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A Family of Trifluoroethoxycarbenes

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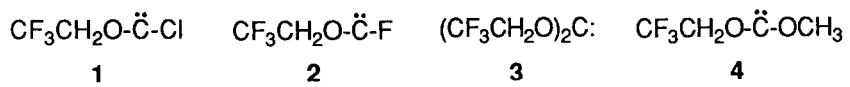
Abstract: The generation and reactions of 4 novel trifluoroethoxycarbenes are described.

Alkoxycarbenes have commanded much attention because the resonance donating electronic properties of the alkoxy substituent stabilizes the singlet state, relative to the triplet,[1] and enhances the singlet's nucleophilicity.[2-4] The latter effect is illustrated by the extraordinary intermolecular nucleophilic selectivity of the bis-oxacarbenes,[5] and the alkyl(or aryl)-alkoxycarbenes,[6] as well as the ambiphilic[2-4] selectivity of the alkoxy(or aryloxy)halocarbenes.[7]

More recently, we showed that the trifluorethoxy group (CF_3CH_2O, TFE), which can be considered a trifluoromethyl-substituted methoxy (MeO) group, modulates or "tunes" the electronic properties of MeO.[8] TFE [σ_R^+ -0.56] is a less effective electron donor than MeO [σ_R^+ -0.66][9] because of the opposed CF_3 inductive effect. As a result, intramolecular reactions of alkylmethoxycarbenes that are electronically suppressed become competitive with their TFE analogues.[8]

It now becomes important to examine the intermolecular chemistry of the TFE carbenes, which ought to be less stabilized and more reactive than analogous MeO carbenes, thereby offering access to many new organofluoro compounds. Some of these may be of biological interest. For example, trifluoroethyl difluoromethyl ether, precursor of the major inhalation anesthetic isoflurane,[10] is commercially prepared by the reaction of difluorocarbene with trifluoroethanol,[11] a process in which trifluoroethoxyfluorocarbene (see below) may intervene.

We are pleased to report here the syntheses of 5 novel trifluoroethoxydiazirines, together with the generation and representative reactions of trifluoroethoxychlorocarbene (TFE-C-Cl, **1**), trifluoroethoxyfluorocarbene (TFE-C-F, **2**), bis-trifluoroethoxycarbene ($(TFE)_2C$, **3**), and trifluoroethoxymethoxycarbene (TFE-C-OMe, **4**).

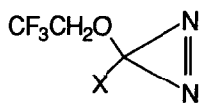


1 **2** **3** **4**

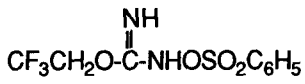
The diazirine precursors (**5a-e**) of this family of trifluoroethoxycarbenes required the prior preparation of N-benzenesulfonyl-O-trifluoroethylisourea (**6**), which was synthesized in 3 steps from trifluoroethanol: (1) conversion to the known[12] trifluoroethylcyanate (BrCN, Et_3N, Et_2O, 5-20°C); (2) reaction of the cyanate with hydroxylamine hydrochloride (MeOH-Et_2O, 0-10°C), affording the known[13] N-OH, N'-hydrochloride precursor of **6**; (3) sulfonylation with $PhSO_2Cl$ (Na_2CO_3, NaOH, H_2O, 0-20°C).[14] After recrystallization from hot benzene-hexane, we obtained a 31% overall yield of **6** (mp, 106-107°C), which was characterized by NMR and elemental analysis.[15]

Graham oxidation[16] of **6** with NaOBr in aqueous DMSO/pentane at 0 to 15°C afforded trifluoroethoxybromodiazirine **5a** (λ_{max} 344, 360 nm, $t_{1/2}$ ~ 6 h, pentane),[17] whereas analogous oxidation with

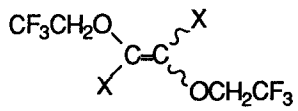
NaOCl gave trifluoroethoxychlorodiazirine **6b** (λ_{max} 344, 360 nm, $t_{1/2}$ ~ 14 h, pentane). Diazirine **5a** was "exchanged" with anhydrous tetra-n-butylammonium fluoride[7a,18,19] in dry DMF (-10 to 0°C, 2 h) yielding trifluoroethoxyfluorodiazirine **5c** (λ_{max} 342, 358 nm, $t_{1/2}$ ~ 2 weeks, pentane). Exchange reactions of **5b** or **5a** with $NaOCH_2CF_3$[8] (DMF, -20°C, 1 h) afforded bis-trifluoroethoxydiazirine **5d** (λ_{max} 344, 358 nm, $t_{1/2}$ ~ 5 h,



5 a, X = Br; **b**, X = Cl
c, X = F; **d**, X = OCH_2CF_3
e, X = OMe



6



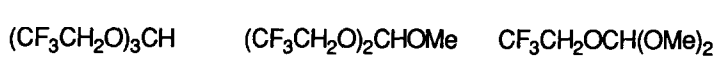
7, X = Cl; **8**, X = F;
9, X = OCH_2CF_3;
10, X = OMe

pentane). Finally, exchange of 3-chloro-3-methoxydiazirine[7c,d] with $NaOCH_2CF_3$ (DMF, -30 to -20°C, 30 min) gave trifluoroethoxymethoxydiazirine **5e** (λ_{max} 352, 366 nm, $t_{1/2}$ ~ 1.6 h, pentane).

The yields of diazirines **5a** and **5b** were ~50% based on **6**, whereas the exchange reactions to diazirines **5c-5e** proceeded in ~80% yields (~40% overall from **6**). Diazirines were used as pentane (or decane solutions) that were dried over $CaCl_2$, and passed through short silica gel columns before use. Their identities follow from their method of preparation,[16,18,19] UV spectra,[16,18,19] decomposition products, and reaction products with alcohols and alkenes.

Thermal, ambient temperature decompositions of solutions (A_{350} ~ 1) of diazirines **5b**, **5d**, or **5e**, and photolytic decomposition (350 nm) of **5c**, gave dimers **7-10**[15] of carbenes **1-4**, respectively. GC (12 m x 0.22 mm bonded SE-30 on vitreous silica) and GC-MS analysis showed that all dimers formed in >95% purity; azines were generally absent suggesting that carbene/diazirine reactions did not occur. The dimers could be purified by preparative GC (SF-96), but isolated yields were low (10-15%, based on **6**) due to their volatility and instability. Except for **9**, GC indicated the presence of Z and E isomeric dimers.

Diazirines **5c-e** were similarly decomposed (see above) in MeOH and /or CF_3CH_2OH, affording carbenes **2-4** which "inserted"[5d] into the solvent OH bonds. Appropriate orthoesters were formed in >95% GC purity; isolated yields (preparative GC) ranged from 5-18%, based on **6**.



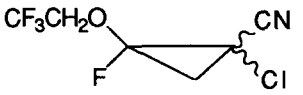
11 **12** **13**

From **5c** (via TFE-C-F) and CF_3CH_2OH, we obtained tris-trifluoroethoxymethane, **11**, identical (GC, GC-MS) with an authentic sample.[11] This product apparently formed from the (unobserved) primary orthoester [$(CF_3CH_2O)_2CHF$] by self-catalyzed alcoholysis with CF_3CH_2OH.[5d] Diazirine **5d** [via $(TFE)_2C$] and CF_3CH_2OH afforded **11**, isolated in 18% yield. From MeOH, we obtained a comparable yield of the previously characterized[5d] "mixed" orthoformate, **12**. Diazirine **5e** (via TFE-C-OMe) also gave **12** upon reaction with CF_3CH_2OH (15% isolated yield), whereas, in MeOH, we obtained the known [5d] dimethoxytrifluoroethoxymethane, **13** (5% isolated yield).

The new diazirines and carbenes were also characterized by the cyclopropanation of alkenes. For example, chlorodiazirine **5b** in acrylonitrile thermally afforded isomeric (1:2.1) cyclopropanes **14** (25°C, 3 d)[15]

in >95% GC purity and 12% isolated yield; about 5% of dimers **7** also formed.With diazirine **5d** [via $(TFE)_2C$], a similar decomposition (25°C, 40 h) afforded cyclopropane **15**[15] (>96% pure by GC, 25% isolated yield), accompanied by <4% of dimer **9**.

14, X = Cl; **15**, X = OCH_2CF_3
16, X = OMe



17

$CF_3CH_2OCHF_2$

18

Similarly, diazirine **5e** (via TFE-C-OMe) and acrylonitrile (25°C, 12 h) gave isomeric cyclopropanes **16** (1:1.3)[15] in greater than 95% purity, isolated in 12% yield. Interestingly, TFE-C-F, from diazirine **5c**, was unreactive toward acrylonitrile; only dimers **8** were found upon photolysis of pentane solutions of **5c** with acrylonitrile (or methylacrylate, 2-methyl-1-butene, or trimethylethylene). However, the more electrophilic[20] α-chloro-acrylonitrile did capture TFE-C-F in acetonitrile, yielding cyclopropanes, **17** (2:1);[15] which were isolated in 18% yield.

Preliminary experiments with other alkenes allow the assignment of provisional philicities[2-4] to the TFE-carbenes. TFE-C-Cl (**1**) adds[21] to tetramethylethylene, trimethlethylene, and acrylonitrile; it is most likely ambiphilic, as is MeO-C-Cl.[7c,d] TFE-C-F (**2**) appears to be nucleophilic (see above), possibly more nucleophilic than MeO-C-F.[7a] $(TFE)_2C$ (**3**) and TFE-C-OMe (**4**) each add to acrylonitrile and methyl acrylate,[21] but not to 2-methyl-1-butene. They also seem to be nucleophilic and qualitatively similar to their analogue, $(MeO)_2C$.[5b] Quantification of the reactivities of these new TFE-carbenes will be reported after we have determined absolute and relative rate constants for their reactions with alkenes and alcohols, but initial absolute rate determinations with several alkenes show that TFE-C-Cl is ~2 orders of magnitude more reactive than MeO-C-Cl.

Finally, in view of the relation of TFE-C-F to the synthesis of isoflurane[10] (see above), we examined the photolysis of **5c** in acetonitrile containing a 5-fold excess of HF-pyridine. Capillary GC and GC-MS revealed >90% of difluoride **18**,[22] identical with an authentic sample.[11] This isoflurane precursor is presumably formed by the reaction of TFE-C-F with HF; benzyloxyfluorocarbene undergoes an analogous reaction.[23] Competition experiments, in which TFE-C-F is forced to choose between pyridine-HF and trifluoroethanol substrates, are in progress and should help to clarify mechanistic problems associated with the commercial synthesis of **18** from CF_2 and trifluoroethanol, where the unwanted orthoester **11** is formed alongside the desired difluoride.[11] The spectroscopy, reactivity, and selectivity of the TFE-carbenes, and the preparation of long-chain fluorinated analogues, are currently under study in our laboratory.

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