# Electrophilic Fluorination Using Elemental Fluorine

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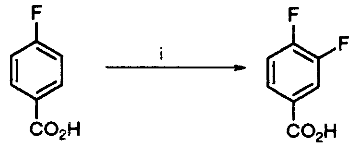
Electrophilic fluorination by elemental fluorine is promoted by the use of protonic acids; formic and sulfuric acids are especially effective.

There is considerable interest in methodology for site specific fluorination of aromatic compounds and recently a range of interesting commercially available electrophilic fluorinating agents have been reported, themselves derived from elemental fluorine.[1] However, fluorine itself is still not generally perceived to be a realistic electrophilic reagent due to its propensity for exothermic radical-chain reactions, although its controlled use as an electrophile would be highly desirable.

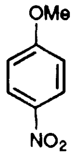
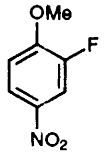
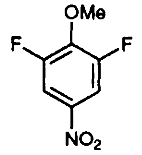
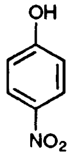
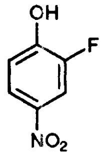
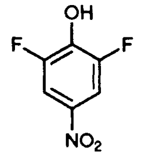
In principle, protonic acids should promote the electrophilic process and, consequently, we have systematically explored the effect of acids in promoting electrophilic reactions of fluorine with a range of aromatic systems. Consequently, we now find that the reactivity of fluorine as an electrophile does indeed vary significantly with the medium and in some cases, dramatically so.



1 2

**Scheme 1** *Reagents and conditions*: i, $HCO_2H$, 10% $F_2$–$N_2$, room temp., 79% conversion, 66% yield

**Table 1** Direct fluorination (10% $F_2$–$N_2$), in formic acid (98%) at room temperature

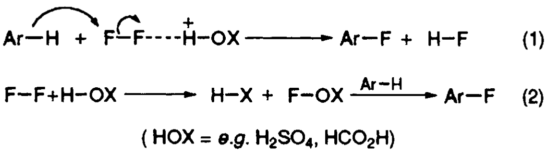
| Substrate | Product(*a*) | Product(*b*) | Conversion(%) | Yield (%) | |
|---|---|---|---|---|---|
| | | | | (*a*) | (*b*) |
|  |  |  | 100 | 50 | 20 |
|  |  |  | 84 | 64 | 10 |

Surprisingly, formic acid (p$K_a$ = 3.8; ε = 58.5) has not been explored as a solvent for fluorinations but we find it is an excellent solvent for this purpose and is potentially useful on an industrial scale. For example, 4-fluorobenzoic acid **1** can be converted smoothly to 3,4-difluorobenzoic acid **2** in 66% yield (79% conversion), with no significant byproducts (Scheme 1).

This is especially significant considering that these reactions are carried out at room temperature *i.e.* against the prevailing feeling that low temperatures are required to control direct fluorinations. Further examples of direct fluorination are shown in Table 1 and this demonstrates quite clearly that fluorine is a viable reagent for synthesis of fluoroaromatic compounds even on the industrial scale.

It is even more surprising that sulphuric acid (p$K_a$ = −3.6; ε = 100) has not been described as a solvent for fluorination, perhaps because of the hazardous nature of hypofluorites derived from fluorination of this medium alone.[2] Nevertheless, we have safely used concentrated sulfuric acid as a medium for fluorination of various aromatic substrates and, furthermore, with a dramatic increase in reactivity. The products depend on the proportion of fluorine passed and pentafluorobenzoic acid can be formed at room temperature (Scheme 2).

Clearly, the isomers obtained demonstrate that fluorine acts as an electrophile under the conditions indicated and, moreover, the effect of acid is an indication that, in some situations, fluorine can be used like other halogens with reactivity being altered by acid catalysis. There are, however, two possibilities for the influence of acid, as illustrated by eqns. (1) and (2) but it is difficult to distinguish between strong acid catalysis, [eqn. (1)] and the *in situ* formation and rapid reaction of hypofluorites derived from the acid [eqn. (2)].

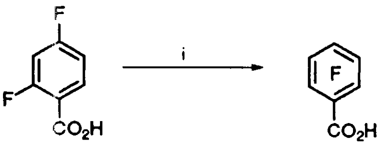


$$\mathrm{Ar{-}H + F{-}F\cdots\overset{+}{H}{-}OX \longrightarrow Ar{-}F + H{-}F} \quad (1)$$

$$\mathrm{F{-}F + H{-}OX \longrightarrow H{-}X + F{-}OX \xrightarrow{Ar-H} Ar{-}F} \quad (2)$$

( HOX = *e.g.* $H_2SO_4$, $HCO_2H$)

These results help to develop the conviction that elemental fluorine can be used as a viable reagent in organic synthesis and forthcoming results will further demonstrate this point.



**Scheme 2** *Reagents and conditions*: i, $H_2SO_4$, 10% $F_2$–$N_2$, room temp., 5%

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## References

1 W. E. Barnette, *J. Am. Chem. Soc.*, 1984, **106**, 452; R. E. Banks and I. Sharif, *J. Fluorine Chem.*, 1991, 207; T. Umemoto and G. R. Tomizawa, *Abstr. Papers ACS*, 1993, **206**, 10 and references therein.

2 M. Lustig and J. M. Shreeve, in *Advances in Fluorine Chemistry*, ed. J. C. Tatlow, R. D. Peacock, H. H. Hyman and M. Stacey, Butterworths, London, 1973, vol. 7.