Bull. Chem. Soc. Jpn., **77**, 549–552 (2004)

Chemoselective Reduction of α,β-Unsaturated Aldehydes, Ketones, Carboxylic Acids, and Esters with Nickel Boride in Methanol–Water#

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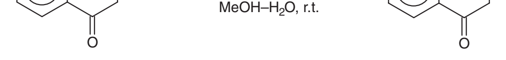
A facile procedure for the conjugate reduction of α,β-unsaturated aldehydes, ketones, carboxylic acids, and esters is reported with nickel boride generated in situ from $NiCl_2 \cdot 6H_2O/NaBH_4$ in methanol–water at ambient temperature.

The conjugate reduction of α,β-unsaturated carbonyl compounds remains an active and widespread area of organic synthesis. Different reagents are reported in the literature, each having its characteristic advantages and disadvantages.[1] Factors such as handling of reagents, strict reaction conditions, temperature maintenance, cost and poor yields of the desired product are some of the drawbacks associated with most of the reagents. Therefore, the development of a mild and selective reducing agent for the conjugate reduction of a variety of α,β-unsaturated carbonyl compounds still attracts a great deal of attention of organic chemists. Nickel boride[2] has been reported as a facile reagent in many reductions. We have also reported the selective deoxygenation of sulfoxides and selenoxides,[3a] the chemoselective reduction of aldehydes and ketones to alcohols[3b] and aromatic nitriles to primary amines,[3c] benzopyrones to 2*H*-1-benzopyran-4-ols,[3d] and the reductive desulfurization of thioureas, benzimidazoline-2-thiones and thiobarbiturates.[3e] With our experience in handling nickel boride, we believed that it must be possible to selectively reduce the conjugate double bonds under appropriate conditions.

Results and Discussion

We report herein a convenient and facile procedure for the selective reduction of the carbon–carbon double bond of α,β-unsaturated carbonyl compounds with nickel boride in methanol–water at ambient temperature. The nickel boride was generated in situ from nickel chloride hexahydrate and sodium borohydride. Chalcone (**Ia**) and 4′-methylchalcone (**Ib**) were chosen as model substrates to investigate the appropriate conditions for selective conjugate reduction. In order to achieve the selective carbon–carbon double bond reduction in chalcones, the molar ratio of substrate to nickel chloride to sodium borohydride was varied, and reactions were attempted in different solvents such as THF, DMF, dichloromethane, ethanol, and methanol. While the reactions of **Ia** and **Ib** in THF, dichloromethane, ethanol, and DMF were either incomplete and/or gave a mixture of products, reactions in methanol showed the predominant formation of dihydrochalcones. Reaction of **Ia** with $NiCl_2$:$NaBH_4$ in a 1:5:2 molar ratio in methanol yielded dihydrochalcone (48%), tetrahydrochalcone (14%), and unreacted starting material (32%). Similarly, the reaction of **Ib** yielded 47% dihydrochalcone, 5% tetrahydrochalcone, and 34% starting material. Thus, methanol appeared to be the solvent of choice for further investigation to achieve the goal. Thereafter, we investigated the role of water as a co-solvent to achieve selective reduction. We observed that **Ia** was regioselectively reduced by nickel boride when the molar ratio of substrate to nickel chloride hexahydrate to sodium borohydride was 1:5:2 in methanol–water to give the corresponding dihydrochalcone (**IIa**) in high yield. Similarly chalcones **Ib** and **Ic** could also be regioselectively reduced to dihydrochalcones **IIb** and **IIc** under these conditions. Chalcones (**Id–m**) with poor solubility in methanol required a higher molar ratio of substrate to nickel boride (1:10:4) for selective reduction of the carbon–carbon double bond (Scheme 1, Table 1). The selective reduction of α,β-unsaturated carbonyl compounds was undoubtedly due to the in situ generation of nickel boride as a reducing species since the reaction of **Ia** with sodium borohydride in a 1:2 molar ratio resulted in the complete reduction of chalcone to tetrahydrochalcone, while **Ia** was recovered unchanged when treated with nickel chloride hexahydrate in a 1:5 molar ratio. The amount of water plays a crucial role in the selective reduction. The use of a higher amount of water caused the reaction to be sluggish and/or incomplete. With lower amount of water, the competitive formation of the alcohol was also observed.

Further, we extended the scope of this reagent to achieve chemoselective reduction of α,β-unsaturated aldehydes, ketones, carboxylic acids, and esters under these conditions. Remarkable chemoselective carbon–carbon double bond reductions were observed in all of these cases, and labile functionalities like aldehyde, ketone, acid, and ester were unaffected



Ia-m **IIa-m**

a : R = R' = R" = H
b : R = R' = H; R" = CH_3
c : R = R' = H; R" = Cl
d : R = OCH_3; R' = R" = H
e : R = R' = H; R" = OCH_3
f : R = R" = H; R' = OCH_3
g : R' = H; R = R" = OCH_3
h : R = CH_3; R' = R" = H
i : R^1 = H; R = R" = CH_3
j : R = R" = Cl; R' = H
k : R = –O–CH_2–O–; R' = R" = H
l : R = –O–CH_2–O–; R' = H; R" = OCH_3
m : R = R' = H; R" = Br

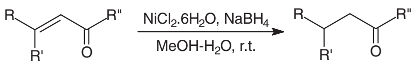
Scheme 1.

Published on the web March 12, 2004; DOI 10.1246/bcsj.77.549

Table 1. Reaction of Chalcones with Nickel Boride at Ambient Temperature in MeOH–H_2O[a)]

Run	Substrate(s)	S:$NiCl_2\cdot6H_2O$:$NaBH_4$	Product[b)]	Time/min	Yield[c)]/%
1	**Ia**	1:5:2	**IIa**	0.25	90
2	**Ib**	1:5:2	**IIb**	0.5	81
3	**Ic**	1:5:2	**IIc**	0.5	90
4	**Id**	1:10:4	**IId**	0.75	88
5	**Ie**	1:10:4	**IIe**	0.5	85
6	**If**	1:10:4	**IIf**	0.75	87
7	**Ig**	1:10:4	**IIg**	1.25	83
8	**Ih**	1:10:4	**IIh**	0.75	87
9	**Ii**	1:10:4	**IIi**	2.5	87
10	**Ij**	1:10:4	**IIj**	3	82
11	**Ik**	1:10:4	**IIk**	0.5	82
12	**Il**	1:10:4	**IIl**	0.5	84
13	**Im**	1:10:4	**IIm**	0.5	76

a) Reactions were performed with 12 mL MeOH and 2 mL water/1 mmol of substrate. b) Products were characterized by IR, NMR, mp and by comparison with authentic compound (wherever applicable). c) Yield refers to the yield of pure isolated product (>98% purity).



R = Alkyl, Aryl; R' = H, Alkyl; R" = H, Alkyl, Vinyl, OH, O alkyl

Scheme 2.

under these conditions (Scheme 2). These results are summarized in Table 2.

It can be inferred from Table 2 that disubstituted α,β-unsaturated aldehydes are selectively reduced faster and also require lower molar ratios than the di- and tri-substituted α,β-unsaturated ketones (runs 15–22). In the case of dibenzylideneacetone, both conjugated bonds were reduced selectively to yield 1,5-diphenylpropan-3-one as the major product. Similarly, cinnamylideneacetophenone underwent selective reduction of both double bonds to yield 1,5-diphenylpropan-1-one. A keto group locked in a transoid conformation, e.g. 2-cyclohexenone, which otherwise requires longer duration for selective hydrogenation,[4,5] underwent fast reduction to cyclohexanone in 1 h with nickel boride. Also, 4-(2-furyl)-3-buten-2-one was reduced selectively to 4-(2-furyl)butan-2-one without any interference from the sensitive furan nucleus. Reduction of α,β-unsaturated acids (runs 23–25) and esters (runs 26, 27) yielded the saturated acids and esters chemoselectively in high yields. α,β-Unsaturated carboxamide, namely cinnamide, and carbonitrile, namely cinnamonitrile, could not be selectively reduced, as their reactions were sluggish and showed the formation of a mixture of compounds.

Chromones could also be selectively reduced with nickel boride in methanol–H_2O to give the corresponding chromanones, though these substrates required comparatively longer reaction times and a higher molar ratio of reagents. On the other hand, flavones seemed to be more difficult to reduce selectively to give flavanones. Thus, flavone and 6-methylflavone were reduced selectively using a higher molar ratio of substrate to nickel boride to the corresponding flavanones in low yield after long reaction times. This could be due to the fact that the carbonyl group and pyrone double bond in flavones are in continuous conjugation with two phenyls, whereas in chromone the double bond has an olefinic character.[6] Slower reductions in the case of cholest-4-en-3-one, chromones, and flavones could also be attributed to the steric bulk of the molecule.

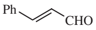
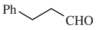
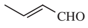
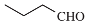
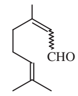
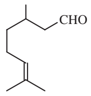
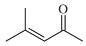
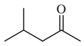
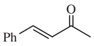
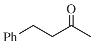
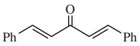
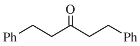
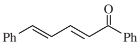
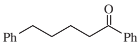
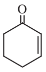
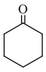
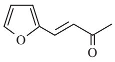
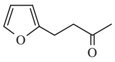
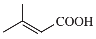
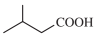
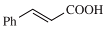
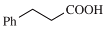
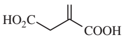
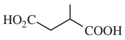
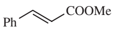
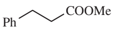
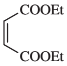
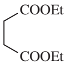
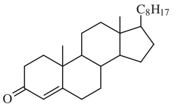
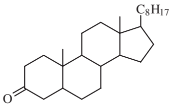
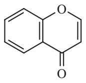
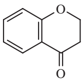
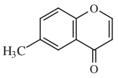
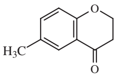
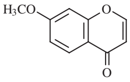
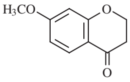
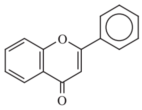
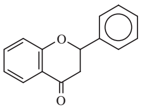
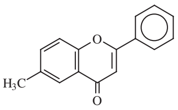
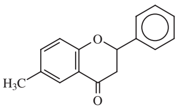
Experimental

All melting points were recorded on a tropical labquip apparatus. IR spectra were recorded on a Perkin-Elmer FT-IR SPECTRUM-2000. NMR spectra were recorded on a FT–NMR model R-600 Hitachi (60 MHz) and Bruker Advance-300 Spectrometer (300 MHz) with TMS as the internal standard. The products were identified by co-TLC (wherever applicable), mp, IR, and NMR spectra.

Starting Materials. Methanol (S.D.Fine), nickel chloride hexahydrate (Thomas Baker), and sodium borohydride (E. Merck) were used in all the reactions. Washing with 5% sodium carbonate solution, drying and distilling under vacuum purified the aldehydes obtained from commercial sources. Distillation or recrystallization purified the commercial ketones. Chalcones were prepared by condensation of corresponding acetophenones with corresponding benzaldehydes by the general procedure of Kohler and Chadwell.[7] Mesityl oxide,[8a] benzylideneacetone,[8b] dibenzylideneacetone,[8b] furfurylideneacetone,[8c] cholest-4-en-3-one[8d] were prepared by methods reported in the literature. Chromone, 6-methylchromone and 7-methoxychromone were synthesized by acid catalyzed cyclization of the appropriately substituted 1-(2-hydroxyphenyl)-1,3-butanediones.[9] Flavone and 6-methylflavone were prepared by a modified Baker–Venkataraman synthesis.[10]

In a typical reaction, a 50 mL round-bottomed flask fitted with a reflux condenser was mounted over a magnetic stirrer and chalcone (**Ia**) (0.208 g, *n* mmol) dissolved in 12 mL of methanol was placed in it. To this was added $NiCl_2\cdot6H_2O$ (5*n* mmol) followed by 2 mL of distilled water. Then $NaBH_4$ (2*n* mmol) was added and the reaction mixture was stirred vigorously at room temperature. The progress of the reaction was monitored by TLC (thin layer chromatography) using petroleum ether:ethyl acetate (90:10; v/v) as an eluent. TLC of the reaction mixture showed the complete disappearance of the starting material after 15 min. A new product having a slightly higher R_f than the starting material was observed, and was believed to be dihydrochalcone. The reaction was quenched with ~10 mL of methanol, and the reaction mixture was filtered through a celite pad (one inch) using a pump and washed with

Table 2. Reactions of α,β-Unsaturated Carbonyls, Carboxylic Acids, Esters, and Benzopyrones with Nickel Boride in MeOH–H_2O[a)]

Run	Substrate(s)	S:$NiCl_2$:$6H_2O$:$NaBH_4$	Time/h	Product[b)]	Yield[c)]/%
14		1:5:2	0.25		70
15		1:5:2	0.25		75
16		1:10:4	1.5		91
17		1:10:4	0.25		82
18		1:10:4	0.5		86
19		1:10:4	0.5		65
20		1:10:4	0.5		88
21		1:10:4	1		75
22		1:5:2	1.5		71
23		1:10:4	0.5		86
24		1:5:2	0.25		90
25		1:10:4	0.25		87
26		1:5:2	0.5		86
27		1:10:4	0.25		96
28		1:25:25[d,e)]	8		61
29		1:15:15[d,e)]	4.5		74
30		1:15:15[d,e)]	4		68
31		1:20:20[d,e)]	4.5		68
32		1:30:30[d,e)]	10		32
33		1:30:30[d,e)]	10		34

a) All reactions were performed with 12 mL MeOH and 2 mL water/1 mmol of substrate, unless mentioned otherwise. b), c) See Table 1. d) Reactions were performed with 12 mL MeOH and 0.25 mL water/1 mmol of substrate. e) Reaction was initially started with 1:5:5 molar ratio, then lots of 5:5 molar ratio of $NiCl_2 \cdot 6H_2O$ to $NaBH_4$ were added at intervals of 2 h to get required molar ratio.

methanol. Water (50 mL) was added to the combined filtrate, which was extracted with dichloromethane (3 × 15 mL). The combined dichloromethane extract was dried over anhyd. $MgSO_4$, decanted through a cotton pad and concentrated on a rotary vacuum evaporator. The product was characterized by mp, IR, and NMR spectra after recrystallization. Reactions of α,β-unsaturated aldehydes, ketones, carboxylic acids, and esters were carried out similarly, but the products were separated by column chromatography using silica gel (100–200 mesh) and petroleum ether/ethyl acetate as eluent.

In case of cholest-4-en-3-one, chromones, and flavones (runs 28–33), the reaction was started with *n* mmol of substrate in 12 mL of methanol and 5*n* mmol of $NiCl_2 \cdot 6H_2O$ placed in a 50 mL round-bottomed flask attached to a reflux condenser and mounted over a magnetic stirrer. The contents of the flask were stirred magnetically and $NaBH_4$ (5*n* mmol) was added to the flask. Thereafter, lots of $NiCl_2 \cdot 6H_2O$ (5*n* mmol) and $NaBH_4$ (5*n* mmol) were added at intervals of 2 h until the starting material completely disappeared (Table 2) as observed by TLC. The reactions were worked up as above, and the products were separated by preparative TLC using petroleum ether:ethyl acetate (75:25; v/v) as an eluent.

This work was supported by CSIR, New Delhi, India (Project No. 01/99/1567/EMR-II) and PS is thankful to UGC for the Junior Research Fellowship Grant.

References

Part of the work was presented at 5th National Symposium in Chemistry, Chemical Research Society of India, Feb. 2003, Chennai, India, p. 7.

1 a) C. Petrier and J.-L. Luche, *Tetrahedron Lett.*, **28**, 2347 (1987). b) F. Alonso and M. Yus, *Tetrahedron.*, **54**, 1921 (1998). c) G. Laval and B. T. Golding, *Synlett*, **2003**, 279. d) S. Saito and H. Yamamoto, *J. Org. Chem.*, **61**, 2928 (1996). e) C. M. Belisle, Y. M. Young, and B. Singaram, *Tetrahedron Lett.*, **35**, 5595 (1994).

2 a) J. M. Khurana and A. Gogia, *Org. Prep. Proced. Int.*, **29**, 1 (1997). b) B. Ganem and J. O. Osby, *Chem. Rev.*, **86**, 763 (1986).

3 a) J. M. Khurana, A. Ray, and S. Singh, *Tetrahedron Lett.*, **39**, 3829 (1998). b) J. M. Khurana and S. Chauhan, *Synth. Commun.*, **31**, 3485 (2001). c) J. M. Khurana and G. Kukreja, *Synth. Commun.*, **32**, 1265 (2002). d) J. M. Khurana and S. Chauhan, *J. Chem. Res., Synop.*, **2002**, 201; *J. Chem. Res., Miniprint*, **2002**, 519. e) J. M. Khurana, G. Kukreja, and G. Bansal, *J. Chem. Soc., Perkin Trans. 1*, **2002**, 2520.

4 H. M. Ali, A. A. Naiini, and C. H. Brubaker, Jr., *Tetrahedron Lett.*, **32**, 5489 (1991).

5 M. Sommovigo and H. Alper, *Tetrahedron Lett.*, **34**, 59 (1993).

6 G. P. Thakar, N. Janaki, and B. C. Subba Rao, *Indian J. Chem.*, **3**, 74 (1965).

7 E. P. Kohler and H. M. Chadwell, *Org. Synth.*, Coll. Vol. **I**, 78 (1994).

8 a) A. I. Vogel's, "Textbook of Practical Organic Chemistry," 4th ed, ELBS/Longman, UK, p. 591. b) A. I. Vogel's, "Textbook of Practical Organic Chemistry," 4th ed, ELBS/Longman, UK, p. 794. c) A. I. Vogel's, "Textbook of Practical Organic Chemistry," 4th ed, ELBS/Longman, UK, p. 795. d) A. I. Vogel's, "Textbook of Practical Organic Chemistry," 4th ed, ELBS/Longman, UK, p. 428.

9 R. Mozingo, *Org. Synth.*, Coll. Vol. **III**, 387 (1994).

10 P. K. Jain, J. K. Makrandi, and S. K. Grover, *Synthesis*, **1982**, 221.