One-Pot Synthesis of *N*-Protected Amino Trifluoromethyl Ketones as Hydrated Hydrochloride Salts via the CsF-Catalyzed Reactions of (Trifluoromethyl)trimethylsilane with *N*-Protected Amino Esters

Rajendra P. Singh and Jean'ne M. Shreeve*

Department of Chemistry, University of Idaho, Moscow, Idaho 83844-2343

Received December 28, 1999

Introduction

It has been known for many years that the incorporation of a fluorine-containing group into an organic molecule dramatically alters its physical, chemical, and biological properties.[1] These changes in properties make them suitable for diverse applications in materials science, and agrochemistry, as well as in the pharmaceutical industry.[2] Biological activity[3] and numerous commercial applications[4] of organo-fluorine compounds have given rise to interest in developing synthetic methods for the selective and efficient incorporation of fluorine or fluorinated groups into organic compounds under mild reaction conditions.

Introduction of fluorine at the α-position in ketones increases the electrophilicity of the carbonyl moiety.[5] When fluorinated ketones were exposed to moisture, hydrates were readily formed.[6] Trifluoromethyl ketones (TFMK)[7,8] are useful enzyme inhibitors. Several methods for this syntheses have been reported[9] but most proceed via trifluoromethylated alcohol intermediates. The disadvantage of this approach is that the alcohol must be oxidized to prepare the desired ketones. Recently, Schofield et al.[10] reported the synthesis of hydrated hydrochloride salts of some amino TFMKs by the reaction of $TMSCF_3$ with oxazolidin-5-one derivatives followed by hydrolysis. But in some attempts final hydrolysis to give the desired products was not successful. Also, this procedure was limited to acyclic amino acids and it was not possible to make oxazolidinone derivatives of cyclic amino acids such as proline. We and others have reported several novel trifluoromethylation reactions[11−16] with various substrates and have successfully substituted the alkoxy group in simple esters with CF_3 by using cesium fluoride catalysis.[17,18] In this study we have extended our trifluoromethylation chemistry to *N*-protected amino esters to prepare amino trifluoromethyl ketones as hydrated HCl salts basically in one-pot reactions and in good isolated yields.

Results and Discussion

Initially, we reacted **1a** with 1.25 equiv of $TMSCF_3$ at room temperature either neat or in glyme in the presence of a catalytic amount of cesium fluoride. The corresponding silyl ketal, **2a**, was formed in essentially quantitative yield. Hydrolysis of **2a** with 6 N HCl gave the hydrated hydrochloride salt of the trifluoromethyl ketone (**3a**). The latter was obtained in 85% yield as a pure product by sublimation at reduced pressure (Scheme 1). Compound **3a** crystallized from acetonitrile as triclinic crystals. The structure and composition of **3a** was confirmed by single-crystal X-ray analysis.

Under similar reaction conditions, *N*-protected amino esters (**1b**−**e**) gave essentially quantitative yields of the corresponding silyl ether intermediates (**2b**−**e**). Hydrolysis with 6 N HCl at room temperature gave the hydrochloride salts of the amino trifluoromethyl ketones as hydrates (**3b**−**e**) (Scheme 2) in >80% yield.

The cyclic amino ester, such as *N*-benzyl-*l*-proline ethyl ester (**1f**), was also found to react with $TMSCF_3$ to produce the corresponding silyl ketal (**2f**) as a diastereomeric mixture in almost quantitative yield. Upon acid hydrolysis, **2f** gave the trifluoromethyl ketone derivative, **3f**, as the hydrated hydrochloride salt in 82% yield (Scheme 3). The enantiomerric purity of **3f** was found to be ∼95%, which is determined by NMR spectral measurements in the presence of Eu(hfc).[19] Similarly, when

(1) (a) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123. (b) Filler, R., Kobayashi, Y., Eds. *Biomedical Aspects of Fluorine Chemistry;* Kodansha Ltd. & Elsevier. Biochemical: Tokyo and Amsterdam, 1982.

(2) (a) Olah, G. A., Chambers, R. D., Prakash, G. K. S., Eds. *Synthetic Fluorine Chemistry*; John Wiley & Sons: New York, 1992. (b) Liebman, J. F., Greenberg, A., Dolbier, W. R., Jr., Eds. *Fluorine-containing Molecules. Structure, Reactivity, Synthesis, and Aapplications*; VCH: New York, 1988. (c) Welch, J. T.; Eshwarakrishanan, S., Eds. *Fluorine in Bioorganic Chemistry*; Wiley: New York, 1991. (d) Filler, R.; Kobayashi, Y.; Yagupolskii, L. M., Eds. *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Elsevier: Amsterdam, 1993.

(3) (a) Kobayashi, Y.; Kumadaki, I. *Acc. Chem. Res.* **1978**, *11*, 197−204. (b) Hansch, C.; Leo, A., Eds. *Substituents Constant for Correlation Analysis in Chemistry and Biology*; John Wiley & Sons: New York, 1997.

(4) (a) Banks, R. E., Smart, B. E., Tatlow, J. C., Eds. *Organofluorine Chemistry, Principles and Commercial Applications*; Plenum Press: New York, 1994. (b) Soloshonok, V. A., Eds. *Enantiocontrolled Synthesis of Fluoro-Organic Compounds: Stereochemical Challenges and Biomedical Targets*; John Wiley & Sons Ltd.: New York, 1999. (c) Kukhar, V. P., Soloshonok, Eds. *Fluorine-Containing Amino Acids: Synthesis and Applications*; John Wiley & Sons Ltd.: New York, 1995.

(5) Linderman, R. J.; Jamois, E. A. *J. Fluorine Chem.* **1991**, *53*, 79−91.

(6) Gelb, M. H.; Svaren, J. P.; Abeles, R. H. *Biochemistry* **1985**, *24*, 1813−1817.

(7) Bégué, J. P.; Bonnet-Delpon, D. *Tetrahedron* **1991**, *47*, 3207−3258.

(8) McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, *48*, 6555−6666.

(9) (a) Abeles, R. H.; Imperiali, B. *Tetrahedron Lett.* **1986**, *27*, 135−138. (b) Patel, D. V.; Rielly-Guavin, K.; Ryono, D. E. *Tetrahedron Lett.* **1988**, *29*, 4665−4668. (c) Edwards, P. D. *Tetrahedron Lett.* **1992**, *33*, 4279−4282. (d) Linderman, R. J.; Graves, D. M. *J. Org. Chem.* **1989**, *54*, 661−668.

(10) Walter, M. W.; Adlington, R. M.; Baldwin, J. E.; Schofield, C. J. *J. Org. Chem.* **1998**, *63*, 5179−5192.

(11) Patel, N. R.; Kirchmeier, R. L. *Inorg. Chem.* **1992**, *31*, 2537−2540.

(12) Singh, R. P.; Kirchmeier, R. L.; Shreeve, J. M. *J. Org. Chem.* **1999**, *64*, 2579−2581.

(13) Singh, R. P.; Vij, A.; Kirchmeier, R. L.; Shreeve, J. M. *J. Fluorine Chem.* **1999**, *98*, 127−132.

(14) Singh, R. P.; Kirchmeier, R. L.; Shreeve, J. M. *Org. Lett.* **1999**, *1*, 1047−1049.

(15) Singh, R. P.; Vij, A.; Kirchmeier, R. L.; Shreeve, J. M. *Inorg. Chem.* **2000**, *39*, 375−377.

(16) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757−786.

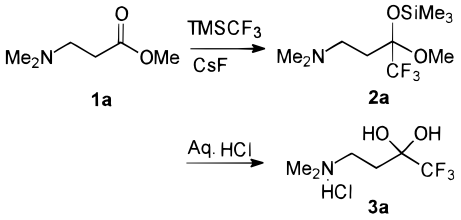
(17) Singh, R. P.; Cao, G.; Kirchmeier, R. L.; Shreeve, J. M. *J. Org. Chem.* **1999**, *64*, 2873−2876.

(18) Wiedemann, J.; Heiner, T.; Mloston, G.; Prakash, G. K. S.; Olah, G. A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 820−821.

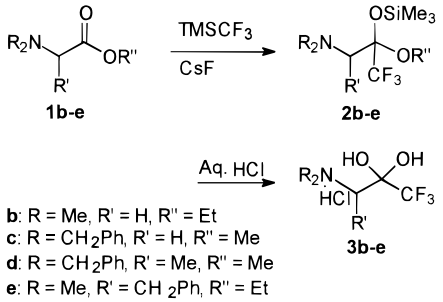
(19) (a) Annunziata, R.; Benanglia, M.; Cinquini, M.; Cozzi, F. *Tetrahedron Asymm.* **1999**, *10*, 4841−4849. (b) Wenzel, T. J.; Zaia, J. *Anal. Chem.* **1987**, *59*, 562−567.

10.1021/jo991972w CCC: $19.00
Published on Web 04/26/2000

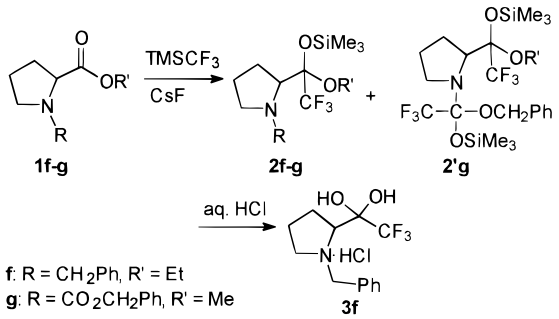
Scheme 1



Scheme 2



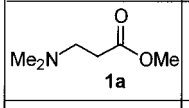
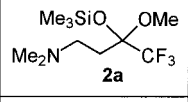
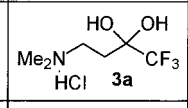
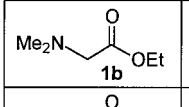
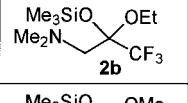
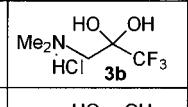
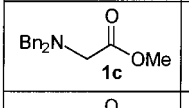
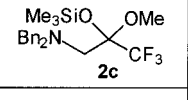
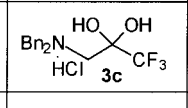
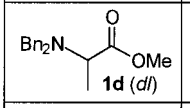
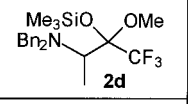
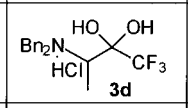
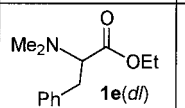
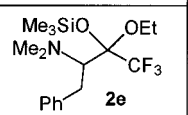
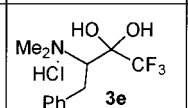
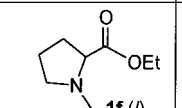
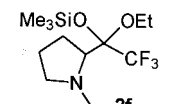
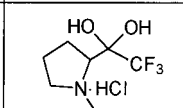
Scheme 3



the *N*-carbobenzyloxy-*l*-proline methyl ester was used as a substrate (**1g**), the desired intermediate (**2g**) was obtained in about 60% yield as a distereomeric mixture based on GC−MS [MS (EI) *m*/*z* (species, rel int) 374 (M^+ − OMe, 4), 373 (M^+ − OMe + H, 6), 336 (M^+ − CF_3, 3), 314 (M^+ − $PhCH_2$, 5), 282 (M^+ − $PhCH_2O_2$, 21), 91 ($PhCH_2$, 100). A second product identified by gas chromatography in about 10% yield was the double addition product **2′g** (as distereomeric mixture) in which CF_3 was added not only to the carbonyl of the methyl ester but also to the carbonyl carbon of the carbobenzyloxy group (MS (EI) *m*/*z* (species, rel int) 516 (M^+ − OMe, 4), 414 (M^+ − $SiMe_3$ + 2Me, 7), 409 (M^+ − $2CF_3$, 3), 91 ($PhCH_2$, 100). The material was not isolated and characterized further. Although deprotection of the methyl group lying on the nitrogen atom might be difficult, removal of benzyl and carbobenzyloxy groups are reported in the literature.[10,20] Therefore, we did not attempt to remove the protecting groups.

Compounds **3a**−**e** (Table 1) were sublimable solids. They were soluble in water, DMSO, DMF, and acetonitrile. In the infrared spectra of **3a**−**e** broad bands in the region 3000−3500 cm^{-1} assignable to ν(OH) and ν(NH) vibrations were observed. In the ^{19}F NMR spectra of **3a**−**e** a single peak appeared in the range δ −77 to −82 (CF_3). The ^1H NMR spectra clearly showed the resonances due to OH and NH protons. They disappeared upon addition of D_2O. In the ^{13}C NMR spectra, the peaks due to the carbonyl carbon in substrates (e.g., **1a**, **1b**) that had appeared in the range from δ 170−173, were shifted upfield to the region δ 90−95 in products (e.g., **3a**, **3b**). These resonances appeared as a quartet with J_{C-C-F} = ∼30 Hz. This upfield shift resulted from the formation of the OH groups and introduction of the CF_3 moiety onto the carbonyl carbon. The CF_3 carbon appeared as a quartet in the region δ 120−126 with $J_{C=F}$ = ∼289 Hz.

Table 1. Reaction of N-Protected Amino Esters with $TMSCF_3$[a]

Substrate	Intermediate[b]	Product	Yield[c] (%)
 1a	 2a	 3a	85
 1b	 2b	 3b	85
 1c	 2c	 3c	83
 1d (*dl*)	 2d	 3d	82
 1e(*dl*)	 2e	 3e	81
 1f (*l*)	 2f	 3f	82

[a] All of the reactions were carried out with 5.0 mmol of substrate, 5.25 mmol of $TMSCF_3$, and 0.1 mmol of CsF in 5 mL of glyme. [b] Yields are >98%. [c] Yields of products.

Conclusion

In conclusion, we have developed an efficient procedure for the synthesis of amino TFMKs as hydrated HCl salts in good isolated yields. At 25 °C, with catalytic amounts of cesium fluoride, *N*-protected acyclic or cyclic amino esters were found to react readily to give the silyl ether intermediates. Upon hydrolysis with HCl, the latter ether gave *N*-protected amino TFMKs as hydrated hydrochloride salts.

Experimental Section

General Comments. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded in $CDCl_3$ on a spectrometer operating at at 200, 50, and 188 MHz, respectively. Chemical shifts are reported in ppm relative to the appropriate standard, $CFCl_3$ for ^{19}F and tetramethylsilane/$CHCl_3$ for ^1H and ^{13}C NMR spectra. IR spectra were recorded using NaCl plates for neat liquids and KBr pellets for solids. Mass spectra were measured on an electron impact 70 eV spectrometer, and high-resolution mass spectra (HRMS) were obtained using a suitable mass spectrometer. Elemental analyses were performed by Desert Analytics Laboratory, Tucson, AZ.

Materials. The substrates, **1a**, **1b**, **1c**, **1d** (*dl*), **1e** (*dl*), **1f** (*l*), **1g** (*l*) cesium fluoride and monoglyme were purchased from

(20) ElAmin, B.; Anatharamaiah, G. M.; Royer, G. P.; Means, G. E. *J. Org. Chem.* **1979**, *44*, 3442−3444.

Aldrich whereas **1c**, **1d**[21a], **1e**[21b] and trimethyl(trifluoromethyl)silane (TMS−CF_3)[22] were prepared by literature procedures. Cesium fluoride was placed in an oven at 200 °C and repeatedly ground until it remained as a finely divided powder. Once this stage is reached, it may be used in the reactions. Storing in the oven at 200 °C retains the compound in a suitable state. No special environmental precautions are necessary.

Characterization of 1c:[21a] mp 40 °C; IR (KBr) 1738 (s, C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.29 (s, 2H), 3.66 (s, 3H), 3.79 (s, 4H), 7.29 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 50.8, 53.3, 57.7, 126.8, 128.7, 129.8, 138.9, 171.8; MS (CI) *m/z* (species, rel int) 270 ($M^+ + H$, 100), 210 ($M^+ - CO_2Me$, 13), 178 ($M^+ - PhCH_2$, 9). HRMS Calcd. for $C_{17}H_{20}NO_2$ ($M^+ + H$): 270.1494. Found: 270.1499.

Characterization of 1e:[21b] highly dense liquid; IR (KBr) 1740 (s, C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (t, 3H, $J = 7$ Hz), 2.37 (s, 6H), 2.96 (dd, 2H, $J = 6$ Hz), 3.37 (t, 1H, $J = 6$ Hz), 4.01 (q, $J = 6.5$ Hz), 7.18 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.2, 35.9, 41.8, 60.0, 69.55, 126.36, 128.2, 129.1, 138.1, 171.3; MS (EI) *m/z* (species, rel int) 221 (M^+, 5), 176 ($M^+ - OEt$, 20), 130 ($M^+ - PhCH_2$, 70), 57 (Me_2NCH, 100).

General Trifluoromethylation Procedure. In a typical reaction, *N*-protected amino ester (5.0 mM) and (trifluoromethyl)trimethylsilane (5.25 mM) were dissolved in monoglyme (5 mL), and CsF (0.1 mM) was added under a dry nitrogen atmosphere. The reaction mixture was stirred at 25 °C for 6 h and was hydrolyzed by reacting with 6 N HCl solution (6 mL) for 3 h. The removal of volatile materials at reduced pressure gave the hydrated hydrochloride salt of the respective amino trifluoromethyl ketone, which was purified by sublimation at reduced pressure.

2a: viscous liquid; ^1H NMR ($CDCl_3$) δ 0.14 (s, 9H), 1.95 (t, 2H, $J = 8$ Hz), 2.18 (s, 6H), 2.34 (t, 2H, $J = 8$ Hz), 3.61 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 1.19, 32.7, 45.4, 50.5, 52.9, 97.5 (q, $J_{C-C-F} = 30.4$ Hz), 123.1 (q, $J_{C-F} = 289.4$ Hz); ^{19}F NMR ($CDCl_3$) δ −80.08 (s); MS (EI) *m/z* (species, rel int) 273 (M^+, 8), 243 ($M^+ - 2CH_3$, 3), 73 ($SiMe_3^+$, 6), 58 ($CH_2NMe_2^+$, 100). HRMS calcd for $C_{10}H_{22}F_3NO_2Si$: 273.1372. Found: 273.1365.

2b: viscous liquid; ^1H NMR ($CDCl_3$) δ 0.16 (s, 9H), 1.16 (t, 3H, $J = 7$ Hz), 2.27 (s, 6H), 2.55 (s, 2H), 3.66 (q, $J = 7$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 1.42, 15.2, 47.2, 58.6, 61.5, 97.5 (q, $J_{C-C-F} = 28$ Hz), 123.1 (q, $J_{C-F} = 290$ Hz); ^{19}F NMR ($CDCl_3$) δ −79.75 (s); MS (EI) *m/z* (species, rel int) 273 (M^+, 88), 258 ($M^+ - CH_3$, 18), 228 ($M^+ - OEt$, 18), 58 (CH_2NMe_2, 100). HRMS Calcd for $C_{10}H_{22}F_3NO_2Si$: 273.1372. Found: 273.1360.

2c: viscous liquid; ^1H NMR ($CDCl_3$) δ 0.17 (s, 9H), 3.30 (s, 2H), 3.51 (s, 3H), 3.85 (s, 4H), 7.31 (m, 10H); ^{19}F NMR ($CDCl_3$) δ −77.36 (s); MS (EI) *m/z* 411 (M^+, 20), 380 ($M^+ - OMe$, 24), 320 ($M^+ - PhCH_2$, 10), 307 [$M^+ - (OMe + SiMe_3)$, 41], 91 ($PhCH_2$, 100).

2d (racemate): viscous liquid; ^1H NMR ($CDCl_3$) δ 0.15 (s, 9H), 1.37 (d, 3H,), 2.33 (q, 1H, $J = 2$ Hz), 3.70 (s, 3H), 3.80 (s, 4H), 7.30 (m, 10H); ^{19}F NMR ($CDCl_3$) δ −77.0 (s).

2f: viscous liquid; ^{19}F NMR ($CDCl_3$) δ −75.35, −75.51 (two peaks due to diastereomeric mixture); MS (EI) *m/z* (species, rel int) 375 (M^+, 15), 330 ($M^+ - OEt$, 20), 306 ($M^+ - CF_3$, 10), 284 ($M^+ - PhCH_2$, 28), 91 ($PhCH_2$, 100), 69 (CF_3, 10).

3a: mp 117−118 °C; IR (KBr) 3500−3000 (br, OH and NH) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.13 (t, 2H, $J = 8$ Hz), 2.62 (s, 6H), 3.19 (t, 2H, $J = 8$ Hz), 5.31 (br, s, 2H), 10.84 (br, s, 1H); ^{13}C NMR (DMSO-d_6) δ 29.2, 42.0, 51.2, 91.6 (q, $J_{C-C-F} = 31$ Hz), 125 (q, $J_{C-F} = 288$ Hz); ^{19}F NMR (DMSO-d_6) δ −79.74 (s). Some selected X-ray crystallographic data for **3a**: crystal system, triclinic; space group, *P*1; unit cell dimensions $a = 9.3685(7)$ Å, $b = 10.4988(8)$ Å, $c = 11.0937(8)$ Å, $\alpha = 94.525(1)°$, $\beta = 106.683(1)°$, $\gamma = 104.850(1)°$; $Z = 4$; $F(000) = 464$; crystal size = 0.10 × 0.20 × 0.35 mm; $R1 = 0.0521$, $wR2 = 0.1141$.

3b: mp 103−4 °C; IR (KBr) 3500−3000 (br, OH and NH) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.90 (s, 6H), 3.46 (s, 2H), 8.07 (br, s, 2H), 10.06 (br, s, 1H); ^{13}C NMR ($CDCl_3$) δ 45.0, 58.3, 90.3 (q, $J_{C-C-F} = 31$ Hz), 122.6 (q, $J_{C-F} = 289$ Hz); ^{19}F NMR ($CDCl_3$) δ −79.8 (s). Anal. Calcd for $C_5H_{11}ClF_3NO_2$: C, 28.65; H, 5.29; N, 6.68. Found: C, 28.48; H, 5.36; N, 6.66.

3c: mp 128−29 °C; IR (KBr) 3500−3000 (br, OH and NH) cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.25 (s, 2H), 4.45 (s, 4H), 5.20 (br, s, 2H), 7.27 (m, 10H), 8.30 (br, s, 1H); ^{19}F NMR ($CDCl_3$) δ −83.9 (s).

3d (racemate): mp 122−23 °C; IR (KBr) 3500−3000 (br, OH and NH) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.24 (d, 3H, $J = 6$H), 3.39 (q, 1H, $J = 2$ Hz)), 3.79 (s, 4H), 6.20 (br, s, 2H), 7.30 (m, 10H), 8.70 (br, s, 1H); ^{19}F NMR ($CDCl_3$) δ −81.20 (s).

3e (racemate): mp 131−32 °C; IR (KBr) 3500−3000 (br, OH and NH) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.37 (s, 6H), 2.95 (d, 2H, $J = 6$ Hz), 6.0o (br, s, 2H), 7.18 (m, 5H), 8.50 (br, s, 1H); ^{19}F NMR ($CDCl_3$) δ −79.48 (s).

3f: mp 109−10 °C; IR (KBr) 3500−3000 (br, OH and NH) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.00 (m, 4H), 3.19 (s, 2H), 3.93 (t, 1H, $J = 6$ Hz), 4.85 (s, 2H), 7.43 (m, 5H), 8.54 (br, s, 2H), 10.61 (br, s, 1H); ^{19}F NMR ($CDCl_3$) δ −81.2 (s). $[\alpha]^{22}_{586} = -34°$ ($c = 1$, DMF); %ee ∼95%. Anal. Calcd for $C_{13}H_{17}ClF_3NO_2$: C, 50.09; H, 5.50; N, 4.49. Found: C, 49.82; H, 5.55; N, 4.30.

Acknowledgment. This work was supported by the National Science Foundation (Grant CHE-9720365) and a NASA Idaho Space Consortium grant. We thank Dr. Gary Knerr and Dr. Ashwani Vij for mass spectra data and single crystal X-ray analysis, respectively.

JO991972W

(21) **)** (a) Gray, B. D.; Jeffs, P. W. *J. Chem. Soc., Chem. Commun.* **1987**, 1329−1330. (b) Bocchi, V.; Casnati, G.; Dossena, A.; Marchelli, R. *Synthesis* **1979**, 961−962.

(22) (a) Nelson, D. W.; O'Reilly, N. J.; Speier, J.; Gassman, P. G. *J. Org. Chem.* **1994**, *59*, 8157−8189. (b) Ramaiah, P.; Krishnamurti, R.; Praksh, G. K. S. *Organic Syntheses*; Wiley: New York, 1998; Collect. Vol. IX, pp 711−715.