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Some Aspects of $NaBH_4$ Reduction in NMP

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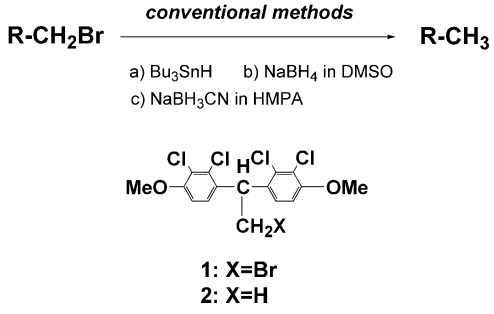
Abstract—In our solvent optimization study of $NaBH_4$ reduction, NMP was found to enhance the reactivity. A chemoselective debromination of the bromide and sulfonates can be attained in the new borohydride reagent system: $NaBH_4$-LiOTf-NMP. This mixed system worked as an alternative to $NaBH_3CN$ and Bu_3SnH for the S_N2 type displacement of alkylbromide and sulfonate. Also mentioned is an expedient reduction of an azide group into amine by $NaBH_4$ in NMP without any additive, which offers a convenient protocol for the direct transformation of halides into amines via azide in one flask. Some examples of other reductions were also presented.

Introduction

In the contemporary synthesis of important drug substances, selection of a suitable solvent or replacement of a harmful reagent is obviously the urgent topic to be concerned. Particularly, safety and ecologically sound systems are demanded for all basic organic transformations from the bench-side synthesis to plant scale production.[1] It is particularly desirable to attain high degree of efficiency by the use of a safe and conventional reagent in the optimized solvent system or with new additives.[2] Recent progress for the improved and chemoselective reduction by $NaBH_4$ is a typical example of this kind.[3] We also focused, among many useful reactions by $NaBH_4$, on the debromination of alkylbromides to alkanes, which is a straightforward hydride substitution, but relatively a few options are available by $NaBH_4$ itself. Actually, we had to carry out a safe conversion of the bromide (**1**) into the alkane (**2**) in our process research on Aripiprazole.[4]

We also extended our attention to the reduction of simple azides into amines. Our aim is to carry out a convenient conversion of the bromides (or chlorides) into amines without isolation of the azide intermediate often claimed to be explosive. Other useful information is also included with regard to the solvent selection in $NaBH_4$ reduction.



Scheme 1. Survey for debromination.

Model Study for Hydride Displacement in NMP

The reduction of alkyl halides and sulfonates by $NaBH_4$ or $NaBH_3CN$ was often carried out in a polar aprotic solvent such as DMSO, sulfolane and HMPA as shown in Scheme 1.[5] Reaction in glyme is also reported.[3e] We were interested in the possibility that common amide solvent might work as a convenient alternative. Although uncontrolled reaction of $NaBH_4$ in *N,N*-dimethylformamide (DMF) was noted in the authentic book,[5a] no report dealt with the utility of its cyclic congener *N*-methylpyrrolidone (NMP, shown below) in $NaBH_4$ reduction. NMP is more stable and less harmful than DMF.

As summarized in the Table 1, $NaBH_4$ showed good solubility in NMP, and debromination reaction of the model bromide (**3**) or mesylate (**4**) did proceed at room

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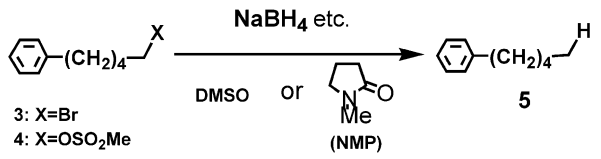
Table 1. Model study for the debromination in NMP



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 eq)	rt, 3 h	70%
5 3 (1.0 g)[d]	$NaBH_3CN$/NMP	~80 °C, 1 h	75%

[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]Compound **3** was added to a solution of $NaBH_4$ in NMP.
[d]Compound **3** was added to a solution of $NaBH_3CN$ in NMP.

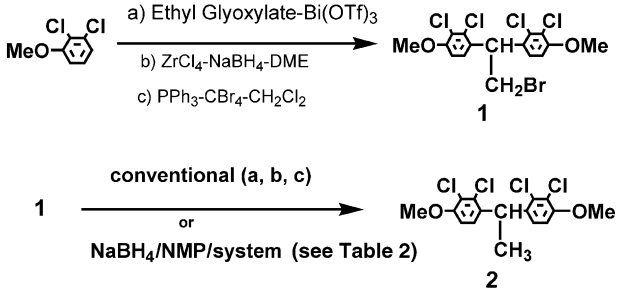
temperature with slight exothermic way (75–78% isolated yields) within 3 h. Reaction of the mesylate (**4**) was somewhat slower and larger amount of reagent was required. In the case of DMSO as a solvent (run 1), a foamy mixture was developed with unpleasant smell. It should be noted the same reaction with $LiBH_4$ in NMP was very slow and took long time to complete the debromination at room temperature. This indicates a well-solvated $LiBH_4$ was no more effective for the reduction of the simple bromide. Our survey indicated the superiority of NMP as a solvent of choice for the hydride displacement reaction by $NaBH_4$. As shown in the last example of Table 1, NMP could supplant hazardous HMPA in the reaction with $NaBH_3CN$ under gentle heating. Numerous examples are known in the literature for the reaction of $NaBH_4$ and $NaBH_3CN$ in polar solvents,[2] but no example has ever been reported on the usefulness of NMP in such reductions.

Debromination of the Bromide (1)

Next, investigation focused on the debromination of **1**[4] with the conditions mentioned above as well as conventional conditions just for comparison. An efficient method for the debromination of **1** into **2** was required in our process research on Aripiprazole and its congeners.[4] Reaction sequence for the preparation of **1** was summarized in Scheme 2 and detailed in Experimental.[6]

Reduction of **1** under various conditions is summarized in the Scheme 2 and Table 2. The routine radical reaction of **1** with 2 equivalents of Bu_3SnH afforded the product (**2**) in 45% yield along with recovered bromide (**1**). Use of excess of tin reagent was effective but inconvenient in a large-scale preparation of **2.** Another protocol using excess $NaBH_4$ in DMSO was satisfactory to give **2** in 60% but again unpleasant work up (smell badly) was an obvious nuisance.

The reaction of **1** with excess $NaBH_3CN$ in HMPA was more reliable to afford **2** in 70% yields after purification.



Scheme 2. Preparation and debromination of **1**.

As expected, the reaction of **1** with $NaCNBH_4$ in NMP gave **2** in high yield after heating at 125 °C for 1 h.

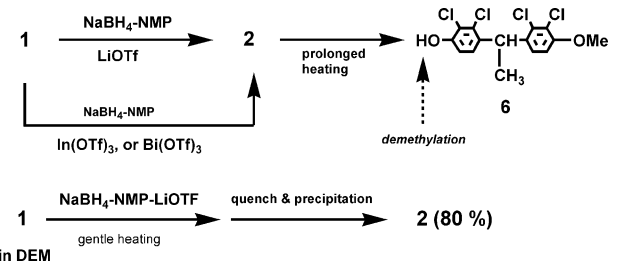
This reaction could be performed up to 100 g scales without any difficulty in the work up stage. Our result thus clearly demonstrated the practical superiority of NMP than the other conventional protocols shown in Scheme 2.

Protocol with Li Salts in NMP

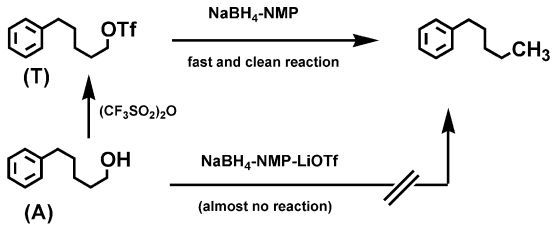
We further searched for the reagent system that is alternative (or supplant) to the toxic reagent $NaBH_3CN$ especially for the conversion of **1** to **2**. Reaction of **1** with $NaBH_4$ in NMP at room temperature was not satisfactory to afford **2** in less than 20% yield after 3 h stirring. We however found that the reduction of **1** with added Li-salt was the most convenient and successful in affording **2** after 10 h stirring at room temperature. In a large-scale reaction with LiCl (0.5~1 equiv), it was found that insoluble NaCl formed a suspension and reaction mixture was heated at 60 °C for the completion. In a search for more effective salt, we found that LiOTf was a convenient alternative. Addition of LiOTf (0.5~1 equiv) resulted in a more homogeneous solution than LiCl and reaction was almost complete at room temperature. In the reactions with 20 g of bromide, it was convenient to warm the mixture (room temperature to 60 °C) to complete the reaction within 1 h. Further heating after the complete consumption of **1** slowly caused a conversion of the initial product (**2**) into the polar product. The tentative structure (**6**), in which demethylation of one methoxy group took place, was most probable. This unwanted side-reaction was completely suppressed by the addition of ethereal co-solvent such as DEM (diethoxymethane, ethylal) as shown below, which is detailed in Experimental.

We are particularly interested in the use of DEM, because of its emerging utility in the process research.[7] The same effect was observed with other metal triflates such as $In(OTf)_3$ and $Bi(OTf)_3$, but obviously LiOTf is most cost effective (Scheme 3).

In order to expand the utility of this protocol, we briefly compared the reaction of the triflate (T) and that of the alcohol (A) as shown below. Reaction of the triflate was fast without any assistance of metal triflate, while



Scheme 3.



Scheme 4.

almost no reaction was observed in the reaction of alcohol even though triflate salt was present in the mixture (Scheme 4).

Reduction of Azides

After the initial progress shown above, we further focused on some advantageous aspect of the reaction in NMP. We observed that the reaction of $NaBH_4$ was faster than that of $LiBH_4$ in NMP in the model experiment with **3** as mentioned. These results prompted us to carry out two successive substitution reactions by sodium salt in NMP.

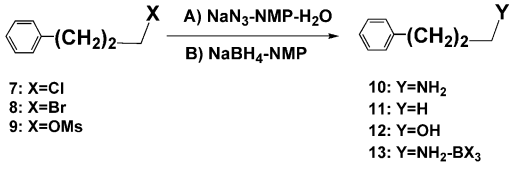
Nucleophilic substitution of halides by NaN_3 affords azide intermediate in NMP, whose reduction might furnish the corresponding amine in one flask by the present reduction. Although a convenient one-pot conversion from halides into amines via azide is reported via Staudinger reaction,[8] no reports have attained such transformation by the use of $NaBH_4$ as the sole reagent. Recent reports indicated some successful reduction of azides to amine by $NaBH_4$ with proper selection of the additives such as $CoCl_2$, $ZrCl_4$, and tin-based reagent.[9] Our improved protocol by the simplest reagent composition without additives are summarized below.

The commercially available phenylpropyl chloride (**7**) and bromide (**8**) were selected as a model to test for our one-pot protocol. Formation of the primary azide from halides in NMP was a conventional pathway as in DMF. We have optimized this step by the addition of H_2O (1∼2 equiv) under careful temperature control (<70 °C). Thus, the reaction of the bromide (**8**) with NaN_3 was a straightforward reaction at 60∼70 °C, while the reaction of the chloride (**7**) required higher temperature than 70 °C. Reduction of the resulting azides was done in one-pot with 2 equiv $NaBH_4$ at

Table 2.

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

Table 3. Azidation-Reduction Sequence in NMP



Substrate	A[a]	B[b]	9[c]	[NMR][d]	By-product[e]
1 7 (2.0 g)	∼70 °C, 3 h	50∼70 °C, 3 h	0∼5%	[7%]	**11**, **13**[f]
2 7 (2.0 g)	∼80 °C, 2 h	50∼70 °C, 2 h	55%	[60%]	**11**
3 8 (2.0 g)	∼70 °C, 2 h	50∼70 °C, 2 h	75%	[75%]	**13**[f] (minor)
4 9 (2.0 g)	∼75 °C, 2 h	50∼70 °C, 2 h	65%	[70%]	**12** (minor)

[a]Substrates (7, 8, 9)-NaN_3 (1.2 equiv)-H_2O were mixed at rt and heated as indicated.
[b]NaBH4 (2 equiv) was delivered at rt and heated as indicated with adequate stirring.
[c]Amine obtained after extractive isolation.
[d]Yields based on NMR analysis of the crude extracts with a standard.
[e]Charaterized by-products are shown.
[f]Isolated by preparative TLC.

temperature around 50 °C. Yields of the free amine after extractive isolation were approximately 75% for bromide (**8**) and 55% for the less reactive chloride (**7**) as shown in the Table 3.

In the case of the chloride (**7**), crude mixture contained starting chloride and reduced 3-phenylpropane (**11**). This side product was obtained in the case of chloride through the reduction with the unreacted chloride. In a separate experiment, direct reduction of the chloride (**7**) by $NaBH_4$ (2 equiv) at 70∼85 °C for 2 h gave **11** in a 65% isolated yield. Reaction of the mesylate (**9**) was also successful, but we observed a small amount of the alochol (**12**) was always accompanied through the hydrolysis of **9** during azide formation under heating.

In this way, we have succeeded in a one-pot conversion of alkyl halide into amine, but caution must be taken to detect side-products present in the mixture including the amine borane complex such as **13**. We are now investigating the utility of this one-pot sequence in a co-solvent system with more demanding secondary halides.

In the related study, we have briefly surveyed on the reduction of acid chlorides into aldehyde with 1 equiv $NaBH_4$ in the presence of amine (TMEDA). Our initial survey indicated a facile conversion of simple acid chlorides (benzoyl chloride or toluoyl chloride) into the corresponding aldehydes at temperature below 0 °C in

ca.50~60% yield after one distillation. In these study, we employed toluene, hexane, DME, TBME, and DEM as a co-solvent. As mentioned before, DEM was a convenient solvent for the direct extractive isolation of the crude product after quench by H_2O.

Conclusion

We have surveyed the reaction of borohydrides in NMP or other solvents as a convenient alternative for the reduction of some halides and azides. Although some explosive reaction of $NaBH_4$ in DMF was reported, we observed no such undesirable reaction in NMP, which is less harmful than DMF. Usually, the reaction mixture formed a homogeneous solution, in which $NaBH_4$ was not easily decomposed. Simple work up (dilution with H_2O) gave nearly pure product as indicated in the experimental procedures shown below. The addition of LiOTf was particularly effective to attain chemoselective debromination of the labile bromide. The present system thus worked as an alternative to $LiBH_4$ and $NaCNBH_3$, both of them obviously hazardous in large-scale operation.

Although NMP was frequently used in the reaction of many transformations as a beneficial solvent, little is known about the behavior of NMP during the reaction. The most characteristic nature of the reduction in NMP was that $NaBH_4$ (or related species) has a long lifetime to reduce halide and azides. Further application to other functionality will give us more insight into the nature of the reduction, as well as comparison with other solvent system, especially with such as ionic liquids, which are now in progress in this laboratory.[10]

Experimental

Material and instrumentation

Chemicals were purchased from the commercial firms indicated and used without further purification. TLC analysis was carried out using Merck silica gel 60 F_{254} plate (Art 5715). ^1H and ^{13}C NMR spectra were measured at 300 and 75 MHz, respectively, with tetramethylsilane as the internal standard. Mass spectra (LR-MS) were recorded with a Shimadzu GCMS-QP1000 spectrometer at 70 eV.

Preparation of the bromide (1)

As in the same procedure described before,[6] ethyl glyoxylate polymer (TCI, 50% in toluene, 40 mL) was concentrated under reduced pressure to obtain neat glyoxylate (ca. 20 g). To this was added solid dichloroanisole (Aldrich, 45.5 g, 257 mmol) and the whole was heated at around 80 °C to form a clear homogeneous solution. To this was then added $Bi(OTf)_3$ powder (1.0 g)[6] and the resulting mixture was gradually heated to 110 °C (ca. 1 h). The mixture was further heated at ~135 °C for 1 h, before cooling to room temperature and dilution with CH_2Cl_2. The insoluble reagent was then recovered through filtration and washing with CH_2Cl_2. The filtrate was directly concentrated to give crude product as a brown oil (61 g). ^1H NMR ($CDCl_3$): δ 1.28 (3H, t, $J=4$ Hz), 3.90 (6H, s), 4.25 (2H, q, $J=4$ Hz), 5.70 (1H, s), 6.82 (2H, d, $J=8.7$ Hz), 6.94 (2H, d, $J=8.7$ Hz). ^{13}C NMR ($CDCl_3$): δ 171.2; 155.4; 134.0; 128.6; 127.2; 122.3; 109.5; 61.5; 56.2; 52.0; 13.9. MS (EI): m/z 436 (M^+).

To a stirred solution of the above ester (61 g, ca. 128.5 mM as ester) in DME (280 mL) was added a powder of $ZrCl_4$ (Merck, 30 g, 128.5 mM) and the suspension was stirred for 30 min.

To this was added very carefully $NaBH_4$ (5 g×2, 264.5 mM) portionwise at room temperature. Resulting suspension was stirred overnight before it was gradually heated to 60 °C. Resulting white mixture was cooled to room temperature and kept in an ice-bath, to which was added AcOEt (10 mL×4) followed by H_2O (10 mL×3) very carefully (gas evolution). Then the mixture was stirred for a while before CH_2Cl_2 (800 mL) was added. The insoluble salts were removed by filtration. The clear filtrate was transferred to a separatory funnel to obtain a clear two-phase solution. Lower organic layer was separated, which was washed with further amount of H_2O. Resulting organic layer was dried over Na_2SO_4 and concentrated to afford the corresponding alcohol colorless oil (50.5 g), which was solidified on standing. ^1H NMR ($CDCl_3$): δ 1.65 (1H, OH), 3.89 (6H, s), 4.08 (2H, d, $J=6$ Hz), 4.97 (1H, t like), 6.82 (2H, d, $J=8.7$ Hz), 7.12 (2H, d, $J=8.7$ Hz). ^{13}C NMR ($CDCl_3$) δ 154.5; 134.2; 131.3; 126.7; 122.3; 109.5; 63.3; 56.2; 47.0. MS (EI): m/z 394 (M^+). MS (EI): m/z 394 (M^+); HRMS: calcd for C16H14Cl4O3: 393.9699; found: 393.9740.

To a stirred solution of the above alcohol (50 g, ca. 120 mM) in CH_2Cl_2 (300 mL) was added Ph_3P (40 g, 152.5 mM) and CBr_4 (50 g, 150.7 mM) under ice-cooling. (an exothermic reaction). Resulting faint yellow mixture was stirred without cooling for 20 h, and further amount of reagents were delivered. Resulting yellow mixture was then concentrated to give a crude residue, which was diluted with toluene (500 mL) and the whole was stirred to precipitate the polar wastes (phosphine oxide). After stirring for 1 h at room temperature and 0.5 h under ice-cooling, the mixture was filtrated to remove polar material. Evaporation of the resulting filtrate then gave a crude product (ca. 35.5 g), which was first triturated with AcOEt/*n*-hexane = 1/4 (ca. 200 mL) to afford crude crystalline crop. Dilution of this solid with AcOEt/*n*-hexane = 1/10 (ca. 200 mL) then gave a white precipitate, which was isolated by filtration followed by washing with *n*-hexane and drying to afford nearly pure bromide (**1**, 21 g). ^1H NMR ($CDCl_3$): δ 3.76 (2H, d, $J=7.5$ Hz), 3.90 (6H, s), 5.17 (1H, d, $J=7.5$ Hz), 6.83 (2H, d, $J=8.2$ Hz), 6.69 (2H, d, $J=8.2$ Hz). ^{13}C NMR ($CDCl_3$): δ 155.2; 134.2; 131.3; 126.3; 126.3; 109.4; 56.2; 46.9; 31.6. MS (EI): m/z 456, 458 (M^+). MS (EI): m/z 456, 458 (M^+); HRMS: calcd for $C_{16}H_{13}BrCl_4O_2$: 455.8855; found: 445.8864.

General procedure for the reduction in NMP (Table 2 entry 3)

To a stirred solution of $NaBH_4$ (Wako, 1.0 g, 2 equiv) in MNP (Wako, 30 mL) was added a solution of bromide (**3**, 3.0 g)[11] in NMP (2 mL) and 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 vigorous gas evolution subsided, the mixture was further diluted with aqueous solvent. Repeated extraction gave products after evaporation of the dried extracts. Through a SiO_2 short column, a nearly pure material was obtained as a colorless oil (**5**, 75%).

$NaBH_3CN$ reduction in NMP

To a stirred solution of $NaBH_3CN$ (Aldrich, 10 g) in NMP (100 mL) was added carefully at 60 °C the solid bromide powder (**1**, 21 g) 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 trituration, a nearly pure material was obtained as a white solid (**2**, 89%). ^1H NMR ($CDCl_3$): δ 1.52 (2H, d, $J=7.2$ Hz) 3.88 (6H, s), 4.82 (1H, q, $J=7.2$ Hz), 6.83 (2H, d, $J=8.2$ Hz), 6.69 (2H, d, $J=8.2$ Hz). ^{13}C NMR ($CDCl_3$): δ 154.5; 136.0; 133.5; 125.5; 122.0; 109.5; 56.2; 39.1; 19.9. MS (EI): m/z 378 (M^+). MS (EI): m/z 378 (M^+); HRMS: calcd for C16H14Cl4O2: 377.9750; found: 377.9750. Anal. calcd for C16H14O2Cl4: C, 50.46; H, 3.72; found C, 50.16; H, 3.75.

Reduction by $NaBH_4$-LiOTf in NMP

To a stirred solution of $NaBH_4$ (3 g) and LiOTf (Strem, 3 g) in NMP (50 mL) was added at room temperature the crystalline bromide (**1**, 10 g) and resulting mixture was stirred at room temperature for 0.5 h (a gentle exothermic reaction) and further at 60 °C for 0.5 h. The mixture was carefully worked up as above. A solid product (ca. 12.5 g) was obtained after evaporation of the dried solvents, which was further purified by SiO_2 column chromatography to give nearly pure material as a white solid (**2**, 88%).

$NaBH_4$ reduction in NMP-DEM

To a stirred solution of $NaBH_4$ (1 g) in NMP (16 mL) was added at room temperature LiOTf (1 g) powder to form a clear solution. A suspension of the bromide (**1**, 3 g) in DEM (TCI, 8 mL) was added in one portion and resulting mixture was kept stirring at room temperature for 0.5 h, followed by warming at around 40 °C. After exothermic process with gas evolution, the mixture was further kept at 60 °C for 1 h. The resulting mixture was cooled in a water-bath and carefully quenched by the addition of H_2O. Further dilution made the product precipitated, which was filtered and washed with H_2O, furnishing nearly pure material as a white solid (**2**, 80%).

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10. In our preliminary survey, aromatic nitro group was reduced to aniline derivative on heating with excess of $NaBH_4$ in NMP. In this reduction, a thermal runaway reaction was observed in the reaction with >20 mM scale, which indicated impractical aspect of $NaBH_4$-NMP system for nitro reduction. Nitrobenzene itself was not reduced to aniline even under forced conditions. Some aromatic esters were also reduced to the corresponding alcohols with excess $NaBH_4$ after prolonged heating. The combination $NaBH_4$-NMP-LiOTf was particularly useful for the reductive amination reaction between aldehydes and anilines. Imine-forming reactions between anilines with aldehydes were successfully carried out in DEM by the aid of LiOTf and $MgSO_4$. Thus, one-pot reductive amination was possible in LiOTf-DEM followed by the treatment of $NaBH_4$-NMP. Progress of this new protocol will be reported in due course. Furthermore, addition of the simplest ionic liquid such as EMIM(OTf) did improve the course of these borohydride reduction.
11. The 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.