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# AROMATIC POLYFLUORO COMPOUNDS LVII [1]. NUCLEOPHILIC REPLACEMENT REACTIONS OF 1, 2, 3, 5-TETRAFLUORO-4-NITROBENZENE, 1, 2, 3, 5-TETRAFLUORODINITROBENZENE AND 1-BROMO-2, 3, 4, 6-TETRAFLUORO-5-NITROBENZENE

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## SUMMARY

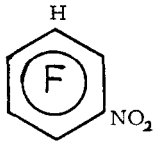
The title compounds have been treated with dimethylamine and sodium methoxide in polar solvents, and the isomer ratios of the products determined. Although attack para to the nitro group is in each case favoured over ortho, it is so by only surprisingly small factors. Structures have mostly been assigned spectroscopically, supported in one case by a chemical proof. The dinitrotetrafluorobenzene is activated sufficiently to react directly with methanol at 35°C, with a pseudo first order rate constant of $(7 \pm 1) \times 10^{-5}$ $s^{-1}$.

## INTRODUCTION

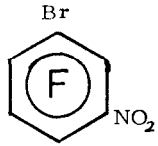
There have been a substantial number of publications [2] concerned with the orienting effects of various substituents in polyfluorobenzenes. Many of these have followed the so-called $I_\pi$ repulsion theory of such effects, and describe attempts to test this theory [3] which thus far has survived these tests well, both in polysubstituted benzenes and latterly, in modified form [4], in polycyclic aromatics [5]. There have been other

contributions to the debate [6], including a purely theoretical one [7] which seeks to explain the results in terms of frontier orbital theory - but see reference [4] -, and one [8] which relies upon a beneficial effect of fluorine meta to the position of attack rather than a destabilising effect of fluorine ortho and para to it.

As a further contribution in this general area we now report on nucleophilic substitution reactions on the tetrafluoronitrobenzenes I to III.




I

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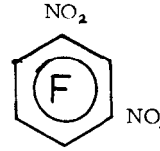
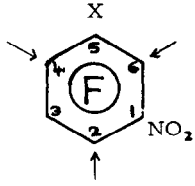


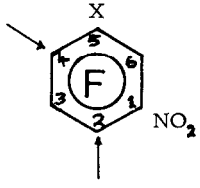

III

There have of course been other studies on polyfluoroaromatic substrates containing nitro groups including, following the early positional studies [9], some kinetic work [10], and it is obvious from these that the most likely positions of attack are those arrowed (ortho and para to $NO_2$).




(non-systematic numbering)

In all our studies reported here we have found no evidence for significant amounts of attack at position 6, even in the case of I, where steric factors ought to favour the position over that in pentafluoronitrobenzene, and so the subsequent discussion revolves around the relative amounts of attack at 2 and 4.



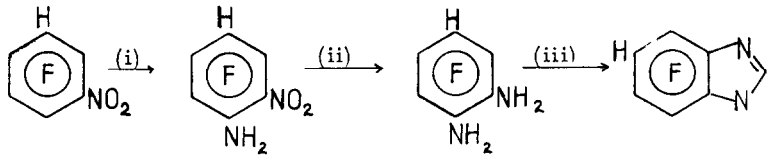

(non-systematic numbering)

RESULTS AND DISCUSSION

The preparations of the substrates were straightforward; 1, 2, 3, 5-tetrafluoronitrobenzene (I) [11] and 1, 2, 3, 5-tetrafluorodinitrobenzene (III) [12] were prepared by the published methods, and 1-bromo-2, 3, 4, 6-tetrafluoro-5-nitrobenzene (II) was synthesised in good yield by electrophilic bromination of I in fuming sulphuric acid.

In the main we have used as nucleophiles sodium methoxide and dimethylamine, both in methanol to reduce the specific dipolar interactions [13], between the nucleophile and the nitro group, often found in non polar media. The relative amounts of the monosubstituted products are shown in Table 1.

Ammonia in ether reacted with I to yield, as by far the major product, 2, 3, 5-trifluoro-6-nitroaniline (Ia), which was reduced and cyclised to the benzimidazole (scheme).




I Ia

SCHEME

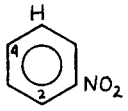
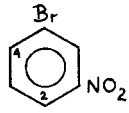
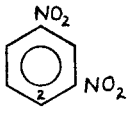
Reagents (i) $NH_3$ in $Et_2O$; (ii) $H_2$, Pd/C; (iii) $H.CO_2H$, reflux

This cyclisation clearly establishes the structure of Ia, and this chemical structure proof goes far to support the spectroscopic structure assignments used in the majority of the other cases. These (Table 2), are based on $^{19}F$ chemical shifts, which have been fitted using the known [14] chemical shift parameters. Although only these, together with elemental analyses (Table 3) are presented as evidence here, coupling patterns in the $^{19}F$ and $^{1}H$ spectra are consistent with the assignments.

The main point of interest found in these reactions is the lack of predominance of attack <u>para</u> to the nitro group in I and II. Thus, for pentafluorobenzene, sodium methoxide in methanol gives, under conditions similar to those used here [15], 8% only of product from <u>ortho</u> attack. Thus, allowing for statistics, if the other substituent in the ring had no

TABLE 1

Results of analyses of product mixture

| Substrate | Reagent | Amounts of monosubstitution products (%) | |
|---|---|---|---|
| | | 2 | 4 |
|  | $NaOMe/MeOH$ | 46 (Ib) | 54 (Id) |
| | $NMe_2H/MeOH$ | 40 (Ic) | 60 (Ie) |
| | $NH_3$ $/Et_2O$ | 95 (Ia) | 5 |
|  | $NaOMe/MeOH$ | 72 (IIa) | 27 (IIc) |
| | $NHMe_2/EtOH$ | 75 (IIb) | 25 (IId) |
| | " $/Et_2O$ (+ trace EtOH) | 89 (IIb) | 11 (IId) |
|  | $NaOMe/MeOH$ | 100 (IIIa) | |
| | $NHMe_2/EtOH$ | 100 | |
| | $NH_3$ $/Et_2O$ | 100 (IIIb) | |

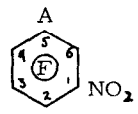
Notes: Analyses by separation, gas chromatography, $^{19}F$ and $^{1}H$ nmr were internally consistent. All figures ± 4%; structures assigned by nmr.

effect, (or, at least, an activating effect much inferior to that of the nitro group) one might expect only about 5% of reaction ortho to the nitro group. Of course, this is a highly oversimplified argument, but it does illustrate the point, since the ability of, for example, the hydrogen atom in I to accommodate significant amounts of $\pi$ charge ought to be much less than that of the nitro group.

The observation in both cases (I and II) of comparable amounts of attack para to the nitro group and para to the other substituent (H or Br) is thus unexpected, although it is in line with results previously obtained from the comparable ortho disubstituted tetrafluorobenzenes [2]. This anomaly also shows up in the comparable studies on 2,4-difluoronitrobenzene [15].

TABLE 2

$^{19}F$ nmr shifts of compounds reported in this work




| Compound number | Substitutents | Position (as above) relative to $NO_2$ group | | | |
|---|---|---|---|---|---|
| | | 2 | 3 | 4 | 6 |
| I | A = H | 138.7 | 161.9 | 121.7 | 121.7 |
| Ia | 2 $NH_2$ | - | 161.7 | 128.0 | 119.8[a] |
| Ib | 2 OMe | - | 155.6 | 126.9 | 124.7 |
| Ic | 2 $NMe_2$ | - | 148.2 | 128.4 | 124.8 |
| Id | 4 OMe | 142.9 | 161.8 | - | 121.7 |
| Ie | 4 $NMe_2$ | 142.2 | 155.6 | - | 121.7 |
| II | A = Br | 139.5 | 158.0 | 117.9 | 116.1[b] |
| IIa | 2 OMe | - | 155.3 | 122,8 | 121.6 |
| IIb | 2 $NMe_2$ | - | 148.3 | 125.7 | 121.8 |
| IIc | 4 OMe | 142.9 | 157.3 | - | 115.7 |
| IId | 4 $NMe_2$ | 143.8 | 149.6 | - | 112.9 |
| III | A = $NO_2$ | 131.9 | 155.7 | 131.9 | 130.5[b] |
| IIIa | 2 OMe | - | 155.0 | 139.0 | 131.0 |
| IIIb | 2 $NH_2$ | - | 158.8 | 137.8 | 128.1 |
| IIIc | 2,4 $(OMe)_2$ | - | 148.8 | - | 136.5 |

All shifts $\phi$*

[a] This spectrum has been reported before: J. Homer and L.F. Thomas, J. Chem. Soc. (B) 1966, 141; see also A. Peake and L.F. Thomas, Chem. Comm. 1966 530.

[b] Data abstracted from P.H. Winson, Ph.D. Thesis, University of Birmingham 1968.

TABLE 3

Elemental Analyses and Characteristics of the Substitution Products

[Numbered as in Table 1]

| Number | Required | | Found | | | m. p. |
|---|---|---|---|---|---|---|
| | C | H | C | H | | |
| Ib | 40.6 | 1.9 | 40.7 | 2.0 | nc | 39.5-41° |
| Ic | 43.6 | 3.2 | 43.5 | 2.8 | nc | 94-95 |
| Id | 40.6 | 1.9 | 40.7 | 2.0 | nc | liquid |
| Ie | 43.6 | 3.2 | 43.4 | 3.0 | nc | liquid |
| IIa + IIc | 29.4 | 1.05 | 29.0 | 2.9 | | liquid |
| IIb + IId | 32.1 | 2.0 | 32.0 | 2.0 | | liquid |
| IIIa | 33.3 | 1.2 | 33.3 | 1.2 | nc | 15° |

This rough equality is made more surprising by our observation that the dinitrobenzene III is very powerfully activated: attempts to make the mono-methoxy compound (IIIa) with methoxide yielded significant amounts of disubstituted material (IIIc). Indeed this substrate, III, reacted with methanol itself at 35°, with a pseudo-first order rate constant of $7 \pm 1 \times 10^{-5}$ $s^{-1}$. (The reaction was followed by $^1H$ nmr, monitoring the aromatic methoxyl peak).

## EXPERIMENTAL

### 1-Bromo-2, 3, 4, 6-tetrafluoro-5-nitrobenzene (II) (nc)

1, 2, 3, 5-tetrafluoronitrobenzene (I) (21.4 g) was stirred and refluxed with fuming $H_2SO_4$ (15 $cm^3$) and $Br_2$ (6.5 $cm^3$) for 1 hr. The reaction mixture was then poured onto crushed ice (200 g) and washed with cold water. The organic layer was washed successively with sodium metabisulphite and KOH solutions before being dissolved in ether and dried ($MgSO_4$). Removal of the solvent gave the crude product (20.6 g), distil-

lation of which gave the title compound b. p. 213-214°C (partial decompn.) (Found: C, 26.4; Br, 29.1; N, 4.8; $C_6BrF_4NO_2$ requires: C, 26.4; Br, 29.3; N, 5.1%).

Reaction of substrates with sodium methoxide. General method.

The nitrobenzene was dissolved in methanol and a solution of sodium methoxide in methanol (1.1 mole ratio on substrate) run in slowly at the ambient temperature. The products were then worked up in the usual way. A portion of the product from 1, 2, 3, 5-tetrafluoronitrobenzene (I) was separated by chromatography on deactivated alumina, using light petroleum /diethyl ether as eluent, before recrystallization. The others were distilled or recrystallised, as appropriate, directly. Nmr analyses were generally performed both on the crude products and on the analytical samples.

Reactions with dimethylamine in methanol were similarly carried out and worked up. Again, only the product from 1, 2, 3, 5-tetrafluoronitrobenzene (I) was separated.

Reactions with ammonia were performed using, as reagent, solutions of ammonia in diethyl ether. In this case, the product from 1, 2, 3, 5-tetrafluoronitrobenzene (I) was again chromatographed and shown (gas chromatography, nmr) to be a single major compound, 2, 3, 5-trifluoro-6-nitroaniline (Ia) (nc) m. p. 65-66°C (Found: C, 37.7; H, 1.5; $C_6H_3F_3N_2O_2$ requires: C, 37.5; H, 1.6%). Traces of starting material and of other products were also present.

Reduction and cyclisation of 2, 3, 5-trifluoro-6-nitroaniline (Ia)

The compound (0.58 g) was hydrogenated in EtOH (20 $cm^3$) over Pd/C. The mixture was poured into ether, filtered, and the solvents removed under reduced pressure to give purple crystals (0.324 g). These were gently refluxed with methanoic acid (90% w/v in $H_2O$; 4 $cm^3$) for 18 h, poured into water (100 $cm^3$) and neutralised ($NaHCO_3$). Isolation via ether extraction gave a crude product (0.283 g, 83%). Recrystalli-

sation (propanone) gave pale brown crystals of 4,5,7-trifluorobenzimidazole m.p. 254-255°C (lit [17] sublimes 210°C) (Found: C, 49.0; H, 1.9 $C_7H_3F_3N_2$ requires: C, 48.8; H, 1.7%).

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