(methine, septet, 1), 7.60 (aromatics, t, 1), 8.33 (aromatic, m, 2), 8.75 (aromatic, m, 1).

Preparation of Alkyl 4-Methylphenyl Ethers (9). A mixture of the appropriate alkyl iodide, **3,** and THF was refluxed under nitrogen fro 16 h. The mixture was then cooled, filtered, and added to water. The aqueous solution was extracted with ether and the ether extracts were washed and dried to give the crude product. ^{13}C NMR data for the compounds are in the Supplementary Material.

9b: 81% yield; bp 140 °C (15 Torr); ^{1}H NMR (CDCl$_3$) δ 1.35 (t, 3), 2.13 (s, 3), 3.95 (q, 2), and an A$_2$B$_2$ aryl region centered at 6.90 (m, 4).

9c: 76% yield; ^{1}H NMR (CDCl$_3$) δ 1.30 (d, 6), 2.25 (s, 3), 4.45 (septet, 1), 6.90 (center of A$_2$B$_2$ aromatic, 4).

Registry No.—3, 1121-70-6; **6a,** 63181-68-0; **6b,** 63181-69-1; **6c,** 63181-70-4; **6d,** 63181-71-5; **7a,** 63181-72-6; **7b,** 63215-75-8; **7c,** 63181-73-7; **7d,** 63181-74-8; **8,** 106-44-5; **9b,** 622-60-6; **9c,** 22921-10-4; **9d,** 33426-69-6; **10,** 119-33-5; **11a,** 618-95-1; **11b,** 618-98-4; **11c,** 6268-23-1; **13,** 63181-77-1; **14d,** 63181-78-2; **16a,** 32136-52-0; sodium nitrite, 7632-00-0; 3-nitrophthalic anhydride, 641-70-3; 4-nitrophthalic anhydride, 5466-84-2; 3-(4-methylphenoxy)-N-phenylphthalimide, 63181-79-3; 3-(4-methylphenoxy)phthalic acid, 63181-80-6.

Supplementary Material Available: A discussion of the ^{1}H and ^{13}C NMR data as well as the ^{13}C NMR assignments for 4–11 and 14d (Tables IV–VI) (9 pages). Ordering information is given on any current masthead page.

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A Direct Synthesis of Phenoxy-Substituted Phthalic Anhydrides by Aromatic Nucleophilic Displacement

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Phenoxides react with nitro-, fluoro-, or chloro-substituted phthalic anhydrides to give phenoxy-substituted phthalic anhydrides. The success of the reaction was dependent upon the reaction conditions employed and the identity of the leaving group (F > Cl > NO$_2$). All three systems suffered from the reaction of the anhydride linkage with solvent (DMF) at higher temperature, and the nitro system was further complicated by reaction of the anhydride linkage with the sodium nitrite by-product. Using the fluoro system, yields of >85% were obtained for the phenoxyphthalic anhydrides.

As part of our continuing effort to understand the reaction of phenoxides with derivatives of nitro-substituted phthalic acids, we investigated the activating effect of the anhydride linkage in phthalic anhydrides. Previous results have shown that phenoxides react with nitro- and halo-substituted phthalimides,[1] nitro-substituted phthalonitriles,[2] and nitro-substituted phthalate esters.[3] The successful reaction of phenoxides with anhydride derivatives would give phenoxy-substituted phthalic anhydrides and would constitute a considerable improvement over existing syntheses (see eq 1 for an example[4]).

Results and Discussion

Reaction of Nitrophthalic Anhydrides. Reaction of 3-nitrophthalic anhydride (**1a**) with sodium phenoxide (Scheme I; X = NO$_2$, Y = H) in DMF at 25 °C produced a mixture of ring-opened acid ester salts **4** and **5** and *no* product (**2**) from nitro displacement. If, after 0.5 h at 25 °C, an equivalent amount of methyl iodide was added to the reaction mixture, the only products formed were the diesters **6** (21%) and **7** (79%)

$$(1)$$
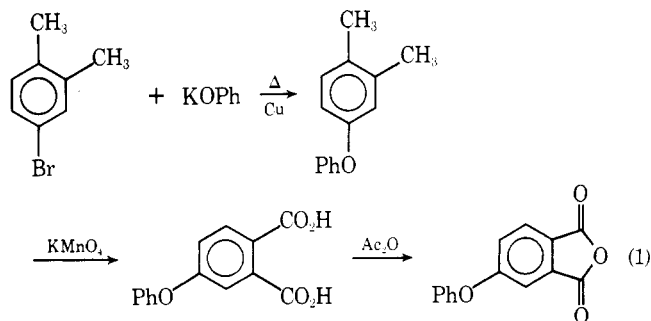
in excellent yield.[5] There was no trace of starting anhydride **1a** or displacement product **2a**. Therefore, in DMF at 25 °C, sodium phenoxide exclusively attacked the carbonyl carbons and, preferentially, the carbonyl α to the nitro group. In addition, because of the total absence of starting material, one can conclude that *if* there was an equilibrium between **1a/3** and **4/5** at room temperature, it was far to the right in favor of **4** and **5**.

Scheme I
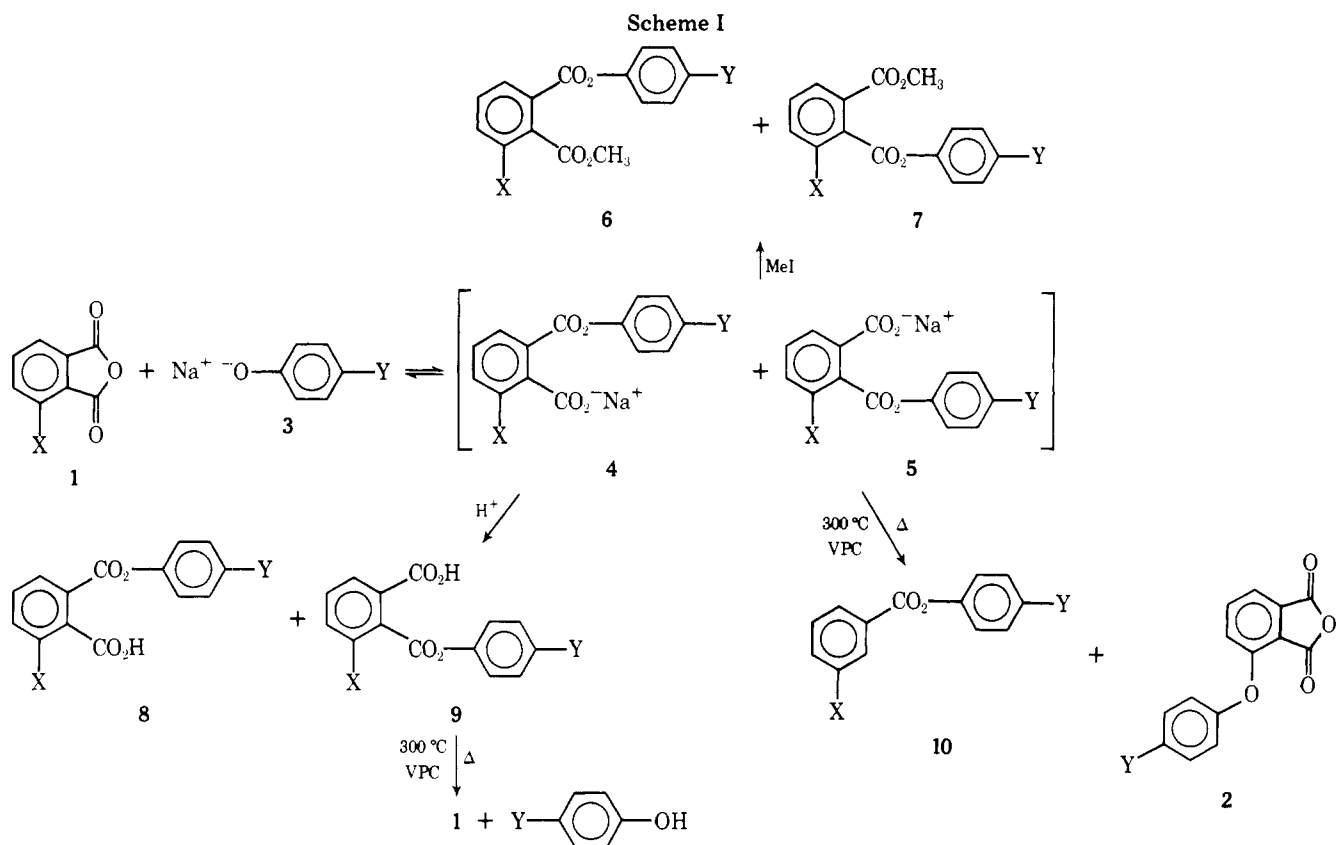
When a reaction mixture containing **4** and **5** was acidified, the mixture of acid esters **8** and **9** was produced. However, VPC analysis of this mixture showed only starting anhydride **1a** and phenol, both of which were apparently formed from ring closure of **8** and **9** in the injection port of the VPC (300 °C). if, however, the initial homogeneous mixture of **4** and **5** in DMF was injected directly into the VPC injection port, then only **2a** and **10** were formed. There was no trace of starting anhydride **1a** or the other possible decarboxylation product phenyl *o*-nitrobenzoate (**11**) observed. Under these conditions, production of **2a** probably resulted from the displacement of the nitro group in **1a** by sodium phenoxide; both of these reagents could have been generated by the thermal ring closing of **4** and **5**.

Compounds **4** and **5** could also be generated by an alternate route. When a sample of the DMF reaction mixture, in which **6** and **7** were produced using CH₃I, was placed directly into the VPC injection port, not only **6** and **7** but also **2a** and **10** were observed. Since it had previously been found that only **6** and **7** were present in a workup involving a methylene chloride extraction of an identical DMF reaction mixture which had been diluted with aqueous HCl, products **2a** and **10** could not have orginated from unreacted salts **4** and **5** in the present example. Instead, we believe these salts were regenerated in the VPC by reaction of sodium iodide with the methyl group of each ester, **6** and **7**, to generate methyl iodide. These salts, **4** and **5**, then decomposed as previously described to give **2a** and **10**. When, in fact, a mixture of authentic samples of **6** and **7** and an equivalent amount of sodium iodide in anhydrous DMF was injected directly into the VPC, **6**, **7**, **2a**, and **10** were all observed. However, if this mixture was added to 1.2 N HCl, then extracted with methylene chloride, and these organic extracts were subjected to VPC analysis, only **6** and **7** were observed.

It is interesting to note that only the meta isomer **10** was formed from the decarboxylation of the mixture of **4** and **5** both during VPC analysis and at elevated temperature in solution. If the mixed ester **6** was stirred with an equivalent amount of sodium iodide in DMF and then injected directly

into the VPC, ester **10** was formed as expected. However, when the experiment was repeated using pure **7**, instead of forming the ortho isomer **11**, only ester **10** was formed. Since the reaction of **7** with sodium iodide at 300 °C should have produced only **5** and no **4**, formation of **10** must have come about from the rearrangement of **5** to **4**. In both cases the yield of decarboxylated product was very low (17–18%), indicating perhaps that the decarboxylation process was not very efficient.[6] In addition, when a mixture of 80% of **9** and 20% of **8** was heated in quinoline with a copper catalyst, a 40% yield of only **10** was produced. This again indicated that a conversion between the salts (or the starting acids) could take place. These results are in agreement with reported literature findings for somewhat similar systems.[8,9]

The fact that **2a** was produced during VPC analysis suggested that the displacement reaction be tried in solution at elevated temperatures. Reaction of sodium phenoxide with **1a** in DMF at temperatures between 80 and 150 °C produced low yields of both **2a** and **10** as well as major amounts of salts **4** and **5**. Although this approach did produce **2a**, the yield was such (5–10%) that the reaction is of little synthetic value. In addition, at these higher temperatures, two other factors complicated the results: (1) reaction of the anhydride linkage with solvent; and (2) reaction of the anhydride linkage with sodium nitrite (vide infra).

The reaction of **1a** with sodium 4-methylphenoxide at room temperature gave very similar results to those described above, except the amount of attack by the nucleophile at the carbonyl α to the nitro group was slightly larger (84% vs. 79%). Repeating the reaction at 78 °C gave **2** (Y = CH₃) and **10** (Y = CH₃) as well as a new product **13**. This diester could result from initial formation of the intermediate **12**, followed by attack of the phenoxide at carbonyl a to give **13** (Scheme II).

Reaction of 4-nitrophthalic anhydride (**14a**) with sodium phenoxide in DMF at 25 °C gave the salts **15** and **16** (see Scheme III; X = NO₂, Y = H). When a homogeneous mixture of **15** and **16** was placed into the 300 °C injection port of a VPC, considerable amounts of starting material **14** were ob-

Scheme II

4 + 5

(X = NO₂, Y = CH₃)   (X = NO₂, Y = CH₃)

12

13
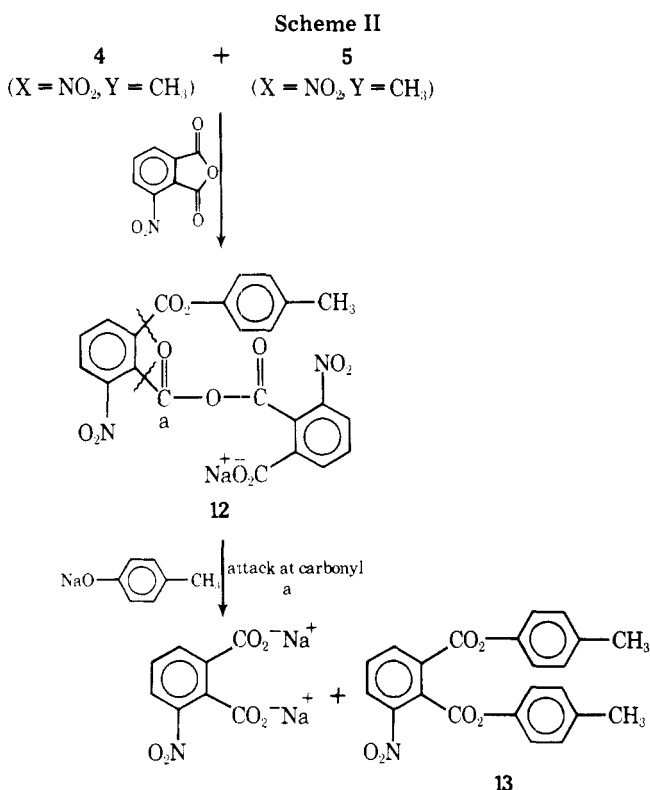
served. This suggests that ring closure of the salts in the 4 system may be considerably more favorable than closure in the 3 system (or the escape of 4-nitrophthalic anhydride from the reaction zone in which it was produced was more efficient). In addition, the amount of decarboxylated product, **19**,[10] was much smaller in this system. Methylation of the salts with methyl iodide produced the esters **17** and **18**. The isomers could not be separated on VPC columns, but ¹³C NMR analysis indicated that two isomers were present in the approximate ratio of 56% (**17**) to 44% (**18**).[11] When the reaction was carried out at 150 °C, two unidentified minor products and a 17% yield of **20** were obtained.

While attempting to improve the yields of the ether products (**2 + 20**) in these reactions, a side reaction was discovered which was highly detrimental to the success of the nitro displacement. It was found that the nitrite ion produced from the displacement rapidly reacts with the anhydride linkage of the

phthalic anhydride derivative to produce the corresponding phthalate salts.[12] Since this nitrite/anhydride reaction destroys the activating anhydride function of the starting materials (**1** and **14**), it interferes with the direct formation of phenoxyphthalic anhydrides by nitro displacement. We therefore became interested in the displacement of other leaving groups.

Reactions of Fluoro- and Chlorophthalic Anhydrides. Reaction of 3-fluorophthalic anhydride (**1b**) with sodium phenoxide in DMF at 25 °C gave the salts **4** and **5** (Scheme I; X = F, Y = H). Reaction of these salts with methyl iodide produced the diesters **7** and **6** in the ratio of 74:26, respectively.[13] The major isomer was assigned on the basis of its ¹³C NMR and by analogy to the 3-nitro system. If, however, a homogeneous solution of **4** and **5** in DMF was injected into a VPC injection port at 300 °C, no decarboxylation product, **10**, was seen and starting material **1b** was regenerated quite efficiently. This suggested that if the reaction were carried out at a higher temperature, an equilibrium between **1c/3** and **4/5** could be established and displacement of the fluoro group could take place to give **2a**.

When a mixture of sodium phenoxide, **1b**, and DMF was heated in a 150 °C oil bath for 30 min, approximately an 85% yield (by VPC) of **2a** was formed. This reaction produced sodium fluoride which, unlike sodium nitrite, appeared to be inert under these reaction conditions. Unfortunately, at these higher temperatures, we found that the solvent, DMF, underwent a reaction with both **1b** and **2a** which slowly destroyed these materials. These results, which are contained in Table I, show that **1b** was much more susceptible to this reaction than **2a**. Although we know the reaction involves ring opening of the anhydride linkage, the resulting products have not yet been identified. However, a 1.2 N HCl workup was used in our control studies and the new product (or the intermediate leading to it) was not hydrolyzed back to the corresponding phthalic acid under these conditions. We are currently attempting to identify these products and determine if the corresponding dimethylamide derivatives are formed.[14] When the reaction between sodium phenoxide and **1b** was repeated in DMF at 150 °C for 20 min, an 87% yield of pure **2a** was isolated by direct precipitation of the reaction mixture into acidic water. This product, **2a**, was not contaminated with any of the corresponding diacid which could have formed from hydrolysis during workup.

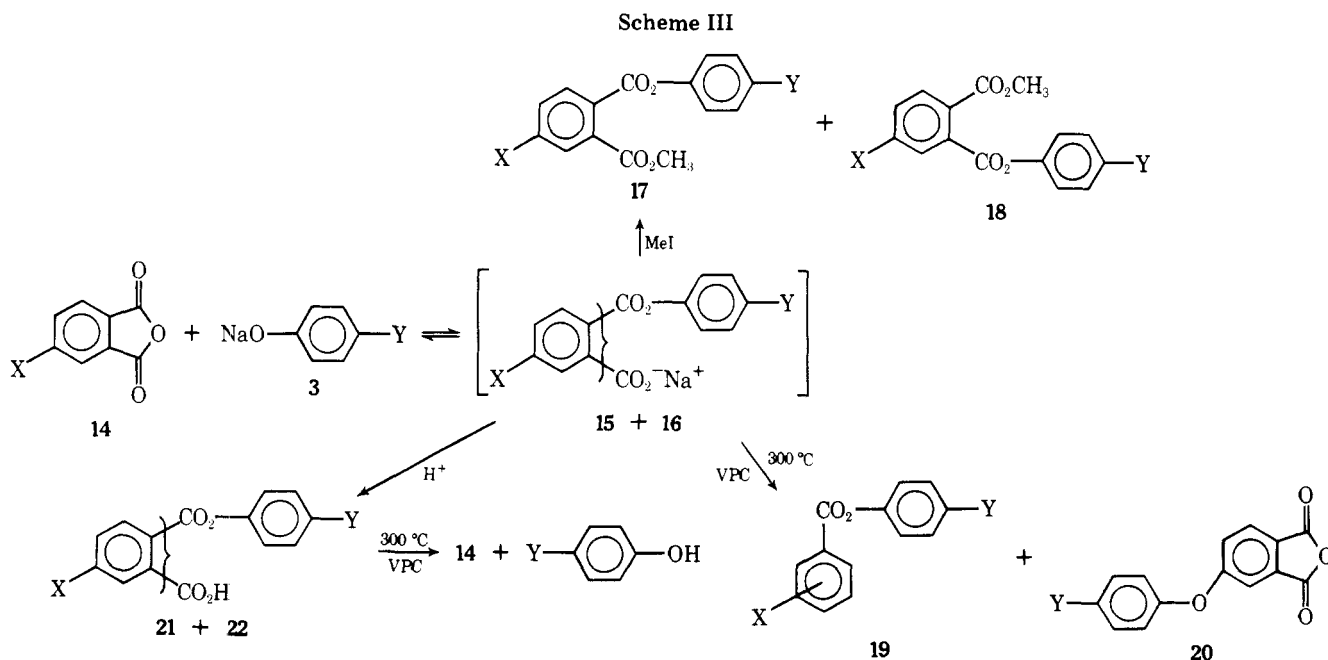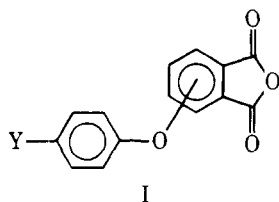Several ether derivatives were synthesized by fluoro dis-

Scheme III

17

18

MeI

14 + 3 ⇌ [15 + 16]

H⁺

21 + 22

$\xrightarrow{\frac{300\ °C}{VPC}}$ 14 + Y—⟨◯⟩—OH

VPC $\searrow$ 300 °C

19

20

Table I. Destruction of Phthalic Anhydrides by DMF at Reflux

Reaction	% destruction		
time, h	1b	1c	2a
1	29	50	11
3	47	75	17
5	62	85	24
7	67	91	27
24	92	100	48

Table II. Synthesis of I by Fluoro Displacement

I

Compd (isomer)	Y	Yield, % (VPC)
2a (3)	H	85–95
2b (3)	CH$_3$	88–92
2c (3)	Cl	80–85
2d (3)	OCH$_3$	65–75
20b (4)	CH$_3$	85

placement (Table II). As can be seen from these results, use of this route allowed the synthesis of derivatives such as 2b and 20b containing groups which would be oxidized in conventional methods.[4]

Reaction of 3-chlorophthalic anhydride (1c) with sodium phenoxide in DMF at 25 °C, as in the fluoro and nitro cases, produced the mixture of salts, 5 and 4, which upon methylation gave an 85:15 mixture of 7/6[15] (Scheme I; X = Cl, Y = H). The isomer assignments were made again on the basis of the ^{13}C NMR data and by analogy to the nitro system. When the reaction was repeated at 150 °C for 5 h, the desired product, 2a, was produced in 44% yield. The formation of 2a by chloro displacement occurred more slowly and in lower yield than by fluoro displacement. However, under these reaction conditions, 24% of the product 2a would have been destroyed by reaction with DMF (raising the possible yield of 2a to 68%) and the remainder of unreacted 1c (theoretically 32%) would have been completely destroyed by solvent reaction (see Table I). This argument is substantiated by the fact that we have isolated sodium chloride in yields of up to 73%

of the theoretical amount. Production of sodium chloride from a route other than by the phenoxide displacement of the chloro group seems unlikely.

Attempts were made to find a solvent system in which 1c and 2a would not be destroyed, but in which displacement would occur. However, none of the solvents tried (DMAC, sulfolane, Me$_2$SO, HMPA, N-methylpyrrolidone, o-dichlorobenzene, acetonitrile, dimethyl sulfone, nitrobenzene, tributylamine, propylene carbonate, or a neat reaction) gave results as good as those in DMF. The use of potassium or lithium phenoxide did not increase the yield of 2a.

Finally, the reaction of 4-chlorophthalic anhydride (14c) and sodium phenoxide was investigated. Reaction of 14 at 150 °C in DMF for 6 h resulted in a 33% yield of 20a (Scheme III; X = Cl, Y = H). Since the 4 isomers are generally less reactive toward displacement than the 3 isomers in these systems,[1] it was not surprising to obtain this lower yield, since more of anhydride 14c would have been destroyed by side reaction with DMF.

In conclusion, we found that the reaction between phenoxides and nitro-, chloro-, or fluorophthalic anhydrides was very dependent upon the reaction conditions employed and the leaving group. In all three systems, reaction with sodium phenoxide at room temperature resulted in opening of the anhydride ring to produce a mixture of acid ester salts (4 and 5 for the 3 isomers, 15 and 16 for the 4 isomers). Upon heating of the reaction mixture, these salts either decarboxylated (X = NO$_2$) or ring closed to varying degrees (X = F, Cl > NO$_2$) to regenerate starting material. The starting material then underwent displacement with phenoxide to give the phenoxy ether derivative with varied success (F > Cl > NO$_2$). Using the fluoro system, yields of >85% were obtained for a variety of ether derivatives. All three systems suffered from the reaction of the anhydride linkage with solvent (DMF) at higher temperatures and the nitro system was further complicated by reaction of the anhydride linkages with the sodium nitrite by-product.

We are currently continuing our studies of the reactions of nucleophiles with nitro and halo phthalic acid derivatives in an attempt to better understand the role of the nitro group in such displacements.

Experimental Section

All ^{1}H NMR spectra were recorded with a Varian Associates T-60 NMR spectrometer using tetramethylsilane as an internal standard and deuteriochloroform or Me$_2$SO-d_6 as a solvent. Infrared spectra were taken on a Perkin-Elmer 457 grating infrared spectrophotometer in chloroform solution or as a KBr pellet. Mass spectra were deter-

Table III. Aryloxy-Substituted Phthalic Anhydride Derivatives[a]
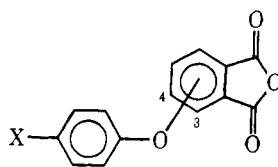
Registry no.	Compd	X	Position of attachment	Mp, °C (solvent)	m/e
54738-86-2	2a	H	3	106–108 (hexane)	240
63181-77-1	2b	CH$_3$	3	117–118 (cyclohexane)	254
63196-07-6	2c	Cl	3	163–164 (benzene/hexane)	274[b]
63196-08-7	2d	OCH$_3$	3	108.5–109 (benzene/cyclohexane)	270
21345-01-7	20a	H	4	112–113 (hexane) (lit. 114–116)[4]	240
63196-09-8	20b	CH$_3$	4	89.5–90 (hexane)	254
63196-10-1	20c	Cl	4	118–118.5 (benzene)	274[b]
63196-11-2	20d	OCH$_3$	4	106–107.5 (benzene/cyclohexane)	270

[a] Satisfactory analytical data (±0.4% for C, H) were reported for all the compounds listed in the table. [b] One-chlorine molecular-ion cluster.

mined on a CEC 21-104 analytical mass spectrometer at 70 eV. Vapor-phase chromatography (VPC) was carried out on a Hewlett Packard 5750 research chromatograph using a 6 ft 10% UC-W98 on 80/100 Chromosorb W column with temperature programming between 150 and 250 °C at 10°/min, unless otherwise indicated. The injection port and detector were at 300 °C. Melting points were determined on a Thomas-Hoover instrument and are uncorrected.

The N,N-dimethylformamide (DMF) was either distilled from CaH$_2$ or purchased in the anhydrous state from Burdick and Jackson Laboratories. All other solvents were dried by standard methods and distilled prior to their use.

VPC yields were calculated as follows. In a typical run equivalent amounts of phenoxide and phthalic anhydride derivatives were mixed with an internal standard (o-terphenyl) in a given solvent (10 mL/g of anhydride) and the solution was heated under nitrogen. Aliquots were removed and added to a mixture of 1.2 N hydrochloric acid and chloroform. The mixture was shaken well, the layers were separated, and the chloroform solution was dried over anhydrous magnesium sulfate. The chloroform solution was subjected to VPC analysis and the yield was calculated from the relative peak areas of standard and product after correcting for detector response differences. Values for the peak areas were obtained by weighing Xeroxed copies of the peak traces.

The starting phthalic anhydride derivatives (1 and 14) were obtained as described previously.[1] The ^{13}C NMR spectra of these materials were obtained and are tabulated in the supplementary material (Table VI).

Preparation of Sodium Phenoxides. The sodium salts of the different phenol derivatives used in this study were prepared from the reaction of freshly prepared sodium methoxide in methanol with the desired phenol derivative.[1] The resulting salts were thoroughly dried and then were stored in a drybox under nitrogen. All salts were weighed in the drybox to avoid contact with oxygen and moisture.

Potassium Phenoxide. Potassium phenoxide was prepared from phenol and potassium tert-butoxide in a dimethylformamide/toluene mixture. The toluene and tert-butyl alcohol were removed by distillation.

Lithium Phenoxide. Lithium phenoxide was prepared from phenol and n-butyllithium in a mixture of benzene and hexane. Dimethylformamide was added and the hexane and benzene were removed by distillation.

Reaction of 3-Nitrophthalic Anhydride (1a) with Sodium Phenoxide. A. Room Temperature. A mixture of 12.46 g of sodium phenoxide, 28.74 g of 1a, and 100 mL of anhydrous DMF was stirred at 25 °C under nitrogen. A dark orange color was initially present, but it quickly faded and a light yellow homogeneous solution was obtained. Analysis of this mixture by ^{13}C NMR indicated the absence of 1a, displacement product 2a, and decarboxylated material 10, and the presence of two acid ester salts 4 and 5.

If this homogeneous solution was injected directly into the VPC, two products were obtained. Collection of these materials by preparative VPC gave samples which were identified as 2a and 10 by comparison to authentic samples (synthesis of these materials is described below).

An aliquot from this reaction mixture was added to a 1.2 N HCl solution and this mixture was extracted thoroughly with methylene chloride. The methylene chloride solution was dried and subjected to VPC analysis. This analysis showed only peaks corresponding to 1a and phenol.

Another aliquot was removed from the reaction mixture and added to 1.2 N HCl, and this time the resulting precipitate was collected and dried to give a mixture of acid esters, 8 and 9, in 88% yield. The assignment of structure was based on the ^{13}C NMR of this mixture, which also showed that no 1a, 2a, or 10 was present.

B. Room Temperature with Methyl Iodide. In order to determine the ratio of 4 to 5 (and 8 to 9), the following experiment was carried out. A mixture of 1.989 g of sodium phenoxide, 3.31 g of 1a, and 33 mL of DMF was stirred at 25 °C under nitrogen. After 30 min, 4.88 g of methyl iodide (2 equiv) was added and the clear yellow solution turned orange in color. This mixture was stirred for 2 h at 25 °C and then an aliquot was removed and added to a 1.2 N HCl solution and the entire mixture was extracted well with methylene chloride. The methylene chloride mixture was subjected to VPC analysis. This showed only a mixture consisting of 21% of 6 and 79% of 7. The remainder of the reaction mixture was poured into 1.2 N HCl and the resulting precipitate was collected by filtration and dried to give 4.40 g (85%) of a mixture of esters 6 and 7. The isomers were separated by preparative VPC and identified by comparison to authentic samples. The ^{13}C NMR spectrum (in Me$_2$SO-d_6) of the isolated mixture displayed all of the peaks for the major isomer (7) and all the peaks

of the protonated carbons of the minor isomer (6). Also, this ^{13}C NMR spectrum indicated that the mixture consisted of 23% of 6 and 77% of 7.

C. Reaction at Elevated Temperature. In a typical run 1.16 g of sodium phenoxide, 1.93 g of 1a, and 1.00 g of o-terphenyl (internal VPC standard) were heated at 150 °C in 20 mL of anhydrous DMF under a nitrogen atmosphere. Aliquots were removed at timed intervals (5 min to 16 h) from this dark black mixture and were worked up as described above. Analysis showed 2a (5–10%), 10 (<5%), and a longer retention time material thought to be the product analogous to 13. Other runs were made at temperatures between 80 and 150 °C and showed very little nitro displacement.

Reaction of Sodium 4-Methylphenoxide with 3-Nitrophthalic Anhydride.[16] A. At Room Temperature. Exactly 1.05 g (0.00808 mol) of sodium 4-methylphenoxide and 1.56 g (0.00808 mol) of 1a were dissolved in 20 mL of DMF. A slight exotherm was noted initially. The ^{13}C NMR spectrum of the resulting solution was recorded and indicated that two acid/ester salts, 4 and 5, had been produced. By analogy with the previous experiments with sodium phenoxide, it was assumed that the major isomer was 5. An estimate (^{13}C NMR) for the ratio of isomers observed was 87 to 13. When the mixture of salts was converted to the corresponding methyl phenyl esters as has been previously described, then VPC analysis indicated an 84 to 16 ratio of products.[17]

The above reaction was repeated at 78 °C for 65 h to give upon workup and isolation 6% of 2b, 1% of 10b, and 6.5% of 13. Products 2b and 10b were identified by comparison to authentic samples. The product 13 was identified from its mass spectrum (m/e 391) and ^{13}C NMR (see supplementary material).

Reaction of 4-Nitrophthalic Anhydride (14a) with Sodium Phenoxide. A. At Room Temperature. A mixture of 5.80 g of 14a and 3.86 g of sodium phenoxide was stirred in 60 mL of DMF at room temperature under nitrogen for 0.5 h. Direct injection of this homogeneous reaction mixture into the VPC allowed the isolation of a small amount of the desired displacement product 20a. In addition, a small amount of 19 contaminated with 20a was collected. This material had identical retention time with both m- and p-nitrophenyl benzoate, which could not be separated under these conditions. Infrared analysis of this mixture (19 and 20a) showed the presence of a nitro group (1530 cm^{-1}) and an ester carbonyl (1745 cm^{-1}). The amount of 19 formed was much smaller than for the decarboxylation of the corresponding 3 isomer.

If the homogeneous reaction mixture was first added to a 1.2 N HCl solution, this mixture was extracted with ether, and the ether extracts were dried, then subjected to VPC analysis, no trace of 19 or 20a was seen. However, there was a peak corresponding to starting material 14a.

B. At Room Temperature with Methyl Iodide. The above reaction was repeated, except that after 4 h of stirring, 2 equiv of methyl iodide were added. The entire mixture was stirred for an additional 4 h. The mixture was worked up with 1.2 N HCl/CHCl$_3$ as described previously to give an 87% yield of 17 and 18. VPC analysis showed only one peak for this mixture. However, ^{13}C NMR showed that two products were present in the ratio of 56:44. The major isomer has tentatively been assigned structure 17 for electronic reasons similar to those used as rationale for the observed product distribution in the 3 system.

C. At Elevated Temperature. A mixture of 5.80 g of 14a, 3.86 g of sodium phenoxide, 2.50 g of o-terphenyl (internal standard), and 60 mL of DMF was stirred at room temperature under nitrogen. The mixture was quickly placed in an oil bath at 170 °C and aliquots were removed at timed intervals between 0.5 and 16 h. These aliquots were worked up with 1.2 N HCl/CH$_2$Cl$_2$ as described previously. VPC analysis indicated the maximum yield of desired product 20a was 17% after 16 h. There was no trace of decarboxylated product(s) 19.

Reaction of 3-Fluorophthalic Anhydride (1b) with Sodium Phenoxide. A. At Room Temperature. These reactions were run exactly as has been described for the nitro system.

B. At Elevated Temperatures. A mixture of 1.18 g of sodium phenoxide, 1.69 g of 1b, and 22 mL of anhydrous DMF was heated at a bath temperature of 170 °C under nitrogen. The solution became homogeneous almost immediately, turned cloudy yellow, and after ca. 10 min turned orange and again became homogeneous. The solution was stirred at reflux for a total of 20 min and after brief cooling, it was added to a mixture of 200 mL of 1.2 N HCl/ice. The resulting white precipitate was removed by filtration and dried to give 2.12 g (87%) of 2a (mp 102–104 °C). This material was identical in all respects with an authentic sample of 2a. Analysis by ^{13}C NMR and IR showed no trace of the ring-opened diacid 23. VPC analysis showed no trace of 1b.

The reaction was repeated several times using *o*-terphenyl as an internal standard. Yields ranged from 85 to 95%. Typical results at 170 and 125 °C are as follows. 170 °C (time, % **2a**) 15 min, 76; 30 min, 85; 45 min, 84; 60 min, 78; 3 h, 79. 125 °C (time, % **2a**) 1 h, 51; 2 h, 56; 3 h, 60; 5 h, 54; 6.5 h, 47.

Reaction of Other Phenoxides with 1b. The solution salt of the phenoxide derived from *p*-chloro-, *p*-methyl-, and p-methoxyphenols was reacted with **1b** at 150 °C exactly as described above. In all cases, the products were isolated and found to be identical with authentic samples prepared by hydrolysis of the corresponding imide (vide infra). The yields of product were determined from VPC analysis using an alternal standard (*o*-terphenyl) (Table II).

Preparation of Authentic Samples. Phenyl *m*-Nitrobenzoate (10, Y = H; X = NO₂). A mixture of 1.88 g of phenol, 40 mL of pyridine, and 3.71 g of *m*-nitrobenzoyl chloride was stirred at room temperature under nitrogen. The solution was heated at 80 °C for 4 h, cooled to room temperature, and poured into ice water. The resulting white precipitate was collected and stirred vigorously with a 5% sodium carbonate solution. The solution was filtered to give 4.365 g of **10** (98% yield). Recrystallization from absolute ethanol gave a sample with mp 90–92 °C (lit.[18] mp 97 °C).

In a similar fashion phenyl *o*-nitrobenzoate (**11**), mp 50–52 °C (lit.[19] mp 52–53 °C), and phenyl *m*-chlorobenzoate, mp 57–58 °C (lit.[20] mp 53 °C), were prepared. ¹³C NMR assignments for all three comounds are in the supplementary material.

Phenyl 2-Carbomethoxy-6-nitrobenzoate (7). Compound **7** was synthesized from methyl 2-carboxy-3-nitrobenzoate[21] in two steps. A mixture of 5.0 g of this acid was stirred with 50 mL of anhydrous DMF under a nitrogen atmosphere at room temperature. To this mixture was slowly added 2.82 g of oxalyl chloride and the solution was stirred for 4 h at room temperature. The solution was cooled in ice and 2.58 g of sodium phenoxide was added, and the mixture was gradually allowed to warm to room temperature. The mixture was stirred for 4 h and was then added to a 1.2 N HCl solution. The resulting oil was extracted well with methylene chloride and the methylene chloride solution was washed well with water, a sodium bicarbonate solution, and a saturated sodium chloride solution. After drying over magnesium sulfate, the solution was concentrated to give an oil which upon stirring with ethanol gave the desired product **7** as a white solid, mp 119–121 °C, in 55% yield. VPC analysis of this material showed only a single component having a different retention time from that of **6** (vide infra). The structure was confirmed by the ¹³C NMR in Me₂SO-*d₆*. Mass spectral analysis of this material showed *m/e* at 270 (2%) for loss of methoxy and *m/e* at 208 (91%) for loss of phenoxy. There was no parent ion at *m/e* 301. Infrared analysis (KBr) of this sample showed strong absorptions at 1765, 1720, 1050, 980, and 890 cm⁻¹, which were absent in **6**.

Anal. Calcd for C₁₅H₁₁O₆N: C, 59.8; H, 3.7; N, 4.6. Found: C, 59.8; H, 3.9; N, 4.7.

Phenyl 2-Carboxymethoxy-3-nitrobenzoate (6). Compound **6** was synthesized from methyl 2-carboxy-6-nitrobenzoate[21] in two steps, exactly as was described for compound **7**. Starting with 9.54 g of methyl 2-carboxy-6-nitrobenzoate, we obtained a 60% yield of **6**, mp 105–107 °C. VPC analysis of this material showed only one compound, which had a different retention time from **7**. The structure was again confirmed by ¹³C NMR spectroscopy in Me₂SO-*d₆*. Mass spectral analysis of this material showed *m/e* at 270 (5%), 208 (100%), and no parent ion at *m/e* 301. Infrared analysis (KBr) of this sample showed strong bands at 1745, 1735, 1260, 1070, and 955 cm⁻¹ which were not present in **7**.

Anal. Calcd for C₁₅H₁₁O₆N: C, 59.8; H, 3.7; N, 4.6. Found: C, 59.9; H, 3.9; N, 4.7.

Synthesis of Phenoxy-Substituted Phthalic Anhydrides by Phthalimide Hydrolysis. The phthalimide derivatives were synthesized exactly as described in ref 1. Hydrolysis of the resulting 3 isomers required either the use of a higher boiling co-solvent or else higher temperatures (130 °C) under pressure. We believe this is due to the formation of a hindered amide acid intermediate from the 3 isomer which is more resistant to further hydrolysis. Higher temperatures could also be used with the 4 isomers to shorten the reaction time. The diacids from the hydrolysis were then ring closed in refluxing acetic acid/acetic anhydride to give the anhydride derivatives (see Table III for physical properties). ¹³C NMR data for the diacids and dianhydrides are contained in the supplementary material in Tables IV and V. Representative examples for the hydrolysis and ring closures are given below.

3-(4-Methylphenoxy)phthalic Acid (24). To 200 mL of ethylene glycol and 40 mL of 25% aqueous NaOH was added 19.74 g (0.060 mol) of *N*-phenyl-3-(4-methylphenoxy)phthalimide. The system was heated at reflux (135 °C in solution) for 18 h and then added slowly to 2000 mL of 1 N HCl with stirring and cooling. The precipitated

solid was filtered, washed with 0.1 N HCl, then with water, and dried in vacuo at 60 °C. The yield of **24** was 15.61 g (96%): ¹H NMR (Me₂SO-*d₆*) δ 2.30 (methyl, s, 3), 6.7–7.7 (aryl, m, 7), 9.2 (–COOH, br s, 2); IR (KBr) C=O 1688 (s) and 1708 (s), OH 2900 cm⁻¹ (br); ¹³C NMR was in accord with the assigned structure (see Table V).

3-(4-Methylphenoxy)phthalic Anhydride (2b). A solution of 54.5 g (0.20 mol) of **24**, 300 mL of acetic acid, and 40.8 g (0.40 mol) of acetic anhydride was heated at reflux for 2 h and then all solvent was removed in vacuo. The residue, after being recrystallized from cyclohexane, gave 39.6 g (78%) of **2b**: mp 117–118 °C; ¹H NMR (CDCl₃) δ 2.33 (methyl, s, 3), 6.7–7.7 (aryl, m, 7); IR (KBr) C=O 1782 (vs), 1840 cm⁻¹ (s); ¹³C NMR was in accord with the assigned structure (see Table IV); UV (Et₂O) λ_max 229 (ε 20 800), 333 nm (ε 5200), λ_shoulder 324 nm (ε 4900).

Anal. Calcd for C₁₅H₁₀O₄: C, 70.9; H, 3.9; mol wt 254. Found: C, 70.8; H, 4.1; mol wt 254 (mass spectrum).

4-(4-Methylphenoxy)phthalic Acid (28). A mixture of 19.63 g (0.0596 mol) of *N*-phenyl-4-(4-methylphenoxy)phthalimide, 19.2 g of 50% NaOH, and 400 mL of H₂O was stirred and heated for 3 h at approximately 170 °C in a pressure bomb. The resulting yellow solution was extracted with ether and then acidified with 400 mL of 3 N HCl. The precipitated product was filtered, washed with a little H₂O, and dried in vacuo. In this way 15.53 g (96%) of **28** was obtained: ¹H NMR (Me₂SO-*d₆*) δ 2.35 (methyl, s, 3), 6.9–7.9 (aryl, m, 7), 10.9 (–COOH, br s, 2); ¹³C NMR was in accord with the assigned structure (see Table V).

4-(4-Methylphenoxy)phthalic Anhydride (20b). A 13.51-g (0.0497 mol) sample of **28** was refluxed for 3 h with 10.2 g of acetic anhydride and 200 mL of acetic acid. Solvent was removed and the product was recrystallized from hexane to afford 10.87 g (86%) of **20b**: mp 89.5–90.0 °C; ¹H NMR (Me₂SO-*d₆*) δ 2.38 (methyl, s, 3), 6.9–8.1 (aryl, m, 7); IR (HCCl₃) C=O 1774 (s), 1847 cm⁻¹ (m); ¹³C NMR spectrum was in accord with the assigned structure (see Table IV).

Anal. Calcd for C₁₅H₁₀O₄: C, 70.9; H, 3.9; mol wt 254. Found: C, 70.9; H, 4.1; mol wt 254 (mass spectrum).

Registry No.—**1a**, 641-70-3; **1b**, 652-39-1; **1c**, 117-21-5; **5** (X = NO₂, Y = H), 63196-17-8; **5** (X = NO₂, Y = CH₃), 63196-18-9; **6**, 63196-23-6; **7** (X = NO₂, Y = H), 3196-19-0; **7** (X = F, Y + H), 63196-20-3; **7** (X = Cl, Y = H), 63196-21-4; **9** (X = NO₂, Y = H), 63196-22-5; **9** (X = NO₂, Y = CH₃), 63196-23-6; **10**, 1906-43-0; **11**, 31042-59-8; **13**, 63196-25-8; **14a**, 5466-84-2; **146**, 319-03-9; **14c**, 118-45-6; **17**, 63196-26-9; **18**, 63196-27-0; **23**, 63196-12-3; **24**, 63181-80-6; **25**, 63196-13-4; **26**, 63196-14-5; **27**, 37951-15-8; **28**, 63196-15-6; **29**, 63196-16-7; **30**, 63196-14-5; sodium phenoxide, 139-02-6; sodium 4-methylphenoxide, 1121-70-6; sodium 4-chlorophenol, 1193-00-6; sodium 4-methoxyphenol, 1122-95-8; phenol, 108-95-2; *n*-nitrobenzoyl chloride, 121-90-4; methyl 2-carboxy-3-nitrobenzoate, 6744-85-0; methyl 2-carboxy-6-nitrobenzoate, 6744-85-0; ethylene glycol, 107-21-1; *N*-phenyl-3-(4-methylphenoxy)phthalimide, 63181-79-3; *N*-phenyl-4-(4-methylphenoxy)phthalimide, 63196-28-1; phenyl *n*-chlorobenzoate, 41998-17-8; *o*-nitrobenzoyl chloride, 610-14-0; *m*-chlorobenzoyl chloride, 618-46-2.

Supplementary Material Available. ¹³C NMR assignments for all starting phthalic anhydrides, phenoxy-substituted phthalic acids, and phthalic anhydrides, and compounds **5, 6, 7, 9, 10, 11, 13, 17,** and **18** (Tables IV–VII) (6 pages). Ordering information is given on any current masthead page.

References and Notes

(1) F. J. Williams and P. E. Donahue, *J. Org. Chem.*, this issue, companion paper.
(2) D. R. Heath and J. G. Wirth, U.S. Patent 3 787 475 (1974).
(3) F. J. Williams, H. M. Relles, J. S. Manello, and P. E. Donahue, *J. Org. Chem.*, this issue, companion paper.
(4) H. A. Vogel and H. T. Olen, U.S. Patent 3 431 240 (1969). For a similar synthetic approach using 3,4-dimethylphenol and p-chloronltrobenzene, see J. D. Seddon, British Patent 1 192 002 (1970).
(5) This ratio was obtained from VPC analysis correcting for detector response difference between the isomers. The ratio of products from ¹³C NMR analysis was 23:77 (see Experimental Section).
(6) Decarboxylation of **4** would give only the carbanionic precursor of **10**; thus, a proton must have been supplied from some additional source to complete the transformation to **10**. The aldehydic proton of DMF might be such a source under these conditions. Since the *predominant*[7] fate of such a carbanion or one which could be a precursor to **11** is completely obscure,

any statement concerning the decarboxylation of **5** is meaningless at this time, even though none of **11** was observed and one would have predicted a priori that **4** should decarboxylate more readily than **5** (for both electronic and steric reasons).

(7) The amount of **2a** and **10** generated by this treatment corresponded to only a very small amount (20–30%) of the molar quantity of **4** and **5** placed into the VPC instrument.

(8) P. S. Mayuranathan, *J. Chem. Soc.*, 493 (1957).

(9) R. Goncalves and E. V. Brown, *J. Org. Chem.*, **19**, 4 (1954).

(10) We could not determine by VPC if this material was the meta or para isomer or a mixture of both.

(11) These assignments are tentative as they were not confirmed by independent chemical analysis.

(12) R. L. Markezich, O. S. Zamek, P. E. Donahue, and F. J. Williams, *J. Org. Chem.*, this issue, companion paper. We also found that when 2 equiv of sodium nitrite are stirred with **1a** in DMF at room temperature, an immediate reaction began (in the form of violent bubbling and a color change from clear to dark yellow) and a 71% yield of the disodium salt of 3-nitrophthalic acid was obtained.

(13) This ratio was obtained by VPC analysis, ignoring possible detector response differences between the isomers. The ratio of products from ¹³C analysis was 64:36.

(14) It has been reported in the literature that DMF will react with anhydrides at elevated temperatures to give dimethylamides: see G. M. Coppinger, *J. Am. Chem. Soc.*, **76**, 1372 (1954); H. Schindlbauer, *Monatsh. Chem.*,

99, 1799 (1968); H. Schindlbauer, *ibid.*, **100**, 1583 (1969); H. Schindlbauer, *ibid.*, **104**, 848 (1973). Preliminary examination by ¹³C NMR of our reaction mixtures indicated the presence of other new compounds in addition to the dimethylamide derivatives.

(15) This ratio was obtained by VPC analysis, ignoring possible detector response differences between the isomers. The ratio of products from ¹³C analysis was 74:26.

(16) All vapor-phase chromatographic (VPC) analyses carried out in this section were conducted with a ⅛ in. × 6 ft 10% SE-30 column programmed from 150 to 290 °C at 10°/min.

(17) These numbers did not take into account possible detector response differences for the isomers.

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(22) For an example of these types of calculations using a substituent parameter approach, see ref 3. For further examples, see: G. L. Nelson, G. C. Levy, and J. D. Cargioli, *J. Am. Chem. Soc.*, **94**, 3089 (1972); K. N. Scott, *ibid.*, **94**, 8564 (1972).

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(24) G. C. Levy, private communication.

Reactions of Fluoride and Nitrite Ions with 4-Nitrophthalimides

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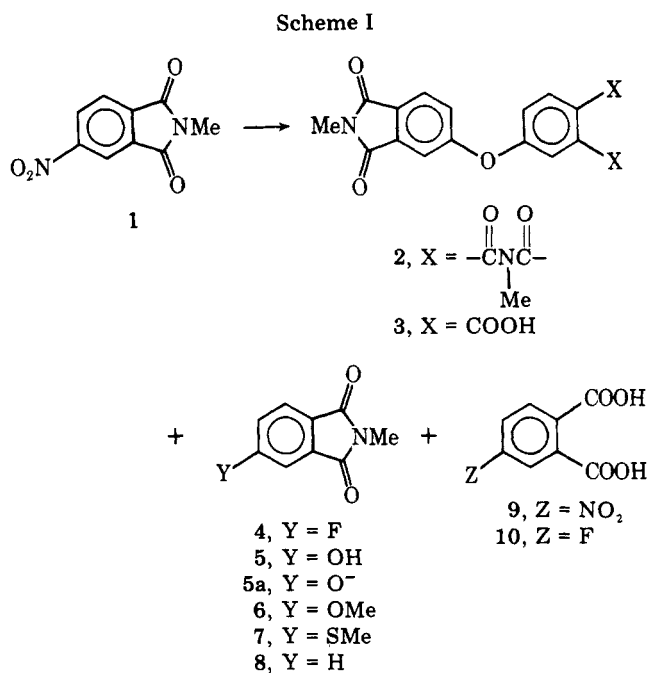
The reaction of 4-nitro-N-methylphthalimide with either fluoro or nitrite salts in an aprotic solvent affords up to a 78% yield of the diaryl ether, 4,4'-oxybis(N-methylphthalimide). When potassium fluoride is used in the reaction, 4-fluoro-N-methylphthalimide can also be isolated. The reaction of 4-fluoro-N-methylphthalimide with potassium nitrite affords the diaryl ether in 75% yield. A possible mechanism for the ether formation is discussed. The intermediate in this mechanism, 4-hydroxy-N-methylphthalimide, has been synthesized and shown to react with either 4-fluoro- or 4-nitro-N-methylphthalimide to afford the diaryl ether. In the reaction with 4-fluro-N-methylphthalimide, potassium fluoride was utilized as a base. Several other minor by-products were identified in the reaction; among them were N-methylphthalimide and 4-substituted phthalic acids. When Me$_2$SO is used as a solvent, 4-thiomethoxy-N-methylphthalimide is also formed.

Recently[1] we reported the reaction of potassium fluoride with 4-nitrophthalic anhydride at elevated temperatures, in which a mixture of 4-fluorophthalic anhydride and dipotassium 4-nitrophthalate is produced. Reaction of 4-nitrophthalic anhydride with potassium nitrite produces dipotassium 4-nitrophthalate as the sole product. In this paper we describe the entirely different behavior of 4-nitro-N-methylphthalimide (1) with potassium fluoride and potassium nitrite.

Heating a solution of 4-nitro-N-methylphthalimide (1) with potassium fluoride in an aprotic solvent such as DMF, Me$_2$SO, or NMP at temperatures of 142–190 °C affords up to a 78% yield of 4,4'-oxybis(N-methylphthalimide) (2) (Scheme I). Instead of potassium fluoride, the use of potassium or sodium nitrite also affords good yields of the bisimide 2. Examples are listed in Table I.

The reaction of nitro compounds to give diaryl ethers is not without precedent. It has been reported[2] that p-nitrobenzonitrile or p-chlorobenzonitrile will undergo a condensation reaction when treated with sodium nitrite in N-methylpyrrolidone to give 4,4'-oxybis(benzonitrile).

After isolation of the bisimide ether 2 by filtration, the filtrate was extracted with methylene chloride and the organic fractions were concentrated in vacuo. The components of this material were separated and identified by GC, GC/MS, and ¹³C NMR analyses. The various products and their yields are listed in Table II.

Scheme I

2, X = $-\overset{\overset{\text{O}}{\|}}{\text{C}}\text{N}\overset{\overset{\text{O}}{\|}}{\text{C}}-$
      |
      Me

3, X = COOH

4, Y = F
5, Y = OH
5a, Y = O⁻
6, Y = OMe
7, Y = SMe
8, Y = H

9, Z = NO₂
10, Z = F

Another compound identified in the reaction mixture when potassium fluoride was used was 4-fluoro-N-methylphthali-