



Cite this: *RSC Adv.*, 2020, 10, 25165

# Iodine-catalyzed efficient synthesis of xanthene/thioxanthene-indole derivatives under mild conditions†

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Received 13th June 2020

Accepted 26th June 2020

DOI: 10.1039/d0ra05217e

rsc.li/rsc-advances

An iodine-catalyzed nucleophilic substitution reaction of xanthen-9-ol and thioxanthen-9-ol with indoles has been developed, providing an efficient procedure for the synthesis of xanthene/thioxanthene-indole derivatives with good to excellent yields. This protocol offers several advantages, such as short reaction times, green solvent, operational simplicity, easily available catalyst and mild reaction conditions. Moreover, this method showed good tolerance of functional groups and a wide range of substrates.

## Introduction

Xanthenes and their analogues including thioxanthenes are important biologically active heterocycles.<sup>1</sup> Natural and synthetic products possessing xanthene moieties exhibit a wide range of biological activities such as antitumor,<sup>2</sup> antibacterial,<sup>3</sup> antifungal,<sup>4</sup> analgesic and antiinflammatory<sup>5</sup> activities. Presently, a number of methods for the functionalized xanthene derivatives have been investigated, some methods particularly for the synthesis of 9-substituted xanthene derivatives.<sup>6</sup> Notably, substitution of the xanthenyl-9-position with an indolyl substituent has received much attention due to the widespread biological and pharmacological activities of indole derivatives.<sup>7</sup> Recently, xanthene-indole derivatives were explored by the nucleophilic substitution of xanthen-9-ol in the presence of catalysts such as AcOH,<sup>8</sup> DDQ,<sup>9</sup> CAN,<sup>10</sup> In(DS)<sub>3</sub>,<sup>11</sup> BmimBF<sub>4</sub>,<sup>12</sup> gluconic acid<sup>13</sup> and 1,3-dichloro-tetra-*n*-butyl-distannoxane.<sup>14</sup> Cozzi also reported the direct substitution of xanthen-9-ol 'on water' without Brønsted or Lewis acid or surfactants, but this reaction must be carried out at 80 °C for long time.<sup>15</sup> However, many of these procedures suffer from certain drawbacks including strong acidic conditions, long reaction times, low yields of products and harsh reaction conditions. In addition, Tsuchimoto reported an indium-catalyzed reductive alkylation of indoles by using carbonyl compounds to obtain alkylindoles with structural diversity.<sup>7d</sup> However, this method was not used

in the formation of xanthene-indole derivatives. Therefore, there is considerable interest in exploring superior catalyst systems which are cheap, stable, environmentally friendly and easy to access.

In recent years, molecular iodine has drawn considerable attention, and been used frequently in many organic reactions. It is widely available, nontoxic, relatively inexpensive, environmentally friendly and highly stable to air and moisture.<sup>16</sup> Iodine catalyzed reactions have resulted in the formation of new C–C,<sup>17</sup> C–O,<sup>18</sup> C–N (ref. 19) and C–S (ref. 20) bonds, and have been recognized as a powerful tool for the synthesis of pharmacologically important heterocyclic compounds.<sup>21</sup> Several methodologies have been reported for the reactions involving the iodine-mediated nucleophilic addition of indole to aldehydes and ketones.<sup>22</sup> However, the reactions about iodine-mediated nucleophilic substitution of alcohols with indoles are seldom.

With these in our mind, we report an efficient synthesis of xanthene/thioxanthene-indole derivatives by iodine-catalyzed nucleophilic substitution of alcohols with indoles under mild conditions in a very short time (Scheme 1). Moreover, this protocol was also used in the substitution of secondary alcohols with indoles or other nucleophiles such as pyrrole, furan and 1,3-dicarbonyl compounds. To the best of our knowledge, there



**Scheme 1** I<sub>2</sub>-catalyzed synthesis of xanthene/thioxanthene-indole derivatives.

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† Electronic supplementary information (ESI) available: Detailed experimental procedures. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra for synthesized compounds or other electronic format. See DOI: 10.1039/d0ra05217e

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are no reports concerning the iodine employed in the substitution of xanthen-9-ol or thioxanthen-9-ol.

## Results and discussion

The reaction of 9*H*-xanthen-9-ol **1a** and indole **3a** was chosen as a model reaction to optimize the reaction conditions. The results were listed in the Table 1. Initially, we investigated the reaction at room temperature under different amounts of iodine in CH<sub>3</sub>CN. In the absence of iodine, the reaction could not proceed in CH<sub>3</sub>CN at room temperature even prolonging reaction time to 1 h (entry 1). To our delight, the reaction proceeded rapidly in the presence of iodine to afford the corresponding substituted product in good yield (entries 2–4), and the investigation indicated that the optimal amount of catalyst was 5 mol% in 85% yield (entry 2). Next, different solvents were also examined in the presence of 5 mol% I<sub>2</sub>. Interestingly, EtOH and CH<sub>2</sub>Cl<sub>2</sub> are tolerated in this reaction (entries 5 and 6). Only H<sub>2</sub>O is turned out to be incompatible for the poor solubility of **1a** in H<sub>2</sub>O (entry 7). Different oxidizing agents including NBS and <sup>t</sup>BuOOH were also examined, but did not show any improvement in the generation of **4aa**. Therefore, the reaction with 5 mol% I<sub>2</sub> in EtOH at room temperature for 5 minutes was found to be the optimal condition.

Under the above optimum reaction conditions, we investigated the substrate scope of the iodine-catalyzed nucleophilic substitution of xanthen-9-ol. Firstly, xanthen-9-ol **1** with different indoles were investigated, and the representative results were listed in Table 2. All substituted indoles with electronic-withdrawing groups or electronic-donating groups proceeded smoothly to afford the desired xanthene-indole derivatives with high or excellent yield. Surprisingly, not only

Table 2 Scope of the reaction of indoles **3** with xanthen-9-ol **1**<sup>a,b</sup>

Product	Yield (%)
4aa	87%
4ab	82%
4ac	84%
4ad	97%
4ae	92%
4af	98%
4ag	81%
4ah	85% <sup>c</sup>
4ai	92%
4aj	86% <sup>c</sup>
4ak	90%
4al	92%
4am	98%
4bn	93%
4ca	91%
4dh	91%
4ea	80%
4fa	90%
4fe	91%
4gh	85%

Table 1 Optimization of the reaction conditions<sup>a</sup>

Entry	Catalyst (mol%)	Solvent	Time (min)	Yield <sup>b</sup> (%)
1	I <sub>2</sub> (0)	CH <sub>3</sub> CN	60	n.d. <sup>c</sup>
2	I <sub>2</sub> (5)	CH <sub>3</sub> CN	5	85
3	I <sub>2</sub> (10)	CH <sub>3</sub> CN	5	81
4	I <sub>2</sub> (15)	CH <sub>3</sub> CN	5	80
5	I <sub>2</sub> (5)	EtOH	5	87
6	I <sub>2</sub> (5)	CH <sub>2</sub> Cl <sub>2</sub>	5	77
7	I <sub>2</sub> (5)	H <sub>2</sub> O	5	n.d.
8	I <sub>2</sub> (5)	EtOH	30	86
9 <sup>d</sup>	I <sub>2</sub> (5)	EtOH	5	84
10	NBS (5)	EtOH	5	84
11	<sup>t</sup> BuOOH (5)	EtOH	60	82

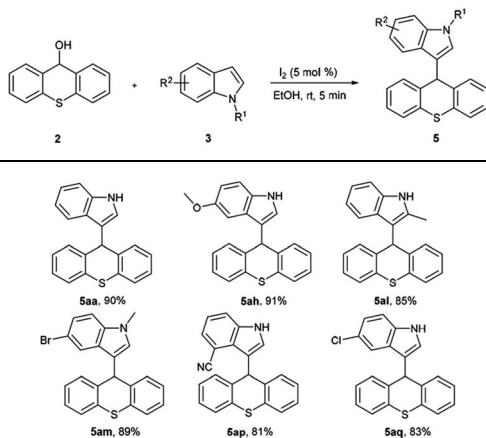
<sup>a</sup> Reaction conditions: **1a** (1.0 mmol) and **3a** (1.0 mmol) in solvent (5 mL) at rt under air. <sup>b</sup> Isolated yield. <sup>c</sup> Not detected. <sup>d</sup> Reaction temperature was 50 °C.

<sup>a</sup> Reaction conditions: **1** (1.0 mmol) and **3** (1.0 mmol) in EtOH (5 mL) at rt under air. <sup>b</sup> Isolated yield. <sup>c</sup> The product was recrystallized from petroleum ether and ethyl acetate.

1- or 2-substituted indoles but also 3-, 4-, 5- or 6-substituted indoles showed high reactivity in our methodology. Moreover, for methyl 1*H*-indole-2-carboxylate, the desired product could be afforded with 90% yield. Substitution of xanthen-9-ol with different substituents such as halogen atoms, CH<sub>3</sub>, CH<sub>3</sub>O, CH<sub>3</sub>CH<sub>2</sub>O and NO<sub>2</sub> groups was conducted, and the targeted products were obtained in good yields.

Subsequently, the reactivity of 9*H*-thioxanthen-9-ol **2** with indoles was also tested for synthesis of thioxanthene-indole derivatives. As shown in Table 3, the reaction proceeded

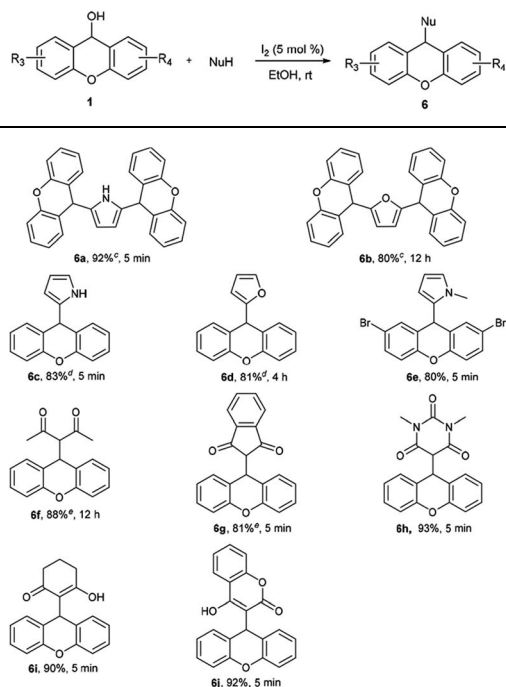


**Table 3** Scope of the reaction of indoles **3** with 9H-thioxanthen-9-ol **2**<sup>a,b</sup>

<sup>a</sup> Reaction conditions: freshly prepared **2** (1.0 mmol) and **3** (1.0 mmol) in EtOH (5 mL) at rt under air. <sup>b</sup> Isolated yield.

smoothly and afforded corresponding substituted product with high yield.

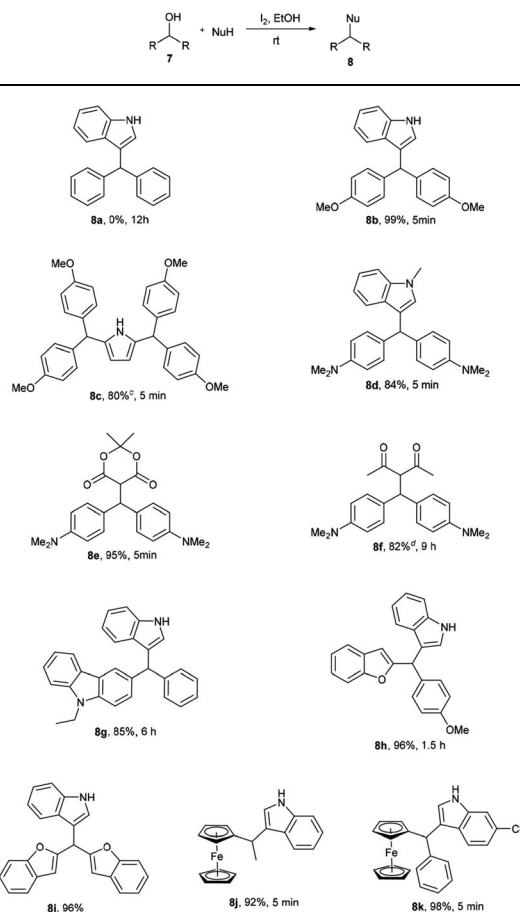
Furthermore, other nucleophiles such as pyrrole, furan and 1,3-dicarbonyl compounds were examined (Table 4).

**Table 4** Scope of the reaction of other nucleophiles with xanthen-9-ol **1**<sup>a,b</sup>

<sup>a</sup> Reaction conditions: **1** (1.0 mmol) and NuH (1.0 mmol) in EtOH (5 mL) at rt under air. <sup>b</sup> Isolated yield. <sup>c</sup> The reaction was performed with 0.5 equiv. of pyrrole or furan. <sup>d</sup> The reaction was performed with 8 equiv. of pyrrole or furan. <sup>e</sup> The product was recrystallized from petroleum ether and ethyl acetate.

Interestingly, the use of 0.5 equiv. of pyrrole or furan gave 2,5-disubstituted pyrrole or 2,5-disubstituted furan in good yields. However, the use of 8 equiv. of pyrrole or furan afforded 2-substituted pyrrole (83%) or 2-substituted furan (81%). 1,3-dicarbonyl compounds such as 2,4-pentanedione, dimedone, 1,3-indanedione, 1,3-dimethylbarbituric acid and 4-hydroxycoumarin were found to be compatible with the reaction conditions, giving the desired products with good to excellent yields.

In addition, the reactivity of other secondary alcohols including benzhydrols and ferrocenyl alcohols were also investigated (Table 5). Diphenylmethanol was not reactive even prolonging reaction time to 12 h. Bis(4-methoxyphenyl) methanol and bis(4-(dimethylamino)phenyl)methanol were suitable substrates and the corresponding products **8b** and **8d** could be obtained in 99% and 84% respectively. The substitution of bis(4-(dimethylamino)phenyl)methanol with pyrrole (0.5 equiv.) also proceeded smoothly to give 2,5-disubstituted pyrrole in 80% yield. To our delight, the heterocyclic derived

**Table 5** Scope of the reaction of other secondary alcohols<sup>a,b</sup>

<sup>a</sup> Reaction conditions: **7** (1.0 mmol) and NuH (1.0 mmol) in EtOH (5 mL) at rt under air. <sup>b</sup> Isolated yield. <sup>c</sup> The reaction was performed with 0.5 equiv. of pyrrole. <sup>d</sup> The product was recrystallized from petroleum ether and ethyl acetate.

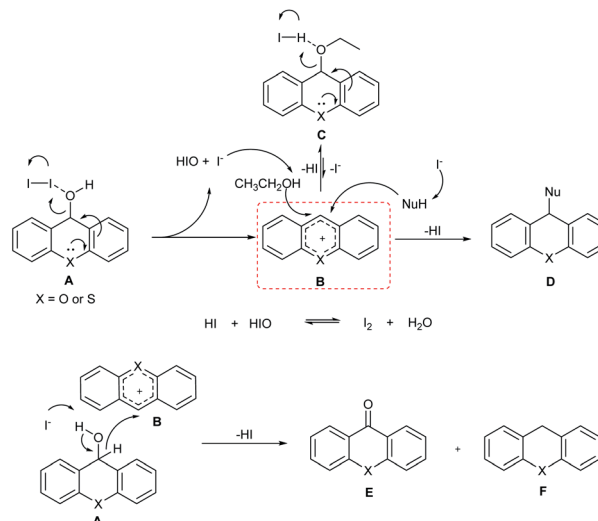


substrates such as di(benzofuran-2-yl)methanol, benzofuran-2-yl(4-methoxyphenyl)methanol and (9-ethyl-9H-carbazol-3-yl)(phenyl)methanol could proceed smoothly in this reaction, affording the desired products with excellent yields. Ferrocenyl alcohols were also good candidate in this transformation to give the desired products **8j** (92%) and **8k** (98%).

The structures of synthesized compounds were confirmed on the basis of IR,  $^1\text{H}$ ,  $^{13}\text{C}$  NMR spectra as well as by comparison with previous reports. For example, compound **4aa** was obtained as white solid. Its molecular formula was determined to be  $\text{C}_{21}\text{H}_{15}\text{NO}$  from the HR-MS at  $m/z$  320.1046  $[\text{M} + \text{Na}]^+$  (calcd 320.1047). Absorption bands at  $3425\text{ cm}^{-1}$  in the IR spectrum of **4aa** were assigned to N-H of indolyl unit. The  $^1\text{H}$  NMR data of **4aa** indicated the presence of a 3-substituted indolyl unit based on the characteristic signals at  $\delta_{\text{H}}$  7.92 (s, 1H), 7.35 (d,  $J = 8.0$  Hz, 1H), 7.30 (d,  $J = 8.0$  Hz, 1H), 7.18 (dd,  $J = 8.8, 1.6$  Hz, 1H), 7.03 (d,  $J = 2.4$  Hz, 1H) and 6.97–6.94 (m, 1H). The  $^{13}\text{C}$  NMR data of **4aa** showed 15 carbon signals.  $\delta_{\text{C}}$  151.33 (2 C), 129.50 (2 CH), 127.73 (2 CH), 124.44 (2 C), 123.13 (2 CH), 116.35 (2 CH) and 35.53 (CH) suggested the existence of 9-substituted xanthenyl moiety.

In order to probe the mechanism of this reaction, control experiments were further conducted (Scheme 2). A 9-ethoxy-9H-xanthene **6k** was obtained when 9H-xanthene-9-ol **1a** was treated solely under the optimized reaction conditions. Subsequently, 9-ethoxy-9H-xanthene was reacted with indole **3a** under the standard conditions; 86% of **4aa** was obtained (Scheme 2b). However, when 9H-xanthene-9-ol **1a** was treated solely under  $\text{I}_2$  (5% mmol) in  $\text{CH}_3\text{CN}$ , 9H-xanthene-9-one and 9H-xanthene formed immediately (Scheme 2c). Meanwhile, the reaction of bis(3-methoxyphenyl)methanol with indole could not proceed under the optimized reaction conditions from room temperature to reflux even prolonging reaction time to 12 h (Scheme 2d).

On the basis of the above experimental outcomes and the previous literature reports,<sup>11,22</sup> a plausible reaction mechanism is presented in Scheme 3. The first step of the process is the coordination of iodine to the hydroxyl function of compound **A**,



Scheme 3 Proposed mechanisms.

thus causing its elimination to give the pyrylium ion **B**. And the  $\text{I}_2$  is transformed to  $\text{HIO}$  and  $\text{I}^-$ . Then, nucleophile attacks the pyrylium ion to generate the corresponding product. On the other hand,  $\text{EtOH}$  as nucleophile can react with pyrylium ion **B** to give **C**, which can transform to pyrylium ion under  $\text{HI}$ . Importantly, the formation of **C** can prevent the redox reaction between **A** and pyrylium ion **B**. Liberated  $\text{HI}$  is further reacted with  $\text{HIO}$  to regenerate  $\text{I}_2$  and complete the catalytic cycle by releasing  $\text{H}_2\text{O}$ . For other secondary alcohols, the results could be explained by the higher stabilization of the generated carbocation.

## Conclusions

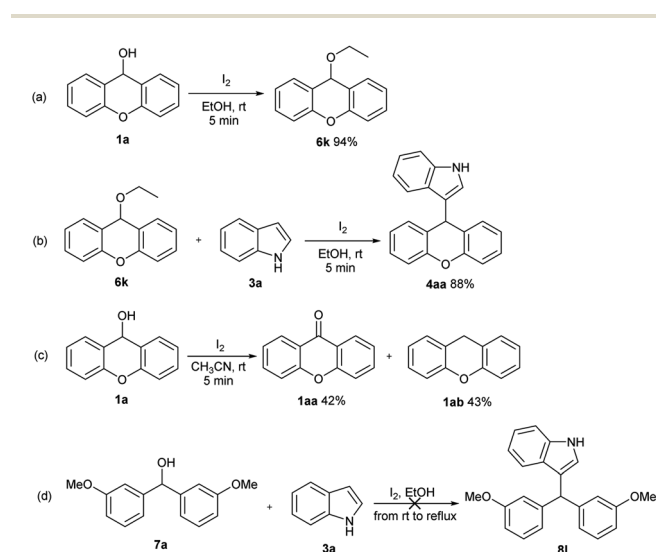
In conclusion,  $\text{I}_2$  in ethanol was found to be effective and green catalyst for the electrophilic substitution reactions of xanthene-9-ol and thioxanthene-9-ol with indoles giving xanthene/thioxanthene-indole derivatives. Using 5 mol%  $\text{I}_2$ , the reactions could proceed efficiently at room temperature in five minutes and afford xanthene/thioxanthene-indole derivatives with good to excellent yield. Moreover, the reactions of xanthene-9-ol with other nucleophilic reagents such as pyrrole, furan and 1,3-dicarbonyl compounds could proceed smoothly. The scope of substrate was also extended to other secondary alcohols such as benzhydrols and ferrocenyl alcohols.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

This work was supported by the National Natural Science Foundation of China (No. 21602050), Applied Basic Research Project of Yunnan (2017FD154), and Yunnan Province Department of Education Fund (2016ZZX218).



Scheme 2 Control experiments.





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