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$NaBH_4$ in *N*-Methylpyrrolidone: A Safe Alternative for Hydride Displacement Reaction

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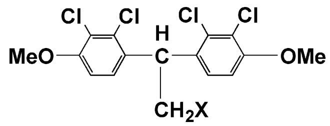
Abstract—Enhanced reactivity of $NaBH_4$ was observed as a solution in *N*-methylpyrrolidone (NMP). Thus, a simple protocol for debromination of alkyl bromide and sulfonate is devised with NMP as a key solvent. Also described is a new mixed borohydride system, $NaBH_4$–LiOTf–NMP, which works as an alternative to $NaBH_3CN$ for the S_N2 type displacement. No reports have ever revealed usefulness of NMP in borohydride reduction. © 2001 Elsevier Science Ltd. All rights reserved.

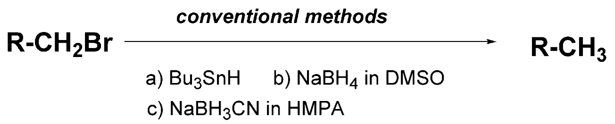
Current trends in synthesis have focused on the efficiency and safety in the operational as well as ecological sense for every conventional synthetic process. Particularly a user-friendly system should be devised for such basic organic transformations as classical aromatic substitution as well as functional group interconversions including oxidation and reduction.[1] We felt that selective reduction by $NaBH_4$ was the case to be re-investigated, because of its low cost and moderate chemoselectivity.[2,3] Among the transformations by $NaBH_4$, we focused on the debromination of alkyl bromides to alkanes, because a few useful methods are available by the use of $NaBH_4$, and actually an improved method was required in our research for the conversion of the bromide (**1**) into the alkane (**2**).[4]



1: X=Br
2: X=H

Reduction of alkyl halides and sulfonates by $NaBH_4$ or $NaBH_3CN$ is best carried out in polar aprotic solvents such as DMSO, DMF, sulfolane and HMPA as summarized in Scheme 1.[3] Reaction in diglyme at high temperature is also reported for the reduction of a variety of functional groups in the presence of inorganic salts.[2f] The major problems with DMSO and DMF are that $NaBH_4$ can form BH_3 in these solvents and have explosive reaction with solvents. The unpleasant smell associated with DMSO is due to the reduction of DMSO to Me_2S by BH_3. We were thus drawn to the possibility that the more stable solvent *N*-methylpyrrolidone (NMP, shown below) might work as an alternative solvent for $NaBH_4$. An explosive runaway reaction of $NaBH_4$ in DMF solution is noted in the textbook,[3a] while no reports have revealed the utility of its cyclic congener NMP in $NaBH_4$ reduction.

To our gratitude, $NaBH_4$ showed comparable or greater solubility in NMP than in DMSO at room temperature. A room temperature debromination of the model bromide (**3**) or mesylate (**4**) did proceed in NMP in a slightly exothermic way (75–80% isolated yields with a trace amount of side products) within 3 h. Reaction with the mesylate (**4**) was somewhat slower and small amounts of the starting material (**4**) were recovered after 3 h, while reaction of the corresponding chloride was



Scheme 1. Initial survey for debromination.

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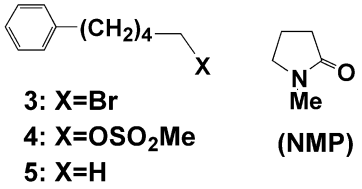
Table 1. Model study in NMP

$$3, 4 \xrightarrow[\text{NMP, DMSO}]{\text{NaBH}_4\text{ etc.}} 5$$

Substrate	Reagents[a]	Conditions	**5** (yields)[b] (%)
1. **3** (1.0 g)	$NaBH_4$/DMSO	rt, 1 h	70
2. **3** (3.0 g)	$NaBH_4$/NMP	rt, 3 h	78
3. **3** (3.0 g)[c]	$NaBH_4$/NMP	rt, 3 h	75
4. **4** (3.0 g)	$NaBH_4$/NMP (4 equiv)	rt, 3 h	70
5. **3** (1.0 g)[d]	$NaBH_3CN$/NMP	~80 °C, 1 h	80



3: X=Br
4: X=OSO_2Me
5: X=H
(NMP)

[a] Reagent (2 equiv) was added portionwise to a solution of **3** or **4**.
[b] Isolated yields after silica gel short path are shown.
[c] **3** was added to a solution of $NaBH_4$ in NMP.
[d] **3** was added to a solution of $NaBH_3CN$ in NMP.

very slow at ambient temperature. Nearly the same result was obtained with DMSO as a solvent, but we observed side reaction with solvent DMSO, which caused a foamy mixture with an unpleasant smell as mentioned. As shown in the last example of Table 1, we also found that NMP could supplant hazardous HMPA in the reaction with $NaBH_3CN$ under heating. The combination of $NaBH_3CN$ and NMP gave us the best result during our search for debromination.

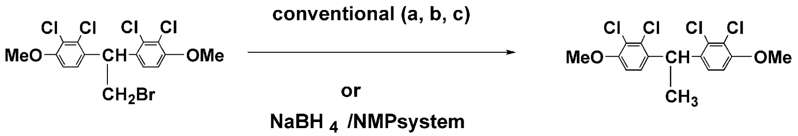
Debromination of 1

Next investigation moved to the debromination of **1**[4] with the above-mentioned conditions as well as conventional conditions. Survey by the reported protocols is summarized in Scheme 2. In the radical reaction of **1** with two equivalents of Bu_3SnH, the product (**2**) was obtained in 45% yield along with recovered bromide (**1**). Use of large excess of tin reagent was successful but inconvenient on a large scale. Another protocol using excess $NaBH_4$ in DMSO was satisfactory to give **2** in 60% yield after chromatographic separation from the polar by-products. Furthermore, unpleasant smell during work up was an obvious nuisance. Another reliable reaction was also attained by the use of excess $NaBH_3CN$ in HMPA affording **2** in 70–80% yield after chromatographic separation. We then substituted HMPA with NMP. To our gratitude, the reaction of **1** with $NaCNBH_4$ in NMP gave **2** in high yield after heating at 120 °C for 1 h (Scheme 2). This reaction could be performed up to 60 g scales without difficulty in the work up stage and no violent reaction was observed.

Although numerous examples are known for the reaction of $NaBH_4$ and $NaBH_3CN$ in polar solvents such as DMSO, diglyme and HMPA,[2] no reports have revealed the usefulness of NMP in debromination reactions.

Optimized protocol in NMP

Encouraged by the initial finding, we further searched for a reagent system that is equivalent (or supplant) to $NaBH_3CN$ in NMP for the conversion of **1** to **2**. Reaction of **1** with $NaBH_4$ in NMP at room temperature was not satisfactory, affording **2** in less than 30% yield after 3 h stirring. Addition of excess LiCl was found to be beneficial as mentioned in other reductions.[3] Thus, the reduction of **1** with $NaBH_4$ in NMP in the presence of LiCl was carried out to afford **2** nearly the same as the case of $NaBH_3CN$ (run 5) after 10–30 h stirring at room temperature. In a large-scale reaction with LiCl, however, it was found that insoluble salt formed a suspension and reaction needed heating at 60 °C for 1 h. We



1 **2**

1	methods	conditions	2 (yields)
1) 4.5 g	a) Bu_3SnH / toluene	reflux, 3hr	45 %
2) 2.5 g	b) $NaBH_4$ / DMSO	~60°, 1hr	60 %
3) 2.5 g	c) $NaBH_3CN$ / HMPA	~100°, 1hr	70 %
4) 21.0 g	$NaBH_3CN$ / NMP	~125 °, 1 hr	89%
5) 2.0 g	$NaBH_4$ / LiCl / NMP	rt, 30 hr	85 %
6) 2.0 g	$NaBH_4$ / LiOTf / NMP	rt, 30 hr	85 %
7) 10.0 g	$NaBH_4$ / LiOTf / NMP	rt~60 °, 1hr	88 %

Scheme 2. Debromination of **1**.

found that LiOTf was a convenient alternative choice. Addition of LiOTf resulted in a more homogeneous solution than LiCl and reaction was almost complete at room temperature. In the reactions with 10–20 g of bromide, it was convenient to warm the mixture (rt to 60 °C) to complete within 1 h. We also observed that further heating after the consumption of **1** slowly caused a conversion of the initial product (**2**) into the polar product, in which further demethylation of one methoxy group took place. Further study is necessary to clarify the role of LiOTf or other related salts in the reduction in NMP.

In summary, we have shown that the reaction of borohydrides in NMP is a convenient alternative for debromination. Increased solubility and reactivity of $NaBH_4$ was attained in NMP as compared to DMSO. Although some explosive reaction of $NaBH_4$ in DMF was reported, we observed no such undesirable reaction in NMP, which is also less harmful than DMF. In most cases, reaction mixture formed a homogeneous solution, in which $NaBH_4$ was stable to effect the debromination at room temperature without any runaway reaction. Simple work up gave nearly pure product as indicated in the experimental procedures shown below. By a fine-tuning with additional Li-salt, a chemoselective debromination of some labile bromides can be attained. The mixed agent ($NaBH_4$–LiOTf–NMP) worked as an alternative to $LiBH_4$ and $NaCNBH_3$, both of which are obviously hazardous in large-scale operations. Very little is known about the behavior of NMP under reduction conditions. We are now investigating the fate of NMP under forced reduction conditions. Further application to other functional groups such as carbonyl and nitro groups is also in progress in this laboratory.[5]

Experimental Details for the Reduction in NMP

General procedure (Table 1, entry 3)

To a stirred solution of $NaBH_4$ (1.0 g, 2 equiv) in NMP (30 mL) was slowly added a solution of bromide (**3**, 3.0 g)[6] in NMP (2 mL). Instantaneous reaction was observed and the resulting mixture was stirred at room temperature for 3 h. The mixture was first diluted with solvent and quenched carefully with H_2O in the cold. After gas evolution subsided, the mixture was diluted with aqueous solvent. Repeated extraction gave products after evaporation of the dried extracts (a trace of products was present in aqueous layer). Through an SiO_2 short column, a nearly pure material was obtained as colorless oil (**5**, 75%).

$NaBH_3CN$ reduction in NMP

To a stirred solution of $NaBH_3CN$ (10.0 g) in NMP (100 mL) was added carefully at 60 °C the solid bromide powder (**1**, 21.0 g)[4] and resulting mixture was stirred at 100–125 °C for 1 h. The mixture was cooled in ice bath and worked up as above. Repeated extraction gave a nearly pure solid product (ca. 23 g) after evaporation of the dried extracts. By a simple crystallization, a nearly pure material was obtained as a white solid (**2**, 89%).

Reduction by $NaBH_4$–LiOTf in NMP

To a stirred solution of $NaBH_4$ (3.0 g) and LiOTf (3.0 g) in NMP (50 mL) was added at room temperature the crystalline bromide (**1**, 10.0 g) and resulting mixture was stirred at room temperature (exothermic reaction) and further at 60 °C for 1 h. The mixture was carefully worked up as above. A solid product (ca.12 g) was obtained after evaporation of the dried solvents, which was further purified by column chromatography to give nearly pure material as a white solid (**2**, 88%).

Acknowledgements

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References and Notes

1. For example, see: Bolm, C.; Beckmannn, O.; Dabard, A. G. *Angew. Chem., Int. Ed. Engl.* **1999**, 907.
2. (a) As recent efforts for various reduction, see: Gevorgyan, V.; Rubin, M.; Liu, J.-X.; Yamamoto, Y. *J. Org. Chem.* **2001**, *66*, 1672 and references therein. (b) Narasimhan, S.; Balakumar, R. *Synth. Commun.* **2000**, *30*, 4387 and references therein. (c) Crich, D.; Neelamkavil, S.; Sartillo-Piscil, F. *Org. Lett.* **2000**, *2*, 4029. (d) Chary, K. P.; Ram, S. R.; Salahuddin, S.; Iyengar, D. S. *Synth. Commun.* **2000**, *30*, 3559. (e) Desai, D. G.; Swami, S.; Hapase, S. B. *Synth. Commun.* **1999**, *29*, 1033. (f) Yang, C.; Pittman, C. U., Jr. *Synth. Commun.* **1998**, *28*, 2027.
3. (a) For an overview, see: Banfi, L.; Narisano, E.; Riva, R. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1995; Vol. 7, p 4522. (b) Hutchins, R. O.; Hutchins, M. K. *ibid*, p 4539.
4. Torisawa, Y.; Nishi, T.; Minamikawa, J. *Org. Proc. Res. Dev.* **2001**, 84 and references cited therein.
5. In our preliminary survey, simple azides and aromatic nitro group were able to reduce to amine derivative in moderate yields on heating with $NaBH_4$–NMP system. Both aldehydes and esters were easily reduced to the corresponding alcohols, while some *N*-aryl lactams were reduced into amines after long time heating in the $NaBH_4$–LiOTf–NMP system. From these initial surveys we speculated that reaction with $NaBH_4$–LiOTf–NMP was almost equally as effective as the $NaBH_4$–$ZrCl_4$ system. A comparative study for $NaBH_4$ reduction in NMP with some additives will be reported in due course.
6. The requisite bromide **3** was prepared from commercially available 5-phenyl-1-pentanol (Aldrich) by the treatment of CBr_4 and PPh_3 in CH_2Cl_2 under cooling.