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A New Method for the Trifluoromethylation of Aromatics*

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SUMMARY

A new method is discribed for introducing a CF_3-group, by a single-step synthesis, into aromatic compounds. This trifluoromethylation is done by means of a mixture consisting of HF/CCL_4 and the aromatic compound. The reaction is thought to be of a Friedel-Crafts type and limited to aromatics which are not substituted by electron withdrawing groups.

INTRODUCTION

Trifluoromethyl aromatics form an important class of compounds, the importance of which is increasing continuously because of the fact that - in active ingredient research, for example - the special properties of the trifluoromethyl group (which are conferred on it by the electron-withdrawing lipophile moiety) enable the biological effects of many types of compound to be improved. Methods for the synthesis of aromatics with CF_3 substituents are therefore of industrial interest.

The known methods for the production of substituted trifluoromethyl aromatics can be divided into two groups. One of the groups comprises all the methods in which a trifluoromethyl aromatic is first produced, either by fluorination of a trichloromethyl aromatic [1] or by reacting an aromatic carboxylic acid with SF_4 [2], and afterwards functionalized in a second reaction.

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* Dedicated to Professor Grünewald on the occasion of his 60th birthday.

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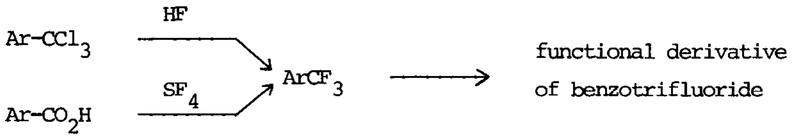


The other group comprises all the methods in which the CF_3 group is introduced into an aromatic as a radical.

$$CF_3\text{-}X \xrightarrow{\text{catalyst}} CF_3\cdot + X\cdot$$

$$CF_3\cdot + ArY \longrightarrow ArCF_3 + Y\cdot$$

The CF_3 radicals are produced either from trifluoroiodomethane [3] or from silver trifluoroacetate [4] . As, however, the CF_3 radicals are not formed at all readily, such substitution reactions require severe conditions and long reaction times. Radical substitution reactions on aromatics have the additional drawback that the product is generally a mixture of a fairly large number of isomers, and often includes polysubstituted derivatives also.

In the course of our work on organofluorine compounds [5] we have found a novel process for the trifluoromethylation of aromatics which substantially eliminates the above-mentioned disadvantages of radical trifluoromethylation. This process complements the methods belonging to the first of the two groups just referred to because CF_3 aromatics, which are difficult or impossible to produce according to those methods, are readily accessible in this particular case.

PROCESS

The process is based on the action of carbon tetrachloride/hydrofluoric acid (CCl_4/HF) on aromatics. The mixture of hydrofluoric acid, carbon tetrachloride, and aromatic is produced in a suitable autoclave at a temperature of about 0 to 10 °C and it is then heated to the desired reaction temperature under pressurized nitrogen.

$$Ar\text{-}H \xrightarrow[HF]{CCl_4} ArCF_3 + 4\ HCl$$

Table 1 gives examples to show how the new process can be used and outlines its range of application.

The trifluoromethylation is carried out with an excess of CCl_4/HF. When molar quantities are used, quantitative conversion is not generally achieved and it is difficult to separate the starting compound and the corresponding benzotrifluoride in some cases. Extending the reaction time generally raises the degree of conversion. Efficient mixing of the two-phase system is also necessary for a high rate of conversion in unit time.

RESULTS AND DISCUSSION

Apart from the reaction products listed in Table 1, no further isomers, no bistrifluoromethyl aromatics, and no difluorochloromethyl aromatics were found in appreciable quantities. As may also be seen from Table 1, the substitution conforms to the laws governing the electrophilic attack on the aromatic and is in some cases more selective, and in a few cases less selective, than other electrophilic substitution reactions (e.g. Friedel-Crafts reactions). The isomer distribution determined by the selectivity of the reaction cannot be influenced by the reaction parameters, e.g. pressure, time, temperature, and concentration. The isomer distribution also remains unchanged if the reaction is terminated prematurely (with the result that a low degree of conversion is obtained). A marked deviation from the general rules of substitution is observed in the case of toluene. In relation to, e.g., the acylation of toluene with acetyl chloride according to Friedel-Crafts the trifluoromethylation of toluene is comparatively unselective. The high proportion of 3-methylbenzotrifluoride is particularly surprising. The trifluoromethylation reactions of 2- and 3-chlorotoluene are highly selective, however. With 4-chlorotoluene the result cannot be predicted, since an isomerization evidently occurs in this case. Under the experimental conditions the 4-chlorotoluene is not isomerized by hydrofluoric acid. The structure of the 'isomerized product' appears plausible but has not been proved. The positions of the methyl and trifluoromethyl groups in relation to one another can be easily detected by catalytic hydrogenation of the chlorine atom attached to the aromatic nucleus.

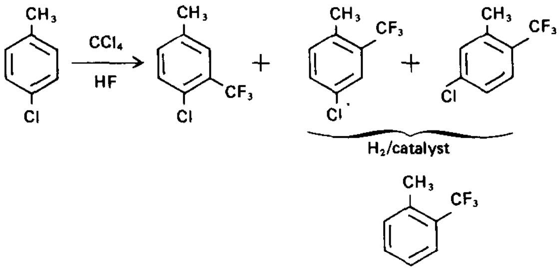
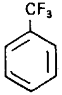
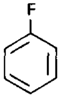
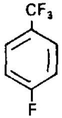
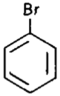
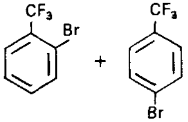
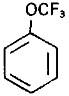
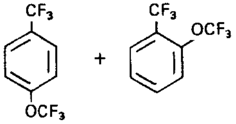
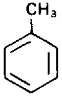
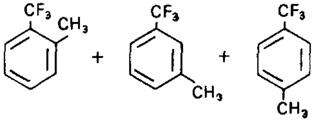
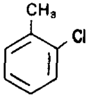
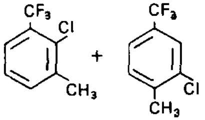


TABLE 1

	Starting compound	Quantities			Time/Temp.	Conversion	Selec-tivity	Products
		Arom. (g)	CCl_4 (ml)	HF (ml)				
1		50	300	250	5h/100°C	100	92	
2		100	500	500	10h/110°C	42	96	
3		500	1800	1700	6h/120°C	63	97	 2 : 1
4		100	500	500	6h/120°C	56	91	 3 : 1
5		500	2000	1000	12h/100°C	~90	67	 13 : 42 : 45
6		300	1200	900	6h/110°C	85	96	 1 : 2

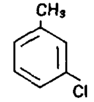
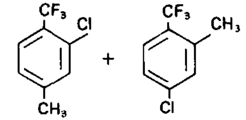
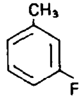
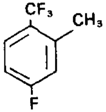
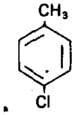
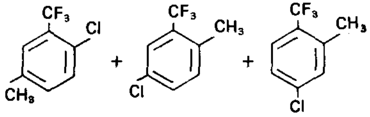
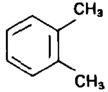
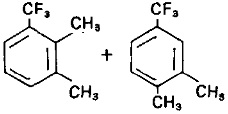
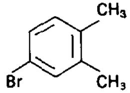
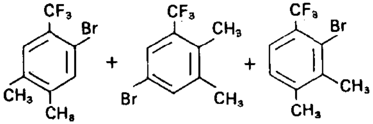
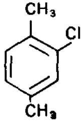
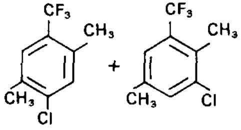
7		860	1500	1500	10h/105°C	95	96	 3 : 1
8		110	600	500	8h/105°C	68	87	
9		250	1200	500	12h/105°C	97	94	 75 : 13 : 12
10		100	800	500	6h/105°C	100	30	 64 : 36
11		550	1600	1600	7h/110°C	93	91	 54 : 21 : 10
12		140	600	500	10h/103°C	95	92	 97 : 3

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TABLE 1 *(cont.)*

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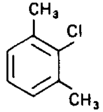
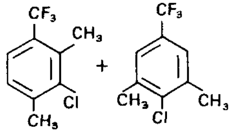
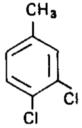
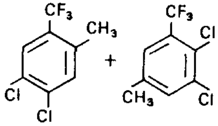
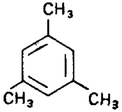
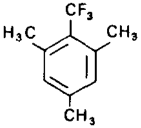
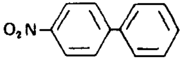
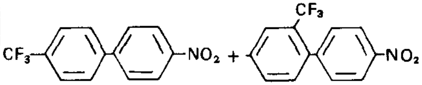
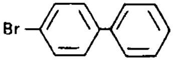
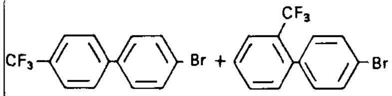
13		180	650	600	10h/101°C	92	90	 84 : 16
14		140	600	500	12h/115°C	25	93	 20 : 3
15		400	1500	1500	20h/93°C	92	65	
16		100	500	500	8h/110°C	92	84	 8 : 6
17		50	350	300	6h/105°C	100	26	 82 : 18

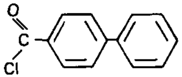
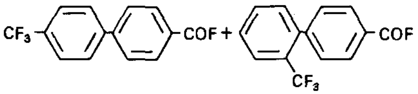
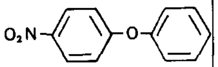
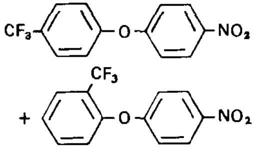
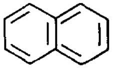
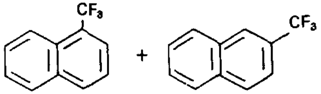
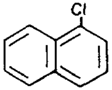
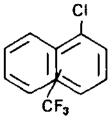
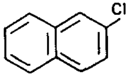
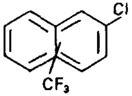
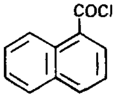
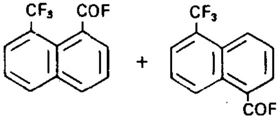
18		100	500	500	6h/110°C	90	53	 9 : 1
19		200	650	650	8h/106°C	93	73	 6 : 4
20		128	600	500	4h/105°C	100	50	 4 : 6
21		750	1900	1600	8h/105°C	95	76	
22		240	1050	650	10h/105°C	100	67	
23		400	1800	1800	7h/109°C	95	80	 8 : 92

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TABLE 1 *(cont.)*

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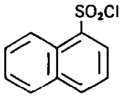
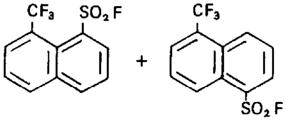
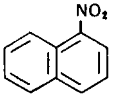
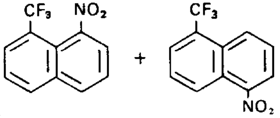
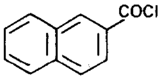
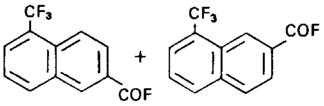
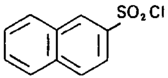
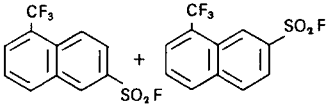
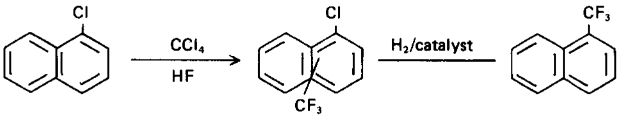
24		400	1800	1800	8h/108°C	100	80	 35 : 65
25		100	400	400	6h/110°C	22	42	 50 : 50
26		100	500	450	7h/110°C	100	90	 65 : 35
27		100	400	500	8h/110°C	100	75	 65 + 35

N.B. The reaction conditions are not in all cases such as to give the optimum yield.

* From all reaction products correct mass spectra are obtained. Isomer ratios are determined by F^{19} nmr and glc. The products are identified by comparison by their F^{19} nmr-spectra with those of authentic examples or by further reactions like hydrolysis or nitration.

As the 4-chlorotoluene was spectroscopically uniform, chlorotrophy must have occurred during the trifluoromethylation. In the trifluoromethylation process the xylenes and halogenated xylenes behave as they do in other electrophilic substitution reactions. Similarly, the biphenyls and diphenyl ethers present a uniform appearance, with a marked selectivity in relation to the p-substitution.

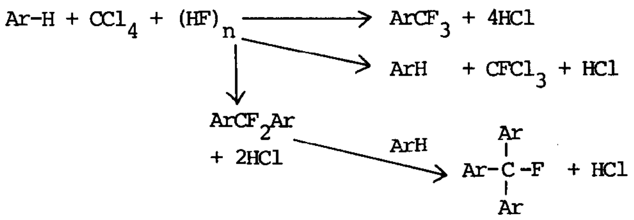
As regards the naphthalenes, only the reactions of 1- and 2-chloronaphthalene are characterized by the formation of complex isomer mixtures. But the proportions of those isomers which give the 1-trifluoromethyl naphtalene after hydrogenolytic removal of the halogen attached to the nucleus are particularly large.



The 2-trifluoromethyl naphthalene is practically impossible to isolate after the hydrogenation.

The fact that the behaviour of the trifluoromethylation reagent CCl_4/HF partly differs from that of other electrophilic reagents is presumably attributable to the 'solvent HF'. The number of experimental findings is not yet sufficient, however, for a comparison which would enable this assumption to be generalized.

The following reaction routes are observed in the trifluoromethylation process with which we are concerned :



$$\begin{tikzcd}
\text{Ar-H} + CCl_4 + (HF)_n \arrow[r] \arrow[dr] \arrow[dd] & ArCF_3 + 4HCl \\
 & ArH + CFCl_3 + HCl \\
ArCF_2Ar + 2HCl \arrow[r, "ArH"] & \text{Ar-}\overset{\text{Ar}}{\underset{\text{Ar}}{\text{C}}}\text{-F} + HCl
\end{tikzcd}$$

It is observed that fluorotrichloromethane is formed to different extents. With aromatics having low degrees of nucleophily this side-reaction is more pronounced; and it becomes the main reaction in the case of aromatics which can no longer be subjected to trifluoromethylation (e.g. nitrobenzene).

Hence the two-fold trifluoromethylation, i.e. the trifluoromethylation of a CF_3 aromatic, is not observed either.

Another side-reaction is the multiple arylation of carbon tetrachloride. But it occurs to a minor extent only. In cases where it becomes the main reaction unfavourable experimental parameters (of concentration and temperature) appear to be responsible for this, from which it follows that the reaction can be influenced in the desired direction by altering these parameters.

The described method for the trifluoromethylation of aromatics is a variant of Friedel-Crafts acylation. It is based on two characteristic properties of anhydrous hydrofluoric acid: its ability a) to catalyze electrophilic substitutions on aromatics of the type given by Friedel-Crafts reactions and b) to serve as a fluorination agent for trichloromethyl groups.

The interpretation of trifluoromethylation as a reaction of the Friedel-Crafts acylation type also agrees with the observation, mentioned above, that aromatics with substituents of the second order cannot be made to react, which they can if the mechanism is radical. Additions of radical-forming agents, e.g. copper salts, influence the reaction adversely, while even small additions of such compounds as sodium fluoride, potassium fluoride, or pyridine suppress the reaction entirely. The ability of hydrofluoric acid to act as Friedel-Crafts catalyst is strongly influenced by even small amounts of such bases.

We interpret this to mean that a complex consisting of an aromatic, carbon tetrachloride, and a solvate envelope of hydrofluoric acid is formed and that, depending on the conditions, this is then able to react in the indicated way. This hypothesis is supported by the fact that, under the conditions under which the trifluoromethylation is generally carried out, carbon tetrachloride fails to react with hydrofluoric acid alone to give fluorotrichloromethane.

In a possible complex with the reagent the aromatic is therefore decisively important. Under these conditions the effect of a reduction of the hydrofluoric acid concentration also becomes understandable: arylation is still possible, but the HF concentration is not sufficient for immediate fluorination of the primary product. Multiple arylations by the primary product are the consequence.

Although the reaction partner consisting of carbon tetrachloride and HF solvate envelope is quite voluminous, sterical factors do not play a decisive part. Thus mesitylene, for example, can be trifluoromethylated with CCl_4/HF without difficulty.

EXPERIMENTAL

At 0 °C the anhydrous hydrofluoric acid and then the mixture of the aromatic and carbon tetrachloride were introduced into a stainless steel autoclave having an agitator, a brine-cooled reflux condenser and a pressure relaxation valve. Nitrogen at a pressure of about 3-5 bar was then introduced and the reactor heated to the desired reaction temperature. The resulting hydrogen chloride was relaxed continuously, but only to such an extent that the hydrofluoric acid remained pressurized. At the end of the reaction the vessel was cooled and the reaction mixture placed on ice, after which the organic phase was separated off. Alternatively the mixture can be subjected directly to fractional distillation in a stainless steel reaction vessel.

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