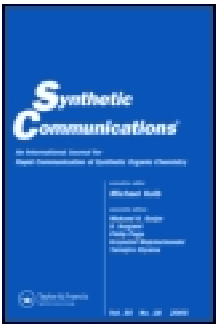

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REDUCTION OF AZIDES TO AMINES WITH BOROHYDRIDE EXCHANGE RESIN - NICKEL ACETATE

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Republic of Korea

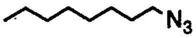
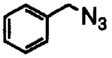
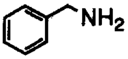
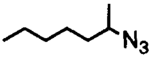
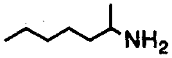
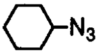
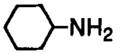
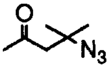
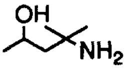
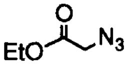
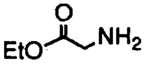
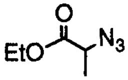
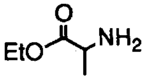
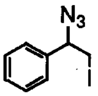
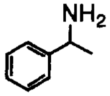
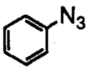
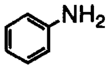
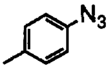
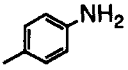
Abstract: Borohydride exchange resin (BER) - nickel acetate system in methanol readily reduces both aliphatic and aromatic azides to the corresponding amines in excellent yields.

Since many azides can be prepared with good regio- and stereocontrol, and subsequent reduction permits a controlled introduction of amino function,[1] the reduction of azides to amines is an important reaction in organic synthesis. Representative reagents are catalytic hydrogenation,[2] lithium aluminum hydride,[3] sodium borohydride,[4] borohydride exchange resin (BER),[5] stannous chloride,[6] and triphenylphosphine.[7] Sodium borohydride has been applied in several ways. Thus although aliphatic azides were reduced to give poor yields of the corresponding amines by sodium borohydride itself,[4a] the yields of amines were improved substantially in the presence of phase transfer agent,[4b] by dropping methanol in tetrahydrofuran,[4c] or in the presence of nickel chloride.[4d,e]

Recently we have studied the reducing properties of BER - $Ni(OAc)_2$ in methanol and demonstrated this system is an excellent reduction system for nitro compounds[8] compared with $NaBH_4$ - $NiCl_2$.[9] BER is much more stable than $NaBH_4$ in methanol in the presence of Ni_2B[10] and yields of amines were better with BER - $Ni(OAc)_2$. Also work up procedure was very simple with BER - $Ni(OAc)_2$. Therefore we applied this system for the reduction of azides and found BER - $Ni(OAc)_2$ is also an excellent reducing agent for azides to the corresponding amines.

As shown in Table 1, BER - $Ni(OAc)_2$ system readily reduced both aliphatic and aromatic azides to the corresponding amines in excellent yields at room temperature. These are much improved yields compared with other $NaBH_4$ reductions[4b-d] which usually give 70 ~ 80% yields for aliphatic azides. Primary, secondary and tertiary azides were all reduced almost quantitatively (entry 1 - 5). Benzyl azide showed no sign of hydrogenolysis (entry 2 and 9). BER - $Ni(OAc)_2$ system tolerated ester (entry 6 and 7), chloro (entry 8), acetal,[8] nitrile,[8] aliphatic epoxide,[11] and tosylate.[11] However, carbon - carbon multiple bonds,[11] ketone,[12] and iodo group were reduced with this system (entry 5 and 9). And in the case of 1-azido-2-iodoethylbenzene, the product, 1-aminoethylbenzene was accompanied by a small amount (< 5%) of 2-phenylaziridine (entry 9).[13] Phenyl azide and 4-tolyl azide were also reduced rapidly to the corresponding anilines quantitatively (entry 10 and 11). BER itself was also reported to reduce these aromatic azides;[5] however, the reduction required a long reaction time (3 - 18 h) at 65 °C. Since azides could be prepared readily from the corresponding bromides, we tested the possibility of one pot synthesis of octylamine from octyl bromide without separating octyl azide. The result (95%) was equally satisfactory as shown in entry 1. BER - $Ni(OAc)_2$ system has another significant advantage over

Table 1. Reduction of Azides to Amines with BER-Ni(OAc)$_2$ in Methanol at Room Temperature[a]

entry	azide	product	yield(%)[b]
1			96(95)[c]
2			95
3			93
4			96
5			95[d]
6			93
7			92
8			92
9			90[e]
10			96
11			95

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[a] BER (50 mmol) was added to the mixture of azide (10 mmol) and Ni(OAc)$_2$ (1 mmol) in methanol. The reaction mixture was then stirred at room temperature for 30 min. [b] Isolated yields of HCl salt. [c] Yield by one pot synthesis from octyl bromide. [d] Reduction was carried out for 1 h. [e] 2-Phenylaziridine (< 5%) was also produced.

other reducing systems. Thus simple separation of BER - Ni_2B by filtration gives the methanol solution of essentially pure products. Just in one case (entry 9), we had to separate 1-aminoethylbenzene from 2-phenylaziridine by silica gel column chromatography.

In conclusion, BER - $Ni(OAc)_2$ system in methanol is a reagent of choice for the reduction of azides to amines because of its excellent yields, good chemoselectivity and simple procedure.

EXPERIMENTAL:

Materials: $NaBH_4$ (98%, Nisso Ventron) was used without further purification. Anion exchange resin (Amberlite IRA-400 [20 - 50 mesh]) was used for supporting polymer of BER. Commercial grade, 99% methanol was used as solvent. All azides were prepared using standard synthetic methods.[14]

Preparation of Borohydride Exchange Resin:[5,15] An aqueous solution of sodium borohydride (1 M, 1 L) was stirred with 200 g of wet chloride-form anion exchange resin (Amberlite IRA-400 [20 - 50 mesh]) for 1 h. The resulting resin was washed thoroughly with distilled water until free of excess $NaBH_4$. The borohydride form anion exchange resin was then dried in vacuo at 60 °C for 5 h. The dried resin was analyzed for borohydride content by hydrogen evolution on acidification with 2 N HCl and the average capacity of BER was found to be 3.3 mmol of BH_4^- per gram. The dried resin was stored under nitrogen in refrigerator (~ 4 °C). The hydride content was constant over 6 weeks.

Reduction of Azide: The reduction of benzyl azide is representative. 15.2 g of BER (30 mmol) was added to the reaction flask containing 0.25 g of $Ni(OAc)_2 \cdot 4H_2O$ (1 mmol) and benzyl azide (1.33 g, 10 mmol) solution in methanol (150 mL) and the mixture was stirred at room temperature for 30 min to complete the reduction. Then the resin was removed by filtration. The filtrate was acidified with 1.67 mL of concentrated HCl (20 mmol) and methanol was evaporated under reduced pressure to give 1.37 g of benzylamine hydrochloride (96%); mp. 252 - 253 °C (lit.[16] 253 °C).

One Pot Synthesis of Octylamine from Octyl Bromide: A slurry of 1.31 g of NaN_3 (20 mmol) in water (5 mL) was added to the reaction flask containing 1.93 g of octyl bromide (10 mmol) solution in methanol (50 mL) and the mixture was refluxed for 6 h to complete the synthesis of octyl azide. The solution was cooled to room temperature, methanol (100 mL) was added and 0.25 g of $Ni(OAc)_2$ (1 mmol) was dissolved in the solution. Then 15.2 g of BER (30 mmol) was added to the reaction flask and the mixture was stirred at room temperature for 30 min to complete the reduction. After the resin was removed by filtration, the filtrate was poured into 150 mL of water and extracted with three 150 mL portions of CH_2Cl_2. The combined extracts were dried with $MgSO_4$ and evaporated under reduced pressure to give 1.23 g of GC pure octylamine (95%); ^1H NMR (CCl_4 + TMS) δ 0.86 - 0.90 (t, 3H), δ 1.22 - 1.38 (s, br, 12H), δ 1.42 - 1.46 (t, 2H), δ 2.65 - 2.75 (s, br, 2H).

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10. In the presence of Ni_2B, $NaBH_4$ decomposes in methanol completely within 5 min, however BER decomposes ~ 30% in 1 h, and slowly thereafter.

11. Unpublished results.

12. Ni_2B is reported to tolerate ketone group. See Ref. 4d.

13. When 1-azido-2-iodoethylbenzene was reduced with lithium aluminum hydride, the product (~80%) contained 2-phenylaziridine and 1-aminoethylbenzene (their relative amounts by NMR were 7 : 3). Hassner, A., Matthews, G. J., and Fowler, F. W., J. Am. Chem. Soc., 1969, 91, 5046.

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