A mild and convenient synthesis of N-carbobenzyloxy ketimines

doi: 10.1039/b605882e

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

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

Received (in Cambridge, UK) 25th April 2006, Accepted 16th May 2006
First published as an Advance Article on the web 1st June 2006
DOI: 10.1039/b605882e

_N_-Carbobenzyloxy (Cbz) ketimines were prepared conveniently from _N_-Cbz amines by oxidation with _N-tert_-butylbenzenesulfinimidoyl chloride.

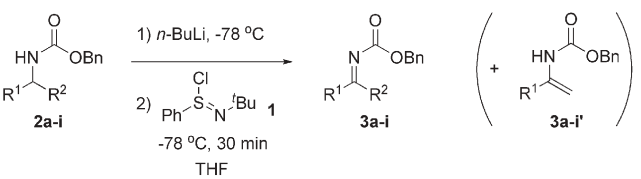
N-Carboalkoxy aldimines are often used as nitrogen-containing electrophiles for carbon–carbon bond forming reactions, especially for highly enantioselective reactions such as the Mannich type reaction[1] and the aza-Henry reaction.[2,3] *N*-Carboalkoxy amines having a chiral tertiary carbon center are 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 aldimines[4] 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 NH_2CO_2Et in the presence of a trace amount of $PhNH_3Cl$ 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*-butylbenzenesulfinimidoyl 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 ^{13}C NMR chemical shift differences[14] 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**

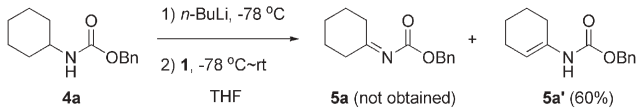


Entry	*N*-Cbz amine	R^1	R^2	Product	Yield (%)
1	**2a**	Ph	Me	**3a**	97
2	**2b**	Ph	Et	**3b**	90
3	**2c**	Ph	*n*-Pr	**3c**	92
4	**2d**	Ph	*i*-Pr	**3d**	94
5	**2e**	1-Naph	Me	**3e**	89
6	**2f**	*p*-MeC_6H_4	Me	**3f**	95[a]
7	**2g**	*p*-ClC_6H_4	Me	**3g**	96
8	**2h**	*p*-$MeOC_6H_4$	Me	**3h**	89[b]
9	**2i**	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).

Division of Pharmaceutical Sciences, Graduate School of Natural Science and Technology, Kanazawa University, Kakuma-machi, 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

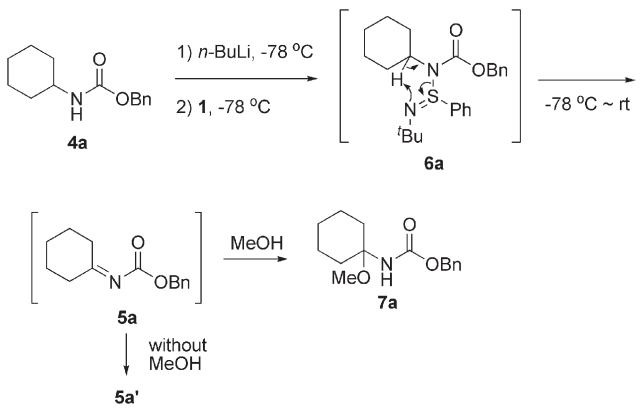


Scheme 1 Oxidation of **4a** with **1** at room temperature.

yellow color of **1** immediately disappeared after the addition of **1** at −78 °C, it was thought that **1** reacted smoothly with the lithium anion of **4a** at −78 °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[16] 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).

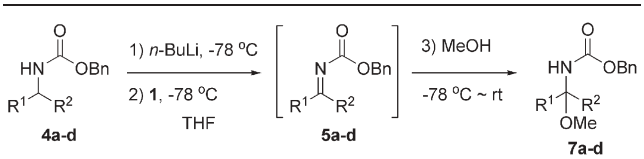
Kugelrohr distillation (290 °C/0.9 mmHg) of **7a** gave ene carbamate **5a′**[17] as a sole product (Scheme 3). Therefore, oxidation of *N*-Cbz amine with **1**, followed by addition of MeOH and successive distillation would give a useful method for preparation of ene carbamates.

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 °C



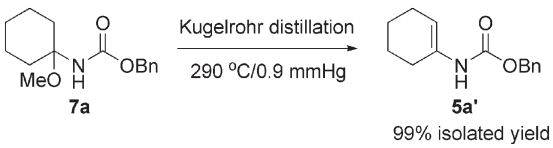
Scheme 2 Mechanism for formation of **5a′**.

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	*N*-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 °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 °C and the mixture was stirred for 30 min. The reaction was then quenched by adding saturated $NaHCO_3$ (5 mL) and the mixture was extracted with EtOAc (three times). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, 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.

¶ The authors thank for the financial support, the Novartis Foundation (Japan) for the Promotion of Science, and this work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan.

1 A. G. Wenzel and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2002, **124**, 12964–12965; S. Matsunaga, T. Yoshida, H. Morimoto, N. Kumagai and M. Shibasaki, *J. Am. Chem. Soc.*, 2004, **126**, 8777–8785.
2 L. Bernardi, F. Fini, R. P. Herrera, A. Ricci and V. Sgarzani, *Tetrahedron*, 2005, **62**, 375–380; X. Xu, T. Furukawa, T. Okino, H. Miyabe and Y. Takemoto, *Chem.–Eur. J.*, 2006, **12**, 466–476.
3 T. R. Wu and J. M. Chong, *Org. Lett.*, 2006, **8**, 15–18; E. M. Ferstl, H. Venkatesan, N. B. Ambhaikar, J. P. Snyder and D. C. Liotta, *Synthesis*, 2002, 2075–2083; V. K. Aggarwal, M. Ferrara, C. J. O'Brien, A. Thompson, R. V. H. Jones and R. Fieldhouse, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1635–1643; B. Wünsch and S. Nerdinger, *Chem. Lett.*, 1998, 799–800; B. Wünsch and S. Nerdinger, *Eur. J. Org. Chem.*, 1998, 711–718.
4 They have been easily prepared by the condensation of alkyl carbamate and aldehyde. See: A. E. Martell and R. M. Herbst, *J. Org. Chem.*, 1941, **6**, 878–887.
5 J. Hoch, *Compt. Rend.*, 1935, **201**, 560–562.
6 M. Sato, *J. Org. Chem.*, 1961, **26**, 770–779.
7 D. M. Colvin and B. C. Uff, *Tetrahedron Lett.*, 1966, **7**, 6079–6081.
8 J. E. Banfield, G. M. Brown, F. H. Davey, W. Davies and T. H. Ramsay, *Aust. J. Sci. Res., Ser. A*, 1948, **1**, 330–342.
9 L. I. Samarai, O. V. Vishnevskii and G. I. Derkach, *Chem. Ber.*, 1969, **102**, 2972–2976.
10 R. Kupfer, S. Meier and E.-U. Wurthwein, *Synthesis*, 1984, 688–690.
11 For other methods, see: R. Reck and J. C. Jochims, *Chem. Ber.*, 1982, **115**, 860–870; S. Ozaki and A. Tamaki, *Bull. Chem. Soc. Jpn.*, 1978, **51**, 3391–3392; W. Lwowski and T. W. Mattingly, Jr., *J. Am. Chem. Soc.*, 1965, **87**, 1947–1958.
12 J.-i. Matsuo, *J. Synth. Org. Chem. Jpn.*, 2004, **62**, 574–583; J.-i. Matsuo, D. Iida, K. Tatani and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 2002, **75**, 223–234; T. Mukaiyama, J.-i. Matsuo and H. Kitagawa, *Chem. Lett.*, 2000, 1250–1251; T. Mukaiyama, A. Kawana, Y. Fukuda and J.-i. Matsuo, *Chem. Lett.*, 2001, 390–391; J.-i. Matsuo, A. Kawana,

Y. Fukuda and T. Mukaiyama, *Chem. Lett.*, 2001, 712–713; J.-i. Matsuo and Y. Aizawa, *Tetrahedron Lett.*, 2005, **46**, 407–410; J.-i. Matsuo and Y. Aizawa, *Chem. Commun.*, 2005, 2399–2401.
13 R. Matsubara, P. Vital, Y. Nakamura, H. Kiyohara and S. Kobayashi, *Tetrahedron*, 2004, **60**, 9769–9784.
14 C. A. Bunnell and P. L. Fuchs, *J. Org. Chem.*, 1977, **42**, 2614–2617.
15 The ^{13}C chemical shifts of alkyl α-carbons of *N*-Cbz ketimines **3** were shifted to higher field, except for **3d**. The stereochemistry of **3d** was ambiguous.
16 Y. H. Suen and H. B. Kagan, *Bull. Soc. Chim. Fr.*, 1965, 1460–1463.
17 Compound **5a′** was prepared *via* the isocyanate. See: S. Machida and I. Tanaka, *Kyoto Kogei Sen'i Daigaku Sen'igakubu Gakujutsu Hokoku*, 1975, **7**, 423 (*Chem. Abs.,* **84**, 122382) and ref. 6 and 13.

