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Photo-induced Friedel-Crafts Reaction. II[1]

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On photolysis of anisol or phenol with chloroacetamide, methoxy- or hydroxyacetamides were easily obtained. This reaction is one of alkylation on aromatic ring with alkyl halide in very mild condition and provides an example of photo-induced Friedel-Crafts reaction. A photorearrangement of phenoxyacetamide to hydroxyphenylacetamides in good yield was observed. Some discussion for mechanisms of these reactions were also described.

A number of compounds containing the novel heterocycles have been obtained from the photochemical reactions of N-chloroacetyl derivatives of aromatic amino acids and pharmacodynamic amines.[3] Although the mechanisms are still unsettled, these unusual photocyclizations and photorearrangements may proceed through the cleavage of the carbon-chlorine bond by the intramolecular assistance of the excited singlet state of the aromatic chromophore. This paper reports the intermolecular photoreaction between either anisol (**1**) or phenol (**6**) and chloroacetamide (**2**), their probable mechanisms and the photorearrangement of phenoxyacetamide (**10**).

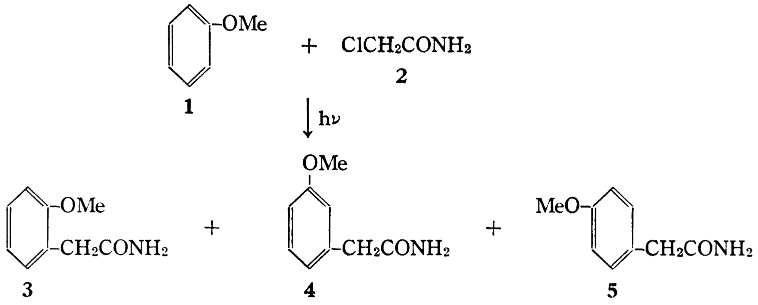

Chart 1

TABLE I. Photolysis of **1** and **2** for 2 hr

Solvent	%		
	3	4	5
Water	20.8	4.34	6.08
	(21.0)	(3.6)	(1.8)
Acetonitril	0.58	0.09	0.03
Dioxane	0.2	0.04	0.03
Acetone	0.03	trace	trace

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1) Part I: O. Yonemitsu and S. Naruto, *Tetrahedron Letters*, **1969**, 2387.

2) Location: *Kita-12, Nishi-6, Sapporo.*

3) O. Yonemitsu, H. Nakai, Y. Kanaoka, I.L. Karle and B. Witkop, *J. Am. Chem. Soc.*, **92**, 5691 (1970), and references cited therein.

An aqueous ethanol solution of anisol (**1**) and **3** equivalents of chloroacetamide (**2**) was irradiated with 10 watt low pressure mercury lamp in nitrogen atmosphere for 2 hr to give the mixture of 2-, 3- and 4-methoxyphenylacetamides (**3**, **4** and **5**), which were separated by silica gel chromatography in yield of 21, 3.6 and 1.8% respectively. In order to examine the solvent effect, this photoreaction was carried out in some aprotic solvents and analyzed quantitatively by gas chromatography, indicating that the reaction was strongly depressed in aprotic solvents (Table I). The similar results was observed in photolysis of phenol (**6**) with **2** (Table II) and even in the photorearrangement of phenoxyacetamide (**10**) (Table III) as mentioned below. This photoreaction is one of alkylation reactions to the aromatic ring with a alkyl halide in very mild reaction condition and provides an example of the photo-induced Friedel–Crafts reaction.[4]

Table II. Photolysis of **6** and **2** for 2 hr

Solvent	%			
	7	**8**	**9**	**10**
Water	39.7 (41.3)	0.3	11.3 (14.2)	0.63
Water with O_2	22.4	3.4	12.5	1.79
Acetonitril	1.07		0.34	3.2
Dioxane	2.6		0.89	2.64

Table III. Photorearrangement of **10** for 2 hr

Solvent	%			
	7	**8**	**9**	**10**
Water	71.0 (66.2)		18.1 (19.0)	3.8
Water with O_2	65.3		24.5	0.94
Acetonitril	15.2		9.2	26.2
Dioxane	18.8		4.0	36.1

Recently, reactions of alkyl and aryl radicals on aromatic nuclei have been considerably investigated,[5] and from the orientation and relative reactivity in the reaction of anisol (**1**) and chloroacetamide (**2**), it might be resonable to assume that this reaction proceeds through the attack of an alkyl radical ($\cdot CH_2CONH_2$) produced by ultraviolet (UV) irradiation on an aromatic ring (mechanism 1).

However, there are other evidences that photolysis of aromatics with electron-donating substituents in aqueous solution produces hydrated electrons[6] and chloroacetic acid is a very

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[4] Ogata, et. al., reported on the photochemical ethoxycarbonylation of benzene with ethyl chloroacetate in the presence and absence of aluminium chloride: Y. Ogata, T. Itoh and Y. Izawa, *Bull. Chem. Soc. Japan*, **42**, 794 (1969). *cf.* A. Tuinman, S. Iwasaki, K. Schaffner and O. Jeger, *Helv. Chim. Acta*, **51**, 1778 (1968).

[5] R. Ito, T. Migita, N. Morikawa and O. Shimamura, *Tetrahedron*, **21**, 955 (1965); J.R. Shelton and C.W. Uzelmeier, *J. Am. Chem. Soc.*, **88**, 5222 (1966); G.E. Corbett and G.H. Williams, *J. Chem. Soc.* (*B*), **1966**, 877.

[6] L.I. Grossweiner and H.I. Joschek, *Advan. Chem. Ser.*, **No 50**, 279 (1965); H.I. Joschek and L.I. Grossweiner, *J. Am. Chem. Soc.*, **88**, 3261 (1966).

mechanism 1

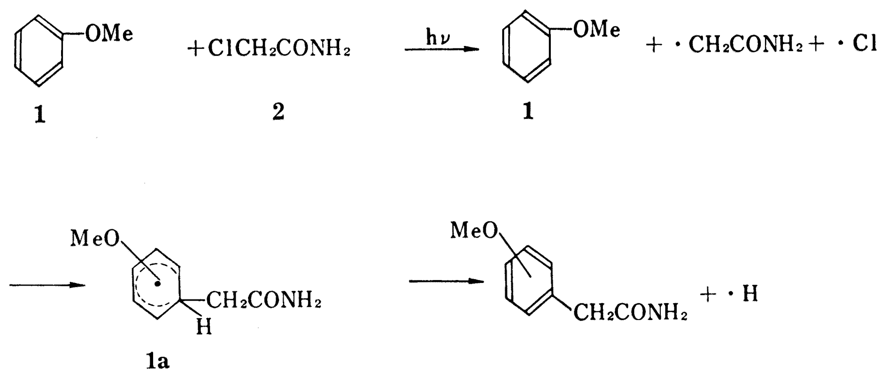

Chart 2

effective electron scavenger in the dissociative electron capture process.[7] The photoreaction of **1** and **2** may therefore proceed by the following mechanism:

$$e^- + ClCH_2CO_2H \longrightarrow \cdot CH_2CO_2H + Cl^-$$

the UV light energy first is absorbed in the aromatic ring, from which an electron transfers to chloroacetamide (**2**) to cleave carbon–chlorine bond, followed by immediate formation of cation intermediate (**1b**), which releases a proton to produce the methoxyphenylacetamides (mechanism 2). In fact there are further facts supporting the second mechanism; that is, the fluorescence of electron-rich aromatics is quenched efficiently by methyl chloroacetate and chloroacetamide in the loosely bound exciplex[8] between irradiated aromatics and quenchers,[9] besides as shown in Table I this photoreaction is strikingly depressed by changing in solvent from water to aprotic organic solvents.[10]

mechanism 2

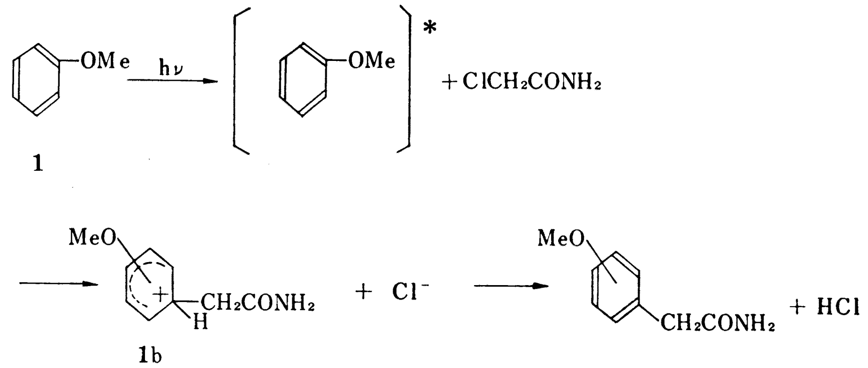

Chart 3

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[7] P.B. Ayscough, R.G. Collins and F.S. Dainton, *Nature*, **205**, 965 (1965); A. Meybeck and J.J. Windle, *Photochem. Photobiol.*, **10**, 1 (1969).

[8] S.L. Murov, R.S. Cole and G.S. Hammond, *J. Am. Chem. Soc.*, **90**, 2957 (1968).

[9] T. McCall, G.S. Hammond, B. Witkop and O. Yonemitsu, *J. Am. Chem. Soc.*, **92**, 6991 (1970).

[10] Optical electron production from aromatic molecules in organic solvents occurs with much lower yields than water.[6]

Phenol (**6**) was also irradiated with 10 watt low pressure mercury lamp and 100 watt high pressure mercury lamp to isolate similar reaction products, 2- and 4-hydroxyphenylacetamides (**7** and **9**). In analytical experiments by gas chromatography small amounts of phenoxyacetamide (**10**) and 3-hydroxyphenylacetamide (**8**) as well as **7** and **9** were detected. Since photorearrangements of aryl ether, in which phenoxy acetic acid[11] and its ester[12] are included, are known, it is reasonable to assume that simultaneous formation of phenoxyacetamide (**10**) from **6** and **2** and successive rearrangement to hydroxyphenylacetamides proceeded as one of the routes of this photoreaction. On photolysis of **10** in aqueous solution, 2- and 4-hydroxyphenylacetamides (**7** and **9**) were actually obtained in *ca.* 90% yield. The existence of **10** in intermolecular reaction between **6** and **2** as welll as the fact that the relative rates of formation of **7** and **9** in both case (Table II and III) are almost same, may also support the above assumption.

In photolysis of phenoxyacetamide (**10**), equimolecular anisol (**1**) was added and the reaction mixture was examined carefully by gas chromatography, but no trace of crossed reaction products (**3**, **4** and **5**) was detected. Moreover the presence of added oxygen, a good scavenger for alkyl radical,[13] did not change the yields of the rearrangement products. These results indicate that this photorearrangement involves a very tightly bound intermediate like that in photo-Fries reaction.[14]

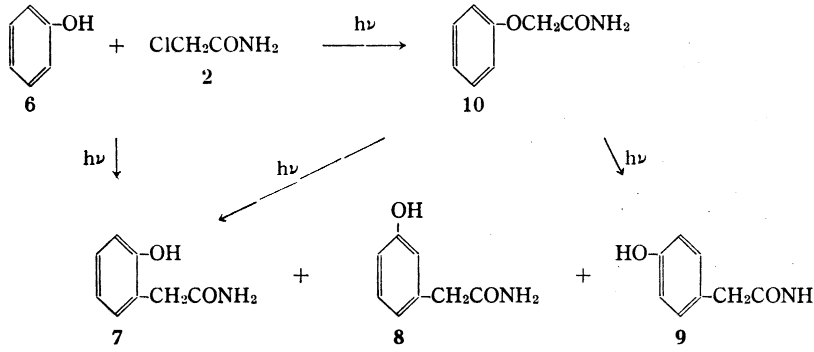

Chart 4

Experimental

All melting points are uncorrected. A 100 watt high pressure mercury lamp (Eikosha PIH-100 from Eikosha Co., Osaka) and 10 watt low pressure lamp from Osawa Shigaisen Kogyo Kenkyujo, Tokyo, were used as light sources for the photoreactions. NMR spectra were measured with the Hitachi H-60 high resolution NMR spectrometer. Mass spectra were determined with the Hitachi RMU-6E double focusing mass spectrometer.

Photoreaction of Anisol (1) with Chloroacetamide (2)——A solution of 81 mg (0.75 mmole) of anisol (**1**) and 210 mg (2.25 mmole) of chloroacetamide (**2**) in 85 ml of water and 10 ml of ethanol was irradiated with a 10 watt low pressure mercury lamp under nitrogen at room temperature for 2 hr. Ten batches totaling a volume of 950 ml were neutralized by the addition of sodium bicarbonate and evaporated *in vacuo* to almost dryness. The residual pale yellow solid was suspended in 10 ml of water and extracted with 40 ml portions of ethyl acetate. The combined extracts were dried over anhydrous sodium sulfate, and evaporated *in vacuo* to leave 1.65 g of a colorless solid. Recrystallization from ethyl acetate to give 0.84 g of recovered chloroacetamide (2). The mother liquor was evaporated to leave 0.81 g of a yellow solid which was chro-

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[11] D.P. Kelly and J.T. Pinhey, *Tetrahedron Letters*, **1964**, 3427.

[12] H. Chaimovich, R.J. Vaughan and F.H. Westheimer, *J. Am. Chem. Soc.*, **90**, 4088 (1968).

[13] J.G. Calvert and J.N. Pitts, Jr., "Photochemistry," J. Wiley & Sons, Inc., 1966, p. 598; D.P. Dingledy and J.G. Calvert, *J. Am. Chem. Soc.*, **85**, 856 (1963).

[14] D. Bellus and P. Hrdlovic, *Chem. Rev.*, **67**, 599 (1967); M.R. Sandner and D.J. Trecker, *J. Am. Chem. Soc.*, **89**, 5725 (1967).

matographed on 30 g of silica gel column to give three fractions. The first fraction which was eluted with methylene chloride was 565 mg of a colorless solid. Recrystallization from ethyl acetate to give 214 mg of **2**. The mother liquor was rechromatographed on 15 g of silica gel column to afford 81 mg of **2** and 174 mg of 2-methoxyphenylacetamide (**3**). The second fraction which was eluted with ethyl acetate was 76 mg of **3**. The third fraction which was eluted with acetone was 131 mg of a colorless solid which was rechromatographed on 15 g of silica gel column. Elution with ethyl acetate to give 10 mg of **3**, 44 mg of 3-methoxyphenylacetamide (**4**) and 22 mg of 4-methoxyphenylacetamide (**5**).

Combined 2-methoxyphenylacetamide (**3**) (260 mg, 21%) was recrystallized from ethyl acetate to give colorless plates mp 124—125°.[15] Mass Spectrum *m/e*: 165 (M^+), 121. IR ν^{Nujol} cm^{-1}: 3370, 3170, 1670, 1660, 1625. NMR $\delta^{\text{acetone-d}_6}$: 3.43 (2H, s), 3.78 (3H, s), 7.0 (4H, m).

The crude 3-methoxyphenylacetamide (**4**) (44 mg, 3.6%) was recrystallized from ethyl acetate to give colorless leaflets, mp 125—126°.[16] Mass Spectrum *m/e*: 165 (M^+), 121. IR ν^{Nujol} cm^{-1}: 3360, 3170, 1665, 1640. NMR $\delta^{\text{acetone-d}_6}$: 3.58 (2H, s), 3.82 (3H, s), 7.0 (4H, m).

The crude 4-methoxyphenylacetamide (**5**) (22 mg, 1.8%) was recrystallized from acetone to give a colorless crystalline powder, mp 181—182°.[17] Mass Spectrum *m/e*: 165 (M^+), 121. IR ν^{Nujol} cm^{-1}: 3340, 3170, 1665, 1640, 1615.

Photoreaction of Phenol (6) with Chloroacetamide (2)——Method A (With a High Pressure Lamp): A solution of 564 mg of phenol (**6**) and chloroacetamide (**2**) in 300 ml of water was irradiated with a 100 watt high pressure mercury lamp under nitrogen at room temperature for 10 hr. The reaction mixture was stirred with 150 mg of silver carbonate to remove the chloride ion and the silver salts were then removed by filtration. The filtrate was evaporated *in vacuo* to a volume of 10 ml and extracted with six 30 ml portions of ethyl acetate. The combined extracts were dried over sodium sulfate and evaporated to leave 1.003 g of a colorless solid which was chromatographed on 50 g of silica gel column. Elution with methylene chloride gave the first fraction of 533 mg of recovered chloroacetamide (**2**).

The second fraction which was eluted with ethyl acetate was 163 mg (18%) of 2-hydroxyphenylacetamide (**7**). Recrystallization from benzene gave colorless small prisms, mp 115—116°.[18] Mass Spectrum *m/e*: 151 (M^+), 134 (base peak), 106. IR ν^{Nujol} cm^{-1}: 3420, 3300, 1670, 1610. UV $\lambda_{\max}^{H_2O}$ nm (log ε): 275 (3.22), 281 (shoulder, 3.30). $\lambda_{\max}^{\text{aq.NaOH}}$ nm (log ε): 293 (3.64).

The third fraction which was eluted with acetone was 192 mg (22.2%) of 4-hydroxyphenylacetamide (**9**). Recrystallization from water gave colorless small prisms, mp 165—169°.[19] Mass Spectrum *m/e*: 151 (M^+), 134 (base peak), 107. NMR δ^{D_2O}: 3.51 (2H, s), 6.84 (2H, d, J=8.3 Hz), 7.19 (2H, d, J=8.3 Hz). UV $\lambda_{\max}^{H_2O}$ nm (log ε): 275 (3.22), 284 (shoulder, 3.15). $\lambda_{\max}^{\text{aq.NaOH}}$: 293 (3.43).

Method B (With a Low Pressure Lamp): A solution of 110 mg of phenol (**6**) and 350 mg of chloroacetamide (**2**) in 80 ml of water was irradiated with a 10 watt low pressure mercury lamp under nitrogen at room temperature for 2.5 hr. Six batches totaling a volume of 480 ml were neutralized by the addition of 588 mg of sodium bicarbonate and evaporated *in vacuo* to volume of *ca.* 10 ml and extracted with five 15 ml portions of ethyl acetate. The combined extracts were dried over anhydrous sodium sulfate and evaporated to leave 1.663 g of a colorless solid which was chromatographed on 45 g of silica gel column. Elution with methylene chloride gave 998 mg of the recovered chloroacetamide (**2**). The second fraction which was eluted with ethyl acetate was 436 mg (41.3%) of 2-hydroxyphenylacetamide (**7**). The final fraction which was eluted with acetone was 151 mg (14.2%) of 4-hydroxyphenylacetamide (**9**).

Photorearrangement of Phenoxyacetamide (10)——A solution of 121 mg of phenoxyacetamide (**10**)[20] in 80 ml of water was irradiated with a 10 watt low pressure mercury lamp under nitrogen at room temperature for 2.5 hr. Four batches totaling a volume of 320 ml were evaporated *in vacuo* to leave a yellow solid which was chromatographed on 15 g of silica gel column. Elution with ethyl acetate to give 320 mg (66.2%) of 2-hydroxyphenylacetamide (**7**) and 92 mg (19.0%) of 4-hydroxyphenylacetamide (**9**).

Photorearrangement of Phenoxyacetamide (10) in the Presence of Anisol (1)——A solution of 7 mg of phenoxyacetamide (**10**) and 5 mg of anisol (**1**) (molar ratio; *ca.* 1:1) was irradiated with a 10 watt low pressure mercury lamp for 1 hr. The reaction mixture was analyzed by gas–liquid partition chromatography (GLPC), which was carried out on a stainless steel column (3 mm × 3 m) containing 5% SE-52 on 60—80 mesh Shimalite W at a column temperature of 190°.[21] No peaks were detected except 2- and 4-hydroxyphenylacetamide (**7** and **9**) and a trace of the starting material (**10**).

Quantitative Analysis by Gas Chromatography——(a) Phenol (**6**) with Chloroacetamide (**2**): A solution in 70 ml of various solvents of 66 mg of phenol (**6**) and 198 mg of chloroacetamide (**2**) was irradiated with

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[15] A.L. Williams and A.R. Day, *J. Am. Chem. Soc.*, **74**, 3875 (1952).

[16] J.A. King and F.H. McMillian, *J. Am. Chem. Soc.*, **68**, 2335 (1946).

[17] W. Wenner, *J. Org. Chem.*, **15**, 548 (1950).

[18] R. Stoermer, *Ann.*, **313**, 86 (1900).

[19] H. Solkowski, *Chem. Ber.*, **22**, 2141 (1889).

[20] C.A. Bischoff, *Chem. Ber.*, **34**, 1836 (1901).

[21] All GLPC data were obtained on the Shimazu Gas Chromatograph GC-4APF equipped with a disk chart integrator using flame ionization detection.

10 watt low pressure mercury lamp. During irradiation oxygen free nitrogen[22] was bubbled through a solution except experiments under oxygen atmosphere. Three ml aliquots were removed after 15, 30, 60 and 120 min, the solvent was removed *in vacuo*, in case of phenolic compounds the residue was methylated with diazomethane in ethanol overnight and subjected to hydrolysis with 3 N potassium hydroxide followed by esterification with diazomethane in methanol. After the addition of 2-methoxynaphthalene as an internal standard, the reaction mixture was analyzed by determining the relative peak areas, correcting from detection response factors determined from analysis of standard solutions of the products and the internal standard. The above mentioned GLPC instrument was used at column temperature of 150°. The results are shown in Table II.

(b) Phenoxyacetamide (**10**): A solution (70 ml) of 53 mg of phenoxyacetamide (**10**) was irradiated and analyzed as in the foregoing experiment. The results are shown in Table III.

(c) Anisol (**1**) with Chloroacetamide (**2**): A solution (70 ml) of anisol (**1**) (76 mg) and chloroacetamide (**2**) (198 mg) was irradiated and analyzed as described above, though in this case methylation process of phenolic compounds with diazomethane was not necessary. The results are shown in Table I.

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[22] A trace of exygen in nitrogen was removed by passage through Fieser's solution; L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," J. Wiley & Sons, Inc., 1967, p. 393.