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Photoinduced Regioselective Lactonization of ortho-Iodobenzoic Acids with Alkenes: Synthesis of 3,4-Dihydroisocoumarin Derivatives

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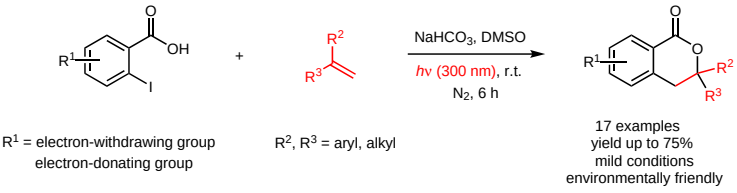

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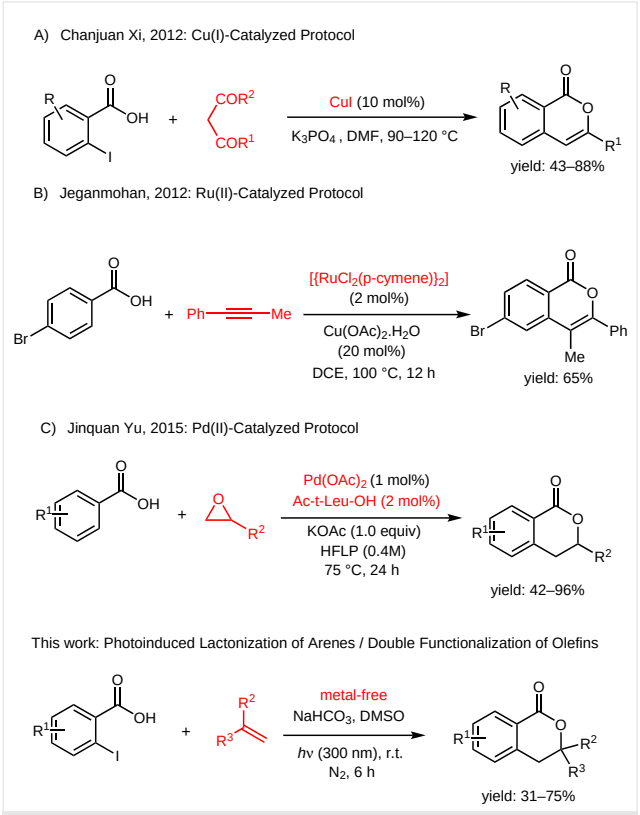
Abstract A photoinduced strategy for the synthesis of a variety of 3,4-dihydroisocoumarins has been realized. The reactions proceeded from *ortho*-iodobenzoic acids and alkenes through a photodehalogenative lactonization with $NaHCO_3$ as the only additive in dimethyl sulfoxide (DMSO) to provide the desired products in moderate to good yields. This method offers a simple, mild, and environmentally friendly route to 3,4-dihydroisocoumarin derivatives.

Key words 3,4-dihydroisocoumarin, *o*-iodobenzoic acids, alkenes, radical lactonization, difunctionalization

Isocoumarins are natural benzolactones that exhibit a wide range of biological activities including antibacterial, anti-inflammatory, and antitumor effects.[1] Among the isocoumarin derivatives, 3-substituted isocoumarins with no substituent at the 4-position exhibit greater biological activities; therefore, research on its synthesis has been widely undertaken.[1d,f,2] Similar to isocoumarins, 3,4-dihydroisocoumarins also possess antibacterial, fungicidal, and HCV protease-inhibitory activities.[3] Through catalytic hydrogenation, isocoumarin can be transformed into 3,4-dihydroisocoumarin, and 3,4-dihydroisocoumarins can be olefinated through halogenation and dehydrohalogenation. By these methods, the reciprocal transformation can be realized by using simple, classical methods of synthesis.

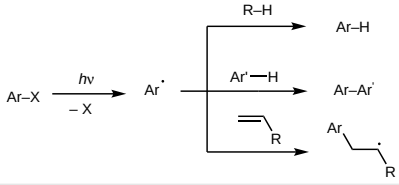
To date, various methods have been developed for the synthesis of isocoumarins. Among them, the most prevalent strategy is the cycloaddition of *o*-halogenated benzoic acids or benzoic acids with alkynes, 1,3-diketones, oxiranes, etc. under the catalysis of Cu,[4] Ru,[5] Rh,[6] Pd,[7,3b] and other transition metals[8] (Scheme 1). For example, the Xi[4a] group disclosed a method for the synthesis of 3-substituted isocoumarin derivatives through the application of 1,3-diketones with *o*-iodobenzoic acid derivatives using CuI as catalyst under heating (Scheme 1, A). The same year, the Jeganmohan[5a] group reported a strategy for the preparation of isocoumarin derivatives with substituents at both 3- and 4-positions, using benzoic acids and alkynes as substrates with a Ru(II) catalyst at high temperature (Scheme 1, B). In



Scheme 1 Synthetic strategies used to form isocoumarin/3,4-dihydroisocoumarin derivatives

addition, with the development of organometallic chemistry, the Yu[6a] group devised a cycloaddition protocol using benzoic acids and oxiranes to achieve 3,4-dihydroisocoumarins in excellent yields. However, they exploited expensive Pd(II) with a similarly expensive ligand as the catalytic agent (Scheme 1, C). Although these reactions afford high yields (>70%) of the target molecules, it should be noted that high temperature is an indispensable condition for the transition-metal-catalyzed reactions. Moreover, transition-metal catalysts are generally expensive and not environmentally sound.

Light is an inexhaustible and nonpolluting energy source; thus, photoinduced reactions play an important role in organic synthesis of natural products, pharmaceuticals, pesticides, and fine organic compounds.[9] Considering all kinds of concerns especially in the environment, a number of studies on the photochemistry of halogenated aromatic compounds have been stimulated, with a significant goal often being to understand whether photolysis is an important measure for these compounds in natural waters or in the atmosphere.[10] Under ultraviolet light (UV) irradiation, the phenomenon of homolytic cleavage of the aryl carbon–halogen bond occurs to afford aryl radicals,[11] which can either abstract hydrogen from a hydrogen atom donor to achieve the aromatization reaction or bond with electron-rich alkenes to realize the difunctional reaction of alkenes (Scheme 2).[12]

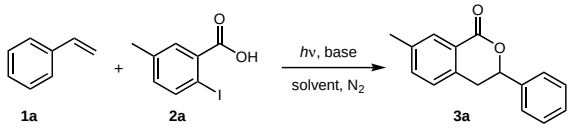


Scheme 2 Photoinduced arylation of alkenes with aryl halides

With this mechanistic hypothesis in mind, we investigated the reaction of 2-iodo-5-methylbenzoic acid (**2a**) and styrene (**1a**) in anhydrous MeCN with $NaHCO_3$ as the only additive. We were pleased to find that, after irradiation with 300 nm UV light (the best absorption of *o*-iodobenzoic acids at 300 nm, see the Supporting Information) for six hours at room temperature, the reaction afforded the desired product 3,4-dihydroisocoumarin (**3a**) in 51% yield. To establish the optimum conditions, we next screened the reaction with respect to three parameters: solvent, light source, and additives.

Screening of solvents showed that the substrate in each case can be consumed completely within six hours, and the highest yield was observed when dimethyl sulfoxide (DMSO) was used as solvent (28–75% yield; Table 1, entries 1–5). Moreover, evaluation of several light sources revealed that 300 nm wavelength light was ideal for the reaction (Table 1, entries 5–7). We speculated that low-energy light

Table 1 Optimization of Reaction Conditions[a]

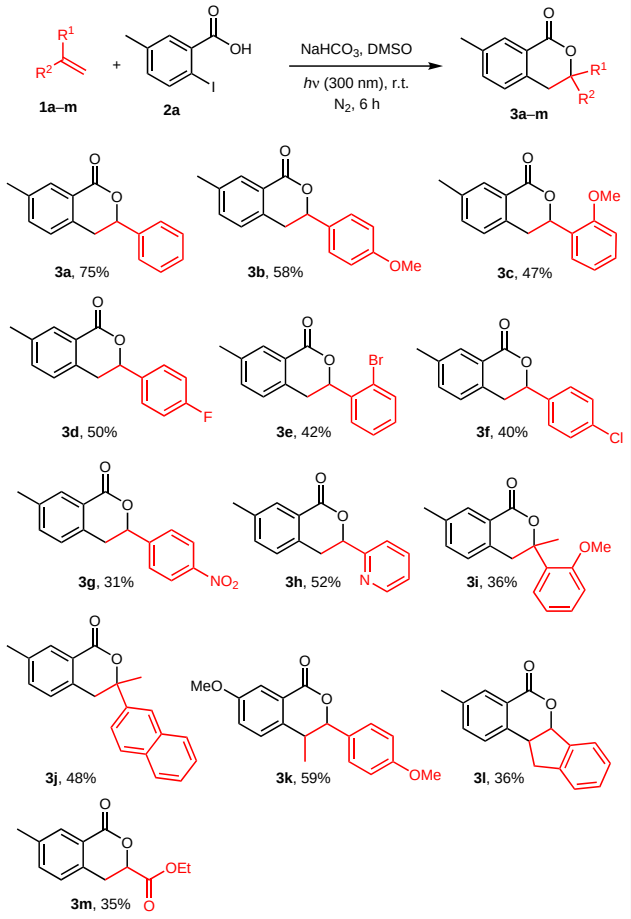


Entry	Base	*hν* (nm)	Solvent	Yield (%)[b]
1	$NaHCO_3$	300	MeCN	51
2	$NaHCO_3$	300	DMF	43
3	$NaHCO_3$	300	CH_2Cl_2	28
4	$NaHCO_3$	300	toluene	39
5	$NaHCO_3$	300	DMSO	75
6	$NaHCO_3$	254	DMSO	57
7	$NaHCO_3$	350	DMSO	0
8	–	300	DMSO	61
9	Na_2CO_3	300	DMSO	63
10	NaOH	300	DMSO	72
11	Na_2HPO_4	300	DMSO	68
12	Et_3N	300	DMSO	0
13[c]	$NaHCO_3$	300	DMSO	21

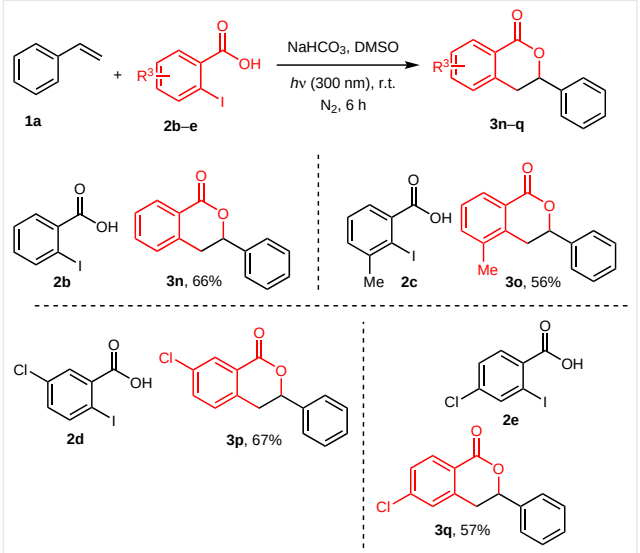
[a] Standard conditions: 2-iodo-5-methylbenzoic acid (**2a**; 0.2 mmol, 1 equiv), styrene (**1a**; 0.8 mmol, 4 equiv), $NaHCO_3$ (0.26 mmol, 1.3 equiv) in anhydrous DMSO (4 mL), *hν* (300 nm), N_2, 6 h.
[b] Isolated yield.
[c] With oxygen.

sources (e.g., 350 nm) were not sufficient to induce this reaction, whereas the use of high-energy light sources (e.g., 254 nm) results in the partial decomposition of the substrates. The choice of inorganic base was also found to have a dramatic effect on the yield, with $NaHCO_3$ proving to be optimal (61–75% yield; Table 1, entries 5, 8–11). When the organic base Et_3N was used, only trace amounts of product were detected (Table 1, entry 12). We speculated that a single-electron transfer process might be involved between **2a** and Et_3N. In addition, when the reaction was exposed to oxygen atmosphere, the yield was reduced to only 21%. Therefore, degassing is an indispensable requirement for this reaction (Table 1, entry 13). Overall, the quartz tube as the reaction vessel, $NaHCO_3$ as the base, 300 nm low-pressure mercury lamp as excitation light source, and nitrogen atmosphere protection appears to be optimal for achieving high efficiency and regioselectivity.[13]

Having identified optimal conditions, we set out to examine the scope of the reaction with respect to alkenes. As shown in Scheme 3, a wide range of styrenes **3b–g** and vinyl heterocycle **3h** could be applied in the reaction. Moreover, the reactions occurred smoothly irrespective of whether the alkene benzene ring was substituted with an electron-donating group (OMe; **3b**, **3c**) or an electron-withdrawing group such as -F, -Br, -Cl, $-NO_2$ (**3d–g**). In general, *ortho*-substituted styrenes provided a lower yield than



Scheme 3 Photocatalytic lactonization of 2-iodo-5-methylbenzoic acid with various alkenes. *Reagents and conditions*: 2-iodo-5-methylbenzoic acid **2a** (0.2 mmol, 1 equiv), alkene (0.8 mmol, 4 equiv), $NaHCO_3$ (0.26 mmol, 1.3 equiv) in anhydrous DMSO (4 mL), *hv* (300 nm), N_2, 6 h.



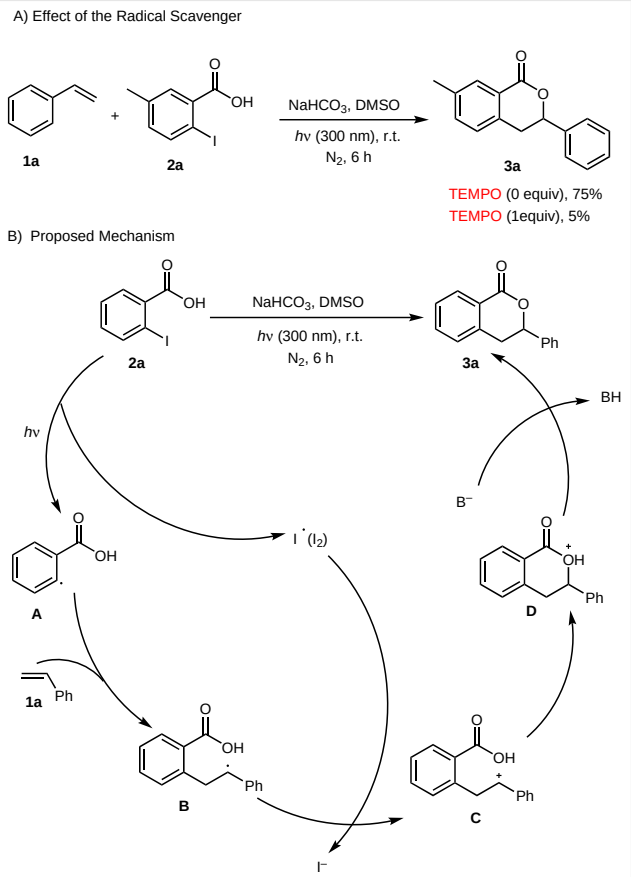
Scheme 4 Photocatalytic lactonization of styrene with various 2-iodobenzoic acids. *Reagents and conditions*: **2b–e** (0.2 mmol, 1 equiv), styrene (0.8 mmol, 4 equiv), $NaHCO_3$ (0.26 mmol, 1.3 equiv) in anhydrous DMSO (4 mL), *hv* (300 nm), N_2, 6 h.

para-substituted styrenes, which might be due to steric hindrance. In cases where alkenes are substituted with two groups at one side of the C=C bond, the products could be obtained in moderate efficiency (**3i**, **3j**). For β-substituted alkenes, the reactions were also well-tolerated under the reaction conditions (**3k** and **3l**). More importantly, an α,β-unsaturated ester was also found to be suitable for the protocol (**3m**).

We then investigated the scope of the reaction with respect to 2-iodobenzoic acid with different substituents; the results are summarized in Scheme 4. Various 2-iodobenzoic acid derivatives, when subjected to the optimal reaction conditions, efficiently led to the products in moderate yields (56–67%). The electronic effect of substituents on the aromatic ring of 2-iodobenzoic acids contributed little to the efficiency of the reaction, whereas the position of the substituents has a slight effect on the yields. When the *para*-position of iodine was substituted, a higher yield could be obtained (Scheme 4, 3a and **3p**). An *ortho*- or *meta*-substituent of iodine decrease the yield slightly (Scheme 4, 3o and **3q**).

To gain a clearer insight into this transformation, a control experiment was carried out by adding radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) to the reaction of **1a** and **2a** under the optimized conditions (Scheme 5, A). As expected, after the addition of TEMPO, the yield of **3a** decreased significantly to 5%. Such a result suggested the involvement of a radical process. Based upon the above results, a reaction mechanism is proposed as shown in Scheme 5, B. Upon UV irradiation, *o*-iodobenzoic acid **2a** undergoes dehalogenation to produce aryl radical **A** and an iodine radical. Aryl radical **A** then adds to alkene **1a** to form radical intermediate **B**. Under the oxidation of iodine radicals, **B** was transformed into cationic species **C**. Subsequent intramolecular cyclization of **C** afforded intermediate **D**, and final product **3a** was produced with the proton of **D** abstracted by the base such as $NaHCO_3$ (Scheme 5, B).

In summary, we have disclosed a new protocol for the synthesis of 3,4-dihydroisocoumarin derivatives through a dehalogenative radical addition process. This method shows good functional group tolerance and high regioselectivity. Due to the commercial availability of the starting materials, the approach is expected to be of great benefit for the synthesis of many organic compounds.



Scheme 5 Exploration of the mechanism

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Supporting Information

Supporting information for this article (experimental procedures and compound characterization data) is available online at https://doi.org/10.1055/s-0036-1588541.

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(13) A mixture of 2-iodo-5-methylbenzoic acid (**2a**; 0.2 mmol, 1 equiv), styrene **1a** (0.8 mmol, 4 equiv) and $NaHCO_3$ (0.26 mmol, 1.3 equiv) in DMSO (4 mL) was put into a quartz reaction tube (10 mL). N_2 was flowed in for 10 min, then the tube was sealed and exposed to illumination with a high-pressure mercury lamp at 300 nm wavelength for 6 h. Water (20 mL) was added to the reaction system and the mixture was extracted with ethyl

acetate (3 × 20 mL). The organic phase was washed with saturated salt water, dried with anhydrous sodium sulfate, and the crude products were obtained under reduced pressure and concentration. The purified products were purified by silica gel column chromatography (PE/EtOAc, 10:1), and the product 7-methyl-3-phenylisochroman-1-one **3a** (75%) was obtained as a pale-yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (s, 1 H), 7.52–7.33 (m, 6 H), 7.17 (d, *J* = 7.7 Hz, 1 H), 5.53 (dd, *J* = 12.0, 3.2 Hz, 1 H), 3.29 (dd, *J* = 16.3, 12.0 Hz, 1 H), 3.10 (dd, *J* = 16.4, 3.2 Hz, 1 H), 2.41 (s, 3 H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 165.6, 138.6, 137.7, 135.0, 134.8, 130.6, 128.6, 128.6, 127.2, 126.1, 124.8, 80.0, 35.2, 21.0. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{15}O_2$: 239.1067; found: 239.1066.