REACTION OF *N*-AMINOPHTHALIMIDE DERIVATIVES WITH ALUMINUM CHLORIDE IN BENZENE†

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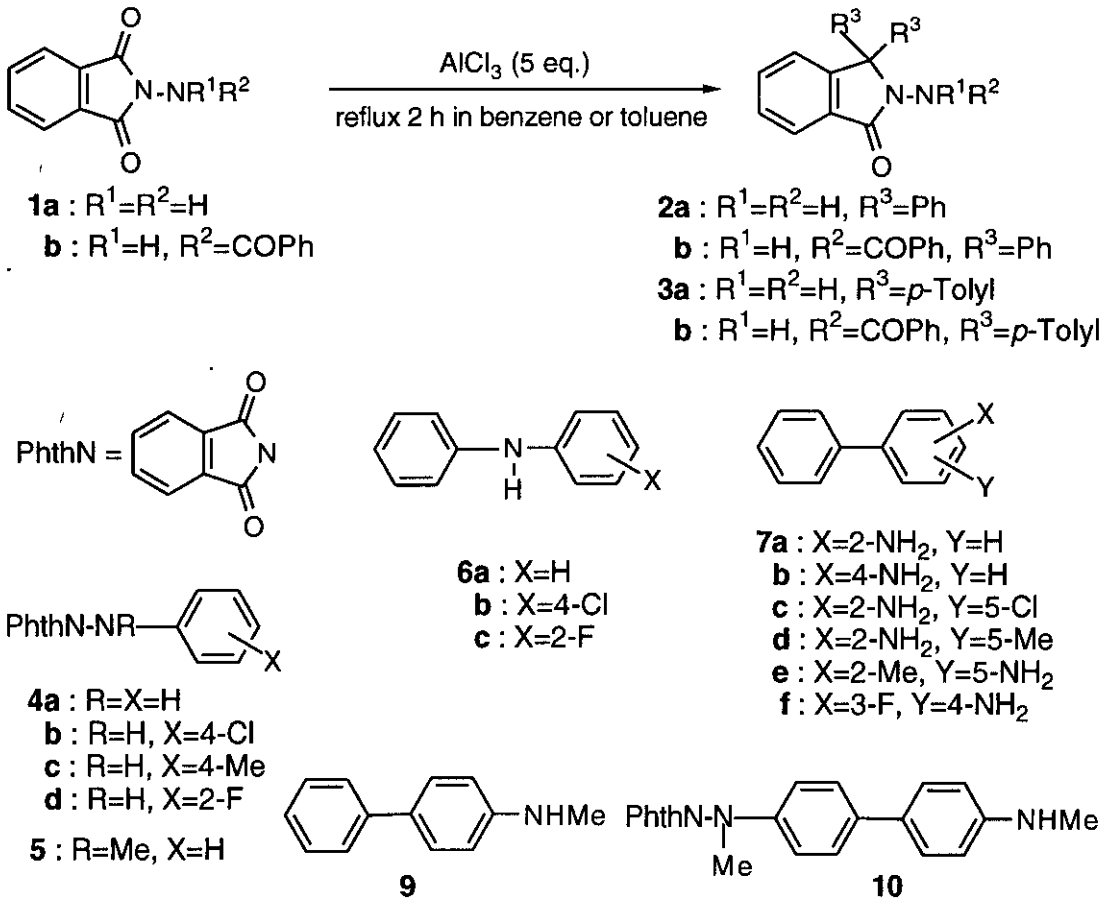
Abstract --- The reaction of *N*-aminophthalimide derivatives with $AlCl_3$ in benzene has been investigated. From *N*-amino- and *N*-benzamidophthalimide (**1a** and **1b**), *N*-amino- and *N*-benzamido-3,3-diaryl-2,3-dihydroisoindol-1-ones (**2**) are obtained in high yield by initial attack of benzene on the imide carbonyl, assisted by the neighboring nitrogen atom. From *N*-arylaminophthalimide derivatives (**4**), the N-N bond is cleaved heterolytically to give an arylnitrenium ion and canonical forms involving the arene which are trapped by benzene to give aminobiaryls and *N*-arylanilines.

Previously we reported that *N*-hydroxyphthalimide reacted with $AlCl_3$ in benzene to give 2-hydroxy-3,3-diphenyl-2,3-dihydroisoindol-1-one, which was transformed to 1,1-diphenyl-1*H*-benzo[*d*][1,2]oxazin-4-one, a ring expanded compound, by heating.[1] In an extension of this work, we investigated the reaction of *N*-aminophthalimide derivatives (**1a** and **1b**) with $AlCl_3$ in benzene, in the expectation that $AlCl_3$-mediated heterolytic cleavage of the N-N bond (a diacylnitrenium ion[2] formation) or Friedel-Crafts type phenylation on the imido carbonyl might occur as was the case of the reaction of *N*-

†This paper is dedicated to the memory of late Professor Shun-ichi Yamada.

hydroxyphthalimide derivatives with $AlCl_3$.[1] Treatment of **1a** with $AlCl_3$ (5 mol eq.) in benzene or toluene at reflux for 2 h gave 2-amino-3,3-diphenyl-2,3-dihydro-isoindol-1-one (**2a**) or its 3,3-*p*-tolyl derivative (**3a**) in high yield. In the case using **1b**, the same Friedel-Crafts type reaction was found to occur at the imido carbonyl to give 2-benzamido-3,3-diphenyl-2,3-dihydroisoindol-1-one (**2b**) and its 3,3-*p*-tolyl derivative (**3b**) in high yield (Scheme 1). However, heating of **2a** and **2b** with $AlCl_3$ in benzene did not lead to ring expansion and recovered starting materials. As phthalimide and *N*-phenylphthalimide do not react with $AlCl_3$ under vigorous reaction conditions,[1] it is evident that the amino or benzamido nitrogen plays an important role for introduction of benzene on the imide carbonyl.

Scheme 1



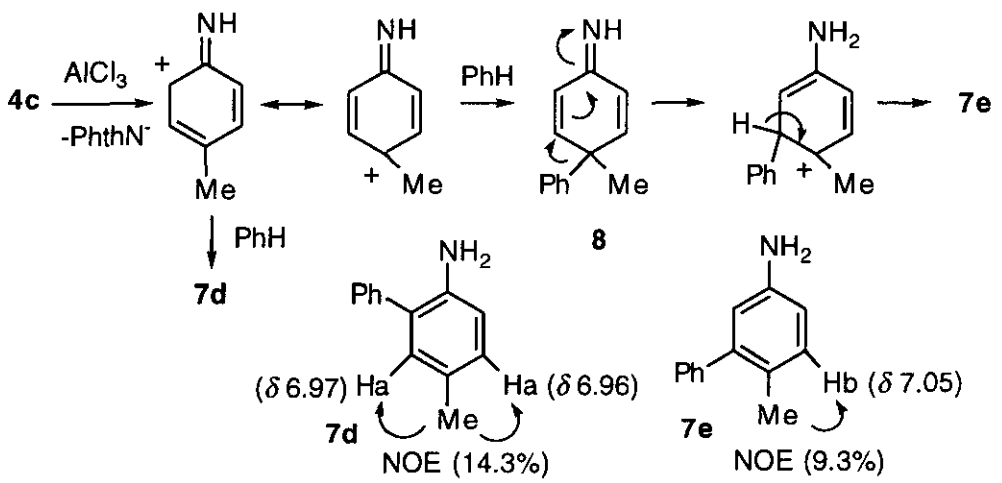
On the other hand, treatment of *N*-phenylaminophthalimide (**4a**) with $AlCl_3$ in benzene did not introduce phenyl groups in the imide carbonyl, but caused heterolytic cleavage of the N-N bond to give a phenylnitrenium ion and a phthalimido anion. This cleavage reaction provides a new source of a phenylnitrenium ion[3] and leads to formation of diphenylamine (**6a**) and 2-amino- and 4-aminobiphenyls (**7a** and **7b**). $AlCl_3$ coordinates with imide carbonyl of **4a** and assists in the elimination of the nucleofugal phthalimide group to produce a phenylnitrenium ion and canonical forms involving the benzene ring, which were trapped by benzene to give the products (**6a**, **7a** and **7b**). In contrast, *N*-phenylaminobenzamide reacted with $AlCl_3$ under reflux for 7 h in benzene and was recovered quantitatively. This is because a benzamido group is not so strong

Table 1. $AlCl_3$-mediated decomposition of *N*-phenylaminophthalimide derivatives (**4**) in benzene at room temperature

Starting material	Reaction time/h	Product (Yield/%)
4a	2	**6a** (21.2), **7a** (16.9), **7b** (57.1)
4b	5[a)]	**6b** (50.3), **7c** (20.8)
4c	1.5	**7d** (51.3), **7e** (24.4)
4d	5[a)]	**6c** (42.5), **7f** (32.9)
5	1	**9** (91.0)

[a)] Reflux

Scheme 2

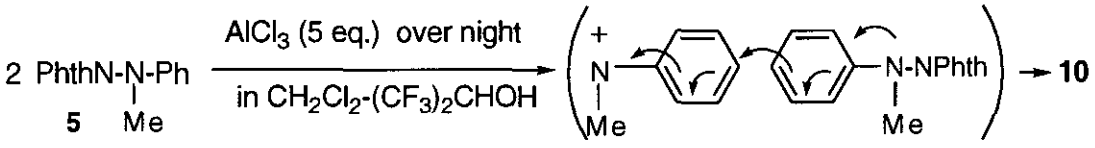


nucleofugal group as a phthalimido group. Several phthalimide derivatives (**4**) reacted in this way and the results are presented in Table 1.

Compound (**4c**) reacted with benzene similarly to give **7d** and **7e**, the regiochemical assignments of which were made on the basis of NOE measurements. When protons of the methyl groups of **7d** and **7e** were irradiated, Ha and Hb alone gave significant NOEs (14.3% and 9.3%, respectively) (Scheme 2). In addition the ^{1}H NMR spectra showed the presence of one proton of **7d** and two protons of **7e** adjacent to nitrogen which was determined by their typical up field chemical shifts. Formation of **7e** will be rationalized by assuming an intermediate (**8**), the phenyl group being a better migrating group than the methyl group (Scheme 2).[4]

From *N*-(*N*-methyl-*N*-phenylamino)phthalimide (**5**), **9** was obtained in high yield. In this case heterolytic cleavage of the N-N bond results in a positive charge exclusively on the *para* position of the methylamino group and *N*-methyl-*N*,*N*-diphenylamine was not detected. Treatment of **5** with $AlCl_3$ in CH_2Cl_2 instead of benzene gave an ambiguous result and 4-chloro-*N*-methylaniline (11.8%) was obtained accompanied with unidentifiable compounds.

Scheme 3



Change a solvent from CH_2Cl_2 to CH_2Cl_2-1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) (1:1) or HFIP alone brought about clear reaction and gave considerable amounts of a condensed product (**10**) (52.3% or 59.3%), the route to which is illustrated in Scheme 3. HFIP is known to have a high ionizing power and low nucleophilicity,[5] and might stabilize a nitrenium ion for further coupling reaction. Formation of **10** suggests that an equimolar coupling reaction with other arenes might be possible under similar reaction conditions.

$AlCl_3$-mediated heterolytic cleavage of the N-N bond of **4a** and **5** provides a new method to generate a phenylnitrenium ion. Other phenylnitrnium ions bearing substituents in the phenyl ring will be produced similarly and the chemistry of them will be published in due course.

EXPERIMENTAL

All the melting points were determined with a Yanagimoto hot-stage melting point apparatus and are uncorrected. ^{1}H NMR spectra were measured at 60 MHz on a JEOL JNM-PNX60SI or at 270 MHz on a JEOL JNM-EX270 spectrometer with tetramethylsilane (Me_4Si) as an internal reference and $CDCl_3$ as the solvent, unless otherwise noted. ^{1}H NMR spectral data are reported in parts per million (δ) relative to Me_4Si. IR spectra were recorded on a JASCO IR 810 spectrophotometer. Mass spectra were obtained with a JEOL JMX-DX 300 spectrometer with a direct inlet system at 70 eV. Elemental analyses were performed in the Microanalytical Laboratory of this University. Compound (**1a**) was purchased from Tokyo Kasei Kogyo Co. Compound (**1b**) was prepared by benzoylation of **1a** in 85% yield, mp 223.5-225 °C (EtOH-AcOEt). ^{1}H NMR (60 MHz, DMSO-d_6) δ 3.20 (1H, s, NH), 7.30-7.69 (3H, m, ArH), 7.69-8.06 (6H, m, ArH); ν_{max}(KBr)/cm^{-1} 3250, 1805, 1740, 1670; m/z 266 (M^+, 2.22), 105 (100). Anal. Calcd for $C_{15}H_{10}N_2O_3$: C, 67.67; H, 3.79; N, 10.52. Found C, 67.43; H, 3.90; N, 10.55. Compounds (**4** and **5**) were prepared by condensation of phthalic anhydride with appropriate hydrazines. **4a**, mp 187-188 °C (EtOH) (lit.,[6] mp 184 °C). **4b**, mp 228-229 °C (AcOEt) (lit.,[6] mp 191 °C). **4c**, mp 198 °C (EtOH) (lit.,[6] mp 196 °C). **4d**, mp 221-222 °C (AcOEt). ^{1}H NMR (60 MHz, $CDCl_3$+DMSO-d_6) δ 6.35-7.19 (4H, m, ArH), 7.69-7.89 (4H, m, ArH), 8.05-8.22 (1H, br s, NH); ν_{max} (KBr)/cm^{-1} 3400, 1795, 1720; m/z 256 (M^+, 100). Anal. Calcd for $C_{14}H_9N_2O_2F$: C, 65.62; H, 3.54; N, 10.93. Found C, 65.62; H, 3.69; N, 10.91. **5**, mp 125-127 °C (AcOEt) (lit.,[6] mp 127 °C).

2-Amino-3,3-diphenyl-2,3-dihydroisoindol-1-one (2a)

To **1a** (400 mg, 2.47 mmol) in benzene (18 mL) was added $AlCl_3$ (1.64 g, 12.3 mmol) under cooling. After refluxing the reaction mixture for 2 h, 10% HCl (25 mL) was added under cooling. The aqueous layer was extracted with ethyl acetate (40 mL x 3), and the combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, and concentrated. The crude product was chromatographed on a column of slica gel with benzene-ethyl acetate (3:1) as the eluent to give **2a** (631 mg, 85.3%), mp 244-245 °C (benzene-hexane). ^1H NMR (270 MHz) δ 3.97 (2H, s, NH_2), 7.19-7.55 (13H, m, ArH), 7.92 (1H, d, J = 6.93, ArH); ν max (KBr)/cm^{-1} 3325, 3275, 3200, 1705, 1685; m/z 300 (M^+, 61.1), 223 (100). Anal. Calcd for $C_{20}H_{16}N_2O$: C, 79.98; H, 5.37; N, 9.33. Found C, 79.69; H, 5.48; N, 9.57.

Compounds (**2b**, **3a** and **3b**) were prepared similarly using **1a** and **1b.**

2b (95.3%), mp 290-291 °C (acetone). ^1H NMR (270 MHz, DMSO-d_6) δ 7.20-7.86 (19H, m, ArH), 10.58 (1H, s, NH); ν max (KBr)/cm^{-1} 3225, 1725, 1690; m/z 404 (M^+, 15.9), 105 (100). Anal. Calcd for $C_{27}H_{20}N_2O_2$: C, 80.18; H, 4.98; N, 6.93. Found C, 80.15; H, 5.15; N, 6.94.

3a (73.8%), mp 162.5-163.5 °C (AcOEt-hexane). ^1H NMR (270 MHz) δ 2.34 (6H, s, CH_3x2), 3.93 (2H, s, NH_2), 7.00-7.56 (11H, m, ArH), 7.89 (1H, d, J = 6.93, ArH); ν max (KBr)/cm^{-1} 3325, 3260, 3200, 1705, 1610; m/z 328 (M^+, 45.4), 237 (100). Anal. Calcd for $C_{22}H_{20}N_2O$: C, 80.46; H, 6.14; N, 8.53. Found C, 80.38; H, 6.23; N, 8.46.

3b (99.0%), mp 246-248 °C (acetone). ^1H NMR (270 MHz) δ 2.09 (6H, s, CH_3x2), 7.00-7.37 (17H, m, ArH), 7.84 (1H, d, J = 7.25, ArH), 10.52 (1H, s, NH); ν max (KBr)/cm^{-1} 3220, 1720, 1680; m/z 432 (M^+, 27.5), 105 (100). Anal. Calcd for $C_{29}H_{24}N_2O_2$: C, 80.53; H, 5.59; N, 6.48. Found C, 80.47; H, 5.71; N, 6.35.

Reaction of *N*-Phenylaminophthalimide (4a) with $AlCl_3$ in Benzene

To **4a** (200 mg, 0.84 mmol) in benzene (20 mL) was added $AlCl_3$ (560 mg, 4.20 mmol) under cooling. After stirring the reaction mixture for 2 h at rt, 10% HCl (5 mL) was added under cooling. After 5 min 10% Na_2CO_3 (25 mL) was added under cooling. The aqueous layer was extracted with ethyl acetate (20 mL x 2), and the combined organic layer was washed with brine (20 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 the eluent to give **6a** (31 mg, 21.2%, mp 51.5-52 °C (lit.,[7] mp 54-55 °C)), **7a** (24 mg, 16.9%, mp 44-46°C (lit.,[8] mp 49-50° C)), **7b** (81 mg, 57.1%, mp 50-51 °C (lit.,[9] mp 53-54.5 °C)), and phthalimide (115 mg, 93.1%, mp 235.5-236.5 °C (AcOEt) (lit.,[10] mp 238 °C)).

Compounds (**4b~d** and **5**) reacted similarly as described above and the products are as follows.

4b, mp 228-229 °C (AcOEt) (lit.,[6] mp 191 °C). ^{1}H NMR (60 MHz, $CDCl_3$+DMSO-d_6) δ 6.36-7.30 (4H, m, ArH), 7.46-7.60 (1H, br s, NH), 7.66-7.83 (4H, m, ArH); ν max (KBr)/cm^{-1} 3360, 1790, 1725; m/z 272 (M^+, 100), 274 (M^++2, 33.2). Anal. Calcd for $C_{14}H_9N_2O_2Cl$: C, 61.67; H, 3.33; N, 10.27. Found C, 61.61; H, 3.47; N, 10.23.

4c, mp 198 °C (EtOH) (lit.,[6] mp 196 °C).

4d, mp 221-222 °C (AcOEt). ^{1}H NMR (60 MHz, $CDCl_3$+DMSO-d_6) δ 6.35-7.19 (4H, m, ArH), 7.69-7.89 (4H, m, ArH), 8.05-8.22 (1H, br s, NH); ν max (KBr)/cm^{-1} 3400, 1795, 1720; m/z 256 (M^+, 100). Anal. Calcd for $C_{14}H_9N_2O_2F$: C, 65.62; H, 3.54; N, 10.93. Found C, 65.62; H, 3.69; N, 10.91.

6b, mp 67-68 °C (hexane) (lit.,[11] mp 66-67 °C).

6c, oil. ^{1}H NMR (270 MHz) δ 5.70-5.88 (1H, br s, NH), 6.78-6.89 (1H, m, ArH), 6.94-7.17 (5H, m, ArH), 7.22-7.38 (3H, m, ArH); ν max (neat)/cm^{-1} 3420, 1620, 1600; m/z 187 (M^+, 100).

7c, mp 68.5-69.5 °C (hexane) (lit.,[12] mp 51 °C). ^{1}H NMR (270 MHz) δ 4.00-4.19 (2H, br s, NH_2), 6.84 (1H, d, J = 8.1, ArH), 7.22-7.34 (2H, m, ArH), 7.36-7.44 (2H, m, ArH), 7.47-7.56 (3H, m, ArH); ν max (KBr)/cm^{-1} 3440, 3420; m/z 203 (M^+, 100), 205 (M^++2, 31.9). Anal. Calcd for $C_{12}H_{10}NCl$: C, 70.77; H, 4.95; N, 6.88. Found C, 70.85; H, 5.06; N, 6.89.

7d, oil. ^{1}H NMR (270 MHz) δ 2.27 (3H, s, CH_3), 3.36-3.69 (2H, br s, NH_2), 6.69 (1H, d, J = 7.7, ArH), 6.96 (1H, s, ArH), 6.97 (1H, d, J = 7.7, ArH), 7.25-7.50 (5H, m, ArH); ν max (KBr)/cm^{-1} 3450, 3370; m/z 183 (M^+, 100).

7e, oil. ^{1}H NMR (270 MHz) δ 2.15 (3H, s, CH_3), 3.45-3.69 (2H, br s, NH_2), 6.56-6.67 (2H, m, ArH), 7.05 (1H, d, J = 7.7, ArH), 7.25-7.41 (5H, m, ArH); ν_{max} (neat)/cm^{-1} 3440, 3370; m/z 183 (M^+, 100).

7f, mp 76-77 °C (hexane). ^{1}H NMR (270 MHz) δ 3.66-3.88 (2H, br s, NH_2), 6.84 (1H, dd, J_1 = 8.1, J_2 = 9.2, ArH), 7.16-7.33 (3H, m, ArH), 7.36-7.44 (2H, m, ArH), 7.49-7.54 (2H, m, ArH); ν_{max} (KBr)/cm^{-1} 3440, 3310; m/z 187 (M^+, 100). Anal. Calcd for $C_{12}H_{10}NF$: C, 76.99; H, 5.38; N, 7.48. Found C, 76.92; H, 5.51; N, 7.43.

9, oil (lit.,[13] mp 38 °C). ^{1}H NMR (60 MHz) δ 2.80 (3H, s, CH_3), 3.26-3.43 (1H, br s, NH), 6.57 (2H, d, J = 7.8, ArH), 6.90-7.90 (7H, m, ArH); ν_{max} (neat)/cm^{-1} 3430; m/z 183 (M^+, 100).

The results are summarized in Table 1.

Reaction of *N*-Methyl-*N*-phenylaminophthalimide (5) with $AlCl_3$ in HFIP

To **5** (100 mg, 0.396 mmol) in $(CF_3)_2CHOH$ (4 mL) was added $AlCl_3$ (264 mg, 1.98 mmol) under cooling. After stirring the reaction mixture for 20 h, 10% HCl (3 mL) was added under cooling. After 5 min 10% Na_2CO_3 (15 mL) was added under cooling. The aqueous layer was extracted with CH_2Cl_2 (20 mL x 2), and the combined organic layer was washed with brine (15 mL), dried over Na_2SO_4, and concentrated. The crude products were chromatographed on a column of slica gel. Elution with ethyl acetate-hexane (1:4) afforded phthalimide (30 mg, 51.1%). Further elution with ethyl acetate-hexane (1:2) afforded *N*-(4'-methylaminobiphenyl-4-ylmethylamino)phthalimide (**10**) (42 mg, 59.3%), mp 250-251 °C (benzene). ^{1}H NMR (270 MHz) δ 2.86 (3H, s, CH_3), 3.45 (3H, s, CH_3), 3.59-3.72 (1H, br s, NH), 6.65 (2H, d, J = 8.4, ArH), 6.82 (2H, d, J = 8.4, ArH), 7.37 (2H, d, J = 8.4, ArH), 7.42 (2H, d, J = 8.4, ArH), 7.77-7.85 (2H, m, ArH), 7.89-7.96 (2H, m, ArH); ν_{max} (KBr)/cm^{-1} 3430, 1790, 1730; m/z 357 (M^+, 100). Anal. Calcd for $C_{22}H_{19}N_3O_2$: C, 73.93; H, 5.36; N, 11.76. Found C, 73.93; H, 5.50; N, 11.54.

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