Fluorodenitration of Some Mildly Activated Nitro-compounds

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1-Fluoro-3-nitrobenzene, 2- and 4-fluoropyridines, and 2-fluorothiazole have been synthesised from the corresponding nitro-derivatives by treatment with fluoride ion in hexamethylphosphoramide or *N*-methyl-2-pyrrolidone.

NUCLEOPHILIC substitution by means of fluoride ion is a common method of synthesis of fluoro-derivatives.[1] Usually chloride, bromide, or toluene-*p*-sulphonate ions [2] are involved as leaving groups in these reactions. Displacements of the nitro-group by fluoride ion have been documented both for aliphatic [3] and for aromatic [4] compounds. As far as the latter class is concerned, only a few cases have been reported in which the mobility of the nitro-group has been tested, by use of fluoride ion in dimethyl sulphoxide or dimethylformamide with highly activated substrates.[4] On the other hand recent studies on S_NAr reactions have shown a high mobility for the nitro-group, which in some cases appears to be comparable or even superior to that of the fluoro-group [*e.g.* second order rate coefficients [5] (k_2 in l mol^{-1} s^{-1}) for reactions of 1-X-2,4-dinitrobenzenes with methoxide ion in methanol at 25 °C for X = NO_2, F, OTs, Cl, and Br are (respectively) 15·4, 17·7, 0·49, 0·029, and 0·019]. Similar results [3] have been obtained for other types of substrates such as 1-X-4-nitrobenzenes and 2-X-benzothiazoles.

We wished to evaluate the scope of the fluorodenitration reaction from a synthetic point of view. We now report experiments with 2- and 4-nitropyridines, with 1,3-dinitrobenzene, and with 2-nitrothiazole. These substrates were chosen with the aim of demonstrating that the present method is general and better than other methods based on exchange reactions which have been used previously. These nitro-compounds are mildly activated towards nucleophiles, and their preparation is straightforward. A summary of the results is reported in the Table.

The convenience of our method is apparent if one considers that 2-fluoropyridine has been previously obtained [6] in *ca.* 50% yield from 2-chloropyridine and fluoride ion in dimethyl sulphoxide at 200 °C for 21 days. Our reaction proceeds at lower temperatures and in shorter times, and higher yields are obtained. By our method 1-fluoro-3-nitrobenzene can be obtained easily from 1,3-dinitrobenzene. The ready synthesis of 2-fluorothiazole contrasts with previous work in which we had experienced considerable difficulty with several methods, including one which was reported to be successful in the case of 5-methyl-2-fluorothiazole.[7]

Fluorodenitration reactions

Reactant	Solvent [a]	Time (h)	Temp. (°C)	Yield (%) of fluoro-analogue
1,3-Dinitrobenzene	NMepy	48	180	40
	HMPT	48	180	45
2-Nitropyridine	NMepy	24	160	55
	HMPT	24	160	60
4-Nitropyridine	NMepy	24	160	20
2-Nitrothiazole	NMepy	24	110	20

[a] NMepy = *N*-methyl-2-pyrrolidone; HMPT = hexamethylphosphoramide.

EXPERIMENTAL

The course of the reactions was followed by g.l.c. The yields reported are those of the final pure product. Usually the materials were separated from the reaction mixture by steam distillation.

We did not observe any reduction of the nitro-function. In the case of 1,3-dinitrobenzene the only isolated material was 1-fluoro-3-nitrobenzene but it is possible that under more drastic conditions the second nitro-group is replaced. As a typical example, the synthesis of 2-fluorothiazole is reported.

2-Fluorothiazole.—A suspension of 2-nitrothiazole (10 g) and dry potassium fluoride (40 g) in *N*-methyl-2-pyrrolidone (50 ml; distilled twice and dried over 4A molecular sieves) was stirred at 110 °C under a slow current of nitrogen for 24 h. The volatile product was trapped in a bath of acetone–solid carbon dioxide. Distillation at atmospheric pressure gave *2-fluorothiazole* (1·5 g, 20%), b.p. 78—80° (Found: F, 19·0. C_3H_2FNS requires F, 18·4%), τ (CCl_4) 2·85 (d, H-4) and 3·00 (q, H-5) ($J_{4,5}$ 4·0, $J_{5,F}$ 1·2 Hz).

The material reacted with methoxide ion in methanol yielding quantitatively the known 2-methoxythiazole.[8]

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