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One-pot synthesis of tryptanthrin by the Dakin oxidation of indole-3-carbaldehyde

Takumi Abe [a], Tomoki Itoh [a], Tominari Choshi [b], Satoshi Hibino [b], Minoru Ishikura [a,*]

[a] School of Pharmaceutical Sciences, Health Sciences University of Hokkaido, Ishikari-Tobetsu, Hokkaido 061-0293, Japan
[b] Faculty of Pharmacy and Pharmaceutical Sciences, Fukuyama University, Fukuyama, Hiroshima 729-0292, Japan

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ABSTRACT

A one-pot approach to indolo[2,1-*b*]quinazolines from indole-3-carbaldehydes through the Dakin oxidation was developed. It was shown that the reaction proceeded through the condensation of indole-3-carbaldehydes with isatoic anhydrides, derived in situ from indole-3-carbaldehydes by the Dakin oxidation, and further oxidation/cyclization steps.

Tryptanthrin (**2a**), first obtained from the sublimation of natural indigo[1] and isolated from the culture of fungus *Candida lipolytica*,[2] is a member of a unique class of alkaloid characterized by a novel indolo[2,1-*b*]quinazoline core. Several related alkaloids, such as candidine (**3**),[3,4] phaitanthrins A (**4**),[4] B (**5**),[4] and C (**6**),[4] and cruciferane (**7**),[5] have also been found in a wide range of natural sources, including plant materials and mammals (Fig. 1). Tryptanthrin (**2a**) and several of its derivatives exhibit antitumor, antimalarial, antiparasitic, and antineoplastic activity, and inhibit COX-2, 5-LOX, and PGE(2) expression.[6–8]

Because of their diverse biological activities and structural intricacy, these alkaloids have been the target of numerous synthetic studies.[9,10] The most common synthetic approach to the indolo[2,1-*b*]quinazoline core depends on the use of isatin, through the reaction of isatin with isatoic anhydride,[11] thermolysis of isatin,[12] cathodic reduction of isatin,[13] the reaction of anthranilic acid with isatin in the presence of $SOCl_2$,[14] and the reaction of isatin with $POCl_3$.[15] Moreover, the reaction of *o*-lithiophenyl isocyanide with isocyanate,[16] I_2/TBHP-catalyzed intramolecular amination,[17] and the insertion of an aryne intermediate to quinazolone[18] have been developed for the synthesis of tryptanthrin. Recently, the construction of **2a** through oxidative dimerization of isatin or indole has been reported, including oxidation of isatin with $KMnO_4$,[19] Cu-catalyzed oxidation of indole,[20] and oxone-induced oxidation of indole-3-carbaldehyde.[21]

The Dakin oxidation is a widely used method for converting various aryl aldehydes to phenols.[22] We recently used this method for a one-pot conversion of a benzaldehyde moiety to the quinone system of calothrixin B.[23] However, the Dakin oxidation of heteroaryl aldehydes has received less attention.[24] In this work, we demonstrate the use of the Dakin oxidation of indole-3-carbaldehydes in the one-pot synthesis of tryptanthrin (**2a**).

Initially, aldehyde **1a** was treated with *m*-CPBA and a 30% aqueous solution of H_2O_2; however, no reaction was observed (Table 1, entries 1–3). Addition of a catalytic amount of $(PhSe)_2$ (0.2 equiv) markedly accelerated the reaction, producing **2a** in 40% yield (entry 4). Furthermore, 30% aqueous H_2O_2 solution was replaced with urea hydrogen peroxide (UHP). Treating **1a** with UHP (10 equiv) in CH_2Cl_2 at room temperature resulted in a complex mixture (entry 5), whereas **2a** was obtained in 55% yield by heating **1a** with UHP (5 equiv) in toluene at 75 °C (entry 8). To our surprise, candidine (**3**) was obtained as a trimerization product in 21% yield by treating **1a** with excess amounts of UHP (10 equiv) in the presence of $(PhSe)_2$ (0.2 equiv) in CH_2Cl_2 at room temperature (entry 9). Candidine (**3**) has so far been prepared by the condensation of **2a** with 3-acetoxyindole in boiling AcOH and piperidine,[25] although the one-pot formation of **3** from **1a** through oxidative trimerization is, to our knowledge, hitherto unknown. The reaction with aldehydes **1b**–**1g** also produced **2b**–**2g** (entries 10, 11, and 13–15), except the reaction of **1d** (entry 12). No products were

* Corresponding author. Tel./fax: +81 133 23 1245.
E-mail address: ishikura@hoku-iryo-u.ac.jp (M. Ishikura).

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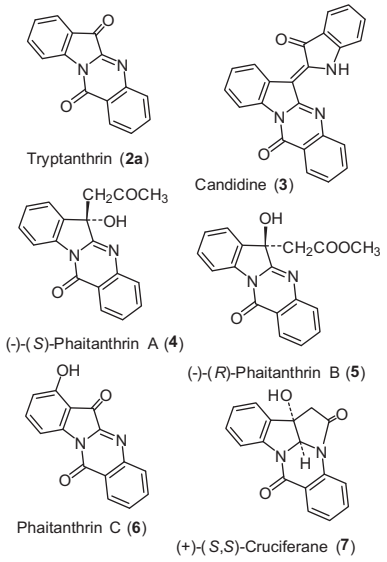
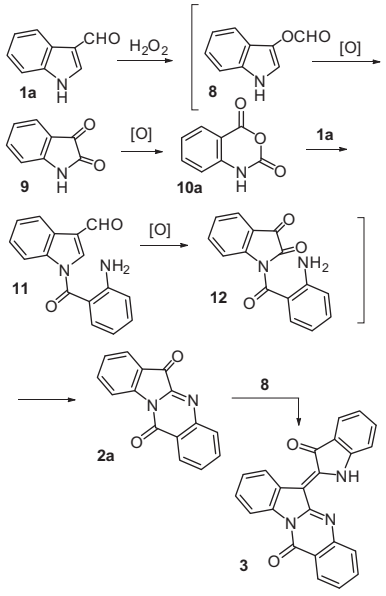


Figure 1. Tryptanthrin (**2a**) and related alkaloids.



Scheme 1. A plausible reaction path.

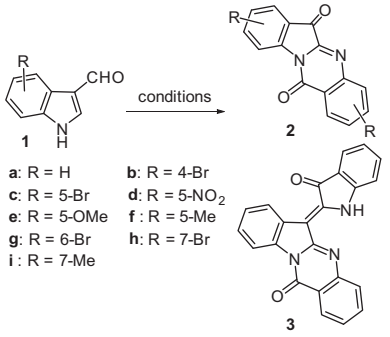
observed in reactions with **1h** and **1i**, which contained a substituent at the 7-position (entries 16 and 17).

Scheme 1 illustrates a plausible reaction path. The Dakin oxidation of **1a** first produces formate **8**, followed by oxidation to isatoic anhydride **10a** via isatin **9**. Then, **10a** reacts with **1a** to form amide **11**, which is converted to **2a** through oxidation of **11** to **12** followed by intramolecular cyclization. The formation of **3** apparently resulted from the condensation of **2a** with **8**. However, **3** was not obtained as a product of the reaction of **2a** with **8** in the presence of UHP and $(PhSe)_2$ in CH_2Cl_2. Therefore, the details of the formation of **3** are being investigated.

To support the proposed mechanism, the following experiments were carried out (Scheme 2). When the oxidation of **1a** with UHP was stopped after 1 h, compounds **1a**, **8**, **10a**, and **11** were isolated from the reaction mixture. The oxidation of **8** produced a trace amount of **2a**, and no isolable products were obtained from the reaction of **9** with **10a**. In contrast, **2a** was obtained in 80% yield from the oxidation of **1a** with **10a**. Furthermore, the oxidation of **11**, through the N-acylation of **1a** with **10a** in the presence of Et_3N, afforded **2a** in 70% yield. However, the attempted oxidation of **1h** with **10a** produced a complex mixture, and the N-acylation of **1h** with **10a** in the presence of Et_3N did not give the corresponding amide **11**. This may be caused by the presence of the Br group at the 7-position of **1h**, which hindered the N-acylation with **10a**.

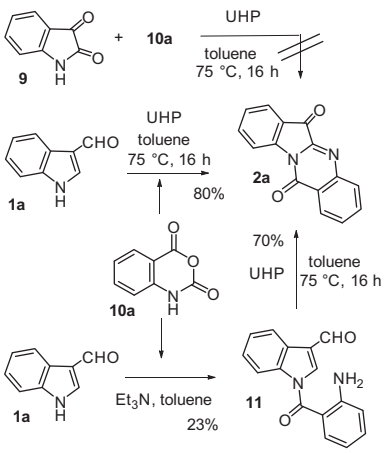
To our knowledge, the one-pot formation of **2a** through oxidation of **1a** with **10a** is unprecedented, although it is well-known that heating **9** with **10a** in the presence of Et_3N in toluene gives **2a**.[26] Compounds **2** are hybrids of **1** and **10**, and substituted alde-

Table 1
Dakin oxidation of indole-3-carbaldehydes **1**



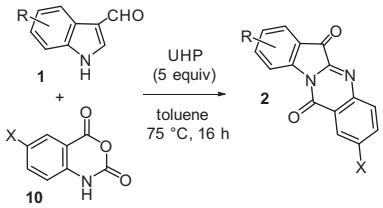
Entry	**1**	Conditions	Yield[a] (%)
1	**1a**	*m*-CPBA (3 equiv), CH_2Cl_2, 0 °C, 3 h	N.R.
2	**1a**	30% aq. H_2O_2 (excess), CH_2Cl_2, rt, 3 h	N.R.
3	**1a**	30% aq. H_2O_2 (excess), TFA (0.2 equiv), CH_2Cl_2, rt, 3 h	N.R.
4	**1a**	30% aq. H_2O_2 (excess), $(PhSe)_2$ (0.2 equiv), CH_2Cl_2, rt, 3 h	40 (**2a**)
5	**1a**	UHP(10 equiv), CH_2Cl_2, rt, 16 h	—[b]
6	**1a**	UHP (5 equiv), neat, 85 °C, 1 h	25 (**2a**)
7	**1a**	UHP (5 equiv), toluene, rt, 16 h	N.R.
8	**1a**	UHP (5 equiv), toluene, 75 °C, 16 h	55 (**2a**)
9	**1a**	UHP (10 equiv), $(PhSe)_2$ (0.2 equiv), toluene, 75 °C, 16 h	21 (**3**)
10	**1b**	UHP (5 equiv), toluene, 75 °C, 16 h	40 (**2b**)
11	**1c**	UHP (5 equiv), toluene, 75 °C, 16 h	48 (**2c**)
12	**1d**	UHP (5 equiv), toluene, 75 °C, 16 h	—[b]
13	**1e**	UHP (5 equiv), toluene, 75 °C, 16 h	62 (**2e**)
14	**1f**	UHP (5 equiv), toluene, 75 °C, 16 h	70 (**2f**)
15	**1g**	UHP (5 equiv), toluene, 75 °C, 16 h	43 (**2g**)
16	**1h**	UHP (5 equiv), toluene, 75 °C, 16 h	—[b]
17	**1i**	UHP (5 equiv), toluene, 75 °C, 16 h	—[b]

[a] Isolated yields.
[b] Complex mixture.



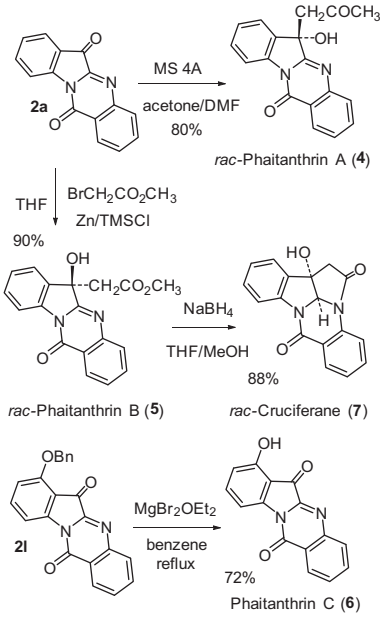
Scheme 2. Experiments to confirm the proposed path.

Table 2
Oxidative coupling of **1** with **10**



Entry	R of **1**	X of **10**	Yield[a] (%)
1	4-Br (**1b**)	H (**10a**)	76 (**2j**)
2	4-Br (**1b**)	Br (**10b**)	71 (**2k**)
3	4-OBn (**1k**)	H (**10a**)	75 (**2l**)
4	5-Br (**1c**)	H (**10a**)	80 (**2m**)
5	5-Br (**1c**)	Br (**10b**)	71 (**2c**)
6	5-Me (**1f**)	H (**10a**)	85 (**2n**)
7	5-Me (**1f**)	Br (**10b**)	70 (**2o**)
8	6-Br (**1g**)	H (**10a**)	70 (**2p**)
9	6-Br (**1g**)	Br (**10b**)	65 (**2q**)
10	7-Br (**1h**)	H (**10a**)	Complex mixture
11	7-Br (**1h**)	Br (**10b**)	Complex mixture

[a] Isolated yields.



Scheme 3. Preparation of alkaloids **4**, **5**, **6**, and **7** from **2a**.

hydes **1** are accessible more easily than substituted isatins. Therefore, the scope of the one-pot oxidation of **1** with **10** was further examined (Table 2). Heating **1** and **10** (1.5 equiv) with UHP in toluene at 75 °C provided tryptanthrin derivatives **2** in good yields (entries 1–9). However, no products were again obtained from the reaction of **1h** (entries 10 and 11).

Next, the conversion of **2a** to (±)-phaitanthrins A (**4**), B (**5**), and C (**6**), and (±)-cruciferane (**7**) was carried out (Scheme 3).[18,27,28] Removal of the benzyl group of **2l** with $MgBr_2OEt_2$ in boiling benzene provided phaitanthrin C (**6**) in 72% yield. Stirring **2a** in acetone and DMF in the presence of molecular sieves 4A at room temperature produced (±)-phaitanthrin A (**4**) in 80% yield. The Reformatsky reaction of **2a** with methyl bromoacetate using Zn and TMSCl was successfully performed to give (±)-phaitanthrin B (**5**) in 90% yield. The reductive cyclization of **5** with $NaBH_4$ in MeOH/THF afforded (±)-cruciferane (**7**) in 88% yield.

In summary, we have demonstrated that the Dakin oxidation of indole-3-carbaldehyde (**1a**) with urea hydrogen peroxide (UHP) produced tryptanthrin (**2a**). The reaction proceeded through the in situ generation of amide **11** from the condensation of **1a** with isatoic anhydride **10a**, followed by oxidative intramolecular cyclization. Moreover, the unprecedented one-pot formation of candidine (**3**) via trimerization in the presence of UHP (10 equiv) and a catalytic amount of $(PhSe)_2$ (0.2 equiv) was also observed. The Dakin oxidation of **1** and **10** was also developed for synthesizing several derivatives of **2a**. Further studies for exploring the scope of the reaction are now in progress.

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