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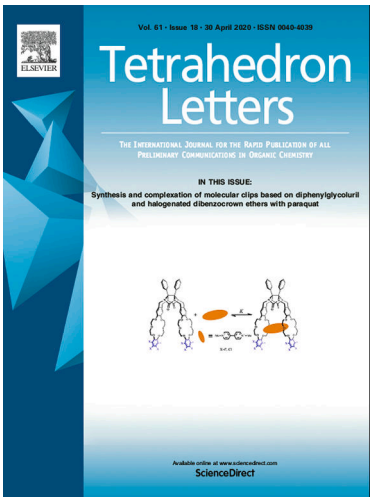


# Synthesis of benzo[*f*]pyrido[1,2-*a*]indole-6,11-diones *via* the $I_2$-promoted reactions of methyl ketones with pyridines and 1,4-naphthoquinone

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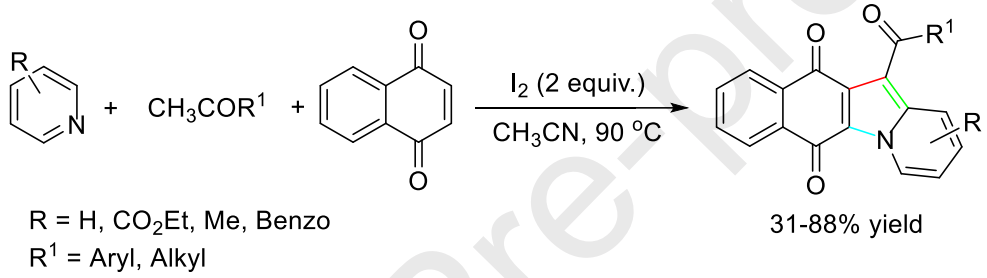
# Synthesis of Benzo[*f*]pyrido[1,2-*a*]indole-6,11-diones *via* the $I_2$-Promoted Reactions of Methyl Ketones with Pyridines and 1,4-Naphthoquinone

Yun Liu,* Hui Xu, Hui Wu*

School of Chemistry and Material Science, Jiangsu Normal University, Xuzhou 221116, Jiangsu, P. R. China

Email: liu__yun3@sina.com




**Abstract:** An effective synthesis of benzo[*f*]pyrido[1,2-*a*]indole-6,11-diones has been achieved *via* the $I_2$-promoted reactions of methyl ketones, pyridines and 1,4-naphthoquinone. In this reaction, either aromatic or aliphatic methyl ketones proceeded well. The advantages of this method include a broad substrate scope, metal-free reaction conditions, and high atom- and step-economy.

**Keywords:** iodine, pyridines, methyl ketones, 2,3-annulated iodolizines, metal-free

Indolizine derivatives exhibit various pharmaceutical activities and play important roles in the development of new pharmaceuticals for the treatment of human diseases [1-5]. Among these compounds, annulated indolizines are found in several naturally occurring alkaloids [6] and have interesting biological activities, as well as optical and electrochemical properties [7]. Consequently, there has been growing interest in the synthesis of annulated indolizines [8-9].

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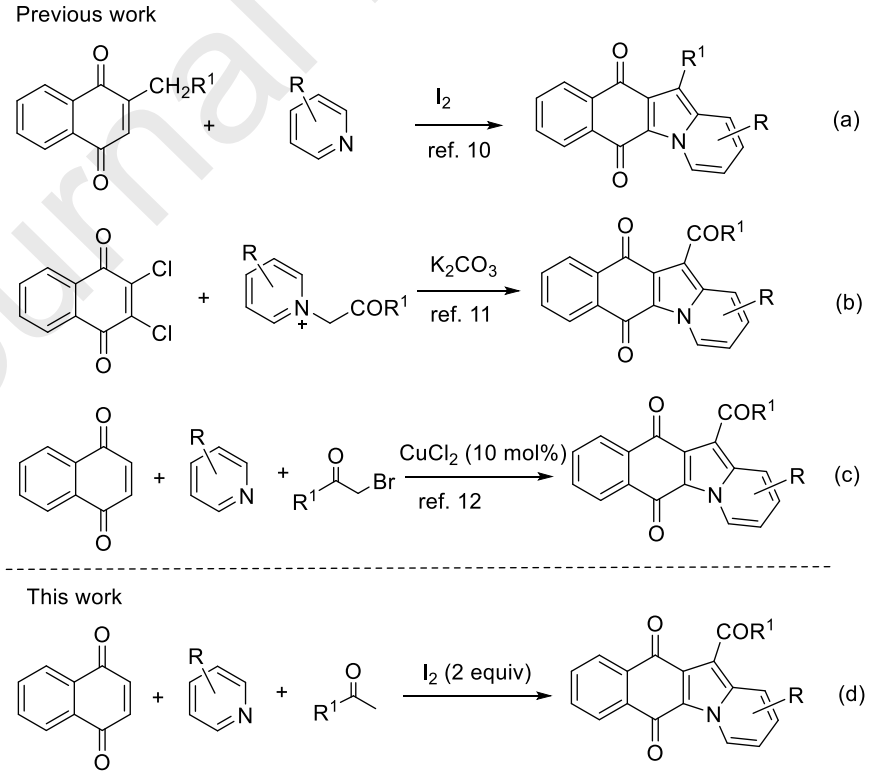
Benzo[*f*]pyrido[1,2-*a*]indole-6,11-diones are naphthoquinone-fused indolizines. Traditional synthetic routes to these compounds usually start from functionalized naphthoquinones (Scheme 1a and 1b) [10-11]. Obviously, the direct synthesis of these compounds from unsubstituted naphthoquinone is more convenient, and our group has reported a synthesis of benzo[*f*]pyrido[1,2-*a*]indole-6,11-diones *via* the copper-catalyzed reaction of 1,4-naphthoquinone with bromides and pyridines (Scheme 1c) [12]. Despite the usefulness of this method, it still requires the preparation or purchase of expensive and irritant bromoketones. Therefore, it is desirable to use more readily-available reactants to replace bromoketones in this reaction.

Molecular iodine has been widely used in organic chemistry [13-14]. As part of our continued interest in heterocycle synthesis [15], herein, we describe an effective synthesis of benzo[*f*]pyrido[1,2-*a*]indole-6,11-diones *via* the iodine-promoted reaction of methyl ketones with pyridine and naphthoquinone under metal-free conditions (Scheme 1d). Due to eliminating the use of bromoketones, this reaction features high atom- and step-economy.

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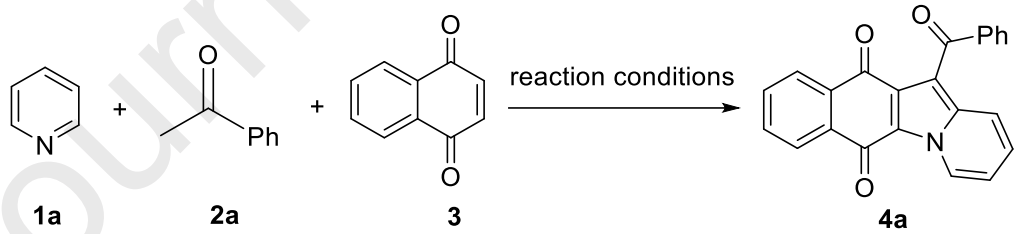
**Scheme 1.** Synthesis of benzo[*f*]pyrido[1,2-*a*]indole-6,11-diones.

To optimize the reaction conditions, we chose the model reaction of pyridine **1a**, acetophenone **2a** and 1,4-naphthoquinone **3**. Initially, by heating a mixture of **1a** (1.5 mmol), **2a** (0.6 mmol), **3** (0.5 mmol) and iodine (0.5 mmol) in DMF at 90 °C for 12 h in a sealed tube, we obtained the desired product **4a** in 58% yield (Table 1, entry 1). Subsequently, we investigated the effect of different solvents and found acetonitrile was the optimal choice (Table 1, entries 1-5). Optimization of the iodine loading showed that 2 equiv. of iodine was necessary to ensure high reaction efficiency, affording **4a** in 78% yield (Table 1, entries 3, 6-7). Adding an external base did not improve the yield (Table 1, entries 8-9). We also tested other iodine reagents instead of molecular iodine, but lower yields were obtained (Table 1, entries 6, 10-11). Finally, we lowered the reaction temperature to 60 °C, but only isolated **4a** in 59% yield (Table 1, entry 12). Therefore, the optimal conditions were determined as heating a mixture of **1a** (1.5 mmol), **2a** (0.6 mmol) and **3** (0.5 mmol) in $CH_3CN$ at 90 °C for 12 h in the presence of 2 equiv. of iodine (Table 1, entry 6).

**Table 1.** Optimization of the reaction conditions.[a]




**1a** **2a** **3** **4a**

| Entry | Solvent | Adduct (eq.) | Base (eq.) | Yield (%)[b] | **4a** |
|---|---|---|---|---|---|
| 1 | DMF | $I_2$ (1) | / | 58 | |
| 2 | DCE | $I_2$ (1) | / | 55 | |
| 3 | $CH_3CN$ | $I_2$ (1) | / | 61 | |

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| | | | | |
|---|---|---|---|---|
| 4 | $C_6H_6$ | $I_2$ (1) | / | 40 |
| 5 | 1,4-Dioxane | $I_2$ (1) | / | 52 |
| **6** | **$CH_3CN$** | **$I_2$ (2)** | **/** | **78** |
| 7 | $CH_3CN$ | $I_2$ (2.5) | / | 78 |
| 8 | $CH_3CN$ | $I_2$ (2) | $K_2CO_3$ (1) | 76 |
| 9 | $CH_3CN$ | $I_2$ (2) | $Cs_2CO_3$ (1) | 77 |
| 10 | $CH_3CN$ | NIS (2) | / | 50 |
| 11 | $CH_3CN$ | ICl (2) | / | 46 |
| 12[c] | $CH_3CN$ | $I_2$ (2) | / | 59 |

[a] Reagents and conditions: **1a** (1.5 mmol), **2a** (0.6 mmol), **3** (0.5 mmol), adduct, base, 90 °C, 12 h, sealed tube. [b] Isolated yields. [c] 60 °C.

With the optimized conditions in hand, we then screened the scope of methyl ketones **2** by reacting with **1a** and **3** (Table 2). Various aromatic methyl ketones **2b-j** were suitable substrates and electronic or steric factors on the benzene ring substituent had little effect on the reaction. For instance, *para*-substituted acetophenones **2b-f** with either electron-donating groups (Me, Et) or electron-withdrawing groups (F, Cl, Br) showed good reactivity and gave products **4b-f** in 73-87% yield. Similarly, acetophenones **2g-j** with *ortho*- or *meta*-substituents reacted equally well, affording products **4g-j** in 65-77% yield. Additionally, aliphatic methyl ketones **2k-l** gave products **4k** and **4l** in good yields. Due to their low boiling points, an excess of the aliphatic methyl ketones was added to the reaction system.

**Table 2.** Scope of methyl ketones **2**.[a,b]

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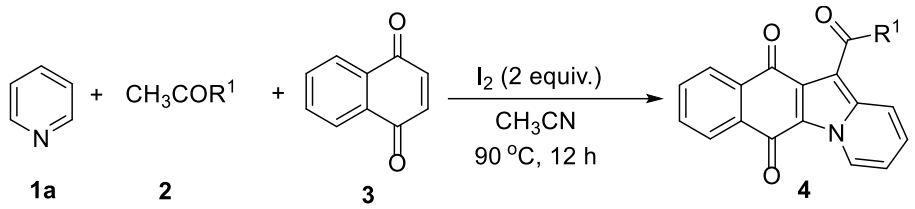
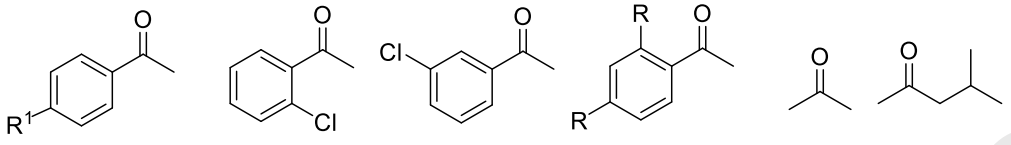
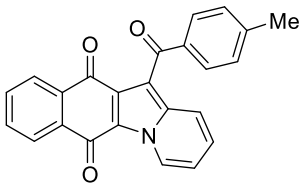


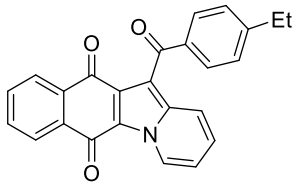

**1a** **2** **3** **4**



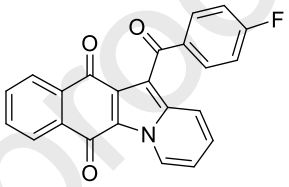
**2b** R=Me **2e** R=Cl **2g** **2h** **2i** R=Cl **2k** **2l**
**2c** R=Et **2f** R=Br **2j** R=Me
**2d** R=F



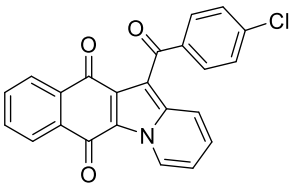
**4b**, 73%



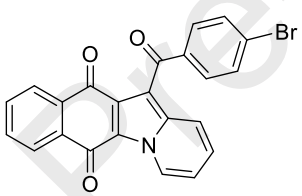
**4c** 75%



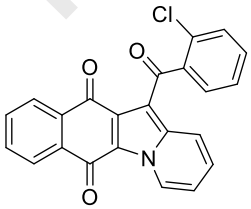
**4d**, 81%



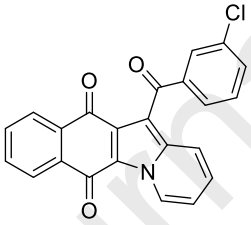
**4e**, 87%



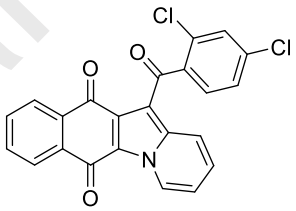
**4f**, 83%



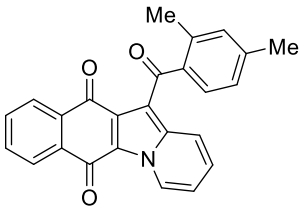
**4g**, 71%



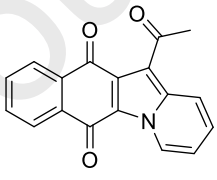
**4h**, 77%



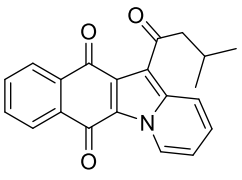
**4i**, 68%



**4j**, 65%



**4k**, 75%[c]



**4l**, 78%[c]

[a] Reagents and conditions: **1a** (1.5 mmol), **2b-l** (0.6 mmol), **3** (0.5 mmol), iodine (1.0 mmol). [b] Isolated yields. [c] 1 mL of the aliphatic methyl ketone was used.

Next, we investigated the scope of the pyridines **1** by reacting with acetophenone **2a** and

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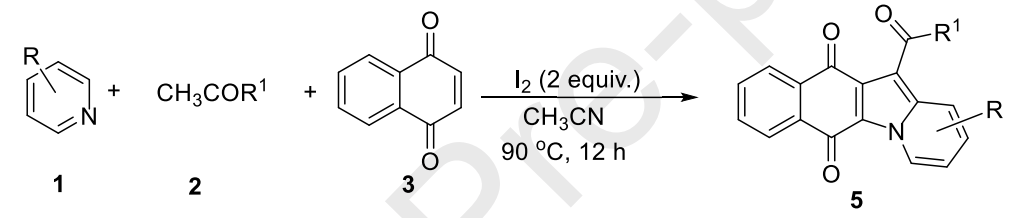
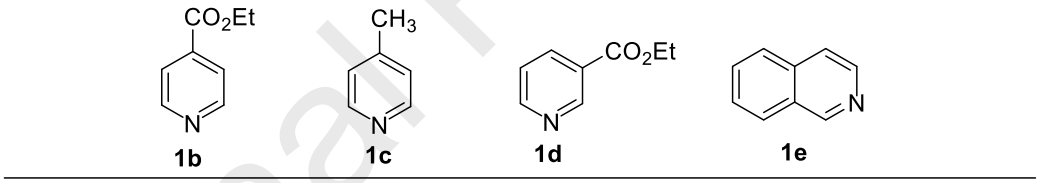
naphthoquinone **3** (Table 3). The reactions of 4-substituted pyridines **1b-c** with different substituents ($CO_2Et$, Me), gave products **5a-b** in good yields. For 3-substituted pyridine **1d**, two isomers **5c** and **5d** were formed in 50% and 31% yield, respectively. Annulated pyridine **1e** also proved to be a good substrate, giving **5e** in 86% yield. To further examine the generality of this protocol, isoquinoline **1e** was reacted with substituted acetophenones and naphthoquinone, affording product **5f-h** in high yields. Aliphatic methyl ketones also afforded products **5i-k** in 62-75% yield. The structures of all compounds were all confirmed by NMR spectroscopy and HPLC, and the spectral data of known compounds **4a** and **5e** were in accordance with our previous reports [11,12].

**Table 3.** Scope of pyridines **1**.[a,b]

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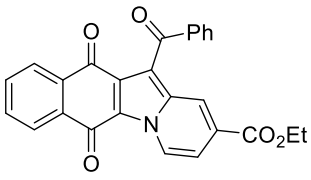
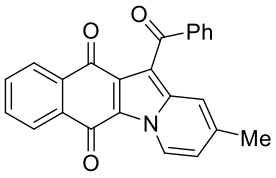
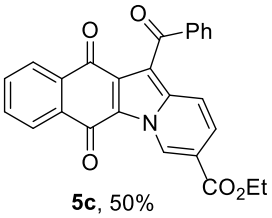


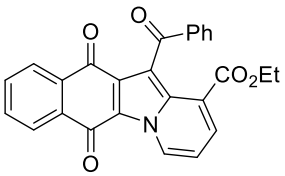

**5a**, 82%



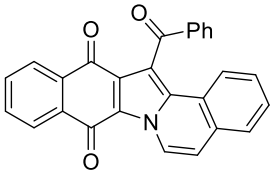

**5b**, 68%[c]



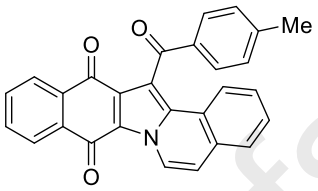

**5c**, 50%



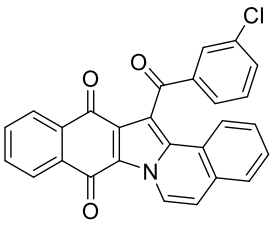

**5d**, 31%



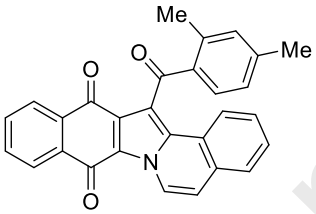

**5e** 88%



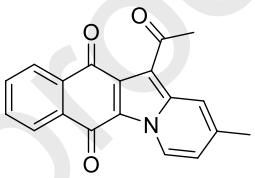

**5f**, 85%



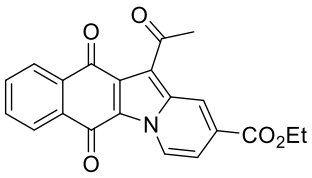

**5g**, 81%



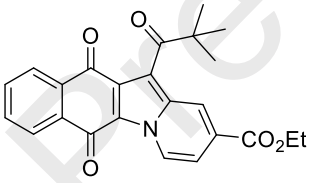

**5h**, 82%




**5i**, 73%[c]




**5j**, 75%[d]




**5k**, 62%[d]

[a] Reagents and conditions: **1b-e** (1.5 mmol), **2** (0.6 mmol), **3** (0.5 mmol), iodine (1.0 mmol). [b] Isolated yields. [c] **2** (3.0 mmol) and iodine (2.0 mmol) in DMF was used. [d] 1 mL of the aliphatic methyl ketone was used.

Control experiments were carried out to shed light on the reaction mechanism. First, pyridinium salt **6** was reacted with naphthoquinone **3** and pyridine **1a**, which gave **4a** in 83% yield (Scheme 2a). Second, pyridinium salt **7** [16] was reacted with acetophenone and pyridine, which gave **4a** in 80% yield (Scheme 2b). These results indicated that **6** and **7** were possible reaction intermediates. Third, we added 1 equiv. of TEMPO into the model reaction, and found the formation of **4a** was not suppressed. This dispelled the radical reaction mechanism (Scheme 2c).

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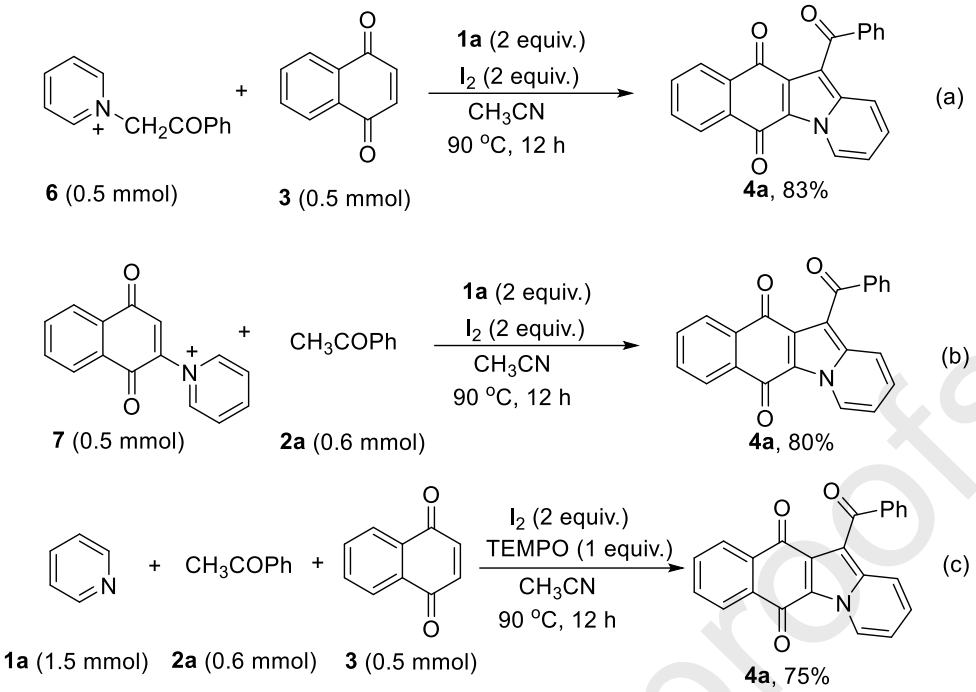


**Scheme 2.** Control experiments.

According to our experimental results and previous literature [12,16,17], a possible mechanism was proposed (Scheme 3). Initially, intermediate **6** is formed from the reaction of **2a** with **1a** with the aid of iodine *via* an Ortoleva-King reaction [17]. Meanwhile, intermediate **7** is generated *via* the reaction of **1a** and **3**. Then, the reaction of **6** with **7** by a cyclization-elimination-oxidation process affords the final product **4a**. In this reaction process, iodine plays a dual role by acting both as a coupling reagent to transfer **2a** to **6**, and as an oxidant to form product **4a** by oxidative aromatization.

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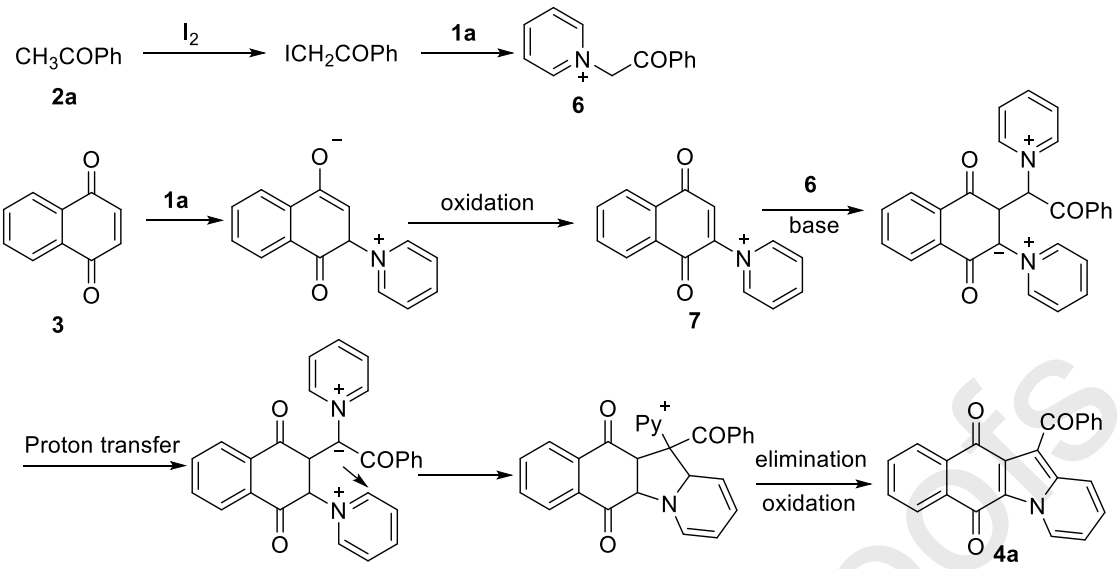


**Scheme 3.** Possible reaction mechanism.

In conclusion, we have reported an efficient and practical protocol for the synthesis of benzo[*f*]pyrido[1,2-*a*]indole-6,11-diones *via* the iodine-promoted reactions of methyl ketones, pyridine, and naphthoquinone. In addition to the high atom- and step-economy, this method also has the advantage of using readily-available methyl ketones instead of the often more difficult to access bromoketones, allowing a substantial expansion of the reaction scope.

**Acknowledgements**

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# Highlights

Synthesis of benzo[*f*]pyrido[1,2-*a*]indole-6,11-diones

Preparation of products in good yields

Broad substituents scope and metal-free conditions

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