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

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N-Carbobenzyloxy (Cbz) ketimines were prepared conveniently from *N*-Cbz amines by oxidation with *N*-tert-butylbenzenesulfonimidoyl 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 reaction¹ and the aza-Henry reaction.^{2,3} *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^{4–11} and most did not have acidic α -protons. Preparation of *N*-carboalkoxy ketimines is more difficult than preparation of *N*-carboalkoxy aldimines⁴ 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 PhNH_2Cl at 90–100 °C,⁵ but it was later found that *N*-carboethoxy ketimines obtained by Hoch's method included ene carbamate.^{6,7} *N*-Carboalkoxy ketimines are also prepared from NH ketimines^{8,9} or *N*-silyl ketimines,¹⁰ though available NH ketimines and *N*-silyl ketimines have been limited to non-enolizable ones; i.e., diaryl and aryl *tert*-butyl ketimines.¹¹

We have found that *N*-tert-butylbenzenesulfonimidoyl chloride (**1**)† oxidized various organic compounds under very mild reaction conditions.¹² 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'**¹³ 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 ¹³C NMR chemical shift differences¹⁴ between the α -carbons of *N*-Cbz ketimines and the corresponding ketones.¹⁵

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

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

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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 MeOH¹⁶ 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 ($290\text{ }^{\circ}\text{C}/0.9\text{ mmHg}$) of **7a** gave ene carbamate **5a'** 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. § 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 ¹	R ²	Product	Yield (%) ^a
1	4a	–(CH ₂) ₅ –		7a	80
2	4b	–(CH ₂) ₄ –		7b	75
3	4c	Me	Me	7c	77
4	4d	Et	Et	7d	91

^a 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. ¶

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 NaHCO₃ (5 mL) and the mixture was extracted with EtOAc (three times). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, 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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