PHOTOCHEMICAL FRIES REARRANGEMENT OF N-PHENYL-2-PYRROLIDONE

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Abstract - Photochemical Fries rearrangement of 1-phenyl-2-pyrrolidone (1) proceeded smoothly in methanol especially in the presence of piperylene. Continuous photo-irradiation of 1 successfully was carried out to raise the yield by utilizing a reaction mixture-circulation system consisting of a spiral quartz cell, a pump, a uv light source and a column packed with appropriate absorbents for the Fries rearranged product (3) and pigments.

Photochemical behaviour of various N-phenyllactams (larger than five-membered ring lactams) was reported by Fischer and his co-worker.[1] According to the report, the photo-Fries rearrangement[2] proceeded smoothly to give the corresponding bicyclic heterocycles except for a case of N-phenyl-2-pyrrolidone (1),[3] which gave 1-phenyl-pyrrole (2)[1] as a major product. So we reexamined the unsuccessful photochemical reaction of 1 in order to obtain the photo-Fries rearranged product, benz[b]azepin-4-ones (3),[4] which could be a possible intermediate for the syntheses of biologically interested N-containing heterocycles. According to the Fischer's report,[1] irradiation of a solution of N-phenyl-2-pyrrolidone (1) in isopropanol by a high-pressure mercury arc lamp gave an almost similar result as that of reported by Fischer[1] except for isolation of a small amount of the photochemical Fries rearranged product (3). On the other hand, we found that irradiation of a methanolic solution of 1 gave a considerable amount of 3 together with *N*-phenylpyrrole (2).

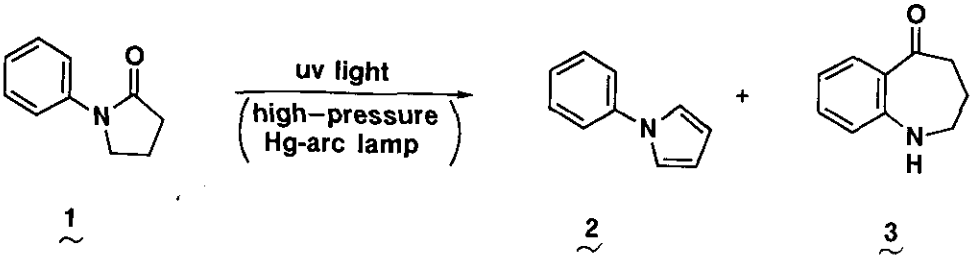

Chart 1

The products (2 and 3) were separated by a silica gel column chromatography, and the structures of 2 and 3 were confirmed by their infrared spectra (ir) and proton nuclear magnetic resonance spectra (^{1}H-nmr; 80 MHz). Thus we examined photochemical behavior of *N*-phenyl-2-pyrrolidone (1) in various solvent systems, and the results are summarized in Table I.

Table I. Irradiation of 1 in Various Solvents

Entry	Solvent	Yield (%)^a	
		3	2
1	benzene	0	0
2	dioxane	6.1	5.0
3	benzene - dioxane (1/1)	3.3	trace
4	methanol	18.3	17.3
5	ethanol	12.8	27.9
6	2-propanol	8.5	39.2
7	methanol - water (4/1)	21.0	23.4
8	methanol - water (3/2)	15.7	15.0
9	dioxane - 1N H_2SO_4 (9/1)	11.5	trace
10	methanol - 1N H_2SO_4 (9/1)	25.7	21.8

a: Isolated yields based on the consumed substrate (1)

The data in Table I indicate that the production of **3** increased in protic and polar solvents and strongly acidic medium, while the formation of **2** could not be supressed even in such solvent systems. Fischer and his co-worker speculated an ionic intermediate in the photochemical Fries rearrangement,[1] so that the the polar solvents effect seems to be rational for explaining the increased production of **3**.[5]

Next we examined photo-irradiation of **3** in the presence of an appropriate photo-sensitizer[6] such as acetone, naphthalene and piperylene (**4**; 1,3-pentadiene) in a methanolic solution. The results are summarized in Table Ⅱ. The photochemical reaction of **1** in the presence of acetone proceeded to give *N*-phenylpyrrole (**2**) with very small amount of by-products. Although naphthalene was almost ineffective, piperylene (**4**) was apparently effective in the formation of the Fries rearranged product (**3**; yield, 47.6 %) under considerable suppression of the formation of **2** and other by-product. It has been known that appropriate unsaturated hydrocarbons such as piperylene (singlet state photosensitizer; radical inhibitor) deactivate triplet excited state in photochemical recaction.[6] The experimental results in Table Ⅱ clearly indicate that *N*-phenylpyrrole (**2**) may be produced *via* the corresponding triplet state.

Table Ⅱ. Irradiation of **1** in Methanol in the Presence of Photosensitizer

Entry	Sensitizer (conc., %)	Isolated Yield (%) **2**	 **3**	 **1**
1	none	5.5	5.8	7.0
2	acetone (25 v/v)	41.0	0	3.6
3	naphthalene (0.01 w/v)	22.0	18.0	42.5
4	piperylene (5 v/v)	trace	47.6	37.5

In all cases in Table **1**, considerable amount of the starting substrate (**1**) remained unchanged in spite of prolonged irradiation. We presumed that absorption of the uv light into **3** might interfere further consumption of **1** by the produced azepinone (**3**) itself and pigments in the photochemical reaction. So it was considered that removal of the product (**3**) and the pigments from the reaction mixture (containing piperylene) may be necessary for improvement of the yield of **3**. Thus we planned the use of a special photochemical reaction apparatus system consisting of a spiral quartz cell (reaction vessel), a uv lamp, a column of acidic ion-exchange resin (Amberlist A-15, H^+ form; absorbent for **3**) and a chromatography pump for circulation of the methanolic reaction solution in the system, and the layout is shown in Figure 1.

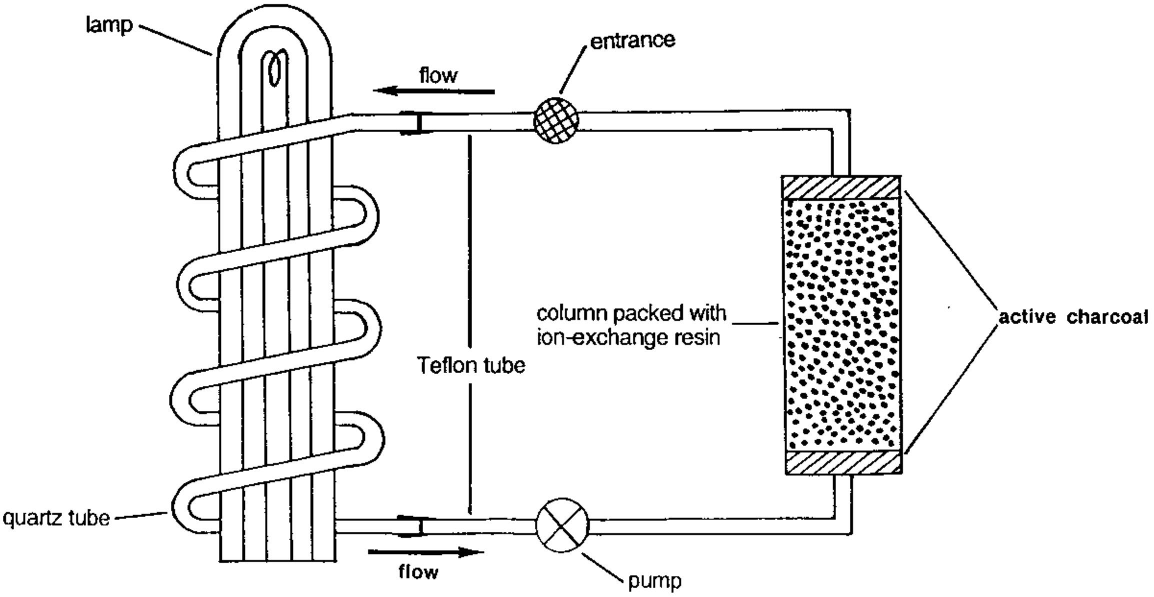

Figure 1

Irradiation experiment by the system was carried out by using 200 ml of 0.5 w/v % methanolic solution of **1** in the presence of piperylene. Consumption of the substrate (**1**) was traced by the high-performance liquid chromatography (hplc). After 24 h irradiation, the substrate (**1**) almost disappeared on tlc, and the yield of **3** reached to 65.0 %.

Generally speaking, continuous removal of interferring substances such as pigments and desired product by using an appropriate circulating reaction system may permit effective and relatively large scale photo-irradiation reaction.

EXPERIMENTAL

N-Phenyl-2-pyrrolidone (1) ----- A mixture of γ-butyrolactone (17.2 g, 0.20 mol), aniline (20.0 g, 0.22 mol) and conc. HCl (5.7 ml) was heated under refluxing at 150 ℃ for 2.5 h, and then at 180 ℃ for 21 h. The cooled reaction mixture solidified, and the solid was successively washed with 10 % HCl and water on a filter and recrystallized from aqueous ethanol to give colorless needles, mp 65 - 66 ℃ (lit.,[3] mp 65.5 - 66.5 ℃). Yield, 29.4 g (83.0 %). Ir (KBr): 1658 cm^{-1} (C=O). Uv λ_{max} (methanol) nm (log ε): 207 (4.12), 245 (4.07). ^{1}H-Nmr ($CDCl_3$) δ ppm: 1.98 - 2.38 (m, 2H, $-COCH_2C\underline{H}_2-$), 2.46 - 2.79 (m, 2H, $-COC\underline{H}_2-$), 3.81 (t, J = 6.5 Hz, 2H, $>NC\underline{H}_2-$), 6.95 - 7.70 (m, 5H, arom.H). Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.22; H, 6.91; N, 8.66.

A Typical Procedure for Irradiation of 1 in Various Solvent ----- Irradiation in Methanol as a Sample ----- A solution of 1 (1.61 g, 10 mmol) in methanol (200 ml) was internally irradiated under N_2 atmosphere for 24 h with a high-pressure mercury arc lamp (100 W). Removal of the solvent under reduced pressure gave a brown oily residue, which was purified by chromatography on silica gel with n-hexane/AcOEt (2/1) to give 2 [83 mg (5.8 %)], 3 [88.3 mg (5.5%)] and 1 [113 mg (7.0 %)]. Structures of these products were confirmed by comparisons of ir and ^{1}H-nmr with those of the authentic samples.

3: mp 68 - 71 ℃. (lit.,[4] mp 69 ℃). Ir (KBr): 3380 (NH), 1660 (C=O) cm^{-1}. Uv λ_{max} (in 95% ethanol) nm (log ε): 206 (sh), 233 (4.31), 258 (3.74), 352 (3.55). ^{1}H-Nmr ($CDCl_3$) δ (ppm): 2.01 - 2.44 (m, 2H, $-COCH_2C\underline{H}_2-$), 2.75 - 2.98 (m, 2H, $-COC\underline{H}_2-$), 3.12 - 3.42 (m, 2H, $>NHC\underline{H}_2-$), 4.70 (br s, 1H, N$\underline{H}$), 6.67 - 7.82 (m, 4H, arom.H).

2: mp 53 - 54 ℃ (lit.,[1] mp 56 ℃). Ir (KBr): no absorption at νNH and νC=O regions. Uv λ_{max} (in 95% ethanol) nm (log ε): 210 (4.50), 250 (4.35).

A Typical Procedure for Irradiation of 1 in Methanol in the Presence of Photosensitizer ----- Piperylene as a Sample ----- A solution of 1 (1.00 g, 6.2 mmol) and piperylene (1.0 ml) in methanol (200 ml) was internally irradiated under N_2 atmosphere for 48 h with a high-pressure mercury arc lamp (100 W). The solvent was removed under reduced pressure, and a solution of the residue in ether was extracted twice with 10% HCl. The ethereal layer was washed with water, dried with Na_2SO_4, passed through a short silica gel column and evaporated to give a crystalline residue [mp 62 - 66 ℃, 375 mg (37.5 %)]. Silica gel tlc of the crude product (n-hexane/ether=1/2) indicated that major constituent was 1 containing trace of 2. The 10% HCl layer was neutralized to about pH 8 by addition of 10 % NaOH, and the resulting mixture was extracted with ether (70 ml × 3). The ethereal layer was dried with Na_2SO_4 and evaporated to give a viscous residue, purification of which with silica gel column chromatography gave pure 3 (476 mg, 47.6 %).

Irradiation of 1 in Methanol in the Presence of Piperylene by Using the Spiral Quartz Cell----- A solution of 1 (1.00 g, 6.2 mmol) and piperylene (1.0 ml) in methanol (200 ml) was introduced into the equipment as illustrated in Figure 1 (spiral quartz cell: ϕ5 mm × 100 cm; ion-exchange resin: Amberlyst A-15 H^+-form, 50 ml; active charcoal for column chromatography (20 - 50 mesh), 2.0 g × 2; pump for usual liquid chromatography) and externally irradiated with a high-pressure mercury arc lamp (100 W) for 24 h under circulation of the solution at a rate of 5 ml/min. After the reaction time, the starting material (1) was almost consumed (checked by tlc). The reaction solution was taken out from the exit of the column by supplying new methanol (250 ml) from the entrance port. Removal of the solvent gave a small amount of viscous residue (67 mg), tlc of which indicated that the residue was a mixture of 1, 2 and several by-products. The ion-exchange resin was taken out on a glass filter and washed with methanol, and then extracted with a mixture of triethylamine/methanol (1/1; 70 ml × 3). Removal of the extract gave a crystalline residue, which was purified by silica gel column chromatography to give pure 3 (650 mg, 65.0 %).

REFERENCES AND FOOTNOTES

1) M. Fischer, Tetrahedron Lett., 1968, 4292; idem, ibid., 1969, 228; idem, Chem. Ber., 1968, 101, 2669; idem, ibid., 1969, 102, 342; M. Fischer and F. Wagner, ibid., 1969, 102, 3486.

2) D. Elad, D. V. Rao, and V. I. Stenberg, J. Org. Chem., 1965, 30, 3252.

3) M. J. Kornet, J. Pharm. Sci., 1979, 68, 350.

4) G. R. Proctor and R. H. Thomson, J. Chem. Soc., 1957, 2302.

5) We examined the effect of substituents on the benzene ring of the N-aryl-2-pyrrolidones. The results indicate that the electron withdrawing substituent such as nitro and chloro groups suppressed the photochemical reactions. Substitution by electron donating group does not improve the yield of benz[b]azepin-5-one derivative. Irradiation of N-(3-substituted phenyl)-2-pyrrolidones afforded the 8-substituted benz[b]azepin-5-ones rather than 6-substituted benz[b]azepin-5-ones. N-Phenyl-1-isoindolone was almost unchanged.

6) For review: K. Tokumaru, "Organic Photochemistry" (Kagakunoryoiki, additional issue No. 93), 1970, p. 281 (Nankodo, Tokyo).

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