New Efficient Conditions for the Reduction with NADH Models

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Received 2 June 1998

Abstract: New conditions were used for the efficient reduction of various nitroalkenes and two prochiral ketones by using NADH mimics. The present procedure is very useful since it does not involve magnesium perchlorate which is replaced by magnesium bromide in THF. High conversions were observed. The new conditions were checked in asymmetric reductions.

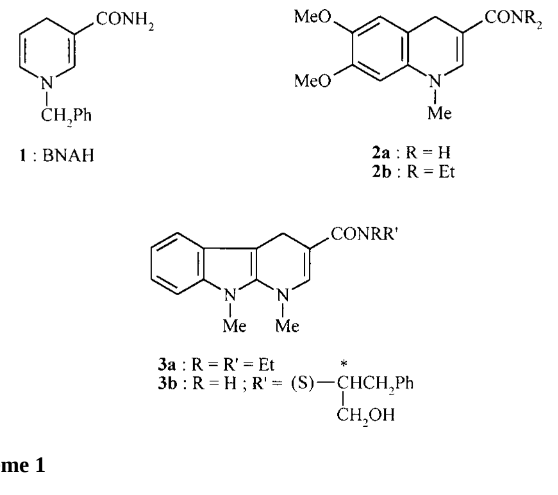
Much effort has been invested to develop NADH mimics that are able to be used in chemoselective or enantioselective reductions.[1] Among these models, BNAH (1-benzyl-1,4-dihydronicotinamide, compound **1**; Scheme 1.) is probably the most popular one. It was shown that reductions with such a reagent are, in general, performed in the presence of divalent metal ions.[2] It was established that the metal ion binds to the substrate and to the 1,4-dihydronicotinamide moiety. The hydride equivalent transfer is promoted through a ternary complex. In reductions with NADH models, it is a common practice to use magnesium perchlorate as a co-catalyst in acetonitrile as solvent.

However, magnesium perchlorate presents some drawbacks: 1) The anhydrous form is rather expensive, 2) it can be hazardous to handle (risk of explosion!).[3]

So, it could be of interest to test the possibility of using more useful metal ions, with a view to developing more convenient procedures.

At this point, it must be mentioned that BNAH, or similar models, are not stable towards side reactions caused by traces of water, which can occur at the 5,6-enamine bond.[4] To overcome this problem, our group developed, a few years ago, new NADH mimics where the 5,6-double bond was included in an electron rich homo or hetero aromatic ring. This approach suppresses the side reactions and favours the hydride equivalent departure through the electron donating effect of the aromatic ring.

Two families of reagents in the quinoline series[5] (compounds **2a** and **2b**, Scheme 1) and in the pyrido[2,3-b]indole series[6] (compounds **3a** and **3b**, Scheme 1) will be used in this paper in the reduction of nitroalkenes and ketones under non-classical conditions *i.e*: no magnesium perchlorate.



Scheme 1

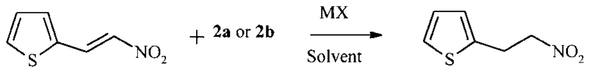
A – Reduction of nitroolefines.

NADH models allow the chemoselective reduction of the double bond, leading to nitroalkanes which are versatile intermediates in synthesis.[7]

1) Reduction of 1-(2-thienyl)-2-nitroethylene.

The results are outlined in Table 1.[8]

Table 1. Reduction of 1-(2-thienyl)-2-nitroethylene



4 **5**

Entry	Model	MX	Solvent	Conversion %
1	**2a**	$Mg(ClO_4)_2$	CH_3CN	100
2	**2a**	$ZnBr_2$	CH_3CN	100
3	**2a**	$ZnBr_2$	THF	100
4	**2a**	$MgBr_2$	THF	100
5	**2b**	$Mg(ClO_4)_2$	CH_3CN	90
6	**2b**	$ZnBr_2$	THF	100
7	**2b**	$MgBr_2$	THF	100

Note: 1) All reactions were performed at room temperature for 24 h in the presence of 3 equivalents of metal salt

2) The reductions were performed in the presence of silica to avoid the formation of tarry material [9]

3) The % conversion was determined by the analysis of the ^{1}H NMR spectrum of the crude reaction product

The main feature is that under soft conditions, reagents **2a** and **2b** are efficient in the reduction of **4** in the presence of zinc bromide or magnesium bromide in various solvents.

In the literature some reactions involving NADH models were performed with zinc bromide especially in kinetic studies.[10] On the other hand, to our knowledge, magnesium bromide has never been used and our results are the first report of the successful reduction of nitroalkenes by NADH models under non-classical conditions.

However, zinc bromide is very much more hygroscopic than magnesium bromide or magnesium perchlorate and the results are not reproducible. Moreover, the reaction conditions with cheap magnesium bromide are cleaner, easy to reproduce, and this salt can be handled in safety.

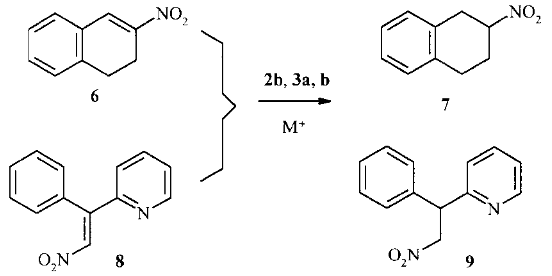
These good results were obtained under conditions where the reaction mixture is not fluid: at the beginning of the reaction magnesium bromide is partly suspended in the solvent. As the reaction progresses the mixture becomes thicker and presents a gelatinous aspect. Under good stirring this behaviour does not perturb the efficiency of the reagent as shown by the obtained results.

So, it was decided to investigate the reduction of other substrates in the presence of magnesium bromide in THF.

2) Reduction of other nitroolefines[8]

Two substrates were studied: 3-nitro-1,2-dihydronaphthalene **6** and (E)-2-phenyl-2-(2-pyridyl)-1-nitroethylene **8**. The ethylenic double bond in these substrates is less reactive than in **4** (steric hindrance). So the reductions were performed at the boiling point of the solvent, using a highly reactive model **3a** previously studied in our laboratory in the pyrido[2,3-b]indole series.[6b]

Table 2. Reduction of nitroolefines **6** and **8**



Entry	Substrate	Model	MX	Solvent	% conversion
8	**6**	**3a**	$Mg(ClO_4)_2$	CH_3CN	10
9	**6**	**2b**	$MgBr_2$	THF	61
10	**6**	**3a**	$MgBr_2$	THF	90
11	**8**	**3a**	$Mg(ClO_4)_2$	CH_3CN	50
12	**8**	**3a**	$MgBr_2$	THF	75
13	**8**	**3b**	$MgBr_2$	THF	60 (e.e. 10 %)[11]

Note: All reductions were performed in refluxing solvent for 48 h in the presence of 2 equivalents of reagent and metal salt

In the case of substrate **6**, it can be observed that model **3a** in the pyrido[2,3-b]indole series was superior to model **2b** in the quinoline series during the reduction in the presence of magnesium bromide in THF (entries 9 and 10). This result justifies the above choice of a model in the indolopyridine series. Once again, the new conditions are more efficient than standard conditions (entries 8 and 10). This behaviour is confirmed in the reduction of substrate **8** (entries 11 and 12).

In the case of substrate **8**, the β carbon in the nitroethylene group is prochiral. The asymmetric reduction of this substrate was previously studied in our laboratory by using another chiral NADH model **3b**.[11] In the presence of magnesium bromide in THF the e.e. was low (entry 13).

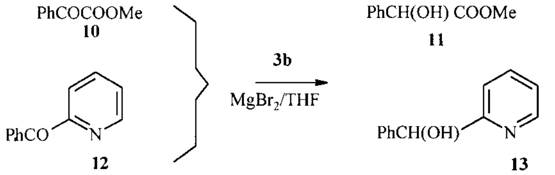
As can be seen in the reduction of nitro-unsaturated substrates like **4**, **6** and **8** the new conditions *i.e.* magnesium bromide in THF gave better yields than magnesium perchlorate in acetonitrile. However the asymmetric reduction of prochiral **8** with **3b** gave a poor e.e.

3) Reduction of prochiral ketones[8]

In order to obtain more information concerning the behaviour of the chiral reagent **3b** in reactions promoted by magnesium bromide in THF we studied two prochiral ketones: methylbenzoylformate **10** which is a classical substrate in asymmetric reductions performed with NADH models and 2-benzoylpyridine **12** which was recently involved in asymmetric reductions performed under various conditions.[12]

As can be seen, the conversion was in all cases quantitative. On the other hand the e.e. were higher by using magnesium perchlorate in acetonitrile than with magnesium bromide in THF. The enantioselective hydride equivalent transfer from the reagent to the substrate is directed by the structure of the ternary complex constructed between the model, the substrate and Mg^{2+} ions.[14] The metal ion is hexacoordinated in this complex and all the ligand-metal bonds ensure the positioning of the partners during the reduction. It can be assumed that, in the case of reductions performed with magnesium bromide in THF (a strongly coordinating solvent) the structure of the ternary complex can be modified by replacing some of the atoms of the reagent or of the substrate involved in the hexa coordinated structure by solvent molecules. As a consequence the positioning of the partners is less well ensured leading to a decreasing of the stereodifferentiation during the hydride equivalent transfer.

Table 3. Reduction of prochiral ketones **10** and **12**



Entry	Substrate	Model	M^{2+}	Solvent	Conversion (%)	e.e. (%)
14	**10**	**3b**	$Mg(ClO_4)_2$	CH_3CN	100	67
15	**10**	**3b**	$MgBr_2$	THF	100	45
16	**12**	**3b**	$Mg(ClO_4)_2$	CH_3CN	100	68
17	**12**	**3b**	$MgBr_2$	THF	100	47

All reductions were performed in refluxing solvent in the presence of 1.5 equivalent of reagent and metal salt. For determination of e.e., see reference 13

Acknowledgement: we thank Sanofi Chimie Co (Gentilly, France) for financial support of this work.

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(5) Reagents **2a** and **2b** are new NADH models which were synthesized in five steps from previously described 6,7-dimethoxyquinoline-3-carbonitrile (Charpentier, P.; Lobrégat, V.; Levacher, V.; Dupas, G.; Quéguiner G.; Bourguignon J. *Tetrahedron Lett.*, **1998**, in press) by following a classical way, i.e.: 1) Conversion of the nitrile group into a carboxylic acid with a 25 % aqueous solution of NaOH at reflux then H_3O^+. 2) The acid chloride was obtained with $SOCl_2$. 3) The acid chloride was treated with NH_3 for **2a** or with $HNEt_2$ for **2b** 4) Quaternization with ICH_3 in CH_3CN 5) Subsequent regioselective reduction of the pyridinium salt with $Na_2S_2O_4/OH^-$

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(8) Typical procedure for reduction of substrates **4**, **6**, **8**, **10** and **12**: the metal salt was added under a nitrogen atmosphere to a solution of reagent model in solvent (5 mL), in the dark (for further information see footnotes in tables 1, 2 and 3 or in text). After reaction, a few drops of water were added and the solution was stirred for 15 min. Diethyl ether (5 mL) was added and the mixture was stirred again for 15 min. The organic layer was separated, dried over magnesium sulfate and concentrated under reduced pressure. In the case of compounds **5**, **7** and **9**, the crude product was analysed by ^{1}H NMR spectroscopy. Compounds **11** and **13** were purified by flash chromatography on silica gel (diethyl ether/cyclohexane 1/1 for **11** and ethyl acetate/cyclohexane 1/4 for **13**) before being submitted to ^{1}H NMR analysis.

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(11) Levacher, V.; Valque, C.; Coupa, S.; Dupas, G.; Quéguiner, G.; Bourguignon, J. *J. Heterocyclic Chem.*, **1996**, *33*, 1211. The e.e. was determined by HPLC on CHIRALCEL OD 10 μ, 250x4.6 mm, flow rate 1 mL/min, hexane/2-propanol 90/10. The temperature was 22 °C at 65 psi and the retention times were 10.82 (minor enantiomer) and 17.35 min (major enantiomer). Absolute configurations were not assigned.

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(13) The e.e. in the reduction of 2-benzoylpyridine was determined by HPLC on CHIRALCEL OD 10 μ, 250x4.6 mm, flow rate 1 mL/min, hexane/2-propanol 95/5. The temperature was 19 °C at 65 psi and the retention times were 15.18 (minor enantiomer) and 16.28 min (major enantiomer). Absolute configurations were not assigned.

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