

## Novel Syntheses of Symmetric Alkyl-substituted $\beta$ -Diketimines with Dimethylsulfate Assisted by Microwave

Saetbyeol Yoon, Byoungki Lee, EungJoon Lee, and Ik Mo Lee\*

Department of Chemistry, Inha University, Namku, Incheon 402-751, Korea. \*E-mail: imlee@inha.ac.kr  
Received May 24, 2013, Accepted July 2, 2013

We present an efficient and new preparative method for the symmetric  $\beta$ -diketimines assisted by microwave. A series of  $N,N'$ -symmetrically alkyl substituted  $\beta$ -diketimines have been synthesized from the reaction of  $O$ -acylation with dimethylsulfate. Higher reproducibility and yield, lower cost and much improved green nature originated from no solvent condition and higher energy efficiency due to faster reaction time are major merits of this new method. In addition to these merits, almost every kind of  $\beta$ -diketimines including alkyl-substituted  $\beta$ -diketimines little reported yet has been successfully prepared. Much wider applications of these compounds in various fields are expected.

**Key Words** : Alkyl-substituted  $\beta$ -diketimines, Dimethylsulfate, Microwave, Condensation reaction,  $\beta$ -Ketoimines

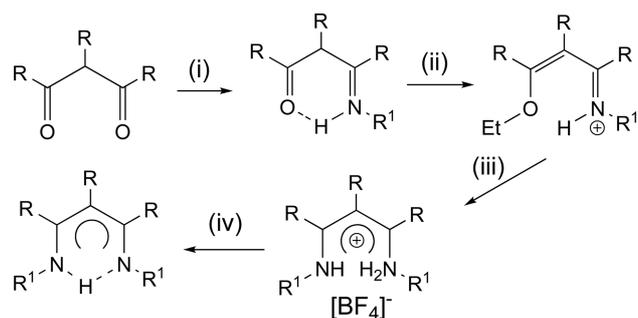
### Introduction

Despite of extensive use of  $\beta$ -diketonate and  $\beta$ -ketoiminate ligands in the coordination chemistry for a long time,<sup>1</sup> their closely related, isoelectronic and isostructural  $\beta$ -diketiminato ligands have received only recent attention and an extensive review<sup>2</sup> has been reported. These ligands are quite interesting in the scope of variation of the substituents on nitrogen, which modifies the steric and electronic effects on the metal center. Since the first synthesis of homoleptic  $M(II)$   $\beta$ -diketiminates ( $M=Co, Ni, Cu$ ) in late 60s,<sup>3</sup> possibility of  $\beta$ -diketiminates as spectator ligands like cyclopentadienyls and  $\beta$ -diketonates was recognized in mid 1990s mainly due to their strong metal-ligand bonds and tunable steric demands.

This feature has been exploited in the development of olefin polymerization catalysts. A Zr complex with a  $\beta$ -diketiminato was reported to show catalytic activity toward ethylene and propylene polymerization<sup>4</sup> and similar catalytic activities were found by Collins.<sup>5</sup> Other results are extensively reviewed in the literature<sup>6</sup> but  $\beta$ -diketiminates with only aryl substituents have been generally adopted.

Aryl-substituted  $\beta$ -diketimines can be easily obtained by simple condensation reaction between  $\beta$ -diketones and primary amines in the presence or absence of acids<sup>7</sup> but some modifications should be taken to avoid the reaction stopping after the first condensation, giving  $\beta$ -ketoimines<sup>8</sup> as shown in Scheme 1. Lithium  $\beta$ -diketiminates can be obtained by the reaction between  $LiCHR_2$  and  $R'CN$ <sup>4,9</sup> or  $R'NC$ <sup>10</sup> and other preparative methods for the  $\beta$ -diketimines are well summarized in the review.<sup>2</sup>

Recently, Schaper *et al.* reported high-yield, one-pot synthesis of alkyl-substituted  $\beta$ -diketimines by using azeotropic removal of water<sup>11</sup> but it requires long reaction time (generally over 18 h) and suffers low yields with bulky substituents. Bradley *et al.* searching for a safe, cost-effective, and amenable method to large scale production, consistent

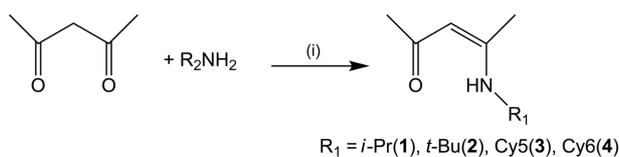


**Scheme 1.** Reagents and Condition: (i)  $NH_2R^1$ ; (ii)  $[Et_3O]BF_4$ ,  $Et_2O$ ,  $-78^\circ C$ ; (iii)  $NH_2R^1$ ,  $Et_2O$ ; (iv)  $NaOMe/MeOH$ .

with electronic grade materials, claimed a general preparative method of alkyl  $\beta$ -diketimines employing dimethyl sulfate with some merits such as no solvent, high yields, and scale up.<sup>12</sup> However, this method requires fractional distillation and still long reaction time (generally 12 h). Some alkyl  $\beta$ -diketimines such as methyl  $\beta$ -diketimine, not very stable at higher temperature, suffer low yields due to thermal decomposition during fractional distillation. Therefore general and convenient synthetic routes for various kinds of  $\beta$ -diketimines, especially with bulky alkyl substituents have not been established yet.

Meanwhile, it was found that  $\beta$ -ketoimines can be easily prepared by the condensation reaction between  $\beta$ -diketones and primary amines assisted by microwave<sup>13</sup> (Scheme 2). As reported, microwave heating has induced much success in organic reactions since the first recognition in the mid 1980s.<sup>14</sup> High yields, clean reactions due to employment of milder and less toxic reagents and solvents, and simple procedures make this technology to be regarded as one of the most important tools in the green organic synthesis.<sup>15</sup>

In order to extend the scope of this new preparative method, synthesis of  $\beta$ -diketimines by application of microwave has been investigated. It is known that  $\beta$ -diketimines with aryl



\*Cy5: Cyclopentyl, Cy6: Cyclohexyl

**Scheme 2.** Reagents and conditions: (i) microwave or RT stirring.

substituents can be prepared more easily than alkyl-substituted ones suffering very low yields with longer reaction time and this may be the reason for a limited application of these alkyl-substituted  $\beta$ -diketimines. Deprotonation of  $\beta$ -diketimines affords anionic bidentate ligands that form a variety of coordination compounds<sup>2</sup> and some derivatives with large substituents can be used to stabilize the main group and transition metal complexes with low oxidation states<sup>16</sup> even though only limited derivatives are available right now.

Herein we report a novel microwave-assisted preparative method of  $\beta$ -diketimines with alkyl substituents, especially bulky ones employing dimethyl sulfate as an alkylating agent assisted by microwave.

## Experimental Section

**General Methods.** All preparations were done without solvent but in some scale-up experiments, some solvent (benzene) was required for the prevention of burn-out. A reaction flask equipped with a condenser was placed in the microwave cavity (CEM Co., Discover). <sup>1</sup>H and <sup>13</sup>C NMR (Varian Unity Inova 400 (400 and 100 MHz, respectively)), and LC-Mass (Varian 1200L Quadruple LC/MS system) were used for the characterization of the prepared compounds (Conditions of LC/MS: Drying gas pressure = 20 psi, Total flow = 0.4 mL/min, nebulizer pressure = 51 psi, Drying gas temperature = 300 °C, fragmentor (capillary) voltage = 52 V).

### Preparation of $\beta$ -Ketoimine Ligands.

**CH<sub>3</sub>COCHC(NHCH(CH<sub>3</sub>)<sub>2</sub>)CH<sub>3</sub> (1):** Acetylacetone (5.00 g, 49.9 mmol) and isopropylamine (3.50 g, 59.9 mmol) was placed in a 100 mL round-bottom flask and the mixture was stirred at room temperature for 1 h. The starting material was evaporated under vacuum and yellow liquid was obtained (yield: 85.7%). <sup>1</sup>H NMR (400 MHz, in CDCl<sub>3</sub>)  $\delta$  1.21 (d,  $J = 6$  Hz, 6H, (CH(CH<sub>3</sub>)<sub>2</sub>)), 1.95, 2.05 (s, 6H, (CCH<sub>3</sub>)), 3.85 (hept.,  $J = 6$  Hz, 1H, NCH), 4.98 (s, 1H, CCH), 10.83 (s, 1H, NH). <sup>13</sup>C NMR (100 MHz, in CDCl<sub>3</sub>)  $\delta$  18.55, 23.78, 28.7, 44.58, 94.85, 161.78, 194.38. ESI-MS: Calcd 141.24 [M<sup>+</sup>], obsd 141.94 [M<sup>+</sup>].

**CH<sub>3</sub>COCHC(NHC(CH<sub>3</sub>)<sub>3</sub>)CH<sub>3</sub> (2):** Acetylacetone (5.00 g, 49.9 mmol) and *tert*-butylamine (4.40 g, 59.9 mmol) in 5 mL of ethanol was placed in a 100 mL round-bottom flask and the flask was sealed with a reflux condenser and placed into microwave cavity (CEM Co., Discover). When microwave was irradiated at a power of 150 W, the temperature was raised from room temperature to 130 °C. Once the predetermined temperature was reached, the reaction mixture was held at that temperature for 1 h. After cooling down to

room temperature, the starting material and solvent were evaporated under vacuum and brown liquid was obtained (yield: 68.5%). <sup>1</sup>H NMR (400 MHz, in CDCl<sub>3</sub>)  $\delta$  1.40 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 1.99, 2.06 (s, 6H, (CCH<sub>3</sub>)), 4.90 (s, 1H, CCH), 11.39 (s, 1H, NH). <sup>13</sup>C NMR (100 MHz, in CDCl<sub>3</sub>)  $\delta$  21, 29.3, 30.8, 52.3, 96.3, 161.8, 194. ESI-MS: Calcd 178.24 [M+Na]<sup>+</sup>, obsd 177.74 [M+Na]<sup>+</sup>.

**CH<sub>3</sub>COCHC(NHC(C<sub>5</sub>H<sub>9</sub>))CH<sub>3</sub> (3):** The same procedures as in compound 2. Dark yellow liquid (yield: 83.3%). <sup>1</sup>H NMR (400 MHz, in CDCl<sub>3</sub>)  $\delta$  1.48-1.80 (m, 8H, C<sub>5</sub>H<sub>8</sub>), 1.95, 1.90 (s, 6H, (CCH<sub>3</sub>)<sub>2</sub>), 3.90 (m, 1H, NCH(Cy5)), 4.95 (s, 1H, CCH), 11.0 (s, 1H, NH). <sup>13</sup>C NMR (100 MHz, in CDCl<sub>3</sub>)  $\delta$  18, 23.8, 28, 34.9, 54, 94.2, 161.8, 193.5. ESI-MS: Calcd 168.25 [M+H]<sup>+</sup>, obsd 167.85 [M+H]<sup>+</sup>.

**CH<sub>3</sub>COCHC(NH(C<sub>6</sub>H<sub>11</sub>))CH<sub>3</sub> (4):** The same procedures as in compound 1. Dark yellow liquid (Yield: 88.0%). <sup>1</sup>H NMR (400 MHz, in CDCl<sub>3</sub>)  $\delta$  1.20-1.92 (m, 10H, C<sub>6</sub>H<sub>10</sub>), 1.98, 1.95 (s, 6H, C(CH<sub>3</sub>)<sub>2</sub>), 3.39 (m, 1H, NCH(Cy6)), 4.95 (s, 1H, CCH), 10.90 (s, 1H, NH). <sup>13</sup>C NMR (100 MHz, in CDCl<sub>3</sub>)  $\delta$  18.3, 23.8, 24.5, 28, 33.7, 51, 94.5, 161.8, 193.6. ESI-MS: Calcd 181.27 [M<sup>+</sup>], obsd 181.75 [M<sup>+</sup>].

### Preparation of $\beta$ -Diketimine Ligands.

**CH<sub>3</sub>C(NCH(CH<sub>3</sub>)<sub>2</sub>)CHC(NHCH(CH<sub>3</sub>)<sub>2</sub>)CH<sub>3</sub> (1a):** In a 100 mL round-bottom flask,  $\beta$ -ketoimines (35.4 mmol) and dimethyl sulfate (35.4 mmol) were placed and the mixture was stirred for 5 min. The flask was equipped with a reflux condenser and placed into microwave cavity (CEM Co., Discover). When microwave was irradiated at a power of 100 W, the temperature was raised from room temperature to 100 °C. Once the predetermined temperature was reached, the reaction mixture was held at that temperature for 1 h. After cooling down to room temperature, primary amines (42.5 mmol, 1.2 equivalents) were added and the mixture was stirred for another 10 min. Methanol solution of sodium methoxide (1 equivalent, 25 wt %. Aldrich Co.) was added to this mixture and the resulting solution was stirred for 1 h. The solvent and starting materials were evaporated under vacuum. The product was washed with pentane (5 mL  $\times$  4) and it is treated with mixed solvents of distilled water (10 mL) and benzene (10 mL). Final product was extracted with benzene and the solvent was evaporated under vacuum. Yellow liquid. <sup>1</sup>H NMR (400 MHz, in CDCl<sub>3</sub>)  $\delta$  1.16 (d,  $J = 6$  Hz, 12H, C(CH<sub>3</sub>)<sub>2</sub>), 1.88 (s, 6H, CCH<sub>3</sub>), 3.65 (hept.,  $J = 6$  Hz, 2H, NCH), 4.37 (s, 1H, CCH), 11.41 (s, 1H, NH). <sup>13</sup>C NMR (100 MHz, in CDCl<sub>3</sub>)  $\delta$  18.91, 24.83, 46.88, 93.66, 158.70. ESI-MS: Calcd. 182.31 [M<sup>+</sup>], obsd. 182.48 [M<sup>+</sup>].

**CH<sub>3</sub>C(NCH(CH<sub>3</sub>)<sub>2</sub>)CHC(NHC(CH<sub>3</sub>)<sub>3</sub>)CH<sub>3</sub> (1b):** The same procedures as in compound 1a. Brown liquid. <sup>1</sup>H NMR (400 MHz, in CDCl<sub>3</sub>)  $\delta$  1.13 (d,  $J = 6$  Hz, 6H, CH(CH<sub>3</sub>)<sub>2</sub>), 1.34 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 1.85, 2.01 (s, 6H, (CCH<sub>3</sub>)<sub>2</sub>), 3.67 (hept.,  $J = 6$  Hz, 1H, NCH(CH<sub>3</sub>)<sub>2</sub>), 4.37 (s, 1H, CCH), 11.67 (s, 1H, NH). <sup>13</sup>C NMR (100 MHz, in CDCl<sub>3</sub>)  $\delta$  19.5, 24.1, 24.9, 35.1, 46.8, 57.2, 94, 159.1. ESI-MS: Calcd 221.19 [M+Na+2H]<sup>+</sup>, obsd 222.67 [M+Na+2H]<sup>+</sup>.

**CH<sub>3</sub>C(NC(CH<sub>3</sub>)<sub>3</sub>)CHC(NHC(CH<sub>3</sub>)<sub>3</sub>)CH<sub>3</sub> (2a):** Brown liquid. <sup>1</sup>H NMR (400 MHz, in CDCl<sub>3</sub>)  $\delta$  1.34 (s, 18H, C(CH<sub>3</sub>)<sub>3</sub>), 1.99 (s, 6H, CCH<sub>3</sub>), 4.37 (s, 1H, CCH), 11.63 (s,

1H, NH).  $^{13}\text{C}$  NMR (100 MHz, in  $\text{CDCl}_3$ )  $\delta$  3.1, 23.1, 52.8, 96.6, 159.1. ESI-MS: Calcd 210.36  $[\text{M}]^+$ , obsd 210.44  $[\text{M}]^+$ .

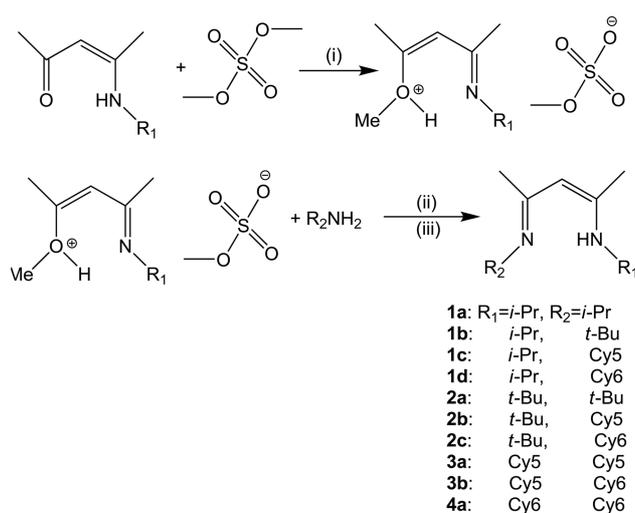
**$\text{CH}_3\text{C}(\text{NC}(\text{CH}_3)_3\text{CHC}(\text{NH}(\text{C}_6\text{H}_{11}))\text{CH}_3$  (2c):** The same procedures as in compound 1a. Yellow liquid.  $^1\text{H}$  NMR (400 MHz, in  $\text{CDCl}_3$ )  $\delta$  1.37 (s, 9H,  $\text{C}(\text{CH}_3)_3$ ), 1.25-1.80 (m, 10H,  $\text{C}_6\text{H}_{10}$ ), 1.85, 2.05 (s, 6H,  $(\text{CCH}_3)_2$ ), 3.30 (br s, 1H,  $\text{NCH}(\text{Cy6})$ ), 4.38 (s, 1H,  $\text{CCH}$ ), 11.60 (s, 1H,  $\text{NH}$ ).  $^{13}\text{C}$  NMR (100 MHz, in  $\text{CDCl}_3$ )  $\delta$  19.5, 22, 25.5, 31.8, 33.7, 52, 57.3, 95.7, 157.9, 163. ESI-MS: Calcd 236.40  $[\text{M}]^+$ , obsd 236.42  $[\text{M}]^+$ .

**$\text{CH}_3\text{C}(\text{N}(\text{C}_5\text{H}_9)\text{CHC}(\text{NH}(\text{C}_5\text{H}_9))\text{CH}_3$  (3a):** The same procedures as in compound 1a. Brown liquid.  $^1\text{H}$  NMR (400 MHz, in  $\text{CDCl}_3$ )  $\delta$  1.43-1.80 (m, 16H,  $(\text{C}_5\text{H}_8)_2$ ), 1.90 (s, 6H,  $(\text{CCH}_3)_2$ ), 3.83 (m, 2H,  $(\text{NCH})_2(\text{Cy5})$ ), 4.40 (s, 1H,  $\text{CCH}$ ), 11.39 (s, 1H,  $\text{NH}$ ).  $^{13}\text{C}$  NMR (100 MHz, in  $\text{CDCl}_3$ )  $\delta$  19.8, 24.1, 35, 57.6, 94, 159.5. ESI-MS: Calcd 234.38  $[\text{M}]^+$ , obsd 234.31  $[\text{M}]^+$ .

**$\text{CH}_3\text{C}(\text{N}(\text{C}_6\text{H}_{11})\text{CHC}(\text{NH}(\text{C}_6\text{H}_{11}))\text{CH}_3$  (4a):** The same procedures as in compound 1a. Yellow solid.  $^1\text{H}$  NMR (400 MHz, in  $\text{CDCl}_3$ )  $\delta$  1.25-1.80 (m, 20H,  $(\text{C}_6\text{H}_{10})_2$ ), 1.93 (s, 6H,  $\text{C}(\text{CH}_3)_2$ ), 3.37 (m, 2H,  $(\text{NCH}(\text{Cy6}))_2$ ), 4.40 (s, 1H,  $\text{CCH}$ ), 11.42 (s, 1H,  $\text{NH}$ ).  $^{13}\text{C}$  NMR (100 MHz, in  $\text{CDCl}_3$ )  $\delta$  18.1, 24, 24.5, 35, 55, 94.5, 159.5, 176. ESI-MS: Calcd 262.43  $[\text{M}]^+$ , obsd 262.53  $[\text{M}]^+$ .

## Results and Discussion

Dimethyl sulfate (DMS),<sup>17</sup> a powerful alkylating agent, has been employed in the methylation of various nucleophiles including hydroperoxides, hydroxamic acids, hydroxyamines, pyridine *N*-oxides, oximes, lactams, phenols, alcohols and carboxylic acids. It is a cheap and high reproducible



**Scheme 3.** Reagents and conditions: (i) microwave; (ii) rt, stirring (iii)  $\text{NaOMe}/\text{MeOH}$ .

agent and potentially safer than other conventional alkylating agent such as triethylxonium tetrafluoroborate.<sup>18</sup> Triethylxonium tetrafluoroborate should be stored in 2-8 °C and it is expensive and sensitive in an air with low reproducibility.<sup>12</sup> Also reactions with this reagent require longer reaction time. Combination of dimethyl sulfate with short reaction time and high yield caused by microwave would be ideal for the new synthetic method.

As expected, various alkyl-substituted symmetric  $\beta$ -diketimines are obtained in a short time with reasonably high yields (Scheme 3) and the results are summarized in Table 1. Generally,  $\beta$ -diketimines can be obtained by the condensation

**Table 1.** Preparation results of  $\beta$ -diketimines

Run No.	Starting Material $\text{MeC}(\text{O})\text{CHC}(\text{Me})\text{NHR}$	Amines $\text{R}'\text{NH}_2$	$\beta$ -diketimines $\text{MeC}(\text{NR})\text{CHC}(\text{Me})\text{NHR}'$	Yield (%)	
				Reaction time (10 min)	Reaction time (2 h)
1	$\text{R} = i\text{-Pr}$	$i\text{-Pr}$	<b>1a:</b> $\text{R} = i\text{-Pr}, \text{R}' = i\text{-Pr}$	78	85
2		$t\text{-Bu}$	<b>1b:</b> $i\text{-Pr}, t\text{-Bu}$	58	49
3		$\text{Cy5}$	<b>1c:</b> $i\text{-Pr}, \text{Cy5}$	(0.48:1:0.52)	(0.44:1:0.57)
4		$\text{Cy6}$	<b>1d:</b> $i\text{-Pr}, \text{Cy6}$	(0.5:1:0.6)	(0.68:1:0.56)
5	$\text{R} = t\text{-Bu}$	$t\text{-Bu}$	<b>2a:</b> $t\text{-Bu}, t\text{-Bu}$	57	68
6		$i\text{-Pr}$	<b>1b:</b> $t\text{-Bu}, i\text{-Pr}$	58 (0:1:0)	52 (1:0.75:0)
7		$\text{Cy5}$	<b>2b:</b> $t\text{-Bu}, \text{Cy5}$	54 (0:1:0)	(0.26:1:0)
8		$\text{Cy6}$	<b>2c:</b> $t\text{-Bu}, \text{Cy6}$	(1:0.89:0)	(1:0.5:0)
9	$\text{R} = \text{Cyclohexylamine}$	$i\text{-Pr}$	<b>1d:</b> $\text{Cy6}, i\text{-Pr}$	(1:0.62:0.84)	(1:0.54:0.62)
10		$t\text{-Bu}$	<b>2c:</b> $\text{Cy6}, t\text{-Bu}$	61	57
11		$\text{Cy5}$	<b>3b:</b> $\text{Cy6}, \text{Cy5}$	(1:0.73:0.18)	(1:0.67:0.40)
12		$\text{Cy6}$	<b>4a:</b> $\text{Cy6}, \text{Cy6}$	74	71
13	$\text{R} = \text{Cyclopentylamine}$	$i\text{-Pr}$	<b>1c:</b> $\text{Cy5}, i\text{-Pr}$	(1:0.43:0.55)	(1:0.4:0.63)
14		$t\text{-Bu}$	<b>2b:</b> $\text{Cy5}, t\text{-Bu}$	(1:0:0.25)	(1:0:0.25)
15		$\text{Cy5}$	<b>3a:</b> $\text{Cy5}, \text{Cy5}$	81	63
16		$\text{Cy6}$	<b>3b:</b> $\text{Cy5}, \text{Cy6}$	(1:0.54:0.45)	(1:0.55:0.40)

Microwave power = 120W, reaction temperature = 100 °C. Ratio = unsymmetric  $\beta$ -diketimines: symmetric  $\beta$ -diketimines ( $\text{R}'$ ): symmetric  $\beta$ -diketimines ( $\text{R}$ ). Ratios were determined by integration of CH peaks in the region of the 4-4.5 ppm obtained from  $^1\text{H}$  NMR spectra.  $\text{p}K_b = 3.37$  ( $i\text{-Pr}$ ), 3.32 ( $t\text{-Bu}$ ), 3.20 ( $\text{Cy5}$ ), 3.30 ( $\text{Cy6}$ ), 9.42 ( $\text{Ph}$ ) (amines used in this study, ref. 21)

reaction between primary amines and  $\beta$ -ketoimines which are conveniently prepared by the method reported earlier.<sup>13</sup> Our method is different from one reported by Bradley by using microwave heating and solvent extraction.<sup>12</sup> This method induces faster reactions with comparable yields (for **1a**, 74%<sup>12</sup> vs. 85%) and potentially safer isolation with thermally unstable  $\beta$ -diketimines.

In the preparation of  $\beta$ -ketoimines, only *t*-butyl amine requires small amount of solvent, EtOH. The remaining reactions with other alkyl amines can proceed without any solvent. Interestingly the order of addition is very important for the higher yield in case of  $\beta$ -ketoimine with *t*-Bu substituent. Addition of *t*-butylamine should be followed after addition of solvent. High reactivity of *t*-butylamine with acetylacetone causes unidentified mixture without solvent. In the preparation of  $\beta$ -diketimines, small amount (2 mL) of solvent, benzene is often required. If the reaction proceeds without solvent, burn-out phenomenon was observed. Initially, various conditions such as 50W/50 °C, 60W/60 °C, and 70W/70 °C (run 9, 39%; run 10, 46%; run 14, 32%) were applied to the 1<sup>st</sup> step of these reactions but no reaction or much lower yields were observed. After several trials, 100W/100 °C was finally chosen as optimal power and reaction temperature for all the reactions.

Several one-pot reactions to produce  $\beta$ -diketimines were also tried but all failed to produce the desired product even though Schaper reported production of mixtures of  $\beta$ -diketimines.<sup>11</sup> Only  $\beta$ -ketoimines can be obtained on stirring without microwave irradiation or reflux. Depending on the nature of amines employed, produced  $\beta$ -ketoimines are different; When isopropyl and other alkyl amines were employed at the same time,  $\beta$ -ketoimine with an *i*-Pr substituent is the major product. (*t*-butyl amine, only *i*-Pr  $\beta$ -ketoimines; cyclopentyl amine, *i*-Pr  $\beta$ -ketoimines: Cy5  $\beta$ -ketoimines = 1:0.61; cyclohexyl amine, *i*-Pr  $\beta$ -ketoimines: Cy6  $\beta$ -ketoimines = 1:0.75; phenyl amine, *i*-Pr  $\beta$ -ketoimines: Ph  $\beta$ -ketoimines = 1:0.57) In order to have some clue for these results, several step reactions have been performed. Early reported failures in various trials to produce alkyl-substituted  $\beta$ -diketimines may be due to one-pot trial.

Dimethyl sulfate reacts with amines so violently to produce solids, possibly ammonium salts which are the exothermic methylation products of amines. <sup>1</sup>H NMR spectra of the products showed that the products are not simple. Two or three new peaks in the range of 3 to 4 ppm appeared depending on the nature of amines. The reactions between dimethyl sulfate and  $\beta$ -ketoimines produce methylation products which is confirmed by MS (Table 2). <sup>1</sup>H NMR spectra were so complicated that they could not be correctly assigned. MS spectra indicated the formation of some dimeric compounds

and they are believed to be formed by the nucleophilic attack of the amine N atom of  $\beta$ -ketoimines on the initial methylation product. This indicates that nucleophilic attack of amines onto the C atom of the carbonyl in the methylation product of  $\beta$ -ketoimines are actually followed after the methylation by DMS.

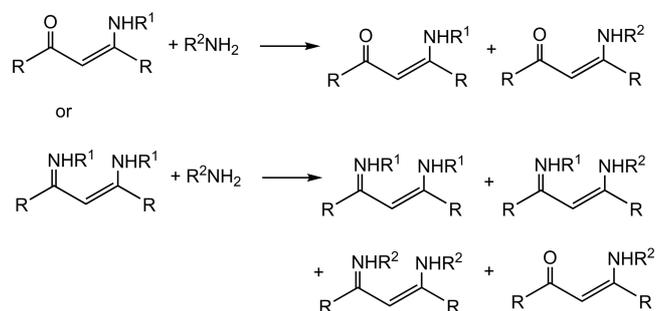
However, as shown in Table 1, pure target products were isolated only in runs 1, 2(or 6), 5, 12, and 15 by following the steps described in Scheme 3. In other words, only symmetrical  $\beta$ -diketimines can be prepared successfully except **1b** and **2c**.

The effect of reaction time on the ratio of products is not quite significant. However, for the symmetric  $\beta$ -diketimines with *i*-Pr and *t*-Bu substituents (run 1 and 5) longer reaction time favors higher yield but the reverse trend is observed in runs 12 and 15 with cyclohexyl (Cy6) and cyclopentyl (Cy5) substituents, respectively. It appears that basicity and steric bulkiness of amines are not critical in the determination of the products. No rational explanation can be made yet.

For the preparation of unsymmetric  $\beta$ -diketimines, the order of alkyl induction appears to be important; as described in Table 1, the ratios are changed depending on the order of induction. It is worthwhile to point out that unsymmetric  $\beta$ -diketimines are obtained in run 2 but a symmetric ones with *i*-Pr and Cy5 substituents are obtained after 10 min in run 6 and 7. After 2 h, mixed products were produced. This indicates that unsymmetric  $\beta$ -diketimines can be obtained by subtle optimization of reaction parameters.

Further exchange of amines after initial formation of  $\beta$ -diketimines clearly happens but it is not clear what the driving force of this trend is. Park proposed several novel routes using cyclic ketimines or ketimines to avoid the mixed products.<sup>19</sup>

In order to understand this trend, reactions between  $\beta$ -ketoimines or  $\beta$ -diketimines and amines (Scheme 4) were investigated. In Table 3, the results of the reactions between  $\beta$ -ketoimines and amines are summarized. Without microwave assistance, amine exchange does not occur in any



**Table 2.** Fragmentation patterns of the selected products of the reactions between DMS and  $\beta$ -ketoimines

$\beta$ -ketoimines	Fragments
<b>1</b>	111.19 ( <b>1</b> + CH <sub>3</sub> - <i>i</i> -Pr), 121.81 ( <b>1</b> + CH <sub>3</sub> - 2 CH <sub>3</sub> ), 140.69 ( <b>1</b> ), 155.28 ( <b>1</b> + CH <sub>3</sub> ), 423.26 (2 × <b>1</b> + DMS - CH <sub>3</sub> )
<b>3</b>	110.98 ( <b>3</b> + CH <sub>3</sub> - Cy5), 123.67 ( <b>3</b> + CH <sub>3</sub> - 2 CH <sub>3</sub> ), 167.79 ( <b>3</b> ), 181.98 ( <b>3</b> + CH <sub>3</sub> ), 443.30 (2 × <b>3</b> + DMS - CH <sub>3</sub> - CH <sub>3</sub> OH), 475.34 (2 × <b>3</b> + DMS - CH <sub>3</sub> )

**Table 3.** Results of the reactions between  $\beta$ -ketoimines and amines

$\beta$ -ketoimines	Amines	Produced $\beta$ -ketoimines <sup>a</sup>		
		rt (no microwave)	1 h (120W, 100 °C)	2 h (120W, 100 °C)
<i>i</i> -Pr	<i>t</i> -Bu	<i>i</i> -Pr: <i>t</i> -Bu = 1:0	1:0	1:0
	Cy5	<i>i</i> -Pr:Cy5 = 1:0	1:0.8	1:1.4
	Cy6	<i>i</i> -Pr:Cy6 = 1:0	1:1.51	1:1.52
	Ph	<i>i</i> -Pr:Ph = 1:0	1:0.17	1:0.23
<i>t</i> -Bu	<i>i</i> -Pr	<i>t</i> -Bu: <i>i</i> -Pr = 1:0.32	1:0.35	1:0.49
	Cy5	<i>t</i> -Bu:Cy5 = 1:0.35	1:1	1:1.98
	Cy6	<i>t</i> -Bu:Cy6 = 1:0.33	1:1.27	1:1.61
	Ph	<i>t</i> -Bu:Ph = 1:0.12	1:0.66	1:0.66
Cy5	<i>i</i> -Pr	Cy5: <i>i</i> -Pr = 1:0	1:0	1:0.05
	<i>t</i> -Bu	Cy5: <i>t</i> -Bu = 1:0	1:0	1:0
	Cy6	Cy5:Cy6 = 1:0	1:0.33	1:0.45
	Ph	Cy5:Ph = 1:0	1:0	1:0
Cy6	<i>i</i> -Pr	Cy6: <i>i</i> -Pr = 1:0	1:0	1:0
	<i>t</i> -Bu	Cy6: <i>t</i> -Bu = 1:0	1:0	1:0
	Cy5	Cy6:Cy5 = 1:0	1:0.8	1:0.83
	Ph	Cy6:Ph = 1:0	1:0.03	1:0.05
Ph	<i>i</i> -Pr	Ph: <i>i</i> -Pr =	0.5:1	0.48:1
	<i>t</i> -Bu	Ph: <i>t</i> -Bu =	1:0.05	1:0
	Cy5	Ph:Cy5 =	0.21:1	0.35:1
	Cy6	Ph:Cy6:Ph-Ph $\beta$ -diketimine =	0.16:1:0.14	0.30:1:0.18
$\beta$ -diketimine (Ph)	<i>i</i> -Pr	Ph-Ph: <i>i</i> -Pr-Ph =		1:0.18
	<i>t</i> -Bu			Ph-Ph diketimine only
	Cy5	Ph-Ph:Cy5-Ph:Cy5-Cy5:Cy-5 $\beta$ -ketoimine =		0.21:1:0.18:0.08

<sup>a</sup>Ratios were determined by integration of CH peaks in the region of the 4-4.5 ppm obtained from <sup>1</sup>H NMR spectra.

combination of amines. With microwave irradiation, it is found that more sterically bulky amines replace less bulky ones in the  $\beta$ -ketoimines. For example,  $\beta$ -ketoimine with *i*-Pr substituent reacts with Cy6 amine to produce  $\beta$ -ketoimine with Cy6 substituent. From the successive reactions employing several amines and  $\beta$ -ketoimines, it is found that the order of exchange ability of amine in the  $\beta$ -ketoimines is as follows; Cy6 > Cy5 > *i*-Pr > Ph > *t*-Bu, which roughly correlates with the steric bulkiness of a substituent except *t*-Bu. Cone angles of PR<sub>3</sub> decrease in the following order; *t*-Bu (182°) > Cy6 (170°) > Cy5 (160-170°) > *i*-Pr (160°) > Ph (145°).<sup>20</sup> Since alkyl amines show similar but higher basicities than aryl amines,<sup>21</sup> basicity may play some role in the reactions with phenyl amine or  $\beta$ -ketoimines with Ph substituent. It is also found that further exchange of amines in  $\beta$ -diketimine with phenyl substituents happens. This shows continuous exchange of amines occurs after formation of  $\beta$ -diketimines even though the extent of exchange is dependent on the nature of amines employed as reported by Park.<sup>19</sup>

In the preparation of  $\beta$ -diketimines with both aryl and alkyl substituents, purification of the products cannot be achieved due to similar properties of the product mixtures even though desired products can be observed in the NMR spectra. We are trying to set up the procedures for the purification but pure unsymmetric  $\beta$ -diketimines with aryl and alkyl substituents are not available yet.

In order to check the possibility of scale-up, yields between

reactions employing 1 g and 5 g starting materials were compared and almost same ones were observed. Further scale-up is under progress.

## Conclusion

A convenient, economic and efficient preparation method for  $\beta$ -diketimines assisted by microwave was successfully developed and it is found that various symmetric  $\beta$ -diketimines with alkyl substituents can be obtained from the reaction of *O*-alkylation by dimethylsulfate in a short time with reasonable to high yields. This method is in green nature due to no solvent and low energy requirement. In addition to this, we conclude that careful optimization of reaction parameters may induce preparation of unsymmetric  $\beta$ -diketimines with alkyl substituents.

**Acknowledgments.** Authors are grateful for the financial support from Inha University (2013).

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