REARRANGEMENT OF N-(TRIFLUOROMETHYL)ANTHRANILOYL FLUORIDE TO 2-(TRIFLUOROMETHYL)ANILINE - KINETIC AND MECHANISTIC OBSERVATIONS

HENRY C. LIN *, BYRON R. COTTER*, JOSEPH F. BIERON** and RAMESH KRISHNAMURTI

Occidental Chemical Corporation, Technology Center, Grand Island, New York 14072 (U.S.A.)

SUMMARY

    Pseudo first order rate constants for the rearrangement of N-(trifluoromethyl)anthraniloyl fluoride (2) to N-[(2-trifluoromethyl)phenyl]carbamoyl fluoride (3) in anhydrous HF have been determined. Increasing HF levels accelerate this process, but increasing KF concentrations retard the reaction. An ionic species has been proposed as the intermediate in the suggested mechanism. Further reaction of 3 with HF proceeded to give 2-(trifluoromethyl)aniline hydrofluoride (4) via an unprecedented expulsion of carbonyl fluoride.

INTRODUCTION

    Klauke [1-3] reported that 2-(trichloromethyl)phenyl isocyanate (1) reacts rapidly with anhydrous hydrogen fluoride to give a rearranged product, N-(trifluoromethyl)anthraniloyl fluoride (2) (Eq 1). We now report a sequence of slower reactions of 2 in liquid hydrogen fluoride which proceed by

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*   To whom correspondence should be addressed.
#   Present address: Lever Research Inc., Edgewater, NJ 07020.
Present address: Department of Chemistry, Canisius College, Buffalo, NY 14208.

initial rearrangement to N-[2-(trifluoromethyl)phenyl]carbamoyl
fluoride (3), followed by an unprecedented solvolysis to expel
carbonyl fluoride and give the hydrofluoride complex of
2-(trifluoromethyl)aniline (4) (Eq 2).
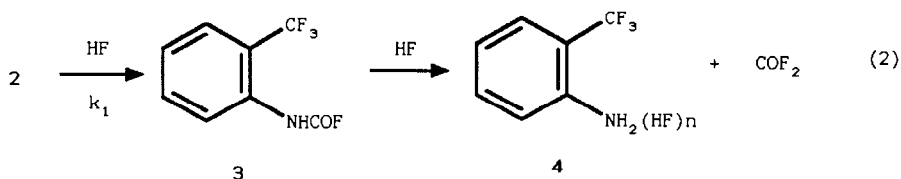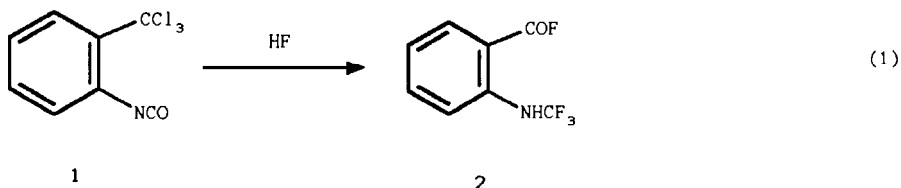
RESULTS AND DISCUSSION

The rate of rearrangement of 2 to 3 depends on the amount
of HF present - increasing the HF content produces a consider-
able increase in the rate of the rearrangement. Table 1 gives
pseudo first order rate constants for the disappearance of 2 as
a function of the amount of HF used. ^{19}F NMR served as a con-
venient means of following the disappearance of 2. By relating
the peak area of the ^{19}F signal of 2 (δ(NHC$\underline{F}_3$): -55.5) against
that of the internal standard (3-fluorotoluene) taken in a
known quantity, the relative amount of unreacted starting mate-
rial was determined. The results showed that upon doubling the
amount of HF, the reaction rate increases by a factor of 3.5.
A greater rate enhancement is seen upon increasing the amount
of HF by a factor of 3 (Table 1). No appreciable acceleration
was observed upon addition of antimony pentafluoride or fluoro-
sulfonic acid which produce superacidic media. However, the
reaction was retarded significantly by the addition of
potassium fluoride (0.7 equiv.). An ionic mechanism may be
involved here. One possibility is that the rate determining

TABLE 1

Pseudo first order rate constants for the disappearance of
N-(trifluoromethyl)anthraniloyl fluoride (2) in anhydrous
hydrogen fluoride[a]

HF/2 Mole ratio	% Unreacted 2[b]	k_1 (sec^{-1})
5	69.5	650
10	28.4	2300
15	13.3	3600

[a] Experiments were conducted at 40 °C under an autogeneous
pressure of 20 psig. [b] Determined by quantitative ^{19}F NMR
analysis of the reaction mixture against 3-fluorotoluene added
as the internal standard.

step is carbocation formation from 2 as shown in scheme 1.
This would explain the rate enhancement observed upon increa-
sing the amount of HF because as the polarity of the reaction
medium increases, formation of ionic species is facilitated.
Carbocations bearing fluorines can be formed in highly acidic
media when they also contain a cation-stabilizing group, such
as a phenyl group [4]. Thus, ionization of 2 would produce
initially, cation 5, which is resonance stabilized as the
iminium ion 6. Two experimental observations in the literature
are relevant to this process. N-(trifluoromethyl)aniline has
been reported to undergo dehydrofluorination upon heating with
potassium fluoride [5]. Arylisocyanide difluorides (Ar-N=CF$_2$)
add HF to give N-(trifluoromethyl)arylamines [6]. Although no
mechanism was proposed, it is reasonable to suggest that di-
fluoroiminium ions of the type 6 are involved in these two pro-
cesses. It also accounts for the strong retarding effect of
fluoride ion which in excess would shift the equilibrium of the
first step back toward 2 (Scheme 1). This resonance-stabilized
system (5⟷6) can exist in equilibrium with the onium ion
(7) by interaction of the oxygen lone pair with the electron-

deficient CF_2-carbon. Fluoride attack at C-1 in **7** would then give the cyclic intermediate (**8**) which under the prevailing strongly acidic conditions could revert to **7** by ionization at C-2. Ionization of the C(2)-F bond in **8** gives onium ion **9** which can also exist as ion **10** due to resonance interaction. Subsequent attack of fluoride ion then gives (**3**). Thus, the observed product is formed by the preferred mode of ionization of proposed intermediate **8** through the ion (**9**⟷**10**) due to resonance stabilization*. The presence of intermediate **8** could not be inferred from the ^{19}F NMR spectrum of the reaction mixture. Conceivably, its equilibrium concentration is too low to permit observation.

In the case of the reaction of **1** [2] with anhydrous hydrogen fluoride, a similar intermediate, such as **10** or **11**, or even a mixture of the two species can be postulated (Scheme 2). Taking intermediate **11** for instance, the C-Cl bond would ionize more readily than the C-F bond to give onium ion **13** (similar to the onium ion **7** shown in Scheme 1) which upon ring opening, followed by fluoride attack would lead to the observed product (**2**).

To determine whether the reverse reaction, **3** to **2**, is significant, 2-(trifluoromethyl)phenyl isocyanate (**14**) was prepared independently by phosgenation of 2-(trifluoromethyl)aniline (**15**). Dissolution of **14** in excess anhydrous HF generated **3** [7] which even after five days in a 46:1 molar ratio of HF and **3**, respectively, at 25 °C showed no measurable amount of **2**.

Further reaction of the carbamoyl fluoride **3** with HF proceeded to give 2-(trifluoromethyl)aniline hydrofluoride (**4**) and carbonyl fluoride. This result was unexpected since carbonyl fluoride has been reported to react with anilines to give the corresponding isocyanates [8]. However, we have confirmed the formation of carbonyl fluoride in the reaction by IR analysis of the gases evolved from the reaction. Furthermore, ^{19}F NMR and GC analysis of the reaction solutions showed that **4** was the major product, even when traces of water which might react with the carbamoyl fluoride **3** were rigorously excluded by pretrea-

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* We thank the Editor for helpful suggestions to clarify the proposed mechanism.
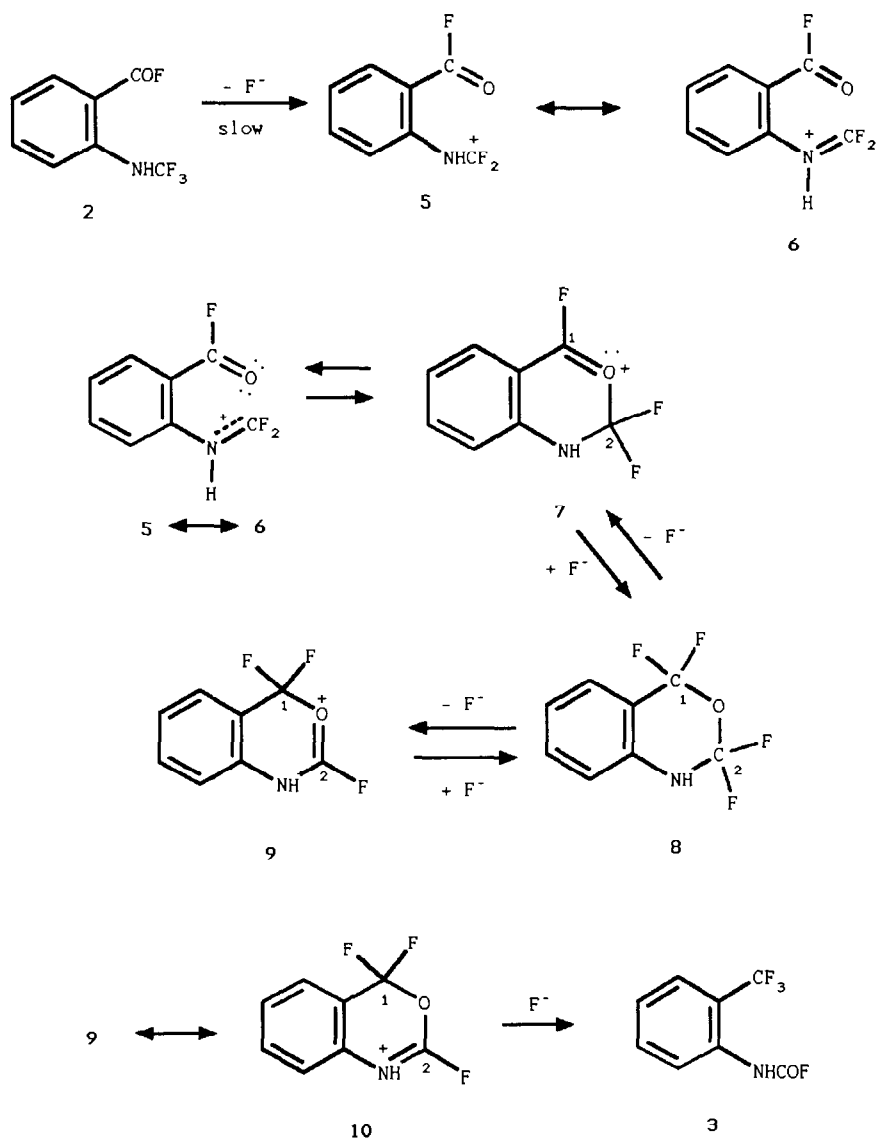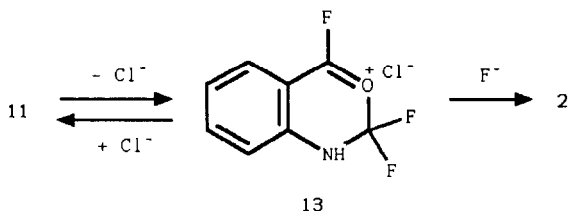
Scheme 1.

ting the HF with thionyl chloride. At lower ratios of HF to **3** (< 5:1), some of the corresponding urea derivative **16** was also formed.

The carbonyl fluoride expulsion appears to be reversible under the reaction conditions. When the reactor was sealed to
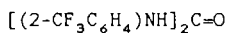
11: X = F

12: X = Cl
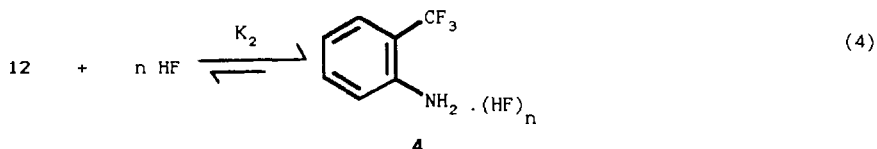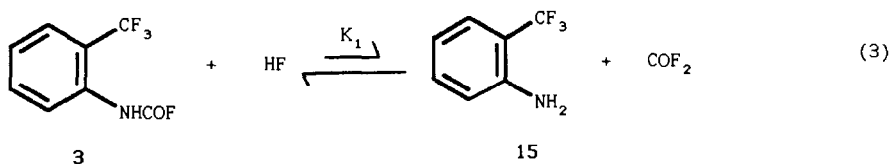

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Scheme 2.

$$[(2\text{-}CF_3C_6H_4)NH]_2C=O$$
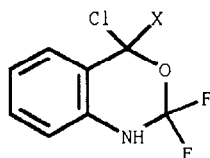
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prevent escape of the carbonyl fluoride, the reaction stopped
at about a 50% conversion, but when left open to allow the HF
to reflux and carbonyl fluoride to escape, complete conversion
to the aniline hydrofluoride **4** occurred. The relatively high
equilibrium concentration of **4** and carbonyl fluoride can be
understood by considering the equilibria involved (eqs 3 and
4). A large K_2 for complexation of aniline with HF would lead
to relatively high equilibrium levels of carbonyl fluoride and
4, even if K_1 is relatively small. Intuitively, one might ex-
pect that the concentration of the free aniline (**15**) in liquid
HF would be so low as to preclude measurement of its reaction
with carbonyl fluoride. However, when a sample of **12** was
dissolved in liquid HF and treated with carbonyl fluoride, the
major product was the carbamoyl fluoride (**3**).

      Carbonyl fluoride expulsion is a relatively general
process. We have carried out the reaction on eight other aro-
matic isocyanates, including phenyl isocyanate and 4-(trifluo-

romethyl)phenyl isocyanate. In the latter two cases, diaryl urea derivatives were formed in much greater amounts than was the case with 2-(trifluoromethyl)phenyl isocyanate. Although the mechanism of urea formation has not been investigated, it appears that the ortho substituent sterically inhibits urea formation.

$$\text{3 (NHCOF, CF}_3) + \text{HF} \;\underset{}{\overset{K_1}{\rightleftharpoons}}\; \text{15 (NH}_2, \text{CF}_3) + \text{COF}_2 \qquad (3)$$

3   15

$$\text{12} + n\,\text{HF} \;\underset{}{\overset{K_2}{\rightleftharpoons}}\; \text{4 (NH}_2\cdot(\text{HF})_n, \text{CF}_3) \qquad (4)$$

4

In summary, therefore, a novel and unprecedented transformation of $\underline{N}$-(trifluoromethyl)anthraniloyl fluoride (2) to 2-(trifluoromethyl)aniline (4) has been observed. Pseudo first order rate constants (given in Table 1) for the rearrangement of 2 to the carbamoyl fluoride (3) have been determined (See Experimental Section). Increasing HF levels accelerates the reaction, but increasing KF concentrations retard the process. An ionic species has been proposed. The rearrangement is postulated to proceed via the cyclic fluorinated intermediate (7) formed in low equilibrium concentrations. Fluoride-induced cleavage of this intermediate to produce the observed product appears to be related to the difference in electrophilic character of the two difluoromethylene carbons. Finally, the hitherto unobserved solvolysis of carbamoyl fluorides, such as 3, to the corresponding aniline hydrofluoride with liberation of carbonyl fluoride is a fairly general process. In the presence of excess HF, the driving force for aniline formation is the large heat of formation of the corresponding hydrofluoride derivative.

EXPERIMENTAL

Instrumentation

Fluorine-19 NMR spectra were recorded at 94.1 MHz using a Varian XL-100 spectrometer equipped with a Nicolet TT-100 Fourier transform unit. The chemical shifts are referenced to fluorotrichloromethane. Quantitative ^{19}F NMR analyses were performed using 3-fluorotoluene (δ ^{19}F -114.9) as the internal standard. IR spectra were obtained with a Nicolet Model 7199 FT-IR spectrophotometer interfaced with a Nicolet 1180 computer and a Nicolet digital plotter. Temperature-programmed (100-250 °C) gas chromatographic analyses were performed using a Hewlett Packard Model HP5840A instrument equipped with a capillary column (0.25 mm X 30 m) and a flame ionization detector. The retention times (in minutes) for the compounds employed in this study are as follows: N-(trifluoromethyl)-anthraniloyl fluoride - 2.77; 2-(trifluoromethyl)aniline - 3.04; 2-(trifluoromethyl)phenyl isocyanate - 3.23; N-[2-(trifluoromethyl)phenyl]carbamoyl fluoride - 3.40; N,N'-bis[2-(trifluoromethyl)phenyl]urea - 12.60.

Reagents

All chemicals employed in this study were commercial materials. They were, if necessary, purified by standard methods. Anhydrous hydrogen fluoride was prepared by treating HF with thionyl chloride according to the procedure of Wiechert[9]. 2-(Trichloromethyl)phenyl isocyanate was prepared by photochlorination of 2-(methyl)phenyl isocyanate according to the literature procedure [10]. N-(trifluoromethyl)anthraniloyl fluoride was prepared according to the procedure of Klauke [11]. N,N'-Bis(2-(trifluoromethyl)phenyl]urea was obtained by the reaction of 2-(trifluoromethyl)aniline with 2-(trifluoromethyl)phenyl isocyanate using acetone as a solvent; mp: 205-207 °C [12] mp: 189-190 °C).

Kinetic Studies

In a typical experiment, a polytetrafluoroethylene (PTFE) reactor containing a magnetic stirring bar was immersed in a dry ice-acetone bath. A predetermined quantity of HF (to attain the appropriate mole ratio of HF/2, see Table 1) was condensed into the reactor through Teflon[R] tubing. The dry ice-acetone bath was then replaced with an ice bath, and the reactor allowed to warm up to 0 °C. The organic substrate was then introduced slowly with vigorous stirring. When the addition was complete, the reactor was either sealed with a Teflon[R] cap for an autogeneous pressure run, or equipped with a cooling condenser maintained at -10 °C using ethylene glycol-water mixture as coolant. The reactor was then warmed to 25 °C. When analyzing the reaction mixture, the reactor was first cooled to 0 °C before withdrawing an aliquot. The sample was then either diluted with acetone for GC analysis or analyzed by ^{19}F NMR spectroscopy using a known weight of 3-fluorotoluene as an internal standard. In the case of N-(trifluoromethyl)anthraniloyl fluoride, the rate of disappearance of the ^{19}F signal for the -NHCF$_3$ group (δ -55.5) was monitored. Concentrations were calculated from the integrated ^{19}F-peak areas of the internal standard and the starting material. Pseudo first order rate constants are given in Table 1.

Detection of Carbonyl Fluoride in the Reaction of 2-(Trifluoromethyl)phenyl isocyanate with Hydrogen Fluoride

Into a PTFE reactor, equipped with a pressure gauge, a valve and a magnetic stirring bar was condensed 3.48 g (0.017 mole) of HF (pretreated with thionyl chloride)as described above. The reactor was cooled in an ice bath and treated with 1.87 g (0.01 mole) of 2-(trifluoromethyl)phenyl isocyanate. After the addition the valve was closed, and the reactor was allowed to warm up to room temperature and stirred for 24 h. The pressure gauge registered a positive reading. The gases in the reactor were vented into a 10 cm IR gas cell equipped with NaCl windows. The resulting FT-IR scan, as compared with that of authentic carbonyl fluoride, confirmed its presence (ν(C=O): 1930 cm^{-1}).

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