Reactions of Phenoxides with Nitro- and Halo-Substituted Phthalimides

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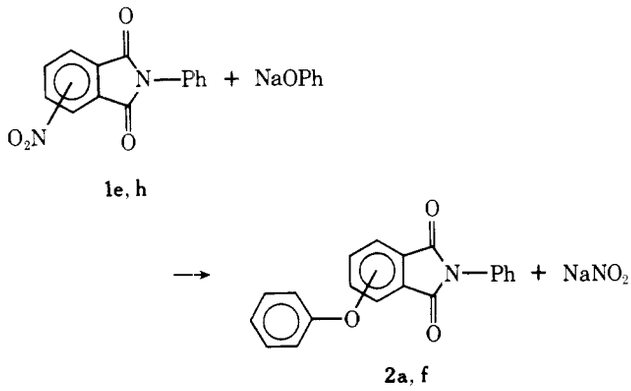
Received November 29, 1976

Phenoxides reacted with nitro- or halo-substituted phthalimide derivatives (1) to give high yields of ether imides (2). The order of leaving group reactivity in these systems was $NO_2 > F > Cl$. 3-Substituted isomers were more reactive toward displacement than the 4-substituted isomers and electron-withdrawing groups on the imide nitrogen slightly increased the rate of displacement. The phenoxy-substituted phthalimides 2 were labile to displacement by other phenoxide nucleophiles. Nitrite ion, a product of the nitro displacement, also reacted with the starting nitrophthalimides, especially at elevated temperatures.

The aromatic nucleophilic displacement of activated nitro groups has been known for many years,[1] but has only recently become a valuable synthetic tool. This reaction has permitted synthesis of many previously inaccessible compounds. Gorvin[2] and Radlmann[3] have demonstrated the displacement of nitro groups activated by ketone groups. Caswell and co-workers[4] have reported displacement by methoxide anion on 3-nitro-*N*-substituted phthalimide derivatives, although yields were low. Aromatic nitro groups are displaced intramolecularly by nitrogen, oxygen, sulfur, and carbon nucleophiles.[5] Beck[6] has displaced nitro groups activated by nitriles, esters, and aldehyde groups. Cyano-activated nitrobenzenes have been converted to phenols.[7] Very recently Kornblum[8] has reported the displacement reactions of nitrobenzenes substituted by a variety of electron-withdrawing groups.

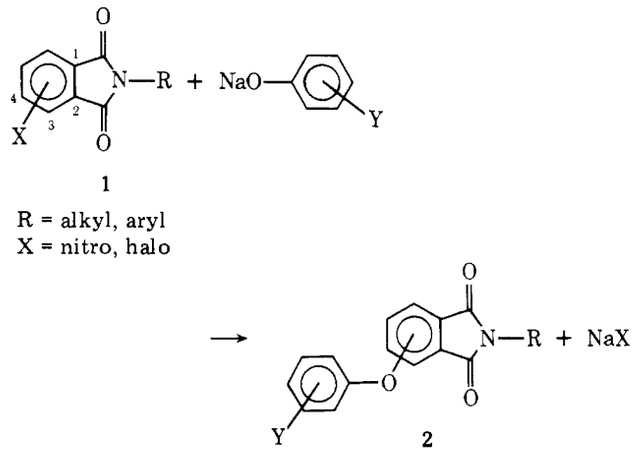
We wish to present our results on the reaction of phenoxide nucleophiles with nitro- and halo-substituted phthalimide derivatives. Wirth and Heath[9] in these laboratories demonstrated that in dipolar aprotic solvents phenoxides react with both 3- and 4-nitro-*N*-phenylphthalimide (**1e** and **1h**) to give the corresponding phenyl ethers **2a** and **2f** in excellent yield.



The potential synthetic utility of this reaction has been explored to learn the following: (1) the effectiveness of the phthalimide ring to activate nitro or halo displacement; (2) the ease of halo vs. nitro displacement in this system; (3) the relative reactivity of different phenolate nucleophiles; (4) the susceptibility of the product ether to further reaction; and (5) the stability of the starting imide and product to the sodium nitrite produced by displacement of the nitro group.

Results and Discussion

The model reaction is shown below. We examined various compounds of formula 1 to obtain information concerning the effect of group R and the orientation of group X. The starting phthalimides were synthesized from the substituted phthalic anhydride and appropriate amine by refluxing in acetic acid.



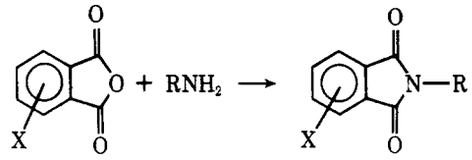
These are described in Table I; ^{13}C NMR data for all starting materials and products are given in the supplementary material. In addition, 4-nitrophthalonitrile (**3**) and diisobutyl 4-nitrophthalate (**4**) were synthesized for comparison. Each was then converted to the corresponding phenyl ether with sodium phenoxide. The products (**2a–g**) are summarized in Table II.

In general, the reactions between sodium phenoxide and the substituted phthalimides 1 proceed quantitatively[10] in DMF or Me_2SO at 25–60 °C. Reaction times varied from <5 min to several hours. The 3- and 4-chloro-*N*-phenylphthalimides (**1a** and **1j**) gave the ethers **2a** and **2f** as the major products (85 and 87% yield, respectively), accompanied by at least two unknown side products, which may arise from attack of phenoxide at the imide carbonyls. Attempts to identify these products are currently under way.

The relative reactivities of the halo–nitro pairs toward sodium phenoxide were determined by competitive experiments in dimethyl sulfoxide. These results are presented in Table III.

Several conclusions can be drawn concerning sodium phenoxide displacement on *these systems*. As Miller pointed out,[11] the order of group mobility in activated aromatic S_N2 reactions depends markedly on the nucleophilic reagent used. When the nucleophilic (or bond-forming) atom belongs to the first horizontal row of the periodic table, the normal mobility order is F > Cl. The nitro group may be either a better or a worse leaving group than the fluorine atom, depending upon the system employed.[12] In the phthalimides, the nitro group is displaced by phenoxide about six to nine times faster than fluorine, depending upon the isomer (3 or 4) and the N substituent. The fluoro derivative reacted approximately four times faster than the chloro derivative in the 4-halo-*N*-methylphthalimide system. Although substitution at nitrogen has little effect on the rate of 3-nitro displacement (there is only a factor of 4 between **1f** and **1g**), the more electron

Table I. Starting Imides Synthesized from Phthalic Anhydride Derivatives[a]

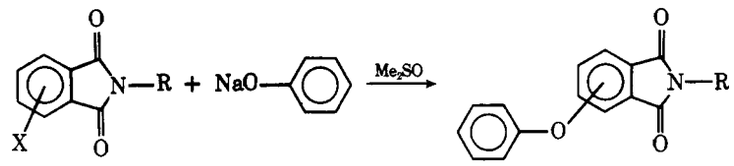


1

Registry no.	Compd	X	R	Mp,[b] °C	Mp, lit	m/e[c]
42899-83-2	1a	3-Cl	C_6H_5	191–192.5	189–190[e]	257 (100)[d]
42899-84-3	1b	3-F	C_6H_5	148–150	151–152[f]	241 (100)
63197-15-9	1c	3-NO_2	4-$CH_3OC_6H_4$	193.5–195[a]		298 (100)
53555-10-5	1d	3-NO_2	4-$CH_3C_6H_4$	151–152.5	154[g]	282 (100)
19065-85-1	1e	3-NO_2	C_6H_5	137–138	138[g]	268 (100)
53555-03-6	1f	3-NO_2	4-ClC_6H_4	193.5–195.5[a]		302 (70)[d]
2593-81-9	1g	3-NO_2	CH_3	111–112	112–113[h]	206 (30)
40392-27-6	1h	4-NO_2	C_6H_5	192.5–194	194[g]	268 (100)
63197-16-0	1i	4-F	C_6H_5	183–184[a]		241 (100)
26491-49-6	1j	4-Cl	C_6H_5	189.5–191[a]		257 (100)[d]
41663-84-7	1k	4-NO_2	CH_3	175–177	175–176[h]	206 (100)
63196-44-1	1l	4-F	CH_3	99–100	99–100[i]	179 (100)
63197-17-1	1m	4-Cl	CH_3	134–135.5	135[h]	366 (100)

[a] Satisfactory analytical data (±0.4% for C, H, N) were reported for all new compounds listed in the table. [b] All samples were recrystallized from ethanol. [c] Value for molecular ion and its relative intensity. [d] One chlorine isotope cluster was observed. [e] G. J. Marriot and R. Robinson, *J. Chem. Soc.*, 134 (1939). [f] R. G. Fowler, L. R. Caswell, and L. I. Sue, *J. Heterocycl. Chem.*, **10**, 407 (1973). [g] M. T. Bogert and L. Boroschek, *J. Am. Chem. Soc.*, **23**, 740 (1901). [h] R. Dabard and J. Tirouflet, *Bull. Soc. Chim. Fr.*, 565 (1957). See also W. Flitsch, *Chem. Ber.*, **94**, 2494 (1961). [i] See ref 19.

Table II. Phenoxy-Substituted Phthalimides[a]



2

Registry no.	Compd	R	Group displaced (X)	Mp,[b] °C	m/e[c]
63197-18-2	2a	C_6H_5	3-NO_2, 3-Cl, 3-F	135–137	315 (91)
63197-19-3	2b	4-$CH_3OC_6H_4$	3-NO_2	178.5–179.5	345 (100)
63197-20-6	2c	4-$CH_3C_6H_4$	3-NO_2	174–176	329 (100)
63197-21-7	2d	4-ClC_6H_4	3-NO_2	172–174	349 (100)[d]
63197-22-8	2e	CH_3	3-NO_2	145–147.5	253 (100)
63197-23-9	2f	C_6H_5	4-NO_2, 4-Cl, 4-F	165–166	315 (100)
63197-24-0	2g	CH_3	4-NO_2, 4-Cl, 4-F	118–119.5	253 (100)

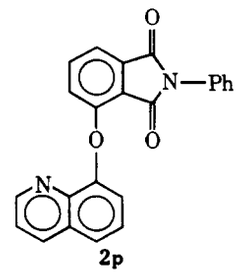
[a] Satisfactory analytical data (±0.4% for C, H, N) were reported for all the compounds listed in the table. [b] All samples were recrystallized from ethanol. [c] Value for molecular ion and its relative intensity. [d] One chlorine isotope cluster was observed.

withdrawing the group attached to the phthalimide nitrogen, the faster is the rate of nitro displacement. Compare **1c** (4′-methoxy) and **1f** (4′-chloro), where the ratio is only 2.[13]

3-Nitrophthalimides react three to five times faster than the 4-nitro isomers; for example, compare **1e** and **1h**, **1g** and **1k**. These small rate differences may reflect the inductive effect of the ortho carbonyl in the 3 isomer, as well as relief of the steric interaction between the 3-nitro group and the ortho carbonyl.[14] The rate ratio drops to 3.2 for the fluoro-substituted *N*-phenyl derivatives, possibly because of a decrease in this steric interaction in the 3 isomer. These rate differences are valid only for this particular solvent (Me_2SO) or possibly the family of dipolar aprotic solvents. In a less polar solvents such as THF, the rate ratio between the 3- and 4-nitro isomers in both the *N*-phenyl and *N*-methyl system was >100. All of these compounds were completely soluble in THF and solubility differences cannot be affecting the relative rates. Thus the dipolar aprotic solvent levels the rate differences between the 3 and 4 isomers found in THF.[15]

Ester carbonyls do not activate nitro-group displacement nearly as well as do the imide carbonyls (**4** vs. **1h**). Cyano groups are much more potent than carbonyls (**1h** vs. **3**). This is also reflected in the ease with which high molecular weight polymer is formed in the reaction of 2,4-or 2,6-dinitrobenzonitrile with bisphenols.[16]

Reactions with Other Phenoxide Derivatives. Various substituted phenoxides reacted cleanly with **1e** to give the ether imides in Table IV. Even 8-hydroxyquinoline gave **2p**



2p

Table III. Relative Reactivity of 1 toward Sodium Phenoxide in Dimethyl Sulfoxide at 25 °C[a]

Compd	X	R	Relative rate (1m ≡ 1)
1m	4-Cl	CH_3	1
1j	4-Cl	C_6H_5	*b*
1a	3-Cl	C_6H_5	*b*
1l	4-F	CH_3	4
1i	4-F	C_6H_5	20
1k	4-NO_2	CH_3	37
1b	3-F	C_6H_5	65
1h	4-NO_2	C_6H_5	130
1g	3-NO_2	CH_3	170
1c	3-NO_2	4-$CH_3OC_6H_4$	340
1d	3-NO_2	4-$CH_3C_6H_4$	430
1e	3-NO_2	C_6H_5	520
1f	3-NO_2	4-ClC_6H_4	670

[a] In this series diisobutyl 4-nitrophthalate (**4**) has a relative rate of <0.5 and 4-nitrophthalonitrile (**3**) has a relative rate of ~7500. [b] An accurate value could not be obtained for this compound because of side reactions. However, we believe its order in the series is correct.

in 82% yield. This reaction thus offers the opportunity to assemble a wide variety of functionalized systems which contain an ether linkage. The ^{13}C NMR chemical shifts for these compounds are tabulated (see supplementary material).

Relative reactivities of substituted phenoxides were determined in competitive experiments in anhydrous dimethylformamide at room temperature (Table V). Electron-releasing substituents increase the rates, but sodium *p*-nitrophenoxide was unreactive. Sodium thiophenoxide reacted over 100 times faster than sodium phenoxide.[17]

Ether Exchange Reactions. An activated ether group may also be displaced.[18] We found the ether imides (**2**) to be susceptible to exchange with other phenoxides to give an equilibrium mixture of ether imides. The position of the equilibrium was related to the nucleophilicities of the phenoxides involved. The enhanced reactivity of sulfur was demonstrated by the fact that the equilibrium lay almost completely toward the 3-(4-methylthiophenoxy)-*N*-phenylphthalimide (**6**). 3-Phenoxyphthalimides react more rapidly than the 4 isomers. Reactions involving the 3 isomers were essentially complete within 1 h at 120 °C in anhydrous dimethylformamide. The rate of phenoxy displacement is slower than chloro displacement. Results of these exchange studies are presented in Table VI.

Reaction with Sodium Nitrite. The reaction of a sodium phenoxide derivative with a nitro-substituted imide produces an equivalent amount of sodium nitrite in addition to an ether imide. The stability of the imide ring in the presence of sodium nitrite was uncertain, so the reactions between the nitro imide or ether imide and sodium nitrite were studied. At 60 °C, 3-nitro-*N*-phenylphthalimide was stable to anhydrous sodium nitrite in dimethylformamide for 2–3 h, although the color changed from light yellow to dark red. A precipitate formed after this time. At 135 °C, darkening and precipitation occurred much faster. The precipitate, identified as disodium 3-nitrophthalate, probably arose from a ring-opening reaction of the nitroimide. The product 3-phenoxy-*N*-phenylphthalimide is stable to sodium nitrite in DMF at 60 °C for 48 h. This imide should be much more stable to ring-opening reactions because of the electron-donating group in the 3 position rather than the electron-withdrawing nitro group. An electron-withdrawing group should activate one imide carbonyl for attack by a nucleophile. We conclude that these displacements by phenoxide should be conducted at as low a temperature and as briefly as possible to minimize the side reactions with nitrite ion.[19]

In summary, the reaction of phenoxides with halo or nitro *N*-substituted phthalimides is an excellent synthetic route to a wide variety of phenoxyphthalimides. In many cases, reaction in dipolar aprotic solvents at room temperature gave quantitative yields of products in <5 min. In Me_2SO or DMF, the relative reactivity of the leaving group was $NO_2 > F > Cl$ and the 3-substituted isomers were more reactive than the corresponding 4 isomers. Substitution of electron-withdrawing groups on the imide nitrogen increased the rate of reaction slightly, as did the use of electron-rich phenoxide derivatives. The phenoxy group of the product was also susceptible to displacement by other phenoxides. At 120 °C ether exchange occurred readily to give equilibrium mixtures of phenoxyphthalimides. Since the nitrite produced in the displacement reaction was also reactive at elevated temperatures, particularly toward the starting nitro imide derivatives, nitro displacements should be performed under mild conditions.

Further studies of the displacement of nitro and halo groups in derivatives of phthalic acid will be presented in subsequent papers.

Table IV. Properties of Phenoxyphthalimides[a] from 1e

Registry no.	Compd	Y	% yield[b]	Mp,[c] °C	*m/e*[d]
63197-25-1	**2h**	*p*-NO_2	72[g]	212–215 (chlorobenzene)	360 (25)
63197-26-2	**2i**	*p*-Cl	98	169–170.5	349 (100)[e]
63181-79-3	**2j**	*p*-CH_3	97	162–163	329 (100)
63197-27-3	**2k**	*p*-OCH_3	94	155.5–157	345 (100)
63197-28-4	**2l**	*m*-CN	98	167.5–168.5	340 (100)
63197-29-5	**2m**	*p*-C(=O)CH_3	94	157.0–158.5	357 (13)
63197-30-8	**2n**	*m*-CO_2H	95	221.5–222.5	359 (100)
63197-31-9	**2o**	*m*-NH_2	85	*f*	330 (100)

[a] Satisfactory analytical data (± 0.4% for C, H, N) or an exact mass determination (for **2m** and **2o**) were reported for all new compounds listed in the table. [b] Phenoxide salts for **2h–2k** were prepared from NaOMe; phenoxide salts for **2l–2o** were prepared from NaOH. See Experimental Section for details. [c] All samples were recrystallized from ethanol unless indicated. [d] Value for molecular ion and its relative intensity. [e] One chlorine isotope cluster was observed. [f] A sharp melting point could not be obtained for this compound. [g] Two unidentified side products were also formed in this reaction.

Table V. Reactivity of 4-Y-C_6H_4ZNa with 3-Nitro-*N*-phenylphthalimide (1e) in Dimethylformamide at Room Temperature

Registry no.	Y	Z	Relative rate (NaOPh ≡ 1)
824-78-2	NO_2	O	<0.01
1193-00-6	Cl	O	0.4
139-02-6	H	O	1
1121-70-6	CH_3	O	3.5
1122-95-8	OCH_3	O	7.7
10486-08-5	CH_3	S	>350[a]

[a] Under these conditions (DMF, 25 °C, 0.5 h) no ether exchange took place even between 3-phenoxy-*N*-phenylphthalimide (**2a**) and sodium *p*-methylthiophenoxide.

Table VI. Ether Exchange Reactions

$$\mathbf{2a} + 4\text{-}XC_6H_4ONa \overset{DMF}{\rightleftharpoons} \mathbf{2h\text{–}k} + C_6H_5ONa$$

X	Starting material	Temp, °C	Time, h	% 2a	% 2h–k
CH_3	**2a**	60	26	44	56
			165	32	68
	2a	120	1	30	70
	2j	60	17	21	79
			140	36	64
	2j	120	1	35	65
OCH_3	**2a**	120	1	23	77
			3	21	79
			16	19	81
	2k	120	1	24	76
			3	21	79
			16	20	80
Cl	**2a**	120	1	85	15
			2.5	84	16
			16	95	5
	2i	120	1	92	8
			2.5	90	10
			16	96	4
NO_2	**2a**	120	1	100	0
			2	100	0
	2h	120	1	100[a]	0

$$\mathbf{2j} + 4\text{-}CH_3C_6H_4SNa \overset{DMF}{\rightleftharpoons} \mathbf{6} + 4\text{-}CH_3C_6H_4ONa$$

Starting material	Temp, °C	Time, h	% 2j	% 6
2j	120	1	3	97
		2	3	97
6	120	1	4	96
		2	4	96
		16	4	96

$$\mathbf{2f} + 4\text{-}CH_3\text{-}C_6H_4ONa \overset{DMF}{\rightleftharpoons} \mathbf{2q} + C_6H_5ONa$$

Starting material	Temp, °C	Time, h	% 2f	% 2q
2q	60	17	7	93
		43	13	87
		67	17	83
		140	26	74
2f	120	1	63	37
		2.25	39	61
		3.75	37	63
		20.5	39	61
2q	120	1	30	70
		2	32	68
		16	34	66

[a] Other side products formed, no **2h** is present.

Experimental Section

Infrared spectra were taken on a Perkin-Elmer 457 grating infrared spectrophotometer in chloroform solution or as a KBr pellet. Mass spectra were determined 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% UCW-98 on 80/100 Chromosorb W column with temperature programming from 200 to 300 °C at 10°/min. Melting points were determined on a Thomas-Hoover instrument and are uncorrected. C, H, N analyses were determined on a Perkin-Elmer 240 C, H, N analyzer.

Anhydrous DMF and Me_2SO were purchased from Burdick and Jackson Laboratories. Toluene and glacial acetic acid were reagent-grade chemicals and were used as purchased. The aniline was distilled before use. The phenol derivatives were used as purchased.

Preparation of Nitro- and Halophthalic Anhydrides. 3- and 4-Nitrophthalic Anhydride. Pure samples of these compounds were prepared by distillation of the reaction mixture obtained from the nitration of phthalic anhydride. We wish to thank N. C. Cook and J. M. Gasaway for a generous supply of these materials.

3-Chlorophthalic anhydride was prepared from 3-nitrophthalic anhydride and chlorine as described by Newman and Scheurer.[20]

4-Chlorophthalic anhydride was prepared from 4-nitrophthalic anhydride and chlorine by the preceding method.

3-Fluorophthalic anhydride was prepared by a toluene/acetic anhydride ring closing of the corresponding diacid, which was purchased from Columbia Chemical Co.

4-Fluorophthalic anhydride was prepared from potassium fluoride and 4-nitrophthalic anhydride.[21] We thank R. L. Markezich for a generous supply of this material.

4-Nitrophthalonitrile (3) was prepared (mp 140.5–142 °C) using the procedure of Drew and Kelly.[22]

4-Nitrodiisobutyl phthalate (4) was synthesized from 4-nitrophthalic anhydride and isobutyl alcohol in refluxing xylene with a trace of *p*-toluenesulfonic acid. The distilled yield was 82%.[23]

Preparation of Nitro- or Halo-Substituted Phthalimide Derivatives 1a–m. Compounds **1a–m**, prepared by refluxing the appropriate phthalic anhydride derivative and desired amine in glacial acetic acid under nitrogen, are described in Table I. The ^{13}C NMR data for these compounds are contained in Table VII (see supplementary material). All compounds had ^1H and infrared spectra consistent with their assigned structures. Detailed experimental conditions are given below for the synthesis of two of these compounds.

3-Chloro-*N*-phenylphthalimide (1a). A mixture of 20.0 g (0.109 mol) of 3-chlorophthalic anhydride and 250 mL of glacial acetic acid was stirred under a nitrogen atmosphere at room temperature. To this stirred mixture was added 10.38 g (0.112 mol) of aniline, and the resulting mixture was slowly heated to reflux. Initially a thick white precipitate formed, but upon heating a homogeneous solution was obtained. The solution was heated at reflux for 3 h and then cooled to room temperature. The white crystals were collected and dried; 26.4 g (94% yield). Recrystallization from absolute ethanol gave mp 191–192.5 °C.

4-Chloro-*N*-methylphthalimide (1m). Methylamine, 0.56 g (0.018 mol), was added to a mixture of 3.00 g (0.016 mol) of 4-chlorophthalic anhydride and 5.0 mL of glacial acetic acid at 0 °C. The mixture was heated at reflux for 2–3 h under nitrogen, then cooled to room temperature and filtered to give 2.85 g (89%), mp 134–135.5 °C (ethanol).

Preparation of Phenoxides. The various sodium phenoxides were prepared from sodium hydroxide or freshly prepared sodium methoxide in methanol and the phenol. The resulting salts were thoroughly dried, stored, and handled under dry nitrogen.

Sodium *p*-Methylphenoxide. Sodium Methoxide Method. Sodium metal, 10.65 g (0.463 mol), was dissolved in 600 mL of anhydrous methanol under nitrogen in an ice bath. Then 50.11 g (0.463 mol) of *p*-methylphenol was added and the clear solution was stirred for 1 h at room temperature. The methanol was removed under reduced pressure. The resulting white powder was dried (0.2 Torr/80 °C) to give 54.1 g (98%).

Sodium *m*-Cyanophenoxide. Sodium Hydroxide Method. A mixture of 1.19 g (0.010 mol) of *m*-hydroxybenzonitrile, 0.80 g of 50% aqueous sodium hydroxide, 23 mL of Me_2SO, and 23 mL of toluene was heated at reflux under nitrogen until no visible traces of water could be seen in the Dean–Stark trap. This trap was then replaced with a recirculating trap (essentially a Dean–Stark trap in which the collected distillate is returned to the pot through a tube in the bottom of the trap) packed with calcium hydride, and the condensed distillate was passed through this trap until no bubbling took place in it. The

toluene was distilled from the system. The mixture was cooled to room temperature and the 3-nitro-*N*-phenylphthalimide was added under nitrogen.

Preparation of Phenoxyphthalimide Derivatives (2a–g). Each of the phthalimide derivatives **1a–m** was stirred with sodium phenoxide in anhydrous dimethyl sulfoxide under nitrogen. All reactions were followed by removing aliquots at timed intervals, adding these aliquots to a methylene chloride/water mixture, and subjecting the methylene chloride solution to VPC analysis. All the reactions were run for 2 h at room temperature except **1a, 1i, 1j, 1k,** and **1m,** which were run at 50 °C. A detailed experimental procedure is given below.

3-Phenoxy-*N*-(4-chlorophenyl)phthalimide (2i). A mixture of 0.9893 g (8.5 mmol) of sodium phenoxide, 2.5810 g (8.5 mmol) of 3-nitro-*N*-(4-chlorophenyl)phthalimide, and 26 mL of anhydrous Me_2SO was stirred under nitrogen at room temperature. After 1 h, an aliquot was added to a methylene chloride/1.2 N hydrochloric acid mixture. This mixture was shaken and the methylene chloride layer was dried and subjected to VPC analysis. The remainder of the reaction mixture was added to 300 mL of 1.2 N hydrochloric acid solution. The white precipitate was collected, washed, and dried; 2.72 g (90%). Recrystallization from absolute ethanol gave the analytical sample, mp 172–174 °C (Table II).

Reaction of 1e with 8-Hydroxyquinoline: Formation of 2p. 8-Hydroxyquinoline, 1.45 g (0.01 mol), was converted to its salt by the sodium hydroxide method. The toluene was distilled from the system and 2.68 g (0.01 mol) of **1e** was added at 60 °C. The mixture was stirred at 60 °C for 6 h and then cooled and added to ice water. The precipitate was collected and dried; 3.01 g (82% yield), mp 195.5–196.5 °C (ethanol). See supplementary material for ^{13}C NMR assignments.

Anal. Calcd for $C_{23}H_{14}N_2O_3$: C, 75.4; H, 3.9; N, 7.6; mol wt 366.1003. Found: C, 74.8; H, 4.0; N, 7.7; mol wt 366.1004 (mass spectrum).

4-(4-Methylphenoxy)-*N*-phenylphthalimide (2q). A mixture of 14.58 g (0.112 mol) of sodium 4-methylphenoxide, 30.0428 g (0.112 mol) of 4-nitro-*N*-phenylphthalimide, and 200 mL of Me_2SO was stirred at 60 °C under a nitrogen atmosphere for 3 h. The mixture was cooled and added to a 1.2 N hydrochloric acid solution. The precipitate was collected and dried to give 34.8 g (94%): mp 177–178 °C (ethanol); ^1H NMR (Me_2SO-d_6) δ 2.35 (methyl, s, 3), 6.9–8.0 (aryl, m, 12); IR (KBr) C=O 1712 (s), 1770 cm^{-1} (m). See supplementary material for ^{13}C NMR assignments.

Anal. Calcd for $C_{21}H_{15}NO_3$: C, 76.6; H, 4.6; N, 4.3; mol wt 329. Found: C, 76.8; H, 4.5; N, 4.2; mol wt 329 (mass spectrum).

4-Phenoxyphthalonitrile. This compound can be prepared from the reaction of sodium phenoxide with 4-nitrophthalonitrile (**3**) in Me_2SO as described in ref 24. We thank D. R. Heath for a sample of this material.

Diisobutyl 4-Phenoxyphthalate (5). A mixture of 5.0 g (0.015 mol) of diisobutyl 4-nitrophthalate (**4**), 1.80 g (0.015 mol) of sodium phenoxide, and 50 mL of DMF was heated at 100 °C for 1 h under nitrogen. The reaction mixture was cooled to room temperature and added to 200 mL of 1.2 N hydrochloric acid. The resulting mixture was extracted well with ether, and the ether extracts were washed with water and a saturated salt solution to give 5.5 g of a light yellow oil. This material was distilled through a short-path distillation column to give 5.1 g (89%) of diisobutyl 4-phenoxyphthalate, bp 198–201 °C (0.53 Torr). See supplementary material for ^{13}C NMR assignments.

Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08. Found: C, 71.1; H, 7.0.

3-(4-Methylthiophenoxy)-*N*-phenylphthalimide (6). A mixture of 1.46 g (0.010 mol) of the sodium salt of *p*-methylthiophenol, 2.51 g (0.010 mol) of 3-chloro-*N*-phenylphthalimide (**1a**), and 25 mL of anhydrous dimethylformamide was stirred at 60 °C under a nitrogen atmosphere. After 2 h, the mixture was cooled to room temperature and poured into 500 mL of 1.2 N hydrochloric acid solution. The precipitate was collected and dried to give 3.35 g (97%), mp 203.5–205 °C (ethyl acetate), of desired product (**6**).

Anal. Calcd for $C_{21}H_{15}NO_2S$: C, 73.02; H, 4.38; N, 4.06; S, 9.28; mol wt 345. Found: C, 73.3; H, 4.6; N, 3.8; S, 9.5; mol wt 345 (mass spectrum).

Competition Experiments: Reactivity toward Sodium Phenoxide (Table III). Anhydrous sodium phenoxide was accurately weighed into a flask under nitrogen. Equimolar amounts of the two compounds being studied and an internal standard (*o*-terphenyl) were then dissolved in enough Me_2SO to make a 10% solution. An aliquot was added to a mixture of 1.2 N hydrochloric acid and chloroform. The chloroform layer was dried, and this solution analyzed to determine the composition of the starting mixture. The Me_2SO solution was then added to the sodium phenoxide and this mixture was stirred under nitrogen at room temperature. After 1 h, an aliquot was analyzed (VPC) as described above. Using the equation presented by Huisgen,[25] the relative rates of reactivity were calculated:

$$\frac{K_A}{K_B} = \frac{\log A_0 - \log (A_0 - x)}{\log B_0 - \log (B_0 - x)}$$

A_0 = initial concentration of A, B_0 = initial concentration of B, $(A_0 - x)$ = amount of A unreacted, and $(B_0 - x)$ = amount of B unreacted.

Competition Experiments: Reactivities of the Nucleophiles (Table V). Two different nucleophiles (10 mmol each) were dissolved in 25 mL of anhydrous dimethylformamide, followed by 2.68 g (10 mmol) of 3-nitro-*N*-phenylphthalimide. The mixture was stirred for 0.5 h at room temperature under nitrogen, and an aliquot of the homogeneous solution was added to 1.2 N hydrochloric acid and extracted well with chloroform. If the reaction mixture was not homogeneous, the entire reaction mixture was so treated. The chloroform solution was dried and subjected to VPC analysis, which was calibrated with standards. Each competition was run in duplicate and the average values were used to calculate the relative reaction rates.

Ether Exchange Reactions (Table VI). All reactions were run in anhydrous dimethylformamide under a nitrogen atmosphere.

Typically, a mixture of 1.0 g (3.0 mmol) of 3-(4-methylphenoxy)-*N*-phenylphthalimide (**2j**) and 0.35 g (3.0 mmol) of sodium phenoxide was stirred with 10 mL of anhydrous DMF under a nitrogen atmosphere. The mixture was placed in a bath at 60 °C and aliquots were added to a mixture of 1.2 N hydrochloric acid and chloroform, as before, and analyzed. Ratios for the two imides were calculated from the corrected peak areas.

The final reaction mixture was poured into 1.2 N hydrochloric acid/ice to give 0.92 g of material. ^{13}C analysis indicated only two compounds were present and proton NMR analysis showed the ratio of **2a/2j** to be 33/67.

Reaction of Sodium Nitrite with 3-Nitro-*N*-phenylphthalimide (1e). A mixture of 0.24 g (3.5 mmol) of anhydrous sodium nitrite, 1.0 g (3.7 mmol) of **1e,** and 10 mL of anhydrous DMF was stirred under nitrogen at 60 °C. Within 15 min, the solution became dark red in color, but no precipitate formed during 3 h. The reaction mixture was cooled to room temperature and poured into a 1.2 N hydrochloric acid/ice mixture. The resulting precipitate was collected and dried to give 0.98 g of yellow powder, identical with the starting material by VPC, IR, and ^1H and ^{13}C NMR.

After 48 h at 60 °C, the reaction mixture was very dark in color and a white precipitate (0.17 g) had formed. This solid was dissolved in water, acidified, and extracted with ether to give 3-nitrophthalic acid. An NMR of the initial white precipitate in D_2O was identical with the NMR of the disodium salt of 3-nitrophthalic acid.

The initial filtrate was poured into a 1.2 N hydrochloric acid/ice mixture; the resulting precipitate (0.65 g) was starting material (IR), but VPC analysis showed the presence of two minor impurities which were not identified.

A mixture of 2.68 g (10 mmol) of imide (**1e**), 0.75 g (10.8 mmol) of anhydrous sodium nitrite, and 50 mL of anhydrous DMF stirred under nitrogen at 135 °C almost immediately turned very red. After 5 min, the solution was dark red-black in color and precipitate formed. After 4 h, at 135 °C, the solution was cooled and filtered to give 1.0 g (39%) of disodium 3-nitrophthalate. The filtrate was poured into a 1.2 N hydrochloric acid/ice mixture and extracted with chloroform. The chloroform extracts gave 1.5 g of a red oil containing many unidentified components.

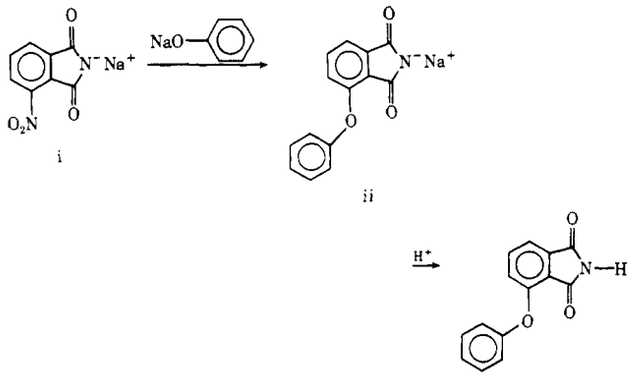
Reaction of Sodium Nitrite with 3-Phenoxy-*N*-phenylphthalimide (2a). A mixture of 1.0 g (3.1 mmol) of **2a,** 0.21 g (3.0 mmol) of anhydrous sodium nitrite, and 10 mL of anhydrous dimethylformamide was stirred under nitrogen at 60 °C for 48 h. The solution slowly turned light yellow, but no detectable precipitate was formed. The cooled mixtures was added to a 1.2 N hydrochloric acid/ice mixture to give 0.95 g of **2a.** No new products were found.

Acknowledgments. We would like to thank H. M. Relles, T. Takekoshi, and J. S. Manello for many helpful discussions concerning this work. In addition, we would like to thank H. M. Relles, J. D. Cargioli, E. A. Williams, and G. C. Levy for their help in obtaining and interpreting the ^{13}C spectra, which have been of great value to us in much of this study.

Registry No.—**2p,** 63197-32-0; **2q,** 63196-28-1; **3,** 31643-49-9; **4,** 53577-26-7; **5,** 63197-33-1; **6,** 58045-38-8; 3-chlorophthalic anhydride, 117-21-5; 3-fluorophthalic anhydride, 652-39-1; 3-nitrophthalic anhydride, 641-70-3; 4-nitrophthalic anhydride, 5466-84-2; 4-fluoro-

phthalic anhydride, 319-03-9; 4-chlorophthalic anhydride, 118-45-6; aniline, 62-53-3; 4-methoxyaniline, 104-94-9; 4-methylaniline, 106-49-0; 4-chloroaniline, 106-47-8; methylamine, 74-89-5; 8-hydroxyquinoline, 148-24-3; sodium, 1440-23-5; *p*-methylphenol, 106-44-5; *N*-phenylphthalimide, 520-03-6.

Supplementary Material Available. Tabulated ^{13}C NMR chemical shifts for all phthalimides contained in Tables I, II, and IV (Table VII) as well as **2p**, **2q**, and **5** (7 pages). Ordering information is given on any current masthead page.



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(9) See, for example, J. G. Wirth and D. R. Heath, U.S. Patent 3 838 097 (1974).
(10) Yields of >95% can be obtained by pouring the reaction mixture into water and recovering the product by filtration. No attempt was made to maximize the yields of these crude products, which were clean by VPC analysis.
(11) J. Miller, "Aromatic Nucleophilic Substitution", Elsevier, New York, N.Y., 1968, p 137.
(12) J. Miller, ref 11, p 165.
(13) Placement of a negative charge on nitrogen causes the reaction to be very sluggish. Displacement of the nitro group from the phthalimide salt (i) by phenoxide to give ii requires heating at 120 °C for 16 h in DMF. Reaction with the corresponding 4 isomer is incomplete after 48 h at 120 °C.
(14) Support for the contention of steric interaction between the 3 substituent and the ortho carbonyl group is found in the ^{13}C NMR spectrum of 3-nitro-*N*-phenylphthalimide (**1e**) (see Table VII). Both carbonyl B and C-2 of this molecule are shifted upfield relative to the calculated values, which suggests steric compression between the nitro and carbonyl group. For a discussion of steric compression shifts, see G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972, p 24.
(15) Perhaps Me_2SO also levels the rate differences between the different leaving groups. Many examples are known. See, for example, ref 11, Chapter 8.
(16) D. R. Heath and J. G. Wirth, U.S. Patent 3 730 946 (1973).
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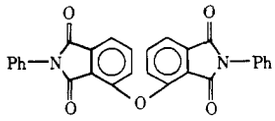

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Reactions of Phenoxides with Nitro-Substituted Phthalate Esters

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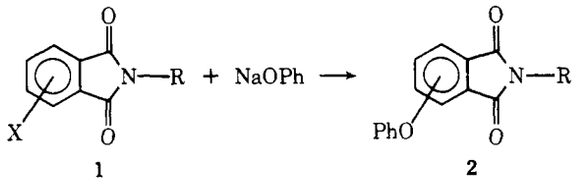
Aromatic nucleophilic nitro displacement by phenoxides on nitro-substituted phthalate esters is discussed. The differences in behavior between the 3-nitro (**5a–d**) and 4-nitro (**4a–d**) isomers were investigated. The 4 isomers gave excellent yields of the phenoxy substituted derivatives **6**. Side reactions were prominent for the 3-nitro isomers in degrees depending on the alkyl groups of the ester function. The majority of the side products can be explained by nucleophilic attack on the alkyl group of the ester, resulting in cleavage of the alkyl–oxygen bond. A rationale for the relative displacement rates of these two isomers is presented.

The reaction of phenoxides with nitro- or halo-substituted phthalimides (**1**) is an excellent synthetic route to ether imide derivatives (**2**).[1] We wish to report the results of studies on the reactions of phenoxides with nitrosubstituted phthalate esters.[2] Examples of aromatic displacement reactions using an ester activating group were reported as early as 1890,[3] but this group was used only in conjunction with other activating groups. The displacement of nitro groups activated by only one ester group was subsequently observed in dipolar aprotic solvents.[4,5] No attack of the nucleophile at either the carbonyl or alkyl group of the ester was observed in any of these systems.



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Results and Discussion

Reactions with Sodium 4-Methylphenoxide. The reaction of sodium 4-methylphenoxide (**3**) with eight dialkyl nitrophthalates (**4a–d** and **5a–d**) was examined to determine