

Selective fluorodenitration of chloronitroaromatics

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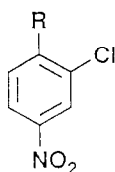
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Abstract

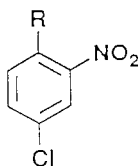
Nucleophilic fluorination of chloronitrobenzenes shows a strong bias for fluorodenitration rather than halogen exchange.

Introduction

Nucleophilic fluorodenitration of chloronitroaromatics has been known for over 30 years but the reaction has been traditionally regarded as an undesirable side-reaction in attempted halogen-exchange reactions on chloronitroaromatics [1]. More recently, however, fluorodenitration has been put forward as a potentially viable route to selective fluorinated aromatic molecules, although successful examples have been largely limited to molecules where the nitro group is highly activated by a combination of electronic and steric (twisting the nitro group out of the plane of the aromatic ring and hence reducing conjugation) effects [2–4]. Little is known of the relative leaving-group abilities of chloro and nitro groups within the same molecule. We now report the first systematic study of the reaction of chloronitroaromatics with F^- which clearly shows that fluorodenitration is preferred to fluoro-dechlorination in wide variety of reactive substrates with the structures I or II.



I



II

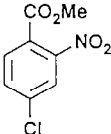
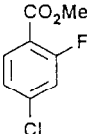
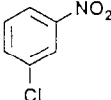
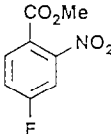
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Results and discussion

Studies on the reactivity of the model substrate II ($R = \text{CO}_2\text{CH}_3$) with different KF reaction systems showed that the KF (2 mol equiv.)/ $\text{Ph}_4\text{P}^+\text{Br}^-$ (0.2 mol equiv.)/DMSO system at 130 °C gave the best yield of fluoroaromatic products (Table 1). Reactions with DMAc or sulpholane as the solvent or in the absence of a phase-transfer catalyst give significantly lower yields. At higher temperatures in sulpholane, decarboxylation to give the chloronitrobenzene was a major reaction pathway. Addition of phthaloyl chloride, used previously to encourage fluorodenitration [5] actually suppressed the fluorination. The major product from the reaction of isomer II ($R = \text{CO}_2\text{CH}_3$) using the optimum conditions was the fluorodenitration product accompanied by trace amount of the Halex product and the decarboxylation product. Isomer I ($R = \text{CO}_2\text{CH}_3$) also gave the fluorodenitration product. Fluorodenitration also predominated in the reactions of other activated chloronitroaromatics (I and II, $R = \text{CF}_3$ and CN, see Table 2).

The nucleophilic fluorination chemistry of the corresponding trifluoromethylsulphones (ArSO_2CF_3) proved to be more complex. In the case of isomer II ($R = \text{SO}_2\text{CF}_3$), the major product was again that derived from fluorodenitration although significant amounts of the difluorosulphone and the fluorodesulphonylation product were also obtained. Fluorodesulphonylation of isomer I ($R = \text{SO}_2\text{CF}_3$) was also observed and in an attempt to study this competitive process we investigated the reaction of this isomer under a variety of conditions (Table 3). As can be seen, excellent selectivity to

TABLE 1
Fluorination of methyl-4-chloro-2-nitrobenzoate

Reaction conditions ^a			Observed products (% by GC methods)			
Solvent	Temp. (°C)	Time (h)				
Sulpholane	220	0.5	—	27	66 ^b	—
Sulpholane	180	5	14	45	38	1.3
DMAc	130	25	62	31	2	5
DMSO	130	26	39	57	1.8	1.8 ^c
DMSO	130	27 ^d	23	72	2.5	0.9
DMSO	130	27 ^e	22	72	3	1 ^f

^aSubstrate/KF/ $\text{Ph}_4\text{P}^+\text{Br}^-$ mole ratio of 1:4:0.1.

^bPlus 5% of methoxy-substituted products.

^cPlus 1.8% of the difluoro product.

^d0.2 mol equiv. $\text{Ph}_4\text{P}^+\text{Br}^-$.

^e0.3 mol equiv. $\text{Ph}_4\text{P}^+\text{Br}^-$.

^fPlus 1.4% of the difluoro product.

TABLE 2
Fluorination of chloronitroaromatics^a

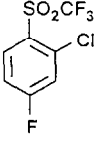
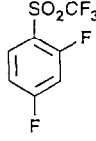
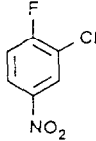
Substrate	Time (h)	Products (% by GC methods)		
	27	 	24 ^b	
	0.5			
	1.0	 	20	
	5			
	0.5	 <p>^aSubstrate/KF/Ph₄P⁺Br⁻ mole ratio of 1:4:0.2; DMSO, 130 °C.</p>		

^bSubstrate/KF/Ph₄P⁺Br⁻ mole ratio of 1:2.2:0.3; DMSO, 130 °C.

the fluorodenitration product can be achieved using either high temperatures with KF or very low temperatures using the homogeneous fluoride source tetra-*n*-butylammonium fluoride (TBAF). Under other conditions, fluorodesulphonylation is a significant side-reaction. If, as seems likely, the rate-

TABLE 3

Fluorination of 2-Cl-4-NO₂C₆H₃SO₂CF₃ using different conditions

Reaction conditions				Observed products (% by GC methods)		
Fluoride	Solvent	Temp. (°C)	Time (min)			
KF ^a	Sulpholane	230	~ 1	100	—	—
KF ^a	Sulpholane	200	~ 1	80	—	7
KF ^a	Sulpholane	170	5	80	10	10
KF ^a	Sulpholane	130	150	56	3	12
KF ^a	DMAc	130	60	63	5	14
KF ^a	DMSO	130	5	78	5	17
TBAF ^b	THF	20	15	67	9	24
TBAF ^b	THF	-78	25	98	—	2

^aSubstrate/KF/Ph₄P⁺Br⁻ mole ratio of 1:2:0.2.^bSubstrate/TBAF mole ratio of 1:5.

determining step in these reactions is the reversible formation of the Meisenheimer intermediate, then these results suggest differences both in the relative rates of formation of the two Meisenheimers and in their relative stabilities in KF and TBAF systems [6]. The much greater discrimination for the fluorodenitration product at lower temperatures (i.e., with more kinetic control) when using TBAF may be a result of the bulkier TBA⁺F⁻ ion pair (compared to a K⁺F⁻ ion pair) experiencing greater steric hindrance in approaching the carbon carrying the CF₃SO₂ group (which is also *ortho* to a chlorine). At higher temperatures (with more thermodynamic control) there is greater discrimination with KF, so that while the Meisenheimer intermediate leading to fluorodenitration is more stable generally, the difference in stabilities between it and the Meisenheimer intermediate leading to fluorodesulphonylation is less when using TBAF.

We are not able to offer an explanation for this, although presumably it is again a result of differences in ion pairing. Clearly changes in the F⁻ reagent can lead to changes in product distribution as well as in the overall rate of reaction.

Experimental

Equipment used

Gas-liquid chromatograms were obtained on a Phillips PU4500 instrument equipped with a Hewlett-Packard 3396A integrator and using OV 101 silicone-supported Chromasorb in the column. Mass spectra were obtained by electron

impact using a VG Analytical Autospec mass spectrometer and a DEC graphic workstation. This was interfaced to a Hewlett-Packard 589011 GC instrument for GC MS analyses. ^1H and ^{19}F NMR spectra were obtained on a Bruker WP80SY spectrometer operating at 80 and 75.4 MHz respectively at 30 °C. ^{13}C NMR spectra were obtained on a JEOL FX90Q spectrometer operating at 22.5 MHz and at 30 °C.

General procedures

Potassium fluoride was dried in an oven at 300 °C for at least 24 h and was then finely ground before use. Tetraphenylphosphonium bromide was dried in a vacuum drying pistol at 60 °C for 24 h before use. All solvents were distilled from calcium hydride and stored under N_2 over activated 4 Å molecular sieves. Tetrabutylammonium fluoride was purchased as the trihydrate then further dried by high-vacuum pumping of the solid maintained at 50 °C in a water bath. The final reagent was an oily liquid and contained (by ^1H NMR methods) 0.5–1.0 mol equiv. H_2O .

Reactions with potassium fluoride

In a typical experiment, the aromatic substrate (0.5 mmol), dried potassium fluoride (2 mmol, 0.12 g) and dried tetraphenylphosphonium bromide (0.05 mmol, 0.2 g) were dissolved in 10 cm^3 of the dried solvent. The flask was fitted with a reflux condenser and nitrogen inlet and taken up to the required temperature (oil bath) with efficient magnetic stirring. Samples were removed periodically, diluted with ether, washed with water and analysed by GC methods.

*Reactions with tetra-*n*-butylammonium fluoride*

The TBAF oil (2.5 mmol) was prepared as described above and then dissolved in 10 cm^3 of dried tetrahydrofuran in a 25 cm^3 flask. The aromatic substrate (0.5 mmol) was added to this solution and the flask fitted with a reflux condenser and drying tube. This was then maintained at 20 °C (water bath) or cooled to -78 °C (Dry Ice/acetone) with stirring. Samples were periodically removed and analysed by GC methods.

In all cases, the final reaction mixtures or products isolated by distillation were analysed by GC/MS and, where necessary, by ^1H , ^{13}C and ^{19}F NMR spectroscopy. The products reported are known compounds and gave spectra consistent with their structures.

Acknowledgements

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