Photoinduced Intramolecular Substitution Reaction of Aryl Halide with Carbonyl Oxygen of Amide Group†

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Photoreaction of *N*-(*o*-halophenyl)acetamide in basic acetonitrile produces an intramolecular substituted product, 2-methylbenzoxazole in addition to reduced product, acetanilide, whereas photoreaction of *N*-(*o*-halobenzyl)acetamide affords a reduced product, *N*-benzylacetamide only. On the basis of preparative reaction, kinetics, and UV/vis absorption behavior, an electrophilic aromatic substitution of aryl halide with oxygen of its amide bond are proposed.

Key Words : *N*-(*o*-Halophenyl)acetamide, *N*-(*o*-Halobenzyl)acetamide, Intramolecular photosubstitution, Photoreduction, Methylbenzoxazole

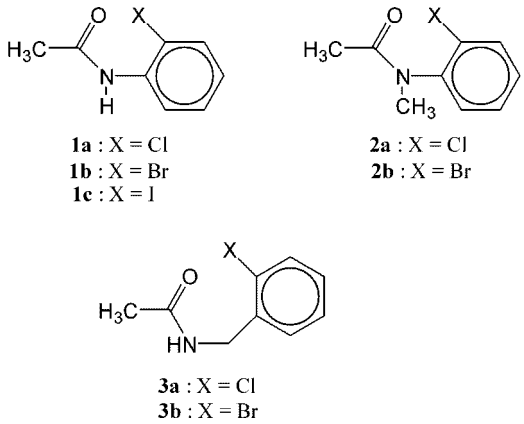
Introduction

We are interested in intramolecular photosubstitution of aryl halide with its amide and thioamide groups. There are a few reports for intramolecular photosubstitution of aryl halide with sulfur of its thioamide: intramolecular photosubstitution of halide ion of *o*-halothioacetanilide and *o*-halothiobenzanilide with sulfur of thioamide group produced 2-methylbenzothiazole and 2-phenylbenzothiazole, respectively;[1-3] intramolecular photosubstitution of halide ion of *N*-(2-chloro-3-pyridinyl)arylamide with sulfur of thioamide yielded 2-phenylthiazolo[5,4-*b*]pyridine.[4] These reactions are straightforward and valuable in synthesis of thiazole derivatives.

We have recently reported intramolecular photosubstitution of *N*-(2-halophenyl)arenecarboxamide and *N*-(2-halophenyl)-cyclohexanecarboxamide with carbonyl oxygen of amide portion to yield 2-arylbenzoxazole and 2-cyclohexylbenzoxazole, respectively,[5-7] and mechanism of the reaction.[5] The mechanism is that at charge-transfer state an electrophilic addition of oxygen of amide group to the halophenyl anion radical to give a cyclohexadienyl anion radical and eventually elimination of halide ion produce pyridinylbenzoxazole. We hope to extend the reaction to *o*-haloacetanilide and clarify the mechanism for intramolecular photosubstitution of *N*-(2-halophenyl)alkanecarboxamide.

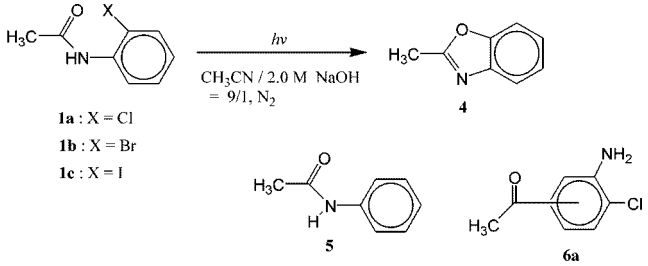
Results and Discussion

Two *N*-(*o*-halophenyl)acetamide (**1a**, **1b**) were synthesized by acetylation of 2-haloaniline with acetic anhydride in weak acidic condition (Scheme 1). *N*-(*o*-Halophenyl)-*N*-methylacetamide (**2a**, **2b**) were prepared by methylation of **1a** and **1b** with methyl iodide in basic acetone.[8] *N*-(*o*-Halobenzyl)acetamide (**3a**, **3b**) were synthesized by acetylation of *o*-halobenzylamine with acetic anhydride in weak acidic condition. The haloarylacetamides **1**, **2** and *o*-halobenzylamides **3** have been identified by the spectral properties (^{1}H NMR, UV, IR, mass spectra) and elemental analyses.



Scheme 1

When an acetonitrile solution of *N*-(*o*-bromophenyl)-acetamide (**1b**) containing aqueous NaOH was irradiated by a Hg lamp under nitrogen, intramolecular substituted product, 2-methylbenzoxazole (**4**) and reduced product, acetanilide (**5**) were obtained in 27 and 13% yields, respectively (Scheme 2). 2-Methylbenzoxazole could be easily identified by the ^{1}H NMR spectra. Four aromatic protons appear at a range of δ 7.20-7.60, whereas methyl protons occur at δ 2.55 as a singlet (Figure 1): two aromatic protons near oxygen



Scheme 2

†This paper is dedicated to Sang-Chul Shim, exceptional scientist, remarkable man.

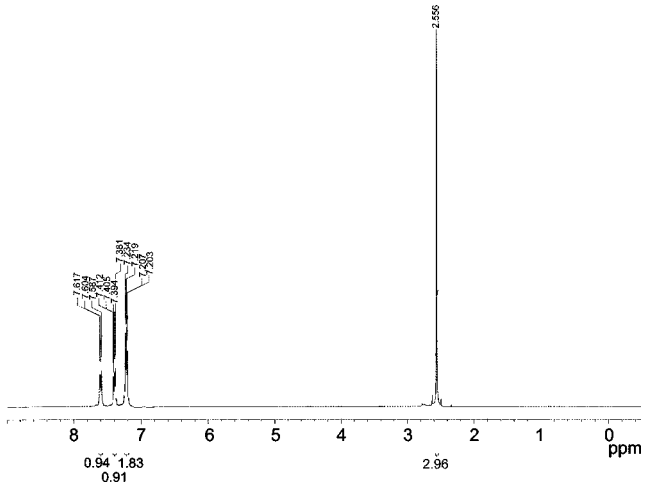


Figure 1. ^{1}H NMR spectra of 2-methylbenzoxazole in $CDCl_3$.

Table 1. Product Yields in the Photoreactions of *N*-(*o*-halophenyl)-acetamide (**1**) and *N*-(*o*-halobenzyl)acetamide (**3**)

Starting compd	Solvent condition	Reation time (min)	Product yield (%)				Recovered (%)
			4	**5**	**6a**	**8**	
1a	CH_3CN/2M NaOH = 9/1	40	10		5[a]		3
1b	CH_3CN/2M NaOH = 9/1	30	27	13			6
1c	CH_3CN/2M NaOH = 9/1	20	4	33			3
3a	CH_3CN/2M NaOH = 9/1	45				27	3
3b	CH_3CN/2M NaOH = 9/1	25				33	8

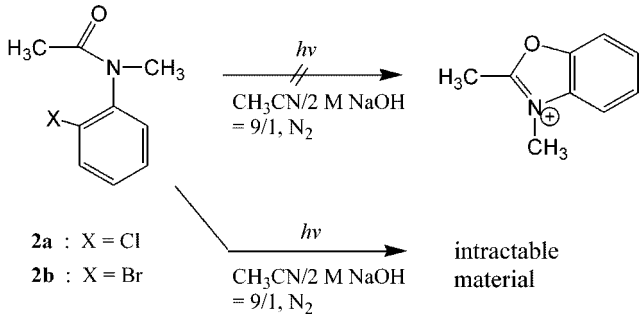
[a]identified by GC/MS only.

and nitrogen of oxazole ring appear at rather low fields (δ 7.60 and 7.40, respectively) and two aromatic protons farther oxygen and nitrogen occur at a little higher field (δ 7.20). Acetanilide was identified by comparing its ^{1}H NMR spectra with that of authentic sample.

The pertinent results of synthetic photoreactions of **1**, **2**, and **3** are shown in Table 1 and Scheme 2. Chloro analog **1a** produced substituted product **4** (10%) and Fries type product **6** (5%).[9] Iodo analog **1c** also produced 2-methylbenzoxazole (4%) and acetanilide (33%).

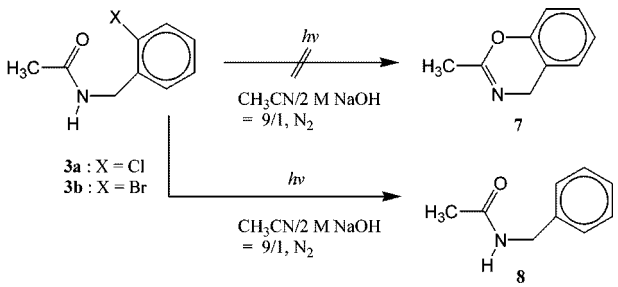
Intramolecular substitution reactions occur in the photoreactions of all halophenyl acetamides **1a**, **1b**, and **1c**, photo-Fries type reaction from only **1a**, and photoreduction reaction from **1c** and **1b**. This results can be explained by the strength of C-X bond: weak C-I bond of **1c** is readily cleaved by excitation to give phenyl and iodine radicals, eventually producing mainly reduced product **5**; strong C-Cl bond of **1a** is inert to the excitation, inducing two alternative reactions, intramolecular substitution leading to benzoxazole **4** and Fries type reactions to **6a**; and medium C-Br bond of **1b** is not only cleaved but also substituted by excitation, eventually producing **4** and **5**.

N-(*o*-Chlorophenyl)-*N*-methylacetamide (**2a**) or *N*-(*o*-bromophenyl)-*N*-methylacetamide (**2b**), which can not exist as imidol form in contrast to **1a-c**, did not produce intramolecular substitution product but intractable materials in the above condition (Scheme 3). This results imply that an imidol form is possibly involved in the intramolecular substitution of **1** as observed in the case of *N*-(*o*-halophenyl)pyridinecarboxamide.[5]



Scheme 3

N-(*o*-Chlorobenzyl)acetamide (**3a**) and *N*-(*o*-bromobenzyl)-acetamide (**3b**) did not produce intramolecular substituted product **7**, but reduced product **8** in the condition (Scheme 4). These substrates can not proceed to a charge-transfer species by excitation because of nonconjugation between the amide group and 2-halophenyl group and thus, reduction reaction occurs exclusively. This results support that conjugated imidolate in a charge transfer state is involved in the intramolecular photosubstitution of **1**.



Scheme 4

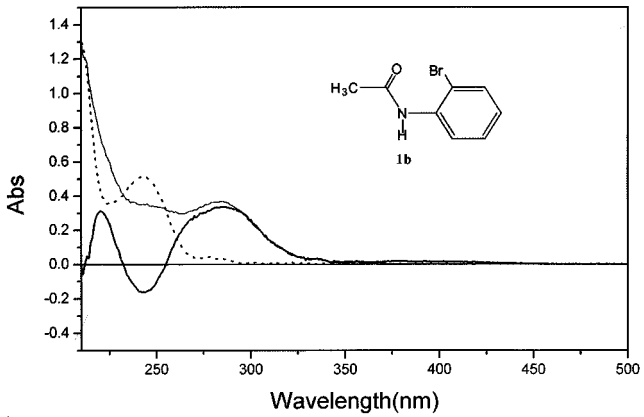


Figure 2. UV/vis absorption change of **1b**: ---, UV/vis absorption spectra of **1b** in acetonitrile; —, that of **1b** in acetonitrile containing NaOH; ━, this spectra was obtained by subtraction of dotted line from the thin line.

Table 2. Relative Rate of the Formation of Products in the Photoreaction of *N*-(2-bromophenyl)acetamide (**1b**)[a] with a monochromatic Light (290 ± 10 nm)

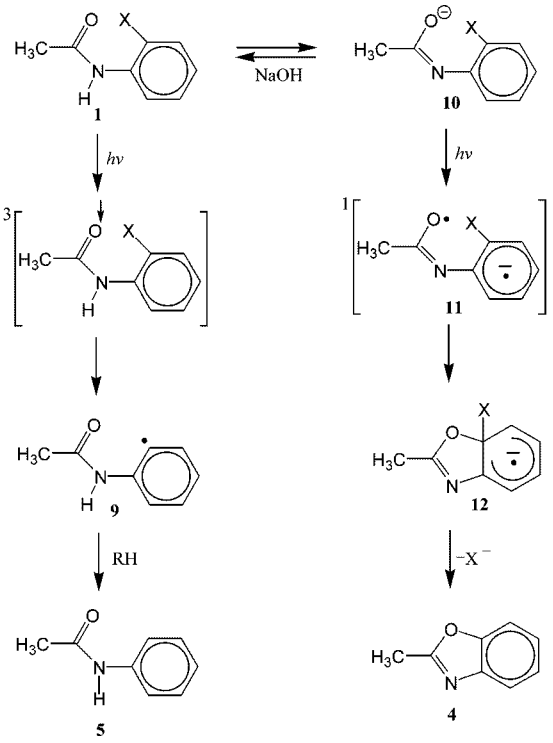
Entry	Medium	Atm	Rel. rate	
			4	**5**
1	CH_3CN	N_2	1.8	0.1
2	CH_3CN/NaOH[c]	N_2	2.7	0.2
3	CH_3CN	O_2	1.8	nd*
4	CH_3CN/NaOH[c]	O_2	2.7	nd*
5	Benzene	N_2	1.0	0.1
6	CH_3OH	N_2	0.8	1.9
7	CH_3CN/Et_3N (2.1 mM)	N_2	2.4	0.5
8	CH_3CN/MMA[b] 5.6 mM)	N_2	2.7	1.2
9	CH_3CN/2 M NaOH[c] Isoprene (0.5 mM)	N_2	2.1	0.4

[a]The concentration of **1b** is 4×10^{-3} M. [b]methyl methacrylate. [c]CH_3CN/2 M NaOH = 13/2. *not detected in GC used.

Blanks reactions were performed. The thermal reaction of **1a** and **1b** under the above conditions for 2 days did not produce a substituted or reduced product. Thus, the reaction that produced 2-methylbenzoxazole and acetanilide are not thermal reactions but photoinduced substitution and reduction reactions.

In order to study the mechanism of the reaction of **1**, the UV/vis absorption behavior and relative rates of **1b** were measured under several conditions (Figure 2 and Table 2). A typical absorption of **1b** in acetonitrile changed to a shapeless spectra in the presence of bases such as NaOH (Figure 2) or KOH (not shown). If subtraction of the typical spectra of **1b** from the shapeless spectra, an absorption peak at about 290 nm appeared. It is believed that the new absorption is due to its charge-transferred singlet state and the state is related to the intramolecular photosubstitution as in the case of *N*-(*o*-halophenyl)pyridinecarboxamide.[5] The conclusion is supported by the following observation that the charge-transferred species could not observed for substrate **2** and **3**, in which charge-transferred excited states are not possible structurally.

In the presence of base, substitution and reduction rates in the photoreaction of **1b** with monochromatic light increased (entries 1, 2). The presence of oxygen did not affect the substitution but reduction (entries 3, 4). This result indicates that singlet states are involved in the substitution and triplet states involved in the reduction. The substitution rate decreased in benzene whereas in methanol, substitution rate decreased and reduction rate increased somewhat. The presence of triethylamine increased both substitution and reduction rate in a small extent. Methyl methacrylate (MMA) or isoprene, radical scavengers did not give an effect on substitution but increased reduction somewhat. Increase of reduction rate in the presence of methanol, MMA, and isoprene can be explained in term of ease availability of hydrogen atom from these substances. No effect of radical scavenger on the substitution implies that the substitution reaction is not a radical-mediated reaction.



Scheme 5

Electrophilic addition and elimination mechanism for the substitution reaction and radical mechanism for reduction reaction are proposed (Scheme 5). The triplet state through intersystem crossing of singlet state of **1** provides energy to cleave C-X bond of **1** homolytically, produce phenyl **9** and halogen radicals, and eventually give reduced product **5**. In base such as NaOH, imidolate anion form **10** is equilibrated in a moderate amount with the keto form. Excitation of the imidolate anions **10** generates singlet charge-transferred species **11**. Electrophilic addition of imidolate radical **11** to 2-halophenyl anion radical to form cyclohexadienyl anion radical **12** and then elimination of halide ion gives substitution product **4**.

Experimental Section

General procedure for the preparation of *N*-(*o*-halophenyl)acetamide (1). In a 20 mL, three-necked, round-bottomed flask with a dropping funnel, thermometer, and condenser is placed 3.4 mL of 2-chloroaniline (0.03 mole). To the stirred solution are added 3.6 mL of acetic anhydride (0.03 mole) slowly within 70 °C and 7 mL of dilute chloric acid (0.1 M). The mixture is stirred at 80 °C for 2 h. The flask is kept at room temperature for 20 min and product isolated by suction filteration. The crystals is washed with water triply. The recrystallization from *n*-hexane gives 4.8 g of *N*-(*o*-chlorophenyl)acetamide.

***N*-(*o*-Chlorophenyl)acetamide (1a)**: yield 4.8 g (88%); mp 87-88 °C; UV (λ_{max} in CH_3CN) 239 nm ($\varepsilon = 1.1 \times 10^4$ L/mole-cm); IR ($CHCl_3$) 3242, 3044, 1663 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.38 (d, J = 7.8 Hz, 1H: C_3-H of Ph),

7.64 (br. s, 1H, NH), 7.38 (d, J = 7.8 Hz, 1H, C_6-H of Ph), 7.28 (t, J = 7.8 Hz, 1H, C_4-H of Ph), 7.04 (t, J = 7.8 Hz, 1H, C_5-H of Ph), 2.25 (s, 3H, CH_3); MS (EI) m/z (rel intensity) 171 (7, M^++2), 169 (20, M^+), 134 (48, M^+-Cl), 127 (100).

Anal. Calcd for C_8H_8ONCl: C, 56.65; H, 4.75; N, 8.26. Found: C, 57.68; H, 4.93; N, 8.11.

***N*-(*o*-Bromophenyl)acetamide (1b)**: yield 5.5 g (80%); mp 92-93 °C; UV (λ_{max} in CH_3CN) 242 nm ($\varepsilon = 8.1 \times 10^3$ L/mole-cm); IR ($CHCl_3$) 3279, 3032, 1660 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.35 (d, J = 7.8 Hz, 1H, C_3-H of Ph), 7.62 (br. s, 1H, NH), 7.55 (d, J = 7.8 Hz, 1H, C_6-H of Ph), 7.34 (t, J = 7.5 Hz, 1H, C_4-H of Ph), 6.98 (t, J = 7.5 Hz, 1H, C_5-H of Ph), 2.17 (s, 3H, CH_3); MS (EI) m/z (rel intensity) 215 (2, M^++2), 213 (2, M^+), 170 (100).

Anal. Calcd for C_8H_8ONBr: C, 44.89; H, 3.77; N, 6.54. Found: C, 45.02; H, 3.75; N, 6.25.

***N*-(*o*-Iodophenyl)acetamide (1c)**: yield 5.9 g (71%); mp 104-105 °C; UV (λ_{max} in CH_3CN) 236 nm ($\varepsilon = 1.2 \times 10^3$ L/mole-cm); IR ($CHCl_3$) 3272, 3028, 1660 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 7.9 Hz, 1H, C_3-H of Ph), 7.79 (d, J = 7.9 Hz, 1H, C_6-H of Ph), 7.36 (br. s, 1H, NH), 7.34 (t, J = 7.9 Hz, 1H, C_4-H of Ph), 6.85 (t, J = 7.9 Hz, 1H, C_5-H of Ph), 2.25 (s, 3H, CH_3); MS (EI) m/z (rel intensity) 260 (13, M^+), 134 (100, M^+-I).

Anal. Calcd for C_8H_8ONI: C, 36.81; H, 3.09; N, 5.37. Found: C, 37.12; H, 2.70; N, 5.03.

Preparation of *N*-(o-halophenyl)-*N*-methylacetamide (2).

N-Methylation of *N*-(*o*-halophenyl)acetamide (**2a**, **2b**) was performed by using Johnstone method[8].

***N*-(*o*-Chlorophenyl)-*N*-methylacetamide (2a)**: yield 0.74 g (81%); UV (λ_{max} in CH_3CN) 272 nm ($\varepsilon = 2.1 \times 10^3$ L/mole-cm); IR ($CHCl_3$) 3062, 2934, 1668 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.53 (dt, J = 9.4 Hz, 1H, of Ph), 7.36 (dd, J = 6.1 Hz, 2H, of Ph), 7.30 (dt, J = 9.4 Hz, 1H, of Ph), 3.20 (s, 3H, N-CH_3), 1.81 (s, 3H, CH_3); MS (EI) m/z (rel intensity) 186 (16, M^++3), 184 (50, M^++1), 148 (100).

Anal. Calcd for $C_9H_{10}ONCl$: C, 58.87; H, 5.49; N,7.63. Found: C, 58.70; H, 5.41; N, 7.43.

***N*-(*o*-Bromophenyl)-*N*-methylacetamide (2b)**: Yield 0.97 g (86%); UV (λ_{max} in CH_3CN) 270 nm ($\varepsilon = 3.2 \times 10^3$ L/mole-cm); IR ($CHCl_3$) 3059, 2932, 1668 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.1 Hz, 1H, C_3-H of Ph), 7.37 (t, J = 8.1 Hz, 1H, C_4-H of Ph), 7.30 (m, 2H), 3.19 (s, 3H, -NCH_3), 1.81 (s, 3H, CH_3); MS (EI) m/z (rel intensity) 229 (4, M^++2), 227 (4, M^+), 148 (100, M^+-Br).

Anal. Calcd for $C_9H_{10}ONBr$: C, 47.39; H, 4.42; N, 6.14. Found: C, 47.43; H, 4.25; N, 6.03.

General procedure for the preparation of *N*-(*o*-halobenzyl)acetamide (3). In a 20 mL, three-necked, round-bottomed flask with a dropping funnel, thermometer, and condenser is placed 0.6 mL of 2-chlorobenzylamine (5 mmole). To the stirred solution are added 1mL of acetic anhydride (10 mmole) solution within 70 °C and 10 mL of chloric acid (0.1 M). The mixture is stirred at 80 °C for 2h. The flask is kept at room temperature for 20 min and the product isolated by suction filteration. The crystals are washed with water. The recrytallization from n-hexane gives 0.85 g of *N*-(o-chlorobenzyl)acetamide (**3a**).

***N*-(*o*-Chlorobenzyl)acetamide (3a)**: yield 0.85 g (75%); mp 60-61 °C; UV (λ_{max} in CH_3CN) 264 nm ($\varepsilon = 2.2 \times 10^4$ L/mole-cm); IR ($CHCl_3$) 3264, 3085, 1642 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.40 (m, 2H), 7.24 (m, 3H), 5.89 (br. s, 1H, NH), 4.05 (d, J = 6.0 Hz, 2H, CH_2), 2.20 (s, 3H, CH_3); MS (EI) m/z (rel intensity) 185 (2, M^++2), 183 (7, M^+), 148 (100).

Anal. Calcd for $C_9H_{10}ONCl$: C, 58.87; H, 5.49; N, 7.63. Found: C, 59.32; H, 5.65; N, 7.32.

***N*-(*o*-Bromobenzyl)acetamide (3b)**: Yield 0.82 g (80%); mp 73-74 °C; UV (λ_{max} in CH_3CN) 267 nm ($\varepsilon = 4.7 \times 10^4$ L/mole-cm); IR ($CHCl_3$): 3298, 3084, 1642 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.1 Hz, 1H), 7.30 (m, 3H), 5.92 (br. s, 1H, NH), 4.53 (d, J = 6.0 Hz, 2H, CH_2), 2.03 (s, 3H, CH_3); MS (EI) m/z (rel intensity) 230 (1, M^++2), 228 (1, M^+), 148 (100).

Anal. Calcd for $C_9H_{10}ONBr$: C, 47.39; H, 4.42; N, 6.14. Found: C, 47.28; H, 4.34; N, 6.02.

Preparative Photoreaction.

Photoreaction of *N*-(*o*-Bromophenyl)acetamide (1b)-General procedure: To a large (500 mL) quartz immersion well photolysis unit with provision for circulation of nitrogen were added 450 mL of acetonitrile, *N*-(*o*-bromophenyl)acetamide (96 mg, 0.45 m mole), and 50 mL of 2 M aqueous NaOH. With nitrogen circulation, the mixture was irradiated with a 450 W mercury lamp (medium pressure) for 30 min. The resulting two-phase mixtures were separated and water layer was extracted with ethyl acetate. The acetonitrile and ethyl acetate portions were together evaporated and analyzed by TLC. The TLC with eluent *n*-Hexane/EA = 5/1 gave two spot; R_f 0.48 and R_f 0.21. The substance of R_f 0.48 is identified as 2-methylbenzoxazole: yield 16 mg (27%); IR ($CHCl_3$) 3050, 1620 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.60 (m, 1H, C_8-H), 7.40 (m, 1H, C_5-H), 7.20 (m, 2H, $C_{6,7}$-H), 2.55 (s, 3H, CH_3); MS (EI) m/z (rel intensity) 133 (100, M^+), 104 (19).

Anal. Calcd for C_8H_7ON: C, 72.16; H, 5.30; N, 10.52. Found: C, 71.93; H, 5.48; N, 10.87.

The substance of the R_f 0.21 is identified as *N*-phenylacetamide: yield 8 mg (13%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.64 (br. s, 1H, NH), 7.50 (d, J = 6.0 Hz, 1H, C_4-H of ph), 7.34 (t, J = 6.0 Hz, 2H, $C_{3,5}$-H of ph), 7.13 (t, J = 6.0 Hz, 2H, $C_{2,6}$-H of ph), 2.20 (s, 3H, CH_3).

Photoreaction of *N*-2-(Chlorophenyl)acetamide (1a) and *N*-2-(Iodophenyl)acetamide (1c): The photoreactions of **1a** and **1c** were carried out for 40 min and 20, respectively as in the case of **1b**. In case of **1a**, photo-Fries type product **6a** (5%) was separated in addition to 2-methylbenzoxazole (10%) and identified by GC/mass only. The products from **1c** were the same as products from **1b**.

Photoreaction of *N*-(*o*-halophenyl)-*N*-methylacetamide, 2: The photoreaction of **2a** and **2b** were carried out as in the case of **1a**. An intractable material was formed from both **2a** and **2b**.

Photoreaction of *N*-(*o*-halobenzyl)acetamide (3): The photoreaction of **3** was carried out as in the case of **1a**. The

TLC of the reaction product give a reduced product, N-benzylacetamide; yield 22 mg (33%); mp 46-47 °C; UV (λ_{max} in CH_3CN) nm; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 6.0 Hz, 1H, C_4-H of ph), 7.34 (t, J = 8.5 Hz, 2H, $C_{3,5}$-H of ph), 7.28 (t, J = 3.0 Hz, 2H, $C_{2,6}$-H of ph), 4.44 (d, J = 5.5 Hz, 2H, CH_2), 2.03 (s, 3H, CH_3); MS (EI) m/z (rel intensity) 148 (100, M^+), 139 (16).

Relative Rate- General Procedure. *N*-(*o*-Bromophenyl)-acetamide (**1b**, 8.5 mg) was dissolved in 10 mL of a solvent such as acetonitrile/2 M NaOH (4×10^{-3} M). The stock solution (2.5 mL) was placed in a UV cuvette and deaerated with argon or oxygen for 20 min. The solution was irradiated with a monochromatic light (290 nm ± 10) for 30 min.

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References

1. Paramasivam, R.; Palaniappan, R.; Ramakrishnan, V. T. *J. Chem. Soc. Chem. Comm.* **1979**, 260.
2. Jayanthi, G.; Muthusamy, S.; Paramasivam, R.; Ramakrishnan, V. T. *J. Org. Chem.* **1997**, *62*, 5766.
3. Bowman, W. S.; Heaney, H.; Smith, P. H. G. *Tetrahedron Lett.* **1982**, *23*, 5093.
4. Couture, A.; Grandclaudon, P. *Heterocycles* **1984**, *22*, 1383.
5. Park, Y.-T.; Jung, C.-H.; Kim, K.-W.; Kim, H. S. *J. Org. Chem.* **1999**, *64*, 8546.
6. Mayouf, A. M.; Park, Y.-T. *J. Photoscience* **2000**, *7*, 5.
7. Park, Y.-T.; Kim, M.-S.; Kwak, Y.-W.; Lee, J.-K.; Yoh, S.-D. *J. Photoscience* **2000**, *7*, 135.
8. Johnstone, R. A. W.; Payling, D. W. *J. Chem. Soc (C)* **1969**, *16*, 2223.
9. Photo-Fries type product was identified by GC/Mass. The regiochemistry of acetyl group on chloroaniline (between *o*- and *p*- and position) is not determined.