Journal of Fluorine Chemistry 132 (2011) 961–964

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Difluoroalkylamines from high temperature vapor phase reactions of nitrogen trifluoride with alkanes, ethers and benzene

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ARTICLE INFO

Article history:
Received 1 July 2011
Received in revised form 15 July 2011
Accepted 19 July 2011
Available online 26 July 2011

Keywords:
Nitrogen trifluoride
Alkyl substitution
Aromatic substitution
Radical abstraction
Difluoroalkylamines

ABSTRACT

At temperatures around 400 °C, nitrogen trifluoride (NF_3) readily reacts with alkanes and benzene as well as ethers. In all cases, products were N,N-difluoroamines. This is in contrast to difluoroamination of benzylic substrates where the initial N,N-difluoroamines underwent eliminations or rearrangements and were not isolated. Cyclic and acyclic alkanes generated N,N-difluoroaminoalkanes. Benzene substituted on the ring to form N,N-difluoroaniline. Ethers reacted to generate α-N,N-difluoroamino ethers. Little direct fluorination was observed.

1. Introduction

1.1. Organic reactions of nitrogen trifluoride

We have previously shown that nitrogen trifluoride (NF_3) can be reacted in a controlled manner with benzylic substrates in a 400 °C vapor phase reactor [1]. Each substrate tested underwent N,N-difluoroamination at the benzylic position. In every case, the initial N,N-difluoroamine was unstable and converted to another functionality. Specifically, toluene produced benzonitrile via HF elimination. Ethylbenzene also produced benzonitrile, but via Beckmann rearrangement. Cumene produced α-methylstyrene via HNF_2 elimination. Diphenylmethane produced benzanilide, again via Beckmann rearrangement. In addition, little or no direct fluorination or radical dimerization was observed.

To further investigate the scope of reactivity of nitrogen trifluoride, we have now investigated NF_3 reactions with acyclic and cyclic aliphatic compounds, cyclic and acyclic ethers, and benzene. The results contrast starkly with the results of reaction with benzylic substrates and we report those results now.

2. Results and discussion

2.1. Reaction of NF_3 with cyclic alkanes

The first substrate chosen for evaluation was cyclohexane, **1**. This compound would be expected to yield a single product as all positions are equivalent and selectivity should not be an issue. In light of the results seen for the reaction of NF_3 with benzylic substrates, we expected an initial difluoroamination to **2**, followed by elimination and Beckmann rearrangement. After hydrolysis during work-up, we expected to isolate ε-caprolactam, **3**, as the principle product (Scheme 1). In fact, we expected lactams and amides to be the products of all reactions with alkanes, cyclic and acyclic respectively.

Gas chromatography of the crude cyclohexane + NF_3 reaction mixture immediately indicated that our suppositions were not correct as the main product was of too short a retention time to be a lactam. After isolation and NMR analysis the product was identified as N,N-difluoraminocyclohexane, **2**! Compound **2** comprised 65% of GC observable products along with 15% cyclohexene. Though difluoroamines were unstable intermediates in the reactions of benzylic substrates at least one difluoroamine is now a stable main product for an alkane.

The reaction sequence we envisioned in Scheme 1 has been stopped short. For a Beckmann rearrangement to occur, an N,N-difluoroamine must first eliminate HF to become an N-fluoroimine. Clearly, this is not occurring and must be the result of the pKa of the α-proton not being of sufficient acidity to support an elimination. For eliminations of α-NF_2 nitriles see references [2,3]. Elimination did not occur under the high temperature, acidic conditions of reaction, nor did it occur during the aqueous and basic (10% KOH) work-up.

These results were duplicated with cyclopentane, **4**, where N,N-difluoroaminocyclopentane, **5**, comprised 56% of products. Interestingly, while some fluorocyclohexane was observed for the

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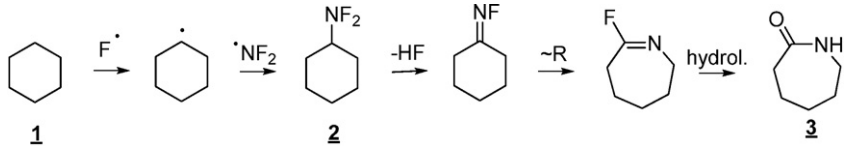
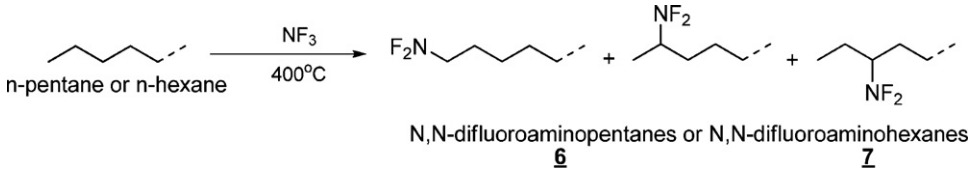
doi:10.1016/j.jfluchem.2011.07.024



Scheme 1. Expected reaction of NF_3 with cycloalkanes.



Scheme 2. Reaction of NF_3 with n-pentane and n-hexane.

cyclohexane reaction, fluorocyclopentane was not observed in the cyclopentane reaction.

2.2. Reaction of NF_3 with acyclic alkanes

Acyclic alkanes such as *n*-pentane and *n*-hexane produced a mixture of the possible N,N-difluoramines as 60–75% of products. The exact regioisomeric ratios have not been determined as two of the isomers coincide on GC and ^{1}H-NMR does not clearly distinguish between those isomers. ^{13}C-NMR does show the existence of all 3 isomers for each substrate. The ^{19}F NMR exhibits one singlet at +55.9 ppm and overlapping quintets at +39.2 ppm. NMR literature for 1-N,N-difluoroaminobutane [4] and 2-N,N-difluoraminobutane [5] indicate a single resonance for each (+54.6 ppm and +52.5 ppm respectively). Our spectra indicate one isomer to have a single resonance while the other two behave more like N-fluorodialkylamines [6], which show predictable F–H splitting. While one may suspect that we have isolated N-fluorodialkylamines, electrospray high resolution mass spectroscopy indicates that the compounds are monoalkyl in nature. The anomalous nature of these ^{19}F spectra will be the subject of future study, pending isolation of the individual isomers. Minor amounts of fluoropentanes and fluorohexanes were observed, respectively (Scheme 2).

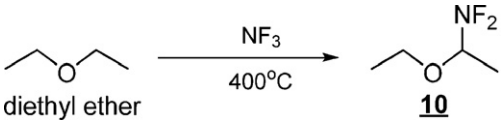
Isobutane (2-methylpropane) produced t-butyl-NF_2, **8**, with accompanying t-butyl fluoride when treated with NF_3.

2.3. Reaction of NF_3 with a cyclic ether

The high temperature reaction of tetrahydrofuran with NF_3 was surprisingly clean. The principle product (57% of GC) was the α-substituted THF, **9** (Scheme 3). Though this compound might appear susceptible to anomeric elimination, it is clearly stable and isolated in the best yield of this study. Compound **9** is previously reported along with ^{1}H NMR spectra [7]. Also known are bis- and tetra-difluoramino substituted furans, which are used in rocket propellants [8–13].

2.4. Reaction of NF_3 with an acyclic ether

The reaction of diethyl ether was as clean as that of THF. Again, the main product observed (87%) was a α-substituted ether, **10**



Scheme 4. Reaction of NF_3 with diethyl ether.

(Schemes 4). The compound **10** has been reported along with ^{1}H NMR spectra [7].

Under the NF_3 reaction conditions, methyl t-butyl ether (MTBE) produced both methanol and t-butyl fluoride. This product pair is clearly the result of HF lysis. However, any HF had to come from difluoroamination, but as no difluoroaminated products were isolated or observed on GC, it is apparent that they are unstable.

2.5. Reaction of NF_3 with benzene

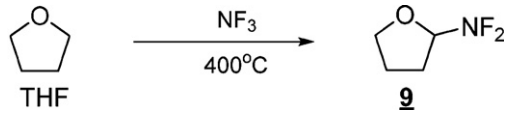
Benzene readily reacted with NF_3 at 400–410 °C. N,N-difluoroaniline, **11**, was accompanied by an almost equal amount (by GC) of fluorobenzene, the two making up 79% of the observed products (Scheme 5). These products were more difficult to separate from the parent reactant (benzene) than the other difluoroalkylamines.

2.6. General reaction behavior

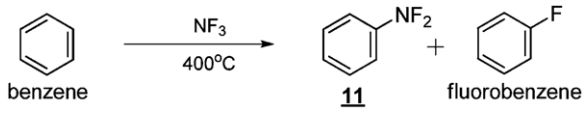
In contrast to the reactions of NF_3 with benzylic substrates, the reaction of aliphatics, ethers and benzene were not accompanied by heavy by-products. In fact, the organic fraction of the product stream was generally clear and only slightly colored. The HF layers were generally dark, but lightened upon neutralization, depositing only small amounts of dark insoluble material.

The exotherm of reaction was much milder and more controllable for these reactions, clearly because there were no HF eliminations occurring. There were no pre-heater detonations as were common for the benzylic substrates and higher concentrations of NF_3 could be used.

Conversions are low (~5%) versus the excess organic substrate. Most NF_3 passes through the reactor unused. Equilibrium calculations show that NF_3 only dissociates to one part per million at 400 °C [14], in which case, our observed reactivity is fairly good. These reactions are, with all intent, uncatalysed. It is not yet understood why these reactions, which exotherm in the front half



Scheme 3. Reaction of NF_3 with tetrahydrofuran.



Scheme 5. Reaction of NF_3 with Benzene.

of the reactor, do not continue reacting through the rest of the reactor bed. It is possible that the generation of HF may inhibit downstream reaction. None-the-less, these conversions are comparable to those attainable for vapor phase O_2 oxidations [15].

3. Conclusion

At 400 °C, NF_3 reacts with *n*-pentane, *n*-hexane, isobutane, cyclopentane, cyclohexane, diethyl ether, tetrahydrofuran and benzene to generate N,N-difluoroalkylamines. There is no reason to believe that this reaction cannot be generalized to include all volatile alkanes and cycloalkanes, ethers and cyclic ethers and substituted benzenes that are stable to HF exposure and high temperatures.

It is the continuing goal of this project to find a means by which waste NF_3 can be utilized in a manner in which valuable products might be generated. In this study, we have discovered a method for the direct and continuous generation of N,N-difluoroamino compounds. While conversions are low, yields are good and products are readily isolated. The easy generation of these N,N-difluoroamino compounds opens the possibility of attempting further substitution of the nitrogen as well as other reactions and we look forward to investigating those possibilities.

4. Experimental

4.1. General

Benzene, cyclopentane, and methyl t-butyl ether were from Aldrich. Cyclohexane, diethyl ether, *n*-hexane, *n*-pentane and tetrahydrofuran were from Aaper. Isobutane was from Bismar, Inc. All substrates were used without further purification or drying. Nitrogen trifluoride was from Fluoromar.

Reactions were performed in a single 1″ (2.5 cm) diameter tubular reactor, 24″ (61 cm) long, as described in our previous publication [1]. A backpressure of 1 atm was maintained for each reaction except for the isobutane reaction where the backpressure of 3 atm was maintained. Product was collected through a cold water condenser, washed with water to remove HF, neutralized with saturated $NaHCO_3$ and dried over Na_2SO_4. Unreacted starting material and product fractions were separated by vacuum fractional distillation.

Products were identified by ^1H and ^{13}C and ^{19}F NMR performed on a Bruker DPX-250. MS was performed on an Agilent 6210 Time-of–Flight spectrometer.

4.2. Cautionary notes

Nitrogen trifluoride is toxic by inhalation and should only be used in a well ventilated environment. It is apparent to us that the N,N-difluoroamino products are toxic as well. In addition, trace by-products may be toxic and concentrated during distillation. The benzene reaction had particularly noxious light by-products.

NF_3 is an oxidant and care must be taken to ensure operations outside the explosivity limits of the NF_3/hydrocarbon mixture. It is advisable that all metal surfaces be fluoride passivated. In our previous study where the NF_3 ratio exceeded 50 mol% and/or reactor inlet temperatures rose much beyond the boiling point of the substrate *detonations were observed* in the preheater system [16].

Anhydrous HF is a by-product of these reactions. Anhydrous HF causes *instantaneous* severe burns to the skin and mucous membranes. HF should be handled with full PPE protection. An ample supply of HF antidote gel should be kept on hand before handling HF. See the reference for burn treatment procedures [17].

4.3. Spectral details

N,N-difluoroaminocyclohexane [**2**] clear, colorless liquid, b.p. 22 °C (~1 mmHg); ^1H-NMR (250 MHz $CDCl_3$/TMS): δ 1.2–1.5 (6H), δ 1.67 (1H), δ 1.8–2.0 (5H), δ 3.34 (m, 1H); ^{13}C-NMR (62 MHz $CDCl_3$): δ 24.0 (s), 25.5 (s), 26.8 (t, J = 7.2 Hz), 73.1 (t, J = 6.0 Hz); ^{19}F-NMR (235 MHz $CDCl_3$): δ + 42.3 (s); IR 2958, 2866, 1446, 995, 943, 920, 850; GC/MS 70 eV, *m*/*z* (rel. int.): 81(100).

N,N-difluoroaminocyclopentane [**5**] clear, colorless liquid, b.p. 20 °C (~1 mmHg); ^1H-NMR (250 MHz $CDCl_3$/TMS): δ 1.67 (m, 4H), 1.87 (m, 4H), 3.93 (tp, 1H, J = 29.6, 6.5); ^{13}C-NMR (62 MHz $CDCl_3$): δ 25.2 (s), 28.2 (t, J = 6.4 Hz), 75.6 (t, J = 5.6 Hz); ^{19}F-NMR (235 MHz $CDCl_3$): δ + 52.9 (s); IR 2958, 2864, 1446, 995, 938, 920, 850; GC/MS 70 eV, *m*/*z* (rel. int.): 69 (100).

N,N-difluoroaminopentanes [**6**] clear, colorless liquid, b.p. 94–95 °C (760 mmHg); ^1H-NMR (250 MHz $CDCl_3$/TMS): δ 0.9–1.1 (3.7H), 1.21 (d, 2H, J = 6.5 Hz), 1.40 (m, 2.4H), 1.68 (mm, 2H), 3.17 (tp, 0.22H, J = 26.2, 6.1 Hz), 3.42 (tm, 0.78H, J = 28.1 Hz);

^{13}C-NMR (1-N,N-difluoroaminopentane) (62 MHz $CDCl_3$): δ 13.7 (s, C-5), 22.5 (s, C-4), 23.8 (t, J = 7.8 Hz, C-2), 29.1 (s, C-3), 66.2 (t, J = 6.3 Hz, C-1);

^{13}C-NMR (2-N,N-difluoroaminopentane) (62 MHz $CDCl_3$): δ 14.0 (s, C-1), 13.2 (t, J = 10.0 = Hz, C-2), 21.2 (t, J = 6.6 Hz, C-1), 33.3 (t, J = 6.8 Hz, C-3), 70.2 (t, J = 6.2 Hz, C-2);

^{13}C-NMR (3-N,N-difluoroaminopentane) (62 MHz $CDCl_3$): δ 10.2 (s, C-5), 19.1 (s, C-4), 77.0 (t, J = 5.3 Hz, C-3);

^{19}F-NMR (235 MHz $CDCl_3$): δ + 55.9 (s), δ + 39.2 (p, J = 579.3 Hz); IR 2958, 2875, 1462, 1370, 953, 860, 844, 810; GC/MS 70 eV, *m*/*z* (rel. int.): 71(100), 55(40).

N,N-difluoroaminohexanes [**7**] clear, colorless liquid, b.p. 25–28 °C (~20 mmHg); ^1H-NMR (250 MHz $CDCl_3$/TMS): δ 0.9–1.1 (3.7H), 1.25 (d, 1.9H, 1.7H, J = 5.6 Hz), 1.3–1.5 (m, 4.0H), 1.6-1.9 (mm, 1.7H), 3.30 (tp, 0.21H, J = 26.8, 6.0 Hz), 3.46 (tm, 0.79H, J = 26.0 Hz); ^{13}C-NMR (62 MHz $CDCl_3$): δ 10.3 (s), 13.3 (t, J = 9.9 Hz), 14.0 (s), 14.1 (s), 14.2 (s), 19.4 (s), 21.8 (t, J = 8.4 Hz), 22.6 (s), 22.8 (s), 24.1 (t, J = 7.8 Hz), 26.6 (s), 27.9 (s), 30.3 (t, J = 7.8 Hz), 30.8 (t, J = 6.9 Hz), 31.6 (s), 66.2 (t, J = 6.3 Hz, 1-NF_2), 70.4 (t, J = 6.3 Hz, 2-NF_2), 75.7 (t, J = 5.4 Hz, 3-NF_2);

^{19}F-NMR (235 MHz $CDCl_3$): δ + 55.9 (s), +39.3 (p, J = 574.0 Hz); IR 2958, 2939, 2866, 1462, 1379, 953, 855, 839, 810; GC/MS 70 eV, *m*/*z* (rel. int.): 85(100), 57(70).

2-N,N-difluoroamino-2-methylpropane [**8**] clear, colorless liquid, b.p. 25 °C (~260 mmHg); ^1H-NMR (250 MHz $CDCl_3$/TMS): δ 1.25 (s, 9H); ^{13}C-NMR (62 MHz $CDCl_3$): δ 22.8 (t, J = 7.2 Hz), 69.6 (t, J = 7.3 Hz); ^{19}F-NMR (235 MHz $CDCl_3$): δ + 28.3 (s); IR 2958, 2875, 1462, 1370, 953, 860; GC/MS 70 eV, *m*/*z* (rel. int.): 194 (100), 179 (100), 164 (72), 149 (25), 119 (18), 91 (34), 77 (22).

α-N,N-difluoroaminotetrahydrofuran [**9**] clear, colorless liquid, b.p. 39 °C (~60 mmHg); ^1H-NMR (250 MHz $CDCl_3$/TMS): δ 2.00 (m, 2H), 1.19 (m, 2H), 4.05 (m, 2H), 5.01 (ddt, 1H, J = 23.5, 18.9, 4.6); ^{13}C-NMR (62 MHz $CDCl_3$): δ 24.0 (s), 27.7 (t, J = 4.6 Hz), 70.7 (s), 100.0 (t, J = 10.3 Hz); ^{19}F-NMR (235 MHz $CDCl_3$): δ + 31.9 (d, J = 66.5 Hz); IR 2975, 2865, 1726, 1461, 1184, 1070, 1032, 912, 865; GC/MS 70 eV, *m*/*z* (rel. int.): 82 (65), 71 (100), 42 (100).

α-N,N-difluoroaminodiethylether [**10**] clear, colorless liquid, b.p. 13 °C (~30 mmHg); ^1H-NMR (250 MHz $CDCl_3$/TMS): δ 1.24 (t, 3H, J = 7.0 Hz), 1.40 (dm, 3H, J = 5.9), 3.72 (dt, 1H, J = 8.2, 7.1), 3.99 (dt, 1H, J = 8.2, 7.1), 4.58 (dq, 1H, J = 18.5, 5.9); ^{13}C-NMR (62 MHz $CDCl_3$): δ 14.8 (t, J = 7.9 Hz), 15.3, 67.8, 97.5 (t, J = 9.4 Hz); ^{19}F-NMR (235 MHz $CDCl_3$): δ + 26.5 (q, J = 523.9 Hz); IR 2984, 2941, 1446, 1382, 1336, 1182, 1149, 1099, 1051, 952, 865; IR 2975, 2865, 1726, 1461, 1184, 1070, 1032, 912, 865; GC/MS 70 eV, *m*/*z* (rel. int.): 80 (65), 73 (100), 61 (21).

N,N-difluoroaminobenzene [**11**] clear, colorless liquid, b.p. 25 °C (60 mmHg); ^1H-NMR (250 MHz $CDCl_3$/TMS): δ 7.50 (m, 3H, J = 6.9 Hz), 7.70 (d, 2H, J = 7.2); ^{13}C-NMR (62 MHz $CDCl_3$): δ 125.4 (q, J = 3.7 Hz),

128.6, 128.9, 140.0; ^{19}F-NMR (235 MHz $CDCl_3$): δ −63.2; IR 3036, 1480, 1036, 860, 673, GC/MS 70 eV, *m*/*z* (rel. int.): 77 (100).

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