

Development of a Practical Synthetic Method for *N*-*tert*-Butoxycarbonyl α -Ketimino Esters

Takuya Hashimoto, Kumiko Yamamoto, and Keiji Maruoka*

Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo-ku, Kyoto 606-8502

(Received December 14, 2010; CL-101059; E-mail: maruoka@kuchem.kyoto-u.ac.jp)

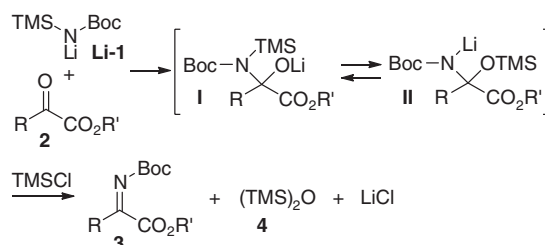
Despite the potential synthetic utility of *N*-Boc α -ketimino esters as prochiral ketimines to give chiral α -tertiary amines, there has been no general method to access these molecules in a practical fashion. We report herein a procedure for the one-step synthesis of *N*-Boc α -ketimino esters starting from the corresponding α -keto esters.

In the realm of asymmetric catalysis aimed at the synthesis of chiral amines, prochiral *N*-Boc aldimines have found unlimited applications building on their good reactivity and ease of deprotection after the planned transformation.¹ However, when it comes to their keto equivalent, *N*-Boc ketimines, there has been essentially no report using these molecules in asymmetric catalysis.^{2d} We assumed that the reason for this deficiency is partially due to the lack of supply of *N*-Boc ketimines² in addition to their elusive nature existing as a tautomeric mixture in the case of ketimines having α -hydrogens,^{2c} despite their high potency as valuable prochiral substrates to produce *N*-Boc-protected chiral α -tertiary amines.³

We report herein the attempt to solve this issue by establishment of a practical synthetic procedure for *N*-Boc α -ketimino esters having no α -hydrogen which are particularly attractive as a robust template for the asymmetric synthesis of α,α -disubstituted α -amino acids.⁴ Our strategy to realize this goal is the use of lithium *N*-Boc-*N*-TMS-amide **Li-1** as a source of the *N*-Boc imino group, designed according to early reports on the synthesis of *N*-TMS and *N*-acyl imines (Figure 1).⁵ Nucleophilic addition of this lithium amide to α -keto ester **2** would give the intermediate **I** which might be in equilibrium with **II**. We anticipated that addition of TMSCl to this intermediate would deliver the corresponding *N*-Boc α -ketimino ester concomitant with the extrusion of disiloxane **4**.

Following this synthetic plan, we actually implemented the synthesis of *N*-Boc α -ketimino esters. After some optimization studies, we settled on the operationally simple one-pot sequential procedure shown in the scheme below (Table 1). Lithium amide **Li-1** could be generated by the reaction of carbamate **1** with butyllithium at -78°C . Exposure of methyl benzoylformate (**2a**) to this solution and subsequent treatment with chlorotrimethylsilane furnished *N*-Boc α -ketimino ester **3a** in 67% yield as a single isomer (Entry 1). This reaction system could also be applied to α -keto esters having bulkier esters, like ethyl ester **2b** and *t*-butyl ester **2c** (Entries 2 and 3). A variety of α -ketimino esters bearing an aromatic substituent were obtained in good yields (Entries 4–10), and even an α -ketimino ester bearing an alkynyl moiety could be synthesized (Entry 11).

The limitation of this procedure is the difficulty to perform the reaction with pyruvate (**2**, R = Me)^{2c} and other alkyl-substituted α -keto esters which might be due to the preferential deprotonation of α -keto esters by **Li-1**. Probably for the same reason, acetophenone could not be employed as well.

Figure 1. Synthetic scheme for *N*-Boc α -ketimino esters.Table 1. Preparation of *N*-Boc α -ketimino esters^a

Entry	R	R'		Yield [%] ^b	Product
1		Me	2a	67	3a
2		Et	2b	80	3b
3		<i>t</i> -Bu	2c	74	3c
4		<i>t</i> -Bu	2d	71	3d
5		<i>t</i> -Bu	2e	73	3e
6		<i>t</i> -Bu	2f	78	3f
7		<i>t</i> -Bu	2g	57	3g
8		<i>t</i> -Bu	2h	54	3h
9		<i>t</i> -Bu	2i	69	3i
10		<i>t</i> -Bu	2j	77	3j
11		<i>t</i> -Bu	2k	79	3k

^aReactions performed at 0.50 mmol scale. ^bIsolated yield.

After the establishment of a practical synthetic method for *N*-Boc α -ketimino esters, we moved our attention to the elucidation of the C=N double bond geometry. To our delight, we could obtain a crystal of **3h** suitable for X-ray crystallo-

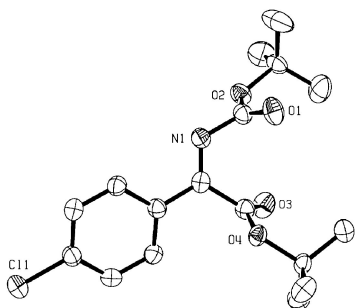


Figure 2. ORTEP representation of **3h** with ellipsoids shown at 50% probability level. Hydrogen atoms are omitted for clarity.

graphic analysis, and the configuration was determined to be *Z*, projecting the Boc group and the ester moiety in a *cis* fashion as shown in Figure 2.⁶

In conclusion, we established an operationally simple synthetic procedure to give *N*-Boc α -ketimino esters in good yield.^{7,8} Research is currently underway to exploit these substrates in the context of catalytic asymmetric synthesis.⁹

This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan. T.H. thanks a Grant-in-Aid for Young Scientists (B).

References and Notes

- 1 *Chiral Amine Synthesis: Methods, Developments and Applications*, ed. by T. C. Nugent, Wiley-VCH, **2010**.
- 2 a) E. Dessipri, D. A. Tirrell, *Macromolecules* **1994**, *27*, 5463. b) A. Armstrong, I. D. Edmonds, M. E. Swarbrick, N. R. Treweek, *Tetrahedron* **2005**, *61*, 8423. c) C. G. Jørgensen, R. P. Clausen, K. B. Hansen, H. Bräuner-Osborne, B. Nielsen, B. Metzler, J. Kehler, P. Krosgaard-Larsen, U. Madsen, *Org. Biomol. Chem.* **2007**, *5*, 463. d) K. Mikami, T. Murase, L. Zhai, S. Kawauchi, Y. Itoh, S. Ito, *Tetrahedron Lett.* **2010**, *51*, 1371.
- 3 For reviews, see: a) M. Shibasaki, M. Kanai, *Chem. Rev.* **2008**, *108*, 2853. b) O. Riant, J. Hannedouche, *Org. Biomol. Chem.* **2007**, *5*, 873. c) P. G. Cozzi, R. Hilgraf, N. Zimmermann, *Eur. J. Org. Chem.* **2007**, 5969. d) S. J. Connon, *Angew. Chem., Int. Ed.* **2008**, *47*, 1176.
- 4 For reviews, see: a) Y. Ohfuné, T. Shinada, *Eur. J. Org. Chem.* **2005**, 5127. b) H. Vogt, S. Bräse, *Org. Biomol. Chem.* **2007**, *5*, 406. c) C. Cativiela, M. D. Díaz-de-Villegas, *Tetrahedron: Asymmetry* **2007**, *18*, 569. d) R. A. Mosey, J. S. Fisk, J. J. Tepe, *Tetrahedron: Asymmetry* **2008**, *19*, 2755.
- 5 a) D. J. Hart, K. Kanai, D. G. Thomas, T. K. Yang, *J. Org. Chem.* **1983**, *48*, 289. b) R. Kupfer, S. Meier, E.-U. Würthwein, *Synthesis* **1984**, 688. c) E. W. Colvin, D. McGarry, M. J. Nugent, *Tetrahedron* **1988**, *44*, 4157.
- 6 The crystal structure has been deposited at the Cambridge Crystallographic Data Centre (CCDC 801250). The data can be obtained free of charge via the Internet at www.ccdc.cam.ac.uk/conts/retrieving.html.
- 7 Use of these *N*-Boc α -ketimino esters in chiral auxiliary based asymmetric aziridination was reported in advance, see: T. Hashimoto, H. Nakatsu, K. Yamamoto, S. Watanabe, K. Maruoka, *Chem.—Asian J.* **2011**, *6*, 607.
- 8 Representative procedure for the synthesis of **3c**: To a stirred solution of *tert*-butyl (trimethylsilyl)carbamate (**1**) (94.7 mg, 0.50 mmol) in THF (4.5 mL) was added 1.6 M hexane solution of butyllithium (313 μ L, 0.50 mmol) at -78°C . After stirring for 1 h, a THF solution of *tert*-butyl benzoylformate (103.1 mg, 0.50 mmol) was added dropwise. The reaction solution was stirred for an additional 5 h, and to this solution was successively added chlorotrimethylsilane (66.6 μ L, 0.525 mmol). The reaction was then gradually warmed to room temperature over 2 h. The mixture was poured into aqueous NaHCO_3 and extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel coated with a dry ice jacket eluting with CH_2Cl_2 (1% triethylamine) to give **3c** as a yellow liquid in 74% yield (113.3 mg, 0.37 mmol).
- 9 Supporting Information is available electronically on the CSJ-Journal Web site, <http://www.csj.jp/journals/chem-lett/index.html>.