Further Insight into the Photochemical Behavior of Aromatic γ,δ-Epoxy Ketones: A New Approach for Synthesis of 4-Methyleneisochromanols

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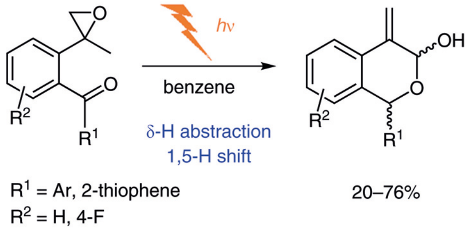

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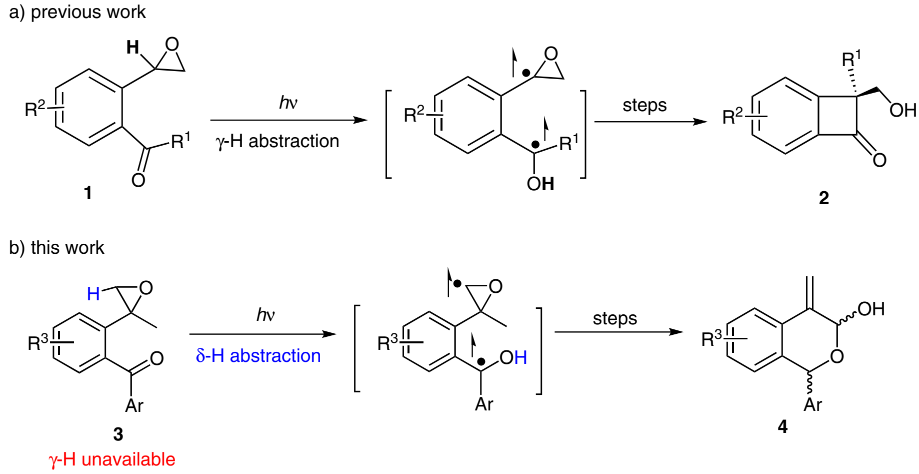
Abstract The photochemical behavior of methyl-substituted aromatic γ,δ-epoxy ketones was investigated by irradiation with a 500 W high-pressure mercury lamp in benzene which led to the formation of 4-methyleneisochromanols through δ-hydrogen abstraction–epoxy rearrangement–1,5-biradical cyclization reactions.

Key words γ,δ-epoxy ketones, photochemical behavior, 4-methyleneisochromanol, epoxy rearrangement, 1,5-biradical cyclization

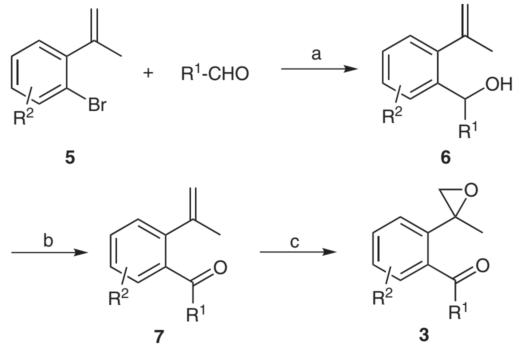
Organic photochemical reactions play an important role in building organic frameworks that are otherwise difficult to make.[1] Considerable research efforts have concentrated on the development of new photochemical reactions. Among them, photochemical studies on epoxides and epoxy ketones have discovered that the type of photoinduced ring opening of epoxides is alternative depending on the substitution and the nature of reactive excited states of substrates.[2] Recently, we have developed a novel and efficient way to prepare polysubstituted benzocyclobutanones and indanones through the investigations on the photochemistry of terminal and substituted aromatic γ,δ-epoxy ketones in which the process involves the abstraction of γ-hydrogen as the typical first step of Norrish type II reaction[3] and the Lewis acid free semipinacol rearrangement–photocyclization cascade reaction (Scheme 1, a).[4] Herein we further investigated the photochemical behavior of substituted γ,δ-epoxy ketones in which the γ-hydrogen is replaced by a methyl group and found that 4-methyleneisochromanol compounds were obtained via initial abstraction of δ-hydrogen instead (Scheme 1, b). Such a conversion provides an easy and quick access to the synthesis of isochro-



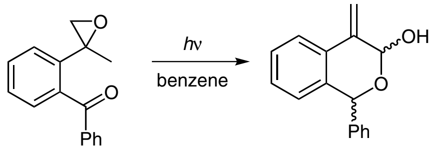
Scheme 1 Previous work and our further investigations.

manol derivatives,[5] the versatile synthetic building blocks of natural products[6] which urges us to investigate this reaction in detail.

Our investigation was started from the synthesis of methyl-substituted γ,δ-epoxy ketone **3a** (R^1 = Ph, R^2 = H) using olefin **5a** (R^2 = H) as the starting material according to the known straightforward steps (Scheme 2). The initial photochemical study on **3a** was conducted by irradiation with a 500 W high-pressure mercury lamp in benzene for 40 minutes which led to a product of 4-methyleneisochromanol **4a** in 52% yield (Scheme 3). The structure of **4a** was determined by its spectroscopic properties, in particular its 1D and 2D NMR spectra.



Scheme 2 Synthesis of γ,δ-epoxy ketones **3**. *Reagents and conditions*: a) *n*-BuLi, THF, –70 °C; b) PCC, CH_2Cl_2; c) Oxone, MeCN, H_2O, 18-crown-6, acetone, $NaHCO_3$, 0 °C.

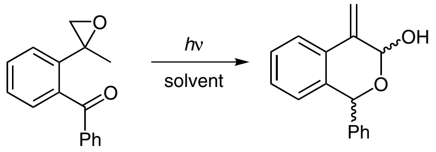


3a 4a

Scheme 3 Initial photochemical studies of **3a**

Based upon the initial result, the optimization of reaction conditions were then conducted by treatment of **3a** with different solvents and wavelengths, and results are listed in Table 1. As it can be seen, the reaction proceeded in anhydrous benzene using a 500 W high-pressure mercury lamp as light source led to the best yield (Table 1, entry 1). In contrast, no reaction was observed when 354 nm wavelength was used which might be due to the difficulty in excitation of the substrate at this wavelength. The complex products were observed when Lewis acids such as $InCl_3$, BF_3·OEt_2 were employed in the reaction as additives (Table 1, entries 2, 7, and 8). Reactions conducted in other solvents, such as acetone and acetonitrile, or undried benzene, led to lower yields (Table 1, entries 4–6). In addition, the reaction also could proceed under air but longer time was needed (Table 1, entry 3).

Table 1 Optimization of Reaction Conditions[a]



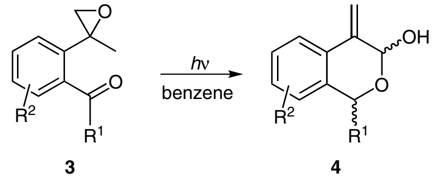
3a 4a

Entry	Solvents	Gas	Wavelength (nm)	Conversion[b]	Yield (%)[c]
1	anhydrous benzene	N_2	>280 (Pyrex)	100	63
2	anhydrous benzene	N_2	354	0	0
3	anhydrous benzene	air	>280 (Pyrex)	100[d]	52
4	normal benzene	N_2	>280 (Pyrex)	100	52
5	anhydrous acetone	N_2	>280 (Pyrex)	100	56
6	anhydrous MeCN	N_2	>280 (Pyrex)	100	55
7	anhydrous benzene, $InCl_3$	N_2	>280 (Pyrex)	100	0
8	anhydrous benzene, BF_3·OEt_2	N_2	>280 (Pyrex)	100	0

[a] Reactions were carried out with **3a** (0.1 mmol) in 10 mL of solvent at r.t.
[b] Irradiated for 40 min.
[c] Isolated yields.
[d] Completed in 100 min.

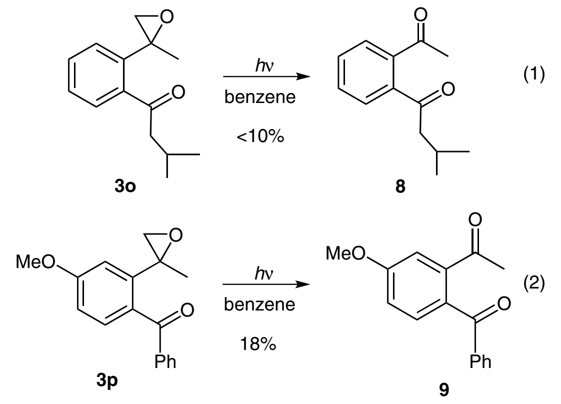
With the optimized reaction conditions in hand, we therefore prepared a series of methyl-substituted aromatic γ,δ-epoxy ketones to investigate the scope of the reaction.[7] As shown in Table 2, the reactions were completed within 30–50 minutes at room temperature to form the desired products in moderate to good yields. The electron effect on the pendent aryl group has no influence on the results of the reactions, for example, when R^1 was an electron-withdrawing or an electron-donating group located at different positions, the corresponding products were obtained in 45–76% yield (Table 2, entries 2–9, 11) with the diastereoisomeric ratio ranging from 1:3 to 3.6. Even if the substrate was highly electron deficient, the desired product also could be prepared in 40% yield (Table 2, entry 10). When the phenyl group adjacent to the epoxy ring was substituted with an electron-withdrawing group, such as F, the reaction still goes smoothly to afford the corresponding products (Table 2, entries 13 and 14). It seems that it is necessary for R^1 to be an aryl group or conjugated group, for example, the corresponding product was formed as the phenyl group was replaced by a thiophene although the yield is not good (Table 2, entry 12). However, the reaction of **3o** led to the diketone compound **8** in very low yield along with other byproducts (Scheme 4, eq. 1) which might result from the decomposition of the starting material. The similar result was also observed on the reaction of the *p*-methoxy phenyl ketone compound **3p** whose lowest triplet state is known as π,π* failed to form the desired isochromanol product but the diketone **9** in 18% yield (Scheme 4, eq. 2).

Table 2 Scope of the Photorearrangement



Entry	Substrate	Time (min)	Yield (%)[a] (dr)[b]
1	**3a** R^1 = Ph, R^2 = H	40	**4a** 63 (1:3.1)
2	**3b** R^1 = 2-FC$_6$H$_4$, R^2 = H	30	**4b** 60 (1:3.4)
3	**3c** R^1 = 3-FC$_6$H$_4$, R^2 = H	40	**4c** 61 (1:3.5)
4	**3d** R^1 = 4-FC$_6$H$_4$, R^2 = H	40	**4d** 70 (1:3)
5	**3e** R^1 = 3-ClC$_6$H$_4$, R^2 = H	40	**4e** 76 (1:3.3)
6	**3f** R^1 = 4-ClC$_6$H$_4$, R^2 = H	40	**4f** 54 (1:3)
7	**3g** R^1 = 3-MeC$_6$H$_4$, R^2 = H	40	**4g** 48 (1:3)
8	**3h** R^1 = 4-MeC$_6$H$_4$, R^2 = H	40	**4h** 57 (1:3)
9	**3i** R^1 = 4-F$_3$CC$_6$H$_4$, R^2 = H	40	**4i** 57 (1:3.6)
10	**3j** R^1 = 3-Cl-4-FC$_6$H$_3$, R^2 = H	40	**4j** 40 (1:2.8)
11	**3k** R^1 = 4-*t*-BuC$_6$H$_4$, R^2 = H	40	**4k** 45 (1:3.5)
12	**3l** R^1 = 2-thiophene, R^2 = H,	40	**4l** 20 (1:3.6)
13	**3m** R^1 = Ph, R^2 = 4-F	50	**4m** 65 (1:3.3)
14	**3n** R^1 = 4-FC$_6$H$_4$, R^2 = 4-F	50	**4n** 32 (1:2.7)

[a] Isolated yields.
[b] The diastereomeric ratios are calculated from their ^{1}H NMR spectra indicating the ratio of between *cis* and *trans* products.



Scheme 4

Based upon the above results and previous work,[4] the reaction mechanism was accordingly proposed and depicted in Scheme 5. A common step is the excitation of the carbonyl group of **3** to form the 1,2-biradical under UV light irradiation via an n,π* triplet state, which was then transformed to 1,5-biradical intermediate **11** after abstraction of a δ-hydrogen of epoxy ring. Epoxy ring opening of **11** led to forming of carbonyl group and the 1,4-biradical of **12**, which then afforded the 1,2-biradical intermediate **13** after the abstraction of hydrogen. Final product **4** was obtained from the formation of the C–C double bond and pyran ring.

In conclusion, the photochemical behavior of methyl-substituted aromatic γ,δ-epoxy ketones in benzene solution was investigated. This protocol provides an easy access to isochromanol derivatives and highlights the application of photochemistry in the realm of organic synthesis. We are continuing to explore the scope of this transformation as well as further mechanistic investigations.

Acknowledgment

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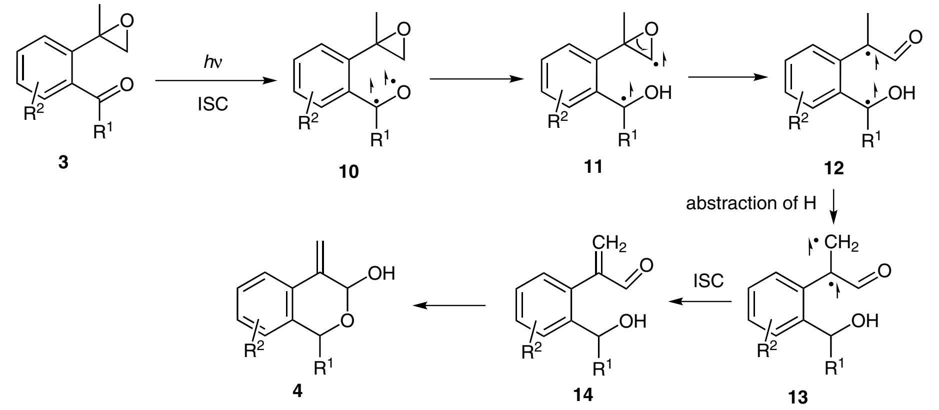

Scheme 5 Proposed mechanism

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1378814.

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(7) **Typical Experimental Procedure for the γ,δ-Epoxy Ketone 3 and Isochromanol 4**
To round-bottomed flask was added olefin **7** (0.2 mmol), acetone (2 mL), H_2O (1 mL), MeCN (1 mL), $NaHCO_3$ (2 mmol), 18-crown-6 (0.002 mmol), the mixture was cooled to 0 °C, and Oxone (0.6 mmol) was dissolved in H_2O and added slowly. After addition, the reaction was stirred at the same temperature until no starting material could be detected by TLC. The mixture was extracted with CH_2Cl_2, the combined organic phase was washed with sat. $NaHCO_3$, brine, and dried over Na_2SO_4, then quickly purified through a neutral Al_2O_3 gel column (PE–EtOAc) to give **3**, which is unstable, refrigerated storage. The γ,δ-epoxy ketone **3** (0.1 mmol) in anhydrous benzene (10 mL) was treated with N_2 for 10 min in darkness, and then irradiated by a 500 W high-pressure mercury lamp with condensate until no starting material could be detected by TLC. The solvent was removed in vacuo, and the residue was purified by silica gel column chromatography (PE–EtOAc) to give the desired product **4**.
1-(4-*tert*-Butylphenyl)-4-methyleneisochroman-3-ol (4k)
Colorless oil. Yield 45%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, 1 H, *J* = 7.8 Hz), 7.42 (d, 2 H, *J* = 7.3 Hz), 7.29 (d, 3 H, *J* = 7.1 Hz), 7.19 (t, 1 H, *J* = 7.4 Hz,), 6.79 (d, 1 H, *J* = 7.7 Hz), 6.07 (s, 0.77 H), 5.91 (s, 0.24 H), 5.85 (s, 0.78 H), 5.82 (s, 0.74 H), 5.79 (s, 0.22 H), 5.67 (d, 0.22 H, *J* = 7.8 Hz), 5.53 (s, 0.22 H), 5.35 (s, 0.77 H), 3.21 (d, 0.20 H, *J* = 7.7 Hz), 3.08 (s, 0.74 H), 1.35 (s, 9 H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.4, 151.3, 141.6, 139.6, 138.1, 137.8, 137.0, 136.7, 131.5, 129.8, 128.5, 128.0, 127.4, 127.3, 126.6, 126.5, 125.5, 124.2, 123.9, 110.8, 107.7, 94.1, 93.9, 79.1, 73.2, 34.6, 31.4. ESI-HRMS: *m/z* calcd for $C_{20}H_{23}O_2^+$: 295.1698 $[M + H]^+$; found: 295.1696.