



## Selective reduction of carbonyl groups in the presence of low-valent titanium reagents



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### ABSTRACT

The chemoselective reduction of several structurally diverse compounds containing carbonyl groups was achieved in the presence of low-valent titanium reagents. This novel synthetic method provides easy access to highly selective reduction of carbonyl groups, and possesses several advantages including one-step procedure, convenient manipulation, good to excellent yields, and short reaction times.

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### Introduction

The selective reduction of functional groups is one of the most important and basic chemical transformations in organic chemistry.<sup>1</sup> The catalytic reduction of carbonyl groups is used to synthesize biologically active compounds, for instance, cyclic amide derivatives, which have good antifungal, antidepressant, and antitubercular activities.<sup>2</sup> The selective reduction of carbonyl groups is an important transformation in chemistry and represents a challenge in both chemical and pharmaceutical industries.

The use of metal hydrides or H<sub>2</sub> with metal catalysts has been widely used in the reduction of carbonyl groups.<sup>3</sup> Numerous methods have been described in recent reports dealing with this type of reduction, using various metal catalysts such as Au,<sup>4</sup> Fe,<sup>5</sup> Ir,<sup>6</sup> Pt<sup>7</sup> or Rh.<sup>8</sup> However, the high costs and limited availabilities of these metals have led researchers to look for inexpensive, easily available, and environmental friendly alternatives. Sodium borohydride (NaBH<sub>4</sub>) has been used for carbonyl reduction under metal- and solvent-free conditions.<sup>9,10</sup> However, this method is suffering from long reaction times and lack of chemoselectivity.<sup>9</sup> Solid acids in combination with NaBH<sub>4</sub> could improve both the reaction rate and chemoselectivity.<sup>10</sup> It can be seen that the selective reduction of carbonyl groups in the presence of other reducible functionalities in a molecule remains a challenge.

The indolin-2-one ring is one of the fundamental heterocycles, widely distributed in a variety of natural and biologically

important molecules.<sup>11</sup> Therefore, several methods for the synthesis of substituted indolin-2-ones have been described,<sup>12</sup> including Wolff–Kishner–Huang method.<sup>13</sup> Recently, some improved methods have been reported,<sup>14</sup> although they remain unsatisfactory with respect to ease of operation, high yield, reasonable reaction time, and general applicability. Thus, there is a need for the development of concise and efficient method for the synthesis of this heterocyclic skeleton.

Low-valent titanium reagents could efficiently promote reductive coupling of carbonyl compounds.<sup>15</sup> There are increased interests of this reagents, and many other functional groups can also be coupled.<sup>16</sup> Recently, we have reported the cyclodimerization of  $\alpha,\beta$ -unsaturated ketones and  $\alpha,\beta$ -unsaturated nitriles promoted by this reagent and yielded functionalized cyclopentanes<sup>17</sup> and cyclopentenes,<sup>18</sup> respectively. It is well known that the carbonyl group can easily be reduced by low-valent titanium reagent to afford only reductive coupling products. However, few literatures report the selective reduction of carbonyl groups promoted by low-valent titanium reagents. As a part of our ongoing research on the synthesis of heterocyclic compounds using low-valent titanium reagents,<sup>19</sup> we report our preliminary results on the chemoselective reduction of the carbonyl group of isatin and several structurally diverse compounds with low-valent titanium reagents.

### Results and discussion

In our preliminary evaluation of the transformation, the reductive reaction of **1a** was evaluated under various conditions and summarized in Table 1. We examined the effects of different low-valent titanium systems. The target compound **2a** was not

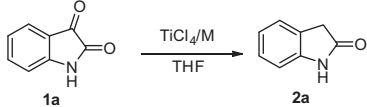
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observed with  $\text{TiCl}_4/\text{Fe}$  (Table 1, entry 1), while it was obtained in 55% yield in the presence of  $\text{TiCl}_4/\text{Al}$  (Table 1, entry 2). We then found that  $\text{TiCl}_4/\text{Zn}$  system gave the best results for the synthesis of **2a** (89% yield, Table 1, entry 3). To further optimize the reaction conditions, similar experiments were carried out using different ratios of **1a** to  $\text{TiCl}_4$  from 1:2 to 1:5. The yield of product **2a** increased as the ratio was increased from 1:2 to 1:3 (Table 1, entries 6 and 3). However, further increases in the ratio to 1:4 and 1:5 failed to improve the yield of product **2a** (Table 1, entries 7 and 8). We also examined the effect of the temperature (Table 1, entries 3 and 9–11), and the highest yield was obtained at room temperature.

Under the optimized conditions, we found that the method was applicable to a broad substrate scope bearing 4-, 5-, 6-, 7-, 4,7-di, 5,6-di and 5,7-disubstitution (Table 2). This method could be applied to isatins with electron deficient groups or electron-rich group. Leading the final products in up to 94% yield. N-substituted isatins were examined under the same conditions. The corresponding 1-(2-hydroxy-1*H*-indol-1-yl)ethanone derivatives **4** were

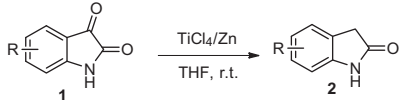
**Table 1**  
Optimization of reductive reaction



Entry	$\text{TiCl}_4/\text{M}$	Ratio <sup>a</sup>	Temp (°C)	Time (min)	Isolated yield (%)
1	Fe	1:3	rt	60	Trace
2	Al	1:3	rt	65	55
3	Zn	1:3	rt	30	89
4	Mg	1:3	rt	60	Trace
5	Sm	1:3	rt	60	42
6	Zn	1:2	rt	30	79
7	Zn	1:4	rt	30	87
8	Zn	1:5	rt	30	60
9	Zn	1:3	40	30	62
10	Zn	1:3	60	30	55
11	Zn	1:3	Reflux	30	42

<sup>a</sup> Ratio of **1a** and low-valent titanium reagent.

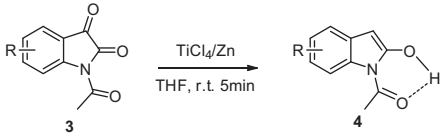
**Table 2**  
Reduction of isatins<sup>20</sup>



Entry	Product	R	Time (min)	Isolated yield (%)
1	<b>2a</b>	H	5	94
2	<b>2b</b>	4-Cl	5	91
3	<b>2c</b>	4-Br	5	93
4	<b>2d</b>	5-Br	6	88
5	<b>2e</b>	5-Cl	5	90
6	<b>2f</b>	5-F	6	87
7	<b>2g</b>	5-CH <sub>3</sub>	10	85
8	<b>2h</b>	6-Br	5	90
9	<b>2i</b>	6-Cl	5	88
10	<b>2j</b>	5,6-F <sub>2</sub>	5	89
11	<b>2k</b>	7-CF <sub>3</sub>	5	90
12	<b>2l</b>	7-Br	5	92
13	<b>2m</b>	4,7-Cl <sub>2</sub>	5	89
14	<b>2n</b>	5-Cl-7-CH <sub>3</sub>	5	86

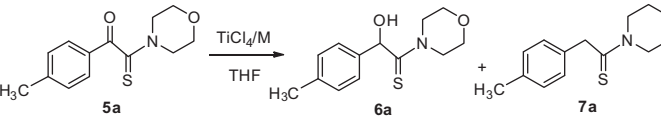
obtained in good yields (Table 3), as a result of hydrogen bonds in 1-(2-hydroxy-1*H*-indol-1-yl) ethanon.

**Table 3**  
Reduction of 1-acetylisatins<sup>20</sup>



Entry	Products	R	Isolated yield (%)
1	<b>4a</b>	H	94
2	<b>4b</b>	5-Cl	91
3	<b>4c</b>	5-F	86

**Table 4**  
Optimization of conditions for selective reduction of 2-carbonylthioacetamides

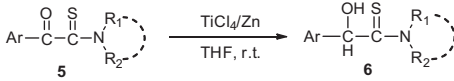


Entry	$\text{TiCl}_4/\text{M}$	Ratio <sup>a</sup>	Temp. (°C)	Time (min)	Yield <sup>b</sup> (%)	
					<b>6a</b>	<b>7a</b>
1	Fe	1:3	rt	20	46	12
2	Al	1:3	rt	15	55	9
3	Zn	1:3	rt	5	91	4
4	Mg	1:3	rt	25	65	11
5	Sm	1:3	rt	30	42	8
6	Zn	1:4	rt	5	87	5
7	Zn	1:2	rt	5	75	4
8	Zn	1:3	40	30	55	24
9	Zn	1:3	60	30	15	62
10	Zn	1:3	Reflux	30	0	88

<sup>a</sup> Ratio of **5a** and low-valent Ti reagent.

<sup>b</sup> The yields were determined by HPLC-MS.

**Table 5**  
Synthesis of 2-hydroxythioacetamide derivatives **6**<sup>21</sup>



Entry	Product	Ar	R <sub>1</sub>	R <sub>2</sub>	Time (min)	Isolated yield (%)
1	<b>6a</b>	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	CH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> CH <sub>2</sub>		5	91
2	<b>6b</b>	4-BrC <sub>6</sub> H <sub>4</sub>	CH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> CH <sub>2</sub>		5	89
3	<b>6c</b>	4-ClC <sub>6</sub> H <sub>4</sub>	CH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> CH <sub>2</sub>		5	85
4	<b>6d</b>	2-ClC <sub>6</sub> H <sub>4</sub>	CH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> CH <sub>2</sub>		5	82
5	<b>6e</b>	4-CO <sub>2</sub> CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	CH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> CH <sub>2</sub>		8	90
6	<b>6f</b>	Naphth-1-yl	CH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> CH <sub>2</sub>		8	89
7	<b>6g</b>	Naphth-2-yl	CH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> CH <sub>2</sub>		10	87
8	<b>6h</b>	Furan-2-yl	CH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> CH <sub>2</sub>		10	85
9	<b>6i</b>	Thiophene-2-yl	CH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> CH <sub>2</sub>		10	86
10	<b>6j</b>	4-ClC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	CH <sub>3</sub>	6	79
11	<b>6k</b>	2-ClC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	CH <sub>3</sub>	8	78
12	<b>6l</b>	Naphth-1-yl	CH <sub>3</sub>	CH <sub>3</sub>	8	84
13	<b>6m</b>	C <sub>6</sub> H <sub>5</sub>	4-CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	H	8	87
14	<b>6n</b>	C <sub>6</sub> H <sub>5</sub>	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>5</sub>	H	8	90

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