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DIRECT FLUORINATION OF PHENOL AND CRESOLS

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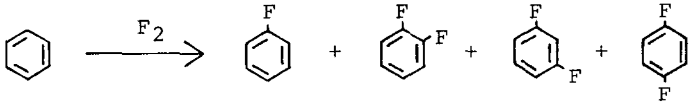
SUMMARY

A study has been made of the reaction of phenol with elemental fluorine using a variety of solvents and reaction temperatures. Yields of o- and p-fluorophenol were obtained as high as 85%. The isomer ratio changed drastically between phenol conversions of 10% and 56%. The o-isomer changed to unidentified polymeric substances at higher conversion, but it might also be assumed that interconversion of some isomers is occuring. The three cresols have also been successfully fluorinated with elemental fluorine. p-Cresol gave some expected 2-fluoroderivative but also formed a fluorocyclohexadienyl ketone.

INTRODUCTION

The usual process for the introduction of fluorine into an aromatic ring is by the Schiemann reaction [1]. However, Grakauskas [2] has shown that the fluorination of benzene with elemental fluorine at -35° led to small amounts of substituted products when relative large ratios of fluorine to benzene were used.



Toluene was fluorinated at -70° and the monofluoro derivatives were obtained in a ratio of 5:4:1 for o, p and meta isomer ;

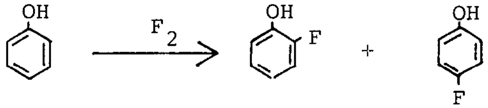
38% of the toluene was converted to a monofluorotoluene. Nitrobenzene gave predominantly the m-fluoronitrobenzene. On the basis of isomer distribution Grakauskas suggested that fluorination occurs via electrophilic aromatic substitution analogous to the ionic reaction of other halogens.

Cacase and Wolf [3] have studied the reaction of benzene, toluene, anisole and nitrobenzene with fluorine at low $[F_2]$:[Substrate] ratios to obtain low conversions, typically 0.1% of fluorine containing products.
They used low reaction temperatures and dilute solutions of substrate in CCl_3F, CH_3CN, C_6F_6 or $C_6F_5CF_3$. Under these conditions they minimized the polymerization and addition reactions characteristic of high $[F_2]$:[Substrate] ratios. They likewise propose a mechanism which involves the attack on the benzene ring by a polarized fluorine molecule leading to a arenium ion,

Fluorophenols are useful precursors to other compounds in the industrial world [4]. It seemed of interest to study the fluorination of phenols under conditions which might lead to high conversions of starting materials. Their reaction with elemental fluorine has not been previously reported. Furthermore it was felt that different conditions from those described previously could lead to conversions to monofluorides which would be sufficiently high to cause this process to be viable as a synthetic method. This paper reports the results of the fluorination of phenol and cresols at various temperatures using various solvents with fluorine introduced to the surface of the solutions.

RESULTS AND DISCUSSION

A study was made of the products formed when phenol was allowed to react with elemental fluorine under a variety of conditions. When 10% solutions, in acetonitrile, tetraglyme, methanol and chloroform were fluorinated at -20° over a period of 90 minutes, conversions of phenol in the order of 51-56% were obtained and yields of the two isomeric fluorophenols as high as 85% were realized.



Appreciably larger amounts of the o-derivative were formed as shown in Table 1 with o-: p-ratios ranging from 1.80:1 in chloroform to 3.64:1 in acetonitrile. These values compare with o:p ratios of the fluorotoluenes of 2:1 and fluoroanisoles of 3:1 obtained at very low fluorine concentration at -78° using CCl_3F as the solvent [3].

It should be noted that a relatively large amount of phenol was converted to products other than o- and p-fluorophenol when water was used as the solvent at a temperature of 5°. The temperature was not a factor in these results for appreciable yields of monofluorides were obtained when trifluoroacetic acid was the solvent.

Changes in reaction temperatures had an effect on the conversion of phenol to products suggesting that the reaction takes place with dissolved fluorine in the solvent.

As shown in Table 2 the highest conversion was obtained at -40°, the lowest temperature employed. A similar trend was noted with tetraglyme. No significant difference in o:p ratios was noted over a 50° range with CH_3CN or a 30° range for tetraglyme.

However, it was found that the isomer ratio changed drastically as the conversion of phenol increased. For example, at -20° in acetonitrile the o:p ratio was 22:1 at 10% conversion and 56% conversion the ratio was 3.6:1 as shown in Figs. 1 and 2. Some of the o-isomer changed to unidentified polymeric substances at higher conversion. In addition to the polymerization, it might be assumed that interconversion of isomers is occuring. However, it requires further study to confirm the mechanism. The reaction temperature has an important effect on the isomer ratio at low conversions. As can be seen from Fig. 1 with acetonitrile at -20°, the o:p ratio is 22:1 while at 10° the ratio is 10:1. These results indicate that o-fluorophenol could be made successfully by fluorination at low temperatures at low conversion rates. When tetraglyme was the solvent the o:p ratio was again much higher initially both at -20° and 0° but at longer times of reaction the ratios approached each other as shown in Fig. 2.

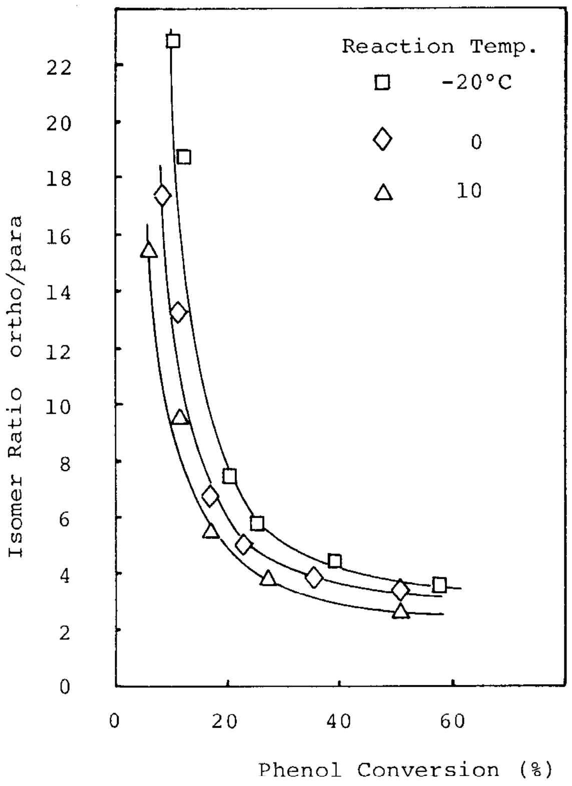


Fig. 1 Fluorination of Phenol in Acetonitrile Temperature Effect on Isomer Distribution of Products

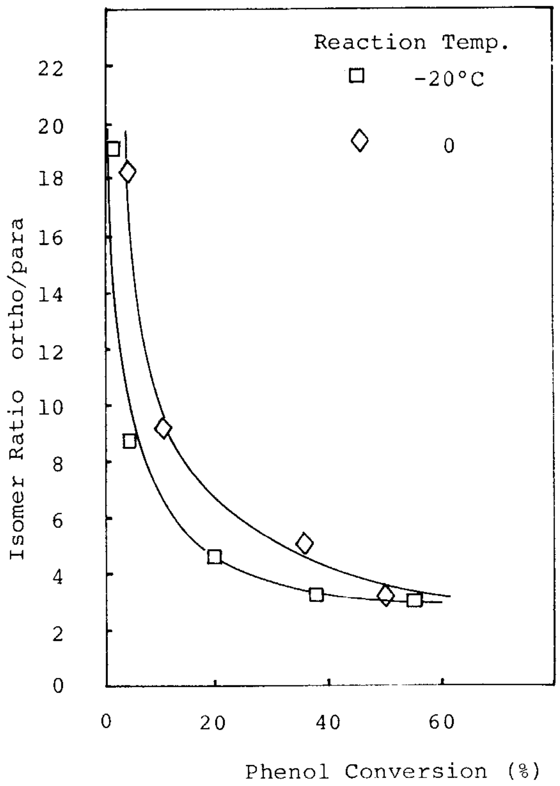


Fig. 2 Fluorination of Phenol in Tetraglyme Temperature Effect on Isomer Distribution of Products

TABLE 1

Fluorination of Phenol in Different Solvents

Reaction Condition		Conv. of Phenol %	Yield %		Isomer Ratio
Temp. °C	Solv.		o-Fluoro phenol	p-Fluoro phenol	ortho/para
-20	CH_3CN	56.1	38.9	10.7	3.64
-20	TG*	53.9	54.7	21.9	2.50
-20	CH_3OH	53.5	47.7	13.3	3.59
5	H_2O	52.9	7.0	2.6	2.69
5	CF_3COOH	52.0	56.1	17.0	3.30
-20	$CHCl_3$	51.4	54.5	30.2	1.80

* Tetraglyme

TABLE 2

Fluorination of Phenol at Different Temperatures

Reaction Condition		Conv. of phenol %	Yield %		Isomer Ratio
Temp. °C	Solv.		o-Fluoro phenol	p-Fluoro phenol	ortho/para
-40	CH_3CN	63.5	42.4	11.0	3.85
-20	CH_3CN	56.1	38.9	10.7	3.64
0	CH_3CN	50.9	34.1	9.0	3.79
10	CH_3CN	44.7	53.9	16.6	3.25
-20	TG	53.9	54.7	21.9	2.50
0	TG	48.9	57.0	22.7	2.51
10	TG	48.5	63.5	24.1	2.64

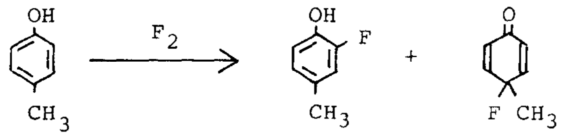
As shown in Table 3 the addition of BF_3 to CH_3CN gave a higher conversion of phenol but no greater yield of monofluorophenols was found. Ferric chloride slowed the reaction in acetonitrile.

Anisole was also fluorinated under conditions similar to those used for phenol. As might be expected from the fact that the methoxy group does not exert as strong an orienting effect in ionic substitution reaction as OH, an appreciable amount of m-fluoroanisole was formed. The ratio of o-fluoroanisole to p-fluoroanisole was 1.67:1 as shown in Table 4. These results compare to a ratio of 3.23:1 reported by Cacase and Wolf at conversion perhaps as low as 0.01% and would suggest that the o-isomer was involved in an equilibrium such as was proposed for the fluorophenols.

The fluorination of o-cresol gave o:p ratio closer to 1:1 as would be expected. As shown in Table 5 conversions were high and the isomer ratio was not greatly affected by changes in solvent and temperature.

m-Cresol afforded a mixture of o-substituted products that could not be separated. However it was determined that the chief o-substituted product was the 2-fluoroderivative. The o:p ratio was largely unchanged by different solvents or different temperatures as shown in Table 6.

The fluorination of p-cresol gave the expected o-derivative but also produced a non-aromatic compound.



The structure of the latter was determined by elemental analysis, ^1H and ^{19}F nmr, infrared and mass spectral studies. The proton signal were assigned as shown in Fig. 3 and ^{19}F spectrum is given in Fig. 4. The infrared spectrum shows the absorption due to the carbonyl group, carbon-carbon bonds and fluorine. The mass spectrum is similar to that of benzoquinone.

TABLE 3

Effect of Catalyst on Fluorination of Phenol

Reaction Condition			Conv. of	Yield %		Isomer Ratio
Temp. °C	Solv.	Catalyst	phenol %	o-Fluoro phenol	p-Fluoro phenol	ortho/para
-20	CH_3CN	——	56.1	38.9	10.7	3.64
-20	CH_3CN	BF_3[a]	64.2	34.4	12.3	2.80
-20	CH_3CN	$FeCl_3$[b]	50.7	42.0	13.6	3.09

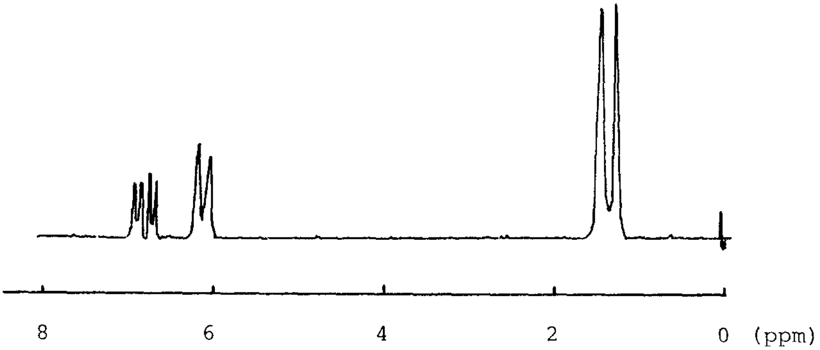
a; 0.026 mole

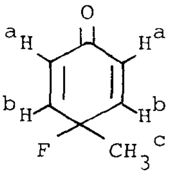
b; 0.030 mole

TABLE 4

Fluorination of Anisole

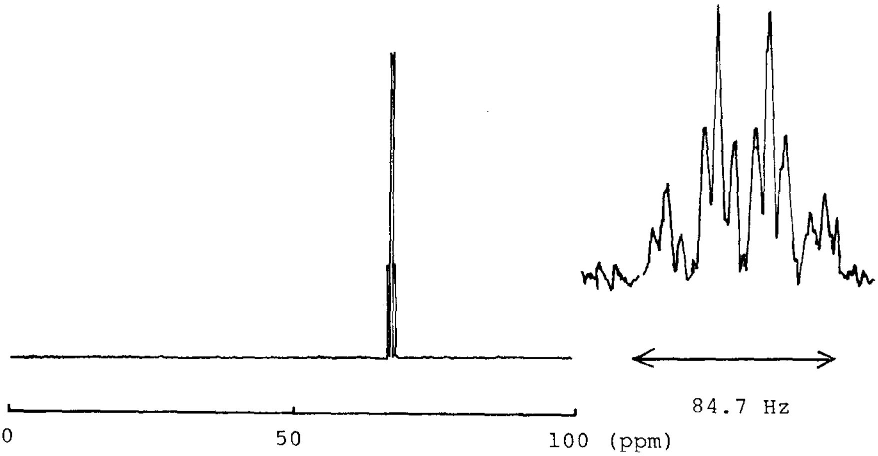
Reaction Condition		Conv. of anisole %	Yield %			Isomer Ratio
Temp. °C	Solv.		o-Fluoro anisole	m-Fluor anisole	p-Fluoro anisole	o/m/p
-20	CH_3CN	65.3	36.9	5.1	22.0	7.2/1.0/4.3





	δ (ppm)	J (Hz)	
H^a	6.1 (d)	J (H^a-H^b)	9.0
H^b	6.8 (d d)	J (H^a-H^b)	9.0
H^c	1.4 (d)	J (H^c-F)	5.9
		J (H^c-F)	22.5

Fig 3 ^1H NMR Spectrum of Compound (B)



δ +68.1* (q t) ppm J ($F-CH_3$) 22.0 (Hz) * Upper field from
J (F-vic H) 5.9 (Hz) ext. TFA

Fig. 4 ^{19}F NMR Spectrum of Compound (B)

TABLE 5

Fluorination of o-Cresol

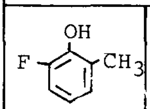
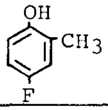
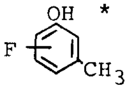
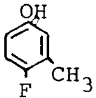
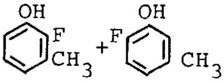
Reaction Condition		Conv. of o-Cresol %	Yield %		Isomer Ratio ortho/para
Temp. °C	Solv.				
0	CH_3CN	65.0	23.1	26.5	0.87
-20	CH_3CN	70.8	22.5	27.5	0.82
0	TG	58.0	28.4	39.7	0.72
-20	TG	65.0	29.2	43.1	0.68
-20	$CHCl_3$	74.7	25.3	26.2	0.97

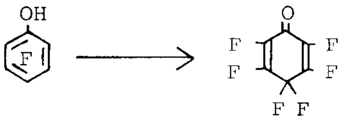
TABLE 6

Fluorination of m-Cresol

Reaction Condition		Conv. of m-Cresol %	Yield %		Isomer Ratio ortho/para
Temp. °C	Solv.		 *		
0	CH_3CN	68.0	46.2	18.4	2.51
-20	CH_3CN	67.7	46.4	20.7	2.24
0	TG	61.7	43.6	23.7	1.84
-20	TG	65.7	40.9	14.6	2.80
-20	$CHCl_3$	68.0	32.7	14.6	2.24

* 

Devynck et al., [5] have obtained a similar compound in 56% yield from the electrochemical oxidation of pentafluorophenol



As shown in Table 7, the choice of solvent has marked influence on the relative amounts of the two products. Conversions were high with all solvents used but the ratio of substitution to addition product changed from 6.27:1 with CF_3COOH to 1.07:1 in tetraglyme. Since the yield of fluorophenol remains constant in all solvents, while that of the ketone varies from 42% in tetraglyme to 6.6% in trifluoroacetic acid, it would appear that the ketone is reacting further. The effect of changes in temperatures with acetonitrile and tetraglyme solvents are recorded in Table 8. More cresol was converted to products at lower temperature. The ratio of A:B was essentially the same in acetonitrile at -0° and -20° but in tetraglyme at -20° significantly larger quantities of ketone were formed.

EXPERIMENTAL

The apparatus used for the fluorination is shown schematically in Fig. 5. The reactor was either made of glass or stainless steel and no significant difference was observed. Fluorine and nitrogen gas flow rates were measured by means of Hasting Mass Flow Meters Model ALL-500.
Both gases were mixed in the mixer which was made of stainless steel and contained spiral mixing rod. Exit gas was passed through a scrubber containing alkali solution and condensed in a cold trap. Vigorous stirring was employed while the fluorine diluted by nitrogen in a ratio of 1:9 was introduced just above the surface of the solutions. The reaction was carried out for 90 minutes for phenol and 120 minutes for cresols and anisole. Samples were withdrawn periodically and analyzed to obtain the data shown in Figs. 1 and 2. The solutions fluorinated consisted of 0.05 mole of substrate dissolved in enough solvent to give a 10% solution. Sodium fluoride or silica gel was added

TABLE 7

Fluorination of p-Cresol in Different Solvents

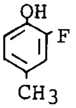
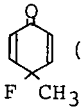
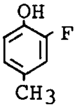
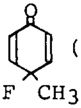
Reaction Condition		Conv. of p-Cresol %	Yield %		Ratio (A)/(B)
Temp. °C	Solv.		 (A)	 (B)	
-20	CH_3OH	70.0	35.0	23.9	1.46
-20	$CHCl_3$	70.9	37.4	8.5	4.40
5	CF_3COOH	68.3	41.4	6.6	6.27
-20	CH_3CN	78.0	38.4	23.1	1.67
-20	TG	69.5	45.3	42.1	1.07

TABLE 8

Fluorination of p-Cresol in Different Temperatures

Reaction Condition		Conv. of p-Cresol %	Yield %		Ratio (A)/(B)
Temp. °C	Solv.		 (A)	 (B)	
0	CH_3CN	69.5	45.3	25.7	1.76
-20	CH_3CN	78.0	39.1	23.1	1.69
0	TG	64.4	38.9	30.6	1.27
-20	TG	69.5	45.1	42.1	1.07

to the solution to minimize the effect of the liberated hydrogen fluoride. The products were separated by the use of vapor phase chromatographic equipment, a Shimadzu GC-R1A Gas Chromatograph with a 3 m x 2 mm column filled with 5% Silicone SE-30 on 80-100 mesh Chromosorb WAW DMCS for phenol and cresols and 30 m x 0.25 mm column filled with Silicone OV-101 (WCOT) for anisole.

Infrared spectra were recorded on a Shimadzu IR-440 Spectrometer. Mass spectra were obtained on a Shimadzu LKB-900 GC-MS Spectrometer. Both ^{1}H and ^{19}F NMR spectra were recorded on a Hitachi R-42 High Resolution NMR Spectrometer; ^{19}F chemical shift was based on trifluoroacetic acid.

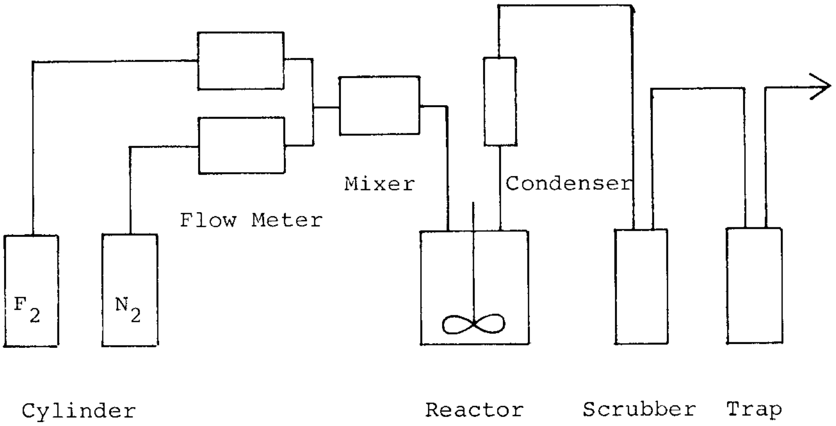


Fig. 5 Schematic Diagram of Reaction Apparatus

The monofluorophenols, cresols and anisoles were known compounds and the isomers were identified by comparison to their known properties and the use of IR and NMR spectroscopy. It was not possible to separate the 2-fluoro-3-methylphenol and the 2-fluoro-5-methylphenol formed from m-cresol.

The new compound produced, 4-fluoro-4-methyl-2,5-cyclohexadienone, was identified by spectral data and elemental analysis.

B.P. 45°C/17 mm Hg, 102°C/760 mm Hg (decompose).
I.R. ; 2940 cm^{-1} (CH_3), 1670 (C=O), 1630 (C=C), 1050 (C-F).
M.S. ; m/e (relative intensity) = 126 (M^+, 70), 111 ($M-CH_3$, 50), 107 (M-F, 20), 98 $M-CO^*$, 96), 97 (M-CO-H, 100), 83 ($M-CO-CH_3$, 60), 72 (30), 57 (25).
Elemental analysis: Calcd., for C_7H_7FO; C, 66.67; H, 5.56; F, 15.07. Found; C, 66.86; H, 5.60; F, 14.91.

In the cold trap cooled to -35°, only a small amount of the solvent was found in each experiments.

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