Notes

Reactions of 4-Nitrophthalic Anhydride with Potassium Fluoride and Potassium Nitrite

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The recent communication by Ishikawa and co-workers[1] on the preparation of 3- and 4-fluorophthalic anhydride from the corresponding nitro compound by fluorodenitration[2,3] prompts us to report our findings in the same area. Ishikawa reports that heating 4-nitrophthalic anhydride (**1**) with 3 mol of potassium fluoride affords 4-fluorophthalic anhydride (**2**). The yields are around 56%, but the authors fail to answer the question of the fate of almost half of the substituted phthalic anhydride.

We find that 3 mol are not necessary; 1 mol will give similar results. We have also elucidated the fate of all the substituted phthalic anhydrides. Nitrite ion produced in the reaction is trapped by the anhydride present, thus lowering the apparent overall yield of the reaction.

Heating 4-nitrophthalic anhydride (**1**) with at least 1 equiv of potassium fluoride at 230–240 °C produced 4-fluorophthalic anhydride (**2**) with the evolution of a red-brown gas. Distillation afforded up to a 62% yield of 4-fluorophthalic anhydride (**2**).

After distillation of the 4-fluorophthalic anhydride, a tan solid remained in the distillation pot. This material was insoluble in organic solvents, but dissolved readily in water. Acidification of an aqueous solution of this solid with hydrochloric acid and extraction with ethyl acetate afforded 4-nitrophthalic acid. The recovery of the 4-substituted phthalic acid was 34%; thus, the overall yield of the exchange reaction was >90%.

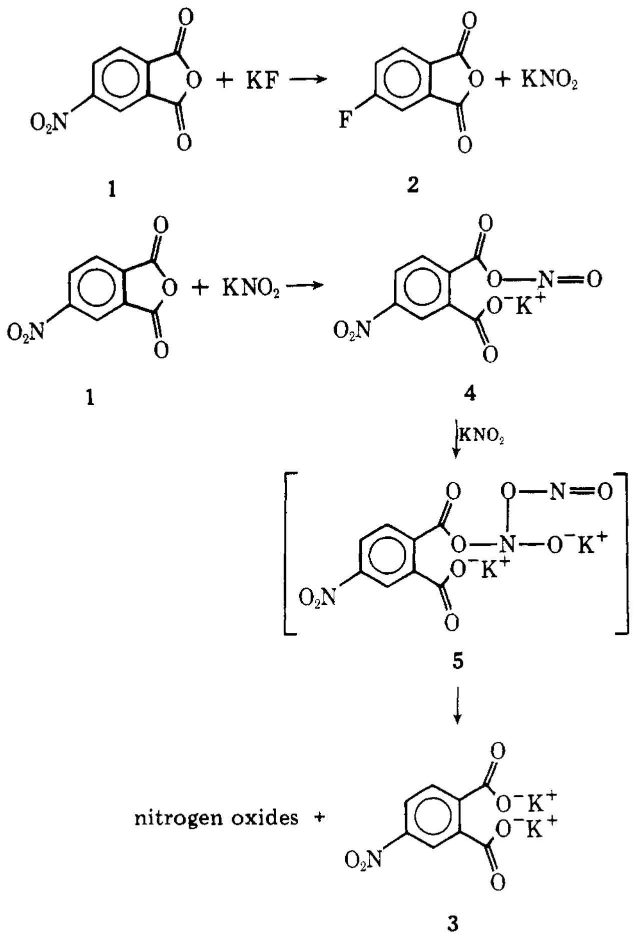
Sodium fluoride failed to give any reaction; heating a mixture of 4-nitrophthalic anhydride and 2 equiv of sodium fluoride for 18 h at 230–260 °C did not produce fluoro compound.

While a 220 °C temperature was necessary to give reaction of potassium fluoride with 4-nitrophthalic anhydride in the melt, the use of an aprotic solvent, such as dimethyl sulfoxide, greatly lowered the temperature required. Thus, reaction of 4-nitrophthalic anhydride with 2 equiv of potassium fluoride in dimethyl sulfoxide was complete within 20 min at 142 °C.

Fluoride exchange will also occur in acetonitrile solvent at 80 °C using the crown ether 2,3:11,13-dibenzo-1,4,-7,10,13,16-hexaoxacyclooctadeca-2,11-diene (dibenzo-18-crown-6) to solubilize the potassium fluoride. The use of crown ethers to solubilize potassium fluoride in acetonitrile and reactions of "naked" fluoride as a nucleophile have been reported.[4] Thus, reaction of 4-nitrophthalic anhydride with potassium fluoride in acetontrile containing dibenzo-18-crown-6 for 43 h afforded the 4-fluorophthalic anhydride, which was isolated as the diacid. Without the crown ether present, no 4-fluoro material was produced.

A possible mechanism for the formation of 4-nitrophthalic acid is shown in Scheme I. Exchange of potassium fluoride with 4-nitrophthalic anhydride affords 4-fluorophthalic anhydride and potassium nitrite. Nitrite ion has two potential reaction sites, and can react by either oxygen or nitrogen attack. Attack by oxygen on 4-nitrophthalic anhydride gives the aroyl nitrite **4**. Attack on **4** by another nitrite ion produces the dipotassium salt of 4-nitrophthalic acid and nitrogen oxides via the intermediate or transition state **5**.

Scheme I. Mechanism for Formation of 4-Nitrophthalic Acid

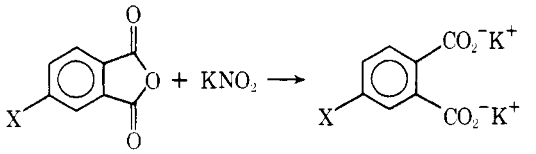


This mechanism is supported by several observations. The dipotassium salt of 4-nitrophthalic acid is formed. The infrared spectrum of the gases given off during the exchange reaction showed bands corresponding to the absorption bands of NO_2. Also, assuming the mechanism in Scheme I, the maximum yield of 4-fluorophthalic anhydride should only be 67%.

The ambifunctional nature of the nitrite ion has been well documented.[5–7] Nitrite ion reacts with alkyl halides to give a mixture of alkyl nitrites and nitroalkanes.[5] It has also been reported[8] that the solvolysis of acetic anhydride is markedly catalyzed by nitrite ions. The rate-determining step involves nucleophilic attack by nitrite ion on the anhydride molecule to produce an intermediate, believed to be acetyl nitrite, which undergoes relatively instantaneous decomposition in the buffered solvent to regenerate nitrite ion.

The reaction of nucleophiles with nitrite ester has been reported by Kornblum and co-workers.[9] In the reaction of primary nitroparaffins with a nitrite ester and sodium nitrite to give carboxylic acids, the sodium nitrite functions as a base to produce the nitro stabilized anion. Nucleophilic attack of this anion on the nitrite ester affords an alkoxide and a nitrosated nitro compound, which breaks down to form a carboxylic acid.

Table I. Reaction of 4-Substituted Phthalic Anhydrides with Nitrite



X	Registry no.	KNO_2/ anhydride (molar ratio)	% yield[a]
–H	85-44-9	2	96
$-NO_2$	5466-84-2	2	71
$-NO_2$		1	35
–F	319-03-9	2	74
–Cl	118-45-6	2	84
$-CH_3$	19438-61-0	2	90

[a] Isolated yield of dipotassium salt of the 4-substituted phthalic acid.

The reaction of potassium nitrite with anhydrides is not limited to 4-nitrophthalic anhydride. Table I lists the results of the reaction of various 4-substituted phthalic anhydrides with nitrite in DMF solution at room temperature. In all cases, there is obtained in good yields the dipotassium salt of the corresponding phthalic acid. In one case, when only 1 mol of potassium nitrite is used, the yield is greatly reduced.

As would be expected, the rate of nitrite attack on the anhydride seems to be determined by the electron-withdrawing ability of the group in the 4 position. Thus in the potassium fluoride exchange reaction, >99% of the attack of nitrite occurs on 4-nitrophthalic anhydride.

Experimental Section

General Procedures. Carbon-13 NMR spectra were recorded on either a Varian XL-100-15 (25.2 MHz) or a Varian CFT-20 (20.0 MHz) NMR spectrometer operating in the Fourier transform (FT) mode with complete proton decoupling. Infrared spectra were measured on a Perkin-Elmer 457 grating infrared spectrophotometer. Mass spectra were obtained on a CEC 21-104 or a Varian-MAT 311 spectrometer operating at 70 eV utilizing the direct inlet system. Vapor-phase chromatography (VPC) was carried out on a Hewlett-Packard 5700A gas chromatograph using a 6 ft × ⅛ in. 3% OV-17 on Chromosorb W column with temperature programming between 100 and 290 °C at 16°/min. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Anhydrous potassium fluoride was obtained from Alfa Chemicals.

Reaction of 4-Nitrophthalic Anhydride with Potassium Fluoride. A flask containing 9.944 g (51.5 mmol) of 4-nitrophthalic anhydride and 6.618 g (114.1 mmol) of anhydrous potassium fluoride was fitted with a distilling head, receiver, and nitrogen inlet and placed into an oil bath at 135 °C. The bath temperature was raised to 235–240 °C and held at this temperature for 60 min. Distillation afforded 5.101 g (60% yield) of 4-fluorophthalic anhydride, bp 205–206 °C (160 mm) [lit.[6] bp 148 °C (20 mm)], as a clear liquid which solidified to give a white solid, mp 74–76 °C (lit.[6] mp 75 °C): IR ($CHCl_3$) 1780, 1856 cm^{-1}; mass spectrum *m/e* 166 (43%, P^+), 122 (100%, $-CO_2$), 94 (100%, $-CO_2$ –CO).

Using only 1 equiv of potassium fluoride at 220 °C for 120 min afforded a 62% yield of distilled 4-fluorophthalic anhydride.

The above reaction was repeated with 34.954 g (0.181 mol) of 4-nitrophthalic anhydride and 21.611 g (0.373 mol) of potassium fluoride to give a 58% yield of the fluoro compound **2**. In the distillation pot was left 33.394 g of a pale tan solid. Carbon-13 NMR showed the organic component of this material to be **3**, the dipotassium salt of 4-nitrophthalic acid. This solid was dissolved in 100 mL of water and extracted with ethyl acetate (2 × 100 mL) to afford 0.197 g of a yellow oil (containing 4-nitro- and 4-fluorophthalic anhydride). The aqueous solution was acidified to pH 1 with concentrated HCl (16 mL, 0.192 mol) and extracted with EtOAc (5 × 150 mL) and ether (2 × 150 mL) to afford 14.190 g (37% recovery) of 4-nitrophthalic acid, mp 163–165 °C (lit.[12] mp 165–166 °C). VPC analysis showed the material to be 95% 4-nitrophthalic acid and 5% 4-fluorophthalic acid. The recovery in this reaction was 95.2%.

Reaction of 4-Nitrophthalic Anhydride (1) with Potassium Fluoride in Me_2SO. A mixture of 3.351 g (17.4 mmol) of 4-nitrophthalic anhydride (1), 2.083 g (35.9 mmol) of anhydrous potassium fluoride, and 8 mL of dry Me_2SO was heated at 142 °C for 35 min under nitrogen. VPC analysis of an aliquot showed that the reaction was over after 20 min. After cooling to room temperature, the reaction mixture was poured into dilute aqueous HCl and extracted with ethyl acetate to afford 3.188 g of a pale yellow solid. The ^{13}C NMR spectrum showed that the material contained 48% 4-fluorophthalic acid, 9% 4-fluorophthalic anhydride, and 43% 4-nitrophthalic acid. Distillation of this material afforded 1.007 g (35% yield) of 4-fluorophthalic anhydride, bp 200–208 °C (160 mm).

Reaction of 4-Nitrophthalic Anhydride (1) with Potassium Fluoride in Acetonitrile Containing Dibenzo-18-crown-6. A mixture of 2.008 g (34.6 mmol) of anhydrous potassium fluoride, 0.458 g (1.3 mmol) of dibenzo-18-crown-6,[10] and 20 mL of dry acetonitrile was refluxed (82 °C) for 30 min under nitrogen and then 3.011 g (15.6 mmol) of 4-nitrophthalic anhydride (1) was added and the refluxing continued. After refluxing for 43 h, the mixture was cooled to room temperature, methylene chloride was added, and the mixture filtered to remove 3.330 g of a solid material. Concentration of the filtrate under vacuum afforded 2.000 g of a mixture containing 82% 4-fluorophthalic anhydride and 18% dibenzo-18-crown-6. To remove the dibenzo-18-crown-6, the material was dissolved in aqueous KOH, extracted with ethyl acetate, and acidified with concentrated HCl to pH 1. Extraction with ethyl acetate afforded 1.195 g (42% yield) of pure (>99% by VPC) 4-fluorophthalic acid, mp 148–150 °C (lit.[11] mp 152–153 °C): IR (KBr) 1706 cm^{-1} (s); mass spectrum *m/e* 184 (16%, P^+), 167 (41%, – OH), 166 (10%, – H_2O), 140 (100%, – CO_2). Exact mass calcd for $C_8H_5O_4F$: 184.0171. Found 184.0170.

The methylene chloride insoluble material was dissolved in water, extracted with ethyl acetate, and acidified with concentrated hydrochloric acid to pH 1. Extraction with ethyl acetate yielded 1.117 g (33.9% recovery) of 4-nitrophthalic acid as a tan solid, mp 163–166 °C (lit.[12] mp 165–166 °C). The ^{13}C NMR showed the material to be >95% 4-nitrophthalic acid.

Reaction of Potassium Nitrite with Substituted Phthalic Anhydride. The following procedures are representative: A mixture of 1.93 g (0.01 mol) of 4-nitrophthalic anhydride, 1.70 g (0.02 mol) of potassium nitrite, and 19 mL of anhydrous DMF was stirred under a nitrogen atmosphere at room temperature. After stirring for 16 h, the reaction mixture was added to 200 mL of diethyl ether, and the resulting precipitate was collected and dried to give 1.32 g (71% yield) of the dipotassium salt of 4-nitrophthalic acid. The material was identified from its ^{13}C NMR (D_2O).

A mixture, 4.0 g (27 mmol) of phthalic anhydride and 4.6 g (54 mmol) of potassium nitrite, was heated up to 200–230 °C over a 110-min period. A brown gas was evolved after heating for 160 min at 200–230 °C; the ^{13}C NMR spectra showed the material to be the dipotassium salt of phthalic acid.

Registry No.—KNO_2, 7758-09-0; KF, 7789-23-3; 4-nitrophthalic acid dipotassium salt, 63196-42-9; 4-nitrophthalic acid, 610-27-5; 4-fluorophthalic acid, 320-97-8; dibenzo-18-crown-6, 14187-32-7; phthalic acid dipotassium salt, 4409-98-7; 4-fluorophthalic acid dipotassium salt, 63196-39-4; 4-chlorophthalic acid dipotassium salt, 63196-40-7; 4-methylphthalic acid dipotassium salt, 63196-41-8.

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