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DIRECT FLUORINATION OF ARYL OXYGEN COMPOUNDS*

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SUMMARY

A study has been made of the reaction of aryl oxygen compounds with elemental fluorine in hydrogen fluoride and acetonitrile. Hydrogen fluoride acted as a good solvent in the reaction of salicylic acid, salicylaldehyde and phenyl salicylate. Salicylalcohol gave a mixture of fluorination and oxidation products. Diphenyl derivatives were also fluorinated and gave mainly monofluoro compounds.

INTRODUCTION

We have previously reported the results of the study of the fluorination of phenol and cresols dissolved in various solvents using elemental fluorine [1].
This paper reports the results of the successful fluorinations of some other aromatic derivatives. These compounds include hydroxy acids, hydroxy aldehyde, hydroxy alcohol, phenyl salicylate and biphenyl derivatives. Their reaction with elemental fluorine has not yet been reported.
We have previously studied the use of hydrogen fluoride as a solvent for the fluorination of uracil and found it was useful for the purpose [2]. Hydrogen fluoride is a material which is economical to use and which is inert to the influence of fluorine.

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In this report we describe the use of hydrogen fluoride as a solvent for the direct fluorinations mentioned above.

RESULTS AND DISCUSSION

A study was made of the comparison of solvents when phenol was allowed to react with large excess of elemental fluorine. When 5 % solutions in hydrogen fluoride, 65 % aqueous hydrogen fluoride and acetonitrile were fluorinated at -10 °C over a period of 120 minutes, conversions of phenol in the order of 90-100 % were obtained.

As shown in Table 1, anhydrous hydrogen fluoride is not a good solvent for the production of monofluorides from phenol itself. Most of the phenol was consumed but only a 35 % yield of fluoro-compounds was obtained, whereas with acetonitrile 77 % of these compounds was formed.

In 65 % aqueous hydrogen fluoride, the yields were substantially better. In a previous paper [1], we have reported the o:p ratio changed drastically in acetonitrile as the conversion of phenol increased. At higher conversion, the ratio decreased.

In hydrogen fluoride, the ratio was quite different from that in acetonitrile.

The ratio is almost 1:1 in hydrogen fluoride whereas it is 2:1 in acetonitrile.

Table 1.

Fluorination of Phenol in Different Solvents

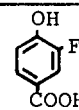
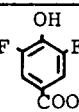
Solv.	Conv. of Phenol %	Yield %			o/p Ratio
					
CH_3CN	90.8	44.4	23.0	10.1	1.93
HF	94.8	14.6	15.1	5.4	0.97
65 % HF	100.0	25.8	25.0	19.5	1.03

Phenol : 0.04 mole, F_2 : 0.12 mole

Table 2 shows the results of fluorination of p-hydroxy benzoic acid in acetonitrile and in hydrogen fluoride at -10 °C. The products were mainly mono and difluoro compounds. As can be seen, the use of both acetonitrile and anhydrous hydrogen fluoride gave good yields of 3-fluoro-4-hydroxy benzoic acid. However, it should be noted that the presence of water in hydrogen fluoride led to the formation of relatively large amounts of difluoro compound even though the conversion of starting material was much less than when anhydrous hydrogen fluoride was used with the same amount of fluorine.

Table 2.

Fluorination of p-Hydroxybenzoic Acid

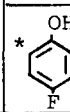
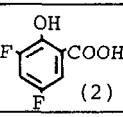
Solv.	Conv. of p-Hydroxy-benzoic Acid %	F_2 mole	Yield %		Ratio (1)/(2)
			 (1)	 (2)	
CH_3CN	63.3	0.0543	59.4	14.4	4.23
CH_3CN	89.0	0.0724	59.6	20.8	2.87
HF	81.8	0.0543	63.2	13.4	4.68
65 % HF	18.5	0.0543	31.2	43.4	0.72

Reaction Temperature : -10 °C
Reaction Time : 90 min. for 0.0543 mole F_2
120 min. for 0.0724 mole F_2
p-Hydroxybenzoic Acid : 0.04 mole

Table 3 shows the results of the fluorination of salicylic acid. Reaction in anhydrous hydrogen fluoride and a 65 % solution of hydrogen fluoride in water also gave different results. In a water solution, only trace of simple fluorinated products were obtained and the starting material was recovered. However, anhydrous conditions led to large conversions and high yields of 5-fluoro-2-hydroxybenzoic acid. Much less difluorination occured in hydrogen fluoride solution than in acetonitrile.

Table 3.

Fluorination of Salicylic Acid

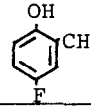
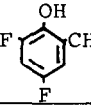
Solv.	Conv. %	F_2 mole	Yield %		Ratio (1)/(2)
			*  (1)	 (2)	
CH_3CN	79.0	0.0543	55.9	21.0	2.69
CH_3CN	94.5	0.0724	62.6	31.0	2.04
HF	83.7	0.0543	72.6	9.8	7.33
65 % HF	23.5	0.0543	trace	trace	----

* Containing some 3-fluoro-salicylic acid

Reaction Temperature : -10 °C
Reaction Time : 90 min. for 0.0543 mole F_2
120 min. for 0.0724 mole F_2
Salicylic Acid : 0.04 mole

Table 4.

Fluorination of Salicylaldehyde

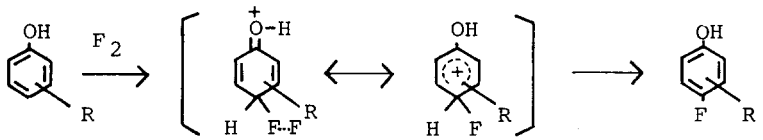
Solv.	Conv. %	F_2 mole	Yield %			5F-isomer / 3F-isomer
						
CH_3CN	62.9	0.0410	22.1	32.1	5.1	1.46
CH_3CN	82.9	0.0615	18.2	28.6	5.9	1.56
CH_3CN	94.9	0.0820	13.9	20.3	9.0	1.46
HF	91.7	0.0615	18.6	60.1	9.1	3.23
65 % HF	96.6	0.0615	6.1	58.9	15.4	9.63

Reaction Temperature : -10 °C
Reaction Time : 60 min. for 0.0410 mole F_2
90 min. for 0.0615 mole F_2
120 min. for 0.0820 mole F_2
Salicylaldehyde : 0.04 mole

The results of the fluorination of salicylaldehyde were interesting as shown in Table 4. It should be noted that essentially no oxidation of aldehyde group to acid occured. This result is somewhat interesting considering the oxidizing power of fluorine and extreme reactivity of the aldehyde group toward oxidizing agents.

In all cases studied more fluorine entered the position para to hydroxy group than ortho. The ratio of products was different in all three solvent systems.

The fluorination of hydroxy substituted benzoic acids and aldehydes might occur by the SE 2' type reaction as suggested by A. P. Wolf et al. [3].



R = COOH, CHO

Scheme

Fig. 1 shows the unusual results of the fluorination of salicyl alcohol. No reaction took place in anhydrous hydrogen fluoride and in hydrogen fluoride-water solution. With acetonitrile, fluorination and oxidation occured at the same time. The yields of expected fluorosalicyl alcohol were low and considerable amounts of fluoro phenols and fluorosalicylaldehydes were obtained. These results show that oxidation of the methylol group to aldehyde occured, followed by a deformylation reaction.

As shown in Fig 2, diphenyl compounds were also fluorinated and gave mainly monofluoro compounds in acetonitrile and in hydrogen fluoride.

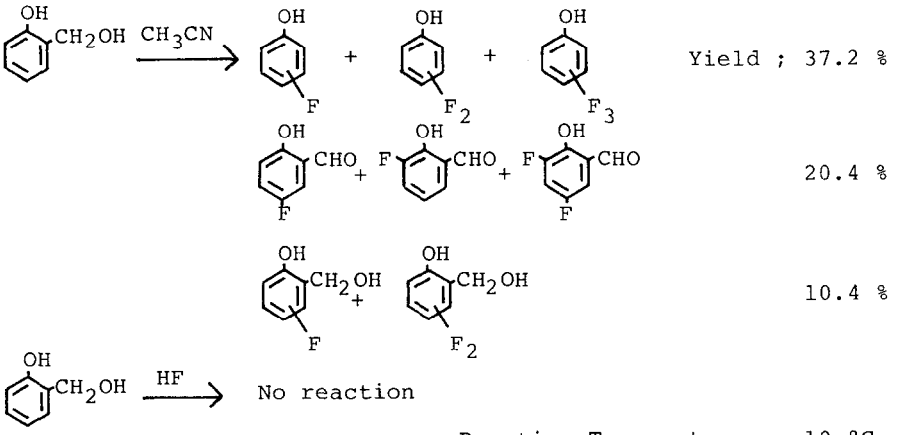


Fig. 1 Fluorination of Salicyl alcohol

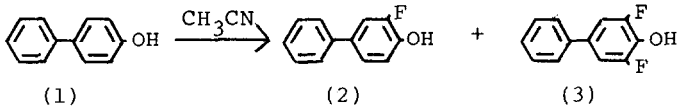
p-Phenyl phenol gave mono and difluoro compounds in acetonitrile and the ratio of mono : difluoro derivative was 2.3 : 1.0. No reaction occured in hydrogen fluoride.
It should be noted that the fluorine always entered the aromatic ring containing the hydroxy group.

The fluorination of 3-phenyl salicylic acid gave only the monofluoro derivative in acetonitrile or in hydrogen fluoride. In hydrogen fluoride, the conversion of 3-phenyl salicylic acid was only 39.7 %. On the other hand, 81 % conversion was obtained in acetonitrile.

Mono and difluoro compounds were also obtained from the reaction of phenyl salicylate.
The ratio of mono to difluoride was 5 : 1 in acetonitrile but only the monofluoro derivative was produced in hydrogen fluoride.

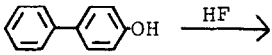
EXPERIMENTAL

The apparatus and procedure used for the fluorination have described in a previous paper [1].



(1) (2) (3)

Yield : 50.1 % 21.5 %



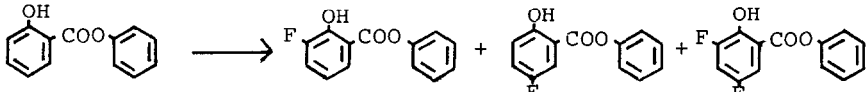
(1)

(4) (5)

Solv. : Yield

CH_3CN : 70.9 %

HF : 93.4 %



(6) (7) (8) (9)

Solv. : CH_3CN, Yield : 44.6 % (7), 29.8 % (8), 13.7 % (9)

HF, Yield : 88.6 % (7 and 8), trace (9)

Reaction Temperature : -10 °C

Reaction Time : 90 min.

Substrate : 0.04 mole

F_2 : 0.06 mole

Fig. 2 Fluorination of Diphenyl Compounds and Phenyl Salicylate

The solutions fluorinated consisted of 0.04 mole of substrate dissolved in enough solvent to give 5 % solution.
The reaction was carried out for 60 minutes to 120 minutes depending on the amounts of fluorine used.

After the reaction, the solvent was removed under reduced pressure, the residue was dissolved in acetone and separated by the use of vapor phase chromatographic equipment with a 3 m x 2 mm column filled with 5 % SE-30 on 80-100 mesh Chromosorb WAW DMCS. The fluoro derivatives of p-hydroxybenzoic acid, salicyli acid, salicyl alcohol and phenol were all known compounds and were identified by comparison with their known properties and by the use of Mass and NMR spectroscopy.

The fluoro derivatives of diphenyl compounds and phenyl salicylate were identified by NMR and Mass spectrometry. The ratio of isomer and the yields were determined by gas chromatography and NMR.

Fluorination of 4-phenyl phenol (1)

4-Phenyl phenol (1) was fluorinated with excess of fluorine Gas chromatography showed the yield of 2-fluoro-4-phenyl phenol (2) and 2,6-difluoro-4-phenyl phenol (3) was 50.1 % and 21.5 % respectively.

2-Fluoro-4-phenyl phenol : MS ; m/e = 188(M^+), 169(M-F), 159 (M-COH), 139(M-COH-HF), 133(M-C_3H_3O).

^{19}F NMR (TFA external) ; δ 60.3 ppm(2F, dd, J = 13.3 Hz).

2,6-Difluoro-4-phenyl phenol (3) : MS ; m/e = 206(M^+), 188(M-F), 177(M-CHO), 159(M-CHO-HF).

^{19}F NMR (TFA external) ; δ 72.9 ppm(2,6F, m).

Fluorination of 3-phenyl salicylic acid (4)

5-Fluoro-3-phenyl salicylic acid (5) was obtained as a main product from the fluorination of 3-phenyl salicylic acid (4). The crude reaction product obtained was dissolved in CH_2Cl_2, treated with 1.5 equimolar amount of N,O-bis(timethysilyl)-acetamide for 1 h at room temperature and analyzed by gas chromatography.

In acetonitrile, the conversion of 3-phenyl salicylic acid (4) was 81.1 % and the yield of fluorinated compound (5) was 70.9 %. Though the conversion was only 39.7 % in hydrogen fluoride, 93.4 % yield was obtained.

MS ; m/e = 361($M-CH_3$), 343($M-CH_2-F$), 295($M-C_4H_3-2CH_3$), 77(C_6H_5), 73[$Si(CH_3)$].
^{19}F NMR (TFA external) ; δ 72.9 ppm(5F, t, J =9.0 Hz).

Fluorination of phenyl salicylate (6)

Phenyl salicylate (6) was also fluorinated and the product analyzed. Gas chromatography and NMR showed the yield of 3-fluorophenyl salicylate (7), 5-fluorophenyl salicylate (8) and 3,5-difluorophenyl salicylate (9) was 44.6 %, 29.2 % and 13.7 % respectively in acetonitrile.
In anhydrous hydrogen fluoride, monofluorophenyl salicylate (7,8) was obtained with 88.6 % yield but only small amount of difluoro derivative (9) was obtained.
3-Fluorophenyl salicylate (7) and 5-fluorophenyl salicylate (8) : MS ; m/e = 232(M^+), 139($M-C_6H_5O$), 111($M-C_6H_5COO$), 94(C_6H_5OH).
^{19}NMR (TFA external) ; δ 47.4 ppm(5F, t, d, J = 9.4, 5.1 Hz), δ 60.1 ppm(3F, d, d, J = 11.0, 4.2 Hz).

3,5-Difluorophenyl salicylate (9) : MS ; m/e = 250(M^+), 157 ($M-C_6H_5O$), 129($M-C_6H_5COO$), 94(C_6H_5OH).

ACKNOWLEDGEMENT

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3 F. Cacace, P. Giacomello and A. P. Wolf, J. Amer. Chem. Soc., 102, 3511 (1981).