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Photochemical conversion of 2,6-dihalo substituted methyl α-phenylcinnamates

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Dedicated to Prof. S. Gudbjarnason on the occasion of his 70th birthday

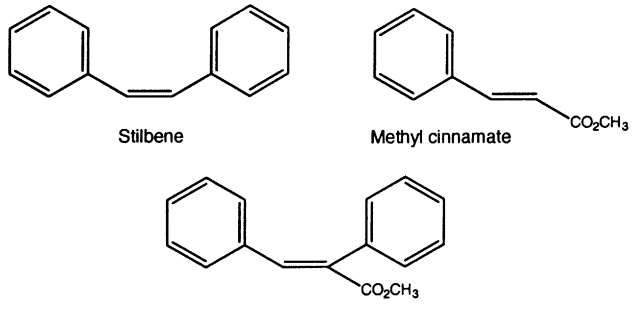
Abstract

Photolysis of methyl α-phenylcinnamate derivatives which have both *ortho* positions of the β-aromatic ring halogenated gives methyl 9-phenanthroates as the only identifiable products in good yields. This photochemical conversion involves a photocyclization with subsequent dehydrohalogenation, and is insensitive to oxygen. The mechanism of this transformation is briefly discussed: electronic factors seem to govern the outcome of the reaction but steric factors are apparently also of importance. The ester group attached to the double bond seems to be essential for the cyclization to take place. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Photochemical synthesis; Photocyclization; Halogenated α-arylcinnamates; Stilbenes; Phenanthrenes

1. Introduction

Methyl α-phenylcinnamate **1** can be viewed as a structural combination of stilbene and methyl cinnamate. Derivatives of the α-phenylcinnamate are known antifungal and antibacterial agents [1,2], and we are interested in the biological [3] as well as the photochemical [4,5] aspects of such compounds.



Methyl α-phenylcinnamate **1**

Methyl α-phenylcinnamate and its derivatives are photochemically active [6] and the expected photoreactions, by analogy with stilbenes and related compounds [7], are *E*/*Z* photoisomerization from the excited singlet state and a ring-closure reaction from the *E* isomers to form reversibly the 4a,4b-dihydrophenanthrene (DHP) derivative **2**. Under oxidative conditions the DHP intermediate is converted to the methyl 9-phenanthroate derivative **3**. These processes are depicted in Scheme 1, using the parent compound methyl α-phenylcinnamate **1** as an example [6]. It is worthy of note that various phenanthrene and dihydrophenenathrene derivatives have recently been reported to show strong antialgal activity [8].

In studying the photochemistry of methyl α-arylcinnamates with variously substituted aromatic rings [4,5], we observed that one of the derivatives differed noticeably as its *E*/*Z* photostationary state (PSS) composition could not be reliably established. This derivative was the only α-arylcinnamate studied that had both *ortho* positions of one of the chlorinated aromatic rings. In this communication, we disclose results which demonstrate that if both *ortho* positions of the β-aromatic ring are halogenated as in **4a**–**c** (Scheme 2), a photocyclization outweighs the *E*/*Z* photoisomerization. The different halogen substituents, chlorine and fluorine, were chosen in order to find out if size and electronegativity affected the outcome of the reaction.

2. Experimental details

The ^1H and ^{13}C NMR spectra were recorded on a Bruker AC250 spectrometer with chemical shift values being reported in parts per million with respect to residual $CHCl_3$ at 7.26 downfield from Me_4Si. All coupling constants (*J*) are given in hertz. IR spectra were recorded on a Nicolet

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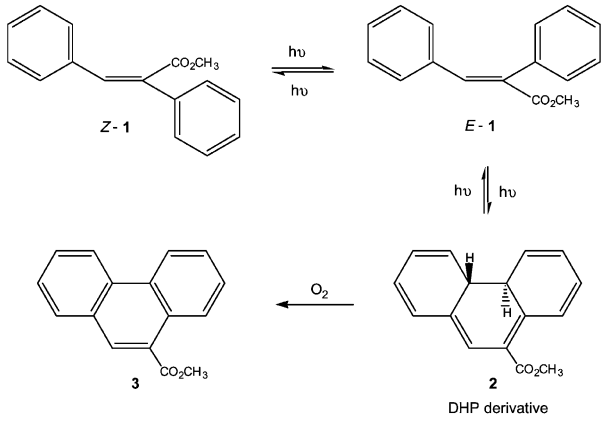
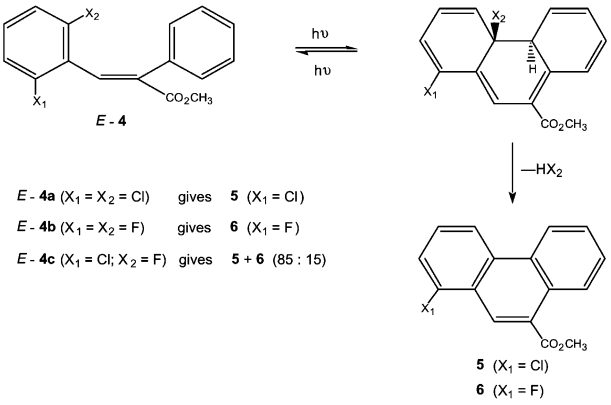


Scheme 1. Photochemical behavior of methyl α-phenylcinnamate.

Avatar 360 spectrometer. The mass spectra were obtained on a Saturn 2000R Instrument from Varian. Melting points were determined in open capillaries on a Büchi 520 melting point apparatus and are uncorrected. Analytical thin layer chromatography (TLC) was performed on 0.25 mm silica gel 60 F254 plates and visualized by UV light. Silica gel from Acros Organics (particle size 0.060–0.200 mm) was used for conventional column chromatography, and flash column chromatography was performed on an instrument from Biotage with pre-packed columns. The photochemical experiments were carried out in hexane from Acros Organics (p.a. grade for the preparative and spectrometric grade for the analytical conversions).

2.1. Synthesis of substrates *4*

The starting compounds (*E*)-**4a**–**c** were prepared by reacting methyl dimethylphosphonophenylacetate [9] with the appropriately substituted aromatic aldehyde in the presence of a base (Wadsworth–Emmons reaction) [2]. This method gave predominantly the *E* isomers, but a chromatographic purification step was necessary in order to obtain pure *E* isomers. The 2,6-dichloro derivative **4a** was most conveniently prepared by using sodium methoxide in refluxing methanol, but for the preparation of **4b**–**c** this base/solvent couple had to be replaced by sodium hydride in ether in order to prevent the replacement of fluorine by methoxide in an aromatic substitution reaction [10].



Scheme 2. Photochemical conversion of dihalogenated methyl α-phenylcinnamate.

The methyl α-phenylcinnamates **4a**–**c** were characterized on the basis of their ^{1}H and ^{13}C NMR spectra, and the *E*/*Z* structural assignments were based on the ^{1}H NMR chemical shifts of the olefinic protons (β-protons). Only the olefinic protons of the *E* isomers are subjected to the anisotropy of the carbonyl group, thereby causing a downfield shift of their signals relative to those of the *Z* isomers [11,12]: the *E* isomer olefinic signals appeared at $\delta = 7.65$–7.70 ppm, whereas those of the *Z* isomers appeared at $\delta = 7.0$–7.2 ppm [13]. The signals for the methyl groups appeared close to $\delta = 3.9$ ppm.

2.2. General procedure for the preparative photolysis of *4*

A solution of **4** (120–150 mg) in hexane (220 ml; approx. 2×10^{-3} M solutions) was irradiated with a 450 W medium-pressure mercury lamp through a water-cooled Pyrex jacket for 2–4 h. The solvent was removed under reduced pressure, and the reaction products were isolated with column chromatography on silica gel with hexane-ethyl acetate (7:3) as an eluent. The products **5** and **6** were characterized on the basis of spectroscopic evidence (^{1}H NMR, ^{13}C NMR, FT-IR, GC/MS).

Methyl 1-chloro-9-phenanthroate (**5**). Yield: 50% of colourless crystals, mp 87–89°C. ^{1}H NMR ($CDCl_3$) δ 4.08 (3H, s), 7.61–7.76 (4H, m), 8.61 (1H, d, *J* 8.1), 8.67–8.74 (1H, m), 8.87–8.94 (1H, m), 8.91 (1H, s); ^{13}C NMR ($CDCl_3$) δ 52.5, 121.6, 123.1, 126.7, 127.4, 127.5 (2C), 127.6, 127.7, 128.0, 128.7, 128.9, 130.4, 133.6, 133.9, 167.9; IR (CCl_4) ν (cm^{-1}) 1721, 1438; GC/MS (70 eV, EI) *m*/*z* (%) 270/272 (M^+, 98/31), 239/241 (100/32), 211/213 (35/15), 176 (45).

Methyl 1-fluoro-9-phenanthroate (**6**). Yield: 55% of colourless oil. ^{1}H NMR ($CDCl_3$) δ 4.06 (3H, s), 7.32 (1H, ddd, *J* 9.8, 7.9 and 0.9), 7.64–7.76 (3H, m), 8.46 (1H, d, *J* 8.5), 8.67–8.74 (1H, m), 8.75 (1H, s), 8.90–8.96 (1H, m); ^{13}C NMR ($CDCl_3$) δ 52.4 (OCH_3), 111.4 (d, J_{CF} 20.8 Hz, CH), 118.4 (d, J_{CF} 3.8 Hz, CH), 119.8 (d, J_{CF} 15.1 Hz, C), 123.8 (CH), 123.9 (d, J_{CF} 6.9 Hz, CH), 126.8 (CH), 127.3 (CH), 128.0 (CH), 128.4 (C), 128.5 (d, J_{CF} 8.8 Hz, C), 129.0 (d, J_{CF} 8.8 Hz, CH), 130.0 (d, J_{CF} 3.1 Hz, C), 133.7 (d, J_{CF} 3.8 Hz, C), 159.8 (d, J_{CF} 253.5 Hz, C), 167.8 (CO); IR (CCl_4) ν (cm^{-1}) 1720, 1462; GC/MS (70 eV, EI) *m*/*z* (%) 254 (M^+, 100), 223 (89), 195 (34), 175 (9).

3. Results and discussion

3.1. Photolysis of *4*

The photolysis of substrates **4a**–**c** afforded, after chromatographic purification, compound **5** or **6** as the sole

identifiable product in 50 and 55% yields, respectively. In the case of **4c**, we isolated a mixture of **5** and **6** with a **5**/**6** ratio of 85:15.

Prior to the above described preparative procedure, the reactions were monitored with HPLC during the irradiation of 1×10^{-4} M hexane solutions of *E*-**4** with pulses from a Lumonics 510 eximer laser (308 nm). The experimental setup has been described in detail elsewhere [4]. The formation of the *Z*-isomers was observed to occur to some extent in all three cases. Furthermore, the HPLC monitoring revealed in all instances the formation of two new major products, one of which disappeared with time, and after 45–60 min the (*E*/*Z*)-**4** had disappeared leaving a mixture composed of one major product with tiny amounts of byproducts. The irradiation of samples that had been flushed with dry nitrogen for 20 min, produced analogous results suggesting that this photochemical reaction was insensitive to oxygen.

3.2. Rationalization

On the basis of the examples studied so far, the introduction of halogen (chlorine and fluorine) into both *ortho* positions of the β-aromatic ring of methyl α-phenylcinnamates apparently has a pronounced effect on the photochemical behavior of these compounds. Once these positions were halogenated, a photochemical ring-closure with an ensuing dehydrohalogenation outweighed the *E*/*Z* photoisomerization.

The mechanism outlined in Scheme 2 is based on the extensively studied mechanism of the photocyclization of stilbenes [7,14]. The Scheme reveals that the photocyclization involves a reversible photochemical conrotatory cyclization from the *E* isomer to form a DHP derivative as an intermediate. This intermediate undergoes a dehydrohalogenation under the nonoxidizing reaction conditions to furnish the fully aromatic compounds **5** and **6**.

Similar photocyclizations with subsequent aromatization under nonoxidizing conditions have been reported for stilbene-type compounds with *ortho* substituents such as bromine and chlorine [15] and a methoxy group [16]. Of particular interest in this context are the findings of Muszkat et al. [17]: they photolysed a series of fluoro substituted stilbenes and observed no photocyclization if one or both of the aromatic rings had fluorine atoms in both *ortho* positions. The comparison of these results with the results presented here implies, that an ester group attached to the double bond facilitates the photocyclization process itself. Furthermore, the photochemical conversion of **4c** is noteworthy because the ring-closure involves the competitive participation of differently substituted *ortho* carbons. As displayed in Scheme 2, the photolysis of **4c** produced predominantly the phenanthroate **5** by expulsion of HF (the ratio of **5**/**6** was 85:15). This is in accord with the observation that the photochemical conversions of **4b** and **4c** were faster than that of **4a** and the byproducts were less pronounced, as judged by HPLC.

For the ring-closure of **1** and **4a**–**c** to take place, steric and electronic factors must come into play. The dominance of ring-closure product channels observed for the halogen substituted cinnamates compared to that observed for the corresponding stilbenes suggests that the major effect is electronic in nature. A less favorable ring-closure for the Cl substituents compared to that for the F substituents might be due to steric effects, considering the difference in the van der Waals volumes V: $V_F = 9.6\,Å^3$ versus $V_{Cl} = 19.9\,Å^3$ [18].

In summary, the conversion of methyl α-phenylcinnamates to phenanthrenes is reported for three derivatives which have chloro and/or fluoro substituents in both *ortho* positions of the β-aromatic ring. The transformation comprises a photochemical ring-closure with an ensuing dehydrohalogenation. The products are formed in acceptable yields and are easily purified.

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