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An efficient high-yield synthesis for perfluorinated tertiary alkyl amines

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Abstract

We wish to report a high-yield synthesis of perfluorinated tertiary amines from their hydrocarbon analogues by direct fluorination. Yields up to 70%, with high purities, have been obtained from certain tertiary amines. This technique will likely develop into a new general method for producing perfluorinated amines.

Keywords: Direct fluorination; Perfluorinated amines; Perfluorotriethylamine; Perfluorotri-*n*-propylamine; Perfluorotri-*n*-butylamine; Perfluorotri-*n*-pentylamine; Perfluoro-*N,N,N′,N′*-tetramethylethylenediamine

1. Introduction

Perfluorinated amines have been known for quite some time, with the first syntheses being reported in 1949 [1]. Tertiary amines were one of the first classes of compounds to be successfully fluorinated using the Simons electrochemical fluorination process [2], and have also been perfluorinated using elemental fluorine [3,4] and cobalt trifluoride [5]. Commercially, perfluorinated amines have been found to be of use in biomedical applications as oxygen carriers in artificial blood [6,7], anesthetics [8], thermal shock test liquids for semiconductors, evaporation coolants, hydraulic fluids, and dielectric fluids for transformers [9].

The electrochemical process is commonly used to produce perfluorinated amines commercially. However, yields of the pure perfluorinated products are typically fair to poor (7–25%) [10]. The desired perfluorinated product is often obtained in a mixture of many partially fluorinated and fragmented, perfluorinated by-products. Identified by-products arise from cleavage, alkylation, isomerization, dimerization, coupling, and cyclization reactions [11]. Separation of the desired product from these by-products is often difficult and very costly.

In the past, we have also been successful at fluorinating tertiary amines. The LaMar fluorination process was used, as recently as 1988, to fluorinate 1,2,2,6,6-pentamethylpiperidine [12]. However, the LaMar process suffered from the same drawbacks encountered by ECF. Yields were low (19%) and many fragmentation by-products were observed.

Using continuous, solution-phase fluorination reaction technology, i.e. the Exfluor-Lagow fluorination process, we have successfully designed a general, high-yield synthesis of perfluorinated tertiary amines, beginning with the hydrocarbon analogues as starting materials. These compounds are reacted with elemental fluorine in chlorofluorocarbon solvents, such as 1,1,2-trichlorotrifluoroethane (Freon® 113). The advantages of this process over the previous LaMar fluorination process and ECF is three-fold. The solvent allows for better thermodynamic relaxation of the substrate to be fluorinated, concentrations of fluorine can be better controlled using precise mass-flow controllers, and the rate of addition of the substrate can be controlled by the use of a metering pump.

2. Results and discussion

Using the Exfluor-Lagow fluorination process, simple and complex tertiary amines have been fluorinated from low to high yields. Both a general scheme (Scheme 1) and a summary (Table 1) of the performed reactions are given.

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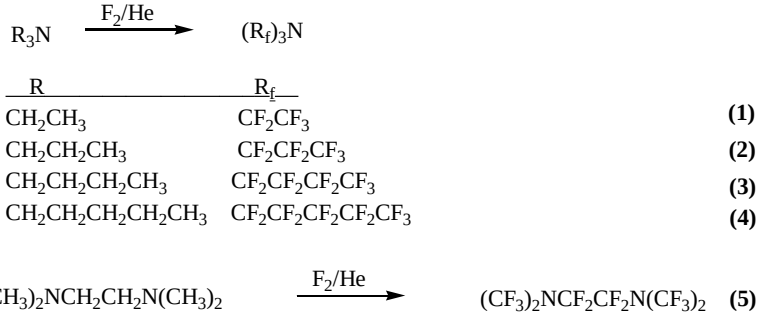

Scheme 1.

Table 1
Yields of perfluorinated amines

Compounds	Reaction temperature (°C)	Yield (%)
$N(C_2F_5)_3$	5	75.2
$N(C_3F_7)_3$	10	72.5
$N(C_4F_9)_3$	15	65.1
$N(C_5F_{11})_3$	20	40.0
$N_2(CF_3)_4(CF_2)_2$	5	20.0

The smaller an alkyl chain is, the lower the temperature needs to reduce the tendency of the fluorination reaction to form unwanted by-products. The concentrations of the fluorine must be initially kept low, by having a high dilution rate of N_2, to slow the fluorination process enough to preserve the carbon–nitrogen bond. As the molecules incorporate more fluorine, more rigorous conditions are required to drive the fluorination to completion. This is achieved by increasing the fluorine concentration through dropping the rate of addition of N_2.

These reactions proceed on a relatively short time scale compared to other direct fluorinations. Care should be taken not to allow the reaction to proceed 1 h past the end of the substrate addition, because allowing the fluorination to proceed beyond this time increases polymerization and cleavage, and produces many other by-products. Once finished, the products can be separated first by simple distillation from the solvent and then vacuum distillation from the other by-products. This bypasses the need for tedious methods of separation and purification that have been necessary by the use of the Simons electrochemical fluorination.

Obtained yields for these tertiary amines are, on average, 20% higher than have been previously obtained by the Simons electrochemical fluorination process and much higher than previously reported for other direct fluorination techniques [10,13]. We observed a general decrease in percent yield as the lengths of the alkyl chains were increased. However, obtained products were very pure. The typical fragmentation products seen with electrochemical fluorination were not observed under these conditions. With further experimentation, this method should be expandable to allow the commercial production of perfluorotertiary amines by the use of solution-phase direct fluorination.

3. Experimental

3.1. General

Triethylamine was purchased from Aldrich (Milwaukee, WI). Tri-*n*-propylamine, tri-*n*-butylamine, and tri-*n*-propylamine were purchased from Alfa Aesar (Ward Hill, MA). Tetramethylethylenediamine was taken from laboratory stock.

Low resolution mass spectrometry was performed on a MAT TSQ-70 spectrometer. High resolution mass spectrometry was performed on a VG analytical ZAB2-E mass spectrometer. $^{13}C\{^{19}F\}$ and ^{19}F NMR spectra were taken on a Varian Unity Plus-300 nuclear magnetic resonance spectrometer. $^{13}C\{^{19}F\}$ NMR spectra were recorded at 75 MHz using C_6D_6 as the lock solvent and internal reference. ^{19}F NMR spectra were recorded at 282 MHz using C_6D_6 as the lock solvent and $CFCl_3$ as the internal reference. ^{19}F NMR chemical shifts are given in ppm with negative values indicating resonances at higher frequencies. Direct fluorinations were performed in a similar manner to the reactions that have been previously described in the literature [15].

Initial care should be taken to avoid exposure to reaction products, as some partially fluorinated amine products have been known to be extremely toxic.

3.2. "Direct fluorination of triethylamine" "perfluorotriethylamine (*1*)"

The fluorination of triethylamine was carried out in a solution-phase fluorination reactor that has been described previously in the literature [14]. The reactor was filled with 350 ml of 1,1,2-trichlorotrifluoroethane (Freon® 113) and 30 g of NaF (0.714 mol), then cooled to 5 °C. The reactor was then purged with N_2 (200 cm^3/min) for 1 h. Triethylamine (2.26 g, 2.23 mmol) was dissolved in 150 ml of Freon® 113 inside a round bottom flask, and then pumped into the purged reactor at a rate of 25 ml/h. During the addition of triethylamine to the reactor, a N_2/F_2 mixture was bubbled through the reactor at a rate of 200, and 50 cm^3/min, respectively. After the solution containing triethylamine was completely pumped into the reactor, the N_2/F_2 flow rate and the temperature was kept constant for an additional 60 min.

The flow rate was changed to 50, and 0 cm^3/min N_2/F_2, respectively, and the reactor was allowed to purge for 4 h. The solution was then filtered to remove any NaF or $NaHF_2$ and the solvent was distilled off.

Distillation of the product (72 °C/760 mmHg) gave a clear, colorless liquid that was analyzed as $N(CF_2CF_3)_3$. CIMS (positive mode) *m/z* (rel. int.) 352 $[M - F]^+$ (36.42). ^{19}F NMR (282 MHz, $CFCl_3$): δ −91.262 (q, 6F, J = 2.5 Hz, NCF_2CF_3), −83.754 (t, 9F, J = 2.5 Hz, NCF_2CF_3). $^{13}C\{^{19}F\}$ NMR (75 MHz, C_6D_6): δ 111.991 (s, C-1), 117.549 (s, C-2).

3.3. "Direct fluorination of tri-n-propylamine" "perfluorotri-n-propylamine (**2**)"

The fluorination of tri-*n*-propylamine was carried out in a solution-phase fluorination reactor that has been described previously in the literature [14]. The reactor was filled with 350 ml of 1,1,2-trichlorotrifluoroethane (Freon® 113) and 30 g of NaF (0.714 mol), then cooled to 10 °C. The reactor was then purged with N_2 (200 cm^3/min) for 1 h. Tri-*n*-propylamine (2.33 g, 0.0162 mol) was dissolved in 150 ml of Freon® 113 inside a round bottom flask, and then pumped into the purged reactor at a rate of 25 ml/h. During the addition of tri-*n*-propylamine to the reactor, a N_2/F_2 mixture was bubbled through the reactor at a rate of 200, and 50 cm^3/min, respectively. After the solution containing tri-*n*-propylamine was completely pumped into the reactor, the N_2/F_2 flow rate and the temperature were kept constant for an additional 60 min. The flow rate was changed to 50, and 0 cm^3/min N_2/F_2, respectively, and the reactor was allowed to purge for 4 h. The solution was then filtered to remove any NaF or $NaHF_2$ and the solvent was distilled off.

Vacuum distillation of the product (60 °C/100 mmHg) gave a clear, colorless liquid that was analyzed as $N(CF_2CF_2CF_3)_3$. CIMS (negative mode) *m/z* (rel. int.) 352 $[M - \text{perfluoroalkyl}]^-$ (100.00); 483 $[M - 2F]^{2-}$ (33.62). Elemental compositions were studied by high resolution mass spectroscopy in chemical ionization mode. Results were consistent with NC_6F_{14} (calculated: 351.980720; found: 351.981318), NC_9F_{19} (calculated: 482.972736; found: 482.971305). ^{19}F NMR (282 MHz, $CFCl_3$): δ −123.520 (s, 6F, $NCF_2\mathbf{CF_2}CF_3$), −86.244 (s, 6F, $N\mathbf{CF_2}CF_2CF_3$), −83.731 (s, 9F, $NCF_2CF_2\mathbf{CF_3}$). $^{13}C\{^{19}F\}$ NMR (75 MHz, C_6D_6): δ 108.215 (s, C-1), 113.926 (s, C-2), 117.441 (s, C-3).

3.4. "Direct fluorination of tri-n-butylamine" "perfluorotri-n-butylamine (**3**)"

The fluorination of tri-*n*-butylamine was carried out in a solution-phase fluorination reactor that has been described in the literature [14]. The reactor was filled with 350 ml of 1,1,2-trichlorotrifluoroethane (Freon® 113) and 30 g of NaF (0.714 mol), then cooled to 15 °C. The reactor was then purged with N_2 (200 cm^3/min) for 1 h. Tri-*n*-butylamine (2.21 g, 0.0119 mol) was dissolved in 150 ml of Freon® 113 inside a round bottom flask, and then pumped into the purged reactor at a rate of 25 ml/h. During the addition of tri-*n*-butylamine to the reactor, a N_2/F_2 mixture was bubbled through the reactor at a rate of 200, and 50 cm^3/min, respectively. After the solution containing tri-*n*-butylamine was completely pumped into the reactor, the N_2/F_2 flow rate and the temperature were kept constant for an additional 60 min. The flow rate was changed to 50, and 0 cm^3/min N_2/F_2, respectively, and the reactor was allowed to purge for 4 h. The solution was then filtered to remove any NaF or $NaHF_2$ and the solvent was distilled off.

Vacuum distillation of the product (75 °C/40 mmHg) gave a clear, colorless liquid that was analyzed as $N(CF_2CF_2CF_2CF_3)_3$. CIMS (negative mode) *m/z* (rel. int.) 452 $[M - \text{perfluoroalkyl}]^-$ (100.00); 633 $[M - 2F]^{2-}$ (14.30). Elemental compositions were studied by high resolution mass spectroscopy in chemical ionization mode. Results were consistent with NC_8F_{18} (calculated: 451.974333; found: 451.974508), $NC_{12}F_{25}$ (calculated: 632.963155; found: 632.964237). ^{19}F NMR (282 MHz, $CFCl_3$): δ −128.231 (s, 6F, $NCF_2CF_2\mathbf{CF_2}CF_3$), −119.674 (s, 6F, $NCF_2\mathbf{CF_2}CF_2CF_3$), −85.204 (s, 6F, $N\mathbf{CF_2}CF_2CF_2CF_3$), −82.880 (s, 9F, $NCF_2CF_2CF_2\mathbf{CF_3}$). $^{13}C\{^{19}F\}$ NMR (75 MHz, C_6D_6): δ 108.628 (s, C-1), 109.780 (s, C-2), 114.520 (s, C-3), 117.346 (s, C-4).

3.5. "Direct fluorination of tri-n-pentylamine" "perfluorotri-n-pentylamine (**4**)"

The fluorination of tri-*n*-pentylamine was carried out in a solution-phase fluorination reactor that has been described previously in the literature [14]. The reactor was filled with 350 ml of 1,1,2-trichlorotrifluoroethane (Freon® 113) and 30 g of NaF (0.714 mol), then cooled to 20 °C. The reactor was then purged with N_2 (200 cm^3/min) for 1 h. Tri-*n*-pentylamine (1.95 g, 8.59 mmol) was dissolved in 150 ml of Freon® 113 inside a round bottom flask, and then pumped into the purged reactor at a rate of 25 ml/h. During the addition of tri-*n*-pentylamine to the reactor, a N_2/F_2 mixture was bubbled through the reactor at a rate of 200, and 50 cm^3/min, respectively. After the solution containing tri-*n*-pentylamine was completely pumped into the reactor, the N_2/F_2 flow rate and the temperature were kept constant for an additional 60 min. The flow rate was changed to 50, and 0 cm^3/min N_2/F_2, respectively, and the reactor was allowed to purge for 4 h. The solution was then filtered to remove any NaF or $NaHF_2$ and the solvent was distilled off.

Vacuum distillation of the product (80 °C/15 mmHg) gave a clear, colorless liquid that was analyzed as $N(CF_2CF_2CF_2CF_2CF_3)_3$. CIMS (negative mode) *m/z* (rel. int.) 552 $[M - \text{perfluoroalkyl}]^-$ (100.00); 783 $[M - 2F]^{2-}$ (7.69). Elemental compositions were studied by high resolution mass spectroscopy in chemical ionization mode. Results were consistent with $NC_{10}F_{22}$ (calculated: 551.967946; found: 551.966807), $NC_{15}F_{31}$ (calculated: 982.953575;

found: 982.953317). ^{19}F NMR (282 MHz, $CFCl_3$): δ −127.303 (s, 6F, $NCF_2CF_2CF_2\mathbf{CF_2}CF_3$), −124.257 (s, 6F, $NCF_2CF_2\mathbf{CF_2}CF_2CF_3$), −118.835 (s, 6F, $NCF_2\mathbf{CF_2}CF_2$-CF_2CF_3), −85.005 (s, 6F, $N\mathbf{CF_2}CF_2CF_2CF_2CF_3$), −82.684 (s, 9F, $NCF_2CF_2CF_2CF_2\mathbf{CF_3}$). ^{13}C{^{19}F} NMR (75 MHz, C_6D_6): δ 108.621 (s, C-1), 110.208 (s, C-2), 110.411 (s, C-3), 114.549 (s, C-4), 117.223 (s, C-5).

*3.6. "Direct fluorination of N,N,N′, N′-tetramethylethylenediamine (TMEDA)" "perfluoro-N,N,N',N'-tetramethylethylenediamine (TMEDA) (**5**)"*

The fluorination of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) was carried out in a solution-phase fluorination reactor that has been described previously in the literature [14]. The reactor was filled with 350 ml of 1,1,2-trichlorotrifluoroethane (Freon® 113) and 30 g of NaF (0.714 mol), then cooled to 5 °C. The reactor was then purged with N_2 (200 cm^3/min) for 1 h.

TMEDA (1.65 g, 0.0142 mol) was dissolved in 150 ml of Freon® 113 inside a round bottom flask, and then pumped into the purged reactor at a rate of 25 ml/h. During the addition of TMEDA to the reactor, a N_2/F_2 mixture was bubbled through the reactor at a rate of 200, and 50 cm^3/min, respectively. After the solution containing TMEDA was completely pumped into the reactor, the N_2/F_2 flow rate was reduced to 10/10 for an additional 16 h and the temperature was held constant. The flow rate was changed to 50, and 0 cm^3/min N_2/F_2, respectively, and the reactor was allowed to purge for 4 h. The solution was then filtered to remove any NaF or $NaHF_2$ and the solvent was distilled off.

Vacuum distillation of the product (90 °C/760 mmHg) gave a clear, colorless liquid that was analyzed as $(CF_3)_2NCF_2CF_2N(CF_3)_2$. CIMS (positive mode) *m/z* (rel. int.) 385 $[M - F]^-$ (100.00); 202 $[M - CF_2N(CF_3)_2]^-$ (72.36). ^{19}F NMR (282 MHz, $CFCl_3$): δ −93.657 (s, 4F, $N\mathbf{CF_2}$), −54.125 (s, 12F, $N\mathbf{CF_3}$).

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References

[1] J.H. Simons, J. Electrochem. Soc. 95 (1949) 47–67.
[2] G.G. Furin, C. Cambaretto, Direct Fluorination of Organic Compounds, Padova, CLEUP, 1996, p. 40.
[3] J.L. Adcock, W.D. Evans, J. Org. Chem. 49 (1984) 2719–2723.
[4] R.J. Lagow, J.L. Margrave, Direct fluorination: a "new" approach to fluorine chemistry, in: S.J. Lippard (Ed.), Progress in Inorganic Chemistry, Wiley/Interscience, New York, 1979, pp. 161–210.
[5] N. Ishikawa (Ed.), Fluorine Compounds, Modern Technology and Application, Mir, Moscow, 1984, p. 592.
[6] L.vC. Clark, E.P. Wesseler, S. Kaplan, C. Emory, R. Moore, D. Denson, Intravenous infusion of *cis–trans* perfluorodecalin emulsions in the rhesus monkey, in: R. Filler (Ed.), Biochemistry Involving Carbon–Fluorine Bonds, vol. 28, American Chemical Society Symposium Series, Washington, DC, 1976.
[7] R.E. Banks, M.G. Barlow, Fluorocarbon and Related Chemistry, vol. 2, The Chemical Society, London, 1974, pp. 98–99.
[8] D.D. Denson, E.T. Uyeno, R.L. Simon Jr., H.M. Peters, Preparation and physiological evaluation of some new fluorinated volatile anesthetics, in: R. Filler (Ed.), Biochemistry Involving Carbon–Fluorine Bonds, vol. 28, American Chemical Society Symposium Series, Washington, DC, 1976.
[9] R.D. Chambers, Fluorine in Organic Chemistry, Wiley, New York, 1973.
[10] D.D. Moldavskii, T.A. Bispen, G.I. Kaurova, G.G. Furin, J. Fluorine Chem. 94 (1999) 157–167.
[11] A. Dimitrov, D. Pfeifer, U. Jonethal, K. Seppelt, J. Fluorine Chem. 82 (1997) 143–150.
[12] H. Huang, D.F. Persico, R.J. Lagow, J. Org. Chem. 53 (1988) 78–85.
[13] D. Velayutham, K. Jayaraman, M. Noel, S. Krishnamoorthy, P. Sartori, J. Fluorine Chem. 115 (2002) 21–26.
[14] T.R. Bierschenk, T.J. Juhlke, R.J. Lagow, H. Kawa, US Patent 5,093,432 (1992).
[15] R.J. Lagow, T.R. Bierschenk, T.J. Juhlke, J. Am. Chem. Soc. 103 (1981) 7340.