path A)

$$Nu^- + BrCF_2X \rightarrow NuBr + CF_2X^-$$

$$CF_2X^- \rightarrow :CF_2 + X^-$$

$$Nu^- + :CF_2 \rightarrow NuCF_2^-$$

$$NuCF_2^- + BrCF_2X \rightarrow NuCF_2Br + CF_2X^-$$

$$NuCF_2^- + \text{"H"} \rightarrow NuCF_2H$$

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However, in the condensation with enamines[7] a radical chain mechanism is involved. No hydrogenated byproduct was obtained. Furthermore, with CF_2BrCl, the only products observed were $NuCF_2Cl$. In the case of charged nucleophiles, the radical chain mechanism, similar to the one proposed by Kornblum[8] and Bunnett[9] can be written as shown in Scheme II.

Scheme II (Path B)

$$Nu^- + BrCF_2X \rightarrow Nu\cdot + BrCF_2X^-\cdot$$

$$BrCF_2X^-\cdot \rightarrow \cdot CF_2X + Br^-$$

$$Nu^- + \cdot CF_2X \rightarrow NuCF_2X^-\cdot$$

$$NuCF_2X^-\cdot + BrCF_2X \rightarrow NuCF_2X + BrCF_2X^-\cdot$$

In the case of $BrCF_2Cl$, the nature of the group introduced on the nucleophile (CF_2Br or CF_2Cl) is a good indication of the mechanism involved: chlorodifluoromethyl compounds are formed by a radical chain process (path B, X = Cl) whereas bromodifluoromethyl derivatives are the result of a carbene chain mechanism (path A, X = Cl).

In this paper we present evidence for the coexistence of the two processes (paths A and B). The condensation of CF_2BrCl with thiophenoxides ArS^- that we described earlier[2,3] was performed in phase-transfer conditions. The fluoro derivatives $ArSCF_2Br$ and $ArSCF_2H$ were the only ones obtained. Soon after, Suda and Hino[10] reported the same type of condensation but in DMF at −40 °C. In these conditions the disubstituted products **2** are formed with $4\text{-}NO_2C_6H_4S^-$ and $4\text{-}ClC_6H_5S^-$.

$$4X\text{-}C_6H_4SNa + BrCF_2Cl \xrightarrow[-40\ °C]{DMF} 4X\text{-}C_6H_4SCF_2SC_6H_4X$$

1a, X = Cl → **2a**, X = Cl
1b, X = NO_2 → **2b**, X = NO_2

The authors postulated an ionic mechanism to explain the formation of **2**.

$$ArSCF_2^- + ArSBr \rightarrow ArSCF_2SAr$$

Another possibility is a radical process. We performed inhibition experiments to check this hypothesis.

Results

Condensation of Sodium *p*-Chlorothiophenoxide with $BrCF_2Cl$. We repeated Suda's work on *p*-chlorothiophenoxide and verified that the disubstituted product **2a** was the major one formed with $BrCF_2Cl$ in DMF at −40 °C. We showed that the formation of **2a** is completely inhibited by *p*-dinitrobenzene,[11] a fact that is in favor of a radical process.

Condensation of Sodium Thiophenoxide with CF_2BrCl. The condensation of sodium thiophenoxide with $BrCF_2Cl$ in DMF at −40 °C, a case that had not been studied by Suda, gives four products: the bromo and hydrogenated derivatives **3** and **4** and the chloro and disubstituted derivatives **5** and **6**.[12]

Table I. Condensation of $BrCF_2Cl$ with C_6H_5SNa in DMF at −40 °C

$BrCF_2Cl/C_6H_5SNa$	3,[a] %	4,[a] %	3 + 4, %	5,[a] %	6,[a] %	5 + 6, %
2/1	9	3	12	5	43	48
2/1 + nitrobenzene[b]	52	2	54	2	5	7

[a] Average values of several experiments (variations for 3 and 6, ± 3%; variations for 4 and 5, ±1%). [b] 1 mol of nitrobenzene per mol of C_6H_5SNa (similar results are obtained if the amount of nitrobenzene is increased).

$$C_6H_5SNa + BrCF_2Cl \xrightarrow[-40\ °C]{DMF} \underset{\mathbf{3}}{C_6H_5SCF_2Br} + \underset{\mathbf{4}}{C_6H_5SCF_2H} + \underset{\mathbf{5}}{C_6H_5SCF_2Cl} + \underset{\mathbf{6}}{C_6H_5SCF_2SC_6H_5}$$

The total yield of the condensation is 60% (see Table I for the proportions of the different products). The addition of nitrobenzene greatly reduces the amount of **6**, which is a good indication of a radical chain process for the formation of this product. Simultaneously the amount of **3** increases, which is in favor of two different processes for the formation of **3** and **6**.

So, in DMF at −40 °C, we observe coexistence of a carbene and a radical chain mechanism in the reaction of thiophenoxide with CF_2BrCl.

Condensation of Sodium Thiophenoxide with CF_2Cl_2. We have been able to perform the condensation of CF_2Cl_2 with sodium thiophenoxide under UV irradiation with a 35% yield.

$$C_6H_5SNa + CF_2Cl_2 \xrightarrow[h\nu]{DMF,\ -40\ °C} \underset{\mathbf{4}}{C_6H_5SCF_2H} + \underset{\mathbf{5}}{C_6H_5SCF_2Cl} + \underset{\mathbf{6}}{C_6H_5SCF_2SC_6H_5}$$

Products **4**, **5**, and **6** are obtained: the yield of **4** and **5** is low (6%), the major product being compound **6** (22%). The fact that the reaction takes places under UV irradiation is in favor of a radical mechanism for the formation of **6**.

Discussion

All these results show that two mechanisms are involved: a carbene chain process leading to $ArSCF_2Br$ and $ArSCF_2H$ (path A, Scheme I) and a radical chain process leading to $ArSCF_2SAr$ (path B′, Scheme III).

Scheme III (Path B′)

$$ArSCF_2Cl^-\cdot \rightarrow ArSCF_2\cdot + Cl^-$$

$$ArSCF_2\cdot + ArS^- \rightarrow ArSCF_2SAr^-\cdot$$

$$ArSCF_2SAr^-\cdot + BrCF_2Cl \rightarrow ArSCF_2SAr + BrCF_2Cl^-\cdot$$

$ArSCF_2Cl^-\cdot$ could partly decompose to $ArSCF_2\cdot$ before reacting with $BrCF_2Cl$ (path B) and then react with ArS^- (path B′) to give $ArSCF_2SAr$. This kind of "bond breaking" of the radical anion intermediate has been recently described by Alonso and Rossi.[13] To understand the difference between DMF solutions and phase-transfer

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(12) Recently Burton and Viemers (D. J. Burton and D. M. Viemers, *J. Fluorine Chem.*, 18, 573 (1981)) described the preparation of **6** by reacting C_6H_5SNa with $C_6H_5SCF_2Br$ in sulfolane. However the characteristics given for **6** are not in agreement with ours.
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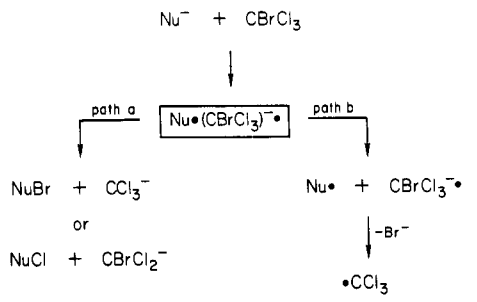
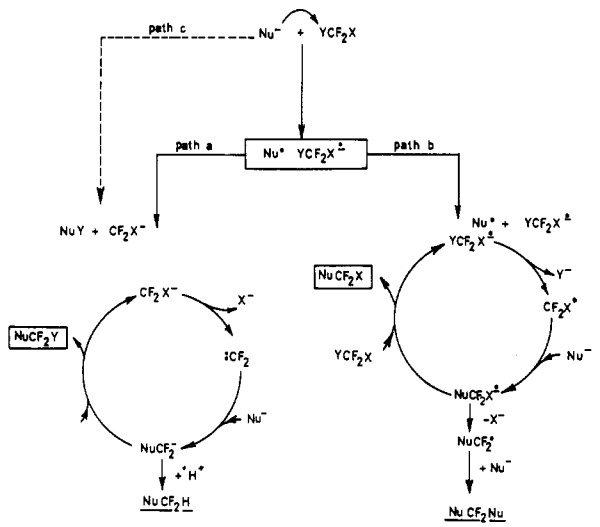
Scheme IV



Scheme V



conditions, a useful comparison with nonfluorinated perhaloalkanes can be made.

Meyers studied the condensation of perhalomethanes CCl_4, CBr_4, and $CBrCl_3$[14,15] with ketones, sulfones, and alcohols in basic medium.

For a given haloalkane CX_3Y, depending on the nucleophile used, either the monohalosubstituted products NuX, NuY are obtained or the trihalomethane-substituted derivative $NuCX_3$ is produced. The authors explained these results by the formation of a radical/radical anion pair (RARP) through a monoelectronic transfer as shown in Scheme IV.

Nucleophiles follow path a when the radicals Nu· are unstable. In this case Nu· reacts in the cage and halogenation occurs to give NuBr (or NuCl). When Nu· is stable, path b is followed. Nu^- reacts with the radical CCl_3· by a radical chain mechanism to give $NuCCl_3$. So Meyers found two mechanisms in the condensation of nucleophiles with perhaloalkanes.

We can also postulate common first step through a monoelectronic transfer (Scheme V). In this hypothesis the intimate radical/radical anion pair should be tight in a solvent like benzene (phase-transfer conditions) and loose in a more polar solvent like DMF. So, in this case, the anion radical $BrCF_2X^-$· can escape from the cage and diffuse in the solvent to give the radical CF_2X· and subsequently the disubstituted derivative $ArSCF_2SAr$. The hypothesis of a cage can explain the different results observed in phase-transfer conditions and in DMF at −40 °C.

It seems clear that the products inhibited by radical scavengers are formed by a single-electron transfer (SET) pathway (Scheme V, path b). The products formed by the carbene process could result either of the same initial SET pathway (Scheme V, path a) or of a nucleophilic attack on the halogen atom (Scheme V, path c). However polyhalomethanes are fairly strong electron-transfer oxidants as judged by their $E°$ values,[16,17] and the SET hypothesis is quite reasonable for the two processes.

Some important differences between nonfluorinated and fluorinated perhaloalkanes appear. No carbene chain process occurs with nonfluorinated perhaloalkanes (Scheme IV, path a); this might be due to the fact that the rate of decomposition of CX_3^- (X = Cl, Br) is much slower than for CF_2X^-.[18-20] Furthermore, the existence simultaneously of the two mechanisms was not observed by Meyers. The condensation of CF_2BrCl with thiophenoxide in DMF at −40 °C is a good example of a competition between carbene and radical chain processes in the same reaction.

We showed[2,3] that phenoxides do not react spontaneously with $BrCF_2X$ but that the reaction is initiated by thiophenoxides. Since phenoxides do not transfer an electron easily,[21] thiophenoxides initiate the reaction by the formation of a radical/radical anion pair and the reaction proceeds.

Conclusion

A general mechanism for the reaction of CF_2X_2 with nucleophiles is represented in Scheme V. Nu^- can be a nucleophile with a net charge like ArO^-, ArS^-, R_3C^-, etc., or an uncharged nucleophile with a doublet on the heteroatom like in C=C—N<, R_3P. For these neutral nucleophilic species the one-electron transfer, in the first step, produces cation radical/anion radical pairs (CRARP) = >C=C—N^+·$BrCF_2X^-$· or R_3P·$^+BrCF_2X^-$· instead of the RARP for charged nucleophiles.

Experimental Section

Proton magnetic resonance spectra (NMR) were recorded on a Perkin-Elmer R24A Model spectrometer and are reported in parts per million (δ) downfield from tetramethylsilane. Fluorine magnetic resonance spectra were obtained on a JEOL Model C60 HL (56.4 MHz) spectrometer and are reported in parts per million (ϕ) upfield from trichlorofluoromethane (solvent $CDCl_3$). Mass spectra were obtained on a AEI MS30 spectrometer at 70 ev.

Bromochlorodifluoromethane ($BrCF_2Cl$) and dichlorodifluoromethane were purchased from Fluorochem. NaH and thiophenols were purchased from Aldrich. DMF (Aldrich) was distilled before use.

All the apparatus were dried and flushed with argon before use. NaH was washed with dry hexane to remove the oil.

Condensation of CF_2BrCl with Sodium *p*-Chlorothiophenoxide. 1. Dry DMF (50 mL) was added, under argon, to NaH (55% in oil, 0.9 g, 0.02 mol) previously washed with hexane. *p*-Chlorothiophenol (2.9 g, 0.02 mol) in 5 mL of DMF was added as drops at room temperature under stirring. After 1 h, argon was bubbled into the solution for 30 mn. The mixture was then cooled to −40 °C and bromochlorodifluoromethane (6.6 g, 0.04

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mol) added quickly. The solution was kept for 1 h at -40 °C and warmed to room temperature for 1 h. The mixture was poured over 100 mL of 15% HCl and extracted with chloroform. The combined extracts were washed with NaOH and water and dried over $MgSO_4$. Chloroform was evaporated. Product **2a** was obtained after crystallization from ether: mp 136-138 °C; 1.2 g (35% yield); ^{19}F NMR ϕ 51 (s). Anal. Calcd for $C_{13}H_8Cl_2F_2S_2$: C, 46.30; H, 2.39. Found: C, 46.30; H, 2.35.

2. Inhibition by *p*-Dinitrobenzene. The same procedure as above was used. *p*-Dinitrobenzene (0.4 g) was added at -40 °C before the introduction of CF_2BrCl. In these conditions, the formation of the disubstituted product **2a** is completely inhibited.

Condensation of CF_2BrCl with Sodium Thiophenoxide. 1. The same procedure as above was used for the condensation of sodium thiophenoxide with CF_2BrCl. Thiophenol (2.2 g, 0.02 mol) and 6.6 g (0.04 mol) of CF_2BrCl are used. After hydrolysis and workup, a bulb-to-bulb distillation was performed at 0.1 mmHg. The light products $C_6H_5SCF_2Br$ (**3**), $C_6H_5SCF_2Cl$ (**5**), and $C_6H_5SCF_2H$ (**4**) are collected (0.8 g; yield 9% **3**; 5% **5**; 3% **4**): ^{19}F NMR **3** ϕ 21.7 (s); **5** 28.4 (s); **4** (90, d, J_{HF} = 60 Hz). Compounds **3** and **4** have been identified by comparison with authentic samples.[3]

From several experiments we have been able to purify $C_6H_5SCF_2Cl$ (**5**): a spinning-band distillation of the mixture of **3**, **4**, and **5** gave pure **5**: bp 82 °C (30 mm); ^1H NMR δ 7 (m); ^{19}F NMR ϕ 28.4 (s). MS, *m/e* 194-196 (M^+), 159 (M - Cl), 109 (M - CF_2Cl). Anal. Calcd for $C_7H_5ClF_2S$: C, 43.19; H, 2.58. Found: C, 42.76; H, 2.50.

The residue of the bulb-to-bulb distillation was distilled; 1.2 g (43% yield) of compound **6** was obtained: bp 110-115 °C (0.1 mm); ^1H NMR δ 8 (m); ^{19}F NMR ϕ 49 (s); ^{13}C NMR ($CDCl_3$) δ 132.4 (CF_2, t, J_{CF} = 315 Hz). Anal. Calcd for $C_{13}H_{10}F_2S_2$: C, 58.21; H, 3.73; F, 14.18; S, 23.88. Found: C, 58.52; H, 3.95; F, 14.16; S, 23.85.

D. J. Burton[12] gives for **6** the following characteristics: bp 103 °C (1 mm); ^{13}C NMR δ 119.2 (t, J_{CF} = 338.3 Hz).

2. Inhibition by Nitrobenzene. The same procedure as above was used. Nitrobenzene (2.4 g, 0.02 mol) was added at -40 °C before the introduction of CF_2BrCl. After hydrolysis and workup, a bulb-to-bulb distillation was performed. The light products **3**, **4**, **5**, and nitrobenzene are collected (5 g). The three fluorinated derivatives (5 - 2.4 = 2.6 g) are analyzed by ^{19}F NMR, which shows that **3** is the major product (more than 95%); yield in **3**, 52%. Distillation of the residue gives 0.15 g of **6** (yield 5%).

Condensation of CF_2Cl_2 with Sodium Thiophenoxide. Dry DMF (130 mL) was added to sodium hydride (55% in oil, 2.18 g, 0.045 mol) previously washed with hexane. Thiophenol (5 g, 0.045 mol) was added as drops. The mixture was poured into a silica vessel. DMF (150 mL) was added, and argon was bubbled into the solution. The mixture was cooled to -40 °C and CF_2Cl_2 (11 g, 0.09 mol) added. The solution was irradiated at -40 °C for 2 h with a high-pressure mercury lamp (TQ Hanau). Hydrolysis and workup were done as described above.

A bulb-to-bulb distillation gives the light products, 1 g (yield 6% **5**; 6% **4**). The residue was distilled at 0.1 mmHg; 1.3 g of **6** was obtained (yield 22%).

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Registry No. **1a**, 18803-44-6; **2a**, 78840-51-4; **3**, 78031-08-0; **4**, 1535-67-7; **5**, 85554-53-6; **6**, 80351-59-3; CF_2BrCl, 353-59-3; CF_2Cl_2, 75-71-8; C_6H_5SNa, 930-69-8; *p*-chlorothiophenol, 106-54-7; thiophenol, 108-98-5; *p*-dinitrobenzene, 100-25-4.

Synthesis of Chain-Extended and C-6′ Functionalized Precursors of the Nucleoside Antibiotic Sinefungin

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Precursors of sinefungin were prepared by chain extension of the blocked adenosine 5′-aldehyde **4** through a carbon-carbon bond to C-5′. Bond formation was accomplished with variously functionalized stabilized ylides. Employment of 2-oxo-3-(triphenylphosphoranylidene)tetrahydrofuran (**7**) gave a nucleoside lactone (**8**) which was converted in several steps to a C-6′ carboxylic acid (**10c**). A Curtius rearrangement of this acid, quenching with benzyl alcohol, allowed the introduction of a C-6′ amino group, blocked as a urethane (**11a**). The chain-ending (C-8′) alcohol was converted to a leaving group and displaced by azide ion and dibenzyl sodiomalonate.

Sinefungin (**1**, SF; see Chart I), a nucleoside antibiotic isolated from *Streptomyces griseolus*, is one of a number of naturally occurring nucleosides containing amino acid residues.[2] The unique feature of sinefungin is that the bond between the amino acid (ornithine) and the nucleoside (adenosine) is a carbon-carbon bond, thus producing a decose as the carbohydrate moiety. Sinefungin is structurally quite similar to *S*-adenosylmethionine (AdoMet) and *S*-adenosylhomocysteine (AdoHcy), with the sulfur in AdoHcy or methylated sulfur in AdoMet being replaced by $CH(NH_2)$. The spatial orientation of the amino group in sinefungin (*S*) is identical with that of the methyl in AdoMet.[3] It has been suggested on the basis of labeling studies that a preformed adenosine derivative and ornithine or a derivative are close biosynthetic precursors of sinefungin.[4] Sinefungin has been found to have activity against fungi, viruses, parasites, and cancer in vitro[5] and has been reported to have in vivo antiviral activity.[6] The wide range of biologic activity of SF may be due to its strong inhibition of a variety of AdoMet-utilizing methyltransferases[5,7-9] or to the inhibition of an enzyme

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