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AROMATIC POLYFLUORO COMPOUNDS—XXXVI[1]

THE REACTIONS OF 2-SUBSTITUTED-TETRAFLUORONITROBENZENES WITH NUCLEOPHILES

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Abstract—Four tetrafluoronitrobenzene derivatives substituted in the 2-position (2-$XC_6F_4NO_2$: X = NH_2, NHMe, NMe_2 and OMe) have each been treated with four nucleophiles (Y = ammonia, methylamine, dimethylamine and sodium methoxide) to give mixtures of 2X-4Y- and 2X-6Y-trifluoronitrobenzenes. Possible reasons for the variation of the ratios of these two products are discussed.

IN OUR studies on nucleophilic replacement in aromatic polyfluoro-compounds, we have encountered several examples of a phenomenon well-known in the general nucleophilic aromatic substitution field. That is, halogen from a position *ortho* to a nitro-group is replaced by amine nucleophiles more rapidly than halogen from a position *para*, whereas the reverse reactivity order holds for alkoxide nucleophiles.[2] For example, pentafluoronitrobenzene reacts with ammonia[3] and methylamine[4] with replacement mainly (~70%) of the fluorine *ortho* to the nitro-group, whilst sodium methoxide in methanol[4] effects replacement mainly (>90%) of the fluorine *para*. The carboxylate[5] and nitroso[6] groups in pentafluorobenzoic acid and pentafluoronitrosobenzene have a similar effect to nitro. This phenomenon has been attributed by many authors,[2b] ourselves[4] included, to enhancement of *ortho* attack in the amine reactions by hydrogen-bonding between the amine and the nitro group. The position is more complex than this, however, as there are a number of examples, seemingly neglected by some of the hydrogen-bonding protagonists, where *ortho* halogen is preferentially replaced by alkoxides as well as by amines; for example, 2,4-dihalogenonitrobenzenes are attacked at the 2-position by all nucleophiles.[7] Change of solvent can also bring about very marked changes in *ortho*:*para* halogen reactivity ratios with both amine and alkoxide nucleophiles.[8,9]

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[1] Part XXXV P. L. Coe, B. T. Croll and C. R. Patrick, *Tetrahedron* **23**, 505 (1967).

[2] [a] R. R. Bishop, E. A. S. Cavell and N. B. Chapman, *J. Chem. Soc.* 437 (1952); [b] S. D. Ross, *Progr. Phys. Org. Chem.* **1**, 31 (1963); [c] J. Bunnett and R. J. Morath, *J. Amer. Chem. Soc.* **77**, 5051, 5055 (1955).

[3] G. M. Brooke, J. Burdon and J. C. Tatlow, *J. Chem. Soc.* 802 (1961).

[4] J. G. Allen, J. Burdon and J. C. Tatlow, *J. Chem. Soc.* 1045 (1965).

[5] J. Burdon, W. B. Hollyhead and J. C. Tatlow, *J. Chem. Soc.* 6336 (1965).

[6] J. Burdon and D. F. Thomas, *Tetrahedron* **21**, 2389 (1965).

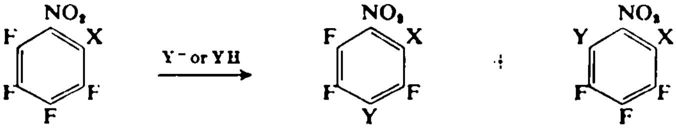
[7] A number of examples are given in J. Bunnett and R. E. Zahler, *Chem. Revs.* **49**, 273 (1951) and in Ref. 2*c*.

[8] J. Burdon, D. Fisher, D. King and J. C. Tatlow, *Chem. Comm.* **65** (1965), and unpublished results.

[9] W. Greizerstein and J. A. Brieux, *J. Amer. Chem. Soc.* **84**, 1032 (1962); N. B. Chapman, R. E. Parker and P. W. Soanes, *J. Chem. Soc.* 2109 (1954).

We have therefore commenced a study of these "anomalous" *ortho*-replacements in the polyfluoroaromatic field. We feel that polyfluoroaromatic compounds offer a wider area of investigation than has been available to previous workers on this problem.

The present paper reports one of our lines of investigation. We have treated four tetrafluoronitrobenzenes further substituted in the 2 position ($2\text{-X}\cdot C_6F_4\cdot NO_2$) with a number of nucleophiles (Y), as indicated in the scheme, to give mixtures of replacement products ($2X,4Y$- and $2X,6Y\text{-}C_6F_3\cdot NO_2$). No other isomeric products were formed,



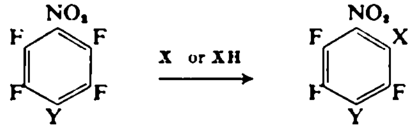
2,4-isomer 2,6-isomer

X and Y = NH_2, NHMe, NMe_2 or OMe.

which is hardly surprising in view of the known powerful activating effect of the nitro-group on *ortho*- or *para*-halogen reactivity.[3,4] We controlled the reactions so that replacement went no further (to any significant extent) than the 2,4- or 2,6-isomer stage.

The 2,4:2,6 isomer ratios were determined by ^1H NMR measurements and by weighing the isolated isomers; the two methods were always in good agreement. The results are summarized in Table 1, together with those obtained previously on pentafluoronitrobenzene. Further experimental data are given in Tables 2 and 3.

The structures of the 2,4-isomers were proved by synthesizing them from the known[3,4] 4-Y-tetrafluoronitrobenzenes. The only disubstituted trifluoronitrobenzene



X and Y = NH_2, NHMe, NMe_2, or OMe

which can arise from both a 2X- and a 4Y-tetrafluoronitrobenzene is the 2,4-isomer. The structures of most of the 2,6-isomers follow from their isolation from *two* 2-X-tetra-fluoronitrobenzenes; for example, 2-amino-6-dimethylaminotrifluoronitrobenzene is the only isomer with this formula which can arise from both 2-aminotetrafluoronitrobenzene (by treatment with dimethylamine) and 2-dimethylaminotetrafluoronitrobenzene (by treatment with ammonia). The structures of the 2,6-isomers with identical amine groups at 2 and 6 were elucidated in earlier work[4] by ^{19}F NMR. The remaining isomer, 2,6-dimethoxytrifluoronitrobenzene, was only investigated by ^1H NMR; the correlation used[10], however, has proved satisfactory for many other aromatic polyfluoro-compounds and for all the new compounds described in this paper. We therefore feel confident that all the products have been correctly identified.

It is obvious from Table 3 that methoxide is the most, and ammonia the least, reactive of the four nucleophiles employed in the study, with methylamine appearing to be a little more reactive than dimethylamine.

The main point of this paper is the 2,4:2,6 isomer ratio. There are two matters to which we wish to draw attention before discussing this, however. First, as can be seen

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[10] J. Burdon, *Tetrahedron* **21**, 1101 (1965).

TABLE 1. 2,4- AND 2,6-ISOMER RATIOS IN THE REACTIONS OF 2-X-TETRAFLUORONITROBENZENES WITH NUCLEOPHILES

2-XC$_6$F$_4$NO$_2$ X =	Nucleophile Y =	Product composition. (relative %)^a 2X-4Y-C$_6$F$_3$NO$_2$	2X-6Y-C$_6$F$_3$NO$_2$
F^b	NH$_2$	48^{c,d}	52^{c,d}
NH$_2$	NH$_2$	56^{c,d}	44^{c,d}
NHMe	NH$_2$	40^e	60^e
NMe$_2$	NH$_2$	57^e	43^e
OMe	NH$_2$	25	75
F^b	NHMe	47^{c,f}	53^{c,f}
NH$_2$	NHMe	60^e	40^e
NHMe	NHMe	45^{c,f}	55^{c,f}
NMe$_2$	NHMe	27^e	73^e
OMe	NHMe	28	72
F^b	NMe$_2$	82^f	18^f
NH$_2$	NMe$_2$	90	10
NHMe	NMe$_2$	75	25
NMe$_2$	NMe$_2$	71^f	29
OMe	NMe$_2$	73	27
F^b	OMe	66^g	33^g
NH$_2$	OMe	70	30
NHMe	OMe	74	26
NMe$_2$	OMe	20	80
OMe	OMe	27^f	73

[a] Accuracy ±5%. [b] The figures for C$_6$F$_5$NO$_2$ are *para*: ½ *ortho* ratios expressed as %'s. [c] By weight only, not ^{1}H NMR. [d] Ref. 3. [e] See text. [f] Ref. 4. [g] Ref. 8.

TABLE 2. REACTIONS OF 4-XC$_6$F$_4$NO$_2$ WITH YH OR Y$^-$ TO GIVE 4X-2Y-C$_6$F$_3$NO$_2$

X	Y	m.p. of product	Analysis			
			Requires		Found	
			C	H	C	H
NH$_2$	NH$_2$	147°	—	—	^{a}	^{a}
NH$_2$	NHMe	149	38·1	2·7	38·2	3·0
NH$_2$	NMe$_2$	108	40·8	3·4	40·8	3·5
NH$_2$	OMe	54	37·8	2·3	37·9	2·4
NHMe	NH$_2$	160	38·1	2·7	37·8	2·8
NHMe	NHMe	124	—	—	^{a}	^{a}
NHMe	NMe$_2$	83	43·2	4·0	43·4	4·4
NHMe	OMe	70	40·7	3·0	40·7	3·2
NMe$_2$	NH$_2$	52	40·8	3·4	40·6	3·8
NMe$_2$	NHMe	63	43·4	4·0	43·3	4·4
NMe$_2$	NMe$_2$	liquid	45·9	4·7	46·2	5·0
NMe$_2$	OMe	liquid	43·2	3·6	43·3	3·6
OMe	NH$_2$	65	37·8	2·3	37·9	2·6
OMe	NHMe	79	40·8	3·0	41·1	3·1
OMe	NMe$_2$	60	43·3	3·6	43·6	3·3
OMe	OMe	liquid^b	—	—	^{a}	^{a}

[a] Known compounds (Refs 3 and 4). [b] Isolated by preparative scale GLC not column chromatography.

TABLE 3. REACTIONS OF 2-$XC_6F_4NO_2$ WITH YH OR Y^- TO GIVE 2X–4Y– AND 2X–6Y–$C_6F_3NO_2$

X	Y	Reaction time	% starting material recovered[c]	m.p. 2,6 isomer[b]	Analysis[a] Requires C	Analysis[a] Requires H	Analysis[a] Found C	Analysis[a] Found H
NH_2	NH_2	[d]	[d]	163°	...	..	[d]	[d]
NH_2	NHMe	2 hr	—	91	38·1	2·7	38·3	3·2
NH_2	NMe_2	24 hr	—	63	—	—	[e]	[e]
NH_2	OMe	2 hr	- -	49	37·8	2·3	38·0	2·3
NHMe	NH_2	48 hr	60	92	38·1	2·7	38·2	2·9
NHMe	NHMe	[d]	[d]	163	—	—	[d]	[d]
NHMe	NMe_2	24 hr	10	35	43·2	4·0	43·4	4·0
NHMe	OMe	2 hr	—	49	40·7	3·0	40·4	3·1
NMe_2	NH_2	30 days	60	63	40·8	3·4	40·8	3·5
NMe_2	NHMe	3 hr	40	35	43·4	4·0	43·2	4·0
NMe_2	NMe_2	24 hr	25	24	45·9	4·7	46·2	5·0
NMe_2	OMe	2 hr	—	liquid	43·2	3·6	43·0	3·5
OMe	NH_2	24 hr	60	49	37·8	2·3	38·1	2·3
OMe	NHMe	3 hr	15	49	40·8	3·0	40·6	3·1
OMe	NMe_2	20 hr	10	liquid	–	- -	[f]	[f]
OMe	OMe	2 hr	- -	liquid[g]	—	—	—	—

[a] Of 2,6 isomers only; the 2,4 isomers were identified by mixed m.p. (Table 2) and/or IR. [b] 2,4 isomers had the same m.p. as those recorded in Table 2. [c] Nearest 5%. No figure means <5%. [d] Known reaction and known compound (Refs 3 and 4). [e] Identified by mixed m.p. and IR only. [f] Identified by IR only. [g] Reaction mixture separated by preparative scale GLC, not column chromatography.

from Table 1, the amount of 2,6-isomer formed in the ammonia–2-dimethylaminotetrafluoronitrobenzene reaction is apparently anomalously low. Of course, the result could be genuine; on the other hand, it could be due to water introduced into the reaction mixture by accidential condensation—ammonia bubbling through ether causes evaporation and hence cooling. Increasing the water content of the reaction mixture might be expected, from other work,[5,8,9] to increase the 2,4-isomer at the expense of the 2,6. Secondly, the reactions were not all carried out in exactly the same solvent mixtures, and, as this has lead to variation in product composition in at least one case[8] before, the value of comparisons between nucleophiles is therefore diminished.

With these provisos, the trend for all four nucleophiles is roughly the same; the percentage of the 2,6-isomer increases with the group *ortho* to the nitro-group in the order $NMe_2 > OMe > NHMe > F > NH_2$. Also, the overall reactivities *roughly* decrease in a similar order (cf. Table 3): $NMe_2 < OMe \sim NHMe < NH_2 \ll F$. A plausible explanation for the reactivity order (excluding of course pentafluoronitrobenzene itself) is apparent from the fact that the order is one of decreasing size; the larger the group *ortho*, the more it can prevent the nitro-group from achieving the coplanarity necessary for the exertion of its full activating effect. Since the reactivity order resembles the 2,6:2,4 isomer ratio order, it is tempting to ascribe the latter to some sort of steric effect also; by what mechanism a steric effect might operate is, of course, another matter. Another feature we cannot explain satisfactorily is the formation of transient colours at the beginning of many of the reactions.

EXPERIMENTAL

Reactions with ammonia

Dry ammonia was bubbled through a soln of the substrate (1 g) in dry ether (300 ml) at room temp for the stated time. The ethereal soln was washed with water, and the washings were extracted with ether. The combined ethereal solns were dried ($MgSO_4$) and evaporated and the product distribution in the residue was determined, where possible, by ^1H NMR (Table 1). The residue was then chromatographed, in ca. 0·3 g portions, on a column (24″ × 1⅛″) of alumina (commercial chromatography grade alumina, deactivated with $\frac{1}{16}$ its wt in water) with light petroleum (b.p. 40–60°) benzene (4:1 v/v) as eluent. Two main product bands separated; the faster running was the 2,6 isomer and the slower, the 2,4. Starting material was recovered in many experiments (Table 3); it always ran more quickly than either the 2,4 or 2,6 isomers. Occasionally very small amounts of more highly substituted products were obtained; these have not been investigated. The 2,6 and 2,4 isomers and any starting material were re-chromatographed with ether as eluent to remove traces of high boiling petroleum fractions. The crude products were then weighed (their relative amounts were always in good agreement with those determined by ^1H NMR) and crystallized from CCl_4 or light petroleum (b.p. 40–60°).

Reactions with methylamine or dimethylamine

The nucleophile (1·8 moles of a 33% w/w soln in EtOH) in dry ether (50 ml) was added over 30 min, with stirring and at room temp, to a soln of the substrate (1 g) in ether (50 ml). Transient colours formed at the beginning of many of the reactions. The reaction mixture was then stirred for the stated time before being worked up as in the ammonia experiment. Liquid products were purified by distillation at ca. 0·1 mm.

Reactions with sodium methoxide

These were carried out as for $MeNH_2$ and Me_2NH. The nucleophile (1·05 moles) was a 1·14N MeONa in MeOH diluted with ether, to a solvent composition of about 6% MeOH in ether (the final solvent composition was thus 3% MeOH in ether). Again, transient colours were observed at the beginning of many reactions.

Reactions of 4-X-*tetrafluoronitrobenzenes with nucleophiles*

These were carried out as described above. (The reaction time for the ammonia reaction was 6 hr, that for $MeNH_2$ and MeONa 2 hr, and that for Me_2NH 24 hr) except that only one main band, that of the 4-X-2-Y-trifluoronitrobenzene, appeared on the chromatography column. Yields were >90% in every case; the results are recorded in Table 2.

Reactions of 2-X-*tetrafluoronitrobenzenes with nucleophiles*

These reactions were carried out as described above; yields were >90% but conversions were occasionally much lower (Table 3). Mixed m.ps between the same compounds prepared in different ways were undepressed, and IR spectra of such compounds were identical. The 2,6:2,4-isomer ratios are recorded in Table 1 and the experimental details and the physical constants for the 2,6 isomers in Table 3.

NMR *spectra*

^1H NMR spectra were measured on a Varian A60 instrument in CCl_4 or acetone soln or on undiluted products. The various side-chains (OMe, NHMe, NMe_2) gave signals in the ranges found for similar compounds,[10] and the fine structure of these signals was as described previously;[10] with one *ortho*-fluorine the signals were doublets, and with two, triplets. Usually a side-chain *ortho* to a nitro-group gave its signal at higher field than the isomeric *para*-compound, and thus enabled the 2,6:2,4 isomer ratio to be determined (Table 1); the parent $2\text{-}XC_6F_4NO_2$ usually gave signals at lower field than either the 2,6 or the 2,4 product. Occasionally the signals overlapped and the ^1H NMR spectrum was not then used to determine the isomer ratio.

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