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The Preparation of 3- and 4-Fluorophthalic Anhydrides by Fluorodenitration

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Synopsis. 3- And 4-fluorophthalic anhydrides were prepared by heating the respective nitrophthalic anhydrides with potassium fluoride with or without an aprotic polar solvent.

Mono and difluorophthalic anhydrides have been synthesized mainly by the oxidation of fluorinated *o*-xylenes.[1,2] However, these preparative routes involve a tedious Balz-Schiemann reaction in order to introduce the fluorine atom into an aromatic ring. A simple preparative method for 3-fluorophthalic anhydride has, however, been reported by Heller, who used a halogen exchange process which involves merely baking 3-chlorophthalic anhydride with potassium fluoride.[3] 3-Chlorophthalic anhydride, on the other hand, is most conveniently prepared by the chlorination of 3-nitrophthalic anhydride,[4] which is obtained by the nitration of phthalic anhydride together with the 4-nitro isomer.[5] In this connection, we examined the fluorination of 3- and 4-nitrophthalic anhydrides directly with potassium fluoride, since fluorodenitration on aromatic nitro compounds is not unusual in the literature.[6,7]

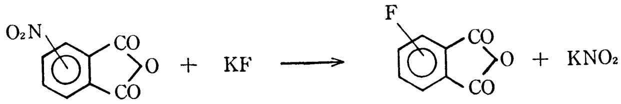
When 3-nitrophthalic anhydride was heated with about three moles of potassium fluoride at 180—190 °C, a temperature which is a little higher than the melting point of the nitro compound, the reaction proceeded smoothly, with the evolution of a brown gas of nitrogen oxide. The reaction was completed within a rather short period, 30—60 min, judging from the gas chromatographic observation. The yield of almost pure 3-fluorophthalic anhydride was about 65%. A higher temperature or a longer reaction time had unfavorable results; for instance, an explosive reaction occurred above 210 °C.

4-Nitrophthalic anhydride was also subjected to a similar process. The nitro group of this compound was less reactive for the fluorination, and the reaction required a higher temperature (190—195 °C) and a longer reaction time (—75 min). This is probably due to the weaker inductive effect of the electron-withdrawing dicarboxyl anhydride group, which is located farther from the nitro group than in the case of the 3-nitro isomer.

Since such polar aprotic solvents as dimethylformamide, dimethylsulfoxide, sulfolane, and hexamethyl phosphortriamide are well known to accelerate nucleophilic aromatic substitutions, including fluorination, we also used these solvents. In these aprotic solvents, the reactions seemed to proceed more easily and a lower temperature (80—90 °C) was enough for them to take place. However, the separation of the products from the reaction mixture was difficult because of their high solubility in these solvents as well as in water. We had to extract them with diethyl ether several times from the reaction mixture after dilution with water. This process made the yield of the fluorophthalic anhydride unreproducible. Further, a part of the fluorophthalic anhydride seemed to be attacked nucleophilically with these solvents.

The results of several runs carried out are shown in Table 1.

Table 1. Fluorodenitration of nitrophthalic anhydrides



[NPA] [FPA]

	Start materials		Reaction conditions			Yield of FPA (%)
	NPA	KF/NPA (molar ratio)	Solvent	Temp. (°C)	Time (min)	
1	3-NO_2	3	—	160—165	60	62
2	3-NO_2	3	—	180	30	66
3	3-NO_2	3	—	190	45	49
4	3-NO_2	3	—	200	30	39
5	3-NO_2	2.5	—	190	30	42
6	3-NO_2	2	—	190	30	16
7	4-NO_2	3	—	190—195	75	56
8	4-NO_2	3	—	200—205	70	52
9	3-NO_2	3	DMF	95	60	42
10	3-NO_2	3	DMSO	80	60	61

Experimental

Nitrophthalic Acids and Their Anhydrides. The nitration of phthalic anhydride was carried out according to the procedure described in Org. Syn.;⁵⁾ it gave pure 3-nitrophthalic acid (mp 214—216 °C (lit,⁵⁾ 215—218 °C)) in a 30% yield after recrystallization from water. This acid was then converted into the anhydride (mp 163—165 °C (lit,⁸⁾ 163—164 °C)) by treating it with acetic anhydride.⁸⁾

From the mixture of isomers of nitro compounds which was obtained from the mother liquors of the recrystallizations, 4-nitrophthalic acid (mp 159—160 °C (lit,⁹⁾ 164—164.5 °C)) was separated *via* esterification.¹⁰⁾ A subsequent treatment with acetic anhydride gave 4-nitrophthalic anhydride (mp 118—119 °C (lit,⁹⁾ 120—120.5 °C)).

Fluorophthalic Anhydrides. *Without Any Solvent*: A typical procedure was as follows. A mixture of 3-nitrophthalic anhydride (4.85 g, 0.026 mol) and potassium fluoride dehydrated by baking (4.35 g, 0.075 mol) was heated in an oil-bath and vigorously stirred for 30 min, keeping the temperature at 180—185 °C. During the reaction, nitrogen oxide gas evolved; it was led into a hood. After cooling, the reaction mixture was treated with benzene, and the fluorinated product was extracted by filtration. The solvent was then evaporated from the filtrate, giving 3-fluorophthalic anhydride (2.72 g, 66%, mp 159—160 °C). Recrystallization from benzene gave pure crystals (mp 161.5—162.5 °C (lit,³⁾ 160 °C)). IR (KBr): 1870, 1855, 1780 (C=O), 1265 (C–F) cm^{-1}. ^{19}F NMR (from int. C_6H_5F in C_6H_6): δ −3.4 ppm.

The reaction between 4-nitrophthalic anhydride and potassium fluoride was run in a similar manner, giving 4-fluorophthalic anhydride (mp 79—80 °C (lit,²⁾ 76—78 °C) (Table 1)). IR: 1855, 1830, 1780 (C=O), 1280 (C–F) cm^{-1}. ^{19}F NMR: δ −13.0 ppm.

With A Solvent: Nitrophthalic anhydride (5 g) and baked potassium fluoride (4.5 g) were heated in a solvent while being mechanically stirred. On cooling, the mixture was diluted with water, made acidic with hydrochloric acid, and extracted with diethyl ether several times. The ethereal extract was dried over magnesium sulfate and evaporated to give fluorophthalic anhydride (Table 1).

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