

# A mild and convenient synthesis of *N*-carbobenzyloxy ketimines†

Jun-ichi Matsuo,\* Yumi Tanaki, Aimi Kido and Hiroyuki Ishibashi\*

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*N*-Carbobenzyloxy (Cbz) ketimines were prepared conveniently from *N*-Cbz amines by oxidation with *N*-*tert*-butylbenzenesulfinimidoyl chloride.

*N*-Carboalkoxy aldimines are often used as nitrogen-containing electrophiles for carbon–carbon bond forming reactions, especially for highly enantioselective reactions such as the Mannich type reaction<sup>1</sup> and the aza-Henry reaction.<sup>2,3</sup> *N*-Carboalkoxy amines having a chiral tertiary carbon center are stereoselectively constructed by these reactions. Given this, *N*-carboalkoxy ketimines should be attractive electrophilic targets for creating chiral quaternary carbon centers; however, only a few *N*-carboalkoxy ketimines have been prepared<sup>4–11</sup> and most did not have acidic  $\alpha$ -protons. Preparation of *N*-carboalkoxy ketimines is more difficult than preparation of *N*-carboalkoxy aldimines<sup>4</sup> because of the lower reactivity of ketones and the tendency of *N*-carboalkoxy ketimines to tautomerize into the corresponding ene carbamates. Hoch reported that *N*-carboethoxy ketimines were prepared from diethyl ketals and  $\text{NH}_2\text{CO}_2\text{Et}$  in the presence of a trace amount of  $\text{PhNH}_3\text{Cl}$  at 90–100 °C,<sup>5</sup> but it was later found that *N*-carboethoxy ketimines obtained by Hoch's method included ene carbamate.<sup>6,7</sup> *N*-Carboalkoxy ketimines are also prepared from NH ketimines<sup>8,9</sup> or *N*-silyl ketimines,<sup>10</sup> though available NH ketimines and *N*-silyl ketimines have been limited to non-enolizable ones; *i.e.*, diaryl and aryl *tert*-butyl ketimines.<sup>11</sup>

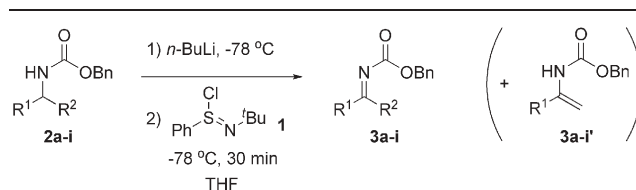
We have found that *N*-*tert*-butylbenzenesulfinimidoyl chloride (**1**)† oxidized various organic compounds under very mild reaction conditions.<sup>12</sup> We expected that the above-mentioned labile *N*-carboalkoxy ketimines would be synthesized under mild conditions by **1**-mediated oxidation of the corresponding *N*-carboalkoxy amines. We describe here the oxidation of a variety of *N*-carbobenzyloxy (Cbz) amines to *N*-Cbz ketimines using **1**.

First, oxidation of *N*-Cbz-1-phenylethylamine (**2a**) to the corresponding *N*-Cbz ketimine **3a** was tried using the following procedure: **2a** was treated with *n*-BuLi in THF at –78 °C and then **1** was added at the same temperature. As expected, the **1**-mediated oxidation of **2a** proceeded rapidly at –78 °C and the desired product **3a** was obtained in 97% yield after chromatography on silica gel. It was noted that ene carbamate **3a'**<sup>13</sup> was not obtained by this procedure. The crystalline product **3a** was stable in a refrigerator for several months, while a part of **3a** tautomerized to **3a'** after keeping the solution of **3a** in chloroform at room

temperature for 10 days. The scope and limitations of the present **1**-mediated oxidation were investigated for the reaction of various *N*-Cbz protected amines **2** giving *N*-Cbz aryl alkyl ketimines **3** (Table 1). *N*-Cbz phenyl ethyl ketimine **3b**, *N*-Cbz phenyl propyl ketimine **3c**, and *N*-Cbz phenyl isopropyl ketimine **3d** were isolated in high yields regardless of the steric hindrance. It was found that yields of *N*-Cbz aryl ketimines **3** depended strongly on the substituents on the phenyl ring. In the presence of an electron-attracting group, such as chloride, ketimine **3g** was isolated in 96% yield as the sole product, while a mixture of ketimine and ene carbamate was obtained in the presence of electron-donating substituents such as methyl and methoxy groups (Entries 6 and 8). It was thought that protonation of the nitrogen atom of the ketimine took place more easily when electron-donating groups were attached to the phenyl ring. In the oxidation of **2i**, having a 3-pyridyl group as an aryl group, ketimine **3i** was obtained along with an ene carbamate **3i'** in 87% combined yield (**3i:3i'** = 79:21). The two compounds **3i** and **3i'** were separated by thin-layer chromatography on silica gel. It should be noted that only one isomer of ketimine was obtained by the present procedure. We speculated that *anti*-*N*-Cbz ketimines were selectively formed, judging from <sup>13</sup>C NMR chemical shift differences<sup>14</sup> between the  $\alpha$ -carbons of *N*-Cbz ketimines and the corresponding ketones.<sup>15</sup>

When the oxidation of *N*-Cbz cyclohexylamine (**4a**) was carried out by the above-mentioned procedure, only the starting material **4a** was recovered. Elevating the reaction temperature to room temperature gave ene carbamate **5a'** in 60% yield, and many by-products were detected by TLC analysis (Scheme 1). Since the

**Table 1** Oxidation of various *N*-Cbz amines **2a–i** to *N*-Cbz ketimines **3a–i**

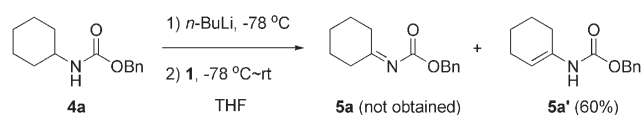


Entry	<i>N</i> -Cbz amine	R <sup>1</sup>	R <sup>2</sup>	Product	Yield (%)
1	<b>2a</b>	Ph	Me	<b>3a</b>	97
2	<b>2b</b>	Ph	Et	<b>3b</b>	90
3	<b>2c</b>	Ph	<i>n</i> -Pr	<b>3c</b>	92
4	<b>2d</b>	Ph	<i>i</i> -Pr	<b>3d</b>	94
5	<b>2e</b>	1-Naph	Me	<b>3e</b>	89
6	<b>2f</b>	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	Me	<b>3f</b>	95 <sup>a</sup>
7	<b>2g</b>	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	Me	<b>3g</b>	96
8	<b>2h</b>	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	Me	<b>3h</b>	89 <sup>b</sup>
9	<b>2i</b>	3-Py	Me	<b>3i</b>	87 <sup>c</sup>

<sup>a</sup> A mixture of **3f** and **3f'** (**3f:3f'** = 61:39). <sup>b</sup> A mixture of **3h** and **3h'** (**3h:3h'** = 75:25). <sup>c</sup> A mixture of **3i** and **3i'** (**3i:3i'** = 79:21).

Division of Pharmaceutical Sciences, Graduate School of Natural Science and Technology, Kanazawa University, Kakumachi, Kanazawa 920-1192, Japan. E-mail: jimatsuo@p.kanazawa-u.ac.jp; Fax: (+81) 76-234-4439; Tel: (+81) 76-234-4439

† Electronic supplementary information (ESI) available: Typical experimental procedures and spectral data for all new compounds. See DOI: 10.1039/b605882e

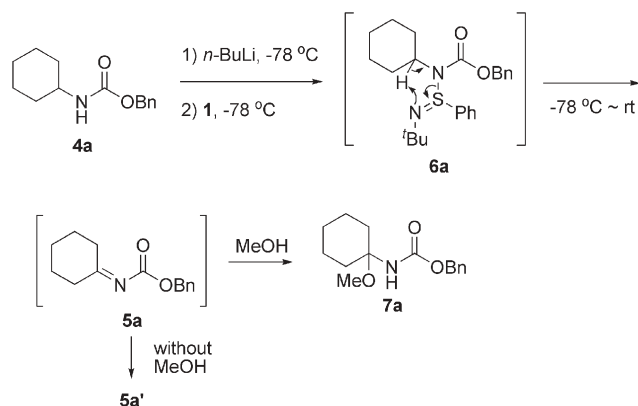


**Scheme 1** Oxidation of **4a** with **1** at room temperature.

yellow color of **1** immediately disappeared after the addition of **1** at  $-78\text{ }^{\circ}\text{C}$ , it was thought that **1** reacted smoothly with the lithium anion of **4a** at  $-78\text{ }^{\circ}\text{C}$  to form an oxidation intermediate **6a**, and that **5a** would be formed during warming to room temperature (Scheme 2). Therefore, we tried to trap the *N*-Cbz ketimine **5a** with MeOH<sup>16</sup> before isomerization of **5a** to **5a'**. In fact, the expected MeOH-addition product **7a** was obtained in 80% yield by generating **5a** in the presence of MeOH (Table 2, Entry 1). This result suggested that dialkyl ketimine **5a** was also formed effectively by the present oxidation. Other cyclic and acyclic dialkyl ketimines were generated by this method and MeOH-addition products were obtained in good to high yields by trapping ketimines with MeOH (Table 2, Entries 2–4).

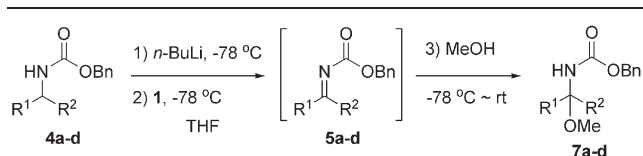
Kugelrohr distillation (290  $^{\circ}\text{C}$ /0.9 mmHg) of **7a** gave ene carbamate **5a'**<sup>17</sup> as a sole product (Scheme 3). Therefore, oxidation of *N*-Cbz amine with **1**, followed by addition of MeOH and successive distillation would give a useful method for preparation of ene carbamates.

Thus, we have established a new method for the preparation of a variety of *N*-Cbz ketimines.<sup>§</sup> Oxidation of *N*-Cbz amines to the corresponding *N*-Cbz ketimines proceeded smoothly at  $-78\text{ }^{\circ}\text{C}$



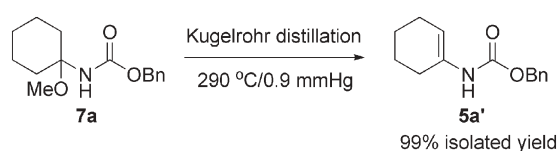
**Scheme 2** Mechanism for formation of **5a'**.

**Table 2** Oxidation of *N*-Cbz amines **4a–d** to *N*-Cbz ketimines **5a–d**, and successive addition of MeOH to give **7a–d**



Entry	<i>N</i> -Cbz amine	R <sup>1</sup>	R <sup>2</sup>	Product	Yield (%) <sup>a</sup>
1	<b>4a</b>	–(CH <sub>2</sub> ) <sub>5</sub> –		<b>7a</b>	80
2	<b>4b</b>	–(CH <sub>2</sub> ) <sub>4</sub> –		<b>7b</b>	75
3	<b>4c</b>	Me	Me	<b>7c</b>	77
4	<b>4d</b>	Et	Et	<b>7d</b>	91

<sup>a</sup> Isolated yield.



**Scheme 3** Formation of ene carbamate **5a'** from **7a**.

using the oxidizing agent **1**; relatively stable *N*-Cbz aryl ketimines were isolated in high yields and labile *N*-Cbz dialkyl ketimines were trapped with MeOH *in situ*. Since a variety of *N*-Cbz ketimines are now available and *anti*-isomers of ketimines were selectively formed by the present oxidation, it is expected that the *N*-Cbz ketimines would be useful synthetic intermediates in organic synthesis and we are now studying carbon–carbon bond forming reactions using them.<sup>¶</sup>

## Notes and references

‡ Commercially available from Tokyo Chemical Industry.

§ Typical procedure (Table 1, entry 1): to a stirred solution of **2a** (100 mg, 0.39 mmol) in dry THF (2 mL) was added a solution of *n*-BuLi (1.59 N in hexane, 0.27 mL, 0.43 mmol) at  $-78\text{ }^{\circ}\text{C}$  under an argon atmosphere. After the resulting pale yellow solution was stirred for 15 min at the same temperature, a solution of **1** (129 mg, 0.60 mmol) in THF (1 mL) was added at  $-78\text{ }^{\circ}\text{C}$  and the mixture was stirred for 30 min. The reaction was then quenched by adding saturated NaHCO<sub>3</sub> (5 mL) and the mixture was extracted with EtOAc (three times). The combined organic extracts were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was purified by thin layer chromatography (silica gel, hexane–AcOEt 5:1) to afford **3a** (96 mg, 97%) as a colorless powder.

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