Perfluoroalkylation of Anilines in the Presence of Zinc and Sulphur Dioxide

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Arylamines are transformed into their *ortho*- and *para*-trifluoromethyl derivatives by the action of trifluoromethyl bromide under slight pressure in the presence of 0.15 equiv. of zinc and sulphur dioxide in dimethylformamide.

Recently, we described the transformation of trifluoromethyl bromide, under slight pressure, into a trifluoromethanesulphinate salt by the action of zinc (or other reductive metal such as cadmium, aluminium, or manganese) and sulphur dioxide in dimethylformamide (DMF).[1] In addition to the classical organometallic mechanism for this kind of condensation,[2–4] we considered a radical process possible, in view of the ease of reduction of sulphur dioxide[5] (Scheme 1).

In order to test for the presence of trifluoromethyl radicals, we have added anilines to this mixture, and indeed observed

Table 1. Perfluoroalkylation products

Arylamine (1)	Perfluoroalkyl halide (2)	Pressure/ bar	Alkylation product (3) orientation[a] (% yield)[b]	Total yield/ %
Aniline	CF_3Br	3—5	2(36); 4(20)	56
4-Methylaniline	CF_3Br	3—5	2(30)	30
2-Chloroaniline	CF_3Br	3—5	4(21); 6(21)	42
3-Methoxyaniline	CF_3Br	3—5	2(21); 4(24); 6(24)	69[c]
1-Aminonaphthalene	CF_3Br	3—5	2(30); 4(20)	50
Aniline	C_4F_9I	1	2(30); 4(30)	60

[a] Of perfluoroalkylation relative to the amino group. [b] For isolated and purified isomers except for perfluorobutylaniline (g.l.c. analysis). [c] 2,6-Bistrifluoromethyl-3-methoxyaniline (4%) was also obtained.

$$\mathrm{Zn} + \mathrm{SO_2} \longrightarrow \mathrm{Zn^+} + \mathrm{SO_2}^{\bullet-}$$
$$\mathrm{SO_2}^{\bullet-} + \mathrm{CF_3Br} \longrightarrow \mathrm{SO_2} + \mathrm{CF_3Br}^{\bullet-}$$
$$\mathrm{CF_3Br}^{\bullet-} \longrightarrow \mathrm{Br^-} + \mathrm{CF_3}^{\bullet}$$
$$\mathrm{CF_3}^{\bullet} + \mathrm{SO_2}^{\bullet-} \longrightarrow \mathrm{CF_3SO_2}^-$$

Scheme 1

$$\underset{(\mathbf{1})}{\mathrm{ArNH_2}} \xrightarrow[\mathrm{Zn/SO_2/DMF}]{\mathrm{R_FX}(\mathbf{2})} \underset{(\mathbf{3})}{\mathrm{R_FArNH_2}}$$

Scheme 2

alkylation of the ring (Scheme 2). In addition to variable amounts of zinc trifluoromethanesulphinate, trifluoromethylanilines were obtained (Table 1).

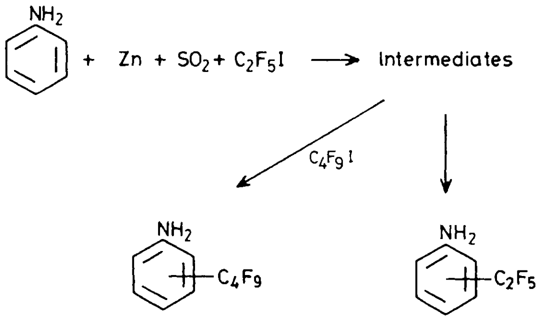
In all the experiments, 0.15 equiv. of Zn and SO_2 and 1.5 mol of CF_3Br per mol of aromatic compound were used. The exothermic reaction was performed in DMF at room temperature during 2 h in a Parr apparatus under a pressure of 3—5 bar of CF_3Br. Usually the HBr formed was neutralized *in situ* by sodium bisulphite or a pyridine derivative.

Similar alkylations were observed with stoicheiometric quantities of aniline and perfluoroalkyl iodides of various chain lengths at atmospheric pressure (Table 1). These perfluoroalkylations do not need stoicheiometric amounts of Zn and SO_2; a decimolar quantity of these reagents is sufficient.

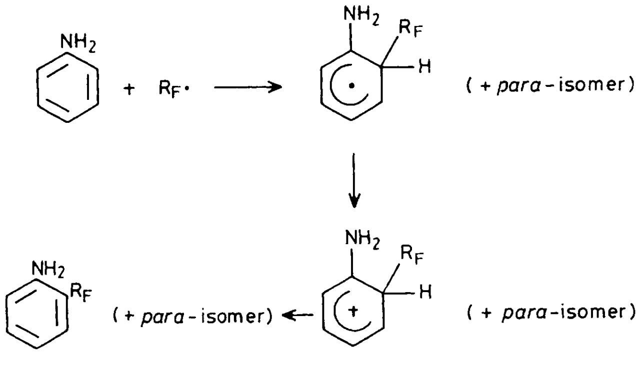
We have observed the initiation of the condensation by an intermediate species in solution, as follows. Into a solution of aniline (10 ml) in 2-methylpyridine (10 ml) and DMF (25 ml), sulphur dioxide (4 g) was bubbled. After addition of zinc powder (1.5 g) the mixture was stirred for 1 min. Then stirring was stopped and half the upper liquid phase was quickly transferred under pressure (nitrogen) through a glass bridge into nonafluorobutyl iodide (10 ml). After 30 min stirring, the mixture was analysed by ^{19}F n.m.r. An *ortho-para* mixture of perfluorobutylanilines was detected and also some zinc perfluorobutanesulphinate.

In a second experiment, the same procedure was applied except that iodopentafluoroethane was bubbled through the solution before sulphur dioxide. Beside 2- and 4-pentafluoroethyl [δ ($ArCF_2$) -113.0 and -113.6 p.p.m.], nonafluorobutylanilines [δ ($ArCF_2$) -110.7 and -111.3 p.p.m.] were detected. The formation of the latter in in agreement with a chain process (Scheme 3).

A third experiment was performed like the second, but nitrobenzene was mixed with the perfluorobutyl iodide. Only pentafluoroethylanilines (formed in the initial mixture) were detected by n.m.r. analysis of the final product mixture. Formation of perfluorobutylanilines was clearly inhibited by the electron scavenger nitrobenzene. This observation is in agreement with the presence of radical intermediates.



Scheme 3



Scheme 4

These experiments can be interpreted as shown in Scheme 4. Capture of the perfluoroalkyl radical by the aromatic nucleus is followed by oxidation of the cyclohexadienyl radical to the corresponding cation, as in other homolytic aromatic substitutions.[6] The oxidant could be a zinc cation or SO_2 (or perhaps R_FX); its reduced form is able to generate perfluoroalkyl radicals (Scheme 1), maintaining a radical chain process. The cyclohexadienyl cation can give the perfluoroalkylated aromatic product by loss of a proton. In the Minisci reaction nucleophilic alkyl radicals alkylate an electron-poor aromatic nucleus. In contrast, the present alkylation by electrophilic perfluoroalkyl radicals works better with electron-rich aromatic compounds.† The selectivity for the

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† Similar perfluoroalkylation of other aromatic compounds (alkylbenzenes and phenols) has been observed, in lower yields than with anilines. From toluene a mixture of 2-, 3-, and 4-trifluoromethyltoluenes was obtained in a total yield of 22%, and ratios of 9 : 4 : 9 (g.l.c. and ^{19}F n.m.r.).

electron-rich *ortho-* and *para*-positions of the arylamines can be explained by the electrophilic nature of this radical, reacting under very mild conditions.

This reaction is the first reported alkylation of anilines by the cheap and easily available trifluoromethyl bromide, leading directly to the base sensitive trifluoromethyl derivatives[7] which are important intermediates for the synthesis of drugs and agrochemicals.[8]‡

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‡ Hitherto, *ortho* and *para*-trifluoromethylanilines have been prepared by reduction of nitrotrifluoromethylbenzenes. Although the nitration of trifluorotoluene can be performed in the classical manner, it leads mainly to the *meta*-isomer (91%).[9] The alkylation of aromatic compounds by carbon tetrachloride in HF has not been described for anilines.[10,11] No direct method for the trifluoromethylation of anilines by perhalogenoalkyl halides is known.[12] Copper-mediated alkylation of an aniline with trifluoromethyl iodide failed.[13] Other preparations of trifluoromethyl aromatic compounds necessitate functional starting materials, *e.g.* transformation of benzoic acids by SF_4,[14] action of *N*-bromosuccinimide and HF on *ortho* thioesters,[15] or Ullmann coupling of a halogenoarene with trifluoromethyl copper[16] or a sodium trifluoroacetate–copper iodide mixture.[17]

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