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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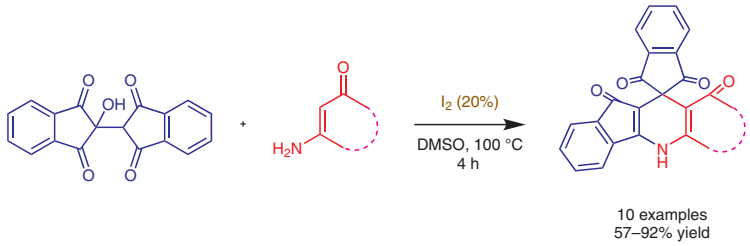
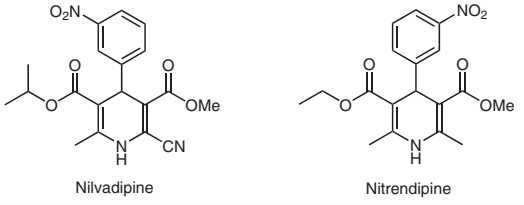


Received: 05.11.2017
Accepted after revision: 16.01.2018
Published online: 01.02.2018
DOI: 10.1055/s-0036-1591918; Art ID: so-2017-d0055-l

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.[1–4] Nitrogen-containing heterocyclic compounds have been of interest for the development of organic synthesisthrough decades.[5–8] 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.[9–12]



Nilvadipine Nitrendipine

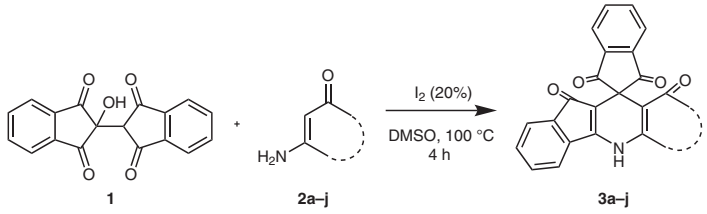
Figure 1 Selected examples of dihydropyridines

Spiro-heterocycles, due to their steric constraints, represent an important class of substances that often have interesting biological properties.[13–15] Among them, spiro-dihydropyridine derivatives serve as important building blocks in a wide range of biologically active compounds.[16] There are several synthetic methods available for the preparation of functionalized dihydropyridines.[17]

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.[18] 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_2SO_4 for addition of phenols,[19] AcOH for enol condensation,[20] triflic acid,[21] acidic magnetic nanoparticle for synthesis of pyrazoles,[22] and silica-sulfuric acid for synthesis of dihydropyridines.[23] 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′-biindan-1,1′,3,3′-tetrone **1** and cyclic enaminones **2a–j** in the presence of molecular iodine under mild reaction conditions to form spiro-dihdydropyridines **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[1,24] 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

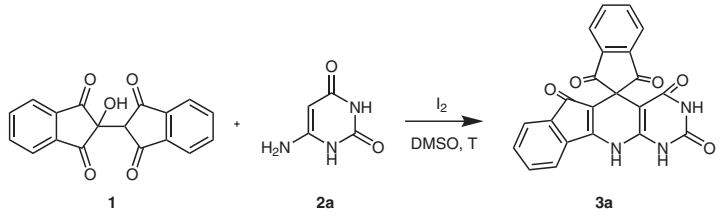
reaction was performed at lower temperatures, the yield decreased dramatically (entries 9 and 10). When solvents such as *N*,*N*-dimethylformamide (DMF) and toluene were examined, again a decrease in the yield of the reaction was observed (entries 11 and 12). Therefore, 20 mol% I_2 in DMSO at 100 °C 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, ^{1}H 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 α,β-unsaturated ketone carbonyl groups, respectively. The ^{1}H-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).

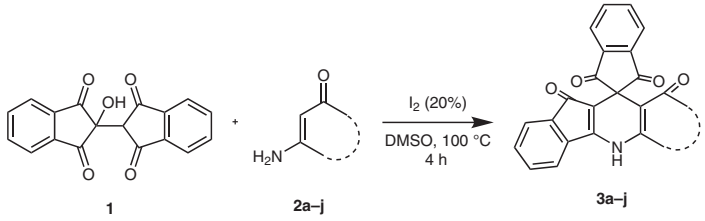
Table 1 Optimization of Reaction Conditions for the Preparation of **3a**[a]



Entry	Solvent	Catalyst	Catalyst (%)	Temp. (°C)	Time (h)	Yield (%)[b]
1	DMSO	none	–	100	24	–
2	DMSO	none	–	120	24	–
3	DMSO	*p*-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
8	**DMSO**	**I_2**	**20**	**100**	**4**	**91**
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

[a] Reagents and conditions: **1** (1 mmol), **2a** (1 mmol), solvent (4 mL), in a capped vial.
[b] Isolated yield.

Table 2 Synthesis of **3a–j**[a]



1 2a–j 3a–j

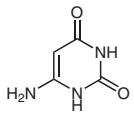
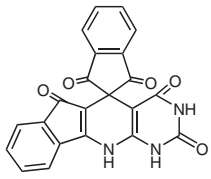
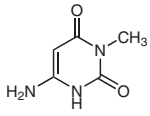
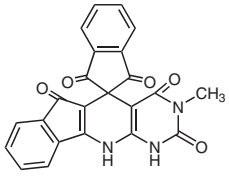
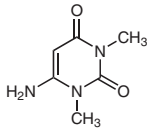
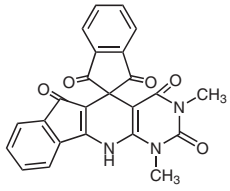
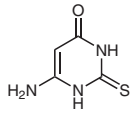
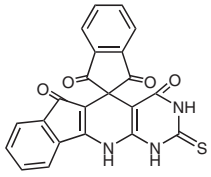
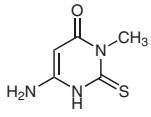
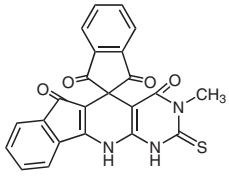
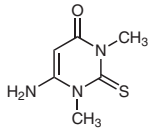
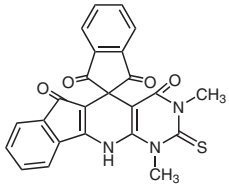
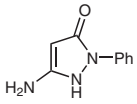
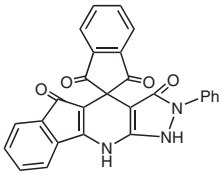
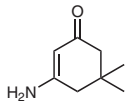
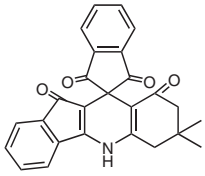
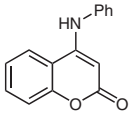
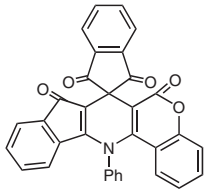
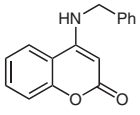
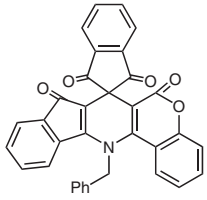
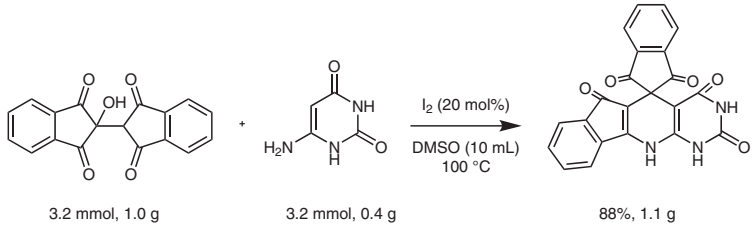
Entry	Cyclic Enaminones		Product		Yield (%)[b]
1	**2a**		**3a**		91
2	**2b**		**3b**		88
3	**2c**		**3c**		85
5	**2d**		**3d**		92
5	**2e**		**3e**		86
6	**2f**		**3f**		80

Table 2 (continued)

Entry	Cyclic Enaminones		Product		Yield (%)[b]
7	2g		3g		73
8	2h		3h		83
9	2i		3i		61
10	2j		3j		57

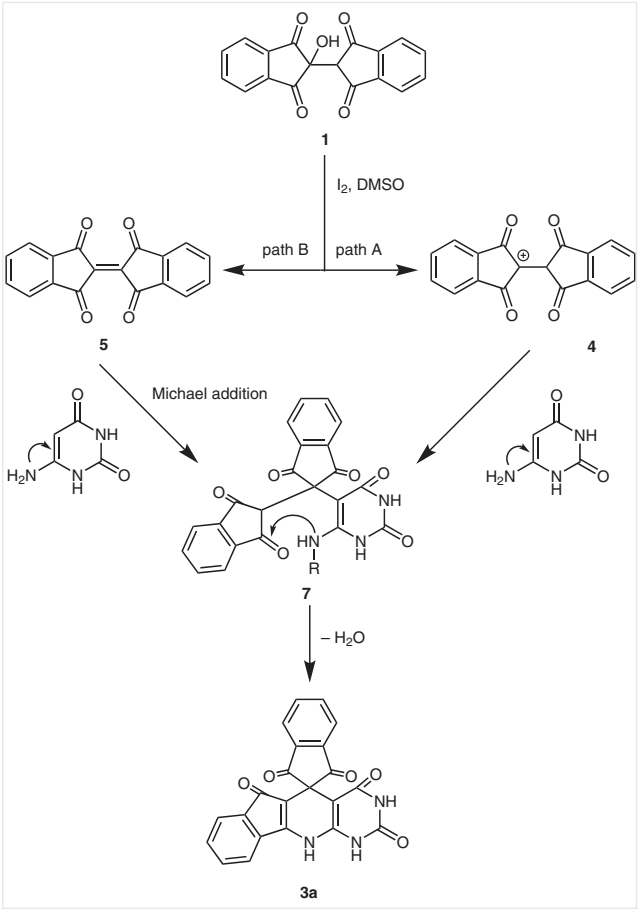
[a] Reagents and conditions: **1** (1 mmol), **2a–j** (1 mmol), DMSO (4 mL), I_2 (20 mol%) in a capped vial.
[b] Isolated yield.



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,[19,21] 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.[25,26] 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-dihydropyrans **3**

Supporting Information

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

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(25) **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**.
(26) **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; ^{1}H NMR (500 MHz, $CDCl_3$): 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); ^{13}C NMR (125 MHz, $CDCl_3$): 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′(1′*H*,3′*H*,11′*H*)-pentaone (3a): Yield: 0.361 g (91%); red powder; mp 212–215 °C (dec.); IR (KBr): 3249, 2917, 1710, 1690, 1666 cm^{-1}; ^{1}H NMR (500 MHz, D_2O): 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); ^{13}C NMR (125 MHz, D_2O): δ = 209, 187, 173, 170, 165, 162, 141, 138, 137, 136, 131, 130, 122, 119, 119, 100, 92, 56; Anal. Calcd for $C_{22}H_{11}N_3O_5$: C, 66.50; H, 2.79; N, 10.58. Found: C, 65.90; H, 2.81; N, 10.61; HRMS: *m*/*z* [M+H]$^+$ calcd. for $C_{22}H_{11}N_3O_5$: 398.0777; found: 398.0775.