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# Chemoselective Deprotection and Deprotection with concomitant reduction on 1,3-Dioxolanes, Acetals and Ketals using Nickel Boride

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## Abstract

An efficient and mild methodology for the reductive deprotection of 1,3-dioxolanes, acetals and ketals to the corresponding aldehydes/ ketones and also deprotection with concomitant reduction to the corresponding alcohols has been achieved in quantitative yields using nickel boride generated *in situ* from nickel chloride and sodium borohydride in methanol. The reactions are chemoselctive as halo, alkoxy and methylenedioxy groups are unaffected.

**Keywords:** Nickel boride, acetals, ketals, aldehydes, acetophenones, alcohols

## 1. Introduction

Protection and deprotection of carbonyl groups are of fundamental importance in the multistep organic synthesis. Usually deprotection is accomplished by treatment with acids or Lewis acids but in some cases sensitivity of substrates to acidic media is a severe limiting factor. Moreover, acetals and ketals tolerate diverse array of nucleophilic and basic reagents.[1] Milder protocols have emerged and reagents such as CAN in neutral or mild conditions,[2] $CeCl_3.7H_2O$,[3] $SmCl_3$/TMSCl,[4] $FeCl_3$,[5] $I_2$-acetone,[6] decaborane in THF,[7] cerium triflate in $CH_3NO_2$,[8] indium triflate[9], iodine-acetone[10], perchloric acid-$SiO_2$[11] have been reported for the deprotection of acetals/ketals. Oxidative cleavage of acetals has been reported.[12] Though numerous methods for the deprotection of acetals and ketals are known, newer

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efficient and chemoselective processes under mild conditions are always useful. However, there is only one report on reductive cleavage (hydrogenolysis) of acetals by $LiAlH_4$-$AlCl_3$.[13] Hydrogenolysis of thioacetals to give reduced products ($–CH_2$-) by nickel boride has been reported.[14] Nickel boride generated *in situ*, has been reported as a reducing agent which acts both as a catalyst and a source of hydrogen.[15] We have investigated its role as a deprotecting and reducing agent for a variety of acetals and ketals.

## 2. Results and discussion

We report herein the reductive deprotection and deprotection with concomitant reduction of a variety of acetals and ketals with nickel boride, generated *in situ*. This is the first report on reductive deprotection of acetals and ketals. 2-(4-Tolyl)-1,3-dioxolane (Ia) was chosen as model substrate. Its reaction with nickel boride using 1:2:2 molar ratio in tetrahydrofuran, dioxane and acetonitrile were incomplete and showed formation of a mixture of products while reaction in methanol was also incomplete but showed the formation of 4-tolualdehyde predominantly besides formation of a small amount of 4-tolyl alcohol (entries 1-4, table 1). The reaction was repeated under reflux and was found to be complete after 4 h and yielded 4-tolualdehyde (84%) and 4-tolyl alcohol (10%) (entry 5, table 1). However, reaction of 2-(4-tolyl)-1,3-dioxolane was complete in 15 min at room temperature using 1:3:3 molar ratio of **Ia**: $NiCl_2$: $NaBH_4$ and 87% of 4-tolualdehyde was obtained after work up (entry 6, table I). A small amount of 4-tolyl alcohol (4%) was also obtained. The reaction of **Ia** using higher amounts of nickel boride at room temperature gave lower yields of 4-tolualdehyde (75%) and higher amount of 4-tolyl alcohol (21%) (entry 7, table 2). No deprotection of **Ia** to 4-tolualdehyde was observed when the reaction was performed with nickel chloride or sodium borohydride separately (entries 8-9, table 1).

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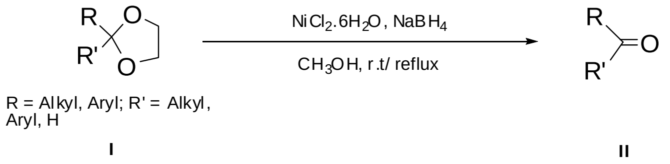
Therefore, the deprotection is undoubtedly proceeding due to the *in situ* formation of nickel boride.

**Table 1: Deprotection of 2-(4-tolyl)-1,3-dioxolane using nickel boride at ambient temperature.**

| Entry | Molar ratio<br>**Ia**:$NiCl_2.6H_2O$:$NaBH_4$ | Solvent | Time (h) | Yield (%)<br>4-$CH_3C_6H_4CHO$ |
|---|---|---|---|---|
| 1. | 1:2:2 | $CH_3CN$ | 24.0 | –[a] |
| 2. | 1:2:2 | Dioxane | 24.0 | –[a] |
| 3. | 1:2:2 | THF | 24.0 | –[a] |
| 4. | 1:2:2 | MeOH | 24.0 | –[a] |
| 5. | 1:2:2 | MeOH | 4.0[b] | 84(10)[c] |
| 6. | 1:3:3 | MeOH | 0.25 | 87(4)[c] |
| 7. | 1:4:4 | MeOH | 0.25 | 75(21)[c] |
| 8. | 1:2:0 | MeOH | 24.0 | –[d] |
| 9. | 1:0:2 | MeOH | 24.0 | –[d] |

[a] Reaction incomplete and a mixture of products was obtained.
[b] Reaction conducted under reflux.
[c] Yield in bracket is of corresponding alcohol.
[d] No reaction was observed.

Subsequently, reactions of different cyclic acetals and ketals (1,3-dioxolanes) have been investigated with nickel boride in methanol at room temperature. All these compounds (Ib-r) underwent successful deprotection using variable amounts of substrate: nickel chloride: sodium borohydride to give high yields of the corresponding aldehydes/ketones (eq 1). All these results are listed in Table 2.



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The halo groups (entries 7-10, 17, table 2) and the methoxy groups (entries 4, 6, table 2) were not affected. Surprisingly, methylene dioxy function (-O-$CH_2$-O-), which is a benzo-1,3-dixolane moiety, was not affected (entry 5, table 2) making this reductive deprotection chemoselective. Furthermore, the reaction proceeded very efficiently with aliphatic ketal (entry 18, table 2). In few cases the reduction of initially formed aldehydes to corresponding alcohols was significant (entries 4, 21, table 2).

With the successful application of using nickel boride as the unmasking agent of cyclic acetals and ketals, we turned our attention to acyclic acetals and ketals. 2-(Dimethoxymethyl)naphthalene (IIIa) was first examined under the optimized reaction conditions (IIIa:$NiCl_2.6H_2O$:$NaBH_4$:: 1:3:3). The reaction regenerated 2-naphthaldehyde in 87% yield within 15 min (entry 19, table 2). A series of other dimethyl acetals and ketals (IIIb-i) also underwent deprotection using the optimised reaction protocol. High yields of corresponding aldehyde or ketone were obtained in all these cases (entries 19-27, table 2) (eq. 2). It was further substantiated that nickel boride is a chemoselective reagent for the deprotection, since reaction of a mixture of 2-(dimethoxymethyl)naphthalene (IIIa) and 2-(diethoxymethyl)naphthalene (IIIj) resulted in selective deprotection of IIIa to give 2-naphthaldehyde. However, this is in contrast to our observation that methoxy group attached to aryl ring is unaffected. Benzyl methyl ether and 9-flurenyl methyl ether also remained unaffected under these conditions. To our surprise the diethyl acetals namely, 1-(diethoxymethyl)-4-methylbenzene and 2-(diethoxymethyl)naphthalene remained unaffected under these conditions and starting materials were recovered quantitatively after 18 h.

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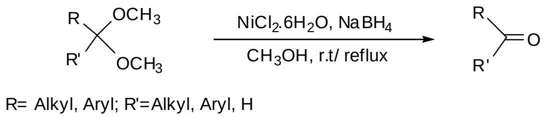

(2)

III II

**Table 2: Deprotection of cyclic/ acyclic acetals and ketals using nickel boride in methanol**

| Entry | R | R’ | Molar ratio S:$NiCl_2.6H_2O$: $NaBH_4$ | Time (h) | Yield (%) **(II)** |
|---|---|---|---|---|---|
| 1. | 4-$CH_3C_6H_4$ (Ia) | H | 1:3:3 | 0.25 | 87(6)[a] |
| 2. | 2-Naphthyl (Ib) | H | 1:3:3 | 2 | 90(7)[a] |
| 3. | 1-Naphthyl (Ic) | H | 1:3:3[b] | 3 | 86 |
| 4. | 4-$CH_3OC_6H_4$ (Id) | H | 1:6:6 | 0.50 | 61(25)[a] |
| 5. | 3-Piperonyl (Ie) | H | 1:6:6 | 0.25 | 86 |
| 6. | 3,4-$(CH_3O)_2C_6H_3$ (If) | H | 1:6:6[b] | 12 | 88 |
| 7 | 4-$ClC_6H_4$ (Ig) | H | 1:12:12 | 1.5 | 78 |
| 8. | 4-$BrC_6H_4$ (Ih) | H | 1:12:12 | 2.5 | 81 |
| 9. | 2-$ClC_6H_4$ (Ii) | H | 1:12:12 | 3 | 77 |
| 10. | 3-$ClC_6H_4$ (Ij) | H | 1:12:12 | 5 | 74 |
| 11. | $C_6H_5$ (Ik) | $CH_3$ | 1:3:3 | 3 | 90(8)[a] |
| 12. | $C_6H_5$ (Il) | $C_3H_7$ | 1:3:3[b] | 3.5 | 88 |
| 13. | 4-$CH_3C_6H_4$ (Im) | $CH_3$ | 1:8:8 | 3 | 88(10)[a] |
| 14. | 4-$CH_3OC_6H_4$ (In) | $CH_3$ | 1:8:8 | 3 | 89 |
| 15. | $C_6H_5$ (Io) | $C_2H_5$ | 1:8:8[b] | 5 | 84 |
| 16. | Fluorenyl (Ip) | H | 1:8:8[b] | 6 | 90 |
| 17. | 4-$ClC_6H_4$ (Iq) | $CH_3$ | 1:12:12 | 4 | 77 |
| 18. | $CH_3$ (Ir) | $C_6H_{13}$ | 1:6:6 | 0.25 | 82 |
| 19. | 2-Naphthyl (IIIa) | H | 1:3:3 | 0.25 | 87(8)[a] |
| 20. | 4-$CH_3C_6H_4$ (IIIb) | H | 1:3:3[b] | 4 | 87 |
| 21. | 1-Naphthyl (IIIc) | H | 1:10:10 | 18 | 60(30)[a] |
| 22. | 4-$BrC_6H_4$ (IIId) | H | 1:10:10 | 0.5 | 75 |
| 23. | 4-$ClC_6H_4$ (IIIe) | H | 1:10:10 | 0.75 | 78 |

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| | | | | | |
|---|---|---|---|---|---|
| 24. | 3-Piperonyl (IIIf) | H | 1:10:10[b] | 3 | 72 |
| 25. | $C_6H_5$ (IIIg) | $CH_3$ | 1:3:3 | 0.25 | 91 |
| 26. | $CH_3$ (IIIh) | $C_6H_{13}$ | 1:6:6 | 0.25 | 90 |
| 27. | 4-$CH_3C_6H_4$ (IIIi) | $CH_3$ | 1:6:6 | 4 | 92(7)[a] |

[a] Yield in bracket represents the yield of alcohol

[b] Reaction conducted under reflux

The deprotection is proposed to be proceeding *via* hydrogenolysis of C–O bond, rather than a hydrolysis mechanism. The deprotection initially involves the cleavage of C–O bond leading to the formation of a geminal diol, which undergoes loss of water molecule to corresponding carbonyl compound. This is in agreement with our observations as no traces of p-xylene, 2-methylnaphthalene or fluorene were detected in the reactions of **Ia, Ib** or **Ip** with nickel boride. The reaction of 2,2-dimethyl-4,5-diphenyl-1,3-dioxolane yielded only 5% of 1,2-diphenylethane and 95% of starting material was recovered unchanged. Also, in conformity with the inertness of the methylene dioxy group (Ie), the starting material was recovered unchanged in the reaction of catechol acetonide, probably because $C_{sp2}$–O bond was difficult to cleave.

The activity and selectivity of nickel boride varies dramatically with small variation in the preparation of nickel boride.[16] This coupled with our observations of formation of small amount of alcohol in a number of reactions, made us to investigate reactions using higher and by varying molar ratios of substrate to nickel chloride to sodium borohydride reagent. Treatment of **Ia** with 1:4:12 molar ratio (Ia:$NiCl_2.H_2O$:$NaBH_4$) in methanol gave 2-tolyl methanol exclusively, in 85% yield within 4 h (entry 1, table 3). Subsequently, various cyclic as well as acyclic acetals and ketals were treated with nickel boride with indicated

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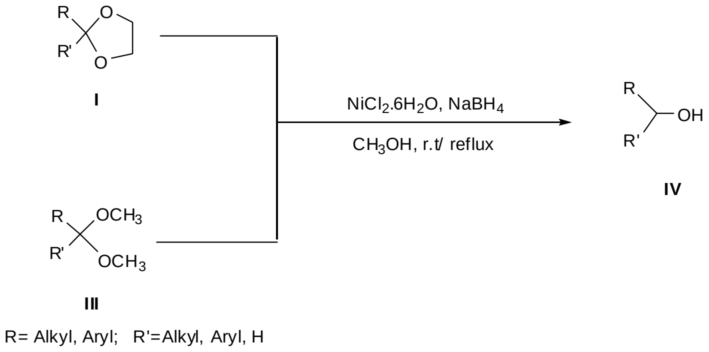
molar ratios in methanol. All theses compounds underwent reduction successfully in 0.25-18 h at ambient temperature to give the corresponding alcohols in high yields at room temperature/ reflux (entries 2-18, table 3) (eq. 3). The results are summarized in Table 3.



(3)

### Table 3: Reduction of cyclic/ acyclic acetals and ketals using nickel boride in methanol

| Entry | R | R’ | Molar ratio<br>S:$NiCl_2.6H_2O$:$NaBH_4$ | Time (h) | Yield (%)<br>**(IV)** |
|---|---|---|---|---|---|
| 1. | 4-$CH_3C_6H_4$ (Ia) | H | 1:4:12 | 4 | 85 |
| 2. | 2-Naphthyl (Ib) | H | 1:5:15 | 1 | 85 |
| 3. | 1-Naphthyl (Ic) | H | 1:3:9[b] | 8 | 70(25)[a] |
| 4. | 4-$CH_3OC_6H_4$ (Id) | H | 1:5:15 | 1 | 66 |
| 5. | 3-Piperonyl (Ie) | H | 1:6:18 | 0.25 | 61(28)[a] |
| 6. | 3,4-$(CH_3O)_2C_6H_3$ (If) | H | 1:6:18 | 0.25 | 82 |
| 7. | $C_6H_5$ (Ik) | $CH_3$ | 1:6:18 | 4 | 81 |
| 8. | $C_6H_5$ (Il) | $C_3H_7$ | 1:6:18[b] | 8 | 85(10)[a] |
| 9. | $CH_3$ (Ir) | $C_6H_{13}$ | 1:6:18 | 24 | 79 |
| 10. | 4-$CH_3C_6H_4$ (Im) | $CH_3$ | 1:6:18 | 0.25 | 91 |
| 11. | 4-$CH_3OC_6H_4$ (In) | $CH_3$ | 1:6:18 | 0.25 | 97 |
| 12. | $C_6H_5$ (Io) | $C_2H_5$ | 1:8:24[b] | 24 | 72 |
| 13. | 2-Naphthyl (IIIa) | H | 1:5:15 | 18 | 80 |
| 14. | 4-$CH_3C_6H_4$ (IIIb) | H | 1:3:9 | 2 | 84 |
| 15. | 1-Naphthyl (IIIc) | H | 1:10:15 | 18 | 82 |
| 16. | $C_6H_5$ (IIIg) | $CH_3$ | 1:3:9 | 0.25 | 91 |

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| | | | | | |
|---|---|---|---|---|---|
| 17. | $CH_3$ (IIIh) | $C_6H_{13}$ | 1:6:18 | 0.5 | 89 |
| 18. | 4-$CH_3C_6H_4$ (IIIi) | $CH_3$ | 1:6:18 | 3 | 90 |

[a] Yield in bracket refers to yield of corresponding carbonyl compound.
[b] Reaction conducted under reflux.

The methylene dioxy group was unaffected even with higher molar ratios of substrate to nickel boride. Also, the chloro and bromo groups were unaffected even under these conditions. The alcohols are indeed obtained from the corresponding aldehydes which could be observed distinctly. The reduction of aldehydes/ ketones has already been reported by us.[17]

## 3. Conclusions

In conclusion, we have shown that nickel boride is a useful reagent for the reductive deprotection of 1,3-dioxolanes, acetals and ketals to give the corresponding aldehydes/ketones or deprotection with concomitant reduction to the corresponding alcohols. The conditions are mild, neutral and tolerate a wide range of functionalities, including methoxy, methylenedioxy and halo groups. The deprotection is believed to be proceeding *via* hydrogenolysis.

## 4. Experimental:

All the melting points (wherever applicable) were recorded on a Tropical Labequip apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer FT-IR SPECTRUM-2000. NMR spectra were recorded on FT-NMR model R-300 Hitachi (300 MHz) with TMS as the internal standard. All the products are reported compounds and were identified by co-TLC, m.p, IR and NMR spectra.

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### 4.1. General procedure for deprotection of cyclic/ acyclic acetals and ketals with $NiCl_2$ and $NaBH_4$

In a typical experiment, 2-(4-tolyl)-1,3-dioxolane (1mmol) and methanol (10 mL) was placed in a 50 mL round-bottomed flask fitted with a water condenser and mounted over a magnetic stirrer. Nickel chloride hexahydrate (3 mmol) was added to the flask, followed by the addition of sodium borohydride (3 mmol) with constant stirring. A vigorous reaction took place and the reaction mixture turned black due to the *in situ* formation of nickel boride. The progress of the reaction was monitored by TLC (petroleum ether: ethyl acetate: 95:5, v/v). After 15 min, the reaction was complete. The reaction mixture was filtered through a celite pad (~1 inch) and washed with methanol (2 x 10 mL). The combined extract was then diluted with water (~50 mL) and extracted with dichloromethane (3 x 10 mL). The combined extract was washed with water and dried over anhyd. $Na_2SO_4$. After concentration on a Buchi rotary evaporator, the product was purified by column chromatography on neutral alumina using petroleum ether: ethyl acetate (97:3, v/v) as eluent. p-Tolualdehyde was obtained as colourless oil in 87% yield. The product was identified by IR and NMR spectra.

### 4.2. General procedure for the reduction of cyclic/ acyclic acetals and ketals with $NiCl_2$ and $NaBH_4$

In a typical experiment, 2-(4-tolyl)-1,3-dioxolane (1mmol), nickel chloride hexahydrate (4 mmol) and methanol (10 mL) were stirred magnetically in a 50 mL round-bottomed flask mounted over a magnetic stirrer. Sodium borohydride (12 mmol) was added to the mixture carefully and the contents were stirred vigorously. The reaction mixture turned black due to the *in situ* formation of nickel boride. TLC analyses (petroleum ether: ethyl acetate:: 95:5,

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v/v) showed complete disappearance of the starting material after 4 h and the formation of a polar product with lower $R_f$ was observed. The reaction mixture was filtered through a celite pad (~1 inch) and washed with methanol (2 x 10 mL). The filtrate was diluted with water (~50 mL). It was extracted with $CH_2Cl_2$ (3 x 10 mL), washed with water (~10 mL), dried over anhydride sodium sulphate and concentrated on a Buchi rotavapour. 4-Tolylmethanol (IIIa) (85 %) was obtained as a white solid. m.p. 60°C (lit. m.p. 60-62°C) and also identified by IR and NMR spectra.

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