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FLUOROMETHOXYDIAZIRINE AND FLUOROMETHOXYCARBENE

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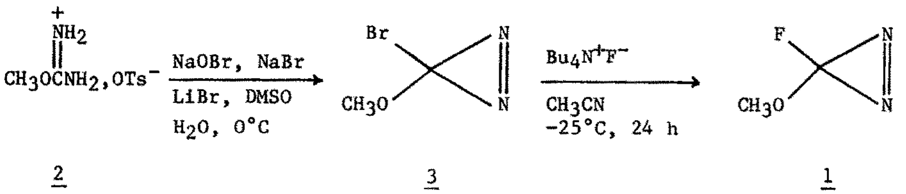
Summary. 3-Fluoro-3-methoxydiazirine was synthesized in ~35% overall yield in a two-step procedure that eschews elemental fluorine.

The triad of carbenes, difluorocarbene (CF_2), fluoromethoxycarbene (FCOMe), and dimethoxycarbene [$C(OMe)_2$], should best illustrate the transition from electrophilic to nucleophilic carbenic reactivity.[1] The electrophilicity[2] of CF_2 and the nucleophilicity[3] of $C(OMe)_2$ are well-documented, but the anticipated ambiphilicity[1] of FCOMe remains unexplored for want of a convenient precursor.

FCOMe appears to form from CF_2 and methoxide ion during the reaction of the latter with chlorodifluoromethane,[4] but the strongly basic conditions are inappropriate for matrix isolation or generalized philicity studies of the carbene. A far better precursor would be 3-fluoro-3-methoxydiazirine, 1, which is reported to thermally decompose with addition of the resulting FCOMe to tetrafluoroethylene in 61.5% yield.[5] Unfortunately, the reported synthesis[6] of diazirine 1 is very inconvenient, involving a low-yield elemental fluorination reaction[7] and a "shatteringly explosive"[6] fluoronitrogen intermediate.

We now disclose a two-step synthesis of 1 that proceeds in 35% overall yield, requires only readily available reagents, and eschews elemental fluorine. Experimental details accompany this brief report.

The reaction sequence is based upon "diazirine exchange" chemistry,[8] and is outlined in eq. (1). O-Methylisourea p-toluenesulfonate, 2,[9] was oxidized to 3-bromo-3-methoxydiazirine in a Graham reaction[10] using freshly prepared sodium hypobromite in aqueous DMSO. Diazirine

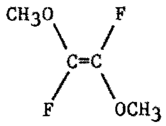


(1)

3, removed as generated by vacuum distillation, was isolated in ~50% yield in CH_3CN solution at -78°C. The new diazirine was characterized spectroscopically[10] by its uv (352 and 362 nm in CH_3CN; 332 sh, 348, and 364 nm in pentane) and ir spectra (1555, 1545, 1240, 1025, 965, and 925 cm^{-1} in pentane)

Without further purification, the bromodiazirine was converted to fluoromethoxydiazirine 1 by exchange[8] with "anhydrous" tetra-*n*-butylammonium fluoride (TBAF)[8,11] in dry CH_3CN (-25°C, 24 h). Vacuum isolation[12] (P~0.01 mm/Hg) in ~2 ml of pentane or other solvent at 77 K afforded ~70% by weight of diazirine 1. Its uv (332 sh, 348, and 364 nm in pentane) and ir (3000w, 2950w, 2850w, 1555s, 1460w, 1300vs, 1220m, 1165s, and 1025s, gas phase) spectra were very similar to the reported descriptions.[5] Additionally, the ^{19}F nmr spectrum featured a singlet at $\delta(CFCl_3/CDCl_3)$ 120.47 (lit.,[5] ϕ^* 121.8).

Thermal decomposition of diazirine 1 (decane, 80°C, 5 h, sealed tube) gave carbene dimer 4 (~57%),[13] azine 5 (~13%),[14] and a third product (~8%) that appears (from mass and ^{19}F nmr spectroscopy) to be the cyclopropane adduct of FCOMe and dimer 4. In the presence of acrylonitrile or methyl acrylate, analogous thermolyses of 1 gave syn/anti isomer mixtures of cyclopropanes 6 and 7, respectively. Each of these 4 cyclopropanes was isolated by gc[15] and characterized by an exact mass measurement and appropriate ^1H and ^{19}F nmr spectra. The isolated yields of 6 and 7 were only 4-6%, but the low yields appear to be due to the volatility of the cyclopropanes and the consequent inefficiency of gc collection; the gc traces were clean, and the cyclopropanes were the dominant products. Photolysis (λ>300 nm) of 1 in methyl acrylate also gave 7, but the crude product mixture was not as clean as that resulting from thermolysis.



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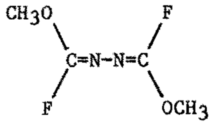

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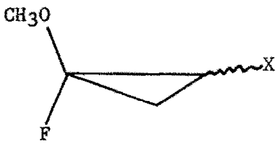

6, X=CN

7, X=COOMe

The formation of products 4, 6, and 7 is consistent with the generation of FCOMe from diazirine 1. Characterization of the philicity[1] of this carbene, and determination of its structure under matrix isolation conditions,[16] await further efforts. The stage is now set by the simple, direct, and efficient preparation of fluoromethoxydiazirine reported here.

3-Fluoro-3-methoxydiazirine

To a cooled solution (0°C) of 3.3 g (13 mmol) of O-methylisourea p-toluenesulfonate, 2,[9] in 80 ml of DMSO containing 7 g of LiBr, was quickly added a fresh NaOBr solution prepared from 6.1 ml (17 g) of bromine, 15 g of NaOH, 50 g of NaBr, and 160 ml of water. The reaction mixture was cooled, stirred magnetically during the addition, and continuously evacuated (P~ 0.01 mm/Hg) for 15 min through a train of 3 traps. The initial (U-tube) trap contained KOH pellets; the second (empty) trap was cooled to -45° to -50°C; and the third trap contained 2-3 ml of dry CH_3CN, cooled to -78°C. A 50% yield of 3-bromo-3-methoxydiazirine (3) collected in the last trap. It was characterized spectroscopically (see above) and used immediately.[17]

Nearly anhydrous TBAF[8,11] was prepared from 6.3 g (18 mmol) of $TBAF \cdot 3H_2O$ (Aldrich) and dissolved in 3-4 ml of dry CH_3CN. This solution was stirred magnetically and cooled to -25°C. The cold, just-thawed CH_3CN solution of 3 was quickly added to the TBAF solution, stirring was continued for 5 min, and then the reaction flask was sealed and stored in the freezer at -25°C for 24 hrs. The product mixture flask was then connected to a vacuum line and "distilled" for 15 min at -20°C/0.01 mm/Hg through a train of 3 traps. The first two traps (at 25° and -78°C) were empty, the third trap (held at -196°C) was charged with 2-3 ml of pentane, CH_3CN, or an alkene. A 70% yield (by weight) of fluoromethoxydiazirine 1 collected in the last trap, and was either characterized spectroscopically or used to generate FCOMe (see above).

Caution. Diazirines 1 and 3 are explosive when neat. Extreme care should be exercised during cold trap procedures when crystalline diazirines are present. Thawing should be carried out so as to dissolve the diazirines at the lowest possible temperature. All operations should be carried out behind safety shields. However, in our hands, solutions of the diazirines have never detonated.

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(12) The reported[5] bp of **1** is ~5°C at atmospheric pressure.

(13) *M^+* at *m/e* 124; ^{1}H nmr, δ($CDCl_3$) 3.76, s; ^{19}F nmr, δ($CFCl_3/CDCl_3$) 135.7, s. The product mixture was separated by gc[15] at 45°C. Dimer **4** was previously reported as the product of thermolysis of neat **1** at 50-95°C,[5] but its characterization was not specified.

(14) *M^+* at *m/e* 152; ^{1}H nmr, δ3.90, s.

(15) We used a 6'x 0.25" 20% SF-96 on 80/100 Chromosorb W Teflon column operated at 55°C.

(16) See, for example, the studies of ClCOMe reported by R.S. Sheridan and M.A. Kesselmayer, *J. Am. Chem. Soc.*, **106**, 436 (1984).

(17) Diazirine **3** is unstable at 25°C; its uv spectrum (pentane) decays within 4 hrs. In contrast, pentane solutions of **1** appear by uv to be stable for at least 24 hrs in the dark at room temperature.

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