



# Reductive coupling of isatins with ketones and aldehydes by low-valent titanium



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## ABSTRACT

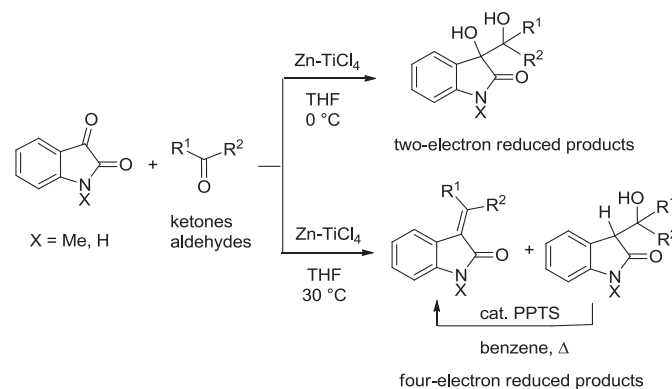
The reductive coupling of isatins with ketones and aldehydes by Zn–TiCl<sub>4</sub> in THF gave two- and four-electron reduced products, 3-hydroxy-3-(1-hydroxyalkyl)oxindoles and 3-alkylideneoxindoles, selectively by controlling the reaction conditions. Although the 3-(1-hydroxyalkyl)oxindoles were also produced as the four-electron reduced products in some cases, these products were readily dehydrated to 3-alkylideneoxindoles. The 3-alkylideneoxindoles derived from aldehydes were formed as mixtures of geometric isomers. The both geometric isomers were isomerized to the equilibrium mixtures by reflux in cat. PPTS/benzene.

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## 1. Introduction

Recently the synthesis and reaction of 3-alkylideneoxindoles attract much attention, since this type of compound exists in a number of biologically important compounds and is a useful precursor for the synthesis of other types of oxindoles.<sup>1–3</sup> Although many methods have been reported to date for the synthesis of 3-alkylideneoxindoles,<sup>1a,2</sup> the use of the reductive cross-coupling of isatins with carbonyl compounds is unprecedented for this purpose. Reductive coupling with low-valent titanium has been well known as a powerful tool for the reductive cross-coupling between two different carbonyl compounds because of its versatility, convenience, and economical efficiency.<sup>4,5</sup> In the course of our recent study on the reductive cross-coupling with low-valent titanium,<sup>6</sup> we report in this paper the reductive coupling of isatins with ketones and aldehydes by low-valent titanium generated from Zn–TiCl<sub>4</sub> (Scheme 1). We found that two- and four-electron reduced products, 3-hydroxy-3-(1-hydroxyalkyl)oxindoles and 3-alkylideneoxindoles, could be prepared selectively by controlling the reaction conditions. In some cases, the four-electron reduced products were obtained as mixtures of two products, 3-alkylideneoxindoles and 3-(1-hydroxyalkyl)oxindoles. However, the latter products were easily transformed to the former by reflux in cat. PPTS/benzene. Therefore, the reductive coupling of isatins with carbonyl compounds provides new synthetic method for

already known 3-alkylideneoxindoles and hitherto unknown 3-hydroxy-3-(1-hydroxyalkyl)oxindoles, which are promising precursors of other oxindole heterocycles.



Scheme 1. Reductive coupling of isatins with ketones and aldehyde by Zn–TiCl<sub>4</sub>.

## 2. Results and discussion

### 2.1. Reductive coupling of isatins with ketones by Zn–TiCl<sub>4</sub>

The reaction conditions of the cross-coupling were scrutinized using *N*-methylisatin (**1a**) and acetone (**2a**) as the substrates and

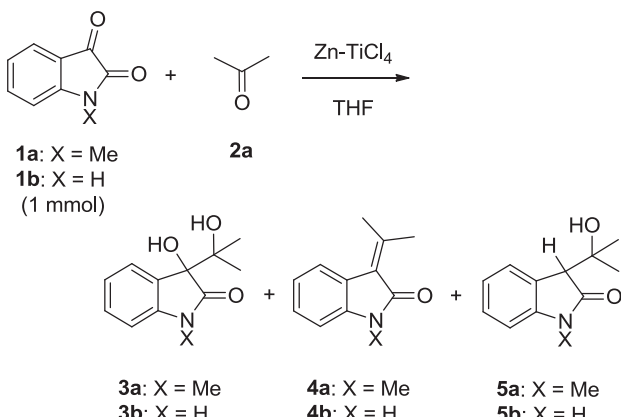
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the results are summarized in Table 1. The molar ratio of Zn/TiCl<sub>4</sub> was fixed to 2/1. Initially, the reaction was carried out with the molar ratio of **1a**/TiCl<sub>4</sub> as 1/1 (condition a) in THF at 0 °C for 1 h with varying the molar ratio of **1a**/**2a** from 1/1 to 1/5 (runs 1–4). In these cases, 3-hydroxy-3-(2-hydroxypropan-2-yl)-1-methylindolin-2-one (**3a**) was obtained in 64–74% yields as the two-electron reduced product together with small amounts of the four-electron reduced products, 1-methyl-3-(propan-2-ylidene)indolin-2-one (**4a**) and 3-(2-hydroxypropan-2-yl)-1-methylindolin-2-one (**5a**). With the ratio of **1a**/**2a** as 1/5 (run 4), **3a** was obtained as the sole product, although the yield was somewhat lowered (64%) and **1a** was recovered (15%). Therefore, the molar ratio of **1a**/TiCl<sub>4</sub> was increased to 1/2 (condition b) to complete the reaction (run 5). This attempt increased the yield of **3a** (71%) and, however, brought about the production of small amounts of **4a** (10%) and **5a** (5%). Consequently, the best yield of **3a** (74%) was obtained with the 1/2 ratio of **1a**/**2a** (run 2). Next, the reaction was performed with the ratio of **1a**/**2a**/Zn/TiCl<sub>4</sub> as 1/2/4/2 (condition b) in THF at 0 °C, 20 °C and 30 °C for 2 h (runs 6–8). From the result in run 6, it found that the further reduction to **4a** and **5a** proceeded considerably even at 0 °C under condition b. Four-electron reduced product **4a** was formed at 30 °C in 70% yield together with **5a** (17%), and **3a** was not obtained (run 8). It was found that dehydration of **5a** gave **4a** quantitatively (vide infra). Therefore, crude product mixture obtained from run 8 was refluxed in cat. PPTS/benzene for 1 h (condition c). Expectedly, **4a** was formed as the sole product in 87% yield (run 9). When isatin (**1b**) was employed in place of **1a**, **3b** (80%) and **4b** (89%) were produced under the same conditions as runs 2 and 9, respectively (runs 10 and 12).

Next, the reductive coupling of **1a,b** with aliphatic cyclic ketones **2b–e** was carried out under the same conditions as runs 2, 7 and 8 (conditions a, b and c) in Table 1 (Table 2). In most cases, 3-hydroxy-

3-(1-hydroxyalkyl)oxindoles **3** were produced selectively in good yields under the condition a. However, the reaction of **1a** with cycloheptanone (**2d**) brought about **3e** in a low yield (38%) probably due to the low reactivity of **2d** at 0 °C (run 6). Especially in the reaction of **1b** with **2d** (run 15), no cross-coupled product could be detected. In these cases, the major products were 3-hydroxyindolin-2-ones **6a,b**. The products **3f** and **3j** were obtained from 4-*t*-butylcyclohexanone (**2e**) as the single diastereomers (runs 8 and 17) and their stereo structures were confirmed to be *cis* by X-ray crystallography (Fig. 1). These results show that the less-hindered equatorial attack of **1a,b** to **2e** proceeded predominantly. In almost all cases, 3-alkylideneoxindoles **4** were formed selectively in good to moderate yields under the condition c. Even in the reactions with **2d** (runs 7 and 16), **4e** and **4i** were formed in moderate yields (41% and 64%). In these cases, the major by-products were indolin-2-ones **7a,b**. These results show that the cross-coupling of **1a,b** with **2d** proceeded at 30 °C (condition b). Incidentally, the reduction of **1a,b** in the absence of **2** under the conditions a and b gave the corresponding two- and four-electron reduced products, **6a,b** and **7a,b**, as shown in Scheme 2.<sup>7</sup> In addition, the reduction of **1a** with benzophenone or acetophenone also gave **6a** and **7a**, and the corresponding cross-coupling products could not be obtained.

**Table 1**  
Reductive coupling of **1a,b** with acetone by Zn–TiCl<sub>4</sub>

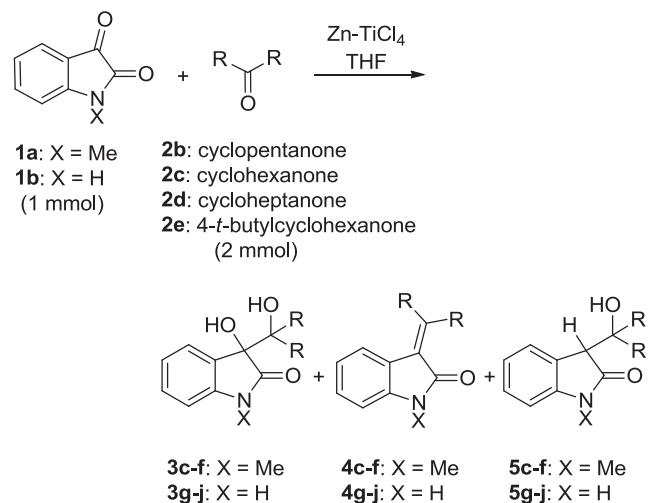


Run	1	2a (mmol)	Condition <sup>a</sup>	Temp (°C)	% Yield <sup>b</sup>			
					3	4	5	
1	1a	1	a	0	a	65	6	—
2	1a	2	a	0	a	74	5	4
3	1a	3	a	0	a	70	6	—
4	1a	5	a	0	a	64	—	—
5	1a	5	b	0	a	71	10	5
6	1a	2	b	0	a	41	37	8
7	1a	2	b	20	a	10	60	21
8	1a	2	b	30	a	—	70	17
9	1a	2	c	30	a	—	87	—
10	1b	2	a	0	b	80	—	—
11	1b	2	b	30	b	—	68	14
12	1b	2	c	30	b	—	89	—

<sup>a</sup> a: **1**/Zn/TiCl<sub>4</sub>=1/2/1, 1 h. b: **1**/Zn/TiCl<sub>4</sub>=1/4/2, 2 h. c: crude product mixture obtained by condition b was refluxed in cat. PPTS/benzene for 1 h.

<sup>b</sup> Isolated yields.

**Table 2**  
Reductive coupling of **1a,b** with **2b–e** by Zn–TiCl<sub>4</sub>



Run	1	2	Condition <sup>a</sup>	% Yield <sup>b</sup>			
				3	4	5	
1	1a	2b	a	c	74	6	5
2	1a	2b	b	c	—	56	34
3	1a	2b	c	c	—	85	—
4	1a	2c	a	d	82	—	—
5	1a	2c	c	d	—	77	—
6	1a	2d	a	e	38	7	—
7	1a	2d	c	e	—	41	—
8	1a	2e	a	f	75	—	—
9	1a	2e	c	f	—	72	—
10	1b	2b	a	g	79	8	4
11	1b	2b	b	g	—	71	22
12	1b	2b	c	g	—	92	—
13	1b	2c	a	h	72	—	—
14	1b	2c	c	h	—	66	—
15	1b	2d	a	i	ND <sup>c</sup>	—	—
16	1b	2d	c	i	—	64	—
17	1b	2e	a	j	64	—	—
18	1b	2e	c	j	—	61	—

<sup>a</sup> a: **1**/Zn/TiCl<sub>4</sub>=1/2/1, 0 °C, 1 h. b: **1**/Zn/TiCl<sub>4</sub>=1/4/2, 30 °C, 2 h. c: crude product mixture obtained by condition b was refluxed in cat. PPTS/benzene for 1 h.

<sup>b</sup> Isolated yields.

<sup>c</sup> Not detected.

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