REACTION OF 1-HYDROXYPHTHALIMIDE DERIVATIVES WITH ALUMINUM CHLORIDE IN BENZENE

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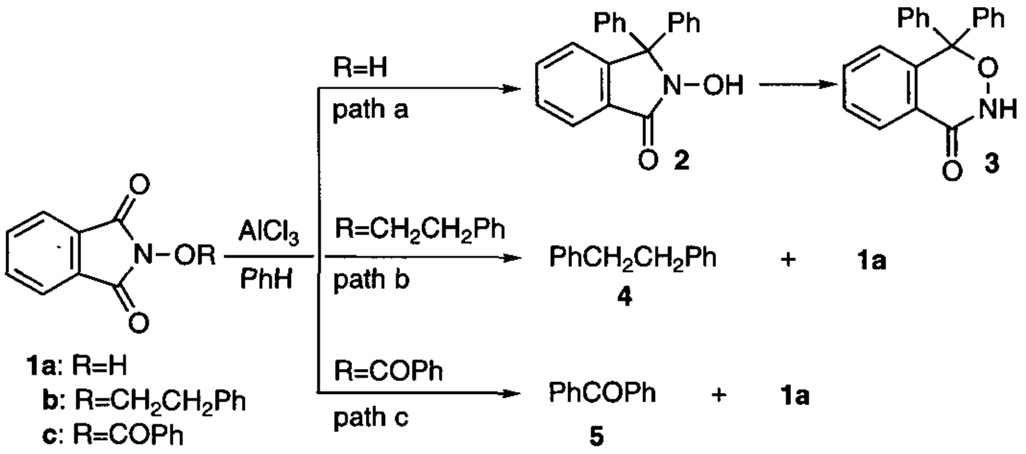
Abstract --- The reaction of 1-hydroxyphthalimide derivatives with $AlCl_3$ in benzene has been investigated. From 1-hydroxyphthalimide (**1a**) 2-hydroxy-3,3-diphenyl-2,3-dihydroisoindol-1-one (**2**) and 1,1-diphenyl-1*H*-benzo[*d*][1,2]oxazin-4-one (**3**) are obtained by initial attack of benzene on the imide carbonyl, assisted by the neighboring oxygen atom. Heating **2** with Lewis acid ($AlCl_3$) in benzene results in ring expansion to afford **3**, while heating **3** with protic acid (H_2SO_4) leads to ring contraction to give **2**. From *O*-(2-phenethyl)- and *O*-benzoyl derivatives (**1b** and **c**), 1,2-diphenylethane (**4**) and benzophenone (**5**) are obtained, respectively, by the heterolytic cleavage of an C-O bond.

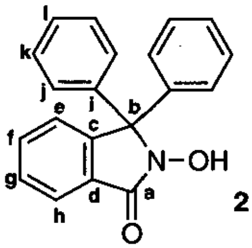
Previously we reported the $AlCl_3$-mediated heterolytic cleavage of the N-O bond of *N*-methoxy-*N*-phenylamides.[1] This cleavage reaction provides a new source of *N*-acyl-*N*-arylnitrenium ions[2] and leads to the nucleophilic intramolecular migration of the methoxy group from the nitrogen to the *ortho* position of the benzene ring.

In an extension of this work, we have investigated the reaction of 1-hydroxyphthalimide derivatives with $AlCl_3$ in benzene, in the expectation that $AlCl_3$-mediated cleavage of the N-O bond might give a diacylnitrenium ion[3] which will be trapped by solvent benzene. However, the results are different from expectation.

When the progress of the reaction of **1a** with $AlCl_3$ in benzene was monitored by tlc, production of two new compounds was observed: compound (**2**), having a lower *Rf* value, was gradually converted to **3** (which has a higher *Rf* value) and disappeared at the end of the reaction (7 h reflux). Isolation of **2** and **3** by silica gel column chromatography was performed and structures of them were determined unambiguously by spectral and X-ray analyses.

Scheme 1. Reaction of 1-hydroxyphthalimide derivatives with $AlCl_3$ in C_6H_6





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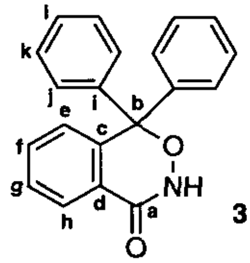

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Table. ^{13}C-Nmr chemical shifts (δ ppm) of **2** and **3**[a)]

position	**2**	**3**
a	164.20	156.57
b	76.12	96.23
c	139.48	141.67
d	unassigned	128.07
i	146.52	146.65
e f g h j k l	123.63 123.97 128.21 128.26 128.37 132.15	122.05 123.88 127.22 128.37 129.04 131.0

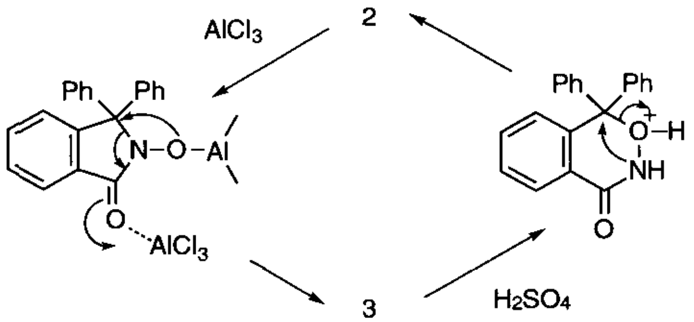
a)The data were taken in $CDCl_3$ at 67.8 MHz.

The ^{13}C-nmr spectrum of **2** shows 8 peaks for aromatic carbons, indicating that two peaks are overlapped. X-ray crystallographic analysis revealed the structure of **2** to be

2-hydroxy-3,3-diphenyl-2,3-dihydroisoindol-1-one. The structure of **3** was determined to be 1,1-diphenyl-1*H*-benzo[*d*][1,2]oxazin-4-one by spectral analyses. ^{13}C-Nmr data are presented in the Table.

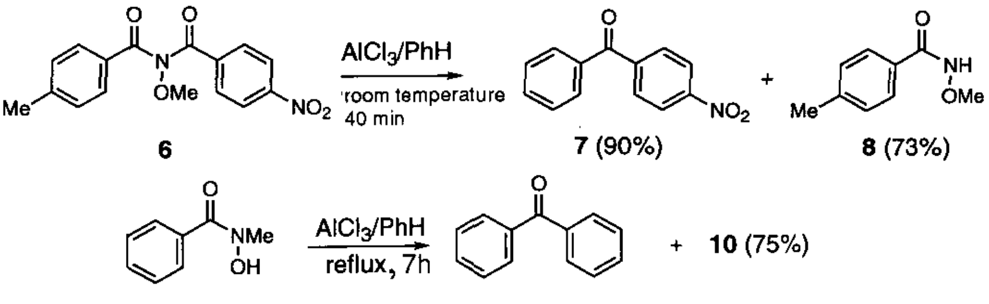
Heating **2** for 7 h with $AlCl_3$ in benzene resulted in ring expansion to afford **3** in 65% yield. On the other hand, heating **3** for 1 h in 30% H_2SO_4-dioxane leads to ring contraction to give **2** in 93% yield. In the reverse reaction, protonation on the oxygen atom induces cleavage of the C-O bond and subsequent recombination forms a C-N bond, as shown in Scheme 2.

Scheme 2. Ring expansion and ring contraction



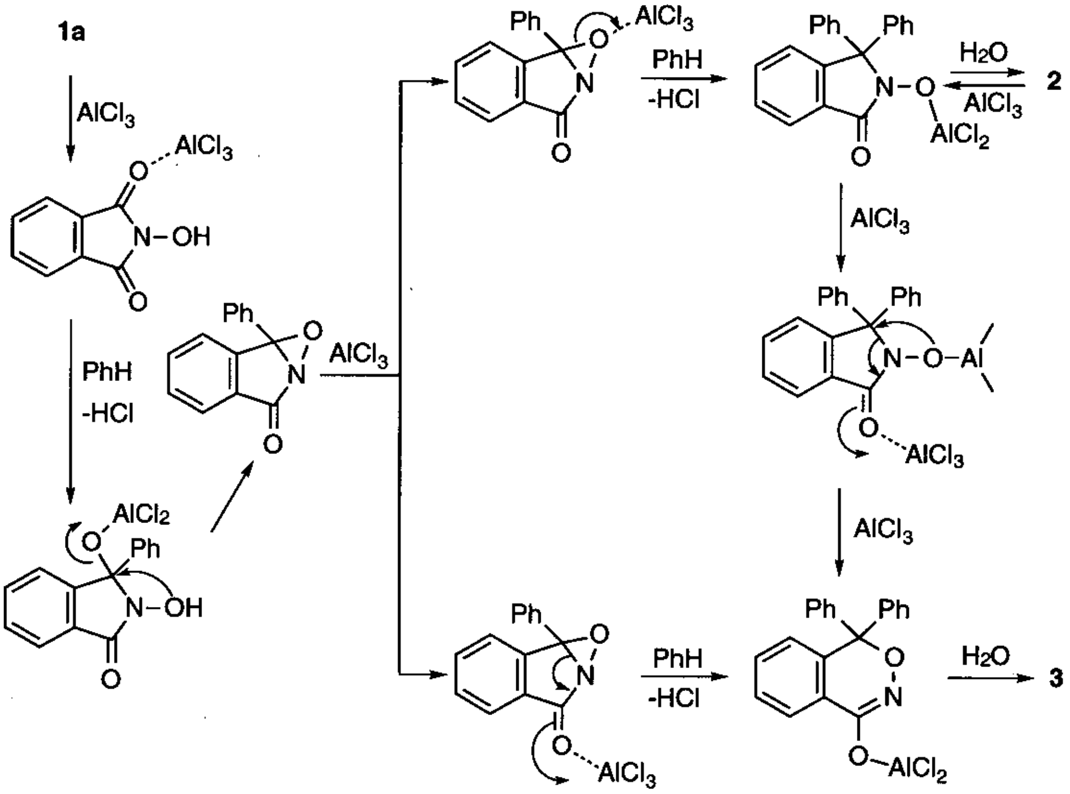
An acyclic *N*-alkoxyimide, *N*-methoxy-*N*-(4-methylbenzoyl)-4-nitrobenzamide (**6**), reacted with $AlCl_3$ in benzene (room temperature, 40 min) to give 4-nitrobenzophenone

Scheme 3. Reaction of 1-hydroxy- and 1-methoxyamide derivatives with $AlCl_3$ in C_6H_6



(**7**) (90%) and *N*-methoxy-4-methylbenzamide (**8**) (73%) (Scheme 3). However, phthalimide (**9a**) and 1-phenylphthalimide (**9b**) do not react with $AlCl_3$ under stronger reaction conditions and the starting materials were recovered quantitatively. *N*-Hydroxy-*N*-methylbenzamide (**10**) reacted with $AlCl_3$ in benzene (7 h reflux) to give benzophenone (**5**) (4%) and starting material (**10**) (75%). These results indicate that the 1-hydroxy group of **1a** activates the imide carbonyl for Friedel-Crafts type reactions. The assumed mechanism is presented in Scheme 4.

Scheme 4. Assumed mechanism



When **1b** was submitted to similar reaction conditions, heterolytic cleavage of the C-O bond and subsequent Friedel-Crafts type phenylation occurred to give 1,2-diphenylethane (**4**) (86%) and **1a** (76%) (path b). Similarly, benzophenone (**5**) (81%) and **1a** (74%) were obtained from the *O*-benzoyl compound (**1c**) (path c).

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. ^1H Nmr spectral data are reported in parts per million (δ) relative to Me_4Si. Infrared 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. Compounds (**1a**, **4**, **5**, **7**, **8**, and **9a**) were purchased from Tokyo Kasei Kogyo Co. Compound (**1c**) and (**9b**) were prepared by the literature methods.[4,5] Compound (**1b**) was prepared from the potassium salt of **1a** and 2-bromoethylbenzene in *N*,*N*-dimethylformamide in 71% yield, mp 93-94 °C (from benzene-hexane). ^1H Nmr δ 3.13 (2H, t, J=6.9, $OCH_2C\underline{H_2}$), 4.40 (2H, t, J=6.9, $OC\underline{H_2}CH_2$), 7.22 (5H, s, ArH), 7.73 (4H, s, ArH); $\nu_{max}(KBr)/cm^{-1}$ 1735; m/z 163 (M^+-104, 12.9%), 105 (100). Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found C, 72.12; H, 5.09; N, 5.20. Compound (**6**) was prepared by the Schotten-Baumann reaction, using 4-nitrobenzoyl chloride and **8**, mp 134-135 °C (benzene-hexane). ^1H Nmr δ 2.35 (3H, s, CH_3), 3.92 (3H, s, OCH_3), 7.12 (2H, d, J=8.0, ArH), 7.55 (2H, d, J=8.0, ArH), 8.28 (4H, s, ArH); $\nu_{max}(KBr)/cm^{-1}$ 1740; m/z 314 (M^+, 3.36), 119 (100). Anal. Calcd for $C_{16}H_{14}N_2O_5$: C, 61.14; H, 4.49; N, 8.91. Found C, 61.10; H, 4.63; N, 8.97.

2-Hydroxy-3,3-diphenyl-2,3-dihydroisoindol-1-one (2) and **1,1-diphenyl-1*H*-benzo[*d*][1,2]oxazin-4-one (3); path a**

To **1a** (200 mg, 1.23 mmol) in benzene (8 ml) was added $AlCl_3$ (817 mg, 6.13 mmol) with cooling. After refluxing the reaction mixture for 1.5 h, 10% HCl (10 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 benzene-ethyl acetate (2:1) afforded **3** (232 mg, 63%), mp 193-195 °C (from benzene-hexane). ^1H Nmr δ 7.11-7.79 (14H, m, ArH), 8.12 (1H, br s, NH); $\nu_{max}(KBr)/cm^{-1}$ 3325, 1675; m/z 301 (M^+, 16.4), 208 (100). Anal. Calcd for $C_{20}H_{15}NO_2$: C, 79.72; H, 5.02; N, 4.65. Found C, 79.80; H, 5.19; N, 4.57. Further elution with the same solvent mixture afforded **2** (65 mg, 18%), mp 206-208 °C (AcOEt). ^1H Nmr δ 7.00-7.67 (14H, m, ArH); $\nu_{max}(KBr)/cm^{-1}$ 3100, 1685; m/z 301

(M+, 14.6), 208 (100). Anal. Calcd for $C_{20}H_{15}NO_2$: C, 79.72; H, 5.02; N, 4.65. Found C, 79.68; H, 5.28; N, 4.92. Compound (**2**) was gradually converted to **3** under the reaction conditions and **3** was obtained in 91% yield when the reaction time was prolonged to 7 h.

Synthesis of 3 from 2

A mixture of **3** (213 mg, 0.708 mmol), 30% H_2SO_4 (10 ml), and dioxane (10 ml) was refluxed for 1 h. After the reaction, H_2O (10 ml) was added and the solution 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 residue was chromatographed on a column of silica gel with benzene-ethyl acetate (2:1) as an eluent to give **2** (198 mg, 93%), mp 205-208 °C.

X-Ray Analysis of 2

#A12001-001 $C_{20}H_{15}NO_2$ F.W.=301, mp 206-208 °C (acetone-CH_2Cl_2)

Crystal data: a=9.584(3) Å, b=9.704(4) Å, c=9.254(2) Å, α=117.64(2)°, β=92.47(2)°, γ=94.90(3)°, V=756.3(4) Å^3, triclinic, $P\bar{1}$, Z=2, Dx=1.32g/cm^3, F(000)=316, μ(Cu Kα)=6.00cm^{-1}.

The diffraction experiment was carried out using a colorless transparent single crystal with dimension of 0.40x0.50x0.30 mm. The diffractometer MXC18(Mac Science) was used with graphite-monochromated Cu Kα radiation (λ=1.5418 Å). The unit cell dimensions were determined from angular setting of 20 reflections (2θ values in the range of 50-60°). 2495 unique reflections (2$\theta \leq$130°) were measured, of which 2465 with Fo>0 σ(Fo) were considered as observed. Absorption corrections were applied to the data.[7] The structure was solved by the direct method using SHELX586[6] and the difference Fourier method. The refinement of atomic parameters was carried out using the full matrix least squares methods.[7] Anisotropic thermal parameters were used for all non-H atoms, while only coordinates of H atoms were refined. The atomic scattering factors were taken from "International Tables for X-ray Crystallography".[8] The final R value is 0.042 (Rw = 0.061).

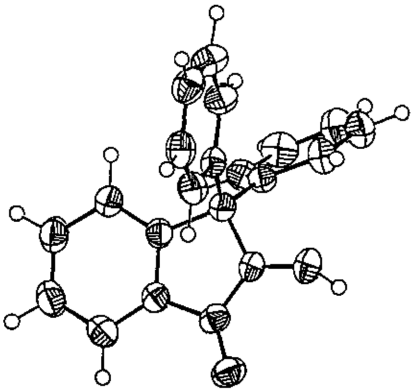


Figure 1. Parallel view of **2**

1,2-Diphenylethane (4); path b

To **1b** (200 mg, 0.80 mmol) in benzene (8 ml) was added $AlCl_3$ (531 mg, 3.98 mmol) with cooling. After stirring the reaction mixture for 0.5 h at room temperature, 10% HCl (10 ml) was added with cooling. The aqueous layer was extracted with CH_2Cl_2 (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 silica gel. First elution with benzene-ethyl acetate (2:1) afforded **4** (124 mg, 86%), mp 46-48 °C (lit.,[9] mp 52 °C), and further elution with the same solvent mixture afforded **1a** (98 mg, 76%), mp 234-236 °C (benzene-AcOEt) (lit.,[10] mp 230 °C).

Benzophenone (5), path c

To **1c** (200 mg, 0.75 mmol) in benzene (8 ml) was added $AlCl_3$ (499 mg, 3.98 mmol) with cooling. After stirring the reaction mixture for 0.5 h at room temperature, 10% HCl (10 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 silica gel. First elution with benzene-ethyl acetate (5:1) afforded **5** (111 mg, 81%), the structure of which was determined by comparison of spectral data with those of an authentic sample. Further elution with the same solvent mixture afforded **1a** (90 mg, 74%), mp 235-237 °C (benzene-AcOEt).

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