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REACTIONS IN ANHYDROUS HYDROGEN FLUORIDE

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SUMMARY

Anhydrous hydrogen fluoride serves as an excellent agent for introducing fluorine into organic compounds, as a solvent and a catalyst with Friedel-Crafts activity. A number of chlorine/fluorine exchange reactions which occur in HF are described, some of which have involved surprising rearrangement processes. New reactions, in which the catalytic action of hydrogen fluoride are utilized, are also discussed.

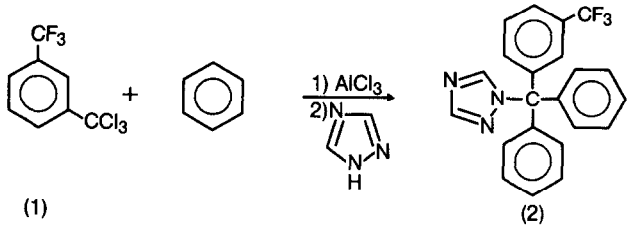
INTRODUCTION

Because of their special chemical and physical properties and their specific biological effects, fluorine containing organic compounds are of fundamental interest in many fields of application. For example, fluorinated compounds are important in medicine as drugs, anaesthetics and synthetic blood plasma, in agriculture as plant protection products, and in the synthesis of polymers, dyestuffs and chlorofluorocarbons[1,2].

Anhydrous hydrogen fluoride is outstanding as a reagent for introducing fluorine into organic compounds, and can act not only as a donor of fluoride ions but also as a solvent and a catalyst with excellent Friedel-Crafts activity [3,4,5,6].This paper gives a survey of some work in this field conducted in our own laboratory.

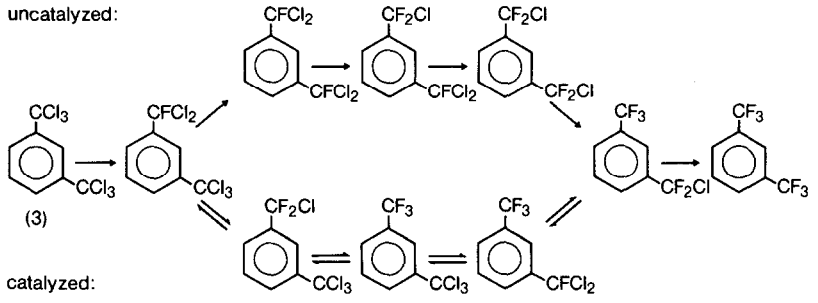
Selective fluorination of aromatic side chains

One of the basic components required for synthesizing the fungicide fluotrimazole (2) (Persulon ®) [7] was meta-trifluoromethylbenzotrichloride (1). It was thus necessary to evolve a practicable method of manufacturing this compound [8].



(1) (2)

In principle, the uncatalyzed fluorination reaction of meta-hexachloro-xylene (3) proceeds in several stages, corresponding to the upper reaction sequence as illustrated in the diagram below.

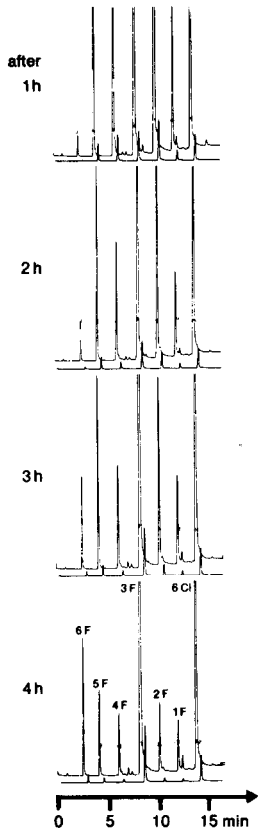


(1)

Since the kinetic conditions favour the formation of mixed fluorinated compounds, there is no possibility of first selectively fluorinating a trichloromethyl group. Selectivity is also excluded by variations in temperature, pressure and time.

Addition of a catalyst such as antimony pentachloride, however, completely alters this situation, introducing a high degree of selectivity into this fluorination reaction. The conversion reaction is then characterized by two

different processes which proceed in a parallel manner. Firstly, the catalytically accelerated exchange of chlorine for fluorine occurs rapidly with the consumption of HF as fluorination reagent, the quantity of HF being chosen to be approximately equivalent to three chlorine atoms. At the same time, the isomerization reactions initiated by the catalyst but proceeding more slowly, commence, which can take place in both inter- and intramolecular fashion. The catalyst thus brings about a state of equilibrium between all the partially fluorinated compounds, following which there is a tendency to formation of m-trifluoromethylbenzotrichloride (1) as the most thermodynamically stable product. This reaction corresponds to the lower reaction sequence shown in the Figure above, which however does not demonstrate the numerous equilibrium states which exist between the compounds. The gas chromatograms and the Table shown below illustrate the course of the reaction.



Batch: 470 g 6 Cl
75 g HF (> = molar ratio 1 : 2,5)
with 0,25% $SbCl_5$ as catalyst
Temp.: 40°C press.: 24 bar

Samples after 0,5 1 2 3 4 5 and 6 h

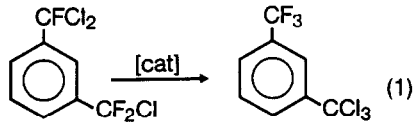
h	6Cl	1 F	2 F	3 F	4 F	5 F	6 F
0,5	9,2	6,7	41,8	17,2	22,3	1,3	–
1	18,0	6,7	28,4	21,3	14,8	8,7	0,5
2	23,3	6,1	18,2	31,4	7,4	10,7	1,7
3	24,5	5,5	12,8	38,3	5,7	9,4	2,6
4	25,5	4,8	9,8	42,5	4,9	7,9	3,2
5	26,2	3,0	4,3	52,7	3,5	4,1	4,1
6	25,8	2,8	3,7	54,4	3,0	3,6	4,7

GC conditions:

3,5 mm 1/8" column
15 % silicone oil Baysilon M 20 000 R (≙ OV 101) on chromosorb W-AW-DMCS, 60 - 80 mesh
temperature program: 80 - 300 °C (15' min)
He-flow: 30 ml/min
thermal conductivity detector, 300 °C

It is apparent that the chlorine/fluorine exchange reaction is practically concluded after 30 minutes. The equilibrium state induced by the catalyst comes about at a much slower rate, reaching a maximum level after about six hours under the specified reaction conditions (1). The equilibrium can naturally be influenced by temperature changes.

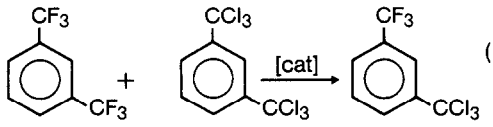
The effect of the catalyst in the isomerization process is demonstrated even more clearly if a pure, partially fluorinated initial compound is treated for instance with antimony pentachloride or aluminium trichloride in the absence of HF. In this case too the halogen transfer reaction takes place, which again results in a state of equilibrium, in which there is a tendency for the thermodynamically more stable trifluoromethylbenzotrichloride (1) to be formed.



(1)

Main product

The transfer reaction can naturally also be applied to the combination of fluorine compounds with non-fluorinated molecules.



(1)

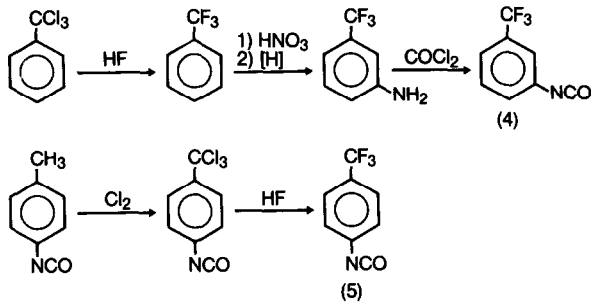
Main product

Selective fluorination can also be performed in compounds with different substitution patterns [8].

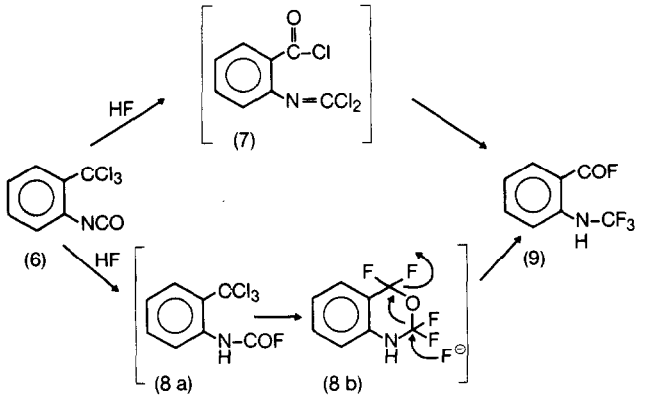
Fluorination of isocyanates and rearrangement reactions

Another important group of substances are the side chain fluorinated isocyanates, which are also used as intermediates in the manufacture of biologically active compounds [9].Synthesis of the meta- and para-trifluoromethylphenyl isocyanates (4) and (5) proceeds through the reaction

sequences described, in which the chlorine/fluorine exchange with HF takes place under moderate conditions and in a virtually quantitative manner [10,11].



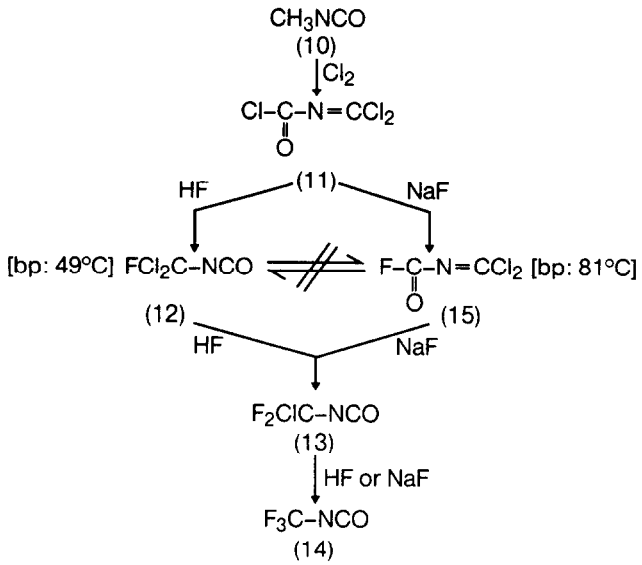
This method is however of no use for synthesizing ortho-trifluoromethylphenyl isocyanate, since in the reaction of o-trichloromethylphenyl isocyanate (6) with HF, a rearrangement process yields N-(trifluoromethyl) anthranilic acid fluoride (9) [12].



A possible interpretation of this reaction is that a thermally induced isomerization of the isocyanate (6) leads to the formation of isocyanide dichloride (7), which is converted into the anthranilic acid derivative (9) through Cl/F exchange and subsequent HF addition to the N=C double bond. It is also possible however that the primary reaction product from HF addition to the isocyanate function is carbamic acid fluoride (8a), which cyclizes in Cl/F exchange to (8b). Under the influence of fluoride ions, the

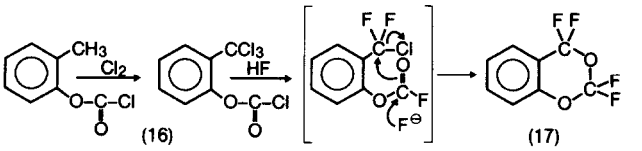
ring opens in the reaction medium HF to form the end product (9), so that finally a migration of oxygen has taken place.

This surprising reaction process has a counterpart in the aliphatic series. In the perchlorination of methylisocyanate (10) it is not the corresponding trichloromethylisocyanate which is formed, but because of chlorotropy, exclusively chlorocarbonyl isocyanide dichloride (11) [13]. Reisomerization in anhydrous HF can then result in the formation of the mono-, di- or trifluorinated isocyanates (12) to (14) [14].



It should be mentioned that when metal fluorides are used as fluorinating agents, fluorocarbonyl isocyanide dichloride (15) can be isolated as a monofluorinated product. Surprisingly, the two compounds (12) and (15) are not in a state of mutual equilibrium and have clearly distinct physical properties.

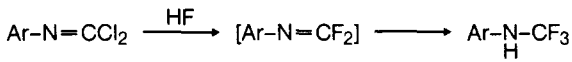
Another example of a chlorine/fluorine exchange with simultaneous rearrangement is the reaction of carbonic ester chloride (16), which cyclizes in HF to give the stable benzodioxin derivative (17) [15].



Ring closure presumably is effected by an intermediate from the fluorination. As a result of primary Cl/F exchange at the ester chloride, the carbonyl group is so strongly polarized as to allow addition of a fluoride anion. The oxygen attacks the positively polarized trihalogen methyl carbon atom nucleophilically, and stabilization into the heterocyclic compound (17) occurs with resulting loss of the chloride anion.

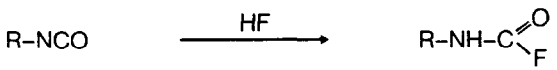
Fluorination and addition reactions

A chlorine/fluorine exchange reaction followed by addition of hydrogen fluoride occurs in the conversion of aromatic isocyanide dichlorides (18) in HF, which results in N-trifluoromethylamines (19). The basicity of the NH group is so greatly reduced by the electronegative CF_3-moiety, that true salts can be formed with tertiary amines [16].



(18) (19)

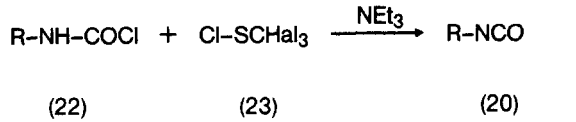
Corresponding addition compounds of aliphatic and aromatic isocyanates and HF can also be obtained in this straightforward manner. In this reaction the carbamic acid fluorides (21) are formed, which are compounds of surprising thermal and chemical stability [17].



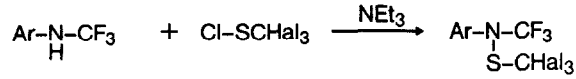
(20) (21)

R=Alkyl, Aryl

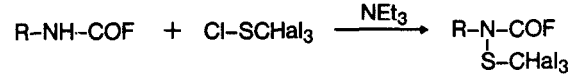
In contrast to carbamic acid chlorides (22), which in the presence of tertiary amines are dehydrochlorinated only into isocyanates (20), the compound types (19) and (21) react with sulfenyl chlorides (23) to form sulfenamides (24) [18] and N-sulfenylated carbamic acid fluorides (25) [9].



(22) (23) (20)



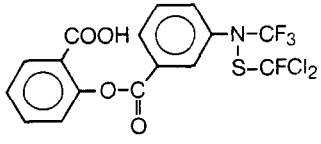
(19) (24)



(21) (25)

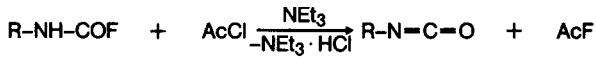
R = Alky, Aryl

These sulfenylation products are themselves biologically active compounds when appropriately substituted in the aromatic nucleus, or serve as valuable intermediates for synthesizing active ingredients. The principle of detoxification of carbamates by N-sulfenylation has been utilized in particular for the synthesis and application of carbamate insecticides [9]. One product derived from the class of compounds (24) is Eulan Asept P ^{R} (26), which has great bactericidal and fungicidal effectiveness, and is used for antimicrobial finishing of textiles [19]. The effectiveness of this product against microorganisms has also earned its importance as a preservative for cut flowers [20].

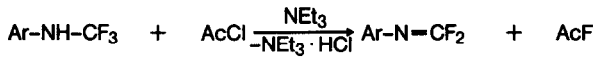


(26)

Under the same reaction conditions as for the sulfenylizations, however, acylation reactions with carboxylic acid chlorides cannot be performed with (19) and (21).



(19)



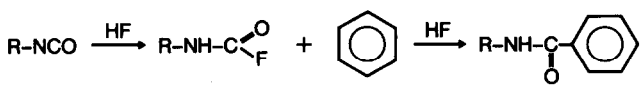
(21) (27)

Whereas the carbamic acid fluorides (19) split to form isocyanates, the N-trifluoromethylamines (21) are converted into isocyanide difluorides (27) or their dimers [21].

Friedel-Crafts reactions in HF

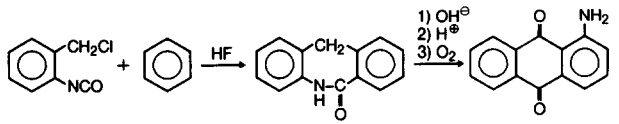
As a reagent with excellent Friedel-Crafts activity, anhydrous hydrogen fluoride displays a number of advantages in relation to the more commonly used Lewis catalysts. Its low boiling point excludes overheating of the reaction mixture, and it also allows easy removal and virtually complete recovery of the excess acid. No secondary reactions such as fluorination of aromatic nuclei or their couplings take place. HF is used on the large scale in petrochemical alkylation processes [22].

A Friedel-Crafts reaction also takes place in the conversion of aromatic hydrocarbons - benzene, to take the simplest instance - with isocyanates in hydrogen fluoride.



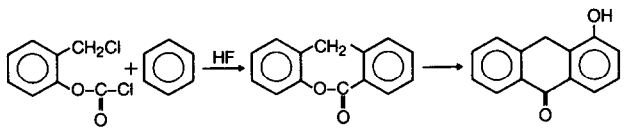
In this type of reaction, the actual Friedel-Crafts acylation is preceded by a reaction whereby HF is added to the isocyanate forming a carbamic acid fluoride [23].

Reference has already been made to ortho-trifluoromethylphenyl isocyanate (6). A preliminary stage in the formation of this compound is o-chloromethylphenyl isocyanate (28), which is readily convertible with benzene in HF. In the primary stage alkylation occurs, followed by acylating cyclization to form the lactam (29). Then, by means of alkaline induced hydrolysis into aminocarboxylic acid, an acidically catalyzed cyclization to anthrone and subsequent oxidation, 1-aminoanthraquinone (30) is formed, which is used as an intermediate in the synthesis of dyestuffs [24].



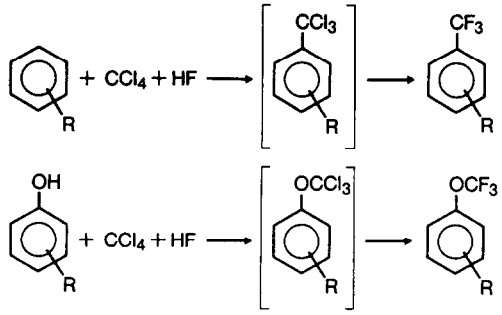
(28) (29) (30)

The conversion of the carbonic acid derivative (31) with benzene in HF, also under acylating conditions, proceeds through oxepinone (32) which can be isolated as an intermediate, to form 4-hydroxyanthrone (33) [25].



(31) (32) (33)

A convincing example of the use of hydrogen fluoride as a specific trifunctional medium - as a solvent, fluorinating agent and Friedel-Crafts catalyst - is the recently developed, advantageous method of synthesizing trifluoromethyl substituted aromatics. Using this process, the classical expedient of side chain chlorination followed by fluorination can be circumvented. In a single stage synthesis, C-alkylation occurs in the tetrachloromethane/hydrogen fluoride system with the use of benzene and its substituted derivatives [26], and O-alkylation occurs when phenols are used, which requires distinctly more stringent reaction conditions [27]. The corresponding trifluoromethyl derivatives are obtained in each case.



R: H, NO_2, Cl, F, CN, CH_3

The important primary stage in this reaction consists in the HF-catalyzed alkylation, in the transitional phase of which a complex of aromatic, tetrachloromethane and hydrogen fluoride is formed. Of the three components present in the reaction mixture, any two reaction partners alone will not react with each other at temperatures up to 150 °C. The second stage then follows in the form of the chlorine/fluorine exchange, which leads to the end product. The importance of the side chain fluorinated aromatics has already been indicated in the beginning.

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