PHOTOCHEMISTRY OF 6-CHLORO-2-PYRIDONES: THE FIRST EXAMPLE FOR ELECTROCYCLIC RING OPENING OF THE PYRIDONE RING SYSTEM[1]

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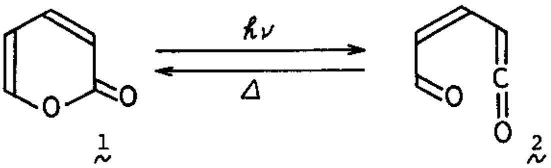
Abstract — Irradiation of 6-chloro-2-pyridone in methanol gave two geometrical isomers (cis and trans) of methyl 4-cyano-3-butenoate and trans isomer of methyl 4-cyano-2-butenoate: this and the related reactions provide the first example for the photochemical electrocyclic ring opening of 2-pyridone ring.

Photochemical behavior of 2-pyridones and 2-pyrones is quite similar in many respects. They gave photo-pyridones and -pyrones through intramolecular cyclization,[2,3] and added intermolecularly to olefins to afford 2+2 adducts[4,5] including the photodimers.[6] By low temperature photolyses, it was revealed that ketene (2) formation from 2-pyrones (1) was a dominant process in the intramolecular reactions, which had not been observed in most room temperature photolyses due to facile reversion to 1 from 2 through thermally allowed electrocyclic ring closure.[3]

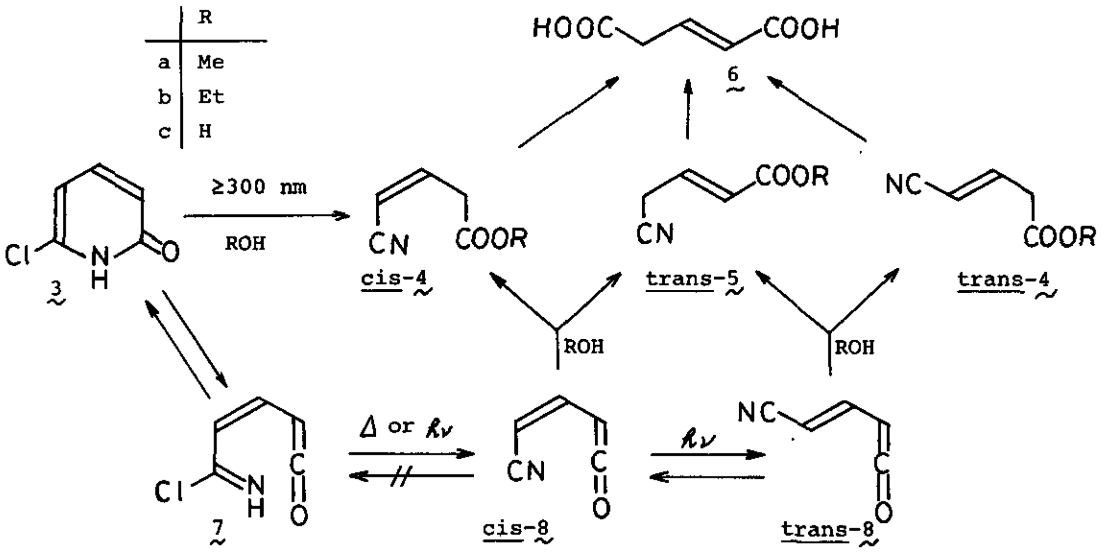


Though the same ring opening reactions are commonly observed in the photolyses of their carbocyclic analogues: ortho-blocked cyclohexadienones,[7] such ketene formation has not been reported for 2-pyridones. Taking into consideration of facile thermal electrocyclic ring closure of diene-ketene containing a non-carbon atom at the other end of the diene system[3,8] to the fully conjugated heterocyclic compounds, we believe that the lack of ketene formation process in the photochemistry of 2-pyridones might be due to the presence of an extraordinary rapid electrocyclic ring closure of the ketenes to the original pyridones.

Here, we report confirmation of the above idea by the photolyses of 6-halo-2-pyridones and provide the first example for the photochemical ring opening of the pyridone system.[9]

Irradiation of *ca*. 8 mM solution of 6-chloropyridin-2(1H)-one (**3**) in methanol gave 61.9% yield of the open chain product as a mixture of two geometrical isomers (*cis*- and *trans*-**4a**) of methyl 4-cyano-3-butenoate and *trans* methyl 4-cyano-2-butenoate (*trans*-**5a**) in an approximate ratio of 5:5:4. The corresponding ethyl esters (*cis*- and *trans*-**4b**, and *trans*-**5b** in an approximate ratio of 5:5:4) were also obtained in 45.9% yield by the photolysis in ethanol. Though these products could not be separated by chromatographic means, their structures and ratios are easily determined from nmr spectra [*e.g.*, olefinic proton of C_4 of methyl 4-cyano-3-butenoates appeared at δ 5.42 (*cis*-**4a**) and 5.40 (*trans*-**4a**) and that of C_2 of *trans*-**5a** at 6.10, whose vicinal coupling constants with the C_3-proton being *ca*. 11 for *cis*-isomer and *ca*. 16 Hz for *trans*-isomer]. Irradiation of *ca*. 8 mM solution of **3** in acetonitrile containing 1.7% volume of water also gave three monocarboxylic acids (*cis*-**4c**, *trans*-**4c**, and *trans*-**5c** in *ca*. 1:1:1 ratio) in the yield of 77.5%. Recrystallization of the mixture from $CHCl_3$ afforded *trans* 4-cyano-2-butenoic acid [*trans*-**5c**: mp 104-108°, δ ($CDCl_3$): 3.32 dd (2H, J=4.8, 1.6 Hz, CH_2), 6.16 dt (1H, J=15.6, 1.6 Hz, C_2-H), 6.87 dt (1H, J=15.6, 4.8 Hz, C_3-H), ν_{max}^{KBr} cm^{-1}: 2260, 1700, 1640]. While all esters are stable and not isomerized each other, the acids (*cis*- and *trans*-**4c**) isomerized slowly to *trans*-**5c** upon standing (the isomerization completed within one week period at room temperature). It should be noted that methylation of *trans*-**5c** with CH_2N_2 in ether afforded a mixture of *cis*-**4a**, *trans*-**4a**, and *trans*-**5a** in *ca.* 3:4:5 ratio.[10] All of the open chain products derived from **3** under these conditions gave *trans* glutaconic acid (**6**: mp 133-135°) by refluxing in 20% aq. hydrochloric acid.

The formation of the products (**4** and **5**) can be rationalized by assuming the ketene (**7**) as a primary photo-product. By elimination of HCl from **7**, the cyano-ketene (*cis*-**8**) would be formed. Since the cyano-ketene can not cyclize to the six-membered ring, it equilibrates photochemically to *trans*-**8**. The photo-equilibration step may compete with addition (either in 1,2- or 1,4-manner) of an alcohol or water to the conjugated ene-ketene function of *cis*- or *trans*-**8** to give the products (**4** and **5**). It is noteworthy that the addition of triethylamine in the irradiation solvent caused a remarkable increase for the rate of formation of the esters. Thus, irradiation of **3** in methanol containing 0.33% volume of triethylamine afforded the three



esters (cis- and trans-4a, and trans-5a in ca. 5:5:5 ratio) in 53.2% yield[11] and the irradiation period for the complete consumption of 3 was shortened to about one-tenth of that in methanol. This fact tells clearly that the step from 7 to cis-8 is accelerated by base and also, in the irradiation in an neutral medium an elimination of HCl from the carbamoyl chloride function in 7 occurs competitively with the cyclization of 7 to the original pyridone (3).[12]

The same photochemical ring opening reaction was also observed even when 6-chloro-1-methyl-2-pyridone (9) was irradiated in methanol to give 33.7% of trans dimethyl glutaconate (10).

The present results provide not only the first example of photochemical electrocyclic ring opening of 2-pyridone ring system, but also chemical means for the *preparation of 4-cyanobutenoic acid derivatives from 6-halo-2-pyridones.*[13]

Experimental

Melting points were determined using a Kofler heating stage and are uncorrected. IR spectra were determined with a Shimadzu IR-420 spectrophotometer, and NMR spectra with a JEOL JNM-C-60 spectrometer with tetramethylsilane as an internal standard. Mass spectra were recorded on a Hitachi M-80 double-focus spectrometer. Photolyses were carried out in a Pyrex immersion apparatus equipped with a Toshiba 400P high-pressure mercury lamp (this corresponds to irradiation at ≥300 nm) cooled internally with running water. All irradiations were carried out under argon or nitrogen with stirring. Column chromatography was performed on silica gel (100-200 mesh) purchased from Kanto Chemical Co., Inc.

General Procedure for Photolyses of 6-Chloropyridin-2(1H)-one (3) ——Typically *the pyridone (3, 300 mg)* was irradiated in 300 ml of solvent at room temperature until almost all of the starting material was consumed (the reaction can be monitored either UV spectroscopically[14] or by t.l.c.). The residue obtained after evaporation of the solvent was separated by column chromatography on silica gel (*ca*. 20 g). Elution with CH_2Cl_2-hexane (1:1 v/v) gave at first the esters (**4a**,**b** and **5a**,**b**) and then the starting pyridone (**3**). Elution with CH_2Cl_2 afforded the carboxylic acids (**4c** and **5c**).

(*a*) Irradiation in methanol: Irradiation of **3** for 10 hr in methanol afforded after chromatographic separation 61.9% of methyl esters (*cis*-**4a**, *trans*-**4a**, and *trans*-**5a** in *ca*. 5:5:4 ratio). IR ν_{CO}^{KBr} cm^{-1}: 1735 with a shoulder peak at 1700. Mass m/e: 125 (M^+). NMR δ ($CDCl_3$): *cis*-**4a**; 3.43 dd (2H, J=7.0, 1.6 Hz, $C\underline{H}_2$), 5.42 dt (1H, J=11.2, 1.6 Hz, C_4-H), 6.59 dt (1H, J=11.2, 7.0 Hz, C_3-H), *trans*-**4a**; 3.22 dd (2H, J=7.2, 1.6 Hz), 5.40 dt (1H, J=16.5, 1.6 Hz, C_4-H), 6.68 dt (1H, J=16.5, 7.2 Hz, C_3-H), and *trans*-**5a**; 3.24 dd (2H, J=4.8, 1.6 Hz, $C\underline{H}_2$), 6.10 dt (1H, J=16.0, 1.6 Hz, C_2-H), 6.72 dt (1H, J=16.0, 4.8 Hz, C_3-H).

(*b*) Irradiation in ethanol: Irradiation of **3** under the same condition as (*a*) except for use of ethanol instead of methanol afforded after comparable irradiation period (10 hr) 45.9% of the corresponding ethyl esters (*cis*-**4b**, *trans*-**4b**, and *trans*-**5b** in *ca*. 5:5:4 ratio). Mass m/e: 139 (M^+). NMR δ ($CDCl_3$): *cis*-**4b**; 3.41 dd (2H, J=6.8, 1.6 Hz, $C\underline{H}_2$), 5.43 dt (1H, J=11.0, 1.6 Hz, C_4-H), 6.59 dt (1H, J=11.0, 6.8 Hz, C_3-H), *trans*-**4b**; 3.20 dd (2H, J=7.0, 1.6 Hz, $C\underline{H}_2$), 5.41 dt (1H, J=16.0, 1.6 Hz, C_4-H), 6.71 dt (1H, J-16.0, 7.0 Hz, C_3-H), and *trans*-**5b**; 3.25 dd (2H, J=5.2, 1.6 Hz, $C\underline{H}_2$), 6.10 dt (1H, J=16.0, 1.6 Hz, C_2-H), 6.72 dt (1H, J=16.0, 5.2 Hz, C_3-H).

(*c*) Irradiation in methanol in the presence of triethylamine: Irradiation of **3** under the same condition as (*a*) except for use of 300 ml of methanol containing 1.0 ml of Et_3N afforded after 1 hr irradiation 53.2% of the methyl esters (*cis*-**4a**, *trans*-**4a**, and *trans*-**5a** in *ca*. 5:5:4 ratio). Its NMR spectrum was identical with that of the ester fraction obtained in (*a*).

(*d*) Irradiation in acetonitrile containing water: Irradiation of **3** under the same condition as (*a*) except for use of CH_3CN (300 ml) containing 5 ml of water afforded 77.5% of the carboxylic acids (*cis*-**4c**, *trans*-**4c**, and *trans*-**5c** in a ratio of *ca*. 1:1:1) as semi-solid. NMR δ ($CDCl_3$-CD_3OD: 5:1 v/v): *cis*-**4c**; 3.50 dd (2H, J=7.0, 1.6 Hz, $C\underline{H}_2$), 5.49 dt (1H, J=11.2, 1.6 Hz, C_4-H), 6.65 dt (1H, J=11.2, 7.0 Hz, C_3-H), *trans*-**4c**; 3.30 dd (2H, J=7.0, 1.6 Hz, $C\underline{H}_2$), 5.47 dt (1H, J=16.0, 1.6 Hz, C_4-H), 6.77 dt (1H, J=16.0, 7.0 Hz, C_3-H), and *trans*-**5c**; 3.32 dd (2H, J=4.8, 1.6 Hz, $C\underline{H}_2$), 6.16 dt (1H, J=15.6, 1.6 Hz, C_2-H), 6.87 dt (1H, J=15.6, 4.8 Hz, C_3-H). Recrystallization of the semi-solid from $CHCl_3$ gave pure *trans* 4-cyano-2-butenoic acid (*trans*-**5c**), mp 104-108°. Its NMR spectrum is identical with that of *trans*-**5c** as shown above. IR ν_{max}^{KBr} cm^{-1}: 2260, 1700, 1640. MS m/e: 111 (M^+). *Anal*. Calcd. for $C_5H_5NO_2$: C, 54.05; H, 4.54; N, 12.61. Found: C, 53.96; H, 4.61; N, 12.48. After 1 week period at room temperature, the mother fraction obtained as above changed to *trans*-**5c** in a quantitative yield.

Irradiation of 6-Bromopyridin-2(1H)-one (11) ——— (*e*) Irradiation in methanol: The pyridone (**11**: 304 mg) in 300 ml of methanol was irradiated for 8 hr. Evaporation followed by column chromatography over silica gel with CH_2Cl_2-hexane (1:1 v/v) as eluent afforded 13.4 mg (4.6%) of a mixture of the esters (*cis*-**4a**, *trans*-**4a**, and trans-5a) whose relative ratio was the same with that obtained in (a) as judged from NMR spectroscopy and 27.5 mg (9.0%) of the starting material. In this case, tars which were absorbed strongly in silica gel were the main component of the product.

(f) Irradiation in methanol in the presence of triethylamine: Irradiation of 11 (300 mg) under the same condition as (e) except for use of 300 ml of methanol containing 1.0 ml of Et_3N for 25 min afforded 67.5% of the methyl esters identical with that obtained in (a).

trans Dimethyl glutaconate (10) ——— A solution of 6-chloro-1-methylpyridin-2-(1H)-one (9: 302 mg) in 300 ml of methanol was irradiated for 10 hr. After column chromatography over silica gel with CH_2Cl_2-hexane (1:1 v/v) as an eluent, 86.0 mg (33.7% based on the consumed 9) of trans dimethyl glutaconate (10) was obtained added to 70.0 mg of the recovered 9. Mass m/e: 158 (M^+). NMR δ ($CDCl_3$): 3.67 and 3.69 s (each 3H, CH_3 x 2), 3.20 dd (2H, J=7.0, 1.6 Hz, CH_2), 5.83 dt (1H, J=15.2, 1.6 Hz), 6.91 dt (1H, J=15.2, 7.0 Hz). The NMR spectrum of 10 was identical with that of the dimethylester obtained from trans glutaconic acid by the usual methylation (CH_2N_2/ether).

Methylation of trans 4-Cyano-2-butenoic Acid (trans-5c) with CH_2N_2 ——— To a solution of trans-5c (101.4 mg) in 7 ml of ether was added an excess of CH_2N_2 in ether. After 5 min, the solvent was removed in vacuo, and the residue was passed through a short column of silica gel with CH_2Cl_2-hexane (1:1 v/v) to give 119.0 mg (96.6%) of methyl esters (cis-4a, trans-4a, and trans-5a in a ratio of ca. 3:4:5 as judged from NMR spectroscopy).

Isomerization of trans 4-Cyano-2-butenoic Acid (trans-5c) to cis and trans 4-Cyano-3-butenoic Acids (4c) in Methanol Containing Triethylamine —— To a solution of trans-5c (10.0 mg) in 2.0 ml of methanol was added 0.1 ml of Et_3N. After 1 hr, the mixture was concentrated in vacuo. The NMR spectrum of the residue in $CDCl_3$-CD_3OD (5:1 v/v) showed that it was a mixture of cis- and trans-4c in ca. 1:1 ratio with a trace amount of the starting material (trans-5c).

trans Glutaconic Acid (6) ——— A solution of 27.5 mg of the esters obtained in (a) in 3.0 ml of 20% aq. HCl was refluxed for 5 hr. After evaporation of the solvent, the residue was taken-up into CH_2Cl_2-methanol (95:5 v/v). Recrystallization of the product obtained after evaporation of the solvent from $CHCl_3$ gave trans glutaconic acid (mp. 130-133°). Identity of the product with an authentic sample was assured by the mixed melting point determination and from comparison of their NMR spectra [δ ($CDCl_3$-CD_3OD; 5:1 v/v): 3.21 dd (2H, J=7.0, 1.6 Hz, CH_2), 5.80 dt (1H, J=15.6, 1.6 Hz), 6.93 dt (1H, J=15.6, 7.0 Hz)].

References and Notes

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9. Very recently, similar photochemical ring opening was observed in some 1-aryl-2-pyrimidones: T. Nishio, K. Kitahara, and Y. Omote, *J. Chem. Soc., Perkin I*, 1981, 943.
10. *trans* 4-Cyano-2-butenoic acid (*trans*-**5c**) isomerized irreversibly to both *cis*- and *trans*-**4c** (ca. 1:1 ratio) in $CDCl_3$ containing Et_3N at room temp. Since *trans*-**5c** was stable in a crystalline state or in $CDCl_3$, the isomerization was deduced to occur *via* the carboxylate ion derived from **5c** as an intermediate. Since methylation by diazomethane also involves a carboxylate ion as an intermediate, formations of *cis*- and *trans*-**4a** may be explained by assuming that methylation of *trans*-**5c** *via* the carboxylate ion occurs competitively with the isomerization.
11. While 6-bromo-2-pyridone (**11**) afforded mostly intractable tars upon irradiation in methanol, the same esters (*cis*- and *trans*-**4a**, and *trans*-**5a** in *ca.* 5:5:4 ratio) were obtained in 67.5% yield by irradiation in methanol containing 0.33% volume of Et_3N.
12. Though it is obvious that triethylamine-catalyzed elimination of HCl from **7** is thermal in nature, it is not clear whether the elimination of HCl from **7** occurs thermally or photochemically in the photolyses of **3** in a neutral medium.
13. The present photochemical reactions of 6-halo-2-pyridones (*e.g.*, **3**) correspond to the reversal of thermal preparation of 6-chloro-2-pyridones from 4-cyano-3-butenoic acid chloride: V. S. Simchen and G. Entenmann, *Angew. Chem.*, 1973, **85**, 155.
14. The pyridone (**3**) shows strong maxima in its UV spectrum: λ_{max}^{MeOH} nm (log ε): 220 (3.78), 278 (3.69), 305 sh (3.13).

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