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Mechanisms of reactions of halogenated compounds Part 7. Effects of fluorine and other groups as substituents on nucleophilic aromatic substitution

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Dedicated to the memory of our good friend and colleague Professor Lyn Williams.

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ABSTRACT

The effect of fluorine as a substituent group on nucleophilic aromatic substitution is discussed, where a fluorine atom located *ortho* to the point of substitution may be of variable activating influence, whereas fluorine located *para* is slightly deactivating and *meta* is activating. A rationale of these effects is presented and evidence to support polar influences by *ortho* fluorine is advanced. The influence of CN, CF_3, CF_2H and CFH_2 is also established by comparison of appropriate measured rate constants and compared with the activation effects of ring nitrogen.

1. Introduction

Polyfluorinated aromatic systems have an interesting 'mirror-image' relationship with the corresponding hydrocarbon compounds, in that the former generally react with nucleophiles, via Meisenheimer complexes [2–5], in contrast to the classical chemistry of aromatic hydrocarbons, that undergo electrophilic substitution, via Wheland intermediates as shown in Fig. 1.

To develop the chemistry of these systems, it is important to understand at least the gross factors that determine the reactivity and orientation of nucleophilic attack in various fluorinated aromatic compounds. In this connection, a curious feature emerged early in the study of these compounds; nucleophilic attack occurs predominantly *para*- to the substituent X in pentafluorobenzene derivatives, Fig. 1, regardless of whether the substituent is electron-withdrawing (activating towards nucleophilic aromatic substitution), hydrogen, or electron-donating (deactivating). Consequently, we endeavoured to determine, by experiment, the separate activating influences of fluorine, as a substituent in a ring, at sites that are *ortho*-, *meta*- and *para*-, Fig. 2, to the point of nucleophilic attack, on a variety of perfluorinated systems, including benzenoid [1,6], pyridine [5], and bicyclic [7,8] derivatives. We have noted a recent publication [9], relating to calculations that are directed to the same problem but has concentrated solely on the thermodynamic stability of the corresponding Meisenheimer complexes. This assumes that the Meisenheimer complex is a good model for the transition state in each case, and that coulombic effects are not important. In this paper, we wish to further demonstrate that neither of these assumptions is valid.

We have previously established [1,2,6] that a fluorine atom that is situated *para*- to the point of nucleophilic attack (Fig. 2) is *slightly deactivating*, whereas fluorine atoms that are situated at corresponding *meta*- and *ortho*- positions are *activating at both sites*. In order to rationalize these findings we used our knowledge of the effect of fluorine as a substituent on carbanion stabilities [5,10].

As indicated in Fig. 3, the stabilizing inductive effect of fluorine on the stability of an attached carbanion is offset by electron-pair repulsions and the overall effect is destabilizing for a planar carbanion, where the repulsion is maximized. Of course, this is the situation for a developing carbanionic transition state during nucleophilic aromatic substitution and it is understandable, therefore, that a *para*-F substituent is slightly deactivating. In an analogous way, a fluorine atom attached to carbon that is adjacent to a carbanionic site in the transition state is strongly stabilizing

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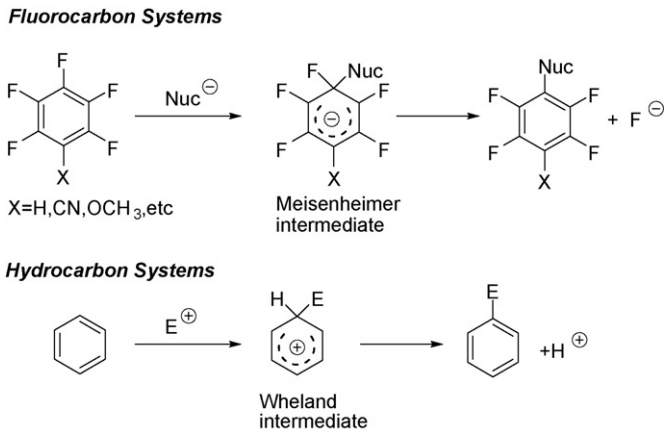


Fig. 1. 'Mirror-image' chemistry.

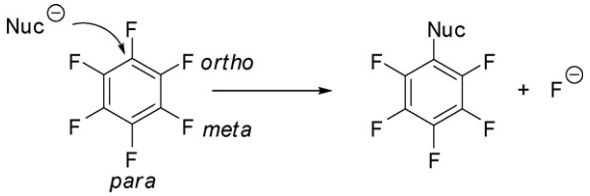


Fig. 2. Activating influences of fluorine.

because electron-pair repulsions are negligible; this is the situation for the effect of a *meta*-F substituent on the developing negative charge in the transition state for nucleophilic aromatic substitution and it is understandable that a fluorine atom at this position is strongly activating.

Intuitively, we might anticipate that a fluorine substituent located at a site that is *ortho*- to the position of nucleophilic attack would have an effect that is similar to that of a *para*-F; but this is not the case. Fluorine substituents at the *ortho*- position are usually activating and may be more activating than at the corresponding *meta*- site, depending on the system. Our rationale of this situation is outlined in Fig. 4: a factor contributing to the reactivity of carbon–fluorine bonds in unsaturated systems is the polarity of the bond. That is, the approach of a nucleophile is aided by ion–dipole interaction, i.e. a coulombic effect, and such effects have been shown previously to change completely the orientation of nucleophilic substitution in some perfluorinated aromatic systems [11]. It seems to

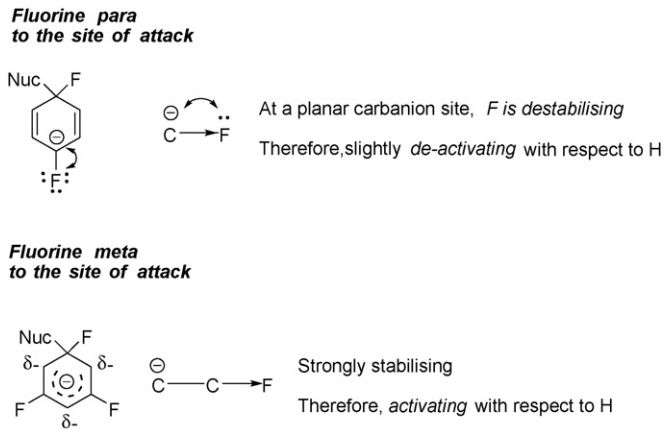


Fig. 3. Effect of fluorine as a substituent *meta* and *para* to the site of nucleophilic aromatic substitution.

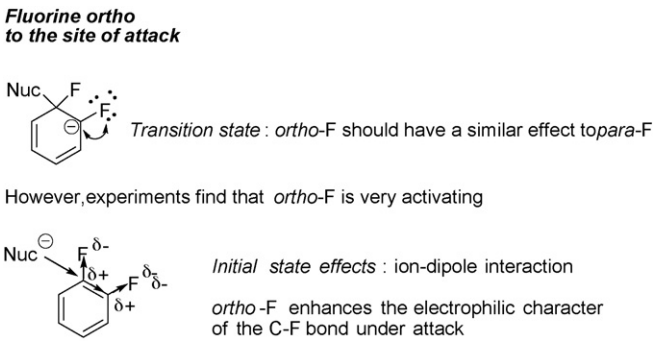
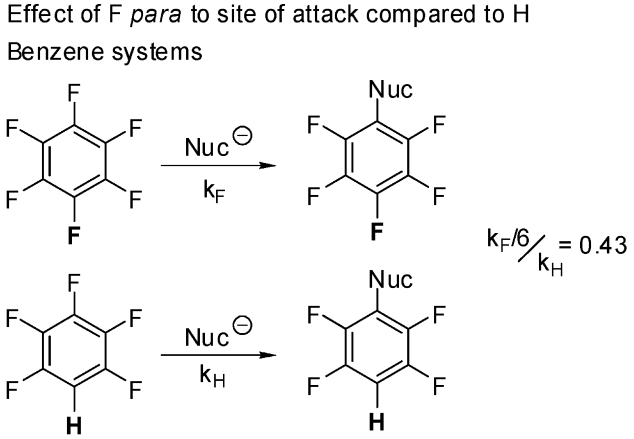


Fig. 4. *Ortho*-activation.

us a short step to conclude that the activating effect of an *ortho*-fluorine is due to enhancing the electrophilic character of the carbon atom that is under attack. Of course, such effects fall off rapidly with distance and it is unlikely that this is a significant factor contributing to activation by a *meta*-fluorine substituent.

This model is open to test, and we have previously done so [12]: according to the Hammond postulate, as the transition state moves closer to the initial-state, that is, if we use a more reactive system, then the *ortho*- (coulombic) effect should become more important, which it does and, conversely, as we make the system less reactive, then the transition state becomes more like the Meisenheimer complex and the *ortho*-activation should become less important. This is indeed the situation that is illustrated in Table 1, where we have compared reactions of methoxide in methanol with systems containing F or H at the corresponding positions. As the system is made much more reactive, comparing benzenoid to the corresponding pyridine systems, then the effect of an *ortho*-F becomes greater than that of a *meta*-F in the pyridine series. In contrast, however, when the much less reactive aniline is used as the nucleophile, then the

Table 1
Relative rates of reaction (k_F/k_H) of systems bearing fluorine or hydrogen at corresponding positions [5,6]



Further results

Nucleophile	Substrates	k_F/k_H		
		ortho	*meta*	*para*
MeONa, MeOH, 58 °C	Benzene systems	57	106	0.43
MeONa, MeOH, 58 °C	Pyridine systems	79	30	0.33
$PhNH_2$, dioxane/H_2O, 58 °C	Pyridine systems	1.8	34	–

Table 2
Effects of ring nitrogen and trifluoromethyl

Effect of ring nitrogen: at various sites (derived from the ratios of *k* values for reactions with ammonia in dioxane) (60:40 v:v, at 25 °C) [13]		
ortho-	*meta*-	*para*- (relative to the site of nucleophilic attack)
0.62×10^5	8.5×10^2	2.3×10^5 (relative to C–H)
[72	1	266] (relative to the *meta*- position)
Effect of trifluoromethyl: at various sites determined from pyridine derivatives [13] (derived from the ratios of *k* values for reactions with ammonia in dioxane) (60:40 v:v, at 25 °C)		
ortho-	*meta*-	*para*- (relative to the site of nucleophilic attack)
2.2×10^3	–	4.5×10^3 (relative to C–H)

activating effect of an *ortho*-F virtually disappears. Thus, our rationale, which incorporates coulombic effects, is quite consistent with our findings, rather than the use of Meisenheimer models only [9] for the transition state which, as we have illustrated, will not account for the variable *ortho*-activation by fluorine.

Development of these ideas has led us to determine the separate activating influences of substituents (e.g. CF_3, CN, etc.) at sites that are *ortho*-, *meta*-, and *para*- to the site of nucleophilic attack, to further compare other significant factors that govern the orientation of nucleophilic aromatic substitution in these systems. In this paper, we report our studies that explore the effects of CF_3, CF_2H, CFH_2, Cl and CN substituents on nucleophilic aromatic substitution processes.

2. Results and discussion

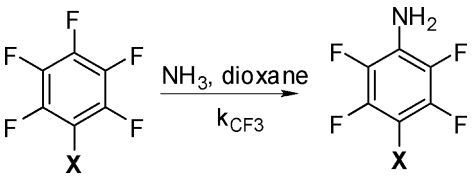
2.1. Effect of CF_3, CF_2H and CFH_2 substituents

We have previously established the activating effects of trifluoromethyl in perfluoroaromatic systems and compared these effects with those of ring nitrogen (Table 2) [13].

Thus, trifluoromethyl is strongly activating but not as activating as ring nitrogen at the corresponding position. Moreover, trifluoromethyl, like ring nitrogen, activates both *ortho*- and *para*-positions to a similar degree. Subsequently, we have explored further the nature of the activating influence of fluorine in the side-chain by comparing the relative effects of CF_3, CF_2H, and CFH_2, in reactions of C_6F_5–X (where X is the substituent group) with ammonia in dioxane/water (60/40), the product in each case being the corresponding 4-amino derivative as determined by ^{19}F NMR. The results are shown in Table 3 and they are very surprising, because the difference in reactivity between CF_2H and CFH_2 are smaller than we would have anticipated.

These results suggest that at least part of the stabilizing influence of fluorine in the substituent groups X, on the forming adjacent planar carbanion, is conformationally dependant. In this way, introduction of the first fluorine would have a significant effect, and then the second would increase the probability of attaining the favourable conformation. However, introducing the third fluorine would not only increase the probability further, but more importantly reduces the possibilities for alternative conformations. A possible scenario would be that the favourable conformation is as shown in Fig. 5, with a C–F bond in plane with the π-bond containing the developing charge in the transition state, and an obvious way of accounting for this stabilizing effect would be to invoke negative hyperconjugation [5] as illustrated in Fig. 5. The possibilities for attaining this favourable conformation are then maximized in the system, X = CF_3.

Table 3
Rate constants for reactions of polyfluoroalkylbenzene derivatives, C_6F_5–X, with ammonia in dioxane/water, 60:40 v:v, at 80 °C



X	Rate constant, *k* (mol^{-1} s^{-1})
CF_3	71×10^{-1}
CF_2H	5.0×10^{-5}
CFH_2	1.1×10^{-5}

2.2. Effect of cyano substituents

We have also explored the activating influence of the CN group at sites that are *ortho*-, *meta*- and *para*- to the site of nucleophilic attack, by comparing appropriate measured rate constants that then enable us to make the comparisons with the activating effect of the trifluoromethyl group shown in Table 4.

Clearly, CN in the *para*- position is significantly more activating than trifluoromethyl, while introduction of a second CN group into the *meta*- position has a relatively small effect. In contrast, two CN groups *para*- to each other are little more activating than two trifluoromethyl groups that are *para*- to each other. This suggests that CN is significantly more activating in the *para*- than in the *ortho*- positions and that CN is much less activating in the *meta*- positions. The comparisons are also consistent with the knowledge that the CN group is activating via conjugative stabilization of the developing negative charge in the transition state.

In further reactions to illustrate these conclusions, using aniline as the reagent (Fig. 6), we have established that 4-chlorotetrafluoropyridine **1** gave product **2** arising from substitution at the 2-position exclusively, replacing fluorine, rather

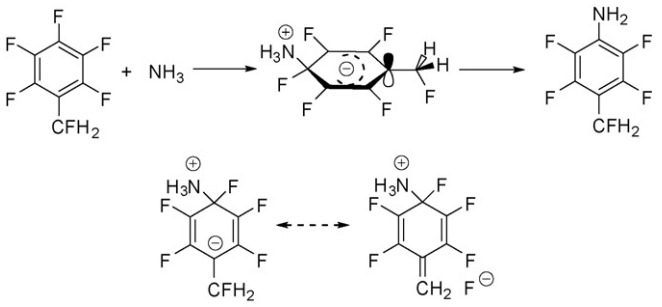
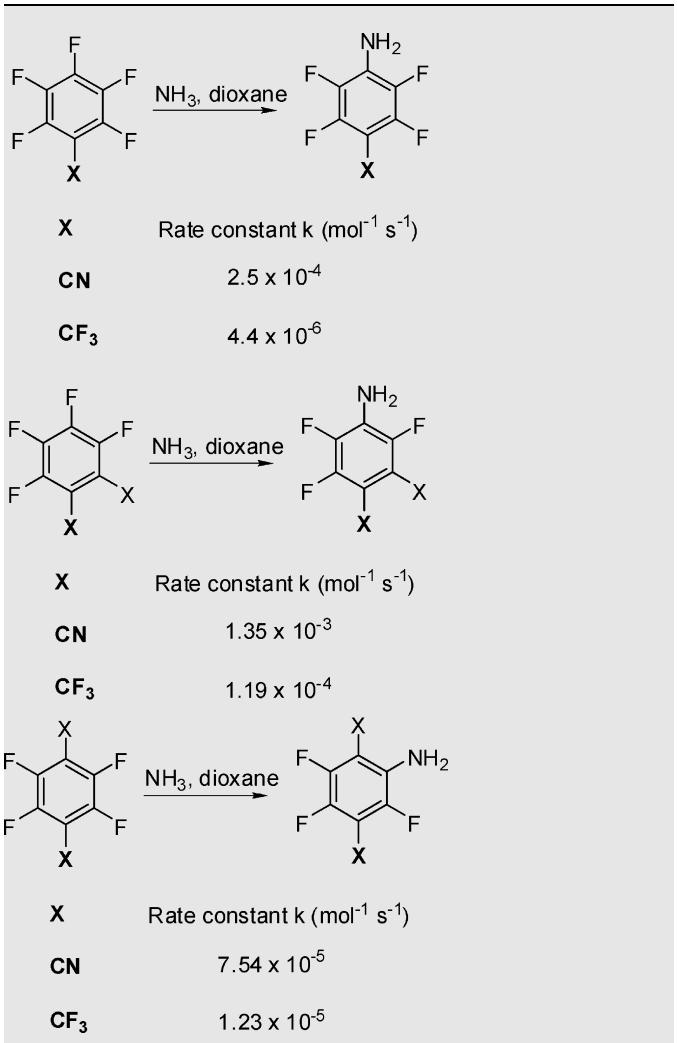


Fig. 5. Conformational dependence of C–F as a stabilizing influence on an adjacent developing carbanion allowing stabilization by negative hyperconjugation.

Table 4
Rate constants (1 mol^{-1} s^{-1}) for reactions of cyano- and trifluoromethyl-benzene derivatives, with ammonia in dioxane/water, 60:40 v:v, at 80 °C



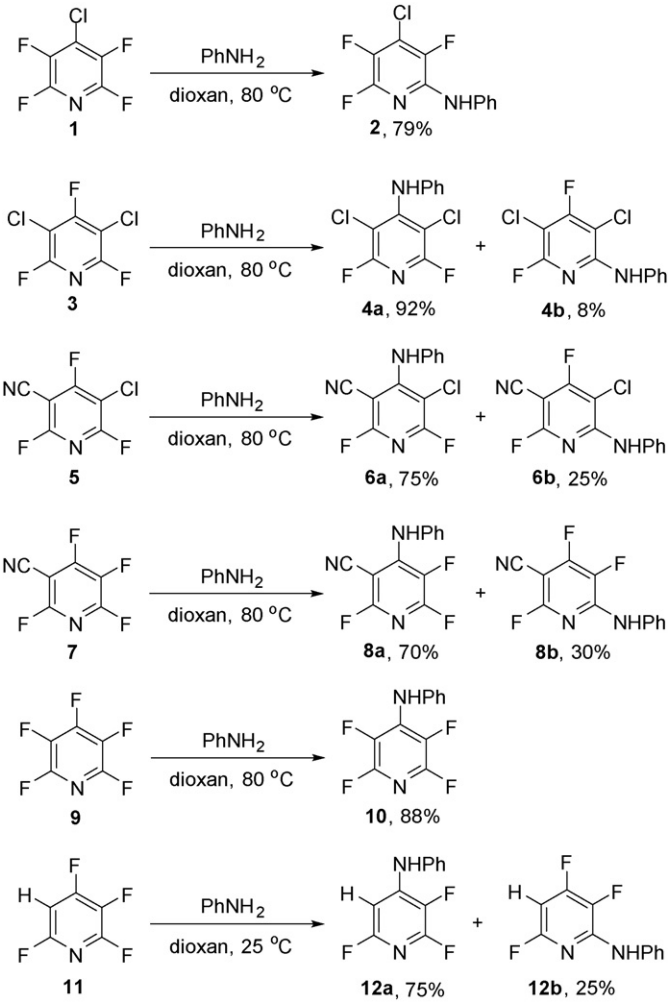


Fig. 6. Orientation of substitution of reactions with aniline.

than chlorine which is attached to the electronically favoured 4-position. 3,5-Dichloro-trifluoropyridine **3** is unusual in that some attack at the 2-position has been reported previously and attributed to steric effects arising from the chlorine atoms which retard attack at the 4-position. In the case of attack by aniline attack at the 4-position occurred preferentially to give **4a** (92%), whereas in 3-chloro-5-cyano-trifluoropyridine **5**, products **6a** and **6b** were formed in a 3:1 ratio. **6b** arises from attack at the 2-position and we may attribute this observation to the superior activating influence of the 5-cyano group, rather than steric effects.

Furthermore, in the case of pentafluoropyridine **9** (Fig. 6), the ring nitrogen has the major influence in determining overall reactivity but is not significantly discriminating between 2- or 4-activation. This is clear from the fact that 2,3,4,6-tetrafluoropyridine **11** gives a mixture of 2- and 4-substitution products because the number of activating fluorine atoms is the same for attack at both sites in this case. However, attack occurs exclusively at the 4-position in pentafluoropyridine simply because this maximizes the number of activating fluorine substituents (two *ortho*-fluorine and two *meta*-fluorine atoms to the site of attack).

3. Conclusions

The gross features of nucleophilic aromatic substitution processes in perfluoroaromatic compounds are now reasonably well understood and the activating effects of various ring substituents are illustrated in the discussion above. This reaffirms the conclusion that a consideration of the relative stabilities of Meisenheimer intermediates alone is insufficient to explain experimentally determined results.

4. Experimental

4.1. General

Except where indicated, all of the compounds described in this paper have been described previously and were synthesised by known methods [3]. Also, reactions of these systems with ammonia have been studied extensively [3] and, therefore, product isomer analysis was carried out by NMR and by gas chromatography, using a gas-density balance detector.

4.2. Kinetic experiments

Rate measurements for reactions with ammonia were carried out at 25 °C using dioxane:water, 60:40 (v:v). Samples were withdrawn at suitable intervals and quenched in a large excess of water, and the remaining base was titrated against standard hydrochloric acid. The infinity value agreed well with that calculated from the weight of material used. Generally, reactions were followed for at least two half-lives and each run was carried out in duplicate. Second-order rate constants were calculated [6] from Eq. (i), where a and b are the initial concentrations of reagent (e.g. ammonia) and substrate respectively, since the reagent becomes protonated by the acid liberated in the reaction.

$$k = \frac{\ln[b(a-2x)/a(b-x)]}{(a-2b)t} \quad \text{(i)}$$

The standard error of the mean in any individual run was ±1% and duplicate runs agreed within ±1%.

Rate measurements for reactions with aniline were carried out by measuring fluoride ion concentrations using a fluoride ion specific electrode, following calibration.

4.3. Reactions with aniline

4.3.1. 4-Chloro-2,3,5,6-tetrafluoropyridine 1

A mixture consisting of aniline (0.93 g, 10 mmol), 4-chloro-2,3,5,6-tetrafluoropyridine **1** (0.93 g, 5 mmol) and dioxane (6 mL) was heated in a sealed tube for 3 days at 80 °C. Work up and purification as above gave *4-chloro-3,5,6-trifluoro-N-phenylpyridin-2-amine* **2** (1.02 g, 79%) as a white solid; (Found: C, 50.9; H, 2.2; N, 10.7. $C_{11}H_6ClF_3N_2$ requires: C, 50.98; H, 2.34; N, 10.83%); δ_F −94.2 (1 F, m, F-6), −143.7 (1 F, m, F-3), −158.5 (1 F, m, F-5).

4.3.2. 3,5-Dichloro-2,4,6-trifluoropyridine 3

A mixture consisting of aniline (0.93 g, 10 mmol), 3,5-dichloro-2,4,6-trifluoropyridine **3** (1.1 g, 5 mmol) and dioxane (6 mL) was heated in a sealed tube for 8 days at 80 °C. Work up gave a mixture of 4-anilino- (**4a**, 92%) and 2-anilino-3,5- (**4b**, 8%) dichlorodifluoropyridine which, after purification by column chromatography (pentane:chloroform, 1:1 v:v), gave *3,5-dichloro-2,6-difluoro-N-phenylpyridin-4-amine* **4a** (1.3 g, 92%) as a white solid; m.p. 73 °C, (Found: C, 48.3; H, 2.1; N, 10.2. $C_{11}H_6Cl_2F_2N_2$ requires: C, 48.03; H, 2.20; N, 10.18%); δ_F −75.2 (m, F-2).

4.3.3. 3-Chloro-5-cyano-2,4,6-trifluoropyridine 5

A mixture consisting of aniline (0.93 g, 10 mmol), 3-chloro-5-cyano-2,4,6-trifluoropyridine **5** (0.8 g, 4 mmol) and dioxane (6 mL) was heated in a sealed tube for 8 days at 80 °C. Work up gave a mixture (1.2 g, 66%), containing the corresponding 4- (**6a**, 75%) and 2- (**6b**, 25%) anilino derivatives, which after purification by column chromatography (dichloromethane:hexane, 60:40 v:v), gave a mixture of isomers; (Found: C, 53.9; H, 2.4; N, 15.7. $C_{12}H_6ClF_2N_3$ requires: C, 54.24; H, 2.26; N, 15.82%). Purification by analytical scale HPLC gave small quantities of each isomer; 5-chloro-2,6-difluoro-4-(phenylamino)nicotinonitrile **6a**; δ_F −61.2 (m, F-6), −65.8 (m, F-2); 5-chloro-2,4-difluoro-6-(phenylamino)nicotinonitrile **6b**; δ_F −58.7 (m, F-2), −94.5 (m, F-4).

4.3.4. 3-Cyanotetrafluoropyridine 7

A mixture containing aniline (0.93 g, 10 mmol) and 3-cyanotetrafluoropyridine **7** (0.88 g, 5 mmol) in dioxane (6 mL) was heated in a sealed tube at 80 °C for 8 days. The NMR spectrum of the crude mixture showed the presence of both the 4-anilino **8a** and the 6-anilino **8b** derivatives in the ratio 7:3. No further purification was carried out.

4.3.5. Pentafluoropyridine 9

A mixture containing aniline (1.03 g, 11 mmol) and pentafluoropyridine **9** (0.93 g, 5.5 mmol) (2:1 molar ratio) in dioxane (6 mL) was heated in a sealed tube at 80 °C for 22 h. The tube was cooled, opened to air, and the contents were extracted by dimethyl ether; the combined extracts were washed with dilute HCl (1 M), dried ($MgSO_4$) and filtered. Removal of the dimethyl ether gave a brown oil and HPLC showed one product, which was purified by column chromatography (silica), using pentane/chloroform (50:50 v:v), to give *4-anilino-2,3,5,6-tetrafluoropyridine* **10** (1.17 g, 88%) as a white solid; m.p. 87 °C (Found: C, 54.8; H, 2.4; N, 11.9. $C_{11}H_6F_4N_2$ requires: C, 54.6; H, 2.5; N, 11.6%); δ_F −95.3 (2 F, m, F-2), −155.75 (2 F, m, F-3). The experiment was repeated, using a reaction temperature of 25 °C, giving the same product in essentially quantitative yield.

4.3.6. 2,3,4,6-Tetrafluoropyridine 11

A mixture consisting of aniline (0.93 g, 10 mmol), 2,3,4,6-tetrafluoropyridine **11** (0.76 g, 5 mmol) and dioxane (6 mL) was stirred for 3 days at 25 °C. The mixture was worked up as described above, giving a brown solid which was shown by ^{19}F NMR and mass spectrometry to contain 2,3,6-trifluoro-*N*-phenylpyridin-2-amine **12a**; δ_F −75.5 (1 F, m, F-2), −96.0 (1 F, m, F-6), −171.6 (1 F, m, F-3); and, 3,4,6-trifluoro-*N*-phenylpyridin-2-amine **12b**; δ_F −71.6 (1 F, m, F-6), −126.3 (1 F, m, F-4), 170.9 (1 F, m, F-3); and, in a 3:1 ratio by ^{19}F NMR.

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