92. Aromatic Nucleophilic Substitution

Part 1

Regiospecific Substitution of the Nitro Groups in 3,5-Dinitrophthalic-Acid Derivatives[1])

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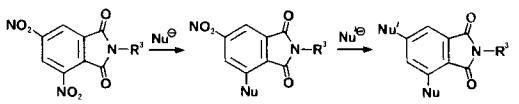
The regioselectivity of nucleophilic substitution of the nitro groups in 3,5-dinitrophthalic anhydrides and 3,5-dinitrophthalimides *(Scheme)* with a variety of nucleophiles (Nu^-) was studied. In all cases, the 3-nitro group was selectively substituted. With excess of the same nucleophilic reagent or with other nucleophiles, the 5-nitro group could subsequently be replaced.

1. Introduction. – The nucleophilic substitution of aromatic nitro groups has attracted increasing attention in recent years [1] for both theoretical [2] and synthetic [3] reasons. The possibility to run such reactions in dipolar aprotic media in high concentrations, with short reaction times, and excellent yields has prompted their introduction into industrial processes. Thus, the substitution reactions of 3- and 4-nitrophthalic-acid derivatives with phenolates and thiophenolates (to give intermediates for the preparation of polymers with excellent properties) have been thoroughly studied [4] *(Scheme)*. We recently used

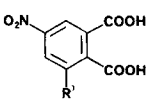
Scheme



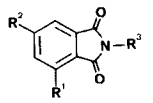
some of these intermediates, *e.g.* 3-(phenylthio)phthalic anhydride (**3a**), to prepare 9-oxo-9*H*-thioxanthene-1-carboxylic-acid derivatives **4** which proved to be excellent photosensitizers and photoinitiators for industrial applications [5]. We have now extended this study to 3,5-dinitrophthalic-acid (**1a**) derivatives and report here our results on the regioselectivity of the substitution reactions with N-, O- and S-nucleophiles and bromide ion.

2. Results. – a) *Substitutions with Thiols and Thiophenols.* The dinitrophthalimides **2a–c** reacted under a variety of conditions with thiols and thiophenols to give the 3-substituted products **2d**, **2f–h**, **5**, and **6** in good yields. With excess reagents, the 3,5-disubstituted products (**2e**, **2i**) were formed. The results are summarized in *Table 1*.

[1]) Presented in part at the Herbstversammlung der Schweizerischen Chemischen Gesellschaft, Berne, October, 1981.

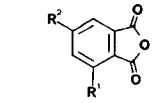


1a $R^1 = NO_2$
b $R^1 = C_6H_5S$

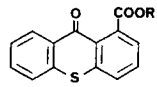


	R^1	R^2	R^3
2a	NO_2	NO_2	H
b	NO_2	NO_2	*p*-tolyl
c	NO_2	NO_2	CH_3
d	C_2H_5S	NO_2	CH_3
e	C_2H_5S	C_2H_5S	CH_3
f	n-$C_{10}H_{21}S$	NO_2	CH_3
g	C_6H_5S	NO_2	H
h	C_6H_5S	NO_2	*p*-tolyl
i	C_6H_5S	C_6H_5S	*p*-tolyl
k	CH_3SO_2	NO_2	*p*-tolyl

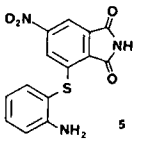
	R^1	R^2	R^3
2l	$C_6H_5SO_2$	NO_2	*p*-tolyl
m	$C_6H_5SO_2$	$C_6H_5SO_2$	*p*-tolyl
n	$C_{10}H_{21}S$	$C_6H_5SO_2$	CH_3
o	$CH{\equiv}CCH_2O$	NO_2	*p*-tolyl
p	(*p*-tolyl)O	NO_2	CH_3
q	OH	NO_2	*p*-tolyl
r	N_3	NO_2	CH_3
s	N_3	N_3	CH_3
t	Br	NO_2	*p*-tolyl



3a $R^1 = C_6H_5S$; $R^2 = H$
b $R^1 = R^2 = NO_2$
c $R^1 = C_6H_5S$; $R^2 = NO_2$
d $R^1 = p$-$CH_3C_6H_4S$; $R^2 = NO_2$
e $R^1 = p$-$CH_3OC_6H_4S$; $R^2 = NO_2$
f $R^1 = p$-$CH_3C_6H_4O$; $R^2 = NO_2$



4 R = H, alkyl



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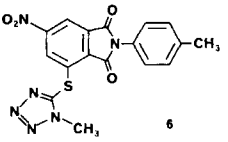

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Table 1. *Substitution of Nitrophthalimides with Thiols and Thiophenols*

Starting material	Reagent	Solvent	Base	Product	Yield[a] [%]
2c	C_2H_5SH	AcOEt	AcONa	**2d**	45
2c	C_2H_5SH	DMF	K_2CO_3	**2e**	82
2c	$C_{10}H_{21}SH$	AcOEt	[b]	**2f**	77
2a	C_6H_5SH	AcOEt	K_2CO_3	**2g**	90
2b	C_6H_5SH	CH_2Cl_2/H_2O[c]	AcONa	**2h**	95
2b	C_6H_5SH	DMSO	–	**2h**	90
2h	C_6H_5SH	DMSO	[b]	**2i**	91
2a	*o*-$NH_2C_6H_4SH$	AcOEt	AcONa	**5**	99
2a	1-Methyltetrazol-5-thiol	DMSO	[b]	**6**	58

[a]) Yield of isolated, pure product; see *Exper. Part* for details.
[b]) With preformed sodium salt.
[c]) With addition of benzyltriethylammonium chloride.

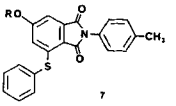
These favourable results with phthalimides prompted us to try the substitution reactions with 3,5-dinitrophthalic anhydride (**3b**) in order to avoid the subsequent hydrolysis to the substituted anhydride. From the literature [4b] it was known that 3-halophthalic anhydrides react with sodium thiophenolates, whereas the reaction with 3-nitrophthalic anhydride was much less satisfactory due to side reactions produced by the nitrite leaving group, *e.g.* attack on the anhydride function or oxidation of the thiophenolate to the corresponding disulfide. Similarly in our case the reactions with dinitrophthalic anhydride **3b** did not proceed satisfactorily. In an attempt to remove the nitrite ion as quickly as possible from the reaction mixture, we used a phase-transfer-catalysed two-phase system [6] (CH_2Cl_2/H_2O). Under these conditions, moderate yields of the substitution products **3c–e** could be obtained from **3b** with thiophenol, *p*-thiocresol, and *p*-methoxythiophenol. The yields could be somewhat improved by the addition of Ac_2O which served to protect the anhydride against hydrolysis.

b) *Substitutions with Sulfinates.* The dinitroimide **2b** reacted with an excess of sodium methanesulfinate in 1,2-dimethoxyethane exclusively at the 3-position to give **2k**. With sodium benzenesulfinate, both mono-adduct **2l** and bis-adduct **2m** could be isolated in

good yields depending on stoichiometry and reaction conditions. Even the less reactive 3-alkylthio-5-nitrophthalimide **2f** reacted with sodium benzenesulfinate to give **2n**.

c) *Substitutions with Alcohols, Phenols, and Acetate.* With aliphatic alcoholates, the dinitroimides **2a–c** did not give satisfactory results. Only propargyl alcohol gave a regioselective substitution to give **2o** from **2b** in moderate yield. With sodium *p*-cresolate, the reaction with the dinitroimide **2c** proceeded smoothly to give the *p*-tolyloxy derivative **2p**. By contrast, the 5-nitro-3-(phenylthio)phthalimide **2h** reacted smoothly with different primary and secondary sodium alcoholates and sodium phenolate in DMSO to give compounds **7** (see *Table 2*). It appears therefore that the difficulties with dinitroimides and alcoholates are due to the 3-nitro group, perhaps to its activating effect on the neighbouring carbonyl group.

Table 2. *Substitution Reactions of* **2h** *with Sodium Alcoholates and Phenolate in DMSO (25°, 1 h) Yielding* **7**



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Product	R	Yield [%]	m.p. (solvent of recrystallisation)
7a	CH_3[a])	84	166–8° (toluene/cyclohexane)
7b	C_2H_5	41	155–7° (CH_3CN)
7c	$(CH_3)_2CH$	83	174–6° (toluene)
7d	CH_2=$CHCH_2$[b])	55	132–5° (C_2H_5OH)
7e	HC≡CCH_2	43	195–7° (CH_3CN)
7f	C_6H_5	55	156–8° (CH_3CN)

[a]) See *Exper. Part* for a representative procedure.

[b]) One equiv. of $NaOCH_3$ was dissolved in allyl or propargyl alcohol and the mixture evaporated to ½ volume before diluting with DMSO *(dry sodium propargyloxide proved to be pyrophoric)*.

The dinitroimide **2b** was smoothly and regioselectively substituted by NaOAc in DMSO to give the hydroxy compound **2q**. This reaction occurred also with $NaHCO_3$, Na_2CO_3, K_2CO_3, and $NaNO_2$ at room temperature, and thus indicates the high reactivity of the 3,5-dinitrophthalimide system towards nucleophilic substitution.

d) *Substitutions with Sodium Azide.* The dinitroimide **2c** gave, depending on stoichiometry and reaction conditions, either regiospecifically the mono-azide **2r** or the bis-azide **2s**.

e) *Substitution with Lithium Bromide.* The dinitroimide **2b** reacted with LiBr in CH_3CN under pressure to give regiospecifically the bromide adduct **2t** (for a similar reaction, see [7]).

3. Discussion. – The 3,5-dinitrophthalic anhydrides and 3,5-dinitrophthalimides are highly reactive towards aromatic nucleophilic substitutions. In all cases studied here, the first nucleophilic substitution occurs exclusively at the sterically more hindered 3-position. This behaviour parallels the higher reactivity of 3-nitro- *versus* 4-nitrophthalic-acid derivatives [4a] [4b]. This striking reactivity difference cannot be explained readily. Molecular models show that, because of steric hindrance, the 3-nitro group cannot be coplanar with the benzene ring. Thus, the conjugation with the aromatic π-system is

partly or totally interrupted, and the C–N bond must be somewhat lengthened and weakened. Consequently, the attack of the nucleophile at the 3-position is favoured by *m*-activation by the 5-nitro group (in addition to the imide function), whereas the 5-nitro group is less or not at all activated by the 3-nitro group.

Similar high regioselectivities were recently reported by *Stirling* and coworkers using dinitro-alkylbenzenes as activated aromatic nuclei and lithium thiolates as nucleophiles [8].

A variety of the novel 3,5-disubstituted phthalic-acid derivatives reported here having λ_{max} in the range of 350–390 nm have useful properties as triplet photosensitizers [9]. In the following paper, we describe the use of these 3,5-disubstituted phthalic acid derivatives as intermediates for the synthesis of a range of thioxanthones.

The technical assistance of Miss *K. Fluri* is gratefully acknowledged.

Experimental Part

1. General Remarks. – M.p. are corrected. IR spectra: absorptions in cm^{-1}. ^{1}H-NMR spectra: chemical shifts in ppm relative to tetramethylsilane (= 0 ppm); coupling constants in Hz. UV spectra: generally $CHCl_3$ as solv.; only the absoption with the longest wavelength is given: λ_{max} in nm (ε_{max}). Sodium salts of phenols and thiols were prepared by dissolving the compound in 1.00 equiv. of 1.00N NaOH, evaporating the solution to dryness, and finally evaporating twice with toluene or xylene (azeotropes).

2. Preparation of 3,5-Dinitrophthalic-Acid Derivatives. – The 3,5-dinitrophthalic acid (**1a**) [10], 3,5-dinitrophthalic anhydride (**3b**) [11] and 3,5-dinitrophthalimide (**2a**) [12] were prepared according to known procedures.

N-Methyl-3,5-dinitrophthalimide (**2c**). *Method A.* The mixture of **1a** (51.22 g, 0.2 mol) and *N,N'*-dimethylurea (8.81 g, 0.1 mol), intimately ground together, was slowly and carefully heated in an open vessel to 180°. The resulting dark transparent melt was held at 180° for further 6 h and then heated to 200° for 1 h. The mixture was cooled, dissolved in CH_2Cl_2/THF, some insoluble material filtered off, and the filtrate evaporated. On recrystallisation from THF-cyclohexane, 42.37 g (84%) of **2c** were obtained, mp. 178–80°. **Warning**: *It is not advisable to repeat this experiment on a larger scale or to heat the reaction mixture too fast or above 200°, since an exothermic decomposition of the dinitro compounds might occur.*

Method B. To a refluxing soln. of **3b** (238.11 g, 1 mol) in 1 l of xylene, *N*-methylformamide (62.02 g, 1.05 mol) was added dropwise over 30 min. After 18 h at reflux, the mixture was concentrated (H_2O and HCOOH being distilled off) until a b.p. of 137° was reached, and the soln. was filtered while hot. From the filtrate, 209.42 g (83%) of **2c** separated out, m.p. 178–80°. IR (CH_2Cl_2): 1805, 1755 (C=O, imide); 1565, 1355 (NO_2). ^{1}H-NMR ($CDCl_3$/(D_6)DMSO): 9.00 (*d*, *J* = 2, H–C(4)); 8.80 (*d*, *J* = 2, H–C(6)); 3.22 (3 *s*, CH_3). Anal. calc. for $C_9N_5N_3O_6$ (251.15): C 43.04, H 2.01, N 16.73; found: C 43.40, H 2.00, N 16.50.

3,5-Bis(ethylthio)-N-methylphthalimide (**2e**). A mixture of **2c** (20 g, 79.6 mmol), ethanethiol (11.4 ml), K_2CO_3 (47 g) and DMF (200 ml) was stirred for 4 h at 25°. The excess of ethanethiol was removed by a stream of dry N_2. The mixture was evaporated at 80° *in vacuo* and the residue acidified with 2N HCl. The suspension was extracted with CH_2Cl_2, the extracts washed with brine, dried over Na_2SO_4, and evaporated. Recrystallisation from cyclohexane gave 18.4 g (82%) of **2e**, m.p. 97–9°. UV: 378 (4400). IR (CH_2Cl_2): 1760, 1705 (C=O, imide). ^{1}H-NMR ($CDCl_3$): 7.35 (*d*, *J* = 2, 1H), 7.22 (*d*, *J* = 2, 1H; H–C(4), H–C(6)); 3.12 (*s*, CH_3N); 3.06 (*q*, *J* = 8, 2 CH_3CH_2S); 1.46, 1.42 (2*t*, *J* = 8, 2 CH_3CH_2S). Anal. cal. for $C_{13}H_{15}NO_2S_2$ (281.39): C 55.49, H 5.37, N 4.98, S 22.79; found: C 55.52, H 5.34, N 5.09, S 22.56.

3-Decylthio-N-methyl-5-nitrophthalimide (**2f**). A mixture of **2c** (20.0 g, 79.6 mmol), sodium decanethiolate (21 g, 107 mmol), and AcOEt (100 ml) was stirred for 3 h at 25°. The mixture was evaporated at reduced pressure, and the residue acidified and extracted into CH_2Cl_2. The org. extracts were washed with brine, dried over anh. Na_2SO_4, and evaporated. Recrystallisation from Et_2O/CH_3OH gave 23.34 g (77%) of **2f**, m.p. 78–81°. UV: 410 (3000). IR (CH_2Cl_2): 1800, 1730 (C=O, imide); 1555, 1360 (NO_2). ^{1}H-NMR ($CDCl_3$): 8.20 (*s*, H–C(4), H–C(6)); 3.19 (*s*, CH_3N); 3.10 (*t*, *J* = 7, CH_2S); 0.9–2.0 (*m*, 19H, CH_2, CH_3). Anal. calc. for $C_{19}H_{26}N_2O_4S$ (378.49): C 60.29, H 6.92, N 7.40, S 8.47; found: C 60.28, H 6.71, N 7,39, S 8.19.

5-Nitro-3-(phenylthio)phthalimide (**2g**). A mixture of **2a** (45.29 g, 191 mmol), K_2CO_3 (83.3 g, 603 mmol), and AcOEt (450 ml) was cooled with stirring to 10°, and thiophenol (22.1 g, 200 mmol) was added in portions. The mixture was stirred at 25–30° for 30 min, then diluted with CH_2Cl_2, washed with 2N HCl and brine, and the org. extract dried over anh. Na_2SO_4 and evaporated. Recrystallisation from toluene gave 51.51 g (90%) of **2g**, m.p. 213–4°. UV: 298 (3440). IR (CH_2Cl_2): 1810, 1770 (C=O, imide); 1560, 1360 (NO_2); 3420 (NH). ^{1}H-NMR ($CDCl_3$): 11.3 (br. *m*, NH); 8.11 (*d*, *J* = 2, H–C(6)); 7.60 (*d*, *J* = 2, H–C(4)); 7.47 (*m*, C_6H_5S). Anal. calc. for $C_{14}H_8N_2O_4S$ (300.29): C 56.00, H 2.69, N 9.33, O 21.31, S 10.68; found: C 55.49, H 2.88, N 9.56, O 21.42, S 10.45.

5-Nitro-3-(phenylthio)-N-(p-tolyl)phthalimide (**2h**). *Method A.* A mixture of 3,5-dinitro-*N*-(*p*-tolyl)phthalimide (**2b**; 820 mg, 2.5 mmol), thiophenol (330 mg, 3 mmol), and benzyltriethylammonium chloride (29 mg, 0.125 mmol) was dissolved in CH_2Cl_2 (15 ml). With vigorous stirring, a soln. of NaOAc (492 mg, 6 mmol) in 4 ml of H_2O was added and the stirring maintained for 20 min. The mixture was diluted with H_2O, the org. layer separated and washed successively with 2N NaOH, then brine, dried over Na_2SO_4 and evaporated. Recrystallisation from toluene gave 930 mg (95%) of **2h**, m.p. 207–9°.

Method B. To a soln. of **2b** (49 g, 0.15 mmol) in DMSO (500 ml), thiophenol (22.5 g, 0.204 mmol) was added with slight cooling (22–23°) during 10 min (evolution of nitrogen oxides). After 30 min at 25°, the mixture was warmed for 4 h at 45°, then cooled and added to 1 l of ice-water. The precipitate was separated, washed with H_2O, and dried *in vacuo*. Recrystallisation from toluene gave 52.2 g (90%) of **2h**, m.p. 208–9°. UV: 402 (4140). IR (CH_2Cl_2): 1790, 1735 (C=O, imide); 1555, 1350 (NO_2). ^{1}H-NMR ($CDCl_3$/(D_6)DMSO): 8.27 (*d*, *J* = 2, H–C(6)); 7.8–7.6 (tot. 7H, C_6H_5S, and H–C(4)); 7.34 (*m*, C_6H_4-(*p*)); 2.42 (*s*, CH_3). Anal. calc. for $C_{21}H_{14}N_2O_4S$ (390.40): C 64.61, H 3.62, N 7.18, S 8.21; found: C 64.30, H 3.81, N 7.32, S 8.45.

3,5-Bis(phenylthio)-N-(p-tolyl)phthalimide (**2i**). A mixture of **2h** (3.9 g, 10 mmol), sodium thiophenolate (1.4 g, 10 mmol), and DMSO (80 ml) was stirred for 1 h at 25°. The mixture was partitioned between H_2O and $CHCl_3$, the org. extract washed with H_2O and brine, dried over $MgSO_4$, and evaporated. Recrystallisation from toluene gave 4.1 g (91%) of **2i**, m.p. 279–80°. UV: 376 (5600). Anal. calc. for $C_{27}H_{19}NO_2S_2$ (453.57): C 71.50, H 4.22, N 3.09, S 14.14; found: C 71.30, H 4.40, N 3.20, S 14.00.

3-(o-Aminophenylthio)-5-nitrophthalimide (**5**). A mixture of **2a** (4.74 g, 20 mmol), NaOAc (5.17 g, 63 mmol), *o*-aminothiophenol (2.63 g, 21 mmol), AcOEt (80 ml), and THF (20 ml) was stirred at 25° for 18 h. The mixture was diluted with THF (30 ml), toluene (60 ml), and H_2O (100 ml). The org. layer was separated, washed with $NaHCO_3$ soln., then brine, dried over Na_2SO_4, and evaporated. Recrystallisation from AcOEt/hexane gave 6.25 g (99%) of **5**, m.p. 210–227° (turns yellow above 100°). UV: 386 (3400). IR (CH_2Cl_2): 3390 (NH, NH_2); 1805, 1765 (C=O, imide); 1560, 1365 (NO_2). ^{1}H-NMR ($CDCl_3$/$(CD_3)_2SO$): 11.25 (br. *s*, NH); 8.08 (*d*, *J* = 2, H–C(6)); 7.53 (*d*, *J* = 2, H–C(4)); 7.4–6.5 (*m*, C_6H_4); 4.6 (br. *s*, NH_2). Anal. calc. for $C_{14}H_9N_3O_4S$ (315.30): C 53.33, H 2.88, N 13.33, S 10.17; found: C 53.27, H 3.03, N 13.34, S 9.88.

3-(1'-Methyltetrazol-5'-yl)thio-5-nitro-N-(p-tolyl)phthalimide (**6**). A mixture of **2b** (655 mg, 2 mmol), sodium 1-methyltetrazol-5-thiolate (304 mg, 2.2 mmol), and DMSO (4 ml) was stirred at 25° for 18 h. The mixture was taken up in H_2O (30 ml), the precipitate separated, washed with H_2O, and dissolved in CH_2Cl_2/H_2O. The org. extracts were washed with brine, dried, and evaporated. Recrystallisation from toluene gave 460 mg (58%) of **6**, m.p. 215–8° (dec.). UV: 360 (2720). IR ($CHCl_3$): 1790, 1730 (C=O, imide); 1550, 1345 (NO_2). ^{1}H-NMR ($CDCl_3$/$(CD_3)_2SO$): 8.49, 8.42 (2*d*, *J* = 1.5, H–C(4), H–C(6)); 7.29 (*m*, C_6H_4); 4.16 (*s*, CH_3N); 2.44 (*s*, CH_3Ar). Anal. calc. for $C_{17}H_{12}N_6O_4S$ (396.38): C 51.51, H 3.05, N 21.20, S 8.09; found: C 51.94, H 3.08, N 20.72, S 7.73.

5-Nitro-3-(phenylthio)phthalic Anhydride (**3c**). To a soln. of **3b** (5 g, 21 mmol) in THF (17 ml), thiophenol (2.78 g, 25.2 mmol) and Ac_2O (4.3 g, 42 mmol) were added. This soln. was added, with vigorous stirring, to a mixture of 30% NaOH (22.4 g) soln., benzyltriethylammonium chloride (47.8 mg, 0.21 mmol), and CH_2Cl_2 (100 ml). After 2 h of stirring, the mixture was diluted with H_2O, the aq. layer separated, acidified, and extracted with CH_2Cl_2. The extracts were dried and evaporated. The residue was heated with Ac_2O in toluene, the resulting soln. evaporated, and the crude product recrystallised from CH_2Cl_2/pentane to give 2.57 g (41%) of **3c**, m.p. 167–9°. UV: 400 (3040). IR (CH_2Cl_2): 1855, 1790 (C=O, anhydride); 1550, 1345 (NO_2). ^{1}H-NMR ($CDCl_3$): 8.31 (*d*, *J* = 2, H–C(6)); 7.74 (*d*, *J* = 2, H–C(4)); 7.57 (*m*, C_6H_5). Anal. calc. for $C_{14}H_7NO_5S$ (301.27): C 55.82, H 2.34, N 4.65, S 10.64; found: C 55.80, H 2.40, N 4.70, S 10.50.

5-Nitro-3-(p-tolylthio)phthalic Anhydride (**3d**). A mixture of **1a** (46.05 g, 180 mmol), Ac_2O (26 g, 250 mmol), and toluene (210 ml) was heated to reflux for 1 h, filtered while hot, and the filtrate evaporated. The residue **3b** was dissolved in CH_2Cl_2 (4.6 l) and *p*-thiocresol (27.4 g, 221 mmol) and Ac_2O (34.7 g, 340 mmol) added. This soln. was added slowly, with vigorous stirring, to a soln. of benzyltriethylammonium chloride (1.9 g, 8.5 mmol) in 50% KOH soln. (190.4 g) during 135 min. After further 90 min of stirring, the mixture was acidified. H_2O and acetone were added to obtain 2 clear phases, and the org. phase was separated, dried, and evaporated. The whole procedure was repeated with the use of Ac_2O (36.7 g) in 200 ml of toluene, then with Ac_2O (21.8 g, 214 mmol), *p*-thiocresol (19.9

g, 161 mmol), benzyltriethylammonium chloride (2.4 g), and 30% NaOH soln. (285 g). The resulting residue was heated with Ac_2O (52.1 g) and toluene (500 ml). Recrystallisation from CH_2Cl_2/pentane gave 20.83 g (39%) of **3d**, m.p. 180–2°. UV: 404 (3600). IR (CH_2Cl_2): 1840, 1770 (C=O, anhydride); 1540, 1340 (NO_2). ^{1}H-NMR ($CDCl_3$): 8.19 (*d*, *J* = 2, H–C(6)); 7.68 (*d*, *J* = 2, H–C(4)); 7.5–7.05 (A_2B_2, C_6H_4); 2.31 (*s*, CH_3). Anal. calc. for $C_{15}H_9NO_5S$ (315.30): C 57.14, H 2.88, N 4.44, S 10.17; found: C 57.30, H 3.00, N 4.50, S 10.10.

*3-(*p*-Methoxyphenylthio)-5-nitrophthalic Anhydride* (**3e**). A soln. of **3b** (12.17 g, 51.1 mmol), 4-methoxythiophenol (10.7 g, 76.6 mmol), and Ac_2O (10.2 g, 100 mmol) in 1350 ml of CH_2Cl_2 was added dropwise, with vigorous stirring, to a soln. of benzyltriethylammonium chloride (1.2 g) in 33% KOH soln. (68.6 g, 408 mmol) and CH_2Cl_2 (50 ml). After 2 h, the mixture was acidified and extracted with CH_2Cl_2. The extracts were dried and evaporated, and the residue heated to reflux with Ac_2O (5.3 g) in toluene (100 ml). The soln. was filtered while hot and evaporated. The residue was extracted several times with boiling cyclohexane from which 5.15 g (31%) of **3e** crystallised, m.p. 143–8°. IR (CH_2Cl_2): 1840, 1780 (C=O, anhydride); 1540, 1335 (NO_2). ^{1}H-NMR ($CDCl_3$): 8.29 (*d*, *J* = 2, H–C(6)); 7.76 (*d*, *J* = 2, H–C(4)); 7.6–6.9 (A_2B_2, C_6H_4); 3.90 (*s*, CH_3O). Anal. calc. for $C_{15}H_9NO_6S$ (331.30): C 54.38, H 2.74, N 4.23, S 9.68; found: C 54.40, H 2.90, N 4.30, S 9.50.

3. Substitutions with Sulfinates. – *3-Methylsulfonyl-5-nitro-*N-(p-*tolyl)phthalimide* (**2k**). A mixture of **2b** (1.64 g, 5 mmol), sodium methanesulfinate [13] (1.02 g, 10 mmol), and 1,2-dimethoxyethane (15 ml) was stirred together at 50° for 6 h. The mixture was evaporated *in vacuo*, the residue dissolved in CH_2Cl_2/H_2O and the org. extracts washed with sat. $NaHCO_3$ soln., dried over Na_2SO_4, and evaporated. Recrystallisation from CH_3CN/toluene gave 1.70 g (94%) of **2k**, m.p. 230–2°. IR ($CHCl_3$): 1798, 1740 (C=O, imide); 1560, 1355 (NO_2); 1380, 1340, 1175, 1145, 1135 (SO_2). ^{1}H-NMR ($CDCl_3/(CD_3)_2SO$): 9.03 (*d*, *J* = 2, H–C(4)); 8.94 (*d*, *J* = 2, H–C(6)); 7.28 (*m*, C_6H_4); 3.50 (*s*, CH_3CO_2); 2.41 (*s*, CH_3Ar). Anal. calc. for $C_{16}H_{12}N_2O_6S$ (360.34): C 53.33, H 3.36, N 7.78, S 8.90; found: C 52.96, H 3.46, N 7.66, S 8.84.

*5-Nitro-3-(phenylsulfonyl)-*N-(p-*tolyl)phthalimide* (**2l**). A mixture of **2b** (3.27 g, 10 mmol), sodium benzenesulfinate (1.81 g, 11 mmol) and DMSO (15 ml) was stirred together at 25° for 6 h. Then 200 ml of H_2O were added, and the mixture was stirred for 1 h. The precipitate was filtered, washed with H_2O, and dissolved in CH_2Cl_2. The org. phase was washed with brine, dried over Na_2SO_4, and evaporated. Recrystallisation from toluene gave 3.70 g (88%) of **2l**, m.p. 262–6°. IR ($CHCl_3$): 1795, 1730 (C=O, imide); 1545, 1345 (NO_2); 1380, 1330, 1170 (SO_2). ^{1}H-NMR ($CDCl_3$): 9.14 (*d*, *J* = 2, H–C(4)); 8.63 (*d*, *J* = 2, H–C(6)); 8.2–7.9, 7.5–7.2 (2*m*, $C_6H_5SO_2$); 7.10 (*s*, C_6H_4); 2.20 (*s*, CH_3). Anal. calc. for $C_{21}H_{14}N_2O_6S$ (422.41): C 59.71, H 3.34, N 6.63, S 7.59; found: C 59.80, H 3.43, N 6.60, S 7.66.

*3,5-Bis(phenylsulfonyl)-*N-(p-*tolyl)phthalimide* (**2m**). A mixture of **2b** (1.64 g, 5 mmol), sodium benzenesulfinate (1.97 g, 12 mmol), and DMSO (20 ml) was stirred at 25° for 2 days after which the mixture was added with stirring to H_2O (200 ml). The precipitate was filtered off, washed with H_2O and dissolved in CH_2Cl_2/acetone. The org. extract was dried over Na_2SO_4 and evaporated. Recrystallisation from acetone/CH_3CN gave 2.32 g (90%) of **2m**, m.p. 150–4°. IR (KBr): 1789, 1730 (C=O, imide); 1375, 1330, 1160 (SO_2). ^{1}H-NMR ($(CD_3)_2SO$): 8.97 (*d*, *J* = 2, H–C(4)); 8.63 (*d*, *J* = 2, H–C(6)); 8.3–7.9 (*m*, 4H), 7.8–7.5 (*m*, 6H; 2 $C_6H_5SO_2$); 7.22 (*m*, C_6H_4); 2.35 (*s*, CH_3). Anal. calc. for $C_{27}H_{19}NO_6S_2$ (517.57): C 62.66, H 3.70, N 2.71, O 18.55, S 12.39; found: C 62.48, H 3.69, N 2.86, O 18.92, S 12.22.

*3-Decylthio-*N-*methyl-5-(phenylsulfonyl)phthalimide* (**2n**). A mixture of **2f** (2 g, 5.28 mmol), sodium benzenesulfinate (1.73 g, 10.57 mmol), and DMF (20 ml) was stirred at 120° for 17 h. The mixture was evaporated *in vacuo* and the residue dissolved in CH_2Cl_2/H_2O. The org. extracts were washed with brine, dried over Na_2SO_4, and evaporated slowly. Thus, 1.83 g (73%) of **2n** separated out, m.p. 91–2°. UV: 388 (3300). IR (CH_2Cl_2): 1790, 1730 (C=O, imide); 1385, 1330, 1175, 1155 (SO_2). ^{1}H-NMR ($CDCl_3$): 7.98 (*d*, *J* = 2), 7.87 (*d*, *J* = 2; H–C(4), H–C(6)); 7.95–7.8 (*m*, 2H), 7.65–7.4 (*m*, 3H; $C_6H_5So_2$); 3.14 (*s*, CH_3N); 3.08 (*t*, *J* = 7, CH_2S); 2.0–0.8 (19H, *n*-C_9H_{19}). Anal. calc. for $C_{25}H_{31}NO_4S_2$ (473.65): C 63.40, H 6.60, N 2.96, S 13.54; found: C 63.17, H 6.39, N 3.58, S 12.73.

4. Substitutions with O-Nucleophiles. – *5-Nitro-*N-*methyl-3-(*p*-tolyloxy)phthalimide* (**2p**). A mixture of **2c** (100 g, 398 mmol), freshly prepared sodium *p*-cresolate (55.4 g), and THF (750 ml) was stirred at 0° for 1 h. The mixture was evaporated *in vacuo*, the residue dissolved in CH_2Cl_2/2N HCl, the org. phase washed with brine, dried over Na_2SO_4, and evaporated. Recrystallisation from toluene gave 95.75 g (77%) of **2p**, m.p. 149–50°. UV: 358 (2560). IR (CH_2Cl_2): 1802, 1750 (C=O, imide); 1565, 1360 (NO_2). ^{1}H-NMR ($CDCl_3$): 8.18 (*d*, *J* = 2, 1H), 7.72 (*d*, *J* = 2, 1H; H–C(4), H–C(6)); 7.18 (*d*, *J* = 9, 2H), 6.90 (*d*, *J* = 9, 2H; C_6H_4); 3.14 (*s*, CH_3N); 2.33 (*s*, CH_3). Anal. calc. for $C_{16}H_{12}N_2O_5$ (312.28): C 61.54, H 3.88, N 8.97; found: C 61.63, H 3.79, N 8.78.

*5-Nitro-3-(2-propynyloxy)-*N-(p-*tolyl)phthalimide* (**2o**). A mixture of **2b** (3.3 g, 10 mmol), K_2CO_3 (1.9 g, 13 mmol), 2-propynyl alcohol (1.1 g, 20 mmol), 2,6-bis(*tert*-butyl)phenol (40 mg, 0.2 mmol), and dioxane (60 ml) was refluxed for 2 h. The mixture was evaporated *in vacuo* and the residue dissolved in CH_2Cl_2/2N HCl. The org.

extracts were washed with $NaHCO_3$ soln., then with brine, dried over Na_2SO_4, and evaporated. Recrystallisation gave 1.3 g (39%) of **2o**, m.p. 169–72°. UV: 345 (5100). IR (CH_2Cl_2): 3330, 2130 (C≡CH); 1795, 1740 (C=O, imide); 1560, 1355 (NO_2). ^{1}H-NMR ($CDCl_3$): 8.37 (*d*, *J* = 2, H–C(4), H–C(6)); 7.29 (*m*, C_6H_4); 5.06 (*d*, *J* = 2, CH_2O); 2.67 (*t*, *J* = 2, C≡CH); 2.40 (*s*, CH_3Ar). Anal. calc. for $C_{18}H_{12}N_2O_5$ (336.30): C 64.29, H 3.60, N 8.33; found: C 63.90, H 3.60, N 8.40.

*3-Hydroxy-5-nitro-*N-*(p-tolyl)phthalimide* (**2q**). A mixture of **2b** (1.64 g, 5 mmol), anh. NaOAc (0.9 g, 11 mmol), and DMSO (8 ml) was stirred at 25° for 24 h. The mixture was diluted with H_2O (100 ml) and extracted with CH_2Cl_2. The extracts were washed with brine, dried over Na_2SO_4, and evaporated. Recrystallisation from toluene gave 1.24 g (83%) of **2q**, m.p. 211–3°. UV: 355 (5500). UV (Na-salt, EtOH): 438 (4200). IR (dioxane): 4000–2600 (br., OH); 1790, 1740 (C=O, imide); 1560, 1355 (NO_2). ^{1}H-NMR ((D_6)DMSO): 12.00 (br. *m*, OH); 8.00 (*d*, *J* = 2, 1H), 7.91 (*d*, *J* = 2, 1H; H–C(4), H–C(6)); 7.29 (*m*, C_6H_4); 2.40 (*s*, CH_3Ar). Anal. calc. for $C_{15}H_{10}N_2O_5$ (298.25): C 60.41, H 3.38, N 9.39; found: C 60.16, H 3.43, N 9.38.

*5-Methoxy-3-(phenylthio)-*N-*(p-tolyl)phthalimide* (**7a**). A 1.0M soln. of $NaOCH_3$ in CH_3OH (110 ml, 110 mmol) was evaporated to dryness and added to DMSO (200 ml). Then, **2h** (39.04 g, 100 mmol) was added, the mixture stirred for 18 h at 25°, then diluted with H_2O (1.5 l) and 2N HCl (10 ml), and extracted with $CHCl_3$. The extracts were washed with H_2O and brine, dried over Na_2SO_4, and evaporated. Recrystallisation from toluene/cyclohexane gave 31.68 g (84%) of **7a**, m.p. 166–8°. UV: 360 (3000). ^{1}H-NMR ($CDCl_3$): 7.7–7.35 (*m*, C_6H_5S); 7.28 (*m*, C_6H_4); 7.07 (*d*, *J* = 2, H–C(6)); 6.35 (*d*, *J* = 2, H–C(4)); 3.68 (*s*, CH_3O); 2.38 (*s*, CH_3Ar). Anal. calc. for $C_{22}H_{17}NO_3S$ (375.44): C 70.38, H 4.57, N 3.73, S 8.54; found: C 70.31, H 4.58, N 3.79, S 8.54.
Similarly prepared were compounds **7b–f** (see *Table 2*).

5. Substitutions with Sodium Azide. – *3-Azido-*N-*methyl-5-nitrophthalimide* (**2r**). A mixture of **2c** (2 g, 7.96 mmol), NaN_3 (0.54 g, 8.36 mmol), and DMF (20 ml) was stirred at 25° for 21 h. The mixture was added to H_2O (200 ml) and 2N HCl (10 ml). The product was extracted into CH_2Cl_2. The extracts were washed with H_2O and brine, dried over Na_2SO_4 and evaporated. Recrystallization from CH_2Cl_2/pentane gave 1.26 g (64%) of light sensitive **2r**, m.p. 123–4°. UV: 358 (4000). IR (CH_2Cl_2): 2140 (N_3); 1785, 1730 (C=O, imide); 1555, 1353 (NO_2). ^{1}H-NMR ($CDCl_3$): 8.35 (*d*, *J* = 2, 1H), 8.21 (*d*, *J* = 2, 1H; H–C(4), H–C(6)); 3.22 (*s*, CH_3). Anal. calc. for $C_9H_5N_5O_4$ (247.17): C 43.73, H 2.04, N 28.33; found: C 43.97, H 2.05, N 28.93.

*3,5-Diazido-*N-*methylphthalimide* (**2s**). The above reaction was repeated using 1.29 g (19.9 mmol) of NaN_3, and the mixture was stirred at 50° overnight. Recrystallisation from CH_2Cl_2/pentane gave 1.34 g (68%) of **2s**, m.p. 153–4° (dried under high vacuum at < 50° and protected from light). UV: 347 (4800). IR (CH_2Cl_2): 2160 (N_3); 1790, 1735 (C=O, imide). ^{1}H-NMR ($CDCl_3$): 7.28 (*d*, *J* = 2, H–C(6)); 6.89 (*d*, *J* = 2, H–C(4)); 3.17 (*s*, CH_3). Anal. calc. for $C_9H_5N_7O_2$ (243.19): C 44.45, H 2.08, N 40.32; found: C 44.57, H 2.23, N 40.31.

6. Substitution with LiBr. – *3-Bromo-5-nitro-*N-*(p-tolyl)phthalimide* (**2t**). A mixture of **2b** (2 g, 6.11 mmol), anh. LiBr (1,06 g, 12,22 mmol), and CH_3CN (10 ml) was heated in a pressure reaction vessel to 160° for 18 h. The mixture was evaporated and the residue dissolved in CH_2Cl_2. The org. extracts were washed with brine, dried over Na_2SO_4, and evaporated. The residue, 1.41 g (64%), was chromatographed with $CHCl_3$ on silica gel to give, after recrystallisation from CH_2Cl_2/pentane, 0.94 g (43%) of **2t**, m.p. 173–5°. IR (CH_2Cl_2): 1790, 1740 (C=O, imide); 1560, 1350 (NO_2). ^{1}H-NMR ($CDCl_3$): 7.71 (*d*, *J* = 2, 1H), 8.62 (*d*, *J* = 2, 1H; H–C(4), H–C(6)); 7.29 (*m*, C_6H_4); 2.21 (*s*, CH_3). Anal. calc. for $C_{15}H_9BrN_2O_4$ (361.15): C 49.89, H 2.51, Br 22.13, N 7.76; found: C 49.98, H 2.68, Br 21.15, N 8.08.

7. Hydrolyses of Phthalimides to Phthalic Acids and Anhydrides. – *5-Nitro-3-(phenylthio)phthalic Acid* (**1b**). *Method A.* A mixture of **2h** (160 g, 410 mmol) and 20% aq. NaOH soln. (1590 ml) was refluxed for 18 h. The mixture was acidified at 10–15° with conc. HCl. The crude amido acid was separated and stirred in conc. HCl (1070 ml) at reflux for 3 h. The mixture was cooled and the precipitate filtered off and dissolved in Na_2CO_3 soln. Neutral products were filtered off, and the filtrate was acidified and cooled. The precipitate was separated and dried over P_2O_5 to give 116.2 g (89%) of **1b**, m.p. 183–5°.

Method B. A mixture of **2g** (3.0 g, 10 mmol) and 1N NaOH (30 ml) was refluxed for 8 h. The mixture was cooled, acidified, and extracted with THF/toluene. The org. extracts were washed with brine, dried over Na_2SO_4, and evaporated to give 3.13 g (98%) of **1b**, m.p. 182–4°. Anal. calc. for $C_{14}N_9NO_6S$ (319.29): C 52.67, H 2.84, N 4.39, S 10.04; found: C 52.90, H 3.20, N 4.30, S 9.80.

The acid **1b** was dehydrated to the anhydride **3c** by refluxing with an excess of Ac_2O in toluene for 1 h. Recrystallisation from CH_2Cl_2/pentane gave 98% of **3c**, m.p. 167–9°.

5-Nitro-3-(p-tolyloxy)phthalic Anhydride (**3f**). A mixture of **2p** (312 mg, 1 mmol) and 1N NaOH (3 ml) was refluxed together for 2 days. The mixture was cooled, acidified to pH 0, heated to reflux for 15 min, cooled, and extracted with THF/toluene. The extracts were dried over Na_2SO_4 and evaporated. The residue was refluxed with

Ac_2O (0.5 ml) in toluene (4 ml) for 5 min. The soln. was evaporated, and the residue gave, recrystallised from CH_2Cl_2/pentane, 250 mg (84%) of **3f**, m.p. 162–8°. IR (CH_2Cl_2): 1870, 1800 (C=O, anhydride); 1560, 1350 (NO_2); 910 (C–O–C). ^{1}H-NMR ($CDCl_3$): 8.36 (*d*, *J* = 2, H–C(6)); 7.88 (*d*, *J* = 2, H–C(4)); 7.31 (*d*, *J* = 9, 2H), 7.05 (*d*, *J* = 9, 2H; C_6H_4); 2.44 (*s*, CH_3). Anal. calc. for $C_{15}H_9NO_6$ (299.24): C 60.21, H 3.03, N 4.68; found: C 59.92, H 3.20, N 4.63.

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