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Synthesis of Tryptanthrins by Organocatalytic and Substrate Co-catalyzed Photochemical Condensation of Indoles and Anthranilic Acids with Visible Light and O_2

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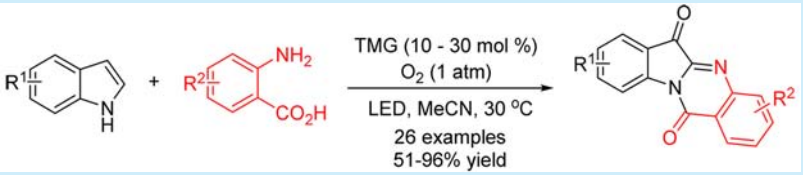
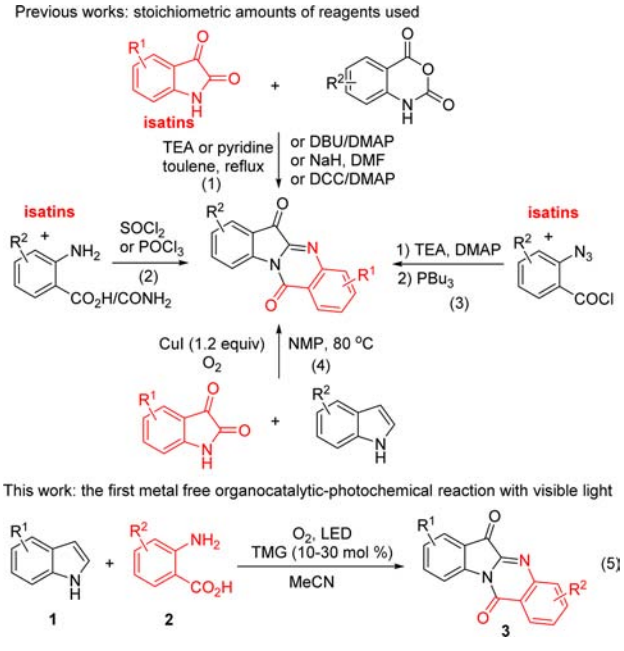
Supporting Information



ABSTRACT: A metal-free catalytic approach to tryptanthrins has been achieved for the first time. The unique process is realized by an organocatalytic and indole and anthranilic acid substrate co-catalyzed photochemical oxidative condensation with visible light and O_2. The truly environmentally friendly reaction conditions enable various reactants to participate in the process to deliver structurally diverse tryptanthrins.

As the emerging "privileged" structure of a unique class of natural products and synthetic substances,[1−7] tryptanthrins exhibit a wide range of biological properties such as antibacterial,[2] antifungal,[3] antiparasitic,[4] antitubercular,[5] antimalarial,[6] and antitumor[7] activities. These intriguing biological properties have triggered considerable interest in the development of useful methods for the synthesis of this valued molecular architecture.[1,8] The strategies involving the coupling of two different partners are highly attractive because they enable the generation of substitution diversity.[9−11] Notable examples include the condensations of isatins with isatoic anhydrides,[10a−c] anthranilic acids/anthranilamides,[10d,e] or 2-azidobenzoyl chlorides[10f] (Scheme 1, eqs 1−3). Furthermore, an efficient Cu-mediated aerobic oxidation reaction of indoles with isatins reported was reported recently by Lu, Wang, and co-workers (eq 4).[10g] Despite these impressive studies, significant synthetic challenges still remain. In these methods, generally stoichiometric amounts of toxic reagents and/or harsh reaction conditions are used. Herein, we disclose the first metal-free organocatalytic approach to tryptanthrins (Scheme 1, eq 5). The process results from the serendipitous study of the photochemical oxidative indole dimerization where benzoic acid was initially used as co-catalyst. We discovered anthranilic acids as new reactants and copromoters in the reaction with indoles to form tryptanthrins. A truly sustainable synthetic protocol using visible light as the light source without requiring external photosensitizer and O_2 as terminal oxidant and cheap 1,1,3,3-tetramethylguanidine (TMG) as organocatalyst is identified. The mild reaction conditions allow for a broad substrate scope and high yields.

Scheme 1. Synthetic Approaches to Tryptanthrins



In light of the fact that visible light is known to be safe, cost-effective, abundant, and a renewable resource, as well as giving potential for previously inaccessible reactions, photochemical processes have undergone a dramatic renaissance of interest in

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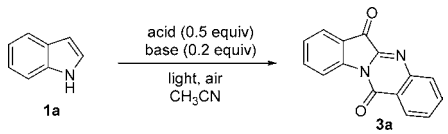
the past few years.[12] In our efforts to develop new organocatalytic transformations, we proposed a novel metal-free-photochemical access to tryptanthrins. In seeking sustainable synthesis, feedstock indoles were chosen as reactant and O_2 as an oxidant. It is noted that O_2 has been widely used in photosensitizer (PS) engaged photoredox transformations.[13] However, because O_2 cannot absorb in the visible region, external PSs such as metal complexes and organic dyes are often used for its activation.[14] We envisioned that reactant indole could serve as a PS,[15] thus eliminating an external PS.

To test the hypothesis, we probed the reaction of indole (**1a**) in the presence of benzoic acid (0.5 equiv) as a co-catalyst and NaOAc (3.0 equiv) as a base in CH_3CN (Table 1). The

Table 1. Exploration of Visible Light Driven Oxidative Formation of Tryptanthrin (3a) from Indole (1a)[a]



entry	acid	base	light, time (h), temp (°C)	yield[b] (%)
1	$PhCO_2H$	NaOAc[c]	CFL, 96, 45	35
2	$PhCO_2H$	NaOAc[c]	LED, 96, 45	45
3	$PhCO_2H$	TEA[c]	LED, 96, 45	trace
4	$PhCO_2H$	DBU[d]	LED, 48, 45	32
5	$PhCO_2H$	TMG[d]	LED, 48, 45	40
6	$PhCO_2H$	TMG	LED, 48, 35	64
7	*p*-TsOH	TMG	LED, 48, 35	<10
8	AcOH	TMG	LED, 48, 35	NR[e]
9	4-$MeOPhCO_2H$	TMG	LED, 48, 35	56
10	4-NH_2PhCO_2H	TMG	LED, 48, 35	NR[e]
11	2-NH_2PhCO_2H	TMG	LED, 48, 35	72
12	$PhCO_2H$	none	LED, 60, 35	NR[e]
13	none	TMG	LED, 60, 35	NR[e]
14	$PhCO_2H$	none	no light, 6o, 35	NR[e]

[a]Reaction conditions: unless specified, a mixture of **1a** (0.3 mmol), acid (0.15 mmol), and base (0.06 mmol) in MeCN (6.0 mL) in an open flask was irradiated by a designated lamp for a specified time. [b]Yields based on ^1H NMR. [c]0.9 mmol was used. [d]0.15 mmol was used. [e]No reaction.

mixture was irradiated by two 14 W compact fluorescent lamps (CFL) in an open flask at 45 °C for 4 d. To our delight, indole (**1a**) slowly dimerized to tryptanthrin (**3a**) in 39% yield (entry 1). The reaction efficiency was further enhanced with LED (light-emitting diode) as light source (45%, entry 2). It was found that the bases were important for the process (entries 2−5). Higher basicity favors the process. TMG was the best base, and the use of 0.5 and even 0.2 equiv at lower temperature delivered comparable or better yields (entries 5 and 6). Moreover, importantly, the acids, particularly substituted benzoic acids, not only affected the reaction efficiency but also changed the course of the reaction (entries 6−11). We found that anthranilic acid (**2a**) furnished the best result (72% yield, entry 11). Furthermore, unlike benzoic acid remaining in the reaction, we observed that anthranilic acid disappeared, indicative that anthranilic acid participated in the reaction as a substrate. The control experiments showed the base (entry 12), the acid (entry 13), and light (entry 14) were all essential for the formation of tryptanthrin (**3a**). This also implies that anthranilic acid serves as a cofacilitator just as benzoic acid does. Consequently, indole (**1a**) and anthranilic acid (**2a**) were chosen as substrates for further investigation of the unexpected process to seek the optimal reaction conditions (Table 2).

Table 2. Optimization of the Reaction Conditions[a]

entry	oxidant	temp (°C)	time (h)	yield[b] (%)
1	air	45	48	54
2	O_2	45	36	72
3	O_2	30	36	83
4	O_2	20	36	69
5[c]	O_2	30	36	86
6[d]	O_2	30	36	67

[a]Reaction conditions: unless specified, a mixture of **1a** (0.45 mmol), **2a** (0.3 mmol), and TMG (0.06 mmol) in MeCN (6.0 mL) in the presence of O_2 was irradiated by a lamp for a specified time. [b]Isolated yields. [c]0.1 equiv of TMG was used. [d]0.05 equiv of TMG was used.

Reducing the ratio from 2.0 to 1.5 (**1a**/**2a**) led to drop in the yield (from 72% to 54%) (Table 2, entry 1). The use of pure O_2 as oxidant led to higher yield (72% yield) and shorter reaction time (entry 2). A higher efficiency (83% yield) was achieved when the reaction was performed at lower temperature (30 °C) presumably due to minimizing side reactions (entry 3). However, further lowering the temperature (20 °C) was unfavorable (69% yield). We next scrutinized the base dosage and found that 10 mol % of TMG could achieve the optimal result (entries 5−6).

With the optimized reaction conditions in hand (Table 2, entry 5), we then probed the scope of the process. The studies revealed that the protocol served as a general approach to the synthesis of structurally diverse tryptanthrins (Table 3). Various substituted indoles were tested and were compatible with anthranilic acid (**2a**). Electron-donating 4- and 5-methylindoles reacted smoothly to give **3b** and **3c** in 73% and 75% yields, respectively (entries 2 and 3). Electron-withdrawing groups (entries 4−6) also worked well with **2a**, although methyl 1*H*-indole-6-carboxylate (entry 5) required 30 mol % loading of TMG and a longer reaction time for 5-cyanoindole (entry 6). It was found that the higher loading of TMG minimized formation of methyl isatin-6-carboxylate and promoted the condensation process. Structural variation of anthranilic acids was probed next. The structures bearing electron-donating (CH_3, CH_3O) and -withdrawing (F, Cl, Br, I, CF_3) groups worked well with indole (**2a**) to furnish the corresponding products (**3g**−**p**) in good yields (51−75%). Moreover, it appears that the position pattern of the substituents (including 3, 4, and 5 positions) on anthranilic acids has limited impact on the reaction (entries 7−16).

Oxidative condensation reactions between various substituted indoles and substituted anthranilic acids were also conducted (Table 3, entries 17−26). It is noted that the broad availability of substituted anthranilic acids rendered us access to various substituted tryptanthrins, including new ones (**3i**−**u**,**z**). Again, a higher loading of TMG (20−30 mol %) was used to inhibit the dimerization and over-oxidation of indoles. Under the reaction conditions, the processes have significant tolerance toward these substituted structures of both substrates,

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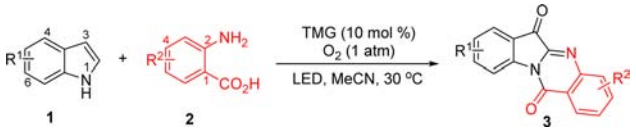
Table 3. Substrate Scope of Oxidative Condensation between Indoles and Anthranilic Acids[a]



1 2 3

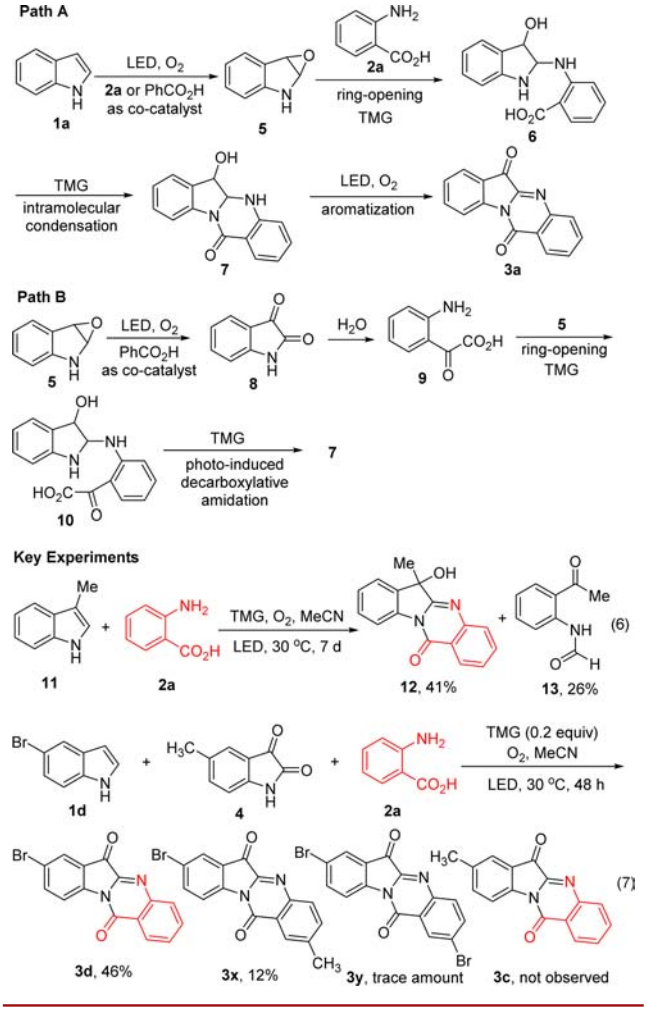
entry	R^1, R^2, 3	time (h)	yield[b] (%)
1	H, H, **3a**	36	86
2	4-Me, H, **3b**	24	73
3	5-Me, H, **3c**	72	75
4	5-Br, H, **3d**	48	81
5[c]	6-CO_2Me, H, **3e**	72	62
6	5-CN, H, **3f**	168	51
7[d]	H, 3-Me, **3g**	24	67
8[d]	H, 5-Me, **3h**	72	71
9[d]	H, 4-F, **3i**	36	64
10	H, 3-Cl, **3j**	36	72
11	H, 4-Br, **3k**	48	74
12	H, 5-Br, **3l**	30	75
13[d]	H, 4-OMe, **3m**	144	72
14[d]	H, 4-CF_3, **3n**	48	70
15[d]	H, 5-CF_3, **3o**	48	51
16	H, 5-I, **3p**	48	61
17[d]	4-Me, 4-F, **3q**	48	80
18[d]	4-Me, 3-Cl, **3r**	48	85
19[d]	4-Me, 5-Br, **3s**	36	76
20[d]	4-Me, 4-OMe, **3t**	120	83
21[c]	5-Me, 4-Br, **3u**	72	67
22[d]	5-Me, 5-Me, **3v**	120	96
23[c]	5-Me, 4-CF_3, **3w**	96	53
24[c]	5-Br, 5-Me **3x**	96	79
25[c]	5-Br, 5-Br, **3y**	48	66
26[c]	5-Br, 4-CF_3, **3z**	48	64

[a]Unless specified, reaction conditions, see Table 2. [b]Yield of isolated product after column chromatography. [c]30 mol % of TMS was used. [d]20 mol % of TMS was used.

indoles (**1**) and anthranilic acids (**2**). A large-scale (3 mmol) synthesis using indoles **1a** and **1d** and anthranilic acid (**2a**) was performed (see Scheme S1). The desired **3a** and **3d** were obtained in good yields (0.62 g and 83% yield for **3a** and 0.77 g and 78% yield for **3d**) using higher power LED (60 W) and longer irradiation time.

A plausible reaction mechanism is proposed for condensation between indoles and anthranilic acids (Scheme 2, path A). With the assistance of anthranilic acid (**1a**), similar to peroxidase-mediated oxidation of 3-alkylindoles,[16] indole (**1a**) was oxidized to indole-2, 3-epoxide (**5**). Intermolecular "N"-centered nucleophilic attack of the epoxide by **2a** promoted by TMG to form ring-opening intermediate **6**. Then, intramolecular amidation between the amino and carboxyl group assisted by TMG furnished the fused ring structure **7**. Finally, oxidative aromatization delivers tryptanthrin (**3a**). An alternative pathway is also possible (path B) based on the observation of the dimerization of indole (Table 1) and formation of **3x** (Scheme 2). Intermediate **5** is further oxidized to isatin (**8**), which then undergoes hydrolysis to form α-oxoacetic acid (**9**).[10g] A similar nucleophilic attack of the epoxide by α-oxo acetic acid (**9**) forms ring-opening **10**, followed by an intramolecular decarboxylative amidation to furnish **7**, which finally aromatizes to deliver **3a**.

Scheme 2. Proposed Catalytic Pathway and Key Experiments



To support the proposed two catalytic pathways, we conducted the preliminary mechanistic investigations by key experiments. Under the same reaction conditions, in the reaction of 3-methylindole (**11**) by blocking the position for further oxidation, product **12** was obtained along with the oxidative ring opening 3-methylindole **13** (Scheme 2, eq 6). This suggests the feasibility of the in situ formation of epoxide **5** followed by its ring opening by anthranilic acid (**2a**) in the formation of tryptanthrin (**3a**) (path A). A small amount of isatin (**8**) was detected by LC−MS from the reaction mixture of indole and benzoic acid (Table 1, entry 6). Furthermore, in a control study, the reaction mixture of 5-bromoindole (**1d**), 5-methylisatin (**4**), and anthranilic acid (**2a**) in a molar ratio of 1:1:1 with 20 mol % of TMG in MeCN was irradiated by an LED lamp under an atmosphere of O_2 for 48 h (eq 7). Compounds **3d** and **3x** were obtained in 46% and 12% yield, respectively, in addition to a trace amount of **3y**, produced from the oxidative dimerization of **1d**. However, compound **3c**, which should be formed from **4** and **2a**, was not detected. Moreover, we did not observe the 5-methylanthranilic acid formed from 5-methylisatin (**4**). The results suggest that isatins are not involved in the proposed reaction mechanism A. They could serve as the surrogate of anthranilic acids rather than indoles. Furthermore, the dimerization product **3y** was observed. Taken together, these indicate that the path B may be in operation.

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In conclusion, we have developed the first metal-free approach to tryptanthrins. The process is catalyzed by an unprecedented binary organo- and photochemical catalysis. Notably, TMG serves as an organocatalyst (base) and the substrate indoles function as a PS while the reactant anthranilic acids assist the oxidation of indoles with visible light. The truly green process using visible light and O_2 as the oxidant under mild reaction conditions enables a wide array of indoles and anthranilic acids to be engaged and produce structurally diverse tryptanthrins. Further understanding of the reaction mechanism and exploration of the strategy for new transformations are under investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03009.

Experimental details and analytical data (PDF)

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Notes

The authors declare no competing financial interest.

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