The Reaction of 2-Trifluoromethyl-3,3-difluorooxaziridine with Some Fluorinated Nucleophiles

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The reaction of the oxaziridine $CF_3\overline{NCF_2O}$ with a variety of fluorinated nucleophiles has been studied. Reactive nucleophiles attack the ring exclusively at nitrogen followed by fluoride elimination to form $CF_3N(Nu)C(O)F$, or isomerization forming $CF_3NFC(O)F$. Subsequent nucleophilic attack in $CF_3NFC(O)F$ is observed in several cases. Three new compounds, $CF_3N[OCF(CF_3)_2]C(O)F$, $CF_3NFC(O)OOCF_3$, and $CF_3NFC(O)OC(CF_3)_3$, were characterized.

In the chemistry of three-membered heterocycles containing two different heteroatoms, the oxaziridine, $CF_3\overline{NCF_2O}$, is the only known perfluoro compound.[2] Because of the often disparate chemistry of perfluorinated compounds compared to their hydrocarbon analogues, the reaction chemistry of $CF_3\overline{NCF_2O}$ is of more than casual interest.

Recently, in an attempt to gain information about the formation of $CF_3\overline{NCF_2O}$ from $CF_3NHCF_2OOCF_3$ and NaF, we carried out reactions of the amine with several metal fluorides.[3] With KF and CsF, the oxaziridine underwent further reaction to form $CF_3NFC(O)F$ and $CF_3N(OCF_3)C(O)F$ in high yield.

$$CF_3\overline{NCF_2O} \xrightarrow{KF} CF_3NFC(O)F$$

$$CF_3\overline{NCF_2O} \xrightarrow{CsF/COF_2} CF_3N(OCF_3)C(O)F$$

These results indicated that the nucleophiles, F^- and OCF_3^-, attacked the nitrogen atom in the oxaziridine. We have carried out reactions between isolated $CF_3\overline{NCF_2O}$ and various fluorinated nucleophiles. It is apparent that the reactivity of $CF_3\overline{NCF_2O}$ to fluorinated nucleophiles is not high, but several reactions proceed in good yield forming novel compounds of the type $CF_3N(R)C(O)F$, where R represents the nucleophile.

Experimental Section

General. All reactions were carried out in glass and stainless-steel vacuum systems as previously described.[2] Amounts of reactants and products were determined by weighing or by PVT measurements assuming ideal gas behavior.

Infrared spectra were recorded in 10-cm glass cells fitted with AgCl windows on P.E. 180 and 337 spectrophotometers. NMR spectra were recorded on a Varian XL-100-15 NMR spectrometer using ~15 mol % solutions in $CFCl_3$ at 30 °C. Chemical shifts are reported in ppm relative to internal $CFCl_3$ (ϕ^* values). Melting points were determined by a modified Stock technique using a calibrated digital thermometer. Vapor pressures were obtained via the isotensiscope principle.[4] Data were analyzed by least-squares fit to linear and quadratic equations with the equation and the extrapolated boiling point reported for the best fit.

Reagents. CsF and NaF were dried by heating under vacuum, followed by treatment of CsF with fluorine at 22 °C. The reagents, $(CF_3)_2CO$, $(CF_3)_3COH$, CF_3CH_2OH, and $(CF_3)_2CHOH$, were from commercial sources and were used as received. The preparations of $CF_3\overline{NCF_2O}$,[2] $CF_3NFC(O)F$,[3] COF_2,[5] CF_3SH,[6] $(CF_3)_2NH$,[7] $(CF_3)_3CONa$,[8] $(CF_3)_3COK$,[8] and CF_3OOH[9] were by literature methods. The alkoxides $NaOCH_2CF_3$ and $NaOCH(CF_3)_2$ were prepared from the alcohols and NaH.

Reactions. Reactions were carried out in 75-mL 304ss reactors or in 100-mL glass bulbs fitted with glass–Teflon valves. Solids (5.0 mmol MF or 1.0 mmol MOR) were placed in the reactors and the vessel was evacuated and then cooled to −196 °C. Volatile reactants (1.0 mmol of each) were then condensed into the reactor and the vessel was allowed to warm to the appropriate temperature. After reactions were complete, the products were passed through cold traps at temperatures calculated to separate the addition product from unreacted starting materials or the isomerized oxaziridine $CF_3NFC(O)F$. In some cases further separation by GLC was required using ss columns packed with 30% Halocarbon 11-21 oil on Chromosorb P.

Characterization of new compounds follows. Other known products were identified by their characteristic IR and NMR spectra. $CF_3N[OCF(CF_3)_2]C(O)F$: bp 61.1 °C; mol wt 314.1, calcd. 315.04; log P(torr) = 6.6988 − 947.11 − 110000 (947.11 = T; 110000 = T^2); ΔH_{vap} = 7.35 kcal/mol; ΔS_{vap} = 22.0 eu; IR 1899 (vs), 1879 (vs), 1863 (vw), 1760 (m), 1570 (vw), 1435 (vw), 1377 (m), 1317 (vs), 1258 (vs), 1224 (s), 1195 (w), 1167 (s), 1160 (s), 1063 (w), 1010 (s), 987 (w), 897 (vw), 808 (vw), 776 (vw), 749 (m), 706 (m), 690 (sh), 535 (w) cm^{-1}; NMR $CF_3^AN[OCF^B(CF_3^C)_2]C(O)F^D$ ϕ^*_A 63.8, (d-d-sep), ϕ^*_B 142.6 (m), ϕ^*_C 78.8 and 78.2 (br), ϕ^*_D 6.9 (br-m), J_{AB} = 10, J_{AD} = 15, $J_{AC} \simeq$ 2 Hz, J_{BD}, J_{BC}, and J_{CD} were not determined. This spectrum is temperature dependent and the values reported are for 30 °C. The relative areas of the signals were as expected. $CF_3NFC(O)OC(CF_3)_3$: bp 84.8 °C; mol wt 368.1, calcd. 365.05; log P(torr) = 7.4200 − 1676.9 + 18607 (1676.9 = T; 18607 = T^2); ΔH_{vap} = 7.20 kcal/mol; ΔS_{vap} = 20.1 eu; IR 1858 (vs), 1837 (vs), 1290 (vs), 1280 (vs), 1250 (s), 1217 (s), 1166 (s), 1135 (sh), 1125 (vs), 1063 (m), 1050 (m), 1004 (vs), 982 (vs), 823 (s), 742 (s), 728 (s), 712 (s), 687 (m), 655 (m), 641 (vw), 614 (m), 582 (w), 540 (m), 519 (vw), 507 (m), 434 (m) cm^{-1}; NMR $CF_3^ANF^BC(O)OC(CF_3^C)_3$ ϕ^*_A 67.2 (d), ϕ^*_B 69.3 (q), ϕ^*_C 70.0 (s), J_{AB} = 10.4, $J_{AC} \simeq J_{BC} \leq$ 0.5 Hz. $CF_3NFC(O)OOCF_3$: mp −114.1 to −113.2 °C; mol wt 228.0, calcd. 231.03; IR 1897 (vw), 1856 (vs), 1378 (w), 1297 (vs), 1250 (sh), 1240 (vs), 1215 (s), 1191 (vs), 1142 (m), 1111 (m), 1054 (s), 1000 (s), 943 (w), 920 (m), 827 (w), 748 (vw), 723 (m), 615 (m) cm^{-1}; NMR $CF_3^ANF^BC(O)OOCF_3^C$ ϕ^*_A 67.9 (d), ϕ^*_B 75.1 (q), ϕ^*_C 69.0 (s), J_{AB} = 11.9, $J_{AC} \simeq J_{BC} \leq$ 0.5 Hz.

Results and Discussion

The reaction of $CF_3NHCF_2OOCF_3$ with CsF indicated that fluorinated oxygen centered nucleophiles could attack nitrogen in $CF_3\overline{NCF_2O}$. To prove this and to see if nucleophiles other than OCF_3^- would react, $CF_3\overline{NCF_2O}$ was allowed to react with $CsOCF_3$ and $CsOCF(CF_3)_2$. In both cases, the salt was first prepared from CsF and the carbonyl compound. Reactions proceed readily at 22 °C giving high yields of the expected compounds after 24 h.

$$CF_3\overline{NCF_2O} + CsOCF_3 \rightarrow CsF + CF_3N(OCF_3)C(O)F \quad (80\%)$$

$$CF_3\overline{NCF_2O} + CsOCF(CF_3)_2 \rightarrow CsF + CF_3N[OCF(CF_3)_2]C(O)F \quad (81\%)$$

The other isolable product, $CF_3NFC(O)F$ (~7%), is probably formed from the direct reaction of the oxaziridine with CsF. The latter is present as unreacted material in the formation of $CsOR_f$ and is formed as the reaction proceeds. The high yields of substituted product indicate that the active fluoride sites on the surface of the CsF are effectively blocked by $CsOR_f$. If $CsOCF_3$ is not preformed, on the same scale after 4.5 h, the products are $CF_3N(OCF_3)C(O)F$ (75%), COF_2(25%), $CF_3\overline{NCF_2O}$ (9%), and $CF_3NFC(O)F$ (4%). Pure CsF under the same conditions completely converts $CF_3\overline{NCF_2O}$ to $CF_3NFC(O)F$ and polymer after only 4 h.

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The uncharacterized polymer formed with $CF_3\overline{NCF_2O}$ and CsF probably results from reaction of $CsOCF_2NFCF_3$ with the oxaziridine. This implies that $CF_3NFC(O)F$ should undergo the usual reaction of an acid fluoride with F_2 in the presence of CsF.[10] This reaction was carried out, but the expected O–F compound was unstable. With 1:1 F_2, CF_3OF[10] and CF_3NF_2[11] were formed in essentially quantitative yield with 50% recovery of $CF_3NFC(O)F$. The following reaction sequence is probably involved.

$$CF_3NFC(O)F + F_2 \xrightarrow{CsF} [CF_3NFCF_2OF]$$

$$[CF_3NFCF_2OF] \longrightarrow CF_3NF_2 + COF_2$$

$$COF_2 \xrightarrow{CsF/F_2} CF_3OF$$

Carbonyl compounds which are known to undergo catalyzed reactions in the presence of CsF, but which do not readily form stable adducts with CsF, are unreactive with the oxaziridine. Thus, reactions with CO_2 and $C_2F_5C(O)F$ in the presence of CsF gave products identical to the reaction of CsF alone and CO_2 and $C_2F_5C(O)F$ were recovered.

The next source of fluorinated nucleophiles tried was fluorinated alcohols and a hydroperoxide. Reaction of CF_3CH_2OH, $(CF_3)_2CHOH$, and $(CF_3)_3COH$ with $CF_3\overline{NCF_2O}$ in the presence of NaF showed no reaction after 24 h. Increasing the nucleophilicity by preforming the sodium salts led to reaction. With $NaOCH_2CF_3$ the reaction could not be controlled and combustion occurred. Sodium hexafluoroisopropoxide gave $CF_3NFC(O)F$ (50%) and five unidentified compounds by GLC. None of these appeared to be the expected product $CF_2N[OCH(CF_3)_2]C(O)F$. However, this result suggests that $CF_3\overline{NCF_2O}$ can be isomerized to $CF_3NFC(O)F$ by nucleophiles other than fluoride. With $NaOC(CF_3)_3$, $CF_3NFC(O)OC(CF_3)_3$ (30%) was obtained with 60% recovery of the unreacted oxaziridine after 24 h. The potassium salt was more reactive resulting in 62% of the same product and no unreacted oxaziridine. These results are explicable by the initial isomerization of $CF_3\overline{NCF_2O}$ by the perfluorinated alcoholate followed by reaction of $CF_3NFC(O)F$ to give the observed products.

$$CF_3\overline{NCF_2O} \xrightarrow{MOC(CF_3)_3} CF_3NFC(O)F$$

$$CF_3NFC(O)F + MOC(CF_3)_3 \rightarrow MF + CF_3NFC(O)OC(CF_3)_3$$

In the case of $KOC(CF_3)_3$, it is possible that KF is responsible for the isomerization of the oxaziridine. However, this is unlikely because NaF does not catalyze this reaction under these conditions and the same product is observed for both sodium and potassium salts of $(CF_3)_3COH$. Neither NaF nor KF should be present in $MOC(CF_3)_3$ initially, based on the method of preparation, and fluorides would have to come from reaction.

The fluorinated hydroperoxide, CF_3OOH, like the fluorinated alcohols, does not react with $CF_3\overline{NCF_2O}$ at 22 °C in the presence of NaF. At 90 °C complete reaction occurs giving COF_2 as the major product with no $CF_3NFC(O)F$ or other heavier compounds. The oxaziridine alone with NaF at 90 °C is consumed forming a variety of low molecular weight products along with $CF_3NFC(O)F$ (40%), and CF_3OOH is known to decompose to COF_2, O_2, and HF at elevated temperatures. Reaction of CF_3OOH with $CF_3NFC(O)F$ at 22 °C in the presence of NaF gives $CF_3NFC(O)OOCF_3$ (99%).

$$CF_3NFC(O)F + CF_3OOH + NaF \rightarrow CF_3NFC(O)OOCF_3 + NaF\cdot HF$$

These results suggest that CF_3OOH partially reacts with $CF_3\overline{NCF_2O}$ at 90 °C, but the product is unstable at this temperature.

Two nonoxygen nucleophiles, $(CF_3)_2NH$ and CF_3SH, were also tried. In the case of $(CF_3)_2NH$, in the presence of NaF, the oxaziridine is consumed along with 35% of the $(CF_3)_2NH$. None of the expected product, $CF_3N[N(CF_3)_2]C(O)F$, was observed. Instead, unreacted $(CF_3)_2NH$ (65%) and $(CF_3)_2NC(O)F$ (35%) were observed as heavier products along with a complex mixture of low molecular weight compounds, including CF_3NO, CF_3NCO, and COF_2. The $(CF_3)_2NC(O)F$ does not arise from the reaction of $(CF_3)_2NH$ with COF_2. This reaction was tried under identical conditions with 100% recovery of the starting materials.[12]

Trifluoromethanethiol and $CF_3\overline{NCF_2O}$ react in the presence of NaF to give CF_3SSCF_3[13] (>90%), CF_3NCO (35%), $(CF_3)_2NH$ (10%), COF_2, and unreacted $CF_3\overline{NCF_2O}$. The major products might be explained by the following reaction scheme.

$$CF_3\overline{NCF_2O} \xrightarrow[NaF]{CF_3SH} [CF_3N(SCF_3)C(O)F]$$

$$\xrightarrow[NaF]{CF_3SH} [CF_3N(SCF_3)C(O)SCF_3] \rightarrow CF_3NCO + CF_3SSCF_3$$

Thus, CF_3SH reacts with the oxaziridine with the nucleophilic displacement at the resultant carbonyl group being faster than the attack of the ring system. Trifluoromethanethiol is known to undergo ready reaction with thiocarbonyl fluorides in the presence of base.[14]

The new compounds prepared in this work are easily identified from the data given in the Experimental Section. However, the ^{19}F NMR of $CF_3{}^AN[OCF^B(CF_3{}^C)_2]C(O)F^D$ requires some discussion. All resonances are broad at 30 °C and exhibit temperature dependence. C shows two separate resonances of equal intensity. Fluorinated amines of the type $(CF_3)_2NR$ exhibit magnetic nonequivalence of the trifluoromethyl groups. If R is ethyl, bulky α substituents strongly effect the spectrum. This nonequivalence has been attributed to a combined hindered inversion and steric hindrance.[15] This explanation is probably correct in our case. An alternative explanation involving nonequivalence due to a carbon–nitrogen double bond in $R_fR_f'N^+{=}C(O^-)F$ seems unlikely. Although the latter is found in $(CH_3)_2NC(O)H$ and related compounds,[16] $(CF_3)_2NC(O)F$, $CF_3N(OCF_3)C(O)F$, and $CF_3N(OR)C(O)F$[17] (OR = variety of alkoxy groups) exhibit sharp spectra with no obvious complications.

In summary, the reactions of $CF_3\overline{NCF_2O}$ with fluorinated nucleophiles proceed similar to related reactions with fluorinated epoxides, with the latter being more reactive.[18] For example, hexafluoropropylene oxide, $CF_3\overline{CFCF_2O}$, reacts with both COF_2 and $C_2F_5C(O)F$ in the presence of CsF, whereas $CF_3\overline{NCF_2O}$ does not react with $C_2F_5C(O)F$. However, this work clearly illustrates the potential of $CF_3\overline{NCF_2O}$ for novel syntheses. The exclusive attack of nucleophiles at nitrogen in $CF_3\overline{NCF_2O}$ is similar to the exclusive attack on the central carbon in $CF_3\overline{CFCF_2O}$. While the latter preference has not been adequately explained, it seems even more surprising that the same preference is found in $CF_3\overline{NCF_2O}$.

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Registry No.—[1,2,2,2-Tetrafluoro-1-(trifluoromethyl)ethoxy]-(trifluoromethyl)carbamic fluoride, 69042-76-8; 2,2,2-trifluoro-1,1-bis(trifluoromethyl)ethyl fluoro(trifluoromethyl)carbamate, 69042-77-9; trifluoromethyl fluoro(trifluoromethyl)carbamoperoxoate, 69042-78-0; 3,3-difluoro-2-(trifluoromethyl)oxaziridine, 60247-20-3; cesium trifluoromethoxide, 2700-82-5; cesium heptafluoroisopropoxide, 13994-52-0; (trifluoromethoxyl)(trifluoromethyl)-

carbamic fluoride, 68986-55-0; fluoro(trifluoromethyl)carbamic fluoride, 68986-54-9; carbonic difluoride, 353-50-4; pentafluoromethanamine, 335-01-3; sodium 2,2,2-trifluoroethoxide, 420-87-1; sodium hexafluoroisopropoxide, 6919-74-0; sodium nonafluoro-*tert*-butoxide, 17526-77-1; potassium nonafluoro-*tert*-butoxide, 29646-16-0; trifluoromethyl hydroperoxide, 16156-36-8; 1,1,1-trifluoro-*N*-(trifluoromethyl)methanamine, 371-77-7; bis(trifluoromethyl)carbamic fluoride, 432-00-8; trifluoromethanethiol, 1493-15-8; bis(trifluoromethyl) disulfide, 372-64-5; trifluoroisocyanatomethane, 460-49-1.

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Ortho Functionalization of Aromatic Amines: Ortho Lithiation of *N*-Pivaloylanilines

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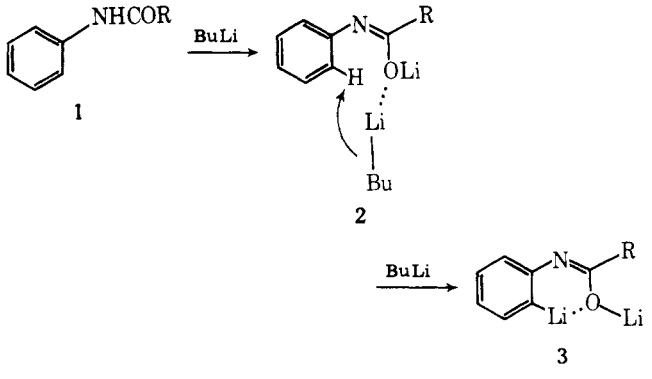
A method is described to convert *N*-pivaloylanilines and toluidines into their *o*-lithio and *o*-(lithiomethyl) derivatives, respectively. These species, in particular those derived from *p*-chloro-, *m*-methoxy-, and *o*-methylaniline, react with a variety of electrophiles (dimethyl disulfide, methyl iodide, DMF, benzaldehyde, trimethylsilyl chloride, acetaldehyde, CO_2) to give ortho-substituted derivatives in very good yield. *N*-Pivaloyl-*m*-anisidine can be functionalized regiospecifically in the 2 position. The pivalamido function is slightly superior to a methoxyl group as an ortho director.

Although electrophilic substitution of anilines, in particular of *N*-acylated derivatives, is feasible,[1,2] the formation of isomers and the marginal yields are synthetically unattractive. More recently a regiospecific ortho alkylation of aromatic amines has been developed based on a Sommelet–Hauser type rearrangement of azasulfonium ylides.[3,4] While the method offers considerable improvement, the reductive removal of the sulfur substituent and the formation of isomers in meta-substituted anilines still present disadvantages. A novel method which permits a specific ortho hydroxyalkylation of secondary anilines and ortho acylation of primary anilines is based on the use of anilinodichloroboranes.[5] While our own work was in progress, Walborsky[6] reported an α addition followed by ortho metalation of phenyl isocyanide. The reaction constitutes, in principle, an ortho metalation of a protected primary aniline but appears to occur only sluggishly relative to other ortho lithiations. We here wish to report on the facile and regioselective ortho lithiation of *N*-pivaloylanilines.

The nitrogen atom in *N,N*-dialkylanilines rates as one of the weakest ortho-directing groups,[7] and lithiation of such substrates can usually be attained only under forcing conditions. The presence of two active hydrogens in primary anilines is a formidable obstacle to nuclear metalation and is presumably the reason for the lack of reports on successful ortho lithiations (cf. ref 6). As part of a systematic search for synthetically useful aniline derivatives as ortho-directing groups, we investigated the suitability of acylated anilines **1**.



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Fundamentally it could be assumed that by analogy with other ortho metalations[7] the oxygen (or nitrogen) atom in the deprotonated species **2** should serve as a ligand for a second equivalent of lithiating agent, thus facilitating a regiospecific protophilic attack on the *o*-hydrogen and formation of the dilithio intermediate **3**. It was evident that the nature of R had to be such that no deprotonation of R could occur. Since lithiation of benzanilide occurs exclusively in the position ortho to the carbonyl group,[8] R could not be aryl. Most alkyl groups had to be excluded as well, based on the acidic character of their α protons.[9] The pivaloyl residue (R = C_4H_9-*t*), however, turned out to be ideal, and the desired reaction occurred readily and under relatively mild conditions. This is illustrated (Scheme I) by the facile lithiation of the *p*-chloro derivative

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