An Approach to the Synthesis of *F*-Tertiary Amines

Ralph J. De Pasquale

PCR, Incorporated, Gainesville, Florida 32602

Received October 24, 1977

F-tertiary amines, industrially important fluids and biomedically important potential artificial blood candidates, can be prepared in high yields as sole products by treating >NCO– containing fluorinated precursors with SF_4/HF at moderate temperatures. Thus the amide $C_7F_{15}CON(CF_3)_2$ and cyclic imide $C_6F_5N(COCF_2)_2CF_2$ are completely converted to the amines $C_8F_{17}N(CF_3)_2$ and $C_6F_5N(CF_2CF_2)_2CF_2$ in 78 and 86% isolated yields, respectively, under appropriate reaction conditions. The consequence of structural variation on yield, reaction rate, and products is discussed.

F-Tertiary amines are commercially important[1] as evaporation coolants, hydraulic fluids, and dielectric fluids for transformers. Recent attention has been focused on fluorocarbons in biomedical applications as potential anesthetics,[2] and in particular *F*-tertiary amines as potential fluid oxygen/CO_2 transport agents in artificial blood.[3]

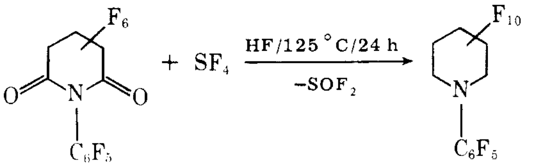
The titled compounds have been isolated from a variety of reactions,[4–7] none of which seem of general synthetic applicability due to low yields and broad product distributions. Their classical preparation[8] involves the electrochemical fluorination of the corresponding hydrocarbon derivative in HF. This method suffers from inconvenience, the inability to prepare unsaturated derivatives, and the difficulty of pure component isolation as well as the disadvantages mentioned above.

Thus, general routes to *F*-tertiary amines using ordinary laboratory equipment are essentially nonexistent, and as a consequence a structual variety of these compounds is inaccessible to experimentalists. These factors prompt this report which describes the preparation of several titled compounds as sole products from the reaction between substrates containing >NCO– groups with SF_4/HF under moderate conditions.

Results and Discussion

The *F*-amide I and imide II[9] were treated with SF_4 in HF in a stainless steel autoclave to afford the corresponding tertiary amines III and IV in 78 and 86% isolated yields, respectively.

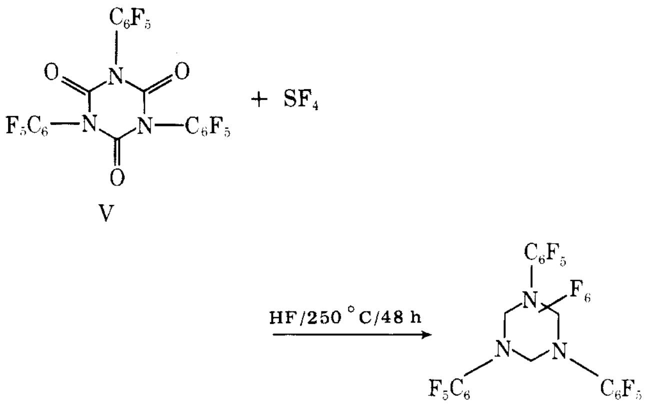
$$\underset{\text{I}}{C_7F_{15}CON(CF_3)_2} + SF_4 \xrightarrow[-SOF_2]{HF/150\,^{\circ}C/18\,h} \underset{\text{III}}{C_7F_{15}CF_2N(CF_3)_2}$$



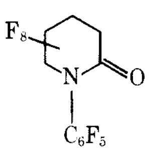
II IV

Crude reaction mixtures were clear, tar-free, and colorless after degassing (–HF, SF_4, SOF_2); VPC showed >98% conversion of the starting materials to the tertiary amines as sole product; i.e., the reactions are essentially quantitative. This is in sharp contrast with similar treatment of hydrocarbon *N,N′*-dialkylamides and related materials which afford low yields[10] of desired products and considerable tarring.[11] Presumably, these yield differences reflect the kinetic stability of the fluorocarbon reactants and products.

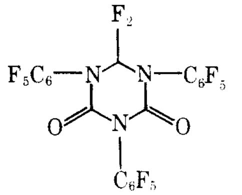
Under more forcing conditions the isocyanurate V[9] is partially converted (10%) to VI in a surprisingly clean reaction (>95% yield). In a similar partial conversion experiment of II → IV (85 °C/15 h/40% conversion) only product and reactant were detected; intermediate lactam VII was not observed. From consideration[12] of the proposed mechanism and the metastable intermediates, i.e., $R_fC(OH)FNR_f{}'_2$ and $R_fC(OSF_3)FNR_f{}'_2$, of the reaction, it is reasonable to assume that VII (and similarly VIII) intervenes in their respective schemes. The relative rates of reaction of these substrates must decrease in the order VII > II > V and as a conservative estimate span four orders of magnitude.



VI

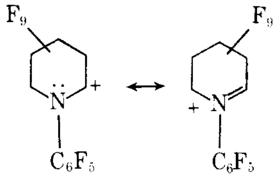


VII



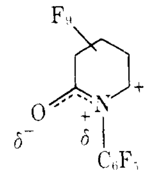
VIII

To digress briefly, hydrocarbon amides (DMF) show a high degree of C–N bond order as evidenced by restricted rotation about the C–N bond; as expected, substitution by an electronegative atom on nitrogen (F for CH_3) decreases[13] the bond order significantly. Even though fluorinated acyclic amide I is freely rotating 25°, rate differences between the cyclic fluorinated derivatives II and VII suggest that $-N\overset{\cdot\cdot}{-}C\overset{\cdot\cdot}{-}O$ interaction cannot be ignored. As positive charge is generated in the rate-determining step, the intermediate and consequently its transition state derived from VII must be of lower energy than those derived from II, i.e.,



is more stable than

0022-3263/78/1943-1727$01.00/0



Rate differences presumably are not attributable to ground-state energies since bond energy estimates indicate that VII is more stable than II. Thus, it is suspected that the rate differences implicate an additive destabilizing effect of an >NCO– resonance interaction adjacent to a carbocation center in the intermediate forming transition state. For comparative purposes the relative rate of SF_4 reaction between II and one of a series of reported[14] fluorinated esters, $C_7F_{15}CO_2CH_2C_2F_5$, was measured in a competitive experiment and found to be $k(\text{II})/k(\text{ester}) = 1.2$ (85 ± 2 °C).

It is notable that treatment of the linear imide IX[9] with SF_4/HF under relatively mild reaction conditions afforded products exclusively resulting from acyl–nitrogen bond fission. The azaolefin product X is extremely moisture sensitive and hydrolyzes to the amide XI in solution or neat.

$$\underset{\text{IX}}{(C_3F_7CO)_2NC_6F_5} + SF_4 \xrightarrow[-SOF_2]{HF/85\ ^\circ C/15\ h} \underset{\text{X (73\%)}}{C_3F_7CF{=}NC_6F_5} + C_3F_7COF$$

$$\text{X} \xrightarrow{H_2O} \underset{\text{XI}}{C_3F_7CONHC_6F_5}$$

Product and reactivity differences between cyclic (II) and linear (IX) imide may be due to a preferred preliminary reaction between IX and HF affording *F*-butyryl fluoride and amide XI which subsequently is converted to X by SF_4 in HF in a relatively facile reaction. Analogous HF induced heterolysis of hydrocarbon[15] or fluorocarbon[16] anhydrides is well documented.

Even though the above reactions have not been subjected to extensive experimental scrutiny, there is no apparent reason why a variety of *F*-tertiary amines derived from *F*-(*N*,*N*-dialkylamides) or *F*-(N-substituted) medium sized cyclic imides could not be prepared by this method.

Experimental Section

General. Vapor phase chromatographic analysis was performed on a Hewlett-Packard Model 700 instrument using an 8 ft × 0.25 in. 15 or 35% PFO-XR on Gas-Chrom R 60–80 mesh column. Infrared spectra were recorded on a Perkin-Elmer Infracord spectrometer. ^{19}F NMR spectra were recorded on a Varian XL-100 spectrometer at 94.1 MHz. The mass spectra were recorded on Model 14-107 Bendix time of flight spectrometer.

Materials. II, V, and IX were prepared according to published procedures.[9] *F*-Azapropene was prepared by static pyrolysis (250–270 °C) of carboxynitroso rubber (C_2F_4, CF_3NO, $HO_2C(CF_2)_3NO$ terpolymer). HF, SF_4, and *F*-octanoyl chloride were supplied by PCR, Inc., and were used without further purification.

Preparation of I. Bis(bis(trifluoromethyl)amino)mercury was prepared from *F*-azapropene according to a literature procedure.[17] This organomercurical (8.7 g, 0.017 mol) was frozen at −183 °C; then *F*-octanoyl chloride (14.9 g, 0.0344 mol) was rapidly added in an atmosphere of nitrogen. The mixture was allowed to warm to 25 °C and maintained at that temperature with stirring for 18 h. At that time the precipitated mercuric chloride was separated by pressure filtration and washed with Freon-113 (3 × 5 mL). Distillation of the resulting mixture gave the titled compound, bp 52–55 °C (12 mm) (11.6 g, 61% yield). The amide was protected from atmospheric moisture. VPC analysis showed <1% impurities: IR (film) 5.6, 7.4, 8.2, 8.7, 9, 9.5, 11, 11.15, 12.95, 14.1 μm; ^{19}F NMR (CCl_4, CF_3CO_2H external) −22.1 (t, 6), 4.1 (t of t, 3), 38.3 (m, 2), 43.1 (m, 9), 44.7 (m, 4), 48.9 (m, 2) ppm.

Anal. Calcd for $C_{10}F_{21}NO$: C, 21.8; N, 2.6. Found: C, 21.6; N, 2.8.

Preparation of III. A 300-mL stainless steel autoclave equipped with a 3000 psi bursting disk was charged with I (8.7 g, 0.016 mol). The vessel was cooled to −183 °C and HF (anhydrous, 40 g) and SF_4 (23.8 g, 0.220 mol) were introduced by vacuum techniques. The autoclave was heated with rocking at 150 °C for 18 h, cooled to 25 °C, vented to atmospheric pressure slowly in a hood (SF_4 and SOF_2 are toxic), and subjected to aspirator vacuum. The contents of the autoclave were diluted with Freon-113 (50 mL) and transferred to a polyethylene flask containing NaF to scavenge residual HF. After overnight storage the colorless solution was decanted and distilled; the fraction bp 64–65 °C (22 mm) (7.1 g, 78% yield) was the desired amine. VPC analysis of the crude reaction mixture in Freon 113 showed >99% conversion of starting material to the sole product. The isolated amine showed the following spectral properties: IR (neat) 7.5, 8.4, 9.2, 9.4, 10.1, 10.9, 13.75, 14.1 μm; ^{19}F NMR (neat, ext. CF_3CO_2H) −24 (t of t, 6), 5 (t, 3), 13.5 (m, 2), 44.9 (m, 10), 49.5 (m, 2) ppm.

Anal. Calcd for $C_{10}F_{23}N$: C, 21.0; N, 2.5. Found: C, 20.7; N, 2.6.

Preparation of IV. In a manner analogous to the above procedure, II (10.0 g, 0.0266 mol), HF (25 g), and SF_4 (32.6, 0.302 mol) were charged into a 300-mL stainless steel autoclave and heated with rocking at 125 °C (24 h). Typical workup afforded IV, bp 93–95 °C (40 mm) (9.5 g, 86% yield), which was >99% pure by VPC: IR (neat) 6.05, 6.6, 7.3, 7.55, 7.8, 7.95, 8.25, 8.4, 8.8, 8.9, 9.3, 9.52, 10.4, 11.15, 13.6 μm; ^{19}F (neat, ext. CF_3CO_2H), 15.6 (m, 4), 55.8 (m, 4), 56.3 (m, 2), 65.0 (m, 2), 73.0 (t of t, 1), 84.7 (m, 2) ppm; MS (70 eV) *m/e* 431, 412, 231, 167, 131, 100, 69.

Anal. Calcd for $C_{11}F_{15}N$: C, 30.6; N, 3.24. Found: C, 30.8; N, 3.47.

Reaction between V and SF_4. V (1.0 g, 1.6 mmol), HF (10 mL), and SF_4 (20.2 g, 0.188 mol) were charged into a 100-mL stainless steel autoclave and heated with rocking for 48 h at 250 °C. Usual workup afforded 1.0 g of a solid, mp 108–140 °C. VPC analysis showed a 1:9 ratio of a sole product to starting material (as a mixture with V): IR (Nujol) 8.25 μm (CF_2); ^{19}F NMR (aetone, ext. CF_3CO_2H) −27 ppm (CF_2); MS (70 eV)–VPC *m/e* 693, 674, 231, 167, 69.

Reaction between IX and SF_4. IX (9.0 g, 0.015 mol), HF (25 mL), and SF_4 (25.0 g, 0.232 mol) were charged in a 300-mL stainless steel autoclave and heated with rocking at 85 °C/15 h. The vessel was cooled to 25 °C and vented through a 3 × 24 in. steel pipe packed with anhydrous NaF pellets and the volatiles were collected at −183 °C and transferred into a gas cylinder. VPC of the volatiles showed a SF_4/SOF_2 product ratio of 8:1; the product was collected by VPC and showed to be C_3F_7COF by comparison of its IR spectrum and VPC retention time to that of an authentic sample. The material remaining in the autoclave was worked up as usual; distillation afforded the azaolefin, X: bp 85–87 °C (41 mm); IR (neat) 5.7, 6.6, 7.4, 8.1, 8.2, 8.8, 9.35, 10, 10.6, 11, 12.1, 13.35 μm; ^{19}F NMR (CCl_4, ext. CF_3CO_2H) −42.9 (m, 1), 3.1 (t, 3), 39.6 (q of d, $J = 9$ and 12.5 Hz, 2), 49 (d, 2), 69.2 (m, 2), 78.5 (m, 1), 84.3 (m, 2).

Anal. Calcd for $C_{10}F_{13}N$: C, 31.5; N, 3.67. Found: C, 31.6; N, 3.6.

X (1.0 g) was dissolved in 25 mL of Et_2O and this solution was slurried with 25 mL of H_2O overnight. The Et_2O layer was separated, dried (Na_2SO_4), and concentrated leaving 0.98 g of the amide XI.[9]

Relative Reaction Rate. The ester $C_7F_{15}CO_2CH_2C_2F_5$ (0.7101 g, 1.301 mmol), imide II (0.2378 g, 0.6140 mmol), and Freon-E4 (standard, 0.5104 g) were charged into a 30-mL stainless steel autoclave along with HF (7.0 g) and SF_4 (2.21 g, 20.05 mmol). The vessel was heated with rocking at 85 ± 2 °C for 15 h, then cooled and worked up in the usual manner. VPC indicated that 0.541 mol of ester and 0.206 mmol of imide remained. This corresponds[14] to $k(\text{imide})/k(\text{ester}) = 1.24$ (not statistically corrected).

Acknowledgments. This work was partially funded by the Air Force under Contract No. F33615-70-C-1343. Thanks are due to Drs. W. S. Brey and R. J. Hanrahan of the University of Florida for obtaining and interpreting the NMR and mass spectral data, respectively.

Registry No.—I, 58955-22-9; II, 58955-21-8; III, 58966-63-5; IV, 58955-19-4; V, 58955-23-0; VI, 58955-20-7; IX, 65465-73-8; X, 654-74-9; bis(bis(trifluoromethyl)amine)mercury, 7276-63-3; *F*-octanoyl chloride, 335-64-8.

References and Notes

(1) R. D. Chambers, "Fluorine in Organic Chemistry", Wiley, New York, N.Y., 1973, p 243.

(2) D. D. Denson, E. T. Uzeno, R. T. Simon, Jr., and H. M. Peters, "Biochemistry

Involving Carbon-Fluorine Bonds", R. Filler, Ed., American Chemical Society Symposium Series 28, Washington, D.C., 1976, pp 190–208.
(3) R. E. Banks and M. G. Barlow, "Fluorocarbon and Related Chemistry", The Chemical Society, London, Vol. 1, 1971, pp 98–99; Vol. 2, 1974, p 204; Vol. 3, 1976, pp 207–209; see also L. C. Clark, Jr., E. P. Wesseler, S. Kaplan, C. Emory, R. Moore, and D. Denson, ref 2, pp 135–169.
(4) R. E. Banks, K. Mullen, and G. E. Williamson, *J. Chem. Soc. C*, 2608 (1968); R. E. Banks, K. Mullen, W. J. Nicholson, C. Oppenheim, and A. Prakash, *J. Chem. Soc., Perkin Trans. 1*, 1098 (1972); R. E. Banks, A. J. Parker, M. J. Sharp, and G. F. Smith, *ibid.*, 5 (1973); R. E. Banks, R. N. Haszeldine, and D. L. Hyde, *J. Chem. Soc., Chem. Commun.*, 413 (1967).
(5) V. S. Plashkin, G. P. Tataurov, and S. V. Sokolov, *Zh. Obshch. Khim.*, **36**, 1708 (1966); *Chem. Abstr.*, **66**, 55354m (1967).
(6) K. E. Peterman and J. M. Shreeve, *Inorg. Chem.*, **14**, 1223 (1975); R. L. Kirchmeier, U. I. Lasouris, and J. M. Shreeve, *ibid.*, **14**, 592 (1975).
(7) R. H. Ogden, *J. Chem. Soc. C*, 2920 (1971).
(8) For reviews, see J. Burdon and J. C. Tatlow, "Advances in Fluorine Chemistry", M. Stacey, J. C. Tatlow, and A. G. Sharpe Ed., Academic Press, New York, N.Y., 1960, p 241; S. Nagase, *Fluorine Chem. Rev.*, **1**, 77 (1967).
(9) R. J. De Pasquale, *J. Fluorine Chem.*, **8**, 311 (1976).
(10) W. R. Hasek, W. C. Smith, and V. A. Englehardt, *J. Am. Chem. Soc.*, **82**, 543 (1960).
(11) F. S. Fawcett and W. A. Sheppard, *J. Am. Chem. Soc.*, **87**, 4344 (1965).
(12) For a recent review on SF_4 chemistry, see G. A. Boswell, Jr., W. C. Ripka, R. M. Scribner, and C. W. Tullock, *Org. React.*, **21**, 1 (1974).
(13) J. Cantacuzene, J. Leroy, R. Jantzen, and F. Dudragne, *J. Am. Chem. Soc.*, **94**, 7924 (1972).
(14) R. J. De Pasquale, *J. Org. Chem.*, **38**, 3025 (1973).
(15) K. Fredenhagen, *Z. Phys. Chem., Abt. A*, **164**, 176 (1933).
(16) G. A. Olah and S. J. Kuhn, *J. Org. Chem.*, **26**, 237 (1961).
(17) J. A. Young, W. S. Durrell, and R. D. Dresdner, *J. Am. Chem. Soc.*, **84**, 2105 (1962).

Energies of the Cycloalkyl and 1-Methylcycloalkyl Free Radicals by the Decarbonylation Method

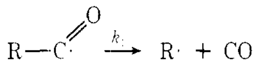
Douglas E. Applequist* and James H. Klug

Department of Chemistry, University of Illinois, Urbana, Illinois 61801

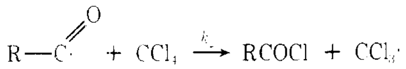
Received December 5, 1977

The relative rates of formation of cycloalkyl and 1-methylcycloalkyl free radicals by decarbonylation of the corresponding acyl radicals have been measured for ring sizes 3–6. The relative rates at 135 °C for cycloalkyl radicals in descending order of ring size from 6 to 3 are 0.268, 0.316, 0.0795, and 0.0121. For the 1-methylcycloalkyl radicals of the same ring sizes they are 14.1, 11.1, 1.18, and 0.542. The relationships of these values to other measures of cycloalkyl radical stabilities are presented and discussed.

The first quantitative measurements of the energies of simple bridgehead radicals were reported by Applequist and Kaplan in 1965.[1] Their method was to measure by analysis of products the competition between decarbonylation of acyl radicals (eq 1) and capture by carbon tetrachloride (eq 2). The



$$R\text{—}\overset{O}{\overset{\|}{C}}\cdot \xrightarrow{k_1} R\cdot + CO \qquad (1)$$



$$R\text{—}\overset{O}{\overset{\|}{C}}\cdot + CCl_4 \xrightarrow{k_2} RCOCl + CCl_3\cdot \qquad (2)$$

rate for eq 2 was assumed constant (independent of R), for which supporting facts and arguments were presented. The acyl radicals were generated from the corresponding aldehydes by reaction with di-*tert*-butyl peroxide. Values of k_1/k_2 were found to correlate with known values of the dissociation enthalpies ($D_{R\text{-}H}$) of simple alkanes to form alkyl radicals, and this correlation was used to propose values of $D_{R\text{-}H}$ for the bridgehead position studies of the following radicals: 90.1 kcal for 1-adamantyl, 91.0 kcal for 1-bicyclo[2.2.2]octyl, and 97.7 kcal for 1-norbornyl.

Subsequently, three groups have investigated the same bridgehead series using a better-known method, the rates of decomposition of *tert*-butyl peresters (eq 3).[2–4] In Table I are

$$RCO_2O\text{-}t\text{-}Bu \rightarrow R\cdot + CO_2 + t\text{-}BuO\cdot \qquad (3)$$

shown their results in the form of relative rates, together with the earlier k_1/k_2 values from decarbonylation. Viewed in this form, the results of the two approaches are strikingly similar, which supports the validity of both methods. The adamantyl, *tert*-butyl, and 1-bicyclo[2.2.2]octyl radicals have roughly the same stability, while the 1-norbornyl radical is destabilized. Some authors[2,3] have attempted to extract evidence for geometric destabilization of even the adamantyl and bicyclo[2.2.2]octyl radicals by factoring out the inductive stabilization of the perester transition states leading to these radicals, but the meaning of such geometric destabilization is unclear now that the geometry of the *tert*-butyl radical is known to be pyramidal and probably close to tetrahedral.[5,6] The point remains, however, that the perester transition states are subject to inductive effects and therefore may be polarized to such an extent that the rates may to some degree reflect carbonium ion stability in addition to radical stability. The extent of such influences in the decarbonylation transition states is entirely unknown, but by the aforementioned technique of empirical correlation with known $D_{R\text{-}H}$ values any polar contribution may be automatically canceled.[1]

In addition to the tenuous advantage of the decarbonylation method in avoiding polar kinetic effects, the method has a large advantage over perester thermolysis in that the latter changes mechanism to a one-bond (–O–O–) cleavage when the alkyl radical is of high energy, and it seems likely that the 1-norbornyl radical is about at (if not beyond) the limit of the range of radicals that can be studied this way.[4,7] The decarbonylation method has been extended to the less stable 1-triptycyl radical[8] ($D_{R\text{-}H}$ = 98.3 kcal) and even further in the present work (vide infra).

Other kinetic approaches to the measurement of bridgehead free-radical energies have also been employed and deserve mention here.

Rüchardt[9–14] has measured the rates of the unimolecular decompositions of symmetrical azo compounds, RN=NR. When the R groups were the bridgehead radicals listed in Table I, the rates at 300 °C in benzene were, relative to each other, much like those in the perester thermolysis: the relative rates of 1-adamantyl/1-bicyclo[2.2.2]octyl/1-norbornyl were (1.00):0.36:0.071.[15] The interpretation is clouded, however, by the fact that even the 1-adamantyl case is slower than the *tert*-butyl case (2,2-azoisobutane) by a factor of 0.02.[15] Rüchardt concluded that the bridgehead cases are slower because the transition state in the endothermic azo decomposition is more advanced so that planarity at the radical center is more closely approached.[9] But to explain the similar relative rates

0022-3263/78/1943-1729$01.00/0 © 1978 American Chemical Society