

FLUORINATION OF 1,2,3-, 1,2,4- AND 1,3,5-TRIHALOBENZENES WITH POTASSIUM FLUORIDE IN DIMETHYL SULFONE

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SUMMARY

Three trifluorobenzenes were prepared by reaction of the corresponding trichlorobenzenes with potassium fluoride or potassium fluoride-cesium fluoride mixtures in dimethyl sulfone. Molar yields were 12.8% for 1,2,3-, 8.3% for 1,2,4- and 56.2% for 1,3,5-. Improved yields of the 1,2,3- (23.9%) and the 1,2,4- (34.0%) trifluorobenzenes were obtained from certain partially fluorinated intermediates. Several chlorofluorobenzene intermediates were obtained in good yields by careful control of the reaction variables. The instability of the polyfluorobenzenes in the halogen-exchange reaction medium explains, in part, why only limited yields of the polyfluorobenzenes are obtained by using this method.

INTRODUCTION

Yakobson *et al.*¹ reacted 1,2,4-trichlorobenzene with potassium fluoride (KF) at 450–460° without the aid of a solvent. They reported a low yield of a complex mixture of chlorofluorobenzene derivatives including some rearranged and reductive dehalogenated products that they attributed to a benzyne intermediate.

We have recently disclosed data on the use of dimethyl sulfone (DMSO₂) as a solvent for the reaction of pentachlorobenzene² and three tetrahalobenzenes³ with KF and mixtures of potassium fluoride and cesium fluoride (KF and CsF). Although reductive dehalogenated products were obtained using a solvent, no rearranged products were found in the reaction mixtures.

The results of the reaction of the three trichlorobenzenes with KF and mixtures of KF and CsF in DMSO₂ are given in this third report in the series on polychlorobenzene studies.

DISCUSSION

The potassium fluoride halogen-exchange reaction on polychlorobenzenes

in dimethyl sulfone has been extended to include the three trichlorobenzene isomers and their partially fluorinated analogs.

Vicinal trichlorobenzene with KF in DMSO₂ gave only monofluoro substitution. Reaction with a KF-CsF mixture produced 1,2,3-trifluorobenzene (12.8% yield) and two difluorochlorobenzenes.

Figure 1 illustrates the 1,2,3-substituted aryl fluorides formed and the percentage composition of the various distillation fractions obtained during the purification of the products.

COMPOSITION OF DISTILLATION FRACTIONS IN PERCENT

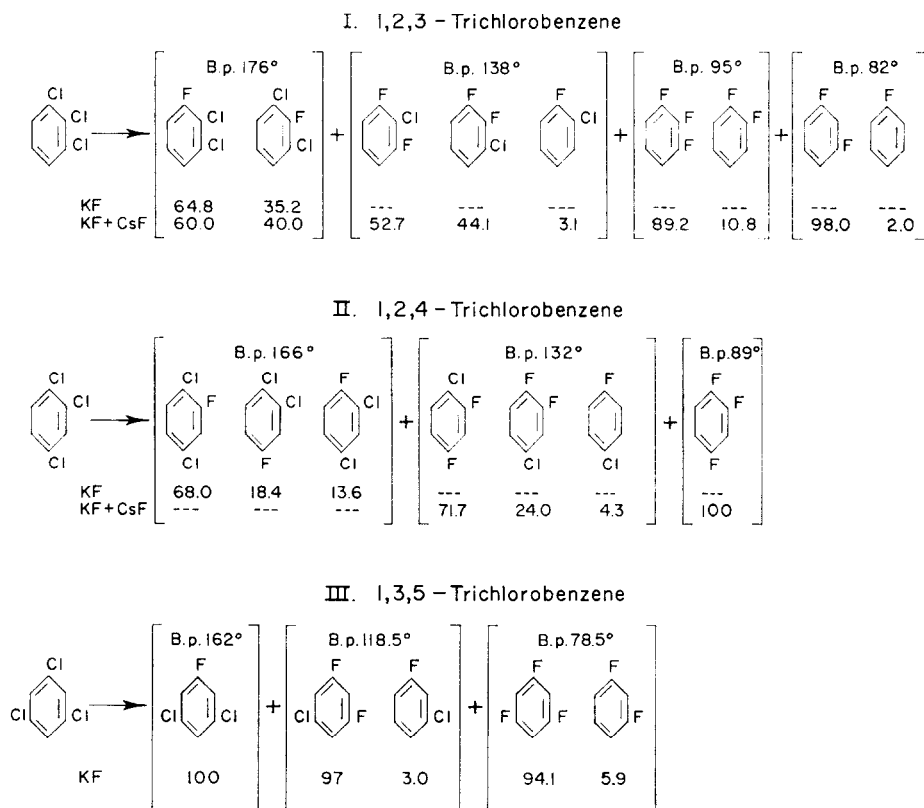


Fig. 1. Fluorination of trichlorobenzenes.

Three hydrogenation products were noted: 1,2-difluorobenzene, 1,3-difluorobenzene and fluorobenzene. The formation of these by-products is attributed to the loss of chlorine rather than fluorine.

The yield of vicinal trifluorobenzene from 2,3-difluorochlorobenzene was 23.9%. This is a nearly two-fold increase over the yield obtained from 1,2,3-trichlorobenzene. 2,3-Difluorochlorobenzene (20.9%) is the only difluoro product in the fluorination of 2,6-dichlorofluorobenzene (Table 1) which strongly suggests that a halogen exchange on 2,6-dichlorofluorobenzene could possibly lead to a good synthesis of vicinal trifluorobenzene. That, of course, is predicated on there being a ready source of the dichlorofluorobenzene.

1,2,4-Trichlorobenzene with KF and DMSO₂ results in mono-, di- and trifluoro-substitution (Table 1). Figure 1 shows the 1,2,4-substituted fluorides formed and the percentage composition of the monofluoro fraction obtained during the purification. The products from another series of fluorination reactions with either KF or KF-CsF mixtures were combined, and the difluoro- and trifluoro-substituted fractions were separated and studied. In this procedure it is assumed that there is only slight deviation in the isomer ratios between runs even though different reagents were used.

The best yield of 1,2,4-trifluorobenzene (34.0%) was obtained from 2,5-difluorochlorobenzene, but only an 8.3% yield was obtained from 1,2,4-trichlorobenzene (Table 1). As 2,5-difluorochlorobenzene is the only expected difluorochlorobenzene isomer not detected among the products from 1,2,4-trichlorobenzene (Fig. 1), it must, if it were formed in the reaction, have been quickly converted to 1,2,4-trifluorobenzene.

Symmetrical trichlorobenzene was reacted with KF in DMSO₂ to give excellent yields of 3,5-dichlorofluorobenzene (54.5%), 3,5-difluorochlorobenzene (47.7%) or 1,3,5-trifluorobenzene (56.2%) simply by varying the reaction conditions. A small quantity (Fig. 1) of 1,3-difluorobenzene was obtained along with the 1,3,5-trifluorobenzene.

All the polyfluorobenzenes were subjected to the conditions of the halogen-exchange reaction in the Parr reactor to determine their stability and to investigate the possibility of isolating reductive dehalogenation products formed by the replacement of fluorine by hydrogen.

Table 2 lists the various polyfluorobenzenes, the reaction conditions to which they were subjected and the percentage recovery of the starting material. These conditions are milder than those required to produce the polyfluorobenzenes from their intermediates (Table 1). The only isolable product as determined by gas chromatography and ¹⁹F NMR spectroscopy was a fraction of the original polyfluorobenzene. It would be difficult, therefore, to find conditions for the halogen-exchange reaction that would be conducive to better yields of the polyfluorobenzenes. No reductive dehalogenation products were found, indicating that 1,4-difluorobenzene produced in the fluorination of 2,5-difluorochlorobenzene and the other reductive dehalogenation products (2-chlorofluorobenzene, 4-chlorofluorobenzene, 1,2-difluorobenzene, 1,3-difluorobenzene and fluorobenzene: see Table 1) can be assumed to be due to a replacement of chlorine rather than fluorine.

TABLE I
FLUORINATION OF TRIHALOBENZENES

Trihalobenzene Cl:F*	Ref. ^a	Moles	KF (Moles)	CsF (Moles)	DMSO ₂ (g)	Temp. (°C)	Time (h)	Method	Products (mole-% yield)						
									Cl ₂ C ₆ H ₃ F	ClC ₆ H ₃ F ₂	C ₆ H ₃ F ₃	ClC ₆ H ₄ F	C ₆ H ₄ F ₂		
<i>I. 1,2,3-Trihalobenzenes</i>															
1,2,3-	—	0.75	3.37	—	480	200	720	A	1,2-3(9.8)* 1,3-2(5.3)	trace	—	—	—	—	—
		0.75	2.37	1.0	480	200	168	B-1	1,2-3(29.0) 1,3-2(19.2)	1-2,6(13.2) 1-2,3(11.0)	—	1-2(0.8)	—	—	
		0.75	3.0	0.35	950	243	168	B-1	1,2-3(10.0) 1,3-2(6.6)	1-2,3(11.7) 48.0	12.8	1-2(0.8)	1,2(1.8) ^b 1,3(2.3)	—	
1,2-3	3	0.48	2.16	0.72	960	265	5.5	B-2	1,2-3(20.0)	—	2.9	1.1 ^c	1,2 ^e	—	
1,3-2	6	0.5	1.25	0.5	600	250	26	B-1	1,3-2(17.8)	1-2,3(20.9)	8.6	—	—	—	
1-2,3	3	0.5	1.0	0.5	1000	265	6	B-2	—	1-2,3(21.2)	23.9	—	—	—	
1-2,6	—	0.4	1.0	0.2	800	265	6	B-2	—	1-2,6(32.5)	9.0	—	—	—	
<i>II. 1,2,4-Trihalobenzenes</i>															
1,2,4-	—	0.75	3.37	—	480	200	504	A	1,4-2(17.3) 1,2-4(4.7)	—	—	—	—	—	
		0.5	4.0	—	320	263	192	B-1	1,3-4(3.4) 1,4-2(17.5)	1-2,4(26.7) 1-3,4(8.9)	2.5	1-4(1.8)	—	—	
		0.5	4.0	—	544	273	240	B-1	1,2-4(4.6) 1,3-4(3.4)	1-2,4(12.4) 1-3,4(4.3)	8.3	1-4(0.7)	—	—	
		0.4	1.02	0.18	500	243	168	B-1	1,4-2(2.0) 1,2-4(0.6)	1-2,4(17.6) 1-3,4(5.9)	4.2	1-4(1.0)	—	—	
1,2,4	7	0.25	1.25	0.12	500	265	6	B-2	1,3-4(1.3)	—	50.2	—	—	—	
1,3,4	7	0.48	2.16	0.72	960	265	6	B-2	1,2-4(6.1)	—	4.2	—	—	—	
1,4-2	8	0.5	2.5	0.5	1000	265	6	B-2	1,3-6(32.4)	—	1.8	—	—	—	
									1,4-2(8.8)	—	32.0	—	—	—	

TABLE I (continued)

1-2,4	9	0.5	1.5	—	1000	265	6	B-2	—	1-2,4(58.8)	2.1	
		0.5	1.25	0.25	1000	265	5	B-2	—	1-2,4(45.0)	7.1	
1-2,5	10	0.5	—	0.5	1000	265	6	B-2	—	1-2,5(34.1)	34.0	1,4(2.5)
		0.5	1.25	0.25	1000	265	6	B-2	—	1-2,5(34.7)	33.2	1,4(2.1)
1-3,4	5	0.5	1.25	0.25	1000	265	6	B-2	—	1-3,4(41.0)	7.0	
III. 1,3,5-Trihalobenzene												
1,3,5-	—	1.5	1.65	—	813	225	240	B-1	1,3-5(54.5) ^d	1-3,5(22.4) ^e	—	
		2.0	8.0	—	670	280	48	B-1	1,3-5(6.6)	1-3,5(47.7)	27.8	1,3(1.7)
		2.0	9.0	1.0	865	275	6	B-1	1,3-5(8.8)	1-3,5(40.5)	31.4	f
		2.0	8.0	—	865	265	168	B-1	—	1-3,5(17.4)	56.2	1,3(4.4)
		2.0	9.0	1.0	1100	290	5	B-1	1,3-5(0.1)	1-3,5(22.2)	43.5	1,3(4.0)

* Numbers preceding hyphen refer to Cl; those after the hyphen refer to F.

^a Lit. Ref. for starting trihalobenzene.

^b Trace of fluorobenzene.

^c Structure not proven.

^d See Ref. 7.

^e See Ref. 11.

^f Not determined.

TABLE 2

STABILITY OF POLYFLUOROBENZENES IN THE HALOGEN EXCHANGE MEDIUM^a

Fluorobenzene		KF	CsF	DMSO ₂	Temp.	Time	Fluorobenzene
Subst.	Moles	(Moles)	(Moles)	(g)	(°C)	(h)	recovered (%) ^b
1,2	0.5	1.0	0.5	410	230	24	73.6
1,3	0.5	1.0	0.5	410	230	24	72.0
1,4	0.5	1.0	0.5	410	230	24	83.5
	0.5	1.0	0.5	410	243	36	69.0
1,2,3	0.2	0.4	0.2	212	230	4.5	33.5
1,2,4	0.2	0.4	0.2	212	230	5	27.9
1,3,5	0.33	0.66	0.33	352	238	5	34.9
1,2,3,4	0.33	0.66	0.33	400	230	5	38.0
1,2,4,5	0.33	0.66	0.33	400	230	24	50.0
1,2,3,5	0.2	0.4	0.2	212	230	5	55.0
Penta-	0.2	0.4	0.2	212	230	5	41.0
Hexa-	0.2	0.4	0.2	212	230	5	35.8 ^c

^a Fluorination method B-2 was used.^b No hydrogenation products were detected in an analysis of the ¹⁹F NMR spectra.^c Contained several unidentified low boiling products.

MATERIALS, METHODS AND PROCEDURES

The trichlorobenzenes 1,2,3- (m.p. 53–54°), 1,2,4- (b.p. 213–214°) and 1,3,5- (m.p. 63–65°) were obtained from commercial sources and were used without further purification.

The potassium fluoride used in these experiments was dried at 120° for 24 h and quickly powdered in a warm mortar. The cesium fluoride (99%) was dried at 120° for 24 h prior to use.

Yields were determined from gas chromatographic data by using a Model 500 F & M gas chromatograph fitted with a 3% silicone rubber (SE-30) column that measured 3 m × 6 mm and a Beckman GC-4 gas chromatograph fitted with a 3% PO-1 (Pierce Chemical Co., Rockford, Ill.) column measuring 1.8 m × 3 mm. Peak areas were determined by use of an Infotronics Integrator. The identity of all of the individual products was established by elemental analysis and by analysis of the ¹⁹F NMR spectra⁴ in conjunction with gas chromatographic retention times. Infrared spectral analysis also aided in structure confirmation.

The halogen-exchange reactions were run in glass apparatus for mild reaction conditions and in a Parr 4501 stainless steel pressure reactor for higher temperature experiments.

*Fluorination**Method A. Glass apparatus*

The trichlorobenzene was added to a slurry of the potassium fluoride and melted dimethyl sulfone (m.p. 109°) in a glass reaction flask. The mixture was

stirred and heated for the times and at the temperatures indicated in Table 1. After the mixture was diluted with water, the fluorinated reaction products were collected by steam distillation.

The crude products were washed successively with conc. sulfuric acid (Sp.G. 1.84), water, 5% aqueous sodium hydroxide solution (1.25 *N*) and again with water. After they were dried over anhydrous magnesium sulfate, they were fractionally distilled in an annular Teflon spinning-band column. They were thus separated into three or four fractions, depending on their boiling range (see Fig. 1). The mono- and difluoro-benzene impurities in each of the trifluorobenzene fractions were separated out by repeated distillations. The components of the higher boiling fractions could not be separated further except by GLC.

Method B. Parr reactor

The trihalobenzene was added to a heated mixture (*ca.* 200°) of dimethyl sulfone and metal fluoride in the autoclave. If solid (method B-1 in Table 1) the trihalobenzene was added directly, but if liquid (method B-2 in Table 1) it was injected into the closed autoclave with a slight nitrogen pressure. The reaction mixtures were allowed to react under autogenous pressure and were stirred at the temperatures and time intervals indicated in Table 1. The reaction products were removed from the reactor by distillation. The crude products were worked up as described above in Method A.

2,6-Difluorochlorobenzene (nc)

A solution of 81.8 g of 2,4-difluoro-3-chloroaniline⁵ in 250 ml of conc. sulfuric acid (Sp.G. 1.84) was prepared. The aniline salt was added at 0° to a stirred solution of 38 g of sodium nitrite in 375 ml of conc. sulfuric acid (Sp.G. 1.84). Diazotization was completed between 0° and 20° by the addition of 200 ml of 85% phosphoric acid. The diazonium salt solution was added to a cooled slurry of 198 g of sodium hypophosphite and 72 g of cuprous oxide in 400 ml of 1:1 (v/v) aqueous sulfuric acid (Sp.G. 1.5). Steam distillation initiated a rapid evolution of nitrogen and 52 g, or a 71% yield, of crude product was collected.

Distillation gave pure 2,6-difluorochlorobenzene, b.p. 132°. Calcd. for C₆H₃ClF₂: C, 48.51; H, 2.01; Cl, 23.87; F, 25.60%. Found: C, 48.57; H, 2.14; Cl, 23.89; F, 25.55%.

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