Photocyclization of Ortho-Substituted Cinnamic Acids

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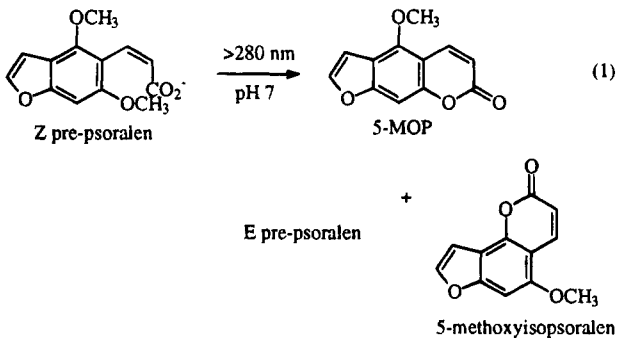
Mono and di (i.e. **2**, **6**) *o*-chloro- and *o*-methoxycinnamic acids undergo photocyclization to give the corresponding coumarins. The reaction occurs in aqueous and organic media, with a prototypical reaction giving evidence of being favored at pH > 6. Cyclization of the dimethoxy acid is relatively inefficient (Φ for the PSS = 0.0015), and a photostationary state of the cis/trans acids is formed early into the reaction. The photocyclization of the dichloro analog is more efficient (Φ exceeds 0.04) and therefore time dependent since product formation competes with trans/cis isomerization. Methyl *o*-chlorocinnamate also photocyclizes (Φ for the PSS = 0.0022 in acetonitrile) but the *o*-methoxy ester is virtually photoinert. It is proposed that the acid photocyclizes through intramolecular nucleophilic attack by the carboxylate group followed by heterolysis of the nucleofuge. Methyl *o*-chlorocinnamate appears to photocyclize through a [4 + 2] cycloaddition of the carbonyl group followed by homolysis of the Cl and Me moieties, possibly through the intermediacy of a ketene as proposed by earlier workers.

Recently we reported a novel photocyclization reaction (eq 1) that allows generation of psoralens *in situ* from water soluble prodrugs.[2] This is of some photobiological importance since psoralens are under active study for the



photodetoxification of blood,[3] an application which has been hindered by the limited water solubility of this family. Because this photocyclization is unprecedented we have explored the generality of the reaction using ortho-substituted cinnamic acids as simpler analogs of the psoralen prodrugs. We have studied the influence of the ortho-substituent and the solvent on the reaction quantum efficiency, with the chemistry discussed herein outlined in eq 2. The photocyclization of several analogous esters has been reported[4] and we present evidence that different mechanisms are operative in the two systems.

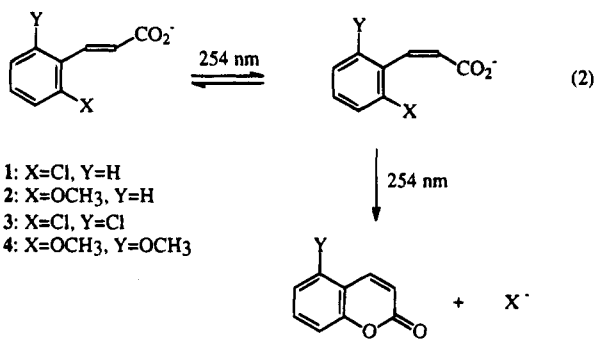
Results and Discussion

Cyclization of Cinnamic Acids. Photolysis of *trans*-**3** and *trans*-**4** in 50 mM phosphate buffer at pH 7 gave rise to concomitant trans → cis olefin isomerization and photocyclization to the coumarin. The results of a time course study are shown in Table 1. Note that the "quantum efficiencies" given in Table 1 represent the net conversion of the original trans acids to the cyclized products, a two photon sequence with cis → trans back reaction potentially competing with ring closure.

Table 1. Quantum Efficiency Data for the Photolysis of 3 and 4[a]

compound	time photolyzed	% conversion	"Φ"[b]
3	30 s	2	0.0092
3	50 s	11	0.026
3	70 s	20	0.036
4	10 min	5	0.0015
4	20 min	11	0.0015
4	30 min	16	0.0015

[a] Photolysis of 0.1 mM acid at 254 nm in 40 mM phosphate buffer pH 7. [b] "Φ" = Molecules of cyclized product formed per photon absorbed by the trans isomer.



There are several features of these data that are significant: (1) the photocyclization of the dichlorocinnamic acid, *trans*-**3**, proceeds over a time scale of seconds whereas the dimethoxy substrate, *trans*-**4**, requires minutes of irradiation; (2) the more rapid rate for **3** is reflected in the quantum efficiencies which, after 70 s, reach a level some 20-fold higher than that seen for **4**; (3) the quantum efficiency for **3** increases with time whereas "Φ" for **4** does not (within the "minutes" time frame). The last fact is readily explained by the expectation that the photostationary state (PSS) of cis/trans isomers for **4** will have been reached well before the appearance of significant product formation, while *cis*-**3** is photocyclizing at a rate which is comparable to the rate of trans to cis isomerization.

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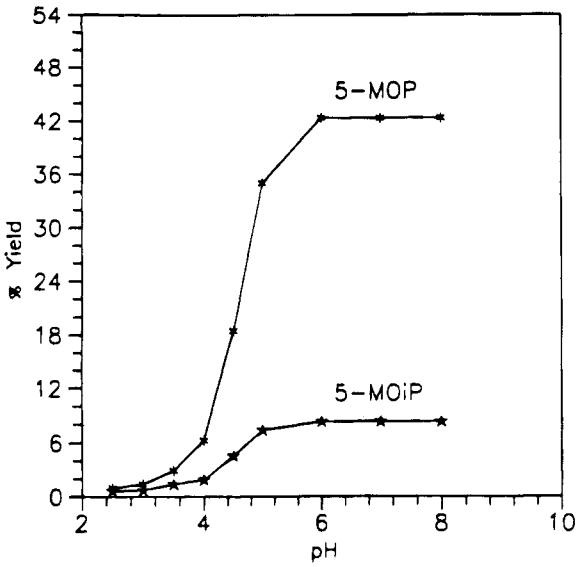


Figure 1. Photocyclization of (*Z*)-3-[5-(4,6-dimethoxybenzofuranyl)]propenoic acid as a function of pH.

Table 2. Quantum Efficiency Data for the Photolysis of Cinnamic Acids 1 and 2 in Various Solvents[a]

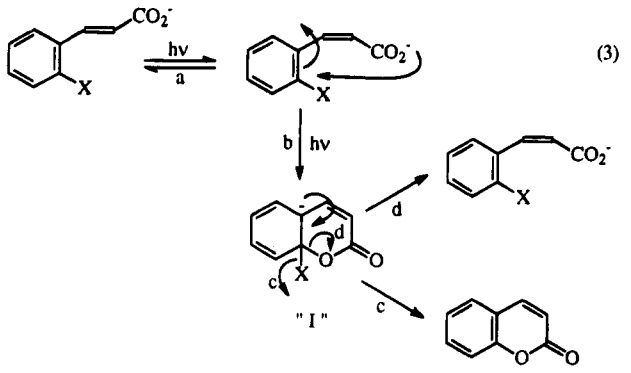
acid, solvent	PSS[b]	$\Phi_{tran\rightarrow cis}$	$\Phi_{cis\rightarrow trans}$	Φ_P[c]	Φ_D[d]	Φ_P/Φ_D
1, buffer pH 7	0.99	0.42	0.56	0.0018	0.0095	0.19
1, acetonitrile	4.1			0.0029	0.0031	0.94
1, methanol	0.70			0.0051	0.019	0.027
1, THF	2.5			0.0011	0.017	0.065
2, buffer pH 7	1.1	0.44	0.48	0.00086	0.0019	0.45
2, acetonitrile	2.4			0.000041	0.0091	0.0034
2, methanol	0.81			0.00024	0.0019	0.13
2, methanol + NaOMe	0.81			0.00043	0.0032	0.13

[a] Photolysis of 0.1 mM acid at 254 nm. Photolysis times for **1** were 15 min in buffer and 10 min in other solvents. Photolysis times for **2** were 15 min in buffer, 30 min in MeOH + NaOAc, 45 min in MeOH, 75–115 min in acetonitrile. [b] Photostationary state cis/trans ratio. [c] Molecules product formed per photon absorbed by cis and trans at PSS. [d] Molecules of cis and trans acid lost per photon absorbed, with the latter averaged from time 0 to the termination of the photolysis.

The monosubstituted analogs, *trans*-**1** and *trans*-**2**, were used to determine the effect of the reaction medium on the quantum efficiencies and PSS ratios; the data are given in Table 2. One notes that the quantum efficiencies for isomerization are comparable for the chloro and methoxy substituents. Their summation to ca. unity is indicative of the prototypical olefin isomerization mechanism in which a common twisted intermediate decays to the two geometric isomers. However, the two substrates differ markedly as to the efficiency of cyclization. As with the disubstituted cinnamic acids, the *o*-chlorocinnamic acid is substantially more reactive, both in appearance of product as well as in disappearance of the acids (with the exception of Φ_D in acetonitrile). It is clear from Table 2 that the mass balance of these reactions is generally poor. The most significant exceptions are for the photolyses of **1** in acetonitrile and **2** in buffer. The former result reflects the unusually high cis/trans ratio at the photostationary state. For none of the reactions are additional products evident by HPLC.

The photolysis of *trans*-**2** in methanol containing sodium methoxide showed only a modest improvement in the cyclization efficiency. In a separate study we found that the formation of 5-chlorocoumarin from **3** at pH 7.0 and pH 8.4 occurred with comparable efficiency. Our most extensive study of this reaction as a function of pH has been carried out with the pre-psoralen in eq 1. The data are shown in Figure 1. It is clear that the cyclization reaction is suppressed at low pH and reaches a plateau at ca. pH 6.

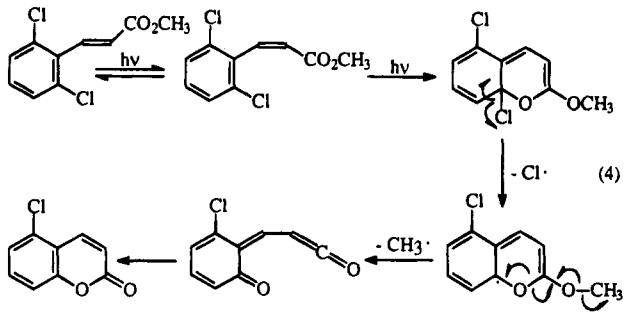
The data discussed above are consistent with nucleophilic attack by the carboxylate anion and heterolysis of the aryl nucleofuge as shown in eq 3. With such a mechanism the overall quantum efficiency of lactone



(3)

formation will depend on the state of ionization of the acid, the olefin PSS, the relative rate of step b vs cis/trans isomerization, and the step c/step d ratio. The need for carboxylate anion is evident in the pH study. With some exceptions, the photostationary states of the cinnamic acids do not vary very widely. Inefficiency is introduced into the reaction to the extent that the cis acid excited state isomerizes back to the trans isomer in competition with step b, but this step is unlikely to be much influenced by the Cl vs MeO aryl substituents. On the other hand, Cl is clearly the better nucleofuge and the correspondingly higher rate for step c will be reflected in a greater net quantum efficiency of ring closure.

Cyclization of Cinnamic Acid Esters. The photocyclization of ortho-substituted cinnamic acid esters was reported some years ago.[4] The proposed mechanism is shown in equation 4 in which there is homolytic dissocia-



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tion of the leaving group and subsequent formation of a ketene. Low temperature IR spectroscopy of a photolysate provided evidence in support of the ketene intermediate. No quantitative data were reported, but comparable reaction rates were observed in polar and nonpolar solvents.

We have prepared the *trans*-methyl esters of compounds **1** and **2** (i.e. *trans*-**5** and *trans*-**6**, respectively) and determined their quantum efficiencies for cyclization in methanol and acetonitrile (Table 3). We found no evidence of cyclization with a methoxy substituent in either methanol or acetonitrile. The *o*-chloro ester also gave no cyclization product in methanol but reacted quite efficiently in acetonitrile. The reaction is very clean with

Table 3. Quantum Efficiency Data for the Photolysis of the Methyl Esters 5 and 6[a]

methyl ester, solvent	PSS[b]	Φ_P[c]	Φ_D[d]
5, methanol	2.3	0	0.0021
5, acetonitrile	2.3	0.0022	0.0024
6, methanol	1.5	0	0.00021
6, acetonitrile	1.8	0	0.00014

[a] Photolysis of 0.1 mM ester at 254 nm. Representative photolysis times were 6.5 min for **5** and 14 for **6**. [b] Photostationary state cis/trans ratio. [c] Molecules or product formed per photon absorbed by cis and trans at PSS. [d] Molecules of cis and trans ester lost per photon absorbed, with the latter averaged from time 0 to the termination of the photolysis.

$\Phi_P \approx \Phi_D$. Both of our primary observations support the proposed mechanism, i.e. one would expect the methoxy-substituted ester, **6**, to resist homolysis of the $ArOCH_3$ bond, and the ketene formed initially from **5** would be diverted by reaction with methanol. In fact, HPLC analysis of the photolysate of **5** in methanol gave a peak with a retention time identical with the expected methyl *o*-hydroxycinnamate.

We find it interesting, and significant, that the *o*-methoxy acid photocyclizes (albeit inefficiently) but that the corresponding ester is unreactive. This is consistent with the homolytic cleavage of the aryl substituent proposed for the ester reaction, since methoxy substituents are not readily lost in this fashion, and lends support to an alternative (i.e. heterolytic) mechanism for the acids. In this regard, the observation that the quantum efficiency for cyclization of the *o*-chloro acid actually increases in acetonitrile relative to water at pH 7 (Table 2), whereas the quantum efficiency for the *o*-methoxy acid decreases with this change of solvent, may have mechanistic significance, i.e. homolytic release of the nucleofuge may play a role in the reaction in organic media.

Experimental Section

Chemicals. The *trans*-cinnamic acids **1**–**3**, *o*-hydroxycinnamic acid, and coumarin were purchased from Aldrich Chemical Co. (Milwaukee, WI) and used as received. HPLC grade acetonitrile and methanol were obtained from Mallinckrodt Specialty Chemical Co. (Paris, KY). Deionized water was distilled using a Corning MP-1 water still. All other chemicals were from J. T. Baker Inc. (Phillipsburg, NJ). Phosphate buffer solutions were prepared from mono and dibasic sodium phosphate.

Instrumentation. HPLC analyses were done using a Varian 5000 liquid chromatograph (7125 Rheodyne injection valve, 100 μL injection loop) with a 10 μm Alltech C8 4.6 × 250 mm stainless steel column, an ISCO V[4] variable wavelength detector, and a Hewlett Packard 3393A integrator. Isocratic analysis was done at 1 mL/min using the following solvent systems. Method A (to analyze for coumarin formation from **1** or **2**): 40% CH_3CN in 2.5 mM phosphate buffer pH 7, 280 nm; method B (to analyze for isomers of **1** or **2**): 20% CH_3CN in 50 mM phosphate buffer pH 7, 236 nm (for **2**), 280 or 254 nm (for **1**); method C (to analyze for 5-chlorocoumarin): 25% CH_3CN in 50 mM phosphate buffer pH 7, 280 nm; method D (to analyze for 5-methoxycoumarin): 20% CH_3CN in 50 mM phosphate buffer pH 7, 280 nm; method E (to analyze for ester isomers or coumarin formation from esters): 50% CH_3CN in 2.5 mM phosphate buffer pH 7, 280 nm. The reported[5] extinction coefficient of 7691 M^{-1} cm^{-1} at 280 nm (MeOH) was used for the HPLC analysis of 5-methoxycoumarin, with 5-chlorocoumarin used as an internal standard. Since pure cis acids and esters were often not available, their quantitation was achieved by photolyzing a sample of 0.10 mM trans acid or ester for ca. 30 s, measuring absorbances at 254 nm and analyzing the solutions by HPLC. All the initial trans samples contained traces of cis isomer estimated to be ca. 4% by HPLC. With this value, and the concentrations of cis and trans isomers after photolysis, one can use the absorbances of the two solutions to generate two Beer's Law equations for time 0 and 30 s. Solving these equations provided extinction coefficients which were then used to determine the photostationary state ratios.

Preparative GLC utilized a Varian 3300 GC chromatograph equipped with a thermal conductivity detector and a 3390A Hewlett Packard integrator. A 15 m SE 30 column at 160 °C was used. The injector and detector temperatures were 250 °C and 210 °C, respectively.

UV absorbances at 254 nm were measured using a Perkin-Elmer Lambda 3D UV/vis spectrophotometer. Analyses were done using 1 cm^2 matched quartz cells. Proton NMR spectra in $CDCl_3$ were recorded on a Varian Gemini-200 spectrophotometer. Melting points were determined using a Fisher-Johns melting point apparatus.

Photolyses. Photolyses with 254 nm light were carried out by placing samples in cylindrical quartz photolysis tubes (13 × 120 mm), degassing with argon and inserting the tubes in a turntable such that they were about 8 cm from an air-cooled Vycor-encased Hanovia 688A-45 low pressure mercury lamp set in a quartz immersion well. These photolyses were done at ambient temperature. Preparative photolyses utilized the same lamp but with the immersion well contained within a Pyrex photolysis vessel. Photolyses with 350 nm light employed a Rayonet Reactor (New England Ultraviolet Co.). Uranyl oxalate actinometry[6] was used to determine lamp intensity which was on average 2.8×10^{16} photons/s. For quantum efficiencies determined well after the establishment of the cis/trans PSS, the calculation of light absorption by the acid or ester presumed a PSS ratio of isomers from the outset.

Preparation of Methyl Esters. The appropriate acid (0.023 mol) and ca. 20 drops of thionyl chloride were dissolved in 100 mL of MeOH and heated at reflux for the time periods described below. The solvent was evaporated and the product purified by vacuum distillation or recrystallization.

Methyl *Trans*-*o*-Chlorocinnamate (5). An amount of 3.98 g (0.020 mol) of liquid product was collected after 3.25 h reflux (87% conversion), bp 71–76 °C, 0.02 mmHg (lit.[7] bp 155 °C, 4.3 mmHg).

Methyl *trans*-*o*-Methoxycinnamate (6). Reaction was done at 0.25 scale described above. An amount of 0.45 g (0.0023 mol) of liquid product was collected after 7.0 h reflux (42% conversion), bp 134 °C, 1.7 mmHg (lit.[7] bp 165–170 °C, 3.0 mmHg).

Methyl *trans*-*o*-Hydroxycinnamate. An amount of 3.72 g (0.021 mol) of a white solid was collected after 2.5 h reflux (91% conversion), mp 133–135 °C (lit.[8] mp 136–137 °C).

***cis*-*o*-Chlorocinnamic Acid.** A 32 mmol solution of methyl *trans*-*o*-chlorocinnamate (**5**) in 300 mL of acetonitrile was placed in a quartz photolysis vessel, degassed with argon, and photolyzed in the Rayonet reactor with 16 350 nm lamps for 8 h with continuous argon bubbling. The solvent was evaporated under reduced pressure at 38 °C leaving a pale yellow liquid mixture of cis and trans isomers (54:46). The mixture was distilled under reduced pressure (81–90 °C, 0.25 mmHg) and methyl *cis*-*o*-chlorocinnamate (304 mg) then collected by preparative GLC. The ester was found to be about 95% pure by ^1H NMR. It was hydrolyzed by heating 300 mg in 5 mL of 20% NaOH in water at reflux for 20 min. The reaction mixture was cooled, and 1 M HCl was added until the solution became acidic and solid began to form. An additional 1–2 mL of acid was added and the filtered product dried at 100 °C for 1.5 h: 260 mg (86%), mp 129–132 °C (lit.[9] mp 136–137 °C). Recrystallization from aqueous ethanol gave no change in melting point.

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***cis-o*-Methoxycinnamic Acid.** A solution enriched to >94% *cis*-**2** was prepared by photolyzing a 0.1 mM solution of *trans*-**2** in 50 mM phosphate buffer pH 7 with 16 350 nm lamps in a Rayonet reactor for ca. 10 min. The cis isomer was not isolated but used *in situ*.

5-Chlorocoumarin. A 1 mmol solution of compound **3** in 500 mL of methanol was placed in a quartz photolysis vessel, degassed with argon, and photolyzed for 30 min with the low pressure mercury lamp. The solution was continuously stirred with a stir motor and bubbled with argon during the photolysis. The solvent was evaporated, the residue redissolved in 40 mL of chloroform, and the organic solution extracted twice with 10 mL of 5% sodium bicarbonate and once with 20 mL of water. The organic solution was dried over sodium sulfate, filtered, and evaporated to dryness. The product was recrystallized with 20% ethanol and dried under vacuum to yield 28.5 mg (32%) of white needles, mp 86–88 °C (lit.[10] mp 92 °C). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.52 (d, 1H), 8.12 (d, 1H), 7.25–7.51 (aromatic, 3H); UV (MeOH) ϵ_{280nm} 12 250 M^{-1} cm^{-1}.

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2,6-Dimethoxycinnamic Acid (4). Malonic acid (0.468 g, 4.5 mmol) and 2,6-dimethoxybenzaldehyde (0.498 g, 3.0 mmol) were stirred in pyridine (0.8 mL) containing piperidine (12 μL) at 100 °C under nitrogen. The suspension dissolved readily upon heating. After 16 h, the light yellow solution was diluted with water (20 mL) and the oil so formed was solidified by trituration and cooled. The white solid was collected by filtration, washed with cold water, and dried to yield 0.530 g (85%) of dimethoxycinnamic acid, mp 154–156 °C (lit.[11] mp 151–153 °C). The solid showed no change in melting point upon recrystallization form ethanol/water.

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