Reductive Dimerization of Azides to Secondary Amines under Hydrogenation Conditions

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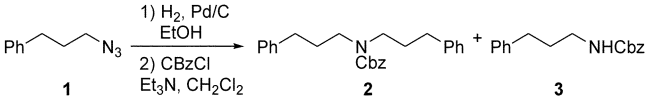
The catalytic hydrogenation of organic functional groups such as imine, nitrile, oxime, azide, nitro, and nitroso into the corresponding amines is a fundamental organic transformation.[1] In the course of our study on the synthesis of polyamines, we used the catalytic hydrogenation for the conversion of a simple azide compound into the corresponding primary amine. We found that a significant amount of an unknown product was always accompanied along with the desired amine depending on reaction conditions. The unknown product was identified to be a secondary amine, which was produced through a "reductive dimerization" process (Equation 1).

$$R\text{-}CH_2N_3 \xrightarrow{H_2,\ Pd/C} RCH_2NHCH_2R \qquad (1)$$

A literature survey indicates that similar reductive alkylation reactions were studied in early nineties in the cases of other functional groups such as amine and cyanide under severe reaction conditions.[2] For example, primary amines such as β-phenylethylamine and cyclohexylamine are converted to the corresponding secondary amines at 200 °C over a nickel catalyst under a pressure of about 100 atm of hydrogen. Also, primary alkyl cyanides are converted to the corresponding secondary amines at 100-150 °C under otherwise similar conditions. Other functional groups such as oximes, nitro, and nitroso derivatives are suggested to undergo a similar reductive dimerization process to form secondary amines because in these hydrogenations imines as the common intermediates are expected. Although similar imine intermediates are expected, the reductive alkylation reaction of azide compounds has not been pursued thereafter. Very recently, Undheim and co-workers observed the reductive dimerization of azides to the secondary amines under mild hydrogenation conditions, and applied the reaction to the synthesiss of an α-bridged bis(glycine) derivative.[3] The conditions of the dimerization reaction, however, have not been studied further. Since the conversion of azide compounds to the primary amines under usual catalytic hydrogenation conditions has been used as a standard procedure in organic transformations, the unexpected reductive dimerization under mild conditions needs to be examined in detail. The reductive dimerization process can also be developed as an alternative route to secondary amine compounds of biological importance.[4] Herein, we wish to report a systematic study on the reductive dimerization process. Our study shows that the reductive dimerization is preferred over normal reduction process, particularly, at high temperature. Also, we observed that a cyanide can be a plausible intermediate for the reductive dimerization in addition to the imine intermediate.[3]

Table 1. Dimerization of azide **1** under different hydrogenation conditions[a]



1 **2** **3**

Entry	Temperature	H_2	Product distribution, **2** : **3**[b]		
			0.1 M[c]	0.25 M[c]	0.5 M[c]
1	0 °C	1 atm	1 : 3.2 (17)	1 : 2.4 (25)	1 : 1.8 (27)
2	30 °C	1 atm	1 : 0.6 (45)	1 : 0.7 (53)	1 : 0.3 (43)
3	50 °C	1 atm	1 : 0.4 (55)	1 : 0.2 (60)	1 : 0.3 (67)
4	80 °C	1 atm	–	–	1 : 0.04 (78)[d]
5	0 °C	2 atm	1 : 1.4 (32)	1 : 3.6 (16)	1 : 2.3 (30)
6	30 °C	2 atm	1 : 1.5 (32)	1 : 0.6 (45)	1 : 0.7 (36)
7	50 °C	2 atm	1 : 0.4 (58)	1 : 0.3 (59)	1 : 0.1 (57)

[a]Catalyst loading: 48-50 mg of 15 wt% Pd/C, 1.0 mmol scale. [b]Determined by GC analysis; Numbers in parentheses mean isolated yields of dimer **2** by column chromatography. [c]Concentration of azide **1** (0.5 mmol in EtOH). [d]2 mmol scale.

We have investigated the reductive alkylation of simple azide **1** under different hydrogenation conditions using Pd/C as the catalyst, by changing the reaction temperature, hydrogen gas pressure, concentration of the reactant, and solvent. The produced amines were in situ protected with a carbobenzyloxy (Cbz) group for the determination of their ratio by GC analysis. The results are summarized in Table 1.

As can be seen from the table, the dimerization product **2** becomes major when the reaction temperature increases. Thus, the simple reduction product **3** was produced as the major component at 0 °C under 1 atm H_2 pressure (Entry 1), whereas it became minor at 50 °C (Entry 3). Also, increasing the reactant concentration from 0.1 M to 0.5 M resulted in the increase of the dimerization product; however, further

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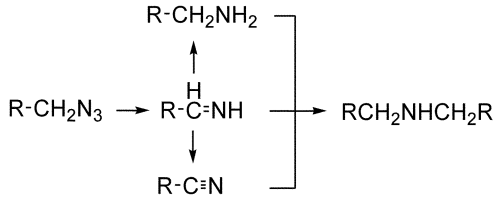
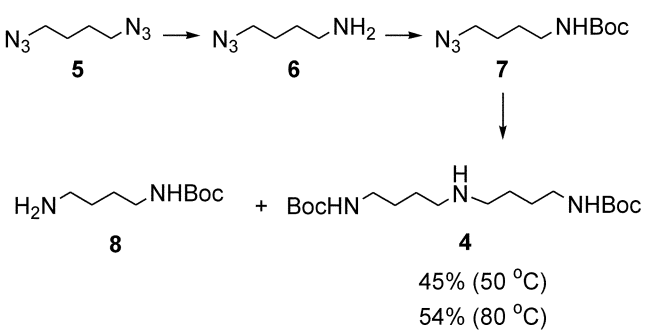


Scheme 1. Plausible intermediates for the dimerization of an azide to the secondary amine.

increasing the concentration from 0.5 M to 1.0 M resulted in a little change. Changing the solvent to THF or MeOH resulted in a lower yield of the dimerization product. Increasing the H_2 pressure from 1 atm to 2 atm resulted in a small change in the product ratio. Thus, under an optimized condition (0.5 M substrate in refluxing ethanol), a maximum yield of 78% can be obtained for the reductive dimerization of azide **1** (Entry 4). This study also indicates that a low temperature and a dilute reactant concentration under 1 atm H_2 pressure are preferred for the simple hydrogenation of an azide to the amine over the Pd/C catalyst. Otherwise, other reduction methods can be used to avoid the reductive dimerization product.[5]

As plausible intermediates of the reductive dimerization process, the corresponding amine, imine, and cyanide can be considered based on the literature data and our own observation (Scheme 1). We were able to observe the formation of a cyanide among the reaction mixture, which is probably produced from the common intermediate imine through a dehydrogenation reaction. A possible mechanism for the reductive dimerization may involve cyanide in addition to imine intermediate that is suggested by Undheim and co-workers.[3] Thus, the amine adds to the cyanide intermediate, generating an adduct, from which extrusion of ammonia and subsequent reduction of the resulting imine bond leads to the dimerization product.

As an extension of the reductive alkylation of azides, we have synthesized homospermidine **4** following the Scheme 2. The diazide **5**, prepared from 1,4-dichlorobutane, was selectively reduced to monoamine **6** by treatment with Ph_3P·HCl in diethyl ether/ethyl acetate. A solution of azido compound **7** (2 mmol) in ethanol (4 mL) was subjected to the reductive alkylation over Pd/C at different reaction



Scheme 2. Synthesis of a protected homospermidine **4** through the reductive dimerization of azide **7**.

temperatures to provide homospermidine **4** in 45% (at 50 °C) and 54% (at 80 °C) isolated yields. Thus, the reductive alkylation can be used for the synthesis symmetrical secondary diamines and polyamines of biological importance.[7]

In summary, the reductive dimerization of azides to secondary amines under hydrogenation conidtions over a commercially available Pd/C catalyst is preferred over the normal reduction process at higher temperature and more concentrated conditions. The reductive dimerization may involve a cyanide as well as an imine as the intermediates.

Experimental Section

A representative procedure for the reductive dimerization. To a bomb reactor were added ethanol (4.0 mL), 1-azido-3-phenylpropane (322 mg, 2.0 mmol), and Pd/C (48 mg, 15 wt %, purchased from Aldrich Co.). The reactor was charged with hydrogen gas (1.0 or 2.0 atm H_2 pressure), and the reaction mixture was vigorously stirred at a given temperature for 3 h. The reaction mixture was filter through a filter paper and concentrated *in vacuo*. The residue was re-dissolved with dichloromethane, and the solution was cooled to 0 °C and then treated with triethylamine (2 molar equiv.), followed by benzyl chloroformate (1.2 molar equiv. with respect to the azide). After completion of the reaction, the reaction mixture was subjected to standard extraction with dichloromethane and purification by column chromatography on SiO_2. The product ratio for the crude extracted mixture was determined by GC analysis using tricosane as the internal standard: HP-1 capillary column, oven temp. 180 → 250 (3 °C/min), injection temp. 250 °C; detection temp. 300 °C; retention time: dimer **2**: t_R = 48.7 min, **3**: 21.1 min.

[Bis(3-phenylpropyl)]carbamic acid benzyl ester (2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.10 (m, 15H), 5.12 (s, 2 H), 3.26 (m, 4H), 2.56 (m, 4H), 1.84 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8, 142.2, 137.6, 129.1, 129.0, 128.9, 128.5, 128.4, 126.5, 67.6, 48.1, 47.4, 33.8, 30.8, 30.5; Mass (EI): calc for $C_{26}H_{29}NO_2$: 387.22; found: 387.22.

Bis[4-(tert-butoxycarbonyl)amino]butylamine (4). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.04 (t, J = 6.3, 4H), 2.58 (t, J = 7.1, 4H), 1.54-1.46 (m, 8H), 1.43 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 79.1, 49.5, 40.4, 28.1, 28.0, 26.9; Mass (EI): calc for $C_{18}H_{37}N_3O_4$: 359.28; found: 359.28.

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