## Molecular Iodine-Catalyzed Imine Activation for Three-Component Nucleophilic Addition Reactions

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**Abstract:**  $\beta$ -Amino ketones and  $\alpha$ -amino nitriles were synthesized from silyl enol ethers and trimethylsilyl cyanides, via a three-component nucleophilic addition reaction with aromatic aldehydes and amines; the reaction was found to be significantly accelerated by molecular iodine under neutral conditions.

**Key words:** molecular iodine, imine activation, three-component reaction, Mannich-type reaction, Strecker-type reaction

Imines are useful intermediates for carbon-carbon bond forming reactions such as nucleophilic addition and imino Diels-Alder reactions. Various nucleophiles have been used with imines to synthesize several useful compounds, such as  $\beta$ -amino ketones and  $\alpha$ -amino nitriles in the presence of Lewis acids.<sup>1</sup> Many of these nitrogen-containing products are not only biologically active but also are of interest within the medicinal community and natural products research.<sup>2</sup> Several Lewis acids in stoichiometric amounts have been found to activate imines towards nucleophilic attack, however, the imine reactants and their corresponding amino products may also act as a Lewis base, resulting in the deactivation of these Lewis acids.<sup>1c</sup> Therefore, typical Lewis acids (such as TiCl<sub>4</sub> and BF<sub>3</sub>·OEt<sub>2</sub>) are required in excess to complete the reaction.<sup>3</sup> In contrast, rare-earth metal triflates can be used in catalytic amounts to activate imines, owing to their stability toward most polar functional groups including Lewis bases such as imines and amines.<sup>4</sup>

In recent years, iodine has emerged as a very effective Lewis acid catalyst for various organic transformations.<sup>5</sup> Iodine is relatively inexpensive compared to other Lewis acids including rare earth metal triflates, and is more tolerant in comparison to typical Lewis acids/bases. Iodine catalysis can also be easily adapted to commercial applications, since its handling does not require special precautions and it is readily reduced to relatively nontoxic iodide during work-up procedures.

While studying ionic polymer-supported Yb(OTf)<sub>3</sub> catalysts for  $\beta$ -amino ketones synthesis,<sup>6</sup> we discovered that iodine containing ionic polymers promoted the reaction by releasing molecular iodine. We decided to explore this phenomenon, and herein, we report the application of cat-

SYNLETT 2005, No. 8, pp 1325–1327 Advanced online publication: 25.04.2005 DOI: 10.1055/s-2005-868487; Art ID: S01705ST © Georg Thieme Verlag Stuttgart · New York alytic molecular iodine in imine activation reactions such as Mannich<sup>1a</sup> and Strecker<sup>1b</sup> for  $\beta$ -amino ketone and  $\alpha$ -amino nitrile synthesis under neutral conditions.

Initially, we tested a two-component reaction of *N*-benzylideneaniline (1) with nucleophiles such as silyl enol ether **2** and trimethylsilyl cyanide (Scheme 1) in the presence of 10 mol% of iodine. Gratifyingly, the  $\beta$ -amino ketone **3** and  $\alpha$ -amino nitrile **4** were readily synthesized in acetonitrile. A more simplified procedure was next identified, wherein benzaldehyde and aniline were used for in situ generation of the imine, reaction with a nucleophile (as exemplified by silyl enol ether **2** and trimethylsilyl cyanide) in the presence of a catalytic amount of iodine resulting in the formation of  $\beta$ -amino ketone **3** and  $\alpha$ -amino nitrile **4**, respectively.



Scheme 1 Iodine-catalyzed two-component reactions

To optimize yields of this multi-component reaction we examined the synthesis of  $\beta$ -amino ketone **5** from 1-naph-thaldehyde, aniline and 1-phenyl-1-trimethylsiloxyethylene (**2**, Table 1) in five organic solvents. Since  $\beta$ -amino ketone **3** obtained from benzaldehyde precipitated during the reaction, we chose the reaction of 1-naphthaldehyde for this study. The reaction with 1-naphthaldehyde is homogeneous and therefore was easy to monitor. Polar solvents were shown to be superior for this reaction and on the basis of HPLC and TLC analysis; the rate of imine formation in methanol was determined to be faster than in acetonitrile or nitromethane. Furthermore, decomposition of **2** to acetophenone was accelerated in acetonitrile and nitromethane compared to methanol; based on this finding methanol was chosen as the best solvent.

Next, we examined the catalytic requirement of iodine for the reaction in methanol (Figure 1). Gratifyingly, 2 mol% iodine was found to be sufficient for catalysis of  $\beta$ -amino ketone synthesis (Table 2). Figure 1 also provides evidence that there is no deactivation or inhibition of iodine catalyst, which is of interest considering that the reactants and/or the amine product might act as a Lewis base.

**Table 1** Three-Component  $\beta$ -Amino Ketone Synthesis and<br/>Conversion (%) in Various Solvents<sup>a</sup>

CHO + PhNH <sub>2</sub>	OTMS + Ph 2	I2 (2 mol%) solvent r.t., 2 h		
Entry	Solvent	Conversion (%)		
1	$CH_2Cl_2$	42		
2	THF	0		
3	MeCN	86		
4	MeNO <sub>2</sub>	55		
5	MeOH	90		



The optimized reaction conditions were used to test a series of three-component reactions for  $\beta$ -amino ketone synthesis. These results are summarized in Table 2. Nine aldehydes and three amines were used for in situ generation of imines, and four silyl enol ethers were used as nucleophiles. All reactions were completed within three hours at room temperature, and corresponding products

Table 2	Iodine-Catalyzed	Three-Component	3-Amino Ketone	Synthesis <sup>7,a</sup>
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R <sup>1</sup> - CHO H	+		+	silvl enol ethers	I <sub>2</sub> (2 mol%)	R <sup>2</sup> , NH
IN ONO		IX INIT2	·		MeOH	
					r +	K K

		1.1.				
Entry	$\mathbb{R}^1$	$\mathbb{R}^2$	Silyl enol ether <sup>b</sup>	<b>R</b> <sup>3</sup>	Time (min)	Yield (%) <sup>c</sup>
1	Ph	Ph	<b>OTMS</b>	0	30	95
2	1-Naphthyl	Ph	$\wedge$	<u>ج</u> بل چ	180	98
3	2-Naphthyl	Ph		· ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~	30	92
4	1-Furan	Ph			60	81
5	4-Methoxyl-Ph	Ph			10	99
6	4-Cyano-Ph	Ph			120	89
7	4-Nitro-Ph	Ph			60	94
8	Ph	Ph	TMSO		30	100 (82:18) <sup>d</sup>
9	Ph	Ph	OTMS	rr rr	30	92 (66:34) <sup>d</sup>
10	Ph	Ph	OTMS		180	81 (37:63) <sup>d</sup>
11 12 13 14	Ph Ph Cyclohexyl Cyclohexyl	Bn <i>n-</i> Bu Ph Bn	OTMS	, start and the	180 180 180 180	0 0 0 0

<sup>a</sup> All reactions were carried out using aldehyde (1.0 mmol), aniline (1.1 mmol) and silyl enol ether (1.1 mmol).

<sup>b</sup> Same silyl enol ether was used in entries 1–7 and 11–14.

<sup>c</sup> Isolated yield.

<sup>d</sup> The number in parenthesis is the ratio of *syn/anti* diastereomers determined by <sup>1</sup>H NMR.



**Figure 1** Activity profile of three-component synthesis of **5** catalyzed by 1–10 mol% of iodine

were obtained in good to excellent yields from aromatic aldehydes and aniline. In some reactions (entries 1, 2, 5, 7 and 8), the resulting products precipitated during the course of the reaction. For entries 8, 9 and 10, the products were obtained as a mixture of *syn/anti* diastereomers. No reaction was observed with aliphatic amines or aldehydes (entries 11-14), we attribute this to the slow formation and unstable nature of the imine formed from either the aliphatic amine examined or the aldehyde.

We also investigated the iodine catalyst in a Strecker-type reaction of imine and cyanide for the production of  $\alpha$ -amino nitriles. This reaction, followed by hydrolysis of the nitrile to a carboxylic acid, is one of the more widely used synthetic routes to α-amino acids.<sup>1b</sup> When trimethylsilyl cyanide was used as a nucleophile instead of silvl enol ether under the same reaction conditions as used for  $\beta$ amino ketone synthesis (aldehyde and aniline), the corresponding  $\alpha$ -amino nitriles were obtained in excellent yields (Table 3). Similar to  $\beta$ -amino ketone synthesis, no reaction took place with aliphatic amines or aldehydes (entry 5-8).

Table 3 Iodine-Catalyzed Three-Component α-Amino Nitrile Synthesis7,a

R <sup>1</sup> -CHO	+ R <sup>2</sup> -NH <sub>2</sub> + TA		(2 mol%)	R <sup>2</sup> ,NH	
K -0110	· K -NH2 · IN		MeOH r.t.	R <sup>1</sup> C	N
Entry	$\mathbb{R}^1$	$\mathbb{R}^2$	Time	e (min)	Yield (%) <sup>b</sup>
1	Ph	Ph	90		97
2	1-Naphthyl	Ph	90		97
3	4-Methoxy-Ph	Ph	30		97
4	4-Cyano-Ph	Ph	60		98
5	Ph	Bn	180		0
6	Ph	<i>n</i> -Bu	180		0
7	Cyclohexyl	Ph	180		0
8	Cyclohexyl	Bn	180		0

<sup>a</sup> All reactions were carried out using aldehyde (1.0 mmol), aniline

(1.1 mmol) and trimethylsilyl cyanide (1.2 mmol).

<sup>b</sup> Isolated yield.

In conclusion, catalytic amounts of iodine were shown to effectively activate imine compounds to undergo Mannich and Strecker-type reactions under neutral conditions. Reactants and amine products did not interfere with the catalytic activity of iodine. We note that the reaction sequence has limitations as it only functions with aromatic aldehydes and amines. The use of iodine as a catalyst in these reactions is preferred to rare earth metal catalysts and typical Lewis acids, because iodine is not only inexpensive but also less sensitive to moisture.

Since iodine provides an easy method for imine activation, we expect that the use of catalytic molecular iodine can be extended to other reactions requiring imine activation.

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- (7) Typical Procedure for β-Amino Ketone and α-Amino Nitrile Synthesis.

To a MeOH solution (10 mL) was added aldehyde (1.0 mmol), aniline (1.1 mmol) and nucleophile (1.2 mmol, silyl enol ether for  $\beta$ -amino ketone or trimethylsilyl cyanide for  $\alpha$ amino nitrile). Upon completion of the reaction (monitored by TLC), aq Na<sub>2</sub>SO<sub>3</sub> (1 mL) and H<sub>2</sub>O (100 mL) were added. The organic compounds were extracted with EtOAc ( $3 \times 20$ mL) from the aqueous solution and the combined extract was dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford pure product, characterized by <sup>1</sup>H NMR, <sup>13</sup>C NMR and mass spectrometry.