(23) K. B. Wiberg and G. Szeimies, *J. Am. Chem. Soc.*, **92,** 571 (1970).
(24) For a review of organosilver chemistry, consult C. D. M. Beverivizk, G. J. M. vander Kerk, A. J. Lensink, and J. G. Noltes, *Organometal. Chem. Rev., Sect. A*, **5,** 218 (1970).
(25) W. R. Moore and B. J. King, *J. Org. Chem.*, **36,** 1882 (1971).
(26) P. G. Gassman and T. J. Atkins [*J. Am. Chem. Soc.*, **94,** 7749 (1972)] have examined the $SnCl_2 \cdot 2H_2O$ catalyzed rearrangement of 1-methyltricyclo[4.1.0.0^{2,7}]heptane and determined the exclusive ring opened product to be 1-methyl-2-norcarene. Evidently, the bridgehead methyl group directs catalyst attack only to those edge bonds *most remote* from the substituent in this instance.
(27) (a) K. B. Wiberg, B. A. Hess, Jr., and A. J. Ashe, III, in "Carbonium Ions", Vol. 3, G. A. Olah and P. v. R. Schleyer, Ed., Wiley, New York, N.Y., 1972, p 1295; (b) J. Haywood-Farmer, *Chem. Rev.*, **74,** 315 (1974); (c) for a recent leading reference, see L. A. Paquette and M. R. Detty, *J. Am. Chem. Soc.*, **99,** 828 (1977).
(28) O. G. Lindsay and C. B. Reese, *Tetrahedron*, **21,** 1673 (1965).
(29) U. Schöllkopf and H.-U. Scholz, *Synthesis*, 271 (1976).

Reaction of Thiophenoxides with Nitro- and Halo-Substituted Phthalimide Derivatives

F. J. Williams* and P. E. Donahue

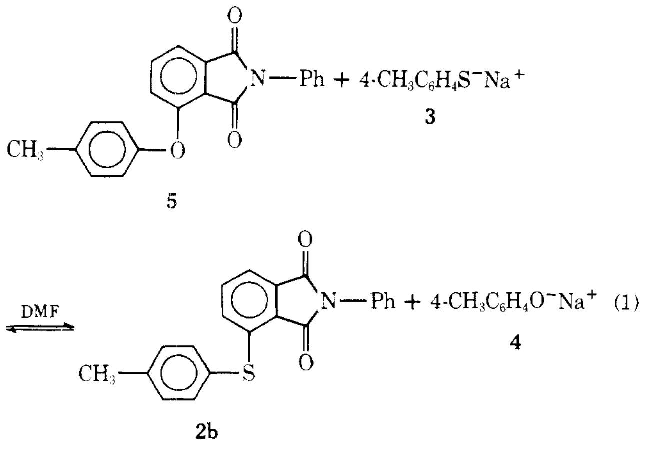
General Electric Research and Development Center, Schenectady, New York 12301

Received June 13, 1977

The reaction of thiophenoxides 3 with nitro- and halo-substituted phthalimide derivatives 1 was studied. In contrast to the reaction of 1 with phenoxides, a variety of inorganic bases, organic amines, and solvents such as THF, EtOH, and CH_2Cl_2 were used successfully in the thiophenol reactions. Using these procedures, a series of previously unknown thioether imides 2 were synthesized and identified with the assistance of ^{13}C NMR analysis. The relative rates of reaction of the different imides with thiophenoxide were measured and the differences in rate between the thiophenoxide and phenoxide nucleophiles are discussed in detail. The 3-substituted nitro derivatives were much more reactive toward thiophenoxide than any of the other systems which were studied. An examination of the formation of disulfides as side products was also made.

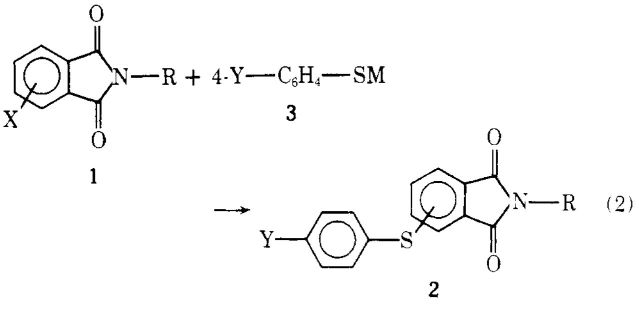
Recent studies by these authors have dealt with the reaction of phenoxide nucleophiles with nitro and halo groups activated by derivatives of phthalic acid. These studies have covered reactions with N-substituted phthalimides,[1] phthalate esters,[2] and phthalic anhydrides.[3] The tremendous nucleophilicity of sulfur in aromatic nucleophilic displacement reactions is well documented.[4] According to Parker,[5] "the thiophenoxide ion is the most powerful nucleophile which has been thoroughly studied in bimolecular SnAr reactions".

Preliminary work[1] has demonstrated that, indeed, in displacement reactions involving the phthalimide moiety as an activating group, thiophenoxide is vastly superior to phenoxide as a nucleophile. For example, in the displacement of the nitro group from 3-nitro-*N*-phenylphthalimide (**1**, X = 3-NO_2; R = Ph) in DMF, sodium 4-methylthiophenoxide (**3**) was found to react >100 times faster than sodium 4-methylphenoxide (**4**). In addition, if a mixture of **3** and 3-(4-methylphenoxy)-*N*-phenylphthalimide (**5**) or **4** and 3-(4-methylthiophenoxy)-*N*-phenylphthalimide (**2b**) was allowed to react in DMF at 120 °C for 1 h, the ratio of **2b** to **5** from either starting mixture was 97 to 3 (eq 1). These experiments suggested that the enhanced reactivity of sulfur might allow us to explore new base and solvent systems with thiophenol derivatives in these displacements.



Results and Discussion[6]

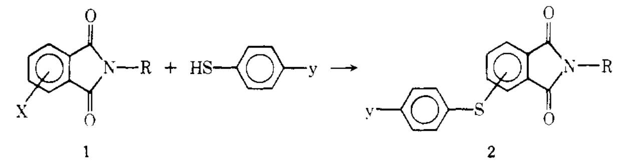
Studies of Base System. Initial work was carried out with the preformed sodium salt of thiophenol (**3**, Y = H; M = Na) or 4-methylthiophenol (**3**, Y = CH_3; M = Na). Reaction of these salts with 3- or 4-substituted nitro, chloro, or fluoro derivatives of **1** (R = alkyl or aryl) in DMF gave essentially quantitative yields of **2** (eq 2). Reactions involving an in situ formation of the anion of 4-methylthiophenol using potassium carbonate or sodium hydroxide as a base gave good yields of **2**. Apparently, the displacement is so rapid with the sulfur nucleophile that the reaction is complete before the base can enter into the hydrolysis reactions with **1** that are seen in the phenol derivatives.[7]



Amine bases were also used in these reactions of **1** where X = NO_2, and essentially quantitative yields of **2** were obtained. These results are in direct contrast to reactions involving 4-methylphenol in which amine bases gave no displacement with any derivatives of **1**. Particularly interesting was the reaction of 4-hydroxythiophenol (**3**, Y = OH; M = H) in which only displacement by sulfur was seen. If amine bases were used with fluoro and chloro derivatives of **1**, only 50% yields of **2** were obtained, even at temperatures of 80 °C. In addition to

0022-3263/78/1943-0250$01.00/0

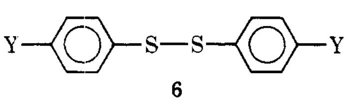
Table I. Displacement Reactions in DMF[a]



Compd	Registry no.	R	Isomer-X	y	Registry no.	Base (temp. °C)	% yield (isolated)	mp (ethanol)
2a	58045-34-4	Ph	3-NO_2	H	108-98-5	NaOH[e] (25)	91[b]	146-148
2b	58045-38-8	Ph	3-F	CH_3	106-45-6	$NaOCH_3$[e] (25)	99	204-205
2g	58045-39-9	Ph	4-NO_2	CH_3		$NaOCH_3$[e] (60)	96	165-167
2g		Ph	4-Cl	CH_3		$NaOCH_3$[e] (25)	98	
2l	64146-71-0	CH_3	4-NO_2	CH_3		$NaOCH_3$[e] (25)	92	135-137
2n	64146-70-9	CH_3	3-NO_2	CH_3		$NaOCH_3$[e] (25)	99	147-148
2b		Ph	3-NO_2	CH_3		K_2CO_3[f] (25)	96[c]	
2l		CH_3	4-F	CH_3		K_2CO_3[f] (25)	81[d]	
2l		CH_3	4-NO_2	CH_3		NaOH[g] (25)	57[d]	
2a		Ph	3-NO_2	H		Et_3N (25)	98	
2c	58045-36-6	Ph	3-NO_2	OH	637-89-8	Et_3N (25)	96	193-195
2b		Ph	3-NO_2	CH_3		Et_3N (25)	99	
2d	58045-35-5	*n*-Bu	3-NO_2	H		Et_3N (25)	92	83-85
2e	64146-09-6	H	3-NO_2	CH_3		Et_3N (25)	93	260-262
2f	64146-68-5	Ph	4-NO_2	H		Et_3N (25)	99	157-159
2g		Ph	4-NO_2	CH_3		Et_3N (60)	98	
2h	64146-67-4	Ph	4-NO_2	Br	106-53-6	Et_3N (60)	87	184-185
2i	64146-66-3	Ph	4-NO_2	OCH_3	696-63-9	Et_3N (60)	98	145-146
2j	64146-65-2	Ph	4-NO_2	Cl	106-54-7	Et_3N (60)	91	177-178
2k		Ph	4-NO_2	F	371-42-6	Et_3N (60)	97	161-163
2l		CH_3	4-NO_2	CH_3		Et_3N (25)	97	
2m		H	4-NO_2	CH_3		Et_3N (25)	86	194-195
2a		Ph	3-NO_2	H		$NaNO_2$[h] (25)	99[c]	
2b		Ph	3-NO_2	CH_3		$NaNO_2$[h] (25)	98	
2a	64146-64-1	Ph	3-NO_2	H		None (25)	51[c]	
2b	64146-72-1	Ph	3-NO_2	CH_3		None (25)	32	

[a] Satisfactory analytical data (±0.4 for C, H, N, S) were reported for all new compounds listed in the table. [b] Reaction run by D. R. Heath in Me_2SO. The displacement was apparently so fast that very little **6** was formed even in this solvent. [c] VPC yield. [d] Yield was low due to samples removed for analysis. [e] Preformed salt—either H_2O or MeOH removed before addition of **1**. [f] Used 1 equiv of granular anhydrous K_2CO_3/1 equiv of thiophenol. [g] Used 1 equiv of sodium hydroxide pellets (97%)/1 equiv of thiophenol. [h] Used 0.02 equiv of anhydrous $NaNO_2$/1 equiv of thiophenol.

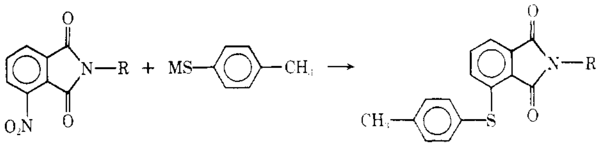
unreacted **1**, a considerable amount of the disulfide **6** (Y = CH_3) was found in these reactions.



6

The addition of a small amount (~2 mol %) of sodium nitrite to a DMF solution of 4-methylthiophenol (**3**, Y = CH_3; M = H) and **1** (R = Ph; X = 3-NO_2) resulted in a rapid reaction at room temperature, and after 1 h a 98% yield of **2** (R = Ph; Y = CH_3) was obtained. A catalytic amount of any number of bases should effect this reaction with the nitrite generated from the displacement functioning as the actual base. Surprisingly, we also found that the displacement could be carried out in DMF with no base present; however, the reaction did not proceed to completion. It is possible that there are traces of dimethylamine in the DMF which function as the base or that perhaps the DMF acts as the base itself. However, in either case the nitrite which is generated apparently does not effectively function as a base, since the reaction does not proceed to completion. This indicates that the cation associated with the base has a definite influence on whether the nitrite generated from displacement can function as a base itself to complete the reaction.[8] The results of these base studies are summarized in Table I. ^{13}C NMR assignments for the compounds **2** are contained in Table VI in the supplementary material.

Table II. Nitro Displacements in New Solvent Systems at 25 °C



R	M	Base	Solvent	Time, h	% yield (isolated)[a]
Ph	H	K_2CO_3	THF	16[b]	98
Ph	H	Et_3N	THF	3	88
Ph	Na	Preformed	CH_2Cl_2	3	95
Ph	Na	Preformed	CH_3CN	1	90
Ph	Na	Preformed	Acetone	1	90
Ph	Na	Preformed	EtOH	3	98
CH_3	H	Et_3N	THF	3	93
CH_3	Na	Preformed	THF	1	87
CH_3	Na	Preformed	CH_2Cl_2	3	97

[a] No attempt was made to maximize the yields. [b] This reaction was carried out at reflux.

Studies of Solvent Systems. The yields of **2** from the reactions of phenoxides with **1** in nondipolar aprotic solvents were generally poor.[1] The exception occurred in the 3-nitro system in which displacements involving **1** (R = Ph; X = 3-NO_2) could be carried out in THF. Thiophenoxides react with 3-nitro derivatives in a variety of solvents such as THF, methylene chloride, acetone, acetonitrile, and ethanol to give excellent yields of **2** (see Table II). Unexpectedly, the 4-nitro isomers of **1** did not react well in these solvents.

The successul use of methylene chloride as a solvent allowed a two-phase reaction to be carried out. Using Adogen 464

Table III. Relative Rates of Reactivity of 1 in Me_2SO at 25 °C[a]

Relative Rates with $4\text{-}CH_3C_6H_4S^-Na^+$ [c]	Compound	Registry no.	Relative Rates with $C_6H_5O^-Na^+$ [d]
1	**1j** ($R = CH_3$; $X = 4\text{-}Cl$)	63197-17-1	1
6	**1a** ($R = Ph$; $X = 3\text{-}Cl$)	42899-83-2	b
8	**1b** ($R = CH_3$; $X = 4\text{-}F$)	63196-44-1	4
8	**1c** ($R = Ph$; $X = 4\text{-}Cl$)	26491-49-6	b
38	**1d** ($R = Ph$; $X = 4\text{-}F$)	63197-16-0	20
190	**1e** ($R = Ph$; $X = 3\text{-}F$)	42899-84-3	65
250	**1f** ($R = CH_3$; $X = 4\text{-}NO_2$)	41663-84-7	37
750	**1g** ($R = Ph$; $X = 4\text{-}NO_2$)	40392-27-6	130
9 400	**1h** ($R = CH_3$; $X = 3\text{-}NO_2$)	2593-81-9	170
16 000	**1i** ($R = Ph$; $X = 3\text{-}NO_2$)	19065-85-1	520

[a] Each series was determined independent of the other and thus the relative value of one in the sulfur series *does not equal* the relative value of one in the oxygen series. Thus, no direct comparison of the rates between the two series should be made. [b] An accurate value for this compound could not be obtained due to the formation of side products. [c] Registry no.: 10486-08-5. [d] Registry no.: 139-02-6.

Table IV

(A) Relative Rate Ratios for Various Leaving Groups for N-Substituted Phthalimide Derivatives 1

Nucleophile	N-R	Isomer	NO_2/Cl	NO_2/F	F/Cl
$4\text{-}CH_3C_6H_4S^-Na^+$	N-Ph	3	2600	84	32
$4\text{-}CH_3C_6H_4S^-Na^+$	N-Ph	4	94	20	5
$4\text{-}CH_3C_6H_4S^-Na^+$	$N\text{-}CH_3$	4	250	31	8
$C_6H_5O^-Na^+$	N-Ph	3		8	
$C_6H_5O^-Na^+$	N-Ph	4		6	
$C_6H_5O^-Na^+$	$N\text{-}CH_3$	4	37	9	4

(B) Relative Rate Differences for 3/4 Isomers

Nucleophile	N-R	Ratio of 3/4 Isomers		
		NO_2	F	Cl
$4\text{-}CH_3C_6H_4S^-Na^+$	N-Ph	21	5	0.75
$4\text{-}CH_3C_6H_4S^-Na^+$	$N\text{-}CH_3$	38		
$C_6H_5O^-Na^+$	N-Ph	4	3	
$C_6H_5O^-Na^+$	$N\text{-}CH_3$	5		

[methyltrialkyl (C_8–C_{10}) ammonium chloride] as a phase-transfer catalyst, an 80% yield of **2n** was obtained from **1** ($R = CH_3$; $X = 3\text{-}NO_2$) and **3** ($Y = CH_3$; $M = H$).

Relative Rates of Reaction. A series of competition reactions was carried out between the various halo- and nitroimides, **1**, with sodium 4-methylthiophenoxide, **3** ($Y = CH_3$; $M = Na$), in Me_2SO at 25 °C. The results of these experiments are presented in Table III along with the relative rates of reactivity for each of these compounds with sodium phenoxide in Me_2SO at 25 °C. Table IV contains a comparison of pairs of leaving groups with respect to displacement by sulfur or oxygen and a comparison of the relative rates of displacement of the 3- and 4-isomer for each leaving group with sulfur or oxygen. From the data in Tables III and IV several trends can be seen: (1) For both sulfur and oxygen nucleophiles, the relative leaving group ability is $NO_2 > F > Cl$. (2) The relative difference between the rate of displacement of nitro and halo is much greater for sulfur than oxygen. (3) Displacements are favored when the leaving group is substituted in the 3-position with both sulfur and oxygen nucleophiles. The exception is for the chloro group with the sulfur nucleophile. (4) When sulfur is the nucleophile, the ratio of rates of displacement of the 3- to 4-nitro group is much greater than when oxygen is the nucleophile. (5) The relative rate of displacement of a 3-substituted nitro group with the sulfur nucleophile is much larger than for any other system studied.

As previously stated,[1] the nitro group can be either a better or worse leaving group than fluorine depending upon the system studied. As evidenced in Table IV, nitro is a better leaving group than fluorine in these systems regardless of whether the nucleophile is sulfur or oxygen. The more highly polarizable and "softer" sulfur nucleophile should prefer attack at a center which is closer to a polarizable group (nitro), and thus the nitro to halo differences should be enhanced with the sulfur nucleophile relative to the less polarizable oxygen nucleophile which favors attack at centers containing "harder", less polarizable groups such as fluoro and chloro. This is in fact the case as illustrated in Tabel IV, where, for example, with compounds **1j** and **1f** the NO_2 vs. Cl difference for sulfur is 250 vs. 37 for the oxygen nucleophile.

The strong inductive effect of the *o*-carbonyl in the 3-isomer (which is not possible in the 4-isomer) should favor displacement in the 3-position over the 4-position. In terms of steric interactions, however, the 3-isomer may be less favored, since approach of the nucleophile is hindered. Thus, the actual rate difference between the 3- and 4-isomers should be lower than if just the electronic effects were important. However, since sulfur is sufficiently polarizable to supply electrons and form bonds with carbon at relatively large separations,[9] there is potentially less chance for steric interaction with the sulfur nucleophile. This polarizability may be very important when the carbon center is attached to a strongly polarizable group such as nitro, and may be further enhanced by the adjacent electron-withdrawing carbonyl group. Thus, when nitro is the leaving group, it is reasonable that the 3-isomer reacts extremely rapidly with the sulfur nucleophile and the resulting 3/4 rate ratio is high (21 for **1j/1g**; 38 for **1h/1f**). It should be noted that the 3-nitro isomer may behave much differently from the 4-isomer, since there is considerable interaction between the 3-nitro oxygen atoms and the carbonyl group which prevents the nitro group from being coplanar with the imide ring. The effect of this change in nitro group configuration on the rate of reactions of the 3- and 4-isomers is unknown.

With the substitution of less polarizable halogen groups, the steric interactions at the 3-position become more important for sulfur and the **3/4** ratio more closely resembles the oxygen ratio (for **1d/1e** the ratio is 5 for sulfur and 3 for oxygen). It is interesting to note that with the sulfur nucleophile the 3-chloro derivative is even slower than the 4-isomer (**1a/1c** = 0.75). Again the lower polarizability of chlorine may enhance the steric effect and, since chlorine is larger than fluorine, this increased steric interaction in the 3-isomer now results in the 4-isomer being slightly more reactive.

We also compared the relative rates of reaction of **1h** ($R = Me$; $X = 3\text{-}NO_2$) vs. **1f** ($R = Me$; $X = 4\text{-}NO_2$) and **1b** ($R = Me$; $X = 4\text{-}F$) vs. **1f** ($R = Me$; $X = 4\text{-}NO_2$) when the sulfur nucleophile was generated by reacting 4-methylthiophenol with triethylamine. The nucleophile generated in this fashion behaved very similarly to sodium 4-methylthiophenoxide (**3**, $Y = CH_3$; $X = Na$) in that the 3-nitro isomer reacted much faster than the 4-nitro isomer and that the nitro derivative was much faster than the fluoro derivative. Likewise, if the nucleophile generated from triethylamine and 4-methylthiophenol was allowed to react with a mixture of **1b** ($R = Me$; $X = 4\text{-}F$) and **1c** ($R = Ph$; $X = 4\text{-}Cl$), it was found that **1c** was 1.1 times faster than **1b** vs. a difference of 1.3 when sodium 4-methylthiophenoxide was used as the nucleophile. Thus, at least for these two methods the manner in which the nucleophile is generated has little influence on the reactivity differences between pairs of imide derivatives.

An attempt was made to determine the relative nucleophilicities of sodium phenoxide and sodium 4-methylthiophenoxide vs. a given phthalimide derivative. If this could be achieved, we could then compare the values for sulfur in Table III directly with those for oxygen. As reported previously,[1] reaction of equal molar quantities of sodium 4-methylphenoxide (**4**) and sodium 4-methylthiophenoxide (**3**, $Y = CH_3$; $M = Na$) with **1i** ($R = Ph$; $X = 3\text{-}NO_2$) in DMF showed only reaction of the sulfur nucleophile. Similar reaction of equal molar amounts of **3** and **4** with **1j** ($R = CH_3$; $X = 4\text{-}Cl$), **1b** ($R = CH_3$; $X = 4\text{-}F$), **1f** ($R = CH_3$; $X = 4\text{-}NO_2$), **1e** ($R = Ph$; $X = 3\text{-}F$), and **1d** ($R = Ph$; $X = 4\text{-}F$) always produced >95% of the product from sulfur displacement. Thus, it is impossible, by our methods, to determine accurately the relative reactivity of **4** to **3** and we can only say that **3** is at least 100 times more reactive than **4** toward displacement in these systems.

Formation of Disulfide Derivatives. During some of our displacement studies we found appreciable amounts of disulfides **6**, and thus we attempted to learn more about their formation. It is well known that thiophenols are very air sensitive and can easily be oxidized to give disulfides. Likewise, reactions carried out with thiophenols in Me_2SO[10] can produce high yields of disulfides. We had noticed that more disulfide was produced in nitro rather than halo displacements and thus we studied the effect of sodium nitrite and unreacted nitro compound[11] on the disulfide formations. These results are summarized in Table V (section A) and indicate that nitrite by itself causes little oxidation of **3** ($Y = CH_3$; $M = H$), but when it is allowed to react with 1.2 N HCl (as in the workup of the displacement reaction) to form nitrous acid considerable coupling occurs to give **6**. In addition, the results also indicate that unreacted nitroimide may be responsible for the formation of **6**.

Reactions carried out between **3** ($Y = CH_3$; $M = Na$) and **1h** ($R = CH_3$; $X = 3\text{-}NO_2$) and **1b** ($R = CH_3$; $X = 4\text{-}F$) demonstrated that if the reactions are carried out under nitrogen using a neutral workup no **6** is produced (Table V, section B). Likewise, it was discovered that when the displacement is slower (as with the halo derivatives) and triethylamine is present considerable coupling takes place[12] (Table V, section B). This side reaction with triethylamine or impurities in the amine is serious enough that in the halo systems the displacement reaction cannot proceed to completion even if a 20% excess of thiophenol is used. This explains the low yields of **2** which are formed from these displacements.

Summary. The reactions of thiophenols with nitro- and halo-substituted phthalimides were found to be much different than similar reactions using phenols. The increased reactivity of the thiophenols permitted the use of inorganic and amine bases as well as many nondipolar aprotic solvents. The thiophenols were found to be extremely reactive with the 3-nitro isomers in comparison to the other nitro- and halo-substituted derivatives. We have extended our studies of thiophenols to nitro and halo derivatives of phthalic anhydride, and these results are presented in a separate paper.

Table V

(A) Coupling of Thiophenol Derivatives **3** ($Y = CH_3$; $M = H$)

Reactants	Time, h	Workup	% **3**	% **6** ($Y = CH_3$)
DMF	1	1.2 N HCl	93	4
	23.5	1.2 N HCl	70	22
DMF, $NaNO_2$	1	1.2 N HCl	0	87
	4	H_2O	83	9
	4	1.2 N HCl	0	78
	23.5	H_2O	59	31
DMF, Nitrobenzene-	1	H_2O	87	11
	4	H_2O	38	50
	23.5	H_2O	0	91

(B) Disulfide Formation during Displacement Reactions

$$\mathbf{1} + \mathbf{3}\ (Y = CH_3) \xrightarrow{DMF} \mathbf{2} + \mathbf{6}\ (Y = CH_3)$$

Imide	M	Time (h)	Workup	% **6**
1h ($R = CH_3$; $X = 3\text{-}NO_2$)	Na	1	H_2O	0
		1	1.2 N HCl	5
1b ($R = CH_3$; $X = 4\text{-}F$)	Na	0.5	H_2O	0
		0.5	1.2 N HCl	0
1h ($R = CH_3$; $X = 3\text{-}NO_2$)	H/Et_3N	1	1.2 N HCl	<2
		1	H_2O	<2
1b ($R = CH_3$; $X = 4\text{-}F$)	H/Et_3N	4.5	H_2O	46
1c ($R = Ph$; $X = 4\text{-}Cl$)	H/Et_3N	16	H_2O	37

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% UC-W98 on 80/100 Chromosorb W column with temperature programming. A variety of different programs were used depending upon the compounds studied. The thioether phthalimides had long retention times and generally required temperatures around 300 °C to be eluded from the column. 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, and sulfur analyses were determined by conventional analytical techniques either in house or by Galbraith.

Anhydrous DMF or Me_2SO were purchased from Burdick and Jackson Laboratories. The acetone, acetonitrile, and ethanol used were reagent grades. The THF used was freshly distilled from sodium benzophenone ketyl. The triethylamine was used as purchased from Eastman. A sample of di-*p*-tolyl disulfide was also purchased from Eastman. The thiophenol derivatives were obtained from commercial sources.

Preparation of Nitro- and Halophthalimides. The majority of nitro- and halophthalimides were prepared as has previously been described[1] by reacting the substituted phthalic anhydride with the desired amine derivatives. The 4-nitro-*N*-methylphthalimide derivative was prepared by nitration of *N*-methylphthalimide.[13] The 3- and 4-nitrophthalimides were purchased from Eastman.

Displacement Reactions—Different Base Systems. In general, the displacements were run by stirring the desired thiophenol and base (or performed thiophenoxide) with **1** and solvent under nitrogen. The reactions were followed by VPC analysis and the products were isolated by addition of the reaction mixture to a 1.2 N HCl/ice mixture followed by filtration. The crude products were recrystallized from ethanol. Analytical data for the compounds **2** are contained in Table I, and ^{13}C NMR shifts are in Table VI (see supplementary material). Specific details for the various methods are given below as well as one detailed example.

(A) Sodium Hydroxide Azeotrope. A mixture of the thiophenol, 50% aqueous sodium hydroxide, Me_2SO, and benzene was heated at reflux under nitrogen while the water was azeotropically removed with the aid of a Dean–Stark trap. After 8 h of reflux, the benzene was removed by distillation and the reaction mixture was cooled to 25 °C. To this mixture was then added the desired imide **1**.

(B) Sodium Methoxide Preformed. The preformed salt of 4-methylthiophenol (Aldrich) was prepared exactly as has been described for 4-methylphenol.[1]

(C) Triethylamine. A mixture of 1.26 g of *p*-hydroxythiophenol (Crown Zellerbach), 2.68 g of 3-nitro-*N*-phenylphthalimide, and 25 mL of DMF was stirred under a nitrogen atmosphere at 25 °C. To this mixture was added 1.40 mL of triethylamine with the aid of a syringe. The color of the solution immediately changed from light yellow to red and then slowly it changed back to light yellow. After 15 min the reaction mixture was added to 1.2 N HCl/ice and **2c** was collected to give 3.35 g (96%) after drying. A sample was recrystallized from ethanol for analytical purposes. In addition to the analytical data presented in Tables II and III, an infrared spectra showed an absorption at 3500 cm^{-1} characteristic of a phenol.

Displacement Reactions—Different Solvents. Besides DMF and Me_2SO, displacement reactions were also run in THF, EtOH, CH_3CN, acetone, and methylene chloride. All of these reaction mixtures were worked up by addition to water followed by filtration of the product, except for methylene chlroide. When methylene chloride was the solvent, the reaction mixture was washed with water and the methylene chloride layer was dried and concentrated to give the desired product. A typical reaction procedure is presented below.

THF 4-NO_2 Isomer. A mixture of 1.34 g of 4-nitro-*N*-phenylphthalimide, 0.80 g of sodium 4-methylthiophenoxide, and 15 mL of THF was heated at reflux under a nitrogen atmosphere for 43 h. Aliquots were removed at 3, 19, and 43 h and analysis indicated an ca. 50% yield of **2**. There was little difference in analysis of the 3- and 43-h point. The VPC analysis indicated large amounts of the disulfide and unreacted nitroimide.

Two-Phase Reaction. A mixture of 2.06 g of 3-nitro-*N*-methylphtahlimide, 1.24 g of 4-methylthiophenol, 0.80 g of 50% aqueous sodium hydroxide, 50 mL of H_2O, 50 mL of methylene chloride, and 0.50 g of Adogen 464 (phase-transfer catalyst from Aldrich) was stirred using a Vibro Mix stirrer. The mixture was kept at room temperature but was not blanketed with a nitrogen atmosphere. After 2 h the stirrer was stopped and an aliquot was removed from the methylene chloride layer. In addition, another aliquot was removed from both the methylene chloride and aqueous layers. Workup of both aliquots and analysis by VPC showed ~80% of 3-*p*-methylthiophenoxy-*N*-methylphthalimide, ~10% of the nitroimide, and ~10% of the disulfide **6**. Extraction of the methylene chloride solutions with aqueous sodium bicarbonate did not alter the product composition, indicating that indeed the materials present were imides and not amide acids which ring closed upon analysis. Further reaction time up to 10 h did not alter the product composition.

Competition Experiments: Reactivity of Nitro or Halo Derivatives toward Displacements by Sodium *p*-methylthiophenoxide. An arbitrary amount of anhydrous sodium 4-methylthiophenoxide was accurately weighed into a flask under nitrogen. An equivalent molar amount of each of the two compounds being studied and an internal standard (*o*-terphenyl) were then dissolved in enough Me_2SO to make a solution containing 10% solids. An aliquot was removed from this solution and added to a mixture of 1.2 N HCl and methylene chloride. After vigorous shaking, the methylene chloride layer was removed and dried, and this solution was then used to determine the composition of the starting mixture. The Me_2SO solution was then added to the sodium 4-methylthiophenoxide and this mixture was stirred under a nitrogen atmosphere at room temperature. After 1 h, an aliquot was removed and worked up as described above. The solutions were then subjected to VPC analysis, and the peak area for each compound was determined. From these measurements and the analysis of the starting mixture, the percentage of reaction for each material was determined and then, using the equation presented by Huisgen,[14] the relative rates of reactivity were calculated. Similar reactions were run in which 4-methylthiophenol/triethylamine were used in place of sodium 4-methylthiophenoxide.

Reactivity of Sodium Phenoxide and Sodium 4-Methylthiophenoxide (3) with Substituted Phthalimide Derivatives. Equal molar amounts of **3** and sodium phenoxide were weighed out under nitrogen and were dissolved in enough DMF (Me_2SO does not give a homogeneous solution) to make a solution containing 10% solids. To this solution was then added an equal molar amount of the desired imide **1** and the reaction was run at 25 °C under nitrogen for 1 h. An aliquot was removed and analyzed as described above. The areas of each product peak were determined and corrected for response differences. From these measurements the relative rates of reactivity were calculated.[13]

Formation of Disulfides. Response factors were determined for di-*p*-tolyl disulfide, and the silylated product of 4-methylthiophenol and BSA. VPC analysis was done using a 150 to 300 °C at 20 °C/min program. In a typical run, a mixture of 0.68 g of 4-methylthiophenol, 0.8357 g of *o*-terphenyl, 0.35 g of sodium nitrite, and 15 mL of DMF was stirred at room temperature under a nitrogen atmosphere. Aliquots were removed at timed intervals and worked up by addition to a CH_2Cl_2/1.2 N HCl or CH_2Cl_2/H_2O mixture. The organic phases were dried and BSA (Aldrich) was added. The resulting solution was analyzed by VPC.

Acknowledgments. We thank H. M. Relles for his many helpful discussions concerning this work and E. A. Williams and J. D. Cargioli for their help in obtaining and interpreting the ^{13}C spectra.

Registry No.—**1**, R = H; X = 4-NO_2, 89-40-7; **1**, R = H; X = 3-NO_2, 603-62-3.

Supplementary Material Available. ^{13}C NMR assignments for all new thiophenoxy-substituted phthalimides (**2**) (3 pages). Ordering information is given on any current masthead page.

References and Notes

(1) F. J. Williams and P. E. Donahue, *J. Org. Chem.*, **42,** 3414 (1977).

(2) F. J. Williams, H. M. Relles, J. S. Manello, and P. E. Donahue, *J. Org. Chem.*, **42,** 3419 (1977).

(3) F. J. Williams, H. M. Relles, J. S. Manello, and P. E. Donahue, *J. Org. Chem.*, **42,** 3425 (1977).

(4) (a) A. J. Parker, in "Organic Sulfur Compounds", Vol. 1, N. Kharasch, Ed., Chapter 11. (b) J. F. Bunnett and W. D. Merritt, *J. Am. Chem. Soc.*, **79,** 5967 (1957). (c) J. F. Bunnett and G. T. Davis, *ibid.*, **80,** 4337 (1958). (d) M. E. Peach, in "The Chemistry of the Thiol Group", S. Patai, Ed., Chapter 15, p 735.

(5) See Reference 4a, page 107.

(6) Some of this work is contained in D. R. Heath and F. J. Williams, U.S. Patent 3 922 284, Nov. 25, 1975.

(7) The ease with which the displacement reaction between 4-methylthiophenol and the phthalimide derivatives (**1**) occurred when carbonate was used as the base suggested that the reaction might also be effected by passing reactants over a basic support contained in a column, providing that the contact time was of sufficient length. A mixture of **1** (R = CH_3; X = 3-NO_2) and 4-methylthiophenol was dissolved in DMF and the solution was passed through a column packed with potassium carbonate. Addition of this DMF solution to water resulted in the isolation of an 89% yield of the desired product **2** (R = CH_3; Y = CH_3). In a similar fashion, a mixture of **1** (R = CH_3; X = 3-NO_2), 4-methylthiophenol, and DMF was passed through a column of Woelm Basic Alumina to give an 85% yield of **2.**

(8) The reaction in which nitrite functions as a base and the reaction with no added base may be specific for derivatives of **1** where X = 3-NO_2. The 4-NO_2 derivatives are much slower toward displacement than the 3-isomers and may not be reactive under these conditions.

(9) See Reference 4a, page 103.

(10) See Reference 4d, G. Capozzi and G. Modena, Chapter 17, p 795.

(11) The oxidation of thiols by nitrobenzene is known. See Reference 4d, Chapter 17, page 800.

(12) The oxidation of thiols is reported to be catalyzed by amines. See Reference 4d, Chapter 17, page 816.

(13) J. Tirouflet and R. Dabard, *C. R. Uebd. Seances Acad. Sci.*, 916 (1956); R. Dabard and J. Tirouflet, *Bull. Soc. Chim. Fr.*, 565 (1957). See also F. J. Williams and P. E. Donahue, submitted for publication in *J. Org. Chem.*

(14) See Reference 1 and U. Burger and R. Huisgen, *Tetrahedron Let.*, **35,** 3057 (1970).