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Efficient synthesis of polysubstituted isochromanones *via* a novel photochemical rearrangement[†]

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A novel and convenient approach to the synthesis of polysubstituted isochromanones is described. Irradiation of 2-formyl phenylalkeno-derivatives with UV light in benzene solution afforded the corresponding products in up to 98% yield. The possible reaction mechanism is proposed and further supported by the isotopic experiments.

Organic photochemical reactions play an important role in the context of green chemistry and/or total synthesis.¹ The photon involved in the procedure can be considered as the ideal clean reagent for organic synthesis in contrast to toxic chemical activators.² Another big advantage of reactions in the excited state is their application in the synthesis of polycyclic or highly functionalized molecules which would be difficult to access with standard chemistry reactions in the ground state.³ Therefore, the field of organic photochemical reactions has received considerable interest from both academia and industry.⁴ During our continuous investigations on the photochemical synthesis of furans or pyrans,⁵ we recently discovered a novel and efficient route to the synthesis of polysubstituted isochromanones via a unique photochemical rearrangement. In this paper, we present what we have learned to date about this unusual and interesting new reaction.

Our preliminary studies focused on the UV irradiation of ethyl 3-(2-formylphenyl)acrylate, a substrate that we expected might undergo a formal retro-Claisen photorearrangement leading to a pyran compound.⁵ Irradiation of (*E*)-ethyl 3-(2-formylphenyl)acrylate (Scheme 1, **1a**) in a benzene solution through Pyrex with a 500 W high-pressure mercury lamp for 1.5 h, to our delight, led to a single product in 89% isolated yield. Based on its spectroscopic properties, in particular its 1D and 2D ¹H NMR spectra, this photoproduct was assigned as the compound **2a** (Scheme 1). The conversion of **1a** to **2a** provides a quick and easy way to synthesise polysubstituted isochromanones. In addition, the lactone and cyclopropanyl

groups of the photoproduct constructed in one step from a simple cinnamic acid ester are versatile building blocks in organic synthesis,⁶ which urged us to investigate this reaction in detail.

Upon initial investigation of the reaction conditions, we were encouraged to treat **1a** with different wavelengths in combination with different solvents (benzene, acetone, acetonitrile, DMF and DMSO), and the results are listed in Table 1. As can be seen, the reaction proceeds efficiently in all employed solvents with 52-89% yield at high conversions. Finally, screening of the conditions on GC showed that the reaction conducted in benzene, using a 500 W high-pressure mercury lamp as the light source through a Pyrex filter, produced the highest yield which were then utilized as the reaction conditions in further investigations.⁷

To explore the scope of this reaction, we prepared a variety of 2-formyl phenylalkeno-derivatives (for preparations see Supporting Information[†]) and subjected them to the reaction conditions, which uniformly afforded the desired photoproduct in good to excellent yields (63-98%; Table 2, entries 1-11). As can be seen, both simple alkyl cinnamate (entries 1 and 2) and bulky alkyl cinnamate (entries 3 and 4) provided the desired products. The presence of substituents at the para or *meta* position of the aldehyde group was tolerated for the reaction independently of their electron-donating or electronwithdrawing effect (entries 5, 6, 9, 10). Irradiation of (Z)-ethyl 3-(2-formylphenyl)acrylate also smoothly afforded the corresponding photoproduct in high yield (entry 11).⁸ It is noteworthy that the formation of photoproduct 2a was affected by the substitutions on the double bond. When the acrylate was tethered with an alkyl group at the β position, the reaction proceeded efficiently (entries 7 and 8) and highest yield was obtained (entry 7), whereas the one containing a methyl group at the α position only afforded the isomerization product

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Scheme 1 Initial photochemical studies of 1a in benzene.

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 Table 1
 Irradiation of 1a in different solvents

Entry	Conditions ^a	Conv. $(\%)^b$	Yield $(\%)^b$
1	Benzene, r.t., 1.5 h	98	89 ^c
2	Acetone, r.t., 1.5 h	88	53
3	Acetonitrile, r.t., 1.5 h	100	68
4	DMF, r.t., 1.5 h	100	74
5	DMSO, r.t., 1.5 h	100	52

^{*a*} A 500 W high-pressure mercury lamp as the light source. ^{*b*} Detected using GC. ^{*c*} Isolated yield after purification by chromatography on SiO₂.

 Table 2
 Photochemical studies on 2-formyl phenylalkeno-derivatives



^{*a*} Isolated yields at complete conversions. ^{*b*} Only the isomerization product obtained.

instead of the desired product (entry 13). The reaction conditions were also tolerant of α , β -unsaturated ketones (entry 12). Although longer a reaction time was involved, the desired photoproduct was obtained in moderate yield.

The photoreaction is not prevented by the addition of stilbene, and no [2+2]-cyclodimerization products were observed during the reaction. Based on the above control experiment results and associated with the behavior of the excited state of cinnamic acid esters that exhibits ineffective dimerization proceeds from the singlet excited state,⁹ it could be proposed



Scheme 2 Isolation of the byproducts 3 and 5.

that the photochemical conversion of **1a** to **2a** most likely proceeds from the $(\pi, \pi^*)^1$ excited state. To add credence to our mechanistic hypothesis, we were fortunate enough to obtain compound **3** and **5** as the byproducts in the case of entries 1 and 3 (Table 2) with isolated yields of 23% and 17%, respectively (Scheme 2). Such products were presumably formed from the intermediate of 1,4-biradicals **4**.

Throughout our investigations, a control experiment was conducted by the irradiation of 1b in which an acetyl group replaced the aldehyde group. As expected, no desired photoproduct was observed, which indicates that the hydrogen of the aldehyde group plays a crucial role in the reaction.

To further support our mechanistic hypothesis, we performed labeling studies using deuterated compound **6** as a substrate. Irradiation of **6** under the same reaction conditions successfully afforded the photoproduct **7**. On the basis of NMR analysis, it was shown that the deuterium atom shifted from the aldehyde group to the cyclopropane (Scheme 3).

Accordingly, we propose a mechanism wherein the double bond of **8** is excited to form the 1,2-biradicals **9** under UV light irradiation (Scheme 4). Sequentially, the abstraction of the hydrogen from aldehyde group affords the 1,4-biradical **10**, which is then transformed to the ketene intermediate **11** *via* the cleavage of the double bond of the aromatic group. Finally, rearrangement of the exocyclic double bonds occurs, regenerating the aromatic ring and forming the lactone and cyclopropane groups in one step, which leads to the final photoproduct **12**.

In a dramatic demonstration of the synthetic potential of the reaction, a solution of 500 mg of (*E*)-ethyl 3-(2-formyl-phenyl)acrylate in 150 mL of benzene was irradiated to 100% conversion to afford an 80% isolate yield of the corresponding photoproduct.



Scheme 3 Deuterium-labeling experiments



Scheme 4 Proposed reaction mechanism.

In summary, we have reported a convenient approach to the synthesis of polysubstituted isochromanones *via* a novel photochemical reaction. The lactone and cyclopropane groups of the photoproducts have potential applications in bioactive molecules synthesis. We are continuing to explore the scope of this transformation as well as further mechanistic investigations.

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