An Intramolecular Photosubstitution Reaction of N-(2,4-Dibromonaphthyl)-arenecarboxamide: Synthesis of 2-Arylnaphthoxazole

In-Soo Bae, Yoo-Shin Kim, and Yong-Tae Park

Department of Chemistry, Kyungpook National University, Daegu 702-701, Korea

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Photoreactions of N-(2,4-dibromonaphthyl)arenecarboxamides in basic medium result in the intramolecular substituted products, 2-aryl-8-bromonaphthoxazoles in moderate yields and further photoreactions of the products afford the reduced products, 2-arylnaphthoxazoles. These reactions are straightforward for syntheses of naphthoxazole derivatives. Since the intramolecular photosubstitution of the bromoarenecarboxamide by the oxygen of its amide group is more effective than the photoreduction of the substituted product, 2-aryl-8-bromonaphthoxazole in basic medium, the intramolecular substituted product, 2-aryl-8-bromonaphthoxazole can be isolated. A charge-transfered excited singlet state of an imidol form of the 2-bromoarenecarboxamide is involved in the photosubstitution, whereas an excited triplet state of the 2-aryl-8-bromonaphthoxazole is closely involved in the photoreduction.

Key Words: Intramolecular photosubstitution, 2-Arylnaphthoxazole, N-(2,4-Dibromonaphthyl)benzamide, Charge-transferred excited singlet state, Photoreduction

Introduction

In 1999, we reported intramolecular photosubstitution reaction of N-(2-halophenyl)pyridinecarboxamide by its amide group. Photoreactions of N-(2-halo-phenyl)pyridine-carboxamides afforded 2-pyridylbenzoxazoles in basic medium. The substitution reaction occurs via an intramolecular aromatic electrophilic addition/elimination mechanism of the charge-transferred excited state from the imidolate anion of the N-(2-halophenyl)pyridinecarboxamide. We recently reported intramolecular photosubstitution reactions of 2'-halobenzenilides and N-(2-halo-phenyl)cyclohexane-carboxamides. Photoreaction of 2'-bromobenzenilide produced 2-phenylbenzoxazole in basic medium. Photoreaction of N-(2-halophenyl)cyclohexanecarboxamide led to 2-cyclohexylbenzoxazole. These reactions are quite peculiar because the halogens of less reactive haloarenes toward nucleophilic aromatic substitution were displaced by oxygen of its amide groups. The reactions are also invaluable for benzoxazole ring formation. Thus, it is necessary to extend and generalize these reactions.

A few similar precedents have been reported. Ramakrishnan and coworkers described that intramolecular photosubstitution of o-halothioacetanilides afforded 2-methylbenzothiozoles. They proposed electron-transfer mechanism. Bowman and coworkers described that intramolecular photosubstitution reactions of o-iodothiobenzenilide and o-iodothioacetanilide yielded 2-phenylbenzothiazole and 2-methylbenzothiazole, respectively. However, these reactions are not completely understood and generalized. This work describes that the intramolecular photosubstitution reactions occurred in the photoreactions of N-(2,4-dibromonaphthyl)-arenecarboxamides in acetonitrile and acetonitrile containing bases, and in situ photoreductions of the substituted products.
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dibromonaphthyl]benzamide (1a, 0.8 mmole) containing 50 mL of aqueous sodium hydroxide (2 M) was irradiated with a Hg-lamp (450 W) for 2 h, intramolecular substitution product, 2-phenyl-8-bromonaphth[1,2-d]oxazole (3a) and its reduced product, 2-phenynaphth[1,2-d]oxazole (4a) were obtained in 31% and 42% yields, respectively (Table 1). No dark reactions were observed in this case and all other cases. Short irradiation (10 min) upon 1a afforded only 2-phenyl-8-bromonaphth[1,2-d]oxazole (3a) in good yield (60%). In acetonitrile without base the photosubstitution reaction of 1a occurred to give 3a (40%). The intramolecular photosubstitution product was readily recognized by IR and MS spectra: imine (C = N) stretching appeared at 1486 cm⁻¹ (KBr), whereas secondary amide N-H and carbonyl stretching of the starting material disappeared; characteristic molecular ion peaks containing one bromine appeared at m/z 325 (40%) and 323 (40%).

Longer irradiation (3 h) upon 1a induced reduction of the intramolecular photosubstituted product (2-phenyl-8-bromonaphth[1,2-d]oxazole) formed initially, to give 2-phenyl-naphth[1,2-d]oxazole in moderate yield (33%, Table 1). The structure of 2-phenynaphth[1,2-d]oxazole was readily determined by MS and ¹H NMR spectra; a molecular ion peak without bromine atom was seen at m/z 245; two clear doublet peaks in aromatic region (δ7.82 and 7.75) ppm were seen in place of an aromatic singlet peak (δ 8.11) of the photosubstitution product, 3a.

When an acetonitrile solution of 2-bromonaphthylpyridinecarboxamide 1b was irradiated with similar system for 15 min, 2-(4-pyridyl)-8-bromonaphth[1,2-d]oxazole (3b) was formed (41%, Table 1). Further irradiation of the reaction mixture produced 2-(4-pyridyl)naphth[1,2-d]oxazole (4b) in 32% yield. Irradiation upon haloarene 1c for 15 min gave 2-(β-naphthyl)-8-bromonaphth[1,2-d]oxazole (3c) in 40% yield. If the irradiation time was longer (4 h), 2-(β-naphthyl)naphth[1,2-d]oxazole (4c) was obtained in 25% yield. Details for identification of these products are given in experimental section. These photoreactions are new and simple for the syntheses of derivatives of naphthoxazole, although several thermal reactions for the naphthoxazole ring formation are known.4

In order to see reaction sequence, the product formation versus irradiation time was studied (see Figure 1). Before the reaction, the peaks at retention time 18.1 and 2.0 min on the GC chromatogram corresponded to starting material 1a and actenonitrile, respectively. After photoreaction for 30 sec, the peak of 1a decreased while a peak at retention time 12.5 min corresponding to intramolecular substitution product 3a increased. For 7 min reaction time, both substituted products 3a and reduced product 4a (retention time 9.3 min) existed. For 10 min reaction time, 4a increased while 3a decreased. After 15 min, only reduced product was shown. These observations implies that intramolecular photosubstitution reaction is precedent to the photoreduction reaction of the intramolecular substituted product 3a.

In order to clarify the reaction mechanism, the UV absorption behavior of 1a was observed in the presence of NaOH and the reactivities were studied under several conditions (Table 2). The absorption maximum of 1a appeared at 293 nm (ε = 1.0 × 10⁴ L/molecm) in acetonitrile. In the presence of NaOH (acetonitrile/2 M NaOH = 9/1) the absorption maximum moved to 327 nm (not shown) as in the case of N-(2-bromophenyl)pyridinecarboxamide.13 We believe that the new absorption maxium is responsible for the formation of the charge-transferred excited singlet state of imidolate anion of 1a.

The relative rates of the formations of 3a was 5 times greater in a basic medium than those in neutral medium acetonitrile (Table 2). In the presence of oxygen, the reduction was affected but substitution. These behaviors were also observed in the reaction of N-(2-halophenyl)pyridinecarboxamide.14 The oxygen effect implies that an excited singlet state is involved in the substitution, whereas an excited triplet state is closely related in the reduction. The effect of

Table 2. The Relative Rates of the product formation in the Photoreaction of N-(2,4-Dibromonaphthyl)benzamide (1a) with a board spectrum of light from a Xenon lamp (400W)

<table>
<thead>
<tr>
<th>solvent</th>
<th>atm</th>
<th>reaction time</th>
<th>Substitution (3a)</th>
<th>Reduction (4a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AN</td>
<td>N₂</td>
<td>1 h</td>
<td>1.0</td>
<td>0.1</td>
</tr>
<tr>
<td>AN/H₂O NaOH</td>
<td>N₂</td>
<td>1 h</td>
<td>5.1</td>
<td>0.6</td>
</tr>
<tr>
<td>AN/H₂O NaOH</td>
<td>O₂</td>
<td>1 h</td>
<td>5.0</td>
<td>0.2</td>
</tr>
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</table>

*The concentration of the substrates used is 3 × 10⁻³ M. *AN/2M-NaOH = 8/2.
base on the reaction can be explained by assuming the involvement of charge-transferred excited singlet state from the imidolate anion of 1a. The assumption was confirmed by observation of reactivities of N-(2,4-dibromonaphthyl)-N-methylbenzamide (2). The phototoreaction of 2 which can not exist as an imidolate form even in the presence of base produced a reduced product 5 only with minor photocyclized product 6 instead of the intramolecular photosubstituted product. Thus, this result implies that imidolate form is necessary for the substitution reaction.

We propose the following mechanism (Scheme 1). The charge-transferred excited singlet state 7 is populated by excitation of imidolate anion of 1a. The singlet state 7 proceeds to anion 8 by addition of oxygen radical of the imidol anion to the carbon bearing bromine substituent of arene anion moiety. The anion 8 gives 3a by eliminating bromide anion. This explanation is the same as that proposed for the intramolecular photosubstitution of N-(2-halophenyl)pyridine-carboxamide.1a Reduction may occur by eliminating bromide ion from anion radical 10, which is produced by charge-transfer to a triplet state of 3a from base \( \text{OH} \), to give a naphthyl radical 11 and then abstracting hydrogen atom of 11 to give final product 4a. This explanation is known as electron-transfer mechanism for the photoreduction of haloarene.5

**Experimental Section**

**Material and General procedure.** \( \alpha \)-Naphthylamine, isonicotinic acid, and 2-naphthoyl chloride (all Aldrich) were used without further purification. General procedure is the same as described elsewhere.1a

**Synthesis of 2,4-Dibromonaphthylamine.** In a 250 mL, three-necked, round-bottomed flask with a mechanical stirrer, dropping funnel, and condenser were placed 3.6 g (2.5 m mole) of \( \alpha \)-naphthylamine and 150 mL of chloroform. To the stirred solution was dropwise added 3 mL of chloroform solution of bromine (0.8 mL, 5 m mole). The mixture was stirred at 50 °C for one day. After evaporating the solvent, purple solids were collected. Crystallization from aqueous methanol gave 7.1 g (purple needle, 94%). mp 118 °C (lit 118 °C).6

**Synthesis of N-(2,4-Dibromonaphthyl)benzamide (1a).** To the pyridine solution of 2,4-dibromonaphthylamine (3 g/50 mL, 10 m mole) in 500 mL flask under ice/water bath, 1.4 mL of benzoyl chloride was added. The mixture was stirred at room temperature for one night. When 300 mL of water was added to the stirred mixture, white solids were obtained. Recrystallization from an aqueous ethanol gave 3.3 g (82%); mp 209 °C; UV (\( \lambda_{\text{max}} \) in CH\(_3\)CN) 233 nm (\( \varepsilon = 1.6 \times 10^4 \) L/mole·cm), 293 nm (\( \varepsilon = 1.1 \times 10^4 \) L/mole·cm); IR (KBr) 3236, 1643, 1513 cm\(^{-1}\); 1H NMR (400 MHz, CDCl\(_3\)) \( \delta \): 8.25 (d, 1H, \( J = 8.5 \) Hz, C\(_{5}'\)-H), 8.06 (d, \( J = 8.5 \) Hz, 2H, C\(_{2,6}'\)-H), 8.05 (s, 1H, C\(_{3}'\)-H), 7.95 (d, \( J = 8.5 \) Hz, 1H, C\(_{8}'\)-H), 7.81 (s, 1H, NH), 7.64 (t, \( J = 8.5 \) Hz, C\(_6'\)-H), 7.59 (t, \( J = 8.5 \) Hz, 1H, C\(_7'\)-H), 7.56 (m, 3H, C\(_{3,4,5}'\)-H); MS m/z (rel intensity) 407 (2, M\(^+\)+4), 405 (3, M\(^+\)+2), 403 (1, M\(^+\)), 326 (35), 105 (92).

Anal. Calcd for C\(_{17}\)H\(_{11}\)ONBr\(_2\): C, 50.41; H, 2.74; N, 3.46. Found: C, 50.64; H, 2.72; N, 3.23.

**Synthesis of N-(2,4-Dibromonaphthyl)4-pyridinecarboxamide (1b).** Isonicotinyl chloride was prepared by refluxing 2.5 g of isonicotinic acid in 20 mL of thionyl chloride for 2 h and then evaporating excess thionyl chloride. To isonicotinyl chloride prepared in situ were added 30 mL of pyridine and 7.5 g (0.0025 mole) of 2,4-dibromonaphthylamine. The mixture was stirred for one night. When 300 mL of water was added, white solids were obtained. Recrystallization from aqueous ethanol gave 5.4 g (67%); mp 184 °C; UV (\( \lambda_{\text{max}} \) in CH\(_3\)CN) 234 nm (\( \varepsilon = 2.0 \times 10^4 \) L/mole·cm); IR (KBr) 3221, 1647, 1516 cm\(^{-1}\); 1H NMR (400 MHz, CDCl\(_3\)) \( \delta \): 8.86 (d, \( J = 6.0 \) Hz, 2H, C\(_{2,6}'\)-H), 8.25 (d, \( J = 8.3 \) Hz, 1H, C\(_{5}'\)-H), 8.04 (s, 1H, C\(_8'\)-H), 7.95 (d, \( J = 8.5 \) Hz, 1H, C\(_8'\)-H), 7.81 (s, 1H, NH), 7.64 (t, \( J = 8.5 \) Hz, C\(_6'\)-H), 7.59 (t, \( J = 8.5 \) Hz, 1H, C\(_7'\)-H), 7.56 (m, 3H, C\(_{3,4,5}'\)-H); MS m/z (rel intensity) 406 (2, M\(^+\)+1), 405 (3, M\(^+\)+2), 403 (1, M\(^+\)), 326 (35), 105 (92).

Anal. Calcd for C\(_{16}\)H\(_{10}\)ON\(_2\)Br\(_2\): C, 47.33; H, 2.72; N, 6.90. Found: C, 50.64; H, 2.72; N, 6.74.

**Synthesis of N-(2,4-Dibromonaphthyl)naphthalene-2-carboxamide (1c).** A pyridine solution (3.3 mL) of 2-naphthoyl chloride (all Aldrich) in 20 mL was added to a solution of 2,4-dibromonaphthylamine (3 g, 10 m mole) and isonicotinyl chloride (2.5 g, 10 m mole) in 50 mL of pyridine. The mixture was stirred at room temperature for one night. When 300 mL of water was added, white solids were obtained. Recrystallization from aqueous ethanol gave 7.1 g (purple needle, 94%). mp 118 °C (lit 118 °C).6

**Scheme 1**
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naphthoyl chloride (1.9 g, 0.01 mole) and 2,4-dibromo-1-naphthylamine (3 g, 0.01 mole) was stirred for one night. When 150 mL of water was added to the mixture, white solids were obtained. Recrystallization from chloroform gave 4 g (90%); mp 242 °C; UV (λmax, CHCl3) 234 nm (ε = 1.7 × 10^4 L/mole·cm); IR (KBr) 3029, 2942, 1653, 1566, 1384 cm

Found: C, 83.45; H, 4.63; N, 5.60.

**2-Phenyl-1,2-dijoxazole (4a):** Yield 82 mg (42%); mp 180 °C; IR (KBr) 3049, 3018, 2951, 1713 cm

Anal. Calcd for C17H11ON: C, 83.45; H, 4.63; N, 5.60.

**Synthesis of N-(2,4-Dibromonaphthyl)-N-methylbenzamide (2):** In a 100 mL flask was dissolved 2 g of N-(2,4-dibromonaphthyl)-N-methylbenzamide in 30 mL of acetone at 50 °C. To the warm solution were added 1.2 g of potassium hydroxide power and 1.2 g of methyl iodide (8 m mole) and the mixture was refluxed for 2 h. After evaporation of solvent and excess methyl iodide, 50 mL of water was added to the residue. The mixture was extracted with chloroform. A column chromatography with hexane/ethyl acetate to give 92 mg of 2-((4-oxazolyl)-8-bromonaphth[1,2-d]oxazole. When the irradiation time was 4 h, 2-(4-pyridyl)naphth[1,2-d]oxazole was only obtained (32%).

**2-(4-Pyril)-8-bromonaphth[1,2-d]oxazole (3b):** mp 180 °C; IR (KBr) 3049, 1602, 1485 cm

Found: C, 83.45; H, 4.63; N, 5.60.

**Preparative photoreaction: Photoreaction of N-(2,4-Dibromonaphthyl)benzamide (1a):** To a large quartz immersion well photolysis unit with provision for circulation, the mixture was irradiated with a 450 W mercury lamp (medium pressure) for 2 h. After evaporation of benzyl alcohol, the mixture was extracted with diethyl ether.

2-Phenyl-8-bromonaphth[1,2-d]oxazole (3a): Yield 58 mg (31%); mp 176 °C; UV (λmax, CHCl3) 350 nm (ε = 2.5 × 10^4 L/mole·cm); IR (KBr) 3049, 1602, 1485, 777, 712 cm

Anal. Calcd for C17H11ON: C, 83.45; H, 4.63; N, 5.60.

**Photoreaction of N-(2,4-Dibromonaphthyl)-4-pyridinecarboxamide (1b):** The irradiation of N-(2,4-dibromonaphthyl)-4-pyridinecarboxamide (1b) for 15 min in the same procedure as in the case of 1a gave 2-(4-pyridyl)-8-bromonaphth[1,2-d]oxazole (41%). While the irradiation time was 4 h, 2-(4-pyridyl)naphth[1,2-d]oxazole was only obtained (32%).

**Photoreaction of N-(2,4-Dibromonaphthyl)-8-bromonaphth[1,2-d]oxazole was only obtained (32%).

**2-(4-Pyril)-8-bromonaphth[1,2-d]oxazole (4b):** mp 166 °C; IR (KBr) 3171, 3047, 1602, 1485 cm

Anal. Calcd for C17H11ON: C, 83.45; H, 4.63; N, 5.60.
Found: C, 83.45; H, 4.63; N, 5.60.

**Photoreaction of N-(2,4-Dibromonaphthyl)naphthalene-2-carboxamide (1c):** Photoreaction of N-(2,4-Dibromonaphthyl)-2-naphthalenecarboxamide in base medium for 15 min produced 2-((β-naphthyl)-8-bromonaphth[1,2-d]oxazole (40%). When the irradiation time was 4 h, 2-(β-naphthyl)-naphth[1,2-d]oxazole was only obtained (25%).

2-Phenyl-8-bromonaphth[1,2-d]oxazole (3c): mp 210 °C; IR (KBr) 3055, 1631, 1579, 1543, 1346 cm

Anal. Calcd for C17H11ON: C, 83.45; H, 4.63; N, 5.60.
Found: C, 83.45; H, 4.63; N, 5.60.
(m, 3H); MS, m/z (rel intensity) 295 (100, M+).

Found: C, 85.61; H, 4.40; N, 4.80.

Photoreaction of N-(2,4-dibromonaphthyl)-N-methylbenzamide (2). Irradiation of N-(2,4-dibromonaphthyl)-N-methylbenzamide (2, 188 mg) for 2 h in the same procedure as in the case of 1a gave N-methyl-N-naphthylbezamide (5), and N-methylbenz[fl]phenanthridone (6) in 14% and 30% yield, respectively.

N-Methyl-N-naphthylbenzamide (5): Yield 16.4 mg (14%): mp 119 ºC; UV (λ_max, CH_3 CN) 286 nm (ε = 2.0 × 10^4 L/mole·cm); IR (KBr) 3056, 2935, 1640, 1593 cm⁻¹; ¹H NMR (400 MHz, CDCl_3) δ 8.03 (d, J = 8.1 Hz, 1H), 7.86 (d, J = 8.1 Hz, 1H), 7.62 (m, 3H), 7.24 (m, 3H), 7.09 (m, 4H), 3.54 (s, 3H); MS, m/z (rel intensity) 261 (50%, M+), 105 (100%).

Anal. Calcd for C_18H_15NO: C, 82.73; H, 5.79; N, 5.36.
Found: C, 82.61; H, 5.41; N, 5.30.

N-Methylbenz[fl]phenanthridone (6): Yield 34.8 mg (30%): mp 136 ºC; UV (λ_max, CH_3 CN) 367 nm (ε = 4.4 × 10^4 L/mole·cm); IR (KBr) 3059, 3045, 2960, 1646, 1608, 1312 cm⁻¹; ¹H NMR (400 MHz, CDCl_3) δ 8.58 (d, J = 8.1 Hz, 1H), 8.30 (m, 3H), 7.80 (m, 6H), 4.07 (s, 3H); MS, m/z (rel intensity) 259 (80%, M+), 258 (100%, M+ -1).

Anal. Calcd for C_18H_13NO: C, 83.37; H, 5.05; N, 5.40.
Found: C, 83.40; H, 5.10; N, 5.42.

Reaction sequence. An acetonitrile solution of 1a containing 2 M-NaOH was irradiated under nitrogen as in the case of the preparative photoreaction of 1a. A small portion of the reaction solution (20 µL), periodically withdrawn, was analyzed on GC (Hewlett-Packard 4890) using a capillary column (30 m × 0.25 mm × 2.25 µm) containing crosslinked PHME. The temperature on oven increased a rate 10 ºC per minute from 200 ºC to 280 ºC. The temperature of injection and detection pots were 240 and 280 ºC, respectively.

Kinetic experiment. An acetonitrile solution of 1a with/without 2 M NaOH (3.0 × 10⁻³ M, 2 mL) was prepared in UV cuvette cell (path length 1 cm), deaerated by nitrogen (or aerated by oxygen), and irradiated by 400 W Xe-lamp for 1 hr. A small portion of the solution (5 µL) was analyzed on GC using the capillary column. The relative rate was measured by comparing the peak area on the GC chromatograph.

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