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Chemoselective conversion of azides to *t*-butyl carbamates and amines

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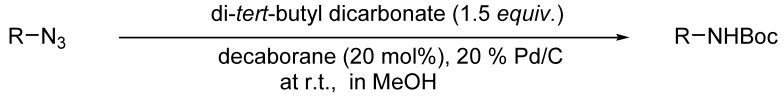
Abstract—Azides were converted to the corresponding carbamates using a system of 20 mol% of decaborane ($B_{10}H_{14}$) and 20 weight% of 10% Pd/C in methanol in the presence of di-*tert*-butyl dicarbonate at rt in high yields and to the corresponding amines using a system of 10 mol% of decaborane and 20 weight% of 10% Pd/C in methanol in the absence of di-*tert*-butyl dicarbonate at rt in high yields.

Reduction of azides has been known as one of the simplest methods for the preparation of primary amines in the organic chemistry.[1] The protection of amines with an appropriate group plays an important role in multi-step synthesis of complex products and also in peptide synthesis. Among the various amine-protecting groups,[2] *t*-Boc group is commonly used due to its chemical stability toward acids, bases and hydrogenation. The most common procedures for the conversion of azides to *t*-butyl carbamates are the catalytic hydrogenation using Pd/C[3] or Rh[4] and the treatment with phosphines[5] such as n-Bu_3P and Me_3P and with 20% Degussa $Pd(OH)_2/Et_3SiH$[6] followed by protection with Boc_2O in one-pot way. The other condition is Fe/NH_4Cl in methanol.[7] However, some of these methods suffer from their own disadvantages. For example, phosphine reagents suffer from drawbacks like unsatisfactory yields with secondary and aromatic azides and require tedious isolation procedures to remove by-products such as phosphine oxide. The other condition is the treatment of azides with indium or zinc powder.[8] However, this method could not be applied to the preparation of carbamates when anhydride such as Boc_2O was used for the reaction.

Decaborane ($B_{10}H_{14}$)[9,10] is a commercially available white solid that decomposes slowly in air and was found to be a quite mild reducing agent in reduction reactions such as reductive amination,[11a] reductive etherification,[11b] and reduction of carbonyls.[11c] As a continuous work of decaborane as a reducing agent, decaborane was applied to the conversion of azides to the corresponding carbamates and amines. Here we wish to report the direct conversion of various azides to the corresponding *t*-butyl carbamates using a system of decaborane and 10% Pd/C in the presence of di-*tert*-butyl dicarbonate in methanol at rt (Scheme 1) and to the corresponding amines using a system of decaborane and 10% Pd/C in the absence of di-*tert*-butyl dicarbonate in methanol at rt (Scheme 3).

A variety of aliphatic and aromatic azides were reduced and protected in one-pot to give the corresponding *t*-Boc carbamates using 20 mol% of decaborane–20 weight% of 10% Pd/C system in methanol at rt in high yields (entries 1–12), as shown in Table 1. The chloro group (entry 14) and nitro group (entries 8, 12 and 14) were remained intact under the reaction conditions. The reaction of 5-nitro-2-azidotoluene (entry13) did not give *t*-Boc carbamate due to the weak nucleophilicity of aniline **2** formed. Instead, two products **1** and **2** were obtained after extended reaction time. Any other trials to protect amine **2** including a protocol of Et_3N, Boc_2O



Scheme 1.

Keywords: azides; amines; protection; Boc_2O; decaborane; Pd/C.

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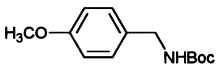
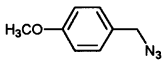
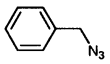
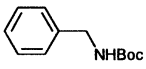
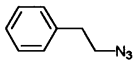
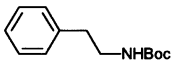
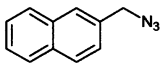
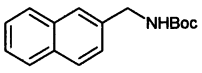
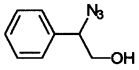
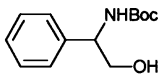
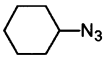
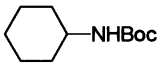
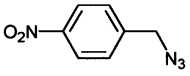
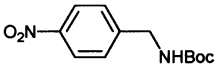
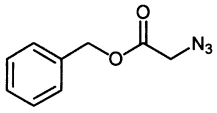
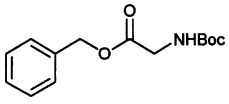
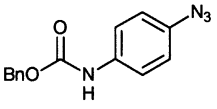
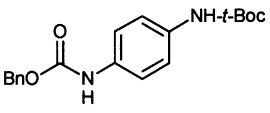
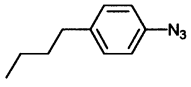
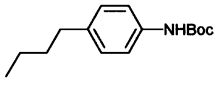
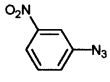
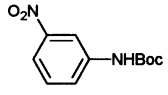
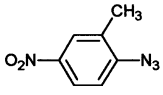
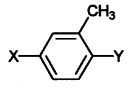
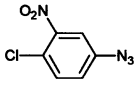
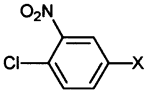
Table 1. One-pot conversion of azides[9] to *t*-butyl carbamates

Entry	Azides	Products	Time	Yield (%)[a]
1			5 h	71
2			8 h	83
3			6 h	87
4			7 h	100
5[9b)]			8 h	92
6			5 h	94
7	$CH_3(CH_2)_9CH_2$-N_3	$CH_3(CH_2)_9CH_2$-NHBoc	5 h	87
8			4.5 h	86
9			8 h	81
10			5 h	86
11			3 h	98
12[b)]			1.5 h	90
13		 **1** X=Y= NH-Boc **2** X=NO_2, Y=NH_2	24 h	**1**: 38 **2**: 57
14		 3 X=NHBOc 4 x=NH_2	3 h	**3** 30 **4** 68

a) Isolated yields. b) 10 mole% of decaborane was used.

and DMAP used for the *t*-Boc protection of less nucleophilic sulfonamide failed.[12] The reaction of 4-chloro-3-nitrophenylazide (entry 14) gave a mixture of protected aniline **3** and aniline **4** due to the weak nucleophilicity of aniline **4**.

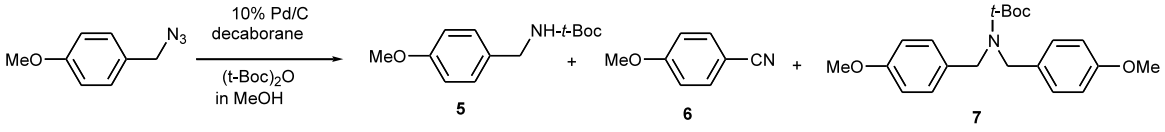
The reaction in methanol was studied using 4-methoxybenzylazide as a model to find the optimum amounts of decaborane. The treatment of 4-methoxybenzylazide with 10 mol% of decaborane and 20% Pd/C in the presence of 1.5 equiv. of di-*tert*-butyl dicarbonate in methanol gave a *t*-Boc-benzylamine (54%), 4-methoxybenzonitrile **6** and bis-(4-methoxybenzyl)-carbamic acid *tert*-butyl ester **7**[13] (Scheme 2, Table 2). It was reported that benzonitrile is formed through dehydrogenation of benzylideneamine generated by dehydrogenation[14] or Curtius rearrangement[15] of benzylazide under the hydrogen deficient condition. The carbamic acid ester **7** is supposed to be formed through the reductive amination of 4-methoxybenzaldehyde dimethyl acetal (or benzaldehyde)[16] generated in situ and 4-methoxybenzylamine followed by the carbamoylation with $(t\text{-Boc})_2O$. When more than 20 mol% of decaborane was used, benzonitrile formation was not observed at all and a little less amount of side product **7** was formed. Therefore, 20 mol% decaborane was the choice of amount in the reaction (entry 2 of Table 2).

The reduction of azides to primary amines was reported recently, but the reaction conditions are still toxic and strong.[17] 10 mol% of decaborane in the absence of di-*tert*-butyl dicarbonate was enough to reduce the electron deficient azides such as phenylazides and sulfonylazide to the corresponding amines (entries 1–6). However, the reduction of aliphatic azides was incomplete under the same conditions, probably due to the formed basic amine, which might act as a poison against the palladium catalyst.[18] To overcome the problem, 5 equiv. of acetic acid and 30% of decaborane (instead of 10 mol%) was used, as shown in Scheme 3 (entries 7–9). Our method is chemoselective against nitrile (entry 4), amide (entry 5), CBZ (entry 6), benzylic ester (entry 7) and nitro groups (entries 1, 2, 3 and 8) (Table 3).

In conclusion, azides were reduced and protected to give the corresponding *t*-Boc carbamates in the presence of di-*tert*-butyl dicarbonate using 20% of decaborane and 20% of Pd/C in good to high yields. However, amines from 4-nitrophenylazide and 4-chloro-3-nitrophenylazide were not protected under the conditions. Using 10 mol% of decaborane and 20% Pd/C, electron deficient azides were reduced to the corresponding amines chemoselectively in high yield. However, 30 mol% of decaborane and 5 equiv. of acetic acid were necessary for the successful reduction of electron sufficient azides such as benzyl azides and alkyl azide.

1. Experimental

A typical conversion procedure of azides to *t*-Boc carbamates: to a solution of 4-methoxybenzylazide (100 mg, 0.61 mmol) in methanol (3 ml) was added di-*tert*-butyl dicarbonate (200.6 mg, 0.92 mmol, 1.5 equiv.), 20 weight% of 10% Pd/C (20 mg) and 20 mol% of decaborane (14.9 mg, 0.12 mmol). The resulting solution was stirred for 5 h at rt under nitrogen. The reaction was monitored by TLC using a solution of ethyl acetate and hexane (1:10). The mixture was filtered through Celite

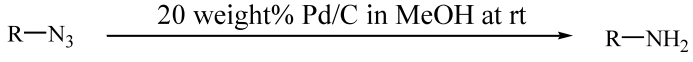


Scheme 2.

Table 2. The reaction[a] of 4-methoxybenzylazide[b] in methanol

Entry	Decaborane (mol%)	Time (h)	Yield
1	10	5	**5**: 79 mg (54%)[c], **6**: 2.8 mg (2%), **7**: 38.2 mg (10.7%)[d]
2	20	5	**5**: 116 mg (80%), **7**: 20 mg (8.7%)
3	30	5	**5**: 120 mg (82%), **7**: 18 mg (7.8%)

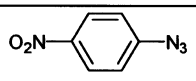
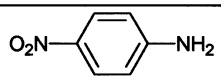
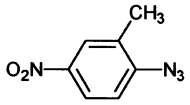
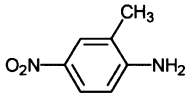
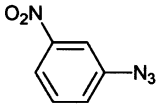
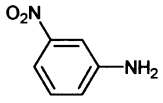
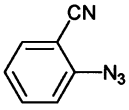
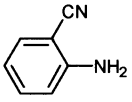
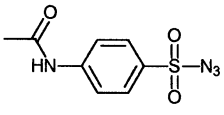
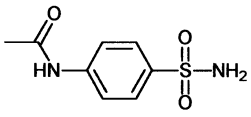
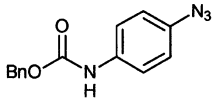
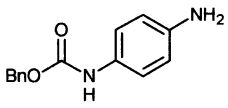
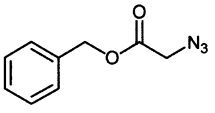
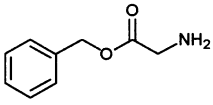
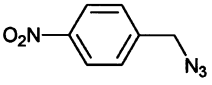
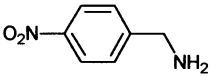
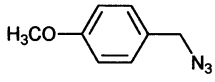
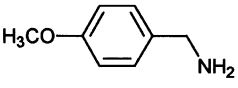
[a] 20 weight% of 10% Pd/C and 1.5 equiv. of di-*tert*-butyl dicarbonate were used.
[b] 100 mg of substrate was used in the reaction.
[c] Isolated yields.
[d] Ratio of **6** and **7** was determined by ^1H NMR spectrum.



Method A: entries 1-6: decaborane (*10 mol%*)
Method B: entries 7-9: decaborane (*30 mol%*), acetic acid (5 *equiv.*)

Scheme 3.

Table 3. Reduction of azides to amines

Entry	Azides	Products	Time	Yield (%)[a]
1			15 min	99
2			1 h	82
3			1.5 h	94
4			2.5 h	91
5			20 min	98
6			5 h	92
7			4 h	93
8			2.5 h	81
9			5 h	79

a) Isolated yields.

bed. The filtrate was then concentrated, chromatographed on silica gel column using a solution of ethyl acetate and hexane (1:7) as an eluent, and concentrated to give a *t*-Boc carbamate as a colorless syrup in 80% yield (116 mg) and bis-(4-methoxybenzyl)-carbamic acid *t*-butyl ester **7** as a syrup in 8.7% yield (20 mg).

A typical procedure of reduction of aryl azides and sulfonyl azides: to a solution of 4-nitrophenylazide (100 mg, 0.61 mmol) in methanol (3 ml) was added 20 weight% of 10% Pd/C (20 mg) and 10 mol% of decaborane (7.4 mg, 0.06 mmol). The solution was stirred for 15 min at rt under nitrogen. The mixture was filtered through Celite and concentrated. The concentrate was chromatographed on silica gel column using a solution of ethyl acetate and hexane (1:4) and concentrated to give 4-nitroaniline as a yellow solid in 99% yield (83.8 mg).

A typical procedure of reduction of aliphatic azides: to a solution of benzyl azidoacetate (100 mg, 0.52 mmol) in methanol (3 ml) was added 20 weight% of 10% Pd/C (20 mg), acetic acid (157 mg, 2.61 mmol) and 30 mol% of decaborane (19.2 mg, 0.16 mmol). After 3 h, the reaction was filtered through Celite bed, concentrated and chromatographed on silica gel column using a solution of 5% methanol in methylene chloride to give benzyl aminoacetate as a colorless liquid in 93% yield (80 mg).

Acknowledgements

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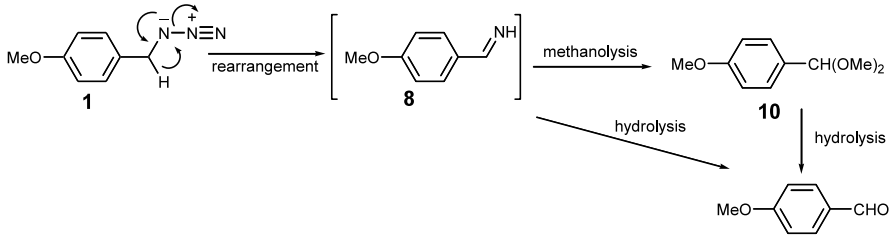

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