

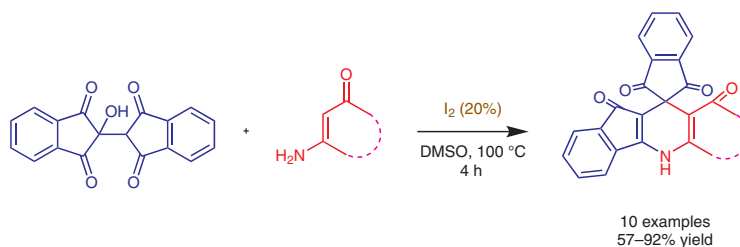
# Iodine as a New Catalyst for the Condensation of 2-Hydroxy-2,2'-bisindan-1,1',3,3'-tetrone with Cyclic Enaminones: Synthesis of Spiro-dihydropyridine Derivatives under Acid-Free Conditions

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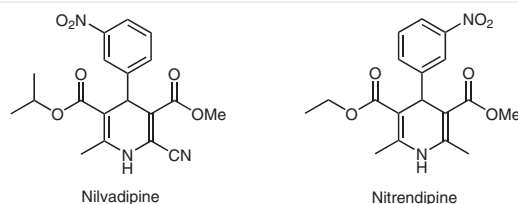
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**Abstract** Iodine has been used as a new catalyst for the synthesis of spiro-dihydropyridine derivatives by the condensation of cyclic enaminones and 2-hydroxy-2,2'-bisindan-1,1',3,3'-tetrone.

**Key words** iodine, aminouracil, spiro-dihydropyridine

The properties of molecular iodine, including its Lewis acidity, lead to a range of applications in organic synthesis.<sup>1–4</sup> Nitrogen-containing heterocyclic compounds have been of interest for the development of organic synthesis through decades.<sup>5–8</sup> Among them, 1,4-dihydropyridines (1,4-DHPs; Figure 1) are an important class of compounds in the field of vasodilation and bronchodilation, being potent calcium antagonists and calcium channel blockers.<sup>9–12</sup>



**Figure 1** Selected examples of dihydropyridines

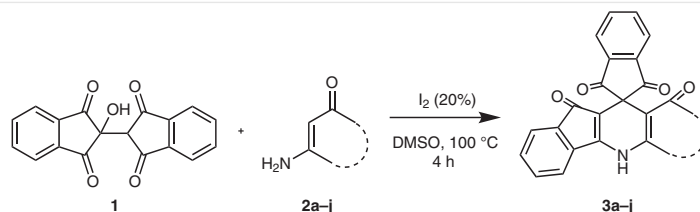
Spiro-heterocycles, due to their steric constraints, represent an important class of substances that often have interesting biological properties.<sup>13–15</sup> Among them, spiro-dihydropyridine derivatives serve as important building

blocks in a wide range of biologically active compounds.<sup>16</sup> There are several synthetic methods available for the preparation of functionalized dihydropyridines.<sup>17</sup>

2-Hydroxy-2,2'-bisindan-1,1',3,3'-tetrone can be readily generated by acid or base catalyzed condensation of ninhydrin with 1,3-indanedione.<sup>18</sup> Activation of 2-hydroxy-2,2'-bisindan-1,1',3,3'-tetrone for electrophilic reactions has been achieved under acidic conditions such as AcOH/H<sub>2</sub>SO<sub>4</sub> for addition of phenols,<sup>19</sup> AcOH for enol condensation,<sup>20</sup> triflic acid,<sup>21</sup> acidic magnetic nanoparticle for synthesis of pyrazoles,<sup>22</sup> and silica-sulfuric acid for synthesis of dihydropyridines.<sup>23</sup> However, the use of acidic conditions can cause rearrangements and can also require high temperatures in some cases.

In the present work, in a continuation of our ongoing research program in the field of synthesis of spiro-heterocyclic compounds, we report the reaction of 2-hydroxy-2,2'-bisindan-1,1',3,3'-tetrone **1** and cyclic enaminones **2a–j** in the presence of molecular iodine under mild reaction conditions to form spiro-dihydropyridines **3a–j** (Scheme 1).

Firstly, 1,3-indandione was reacted with ninhydrin in the presence of triethylamine in EtOH at room temperature, to afford 2-hydroxy-2,2'-bisindan-1,1',3,3'-tetrone **1**. The reaction of compound **1** was tested initially with 6-aminouracil in dimethyl sulfoxide (DMSO) at 120 °C without catalyst. However, these conditions did not afford the desired product **3a** (Table 1, entry 2). The use of an acidic catalyst such as *p*-TSA or acetic acid gave **3a** in moderate yields (entries 3 and 4). Our group has previously used molecular iodine as a catalyst<sup>1,24</sup> and when we examined the use of iodine in DMSO at 120 °C the reaction proceeded in excellent yield (entry 5). To study the effect of temperature, an additional experiment was performed at 100 °C, resulting in 91% yield of **3a** after 4 hours (entry 8). However, when the



**Scheme 1** Synthesis spiro-dihydropyridines

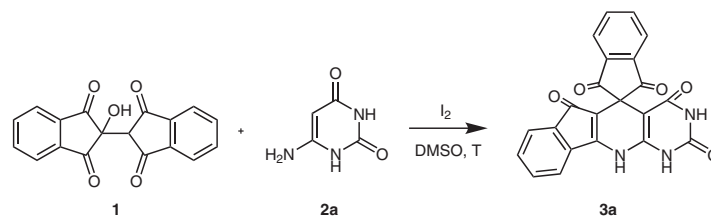
reaction was performed at lower temperatures, the yield decreased dramatically (entries 9 and 10). When solvents such as *N,N*-dimethylformamide (DMF) and toluene were examined, again a decrease in the yield of the reaction was observed (entries 11 and 12). Therefore, 20 mol%  $I_2$  in DMSO at 100 °C was established as the optimal conditions for the current methodology.

To investigate the scope of this reaction, a range of cyclic enaminones was used; the results are summarized in Table 2. All derivatives **3a–j** were obtained in high yields, although in the case of compounds **3i** and **3j** the yield of the reaction decreased slightly, presumably because the nitrogen of the 6-aminocoumarin is further substituted and therefore more sterically hindered.

All novel compounds **3a–f** were fully characterized by elemental analysis, IR,  $^1H$  NMR,  $^{13}C$  NMR spectroscopic analysis and HRMS. For example, the HRMS spectrum of **3a** displayed  $m/z$   $[M+H]^+$  at 398.0775 and the IR spectrum showed absorption bands at 3249, 1710, 1690, and 1666  $cm^{-1}$  assigned to NH stretching and five-membered ketone, amide, and  $\alpha,\beta$ -unsaturated ketone carbonyl groups, respectively. The  $^1H$ -decoupled  $^{13}C$  NMR spectrum of **3a** showed 18 distinct resonances, with a signal at 56 ppm being attributed to the spiro-carbon.

Finally, to investigate the scalability of our reaction, the reaction was conducted on a gram scale under the optimized reaction conditions and no significant changes in either reaction time or yield were observed (Scheme 2).

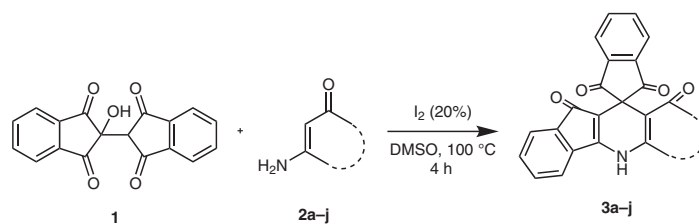
**Table 1** Optimization of Reaction Conditions for the Preparation of **3a**<sup>a</sup>



Entry	Solvent	Catalyst	Catalyst (%)	Temp. (°C)	Time (h)	Yield (%) <sup>b</sup>
1	DMSO	none	–	100	24	–
2	DMSO	none	–	120	24	–
3	DMSO	<i>p</i> -TSA	100	120	12	42
4	DMSO	HOAc	100	120	12	37
5	DMSO	$I_2$	100	120	12	94
6	DMSO	$I_2$	20	120	12	92
7	DMSO	$I_2$	10	120	12	65
<b>8</b>	<b>DMSO</b>	<b><math>I_2</math></b>	<b>20</b>	<b>100</b>	<b>4</b>	<b>91</b>
9	DMSO	$I_2$	20	80	4	44
10	DMSO	$I_2$	20	50	4	23
11	DMF	$I_2$	20	100	4	67
12	toluene	$I_2$	20	100	4	35

<sup>a</sup> Reagents and conditions: **1** (1 mmol), **2a** (1 mmol), solvent (4 mL), in a capped vial.

<sup>b</sup> Isolated yield.

Table 2 Synthesis of 3a–j<sup>a</sup>

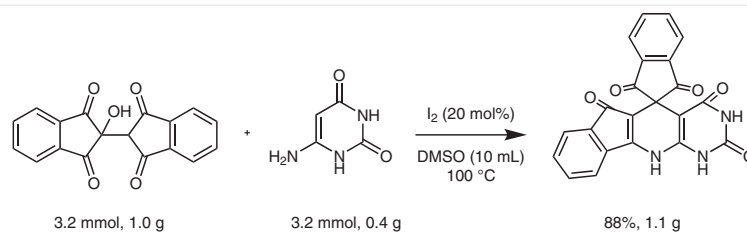
Entry	Cyclic Enaminones	Product	Yield (%) <sup>b</sup>
1	<b>2a</b> 	<b>3a</b> 	91
2	<b>2b</b> 	<b>3b</b> 	88
3	<b>2c</b> 	<b>3c</b> 	85
5	<b>2d</b> 	<b>3d</b> 	92
5	<b>2e</b> 	<b>3e</b> 	86
6	<b>2f</b> 	<b>3f</b> 	80

Table 2 (continued)

Entry	Cyclic Enaminones	Product	Yield (%) <sup>b</sup>
7	2g 	3g 	73
8	2h 	3h 	83
9	2i 	3i 	61
10	2j 	3j 	57

<sup>a</sup> Reagents and conditions: **1** (1 mmol), **2a–j** (1 mmol), DMSO (4 mL), I<sub>2</sub> (20 mol%) in a capped vial.

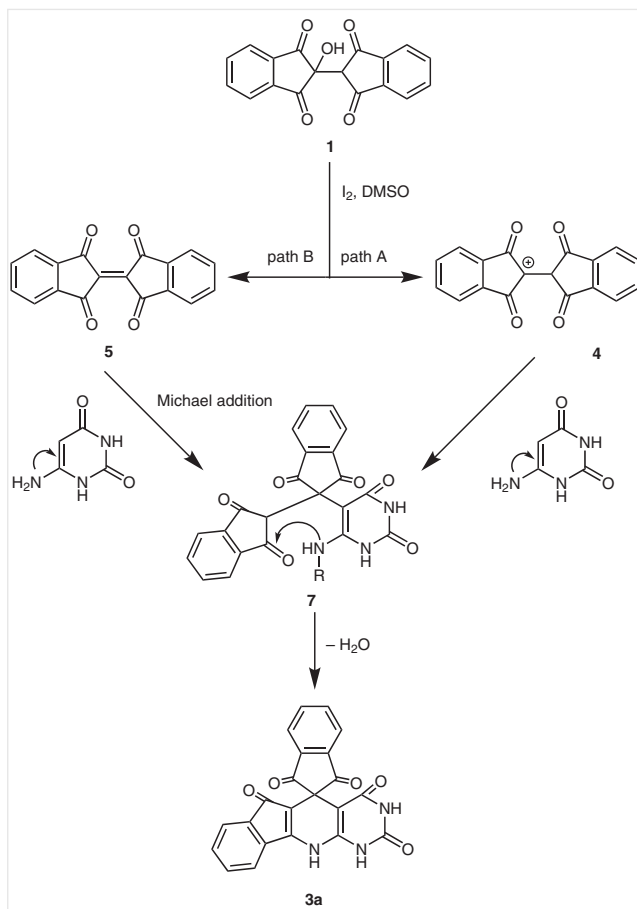
<sup>b</sup> Isolated yield.



Scheme 2

Although we have not established the mechanism of the reaction experimentally, a plausible mechanism is proposed in Scheme 3. The reaction between molecular iodine and hydroxy compound **1** could produce two intermediates, Path A gives intermediate **4**, which is reported to be formed under acidic conditions,<sup>19,21</sup> and Path B leads to intermediate **5**. Michael addition of enaminone **2a** to either the double bond of **4** or the carbocationic center of **5** gives intermediate **7**, which undergoes intramolecular cyclocondensation to produce the desired product.

In conclusion, we have developed an efficient methodology for the synthesis of spiro-dihydropyridines in high yield from 2-hydroxy-2,2'-biindan-1,1',3,3'-tetrone as starting material.<sup>25,26</sup> Activation of 2-hydroxy-2,2'-bisindan-1,1',3,3'-tetrone with molecular iodine as a mild catalyst under acid-free reaction conditions and a simple work-up procedure are features of this method.



**Scheme 3** Proposed mechanism of formation of spiro-dihydropyridans **3**

## Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0036-1591918>.

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- Typical procedure for the synthesis of spiro-dihydropyridines 3a–j:** A mixture of 2-hydroxy-2,2'-bisindan-1,1',3,3'-tetrone **1** (1 mmol), cyclic enaminone **2a–f** (1 mmol) and molecular iodine (20 mol%) in DMSO (4 mL) was stirred at 100 °C for 4 h. After completion of the reaction (monitored by TLC, ethyl acetate/*n*-hexane, 1:2) the reaction mixture was allowed to cool to room temperature. Water was added and the precipitate was filtered off and washed with acetone to give the product **3a–j**.
- Synthesis of 2-hydroxy-2,2'-bisindan-1,1',3,3'-tetrone 1:** A mixture of 1,3-indandione (10 mmol), ninhydrin (10 mmol), and triethylamine (1 mmol) in EtOH (50 mL) was stirred at room temperature for 5 h. The precipitate was filtered and washed with EtOH (2 × 5 mL) to give **1**. Yellow powder; mp 187–190 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 8.00–7.93 (m, 2 H, Ar), 7.92–7.83 (m, 6 H, Ar), 5.47 (s, 1 H, OH), 3.96 (s, 1 H, CH); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ = 197, 196, 142, 141, 137, 136, 124, 124, 76, 53.

**Analytical data for spiro[indene-2,5'-indeno[2',1':5,6]pyrido[2,3-d]pyrimidine]-1,2',3,4',6'(1H,3H,11H)-pentaone (3a):** Yield: 0.361 g (91%); red powder; mp 212–215 °C (dec.); IR (KBr): 3249, 2917, 1710, 1690, 1666 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O): δ = 7.89–7.85 (m, 4 H, Ar-H), 7.36 (d, *J* = 6.9 Hz, 1 H, Ar-H), 7.24–7.17 (m, 2 H, Ar-H), 7.00 (d, *J* = 6.9 Hz, 1 H, Ar-H); <sup>13</sup>C NMR (125 MHz, D<sub>2</sub>O): δ = 209, 187, 173, 170, 165, 162, 141, 138, 137, 136, 131, 130, 122, 119, 119, 100, 92, 56; Anal. Calcd for C<sub>22</sub>H<sub>11</sub>N<sub>3</sub>O<sub>5</sub>: C, 66.50; H, 2.79; N, 10.58. Found: C, 65.90; H, 2.81; N, 10.61; HRMS: *m/z* [M+H]<sup>+</sup> calcd. for C<sub>22</sub>H<sub>11</sub>N<sub>3</sub>O<sub>5</sub>: 398.0777; found: 398.0775.