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Cu-Catalyzed Synthesis of Tryptanthrin Derivatives from Substituted Indoles

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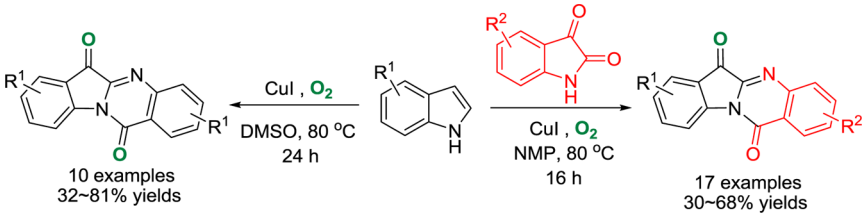
ABSTRACT



A concise method for the preparation of tryptanthrins from indoles *via* the copper-catalyzed aerobic oxidation is described. The reactions can be carried out under mild reaction conditions with varying functional group tolerance.

Tryptanthrin can be formed by *Candida lipolytica* in the presence of tryptophan.[1] Its structure is slightly twisted with aromatic character according to its single crystal analysis.[2] IUPAC numbering of the tryptanthrin ring is shown in Figure 1. Tryptanthrin and its derivatives are indoloquinazoline alkaloids found in many kinds of plants.[3] There are eight indoloquinazolines in the methanol extraction of *Phaius mishmensis*. They are tryptanthrin and its analogues phaitanthrins A−E, methylisatoid, and candidine. Among these compounds, tryptanthrin was documented with excellent cytotoxicity against human breast carcinoma (MCF-7), lung carcinoma (NCI-H460), and central nervous system carcinoma (SF-268) cell lines.[4] Several tryptanthrin derivatives were found to exhibit remarkable antileishmanial activity and are potential succedaneums of sodium stibogluconate (Pentostam) and meglumine antimonate (Glucantime), which are the current treatments for leishmaniases yet showing hazardous side effects and even alarming cardiotoxicity.[5] More recently, it was also discovered that tryptanthrins are potential antitubercular agents.[6]

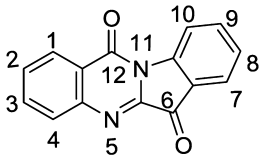


Figure 1. Structures of tryptanthrin and its IUPAC numbering.

Due to the scarcity of the natural existence of tryptanthrins as well as their unique bioactivities, the synthesis of this important class of heterocycles has attracted extensive attention (Scheme 1). Classically, tryptanthrin can be constructed from isatin. For example, cathodic reduction of isatin afforded tryptanthrin in moderate yield.[1b] Treatment of isatin with $POCl_3$[4,7] or $KMnO_4$[8] could also lead to the formation of tryptanthrin. However, the structural diversity of tryptanthrins is much confined by these methods due to the single starting material. The diversity could be achieved by the condensation between isatins and isatoic anhydrides in the presence of triehtylamine[9] or in aqueous β-cyclodextrin solution.[10] An alternative condensation is the one between isatin and *ortho*-aminobenzoic acid in

(1) (a) Lee, E. S.; Park, J. G.; Jahng, Y. *Tetrahedron Lett.* **2003**, *44*, 1883–1886. (b) Batanero, B.; Barba, F. *Tetrahedron Lett.* **2006**, *47*, 8201–8203.

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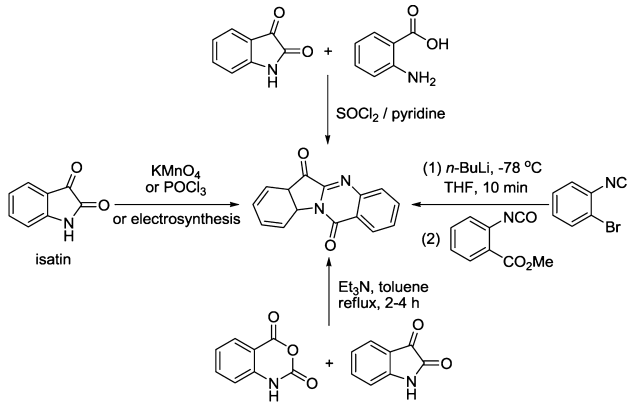
10.1021/ol401144m

the presence of $SOCl_2$.[11] The lithiation of *ortho*-bromophenyl isocuanide, followed by the addition of electrophilic methyl 2-isocyanatobenzoate, is an unusal method.[12]

Scheme 1. Literature Methods Leading to Tryptanthrins



In our previous research, indole (**1a**) was dimerized to tryptanthrin (**2a**) in 46% yield in DMF under air at 100 °C for 34 h, accompanied by 3-formylindole in 16% yield.[13] Based on this result and motivated by the significance of tryptanthrin and its derivatives, we optimized reaction conditions in order to achieve the highly selective formation of **2a** (see Table S1). Initially, an oxygen atmosphere was found to be necessary (Table S1, entries 1−3). With the oxygen balloon, tryptanthrin was isolated in 52% yield while it could not be detected when the reaction was conducted under nitrogen. However, other oxidants, such as *t*-BuOOH, DDQ, BPO, DTBP, and *m*CPBA, did not produce satisfactory yields (Table S1, entries 4−8). Cuprous iodide was found to be the best catalyst when compared to other cuprous salts, such as CuBr, CuCl, and Cu_2O (Table S1, entries 9−11). It is worth mentioning that cupric salts, such as $CuBr_2$, $CuCl_2$, and $Cu(OAc)_2$, work for the reaction, but with lower yields (Table S1, entries 12−14). The suitable amount of CuI was determined to be 1.2 equiv by gradually varying the ratio of CuI to indole (Table S1, entries 15−18). A breathtaking yield was obtained when DMSO was used (Table S1, entries 19−22). In this case, formylation on the 3-position of indole was efficiently inhibited. Finally, the reaction temperature and time were optimized to be 80 °C and 24 h, respectively (Table S1, entries 23−26). Thus, the optimal reaction conditions were established (Table S1, entry 19).

(8) Honda, G.; Tabata, M. *Planta Med.* **1979**, *36*, 85–86.
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(10) Kumar, A.; Tripathi, V. D.; Kumar, P. *Green. Chem.* **2011**, *13*, 51–54.
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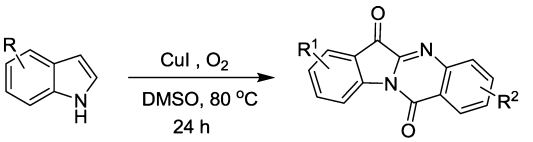
Scheme 2. Oxidative Self-Condensation of Indoles



1a R = H
1b R = 5-CH_3
1c R = 5-OCH_3
1d R = 5-Cl
1e R = 5-Br
1f R = 5-F
1g R = 4-Cl
1h R = 4-CH_3
1i R = 7-CH_3
1j R = 6-CO_2CH_3

2a R^1 = 2-H, R^2 = 8-H, 81%
2b R^1 = 2-CH_3, R^2 = 8-CH_3, 70%
2c R^1 = 2-OCH_3, R^2 = 8-OCH_3, 61%
2d R^1 = 2-Cl, R^2 = 8-Cl, 60%
2e R^1 = 2-Br, R^2 = 8-Br, 51%
2f R^1 = 2-F, R^2 = 8-F, 71%
2g R^1 = 1-Cl, R^2 = 7-Cl, 72%
2h R^1 = 1-CH_3, R^2 = 7-CH_3, 68%
2i R^1 = 4-CH_3, R^2 = 10-CH_3, 59%
2j R^1 = 3-CO_2CH_3, R^2 = 9-CO_2CH_3, 32%

Under the optimized reaction conditions, we tested various indoles (Scheme 2). Indoles **1b**−**1f**, with either an electron-donating (CH_3, CH_3O) or electron-withdrawing (F, Cl, Br) group on its 5-position, worked for this reaction and provided corresponding tryptanthrin derivatives in the yields ranging from 51% to 71%. 4- and 7-Methyl indoles furnished **2h** and **2i** in 68% and 59% yields, respectively. When methyl 1*H*-indole-6-carboxylate (**1j**) was used, **2j** was obtained with a much lower yield (32%) along with 3-iodoindole as the byproduct (43% yield). With a strong electron-withdrawing group attached to indole, 5-cyanoindole and 5-nitroindole afforded 3-iodo-5-cyanoindole (58% yield) and 3-iodo-5-nitroindole (40% yields), respectively, without the desired tryptanthrin.

Since isatins (indoline-2,3-diones) were speculated to be the key intermediate for the formation of tryptanthrins, we then turned our attention to the two-component condensation between indoles and isatins in order to afford tryptanthrins with a broad diversity. In the primary examination, it was exciting to find that the reaction of **1a** with 5-methylindoline-2,3-dione (**3b**) in DMSO in the presence of CuI and oxygen yielded tryptanthrin **4a** (Scheme 3). The structure of **4a** was unambiguously determined by single crystal analysis (Figure 2). After the reaction conditions were screened for the best formation of **4a**, NMP was found to be the optimal solvent (Table S2).

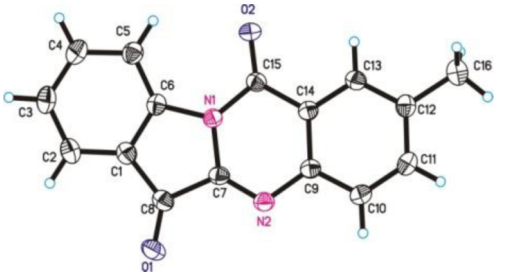
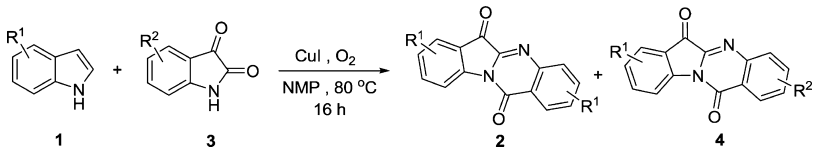


Figure 2. X-ray crystal structure of compound **4a**.

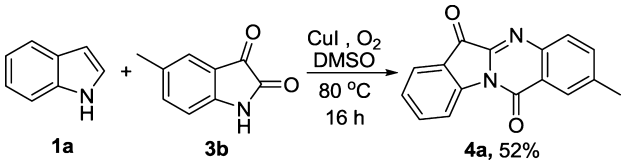
Table 1. Oxidative Condensation between Indols and Isatins[a]



entry	**1** (R^1)	**3** (R^2)	**2** (yield, %)[b]	**4** (R^1, R^2) (yield, %)[b]
1	**1a** (H)	**3b** (5-CH_3)	–	**4a** (H, 2-CH_3) (60)
2	**1b** (5-CH_3)	**3a** (H)	–	**4b** (8-CH_3, H) (68)
3	**1c** (5-OCH_3)	**3a**	–	**4c** (8-OCH_3, H) (53)
4	**1d** (5-Cl)	**3a**	**2d** (11)	**4d** (8-Cl, H) (47)
5	**1e** (5-Br)	**3a**	**2e** (13)	**4e** (8-Br, H) (42)
6	**1g** (4-Cl)	**3a**	**2g** (12)	**4f** (7-Cl, H) (49)
7	**1h** (4-CH_3)	**3a**	–	**4g** (7-CH_3, H) (67)
8	**1i** (7-CH_3)	**3a**	**2i** (15)	**4h** (10-CH_3, H) (41)
9	**1j** (6-CO_2CH_3)	**3a**	**2j** (9)	**4i** (9-$COOCH_3$, H) (47)
10	**1c**	**3b**	–	**4j** (8-OCH_3, 2-CH_3) (53)
11	**1d**	**3b**	**2d** (25)	**4k** (8-Cl, 2-CH_3) (30)
12	**1e**	**3b**	**2e** (11)	**4l** (8-Br, 2-CH_3) (35)
13	**1h**	**3b**	**2h** (<5)	**4m** (7-CH_3, 2-CH_3) (59)
14	**1i**	**3b**	**2i** (<5)	**4n** (10-CH_3, 2-CH_3) (52)
15	**1b**	**3c** (5-OCH_3)	**2b** (12)	**4o** (8-CH_3, 2-OCH_3) (38)
16	**1b**	**3d** (5-Cl)	**2b** (29)	**4p** (8-CH_3, 2-Cl) (31)
17	**1b**	**3e** (5-Br)	**2b** (15)	**4q** (8-CH_3, 2-Br) (30)
18	**1a**	**3f** (5-NO_2)	**2a** (39)	–
19	**1k** (5-CN)	**3a**	**ND**	**ND**
20	**1l** (5-NO_2)	**3a**	**NR**[c]	**NR**[c]

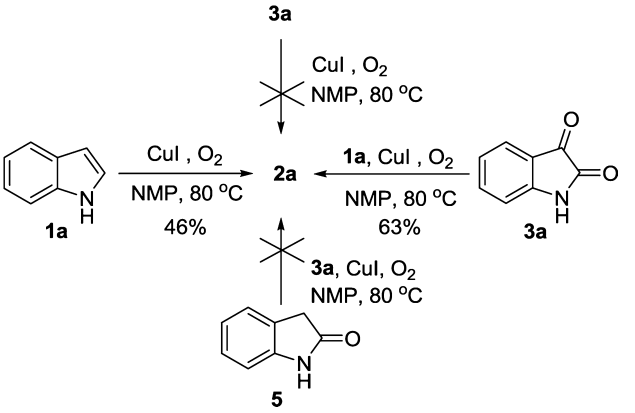
[a] Reaction conditions: **1** (0.25 mmol), **3** (0.25 mmol), CuI (0.3 mmol), NMP (2 mL), O_2, 80 °C, 16 h. [b] Isolated yields refer to **1**. [c] NR = no reaction.

Scheme 3. Formation of Compound **4a**



Subsequently, we investigated the substrate diversity for the oxidative condensation between indoles **1a**–**1l** and isatins **3a**–**3f**, and the results are listed in Table 1. When isatin **3a** was used, indoles (**1b**–**1j**) worked for the reaction and afforded corresponding **4b**–**4i** in yields from 41% to 68%. An electron-donating group on the 5-position of indole (**1b**, **1c**) fostered the reaction giving higher yields (Table 1, entries 1–4). A methyl group on the 7-position of indole (Table 1, entry 7) afforded **4h** in 41% yield. Less reactive indoles (**1d**, **1e**, **1g**, **1i**, and **1j**), affected by either electron-withdrawing or steric hindrance, produced the self-condensation products along with the desired products (Table 1, entries 4–6, 8, and 9). Similar phenomena were observed from these indoles with 5-methyl isatin (**3b**) (Table 1, entries 11–14). It was noticeable that relatively lower yields were obtained in cases of isatins with either a strong electron-donating or -withdrawing group on its 5-position (Table 1, entries 15–17). Reaction of indole

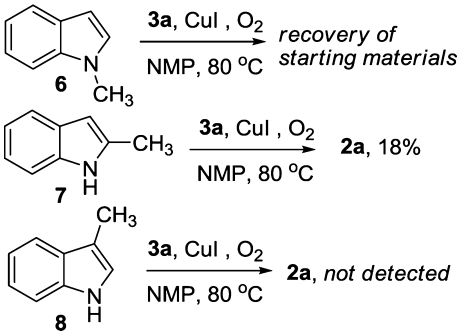
Scheme 4. Controlled Experiments with **1a**, **3a**, and **5**



(**1a**) with 5-nitroisatin (**3f**) only yielded the self-condensation product **2a** (Table 1, entry 18), while reactions of isatin (**3a**) and 5-nitroindole (**1k**) or 5-cyanoindole (**1l**) did not afford any expected alkaloids with the recovery of starting materials (Table 1, entries 19 and 20).

Controlled experiments were carried out in NMP. In the solvent of NMP, both the formylation of indole in DMF and possible oxidation by DMSO could be avoided. Using an equivalent molar ratio of indole (**1a**) and isatin (**3a**), a better yield (63%) of **2a** could be obtained than the

Scheme 5. Controlled Experiments with **6**, **7**, and **8**



yield (46%) obtained from self-condensation of indole (Scheme 4). However, the reaction did not occur when the substrate was only the isatin (**3a**). By using indolin-2-one (**5**) instead of indole, no desired condensation product was detected, only the recovery of isatin.

With shifting of the methyl group on the indole ring from the 1- to 2- and finally to the 3-position, tryptanthrin was only isolated in 18% yield in the case where 2-methylindole (**7**) was used (Scheme 5). Neither 1-methylindole (**6**) nor 3-methylindole (**8**) afforded tryptanthrin, which indicated that the necessity of both N−H and C(3)−H of indole in the reaction.

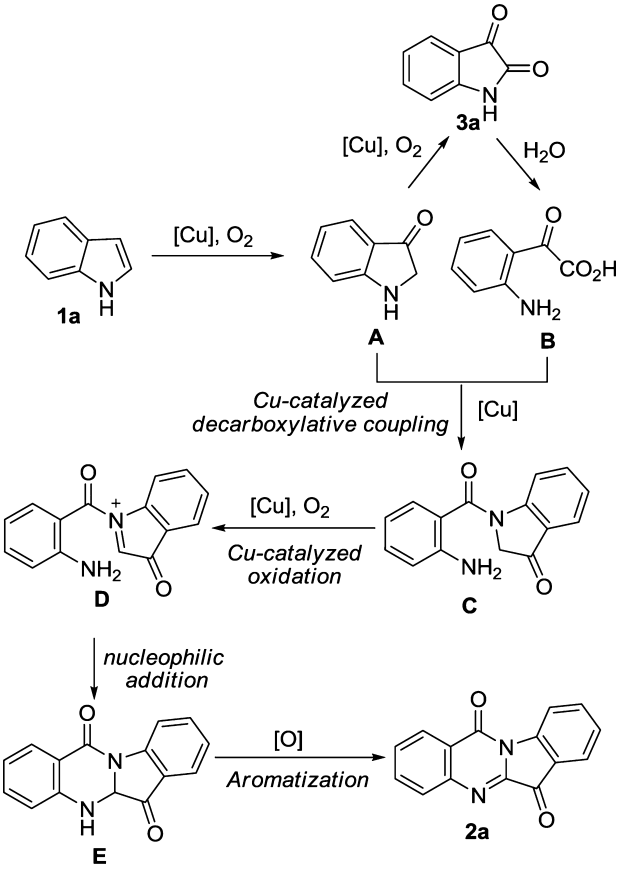
Based on these results, we postulated a possible mechanism for this transformation as shown in Scheme 6. Initially, **1a** was aerobically oxidized to indolin-3-one (**A**), which could further oxidize to isatin (**3a**).[14] Then, **3a** underwent hydrolysis to form α-oxoacetic acid **B**. Copper-catalyzed decarboxylative coupling between **A** and **B** furnished **C**.[15] **C** was sequentially oxidized to imminium **D** *via* copper-catalyzed oxidation. Then, intramolecularly nucleophilic addition of amino to imminium formed the fused ring intermediate **E**. Finally, **2a** was obtained after dehydrogenative aromatization of **E**. In the whole process, C(3)−H of indole is necessary for the oxidation of indole, while N−H of indole is required for the copper-catalyzed decarboxylative coupling. For the reaction of 2-methylindole (**7**) with **3a** to give **2a** in 18% yield (Scheme 5), the aromatization could occur by elimination of methane.[16]

(14) For examples for oxidation of indole to indolin-3-one and isatin, see: (a) Tatsugi, J.; Tong, Z.; Izawa, Y. *ARKIVOC* **2001**, No. i, 67–73. (b) Burd, V. N.; Bantleon, R.; van Pee, K. H. *Appl. Biochem. Microbiol.* **2001**, *37*, 248–250.

(15) For examples for decarboxylative coupling, see: (a) Goossen, L. J.; Rudolphi, F.; Oppel, C.; Rodriguez, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 3043–3045. (b) Yu, L.; Li, P. H.; Wang, L. *Chem. Commun.* **2013**, *49*, 2368–2370.

(16) For an example for elimination of methane, see: Schmittel, M.; Steffen, J. P.; Angel, M. W.; Engels, B.; Lennartz, C.; Hanrath, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1562–1564.

Scheme 6. Proposed Mechanism



In conclusion, we developed a concise method for the preparation of tryptanthrins from indoles. The cascade process is believed to involve copper-catalyzed aerobic oxidation of indole, hydrolysis of amide, the copper-catalyzed decarboxylative coupling, intramolecularly nucleophilic addition, and oxidative aromatization. The reactions could be carried out under mild reaction conditions with varying functional group tolerance. Moreover, the substituent diversity could be quickly expanded by the condensation between the substituted indoles and the substituted isatins *via* this strategy.

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Supporting Information Available. Experimental procedures, characterization data as well as ^{1}H and ^{13}C NMR spectra for all products, and crystallographic information file (CIF) for compound **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.