A New Method for the Synthesis of *N*-t-Butoxycarbonyl protected α-Alkoxy Amines from Allylamines under Neutral Conditions

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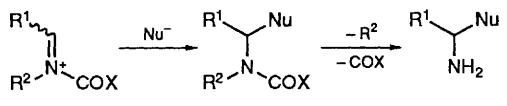
Treatment of the Boc protected allylamines (**4**) with rhodium catalysts in the presence of alcohols produces *N*-Boc substituted α-alkoxy amines (**5**) in high yields, which can be used as a synthetic equivalents of activated imines having an easily deprotectable Boc group.

The reactivity of the carbon–nitrogen double bond of imines towards nucleophiles is low in comparison with that of the carbon–oxygen double bond of aldehydes and ketones. To overcome this difficulty, either 'activated' imines (iminium ions)[1—3] or 'activated' nucleophiles[4—6] are frequently used in organic synthesis. As examples of 'activated' imines, a number of acyliminium ions (**1**) have been developed, and nucleophilic attack takes place readily to give *N*-alkyl(R^2)-carbamates (**2**) in good yields (Scheme 1). However, we encountered a serious problem when we tried to obtain the desired primary amine (**3**); it was difficult to remove the two substituents (R^2 and XCO groups) attached to nitrogen under synthetically acceptable mild conditions. It is desirable to develop a synthetic method for new 'activated' imines having easily deprotectable substituents on nitrogen.

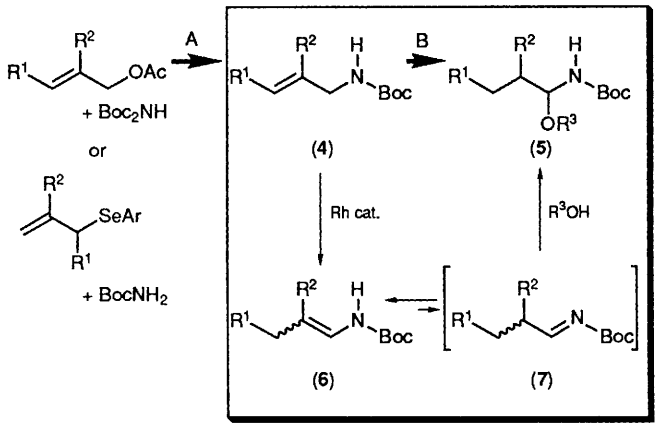
We report a new method for the synthesis of α-alkoxy amines (**5**), synthetic equivalents of the t-Boc[7] attached[8] enolizable imine (**7**), from *N*-Boc protected allylic amines under neutral conditions (Scheme 2). Our synthetic strategy is as follows. Step A: the Boc protected allylic amines (**4**) are prepared from either allylic selenides with $BocNH_2$ by using *N*-chlorosuccinimide,[9] or allylic acetates with Boc_2NH by using a palladium catalyst.[10] Step B: the unsaturated moiety is rearranged to form a carbon–nitrogen double bond from the



(1) (2) (3)

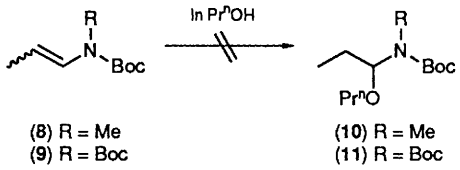
X = alkyl or alkoxy
R^2 = alkyl

Scheme 1

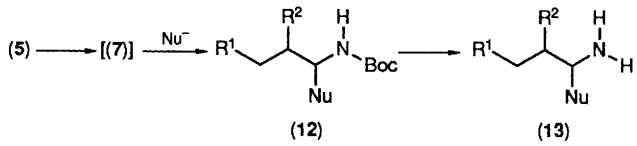


a; $R^1 = R^2 = H$
b; $R^1 = Me, R^2 = H$
c; $R^1 = H, R^2 = Me$

Scheme 2



Scheme 3



Scheme 4

Table 1. Synthesis of (5) from (4) [*via* (6)].

Entry	Substrate	Solvent	*T*/°C	Time	Yield (%) (5)[a]	Yield (%) (6)
1	(4a)	Pr^nOH	100	8 h	77[b]	0
2	(4a)	Pr^nOH	100	3 h	3[b]	80
3[c]	(4a)	THF	100	6 h	—	98
4[c]	(4a)	MeOH	65	12 h	11	78
5[c]	(4a)	MeOH	100	12 h	82	0
6[c]	(4b)	MeOH	120	6 d	60	0
7[c]	(4c)	MeOH	120	6 d	4	70
8	(4b)	MeOH	80[d]	6 d	84	0
9	(4c)	MeOH	80[d]	20 d	59	29
10	(6a)	Pr^nOH	100	5 h	90[b]	—
11	(6a)	Pr^nOH	100	5 h	90[b]	—

[a] R^3 = Me unless otherwise noted. [b] R^3 = Pr^n. [c] Carried out in a sealed tube. [d] Under 10 kbar pressure.

carbon–carbon double bond by using a transition-metal catalyst[11] under neutral condition and the resulting unstable double bond is trapped with an alcohol and isolated in the stable form (5). We first attempted the double bond isomerization of the Boc attached allylamine (4a) by using rhodium catalysts (Table 1).

Conversion of (4a) to (5a) was observed with 4 mol% of the hydride complex $[RhH(PPh_3)_4]$ in the presence of propanol (entry 1). When the reaction was stopped at an earlier stage (entry 2), or when an aprotic solvent, tetrahydrofuran (THF), was used (entry 3), the enecarbamate (6a) was obtained instead of (5a). A mixture of (6a) and (5a) was obtained in methanol (entry 4) presumably owing to the lower boiling point of methanol. When the reaction was carried out in a sealed tube at 100 °C, (4a) was converted to (5a) in satisfactory yield (entry 5).

Next, extension to substituted allylic systems was examined. Under the same conditions as for entry 5, the protected allylic amine (4b) was not converted to (5b), and the starting material was recovered. At 120 °C, the starting material (4b) was completely consumed and the desired alkoxy amine (5b) was obtained in 60% yield along with several unidentified byproducts (entry 6). Although the protected allylic amine (4c) was converted to the enecarbamate (6c) in 70% yield at 120 °C, only a trace of the desired (5c) was obtained (entry 7). Use of higher temperatures and/or longer reaction periods gave many unidentified byproducts probably because of the lability of Boc group under these conditions. Use of high pressures[12] solved this problem. The reaction of (4b) in methanol at 80 °C for 6 days under 10 kbar gave (5b) in 84% yield (entry 8). Similarly, (4c) produced (5c) in 59% yield (entry 9).

The typical procedure is as follows. A mixture of the *N*-Boc allylic amine (4) and 4 mol% of $[RhH(PPh_3)_4]$ in the alcohol was refluxed or heated, and the resulting mixture was filtered through Florisil to removed residual metal catalyst. The filtrate was concentrated and the residue chromatographed on alumina to give the desired alkoxy amine (5). Thus, the present reaction and its purification procedure requires neither aqueous work-up nor use of strong acidic conditions.

Regardless of the presence or absence of rhodium catalysts, treatment of the purified enecarbamate (6a) with propanol under reflux gave the corresponding alkoxy amine (5a) in an essentially quantitative yield (entries 10 and 11). In contrast, a similar reaction of the fully *N*-protected enecarbamate (8) and (9), which cannot adopt a tautomeric structure like (7), did not give (6), but the starting materials were recovered (>90%) either with or without rhodium (Scheme 3). Based on the above experimental results, we propose the reaction mechanism shown in Scheme 2. The rhodium complex effectively catalyses the double-bond migration from (4) to (6). The tautomerism of (6) to (7) occurs without rhodium. The equilibrium between (6) and (7) strongly favours (6) under neutral conditions. At higher temperatures and/or high pressures, a small amount of (7) is formed, which is immediately trapped with alcohols to give (5). We believe that this type of equilibrium between (6) and (7) under neutral or slightly basic conditions has not been taken into consideration previously. It was believed that the conversion of enecarbamates to alkoxy amines requires acidic conditions *via* the iminium ion (1; R^2 = H).[2]

In conclusion, we have discovered, for the first time, the conversion of an enecarbamate (6) to an α-alkoxy amine (5) under neutral conditions. Synthesis of (5) from allylamines is also available *via* rhodium-catalysed isomerization. A new 'activated' imine (7) can be generated from (5), which gives (12) upon treatment with nucleophiles (Scheme 4). Conse-

quently, the present finding opens a door to the synthesis of primary amines (**13**) through (**5**) starting from (**4**).

Received, 14th May 1990; Com. 0/02112A

References

1 J. Yamada, H. Satô, and Y. Yamamoto, *Tetrahedron Lett.*, 1989, **30**, 5611; Y. Yamamoto and M. Schmid, *J. Chem. Soc., Chem. Commun.*, 1989, 1310.
2 W. N. Speckamp and H. Hiemstra, *Tetrahedron*, 1984, **40**, 4367.
3 J. Sisko and S. M. Weinreb, *J. Org. Chem.*, 1990, **55**, 393.
4 Y. Yamamoto, S. Nishii, K. Maruyama, T. Komatsu, and W. Ito, *J. Am. Chem. Soc.*, 1986, **108**, 7778.
5 Y. Yamamoto, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 947.
6 Y. Yamamoto, *Aldrichimica Acta*, 1987, **20**, 45.
7 B. F. Lundt, N. L. Johansen, A. Vølund, and J. Markussen, *Int. J. Peptide Protein Res.*, 1978, **12**, 258.
8 For other methods for the synthesis of Boc attached alkoxy amines: T. Shono, N. Kise, F. Sanda, S. Ohi, and K. Yoshida, *Tetrahedron Lett.*, 1989, **30**, 1253: D. Seebach, R. Charczuk, C. Gerber, P. Renaud, H. Berner, and H. Schneider, *Helv. Chim. Acta*, 1989, **72**, 401.
9 R. G. Shea, J. N. Fitzner, J. E. Fankhauser, and P. B. Hopkins, *J. Org. Chem.*, 1984, **49**, 3647.
10 R. D. Conell, T. Rein, B. Åkermark, and P. Helquist, *J. Org. Chem.*, 1988, **53**, 3845.
11 J. K. Stille and Y. Becker, *J. Org. Chem.*, 1980, **45**, 2139; K. Tani, S. Yamagata, S. Akutagawa, S. Kumobayashi, T. Taketomi, H. Takaya, A. Miyashita, R. Noyori, and S. Otsuka, *J. Am. Chem. Soc.*, 1984, **106**, 5208.
12 Y. Yamamoto, *Chem. Lett.*, 1987, 945: Y. Yamamoto and K. Maruyama, *J. Am. Chem. Soc.*, 1983, **105**, 6963; Y. Yamamoto, K. Maruyama, and K. Matsumoto, *J. Chem. Soc., Chem. Commun.*, 1984, 548.