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Photochemical studies on aromatic γ , δ -epoxy ketones: efficient synthesis of benzocyclobutanones and indanones[†]

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Irradiation of terminal aromatic γ , δ -epoxy ketones with a 450 W UV lamp led to Norrish type II cyclization/semi-pinacol rearrangement cascade reaction which formed the benzocyclobutanones containing a full-carbon quaternary center, whereas irradiation of substituted aromatic γ , δ -epoxy ketones led to the indanones through a photochemical epoxy rearrangement and 1,5-biradicals cyclization tandem reaction.

Light is regarded as a powerful energy source for chemists to synthesize polycyclic or highly functionalized molecules avoiding toxic reagents. Therefore, organic photochemistry has received considerable interest from both academia and industry.¹ For example, many research efforts have concentrated on the photochemical behavior of epoxy ketones. Compared with well established results of the photochemistry of α,β -epoxy ketones² and β , γ -epoxy ketones, ³ attempts to study γ , δ -epoxy ketones are still at an early stage.⁴ Photochemical studies on epoxy and epoxy ketones have demonstrated that the type of photoinduced ring opening of epoxy is alternative depending on the substitution and the nature of reactive excited states of substrates.^{1a} Therein, by the way of heterolytic C-C bond cleavage of the epoxy group, pyrans or furans would be formed.^{2b,5} As our aim to continuously explore new and versatile methods to prepare furans and other synthetic units,⁶ recently, we discovered a novel and efficient way to prepare polysubstituted benzocyclobutanones and indanones during the investigations on the photochemistry of aromatic γ , δ -epoxy ketones in solution. More importantly, the formation of benzocyclobutanones was generated from a Norrish type II photocyclization⁷/Lewis acid-free semipinacol rearrangement cascade reaction. In this communication, we present what we have learned to date about these new and serendipitous discoveries.

Our preliminary studies focused on the photochemical behavior of aromatic γ , δ -epoxy ketone **1a** (Scheme 1) through irradiation of **1a** in benzene solution with a 450 W medium-pressure



Scheme 1 Initial photochemical studies of 1a in benzene solution.

mercury lamp using a Pyrex filter. Initially, the irradiation of **1a** was supposed to form a benzopyran *via* C–C bond cleavage of the epoxy group. However, based on the 1D and 2D NMR spectral analysis, the photoproduct was assigned to the benzocyclobutanone **2a** containing a full-carbon quaternary center which was isolated in 63% yield. Obviously, more complex reaction pathways have to be considered for this unique photochemical reaction. Importantly, the conversion of **1a** to **2a** provided an easy and quick access to the synthesis of polysubstituted benzocyclobutanones, the versatile synthetic building blocks in total synthesis of natural products, from simple and readily available substrates,⁸ which urged us to investigate this reaction in detail.

Upon initial investigations on the reaction conditions, we were encouraged to treat **1a** with a series of wavelengths⁹ in combination with different solvents (anhydrous benzene, acetone, acetonitrile, and dichloromethane). Gas chromatography (GC) analysis showed that the reaction proceeded in anhydrous benzene upon using a 450 W medium-pressure mercury lamp as a light source through a Pyrex filter and led to the photoproduct **2a** in 73% yield. Notably, no reaction was observed when Lewis acids were employed in the reaction, such as TMSOTf, InCl₃, AlBr₃.

We therefore prepared a series of aromatic γ , δ -epoxy ketones (for preparations see ESI†) and subjected them to the optimized reaction conditions. As shown in Scheme 2, the reactions were completed within 25–30 minutes at room temperature and formed the desired products in moderate to good yields. The electron-withdrawing and electron-donating groups on \mathbf{R}_1 are tolerated under the reaction conditions giving the desired products in good yields (**2c** and **2d**). An aryl group is necessary for the initial excitation of the carbonyl group to the 1,2-biradicals, because only the diketone compound was obtained when the alkyl group replaced the aromatic group

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Scheme 2 Photochemical studies of aromatic terminal γ , δ -epoxy ketones 1 in benzene solution.



Scheme 3 Photochemical studies on substituted epoxide 3a in benzene solution.

in the reaction (I). The presence of electron-withdrawing or electron-donating groups at the *para* position of the epoxy group had no influence on the results, because the desired products were smoothly formed in synthetically useful yields (**2e**, **2f** and **2i**). While the presence of an electron-withdrawing group at the *para* position of the ketone was tolerated under the reaction conditions (**2g** and **2h**), the *p*-methoxy-phenyl derivative, whose lowest triplet state is undoubtedly π,π^* in nature,¹⁰ failed to react (**2j**).

Throughout our investigations, the substituted epoxy compound **3a** was also synthesized to examine the influence of a terminal substituent (Scheme 3). Interestingly, irradiation of compound **3a** under the same conditions led to a polysubstituted indanone compound **4a** with *syn*-Ph, Me groups as the sole product. The stereochemistry of **4a** was determined by its spectroscopic properties, in particular its 1D and 2D ¹H NMR spectra. In comparison to the results of the terminal epoxide **1a**, obviously, different reaction pathways have to be considered in this case.

To explore the scope of this reaction, a variety of substrates were also synthesized and subjected to the reaction conditions. As expected, all of the substrates uniformly afforded the indanones in good yields and excellent diastereoselectivity after irradiation for 25–30 minutes (Scheme 4). The presence of electron-withdrawing groups at the *para* position of the aroyl groups was tolerated under the reaction conditions and as high as 84% yield was obtained (**4c**, **4e** and **4f**). The substitutions at the δ -position of the epoxide have influence on the reaction result, *e.g.*, higher yield was obtained when two δ -hydrogen atoms were replaced by methyl groups (**4d**) in comparison to the results of **4a** and **4b**. Interestingly, irradiation of the substrate with a phenyl group substituted at the δ -position directly led to 2,3-diphenylindanone (**II**), which possibly was



Scheme 4 Photochemical studies on substituted epoxides 3 in benzene solution.



Scheme 5 Proposed mechanism for the formation of 2 and 4.

generated from the sequential dehydration of the corresponding β -hydroxyl indanone photoproduct. Notably, the *p*-methoxy phenyl ketone compound ($R_4 = p$ -OMe) failed to react owing to its lowest π,π^* triplet state albeit irradiation was for a longer time.

During the course of our investigations, a control experiment was conducted by irradiation of the substrate **1b** in which the γ -hydrogen was replaced by a methyl group (Scheme 1) under the same reaction conditions. As predicted, no corresponding indanone product was formed (Scheme 1, **2b**), which indicated that the γ -hydrogen plays a crucial role in the process of this reaction.

Accordingly, a proposed mechanism for the formation 2 and 4 is depicted in Scheme 5. A common step for the two pathways is the excitation of the carbonyl group of 5 to form the 1,2-biradicals under UV light irradiation via an n,π^* triplet state, which then transformed to 1,4-biradicals intermediate 6 after γ -hydrogen abstraction. The formation of 1,4-biradicals 6 features the first step of photochemical Norrish type II reaction¹¹ which then cyclized to yield the epoxy cyclobutanol **8** in the case of a terminal epoxide (R_2 , $R_3 = H$). Sequentially, the intramolecular hydrogen-bond involved in 8 promoted a semipinacol rearrangement reaction¹² through the epoxy ring opening accompanied by the migration of the aromatic group to form the final product 2. While for the case of a substituted epoxide (R_2 or $R_3 \neq H$), 1,4-biradicals 6 tended to form the 1,5-biradicals 7 via an epoxy rearrangement due to the stabilization of the radical at the δ -position. This is consistent with the result that higher yield was obtained when two methyl groups replaced the δ-hydrogen (Scheme 4, 4d). Finally, 1,5-biradicals cyclization reaction took place to afford the photoproduct 4.





Scheme 6 Diastereoselectivity model of 4a.

The diastereoselectivity of the formation of **4** could be rationalized using **4a** as the substrate through theoretical calculations. Based upon DFT calculations (B3LYP/6-311), the Dreiding models showed that the intermediate **7a** adopts a conformation with the lowest energy in which the Me group on C5 is located in the plane of C==O, C4–C5 and C5–Me, and *syn* to the phenyl group on C1 (Scheme 6). Sequential ring closure through the C–C bond formation between C1 and C5 led to the final product **4a** with *syn*-phenyl, Me groups.

Benzocyclobutanone and indanone derivatives are versatile synthetic intermediates in total synthesis of natural products with a variety of types of carbon skeletons.¹³ Therefore, to demonstrate the synthetic potential of the photochemical formation of these compounds, a solution of 500 mg of aromatic γ , δ -epoxy ketone **1a** and **3a** in 150 mL of anhydrous benzene was irradiated to 100% conversion to afford **2a** and **4a** in 67% and 59% yield respectively.

In conclusion, the photochemistry of terminal and substituted aromatic γ , δ -epoxy ketones in benzene solution was investigated. The work reported in this communication provides an easy access to benzocyclobutanones and indanones, 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.

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