Pergamon

Tetrahedron Letters, Vol. 38, No. 12, pp. 2129-2132, 1997

0040-4039/97 \$17.00 + 0.00

PII: S0040-4039(97)00324-9

A New Facile Method for the Chemoselective Reductive Transformation of Azides to *N*-(*tert*-Butoxycarbonyl)amines

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Abstract: A new chemoselective procedure for the reductive transformation of organic azides to the corresponding *N*-(*tert*-butoxycarbonyl)amino derivatives using triethylsilane and di-*tert*-butyl dicarbonate in the presence of a catalytic amount of 20% Degussa $Pd(OH)_2/C$ is described.

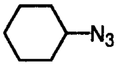
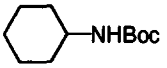
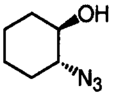
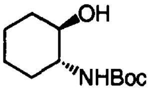
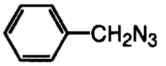
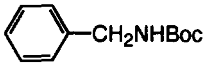
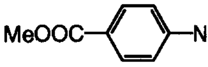
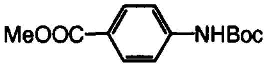
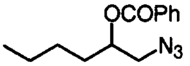
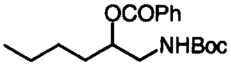
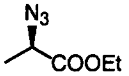
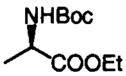
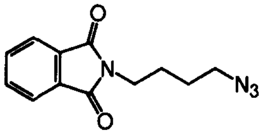
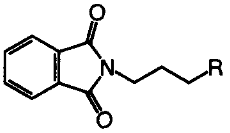
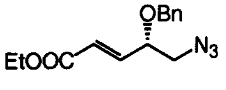
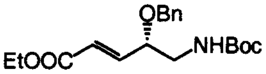
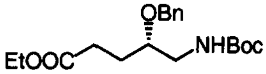
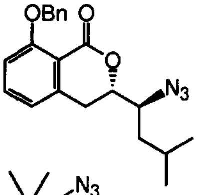
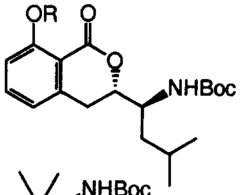
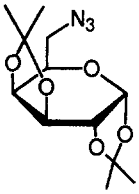
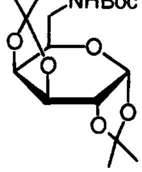
Organic azides are an important class of compounds, particularly for producing primary amines via reductive transformation, and several reducing agents have been developed to date.[1, 2] In a closely related field, protection of amines with appropriate protecting agents also plays an important role in multistep synthesis.[3] Among the various amine-protecting groups, the *tert*-butoxycarbonyl (Boc) group is frequently used due to its chemical stability to acids, bases, and hydrogenation. Based on this background, it is reasonable to consider that the combination of azide reduction and *N*-Boc-protection should offer an efficient approach to the manipulation of organic amino compounds. To our surprise, however, little attention has been paid to this type of synthetic strategy. Indeed, there has been only one report by Saito et al., which involved the use of di-*tert*-butyl dicarbonate (Boc_2O) under conditions of catalytic hydrogenation.[4] Recently, Afonso reported an alternative one-pot procedure using reduction with *n*-Bu_3P followed by reaction with Boc_2O.[5]

In our studies on the synthesis of biologically interesting natural products,[6] we required an efficient method for achieving the chemoselective transformation of azides to the corresponding *N*-Boc-protected amines. Despite our extensive efforts to confirm the feasibility of the above procedures, we only found that they were incompatible with other reducible functionalities or required a tedious workup to remove any by-products. After surveying newer reagent systems, we found that the use of triethylsilane[7, 8] and palladium catalysts in the presence of Boc_2O was highly favorable for our purpose (Scheme 1). We describe here the general applicability of this method.

$$\mathrm{R{-}N_3} \quad + \quad \mathrm{Boc_2O\ (1.5\ equiv)} \quad \xrightarrow[\substack{\text{20\% Degussa Pd(OH)}_2\text{/C} \\ \text{EtOH}}]{\text{Et}_3\text{SiH (1.5 equiv)}} \quad \mathbf{R{-}NHBoc}$$

Scheme 1

Table 1. Reductive Transformation of Azides to *N*-Boc-Protected Amines[a]

Run	Organic Azide	Temp (°C), Time (h)	Product (Mp, °C) ref.	Yield, %[b]
1	 **1**	50, 28	 **11** (73-74.5)[10]	75
2	 **2**	50, 19	 **12** (96-97)[11]	76
3	 **3**	rt, 15	 **13** (56-57)[5]	93
4	 **4**	50, 36	 **14** (109[c])[12]	99
5	 **5**	rt, 19	 **15** (68-70.5)	92
6	 **6**	rt, 0.5	 **16** (oil)[13]	98
7	 **7**	rt, 8	 **17** ($R = CH_2NHBoc$, 112-112.5) **18** (R = CN, 64-66)	64 35
8	 **8**	rt, 1	 **19** (oil)	84
9		rt, 4[d]	 **20** (oil)	81
10	 **9**	50, 18	 **21** (R = H, 126-128) **22** (R = Bn, 92.5-94)	81 15
11	 **10**	rt, 18[e]	 **23** (122-123)	77

[a] Unless otherwise noted, all reactions were performed using 20% Degussa $Pd(OH)_2/C$ (10 mg/mmol), Et_3SiH (1.5 equiv), and Boc_2O (1.5 equiv) in EtOH. [b] Isolated yield. [c] Sublimed. [d] Hydrogen gas was used in place of Et_3SiH. See ref. 4. [e] 20% Degussa $Pd(OH)_2/C$ (20 mg/mmol) and Et_3SiH (2 equiv) were used.

The results are summarized in Table 1.[9] A variety of azido compounds were efficiently reacted with triethylsilane (1.5 equiv) and Boc_2O (1.5 equiv) in the presence of a catalytic amount of 20% Degussa $Pd(OH)_2/C$[14] to provide the corresponding *N*-Boc-protected amines. A brief examination of the reaction conditions revealed that the reactions were best achieved in ethanol as a solvent.[15] Normally, the reactions proceeded at room temperature without any difficulty, but with less-reactive substrates such as **1**, **2**, **4**, and **9**, it was necessary to conduct the reactions at 50 °C to achieve good results (runs 1, 2, 4, 10).

It should be emphasized that in the absence of Boc_2O, all of these reactions were unsuccessful and mainly resulted in recovery of the starting materials.[8] These results seem to indicate that once the amino compounds were formed, they acted immediately as a catalytic poison.[16] This was also true when triethylamine or 4-dimethylaminopyridine was added to this system as a promoter.

The successful results obtained with substrate **8** reflect the excellent chemoselectivity of this method even in the presence of ester, olefinic, and benzyl protective groups (run 8). When the same reaction was conducted under hydrogen gas atmosphere according to the literature procedure,[4] the concomitant reduction of a conjugated double bond was unavoidable (run 9). Similar selectivity was also observed for compounds **4-7** and **9** (runs 4-7, 10). Conversion of **5** to **15** proceeded smoothly without acyl migration (run 5). In the reaction using **7**, a considerable amount of nitrile **18** was formed as a by-product (run 7). This type of palladium-catalyzed decomposition of azides to nitriles has been reported previously.[17] Nevertheless, this unusual behavior of **7** must be regarded as an exceptional example, since no similar products were obtained for other primary azides such as **3**, **5**, **8**, and **10**. In contrast to the case with **8**, when **9** was used as the substrate, concomitant debenzylation of a phenol ring was observed as a major process (run 10). This reflects the labile nature of the benzyl phenyl ether due to the presence of an *ortho*-carbonyl function.[18]

In conclusion, we have developed a convenient method for transforming azides to *N*-Boc-protected amines under fairly mild conditions. We believe that the reagent system described here has tremendous potential for use in organic synthesis due to its high chemoselectivity, efficiency, and simplicity. The application of this method to the synthesis of natural products is currently underway.

Typical experimental procedure: To a stirred mixture of benzyl azide (**3**) (133 mg, 1 mmol), Boc_2O (327 mg, 1.5 mmol), and 20% Degussa $Pd(OH)_2/C$[14] (9 mg) in EtOH (3 mL) was added Et_3SiH (240 μL, 1.5 mmol) at room temperature. When Et_3SiH was added, a slightly exothermic reaction and gas evolution were observed. After stirring for 15 h, the mixture was filtered through Celite and the filtrate was concentrated in vacuo. The crude product was purified by silica gel column chromatography (hexane/AcOEt = 4 : 1) to give *N*-Boc-benzylamine (**13**) (193 mg, 93%) as colorless plates (recrystallized from Et_2O-hexane; lit.[5] mp 55.5-56 °C).

Acknowledgement. The present work was supported in part by Scientific Research Grants from the Ministry of Education, Science and Culture of Japan.

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(*Received in Japan* 24 *January* 1997; *revised* 10 *February* 1997; *accepted* 14 *February* 1997)