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# Molecular iodine catalyzed transfer hydrogenation: reduction of aldimines, ketimines, and $\alpha$ -imino esters



Department of Chemistry, Gakushuin University, 1-5-1 Mejiro, Toshima-ku, Tokyo 171-8588, Japan

#### ARTICLE INFO

### ABSTRACT

the corresponding amines in excellent yields.

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Amines and their derivatives are of central importance in many aspects, such as constitutional chemotypes and underlying structural motifs in agro-pharmaceutical, biological, and synthetic chemistry.<sup>1</sup> An interesting class of such compounds is the glycopeptides antibiotics,<sup>2a</sup> which are represented by aryl glycines. Examples of biologically active compounds synthesized using aryl glycines as building blocks include amoxicillins,<sup>2b</sup> nocardicins,<sup>2c</sup> cephalecins,<sup>2d</sup> galipinine,<sup>2e</sup> and cuspareine.<sup>2f</sup> The synthesis of amines and their derivatives, thus, is an active field in modern organic synthesis. The most direct approach for the synthesis of amines is the reduction of C=N bonds, such as ketimines and  $\alpha$ -imino esters, by means of metal-catalyzed hydrogenation<sup>3</sup> or hydrosilylation.<sup>4</sup>



Scheme 1. Reduction of aldimines, ketimines and α-imino esters.

The transfer hydrogenation using hydrogen donors offers advantages over the hydrogenation using molecular hydrogen: it can be performed under safe and mild conditions in many cases,

#### Table 1

Optimization of the reaction conditions<sup>a</sup>

An efficient and practical protocol for the reduction of aldimines, ketimines, and  $\alpha$ -imino esters in the

presence of catalytic amount of molecular iodine with Hantzsch ester at ambient temperature afforded



Entry	Solvent	I <sub>2</sub> (mol %)	Yield <sup>b</sup> (%)
1	Dichloromethane	2	80
2	Dichloromethane	5	98
3	Dichloromethane	10	76
4	Acetonitrile	5	69
5	Tetrahydrofuran	5	85
6	Toluene	5	71
7	Ethyl acetate	5	67

<sup>a</sup> All the reactions were performed using aldehyde (0.10 mmol), amine (0.11 mmol), Hantzsch ester (0.12 mmol) and iodine (0.005 mmol) in solvent C = 0.1 M. <sup>b</sup> Isolated yield.





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<sup>\*</sup> Corresponding author. Tel.: +81 3 3986 0221; fax: +81 3 5992 1029. E-mail address: takahiko.akiyama@gakushuin.ac.jp (T. Akiyama).

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**Table 2** Molecular iodine catalyzed reduction of aldimines<sup>a,b</sup>

<sup>a</sup> All the reactions were performed using aldehyde (0.10 mmol), amine (0.11 mmol), Hantzsch

ester (0.12 mmol) and iodine (0.01 mmol) in solvent C = 0.1 M.

<sup>b</sup> Isolated yield.

and has been applied to the reduction of imines,  $\alpha$ -imino esters, and quinolines by means of organocatalysts such as Hantzsch ester<sup>5,6</sup> and benzothiazoline.<sup>7</sup>

Recently, molecular iodine has attracted much attention as a catalyst for organic transformations because it is inexpensive, nonmetallic, and readily available.<sup>8,9</sup> The usefulness of molecular iodine is as a mild Lewis acid. Due to the mild Lewis acid character, Mannich-type reaction,<sup>10a</sup> allylation reaction of allylsilane to aldehyde,<sup>10b</sup> and aldimine,<sup>10c</sup> and Michael reaction<sup>10d</sup> were successfully achieved by means of iodine. The iodine catalyzed reduction of imines, ketimines, and  $\alpha$ -imino esters via transfer hydrogenation, however, has not been examined so far to the best of our knowledge.

We wish to report herein an efficient and flexible protocol for the reduction of aldimines, ketimines, and  $\alpha$ -imino esters. This mild and neutral reaction is mediated by a catalytic amount of molecular iodine and Hantzsch ester as the hydrogen source (Scheme 1).

To this end, we set out to perform short screening for the reaction conditions. As the model reaction, 4-nitrobenzaldehyde 4, aniline 5, and Hantzsch ester 2 (1.2 equiv) were treated with a catalytic amount of iodine in dichloromethane at room temperature (Table 1). An optimum catalytic amount of 5% mol  $I_2$  afforded the desired product in excellent yields. Further studies established that  $CH_2CI_2$  is the solvent of choice.

With the optimized reaction conditions in hand, we then evaluated the scope of the reaction using a series of amines and aldehydes. All the substrates smoothly reacted to give the corresponding secondary amines in excellent yields (Table 2). Aromatic amines, including PMP (*p*-methoxyphenyl) amines containing both electron-donating as well as electron-withdrawing groups, were well tolerated (entries 1–4). The steric and electronic properties of aromatic aldehydes had no apparent influence on the yields. Heteroaromatic and aliphatic aldehydes also afforded the desired amines efficiently (entries 10–12).

Next, we examined the generality of this protocol for the reduction of ketimines derived from acetophenone derivatives (Table 3). After the optimal reaction conditions were established, namely, 10% catalyst loading, room temperature, and use of dichloromethane as solvent, the substrate generality was probed using a range of ketimines. As illustrated in Table 3, electron-deficient and electron-rich aromatic *N*-phenyl ketimines underwent facile reduction



 Table 3

 Molecular iodine catalyzed reduction of ketimines<sup>a,b</sup>

<sup>a</sup> All the reactions were performed using ketimine (0.10 mmol), Hantzsch ester (0.12 mmol) and iodine (0.005 mmol) in solvent C = 0.1 M.

<sup>b</sup> Isolated yield.

to yield the desired products in high yields (entries 3–7). Gratifyingly, ketimines bearing a relatively bulky R group, such as naphthyl and indanyl groups, were well tolerated (entries 8 and 9). An aldimine derived from acetophenone and benzylamine did not give the reduction product. Hence, use of *N*-aryl imine is essential.<sup>11</sup>

To further demonstrate the applicability and chemoselectivity of this iodine catalyzed transfer hydrogenation method, we next investigated the reduction of  $\alpha$ -imino esters.  $\alpha$ -Imino ester 15 underwent reduction under the influence of 5% of I2 in the coexistence of 1.2 equiv of Hantzsch ester at room temperature in dichloromethane for 24 h to give corresponding  $\alpha$ -amino ester **12b** in 87% yield. A range of substituted imino esters were successfully reduced with remarkably high yields (Table 4). Aryl substrates next to the imine carbon, having either electron-withdrawing or electron-donating functional group, were competent substrates (entries 5, 7-10). On the other hand, replacing the PMP group on the imine nitrogen with phenyl or other substituted arenes has rather less significant impact on the yields of the products (entries 3 and 4). In the presence of aliphatic substituent, the reaction rate was slightly reduced although the desired product was also obtained in good isolated yields (entry 11).

1,2,3,4-Tetrahydroquinolines are of great synthetic importance in pharmaceuticals, agrochemicals, and natural products, particularly in alkaloids as key structures.<sup>1d</sup> The regioselective reduction of readily available quinoline derivatives is the most sought after method to prepare these biologically important compounds.<sup>5d</sup> We therefore evaluated the utility of the iodine-catalyzed transfer hydrogenation of quinoline **13**, in view of the possibility of extending this method to the synthesis of tetrahydroquinolines. To our delight, desired tetrahydroquinoline **14** was obtained in 97% yield using 10 mol % of iodine and 2.1 equiv of Hantzsch ester **2** as the hydrogen source after 24 h at room temperature (Scheme 2).

It should be noted that the present reduction of ketimines,  $\alpha$ imino esters, and quinoline proceeded smoothly at room temperature, in contrast to some of the previous reported reactions that required a higher temperature.<sup>6</sup>

In order to exclude the possibility that the present reaction was catalyzed by HI generated in situ,  $\alpha$ -imino ester **15** was treated with iodine (5 mol %), sodium hydrogen carbonate (20 mol %), and Hantzsch ester **2** (1.2 equiv) in dichloromethane at room temperature under the optimized conditions. The reaction afforded  $\alpha$ -amino ester **12b** in 76% yield, as expected (Scheme 3). This reaction further underscored the potential of the proposed activation of imine in the presence of molecular iodine as a mild Lewis acid, followed by hydrogen transfer from Hantzsch ester **2** to result in desired amine **12b**.

In conclusion, we have developed an efficient and practical protocol for the reduction of aldimines, ketimines, and  $\alpha$ -imino esters in the presence of the catalytic amount of molecular iodine using transfer hydrogenation at room temperature. This method is equally effective for both cyclic and acyclic substrates. The simple



Table 4 Molecular iodine catalyzed reduction of  $\alpha$ -imines esters<sup>a,b</sup>

<sup>a</sup> All the reactions were performed using  $\alpha$ -imino ester (0.10 mmol), Hantzsch ester (0.12 mmol) and iodine (0.005 mmol) in solvent *C* = 0.1 M.

<sup>b</sup> Isolated yield.

operation procedure, mild reaction conditions, use of an easily available catalyst, impressive yields, and short reaction times are the notable offered by this method.



Scheme 2. Molecular iodine catalyzed reduction of quinoline.



Scheme 3. Molecular iodine catalyzed reduction of α-imino ester 15.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.05. 071.

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