REACTION OF *N*-PHENOXYPHTHALIMIDE DERIVATIVES WITH ALUMINUM CHLORIDE IN BENZENE

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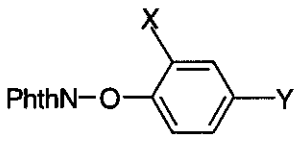
Abstract --- *N*-Phenoxyphthalimides react with $AlCl_3$ in benzene to form products of intramolecular N-C and intermolecular C-C bond formation *via* aryloxenium ion intermediates. *N*-Phenoxy derivatives having an electron-withdrawing substituent on the *para* position react with solvent benzene on the imide carbonyl, assisted by the neighboring oxygen atom, to produce *N*-(4-substituted phenoxy)-3,3-diphenyl-2,3-dihydroisoindol-1-ones.

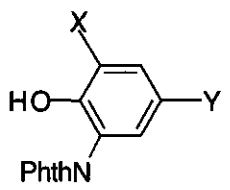
It was reported that aryloxenium ions are generated from the thermolysis of *N*-aryloxypyridinium salts[1] and from the acid-catalyzed solvolysis of *N*-aryloxy-arylamides or -benzenesulfonamides in the presence of trifluoroacetic acid (TFA) and trifluoromethanesulfonic acid (TFSA).[2] In this article we report that $AlCl_3$-mediated decomposition of *N*-aryloxyphthalimides (**1**) provides a new source of aryloxenium ions and leads to formation of C-C bonds in their reactions with benzene and of N-C bonds with a phthalimide anion.

Previously we reported the $AlCl_3$-mediated heterolytic cleavage of N-O bond of *N*-phenoxybenzamide derivatives, which induced intramolecular migration of the benzamide group from the oxygen to the *ortho* position of the phenyl group *via*

acylnitrenium ion intermediates.[3] In an extension of this work, we have investigated the reaction of **1** with $AlCl_3$ in benzene. Trapping studies using solvent benzene are often used for evidence of the intermediacy of an aryloxenium ion.[2]



1 a : X=Y=H
b : X=H, Y=Cl
c : X=Y=Cl
d : X=H, Y=Me
e : X=H, Y=NO_2
f : X=H, Y=CN



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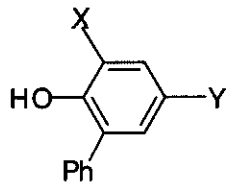
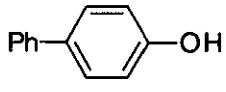


3 a : X=Y=H
b : X=H, Y=Cl
c : X=Y=Cl
d : X=H, Y=Me



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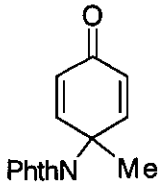

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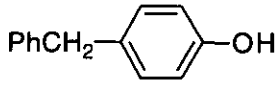

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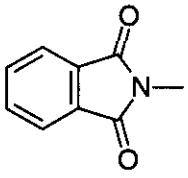
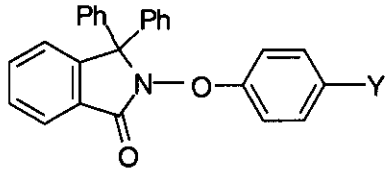
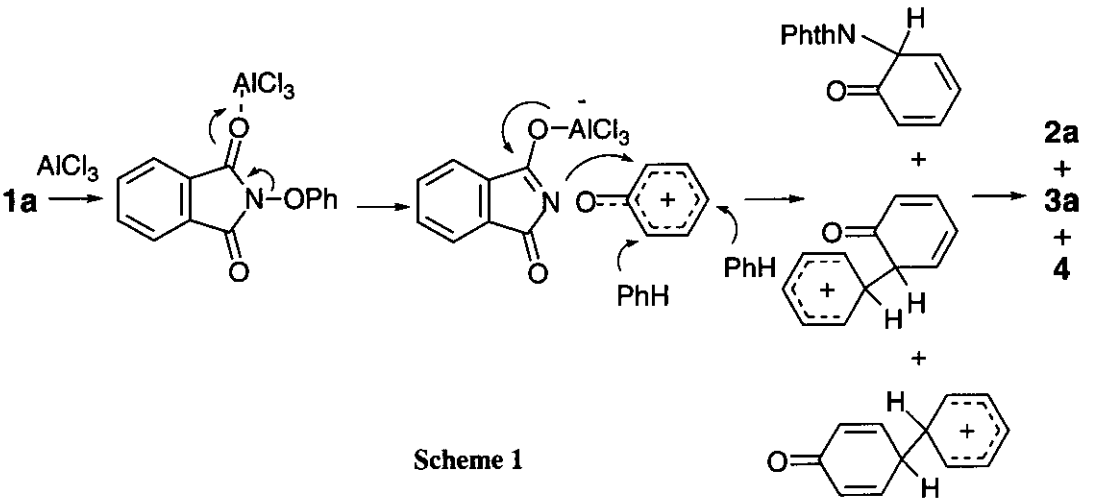


= PhthN-



7 : Y=NO_2, **8** : Y=CN

Treatment of *N*-phenoxyphthalimide (**1a**) with $AlCl_3$ in benzene at room temperature for 1 h gave *N*-(2-hydroxyphenyl)phthalimide (**2a**) (37%) and 2- and 4-hydroxybiphenyls (**3a** and **4**, 26% and 15%, respectively), and in CH_2Cl_2 **2a** (66%) was obtained as a main product along with 4-chlorophenol (31%) under the same reaction conditions. We have investigated the reaction of **1a** with $ZnCl_2$, $Zn(OAc)_2$ and $BF_3 \cdot OEt_2$ instead of $AlCl_3$ in CH_2Cl_2 for 10~18 h at room temperature and the starting material was recovered quantitatively. Several *N*-phenoxyphthalimide derivatives (**1a~f**) reacted in benzene using $AlCl_3$, and the results are presented in Table 1 and Scheme 1.



Scheme 1

Table 1. Reaction of *N*-phenoxyphthalimides (**1**) with $AlCl_3$ (5 equiv.) in benzene at room temperature

Entry	Starting compound	Time/h	Product (yield, %)
1	**1a**	1	**2a** (37), **3a** (26), **4** (15)
2	**1b**	1	**2b** (19), **3b** (46)
3	**1c**	0.5	**2c** (38), **3c** (51)
4	**1d**	1	**2d** (42), **3d** (14), **5** (15), **6** (19)
5	**1e**	3[a]	**7** (74)
6	**1f**	1[b]	**8** (64)

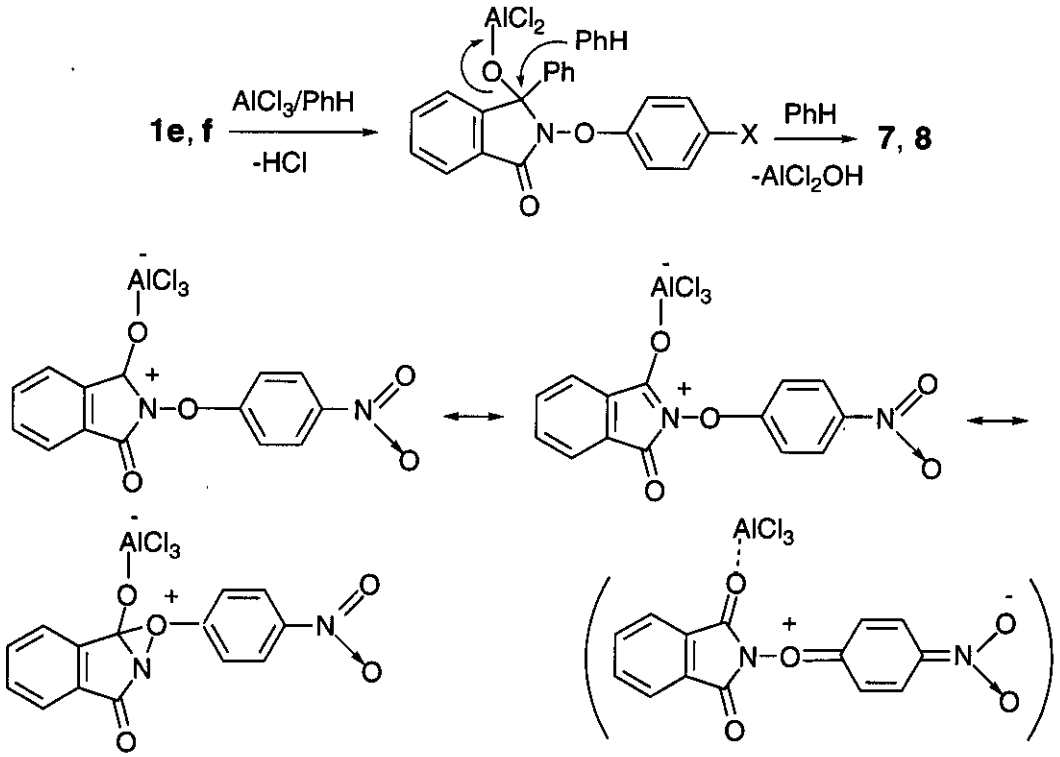
[a] Oil bath temperature 60 °C. [b] Oil bath temperature 80 °C.

$AlCl_3$ coordinates with an imide carbonyl of **1a** and assists in the elimination of the nucleofugal phthalimide group to produce a phenoxenium ion, which was trapped intramolecularly by a phthalimide anion to give **2a** or trapped intermolecularly by benzene and chloride ion to give **3a**, **4** and 4-chlorophenol. *N*-Phenylphthalimide which would arise from reaction of a phthalimide cation (a diacylnitrenium ion)[4] or a phthalimide radical[4] with benzene could not be detected in the reaction mixture at all. In the case of **1d**, formation of products (**5**) and (**6**) is explained in terms of increased resonance forms of the phenoxenium ion, the positive charge of which is extended to the methyl group.

The phenoxenium ion produced from **1a-d** reacted with benzene on the phenyl group, not on the oxygen atom. Abramovitch *et al.* reported that 4-nitrophenoxenium ion produced by thermolysis of the corresponding pyridinium tetrafluoroborate at 180 °C

reacted with anisole on the oxygen atom to afford 4-nitro-4'-methoxydiphenyl ether.[1a, c] Shudo *et al.* reported that *N*-tosyl-*O*-(4-nitrophenyl)hydroxylamine did not react with benzene in the presence of TFA alone, and reacted with benzene on the phenyl group in the presence of a mixture of TFA and TFSA (5 : 1) in prolonged reaction time to afford 2-hydroxy-5-nitrobiphenyl (41%).[2a]

In our case, the electron density of the oxygen atom of the phenoxy groups in **1e** and **f** was decreased by the strong electron-withdrawing effect of the substituents and prevented heterolytic cleavage of the N-O bond to produce a phenoxenium ion (Scheme 2, parentheses). Instead, one of the imide carbonyls was phenylated to afford **7** and **8**. As phthalimide and *N*-phenylphthalimide did not react with $AlCl_3$ under reflux in benzene and the starting materials were recovered quantitatively, it is evident that the oxygen atom of the phenoxy groups participates in the resonance to activate the imide carbonyl for Friedel-Crafts type phenylation as was the case of the reaction of *N*-hydroxyphthalimide and $AlCl_3$.[5] The proposed mechanism is presented in Scheme 2.



Scheme 2

In conclusion, $AlCl_3$-mediated decomposition of *N*-phenoxyphthalimides in benzene led to generation of an aryloxenium ion, to which regioselective intramolecular migration of a resulting phthalimide anion and intermolecular trapping of solvent benzene occurred. On the other hand, *N*-phenoxy derivatives having an electron-withdrawing substituent on the *para* position reacted with benzene on the imide carbonyl, assisted by the neighboring oxygen atom, to produce *N*-(4-substituted phenoxy)-3,3-diphenyl-2,3-dihydroisoindol-1-ones.

EXPERIMENTAL

Melting points are uncorrected and were taken on a Yanagimoto hot-stage melting point apparatus. ^{1}H NMR spectra were measured at 60 MHz on a JEOL JNM-PMX60SI or at 270 MHz on a JEOL JNM-EX270 spectrometer with tetramethylsilane (Me_4Si) as an internal reference and $CDCl_3$ as the solvent. IR spectra were recorded on a JASCO IR810 spectrophotometer. Low and high resolution mass spectra (MS) were obtained with a JEOL JMS-DX300 spectrometer with a direct inlet system at 70 eV. Elemental analyses were performed in the Microanalytical Laboratory of this University.

The following compounds are known: **1a**, mp 145-147 °C (lit.,[6] mp 143.5-145 °C); **2a**, mp 219-221 °C (lit.,[7] mp 220 °C); **3a**, mp 53-55 °C (lit.,[8] mp 56 °C); **3d**, mp 68-69 °C (lit.,[9] mp 67.5-68.5 °C); **4**, mp 166-168 °C (lit.,[10] mp 165.1 °C); **6**, mp 84 °C (lit.,[11] mp 84 °C). Compounds (**1b~d**) were synthesized by the Schotten-Baumann reaction of phthalyl chloride with the corresponding phenoxyamine in dichloromethane-pyridine with cooling. Compounds (**1e** and **f**) were synthesized by heating a mixture of phthalic anhydride and the corresponding phenoxyamine in acetic acid for 1 h. These phenoxyamines were synthesized by the literature and patent methods.[12] Physical constants and microanalytical data for new compounds are listed in Tables 2, 3 and 4.

Reaction of *N*-phenoxyphthalimide (1a) with $AlCl_3$ in benzene. A typical procedure

To **1b** (200 mg, 0.731 mmol) in benzene (8 mL) was added $AlCl_3$ (487 mg, 3.65 mmol) with cooling. After stirring the reaction mixture for 1 h at rt, 10% HCl (20 mL) was

added with cooling. The aqueous layer was extracted with ethyl acetate (20 mL x 2), and the combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, and concentrated. The crude products were chromatographed on a column of slica gel. First elution with hexane-ethyl acetate (2 : 1) afforded **3b** (68 mg, 46%), oil (lit.,[13] mp 38.5-39 °C); ν_{max}(neat)/cm^{-1} 3540, 3440, 1485, 1405, 1265; δ_H ($CDCl_3$) 5.22 (1H, s, OH), 6.90 (1H, d, *J*=9Hz, ArH), 7.18-7.24 (2H, m, ArH), 7.38-7.52 (5H, m, ArH); *m/z* 204 (M^+, 100), 206 (M^++2, 33.0); HRMS (found): 204.0342 (204.0339). Further elution with the same solvent mixture afforded phthalimide (42 mg) and **2b** (19 mg, 19%), mp 258 °C (EtOH) (Tables 3 and 4).

Table 2. Physical constants and microanalytical data of starting compounds

Compound	mp/°C	Solvent	Molecular formula	Found (%) C	H	N	Required (%) C	H	N
1b	141-143	AcOEt-hexane	$C_{14}H_8NO_3Cl$	61.28	3.08	5.13	61.44	2.95	5.12
1c	169-170	hexane	$C_{14}H_7NO_2Cl_2$	54.29	2.48	4.45	54.57	2.29	4.55
1d	127-128	benzene-hexane	$C_{15}H_{11}NO_3$	70.96	3.05	5.46	71.14	2.84	9.86
1e	233.5-234	AcOEt	$C_{14}H_8N_2O_5$	59.14	3.05	9.73	59.16	2.84	9.86
1f	222-223	AcOEt	$C_{15}H_8N_2O_3$	68.26	3.29	10.62	68.18	3.05	10.60

Reaction of *N*-(4-nitrophenoxy)phthalimide (1e) with $AlCl_3$ in benzene

To **1e** (200 mg, 0.704 mmol) in benzene (8 mL) was added $AlCl_3$ (469 mg, 3.53 mmol) with cooling. The reaction temperature was raised to 60 °C (oil bath). After stirring the reaction mixture for 3 h, 10% HCl (15 mL) was added with cooling. The aqueous layer was extracted with ethyl acetate (30 mL x 2), and the combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, and concentrated. The crude products were chromatographed on a column of slica gel with benzene-ethyl acetate (5 : 1) as an eluent to afford *N*-(4-nitrophenoxy)-3,3-diphenyl-2,3-dihydroisoindol-1-one (**7**) (220 mg, 74%), mp 188-190 °C (AcOEt-hexane) (Tables 3 and 4).

Table 3. Spectral data for products

Compound	ν_{max}/cm^{-1} (KBr)	δ_H	*m/z* (M^+)
2b	3400, 1790	7.01 (1H, d, *J* 8.80, Ph), 7.38 (1H, dd, J_1 8.80, J_2 2.93, Ph)	273 (M^+, 77%)
	1720	7.44 (1H, d, *J* 2.93, Ph), 7.87-8.03 (4H, m, Ph)	275 (M^++2, 26%)
		10.19 (1H, s, OH)	
2c	3450, 3340	5.93 (1H, s, OH), 7.23 (1H, d, *J* 2.5, Ph)	307 (M^+, 78%)
	1800, 1740	7.47 (1H, d, *J* 2.5, Ph), 7.78-7.86 (2H, m, Ph)	309 (M^++2, 51%)
		7.93-8.02 (2H, m, Ph)	
2d	3440, 1790	2.33 (3H, s, CH_3), 5.60 (1H, s, OH)	253 (M^+, 100%)
	1720	6.98 (1H, d, *J* 8.42, Ph), 7.10 (1H, s, Ph)	
		7.13 (1H, d, *J* 8.06, Ph), 7.71-7.84 (2H, m, Ph)	
		7.92-8.00 (2H, m, Ph)	
3c	3510, 1570	5.67 (1H, s, OH), 7.22 (1H, d, *J* 2.6, Ph)	238 (M^+, 100%)
	1500	7.34 (1H, d, *J* 2.6, Ph), 7.36-7.54 (5H, m, Ph)	240 (M^++2, 64%)
5	1780, 1720	1.99 (3H, s, CH_3), 6.30 (2H, d, *J* 10.26, -CH= x 2)	253 (M^+, 100%)
	1670, 1640	7.29 (2H, d, *J* 10.26, -CH= x 2), 7.70-7.90 (4H, m, Ph)	
7	1740, 1590	6.68 (2H, d, *J* 9.0, Ph), 6.97-8.80 (16H, m, Ph)[a]	422 (M^+, 15%)
	1490		
8	2240, 1740,	6.63 (2H, d, *J* 9.0, Ph), 7.00-8.00 (16H, m, Ph)[a]	402 (M^+, 35%)
	1600		

[a] 60 MHz.

Table 4. Physical constants and microanalytical data of products

Compound	mp/°C	Solvent	Molecular formula	Found (%)			Required (%)		
				C	H	N	C	H	N
2b	258	EtOH	$C_{14}H_8NO_3Cl$	61.16	3.17	5.20	61.44	2.95	5.12
2c	199-200	benzene	$C_{14}H_7NO_3Cl_2$	54.53	2.50	4.49	54.57	2.29	4.55
2d	190-192	benzene	$C_{15}H_{11}NO_3$	70.99	4.48	5.50	71.14	4.38	5.53
3c	52-54	pentane	$C_{12}H_8OCl_2$	60.04	3.64	0.00	60.28	3.37	0.00
5	139-140	hexane-benzene	$C_{15}H_{11}NO_3$	71.07	4.55	5.51	71.14	4.38	5.53
7	188-190	AcOEt-hexane	$C_{26}H_{18}N_2O_4$	73.88	4.45	6.61	73.92	4.29	6.63
8	215-217.5	benzene	$C_{27}H_{18}N_2O_2$	80.82	4.71	6.90	80.58	4.51	6.96

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