Some synthetic applications of nickel boride at ambient temperature^Ψ

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Introduction

Nickel boride was first reported by Schlesinger and Brown¹ in 1949 and is formed by the reaction of nickel(II) salt with sodium borohydride. In 1951, Paul *et al.*² reported that nickel boride was useful for catalytic hydrogenation. Later Schlesinger *et al.*³ reported a simple synthesis of nickel boride in aqueous medium. The reaction of nickel chloride and sodium borohydride can be represented as shown in eq. (1).

This opened a new area for chemists to unfold the applications of this catalyst. Small variations in the method of preparation can dramatically effect the activity, sensitivity, physical and chemical properties of the boride. Nickel boride is non-magnetic and non-pyrophoric⁴. It can be filtered, stored moist without problem, but when dry, it becomes pyrophoric⁵. The actual composition of borides prepared from nickel salts depends to a great extent on the specific mode of preparation. Maybury *et al.*⁵ analyzed nickel boride prepared in ethanol using excess NaBH₄ and concluded that Ni₂B inadequately represents its composition. Besides containing solvent and adsorbed H₂ which was released upon heating, the solids were contaminated with tightly trapped NaCl. On the basis of metal : boron ratio and the amounts of H₂ evolved, the formula (Ni₂B)₂H₃ was suggested. X-ray photoelectron spectroscopy⁶ has revealed that the activity of the catalyst depends on the form of surface nickel and boron. Surface contamination by spectator ions such as Na⁺ and Cl⁻ dramatically reduces the activity. The activity of various nickel boride catalysts has been correlated to the surface areas of undispersed catalyst⁷.

Nickel boride⁸ has been used for the reduction of alkenes and alkynes; reduction of heteroarenes e.g. quinolines, isoquinolines, quinoxalines and quinaldines; dehalogenation

of α-haloketones; reaction of α-chloro nitro compounds; coupling of alkyl iodides with α,β-unsaturated esters and α-haloesters with olefins; deprotection of silyl ethers, tosylates and anhydrides. It has also been employed for the reduction of different nitrogen functionalities, e.g. aliphatic, aromatic and heterocyclic nitro compounds, oximes, nitriles, azides etc.; desulfurization of thioketals, mercaptans (alkyl, aryl and heterocyclic), thioethers and sulfoxides. Deselenization of selenides and selenoxides to the corresponding hydrocarbons is reported with nickel boride.

Nickel boride has been used as a heterogeneous catalyst in a number of hydrogenation reactions⁸. Lately it has been used not only as a catalyst but also as a source of hydrogen. It is superior to many metal catalysts. Its advantages include its low cost, ease of preparation, handling, non-pyrophoric nature and simple removal from a reaction mixture by filtration. It behaves differently under different reaction conditions. The product(s) depend greatly on (i) the molar ratio of the substrate to nickel boride or substrate to NiCl₂ to NaBH₄, (ii) the solvent/solvent mixture, (iii) whether the catalyst is preformed or is formed *in situ*, and (iv) temperature of the reaction. In view of its various advantages over other catalysts coupled with the fact that it could be used not only as a catalyst but also as a source of hydrogen, we decided to investigate some of its newer applications in organic synthesis which are summarized below.

Deoxygenation of sulfoxides and selenoxides with nickel boride⁹

It was reported that nickel boride brings about reductive desulfurization and deselenization of sulfoxides and selenoxides to the corresponding hydrocarbons. However we believed that it may be possible to deoxygenate the sulfoxides and selenoxides selectively to give the corresponding sulfides and selenides under appropriate conditions. Therefore a number of reactions were carried out using diphenyl sulfoxide as a model substrate to

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delineate the conditions. After various attempts, we have successfully achieved the selective deoxygenation of sulfoxides and selenoxides with nickel boride (eq. (2)). The sulfones are not effected under these conditions. Nickel boride undergoes loss of activity upon aging.

X = S, Se

The deoxygenations are proposed to be proceeding by an oxidative-addition and reductive elimination pathway given below.

Rapid reduction of carbonyls with nickel boride at ambient temperature¹⁰

It has been reported that nickel boride does not effect the aldehydes as such. However, aldehydes can be reduced selectively in the presence of ketones using nickel boride-chlorotrimethylsilane (CTMS). Since nickel boride behaves differently under different reaction conditions, we decided to investigate reactions of various carbonyl compounds with nickel boride to achieve rapid reduction. After carrying out number of reactions with model substrates by changing molar ratios and solvent etc., we observed that aldehydes (**1**) could be reduced rapidly with nickel boride generated *in situ* from anhyd. NiCl_2 and NaBH_4 in dry THF at RT to the corresponding alcohols (**2**) (eq. (3)). Similarly a variety of ketones viz. diaryl, alkyl, fused, dialkyl and cyclic (**3**) were reduced to the corresponding alcohols (**4**) (eq. (4)).

Sterically hindered ketones like Δ^5 -cholesten-3-one and camphor are efficiently reduced. Δ^5 -Cholesten-3-one yielded β -cholesterol and no epimerization was observed at C-3. The catalyst loses its activity with time as the starting benzophenone was recovered unchanged on reaction with preformed nickel boride after 72 h. Nitrogen contain-

ing carbonyl compounds could not be reduced efficiently. The amides and esters were not affected under these conditions. The formation of hydrocarbons in the reactions of 9-anthrone and xanthone has been shown to be proceeding by the subsequent reactions of initially formed alcohols with nickel boride.

Reduction of benzopyrones with nickel boride in methanol at ambient temperature¹¹

Benzopyrones and 2*H*-1-benzopyran-4-ols are important class of naturally occurring compounds and are found in nature as their glycosides. Some of these hydroxyflavans such as phytoalexins possess antifungal activities, while various analogs of 2*H*-1-benzopyran-4-ols are antihypertensive, cardiovascular agents, bronchodilators and immunomodulators. 2*H*-1-Benzopyran-4-ols can be prepared from benzopyrones by reduction with different reagents. Benzopyrones containing α,β -unsaturated carbonyl groups such as flavones, chromones and isoflavones are somewhat resistant to reduction and yield mixture of compounds. In view of their importance, we investigated the reduction of various benzopyrones with nickel boride.

Therefore, reactions were carried out with model substrates by changing the molar ratio of reagent, solvents and temperature to achieve the desired results. After various attempts, we have been able to successfully reduce flavones (**5**), chromones (**7**) and isoflavones (**9**) to give corresponding benzopyran-4-ols (**6**, **8** and **10**) (eqs. (5–7)). Reduction of dihydro benzopyrones, viz. flavonone (**11**), chromanones (**12**), and isoflavanones (**13**) also gave the corresponding benzopyran-4-ols (eqs. (5–7)) with nickel boride in methanol at ambient temperature. The involvement of nickel boride was confirmed by blank reactions of flavone and chromone with NaBH_4 and nickel chloride individually under identical conditions.

It was observed that higher molar ratios are required for the reduction of flavones (**5**) compared to chromones (**7**) probably due to the fact that carbonyl group and pyrone

bond in flavones (**5**) are in continuous conjugation with the two phenyls unlike chromones (**7**) in which the double bond has an olefinic character. However, we could not achieve selective reduction of flavones, chromones and isoflavones to give flavanones, chromanones and isoflavanones, respectively despite various attempts. The reduction of flavones, chromones and isoflavones to flavan-4-ols, chroman-4-ols and isoflavan-4-ols has been shown to be proceeding via the corresponding flavanones, chromanones and isoflavanones. The subsequent reduction of flavanones, chromanones and isoflavanones is much faster (eqs. (5–7)).

All 2*H*-1-benzopyran-4-ols obtained from different benzopyrones were studied for the stereochemistry of the dihydropyran ring using ¹H NMR (300 MHz). The flavan-4-ols (**6**) obtained from flavones (**5**) and flavanones (**11**) showed the products to be 2,4-*cis*-flavan-4-ols (β) isomers. The chemical shifts and the splitting patterns for the heterocyclic ring protons are in agreement with literature value. The coupling constants for the flavan-4-ols are consistent with either half chair or sofa conformation of the heterocyclic ring in which the 2-aryl group is equatorial (**14** and **15**).

The chemical shifts and splitting patterns of the isolated isoflavan-4-ols are also in agreement with the reported data. The 3-H was shown to be axial (3-aryl group equatorial) and the 4-H as equatorial. Similarly 2-methylchroman-4-ol and 2,6-dimethylchroman-4-ol have been identified as the *cis* isomers based on ¹H NMR.

Rapid reduction of nitriles to primary amines with nickel boride¹²

Sodium borohydride does not reduce groups like ester, nitro, amides and nitriles unlike lithium aluminium hydride which offers little selectivity in reductions. Nickel boride was reported as a catalyst in the reduction of nitriles under hydrogen atmosphere. The yields are very poor even after prolonged reaction times e.g. only 56% of benzonitrile was reduced under hydrogen atmosphere after 48 h using nickel boride as catalyst. We decided to investigate the application of nickel boride to reduce the robust cyano group without hydrogen atmosphere.

A simple, facile and convenient procedure for the re-

duction of robust cyano group in aromatic nitriles (**16**) to benzylic primary amines (**17**) in high yields is reported with nickel boride generated *in situ* at ambient temperature. The reductions have been carried out in dry ethanol. The reductions are very rapid and are complete in ~5 min (eq. (8)).

Reductions carried out with hydrated NiCl₂ and 95% ethanol gave lower yields of the corresponding primary amines. There was very little reduction of benzonitrile with sodium borohydride even after 24 h. The reductions are undoubtedly due to the involvement of nickel boride formed *in situ*. Reductions were slower in tetrahydrofuran and dimethylformamide, and also yielded a complex mixture with lower yields of the corresponding primary amines.

Small amounts of secondary amines (**18**) were also formed in the reactions. The formation of secondary amines could not be eliminated completely despite attempting reactions under different conditions. The secondary amines are formed from the primary amines obtained initially as confirmed by an independent reaction of benzyl amine with nickel boride. The reductions are chemoselective as halo (chloro and bromo), methoxy, dimethylamino, olefinic and naphthyl ring were unaffected under our reaction conditions. The stoichiometry of substrate to nickel chloride to sodium borohydride, the reaction solvent and the temperature play an important role in the outcome of the reaction products.

Desulfurization of thioureas and 2(1*H*)-benzimidazoline thiones¹³

Desulfurization of thioureas is reported with different reagents but the results are not consistent, e.g. unsubstituted thioureas gave formamidine hydrochloride in presence of ammonium chloride or a mixture of methane, ammonia and methylamine, *N*-(*o*-tolyl) thiourea gave *o*-toluidine, *N,N'*-di- and *N,N,N'*-trisubstituted thioureas have been reported to yield corresponding formamidines, while *N*-monosubstituted thioureas gave *N,N'*-disubstituted formamidines.

We have carried out reductive desulfurization of diaryl thioureas (**19**), monoaryl thioureas (**22**), dialkyl thioureas (**23**) and benzimidazoline thiones (**25**) with nickel boride in dry methanol at ambient temperature. The diaryl thioureas (**19**) underwent complete reductive desulfurization with concomitant cleavage of carbon-nitrogen bond to give the anilines (**20**) and *N*-methyl anilines (**21**) in nearly equal ra-

tios (eq. (9)). Reactions with hydrated nickel chloride and ordinary methanol were very slow. Diaryl thioureas were recovered unchanged when treated with nickel chloride or sodium borohydride. The reaction of *N,N'*-di-(*p*-bromophenyl) and *N,N'*-di-(*p*-iodophenyl) thioureas showed the formation of corresponding halogenated and dehalogenated anilines. The dehalogenated anilines were formed by competitive dehalogenation. However, complete dehalogenation could not be achieved in either case despite using high molar ratios of substrate to nickel boride or at low temperatures. Monoaryl thioureas (**22**) also underwent reductive desulfurization with concomitant carbon-nitrogen bond cleavage (eq. (10)) under the above reaction conditions. The anilines were obtained in higher yields compared to *N*-methyl anilines. This suggests that reductive

cleavage of carbon-nitrogen bond adjacent to aryl group is preferred over C-NH₂ bond. The dialkyl thioureas did not react as fast as diaryl thioureas and also showed the formation of a mixture of products under these conditions. After modifying reaction conditions, it was observed that

dialkylthioureas could be reductively desulfurised to the corresponding formamidines (**24**) (eq. (11)).

The formation of formamidines prompted us further to investigate the reactions of cyclic thioureas. Thus reaction of 2(1*H*)-benzimidazoline thione (**25a**) was carried out with nickel boride and yielded benzimidazole (**26a**). Subsequently, reactions of *N*-methyl-2(1*H*)-benzimidazoline thione (**25b**) and *N*-phenyl-2(1*H*)-benzimidazoline thione (**25c**) yielded *N*-methyl- and *N*-phenyl benzimidazole (**26b** and **26c**), respectively (eq. (12)).

Reductive desulfurization of 2-thiobarbiturates with nickel boride in dry methanol¹³

Hexahydropyrimidine-4,6-diones constitute an important class of pyrimidine derivatives, some of which are known for their pharmaceutical importance. There has been a great deal of interest in the synthesis of these compounds. These important compounds have been synthesized by two different approaches. The first approach is condensation of malonic acid derivatives and the second approach is reduction of barbiturates and 2-thiobarbiturates (2-thioxo-2*H*, 5*H*-pyrimidine-4,6-diones) to give hexahydropyrimidine-4,6-diones. We decided to explore the potential and versatility of nickel boride for the reductive desulfurization of 2-thiobarbiturates so as to develop a new and general method for the synthesis of hexahydropyrimidine-4,6-diones.

Reactions were carried out with model substrates to determine reaction conditions for the quantitative desulfurization. It was observed that various 2-thiobarbiturates (**27**) can be quantitatively desulfurized with nickel boride generated *in situ* with varying molar ratios of substrate to nickel chloride to sodium borohydride in dry methanol at ambient temperature to give corresponding hexahydropyrimidine-4,6-diones (**28**) (eq. (13)). The rate of desulfurization depends on the molar ratio of substrate to nickel chloride to sodium borohydride.

Involvement of nickel boride in the dethiation of thiobarbiturates was confirmed by blank reactions. Reaction with hydrated nickel chloride in ordinary methanol as well as with lower molar ratios of substrate to nickel boride resulted in poor yields compared to reactions under anhydrous conditions. Competitive debromination was observed in the reaction of 1,3-di(4-bromophenyl)-2-thiobarbituric acid. Reaction of 1,3-di(4-bromophenyl)-2-thiobarbituric acid in higher molar ratios resulted complete debromination to yield 1,3-diphenylhexahydropyrimidine-4,6-dione. However, no competitive dechlorination was observed in the reactions of 1,3-di(4-chlorophenyl)-2-thiobarbituric acid even with higher molar ratio of substrate to nickel boride.

The desulfurization of 1,3,5-triphenyl-2-thiobarbituric acid required a very high molar ratio of the reagent compared to other analogues due to steric crowding of the three phenyl rings. The substitution pattern in the pyrimidine ring

at C-5 or at either of the nitrogen atoms does not play any role in the final outcome of the desulfurized product unlike desulfurization reactions reported with Raney nickel, wherein 5-monosubstituted-2-thiobarbiturates are reported to give corresponding 4,6-dihydroxypyrimidines. In our reactions of unsubstituted 2-thiobarbituric acid, 5-monosubstituted-2-thiobarbituric acid and 5,5-disubstituted-2-thiobarbituric acids with nickel boride, only the corresponding hexahydropyrimidine-4,6-diones were obtained in high yields. This method has been utilized to prepare 5-ethyl-5-phenylhexahydropyrimidine-4,6-dione, a well known antiepileptic agent, in 81% yield compared to 30–45% yield using Raney nickel and 1,3-diphenyl hexahydropyrimidine-4,6-dione in 85% yield compared to reported yield of 30% using Raney nickel. Nickel boride shows high selectivity towards desulfurization as carbonyl groups are not effected. The desulfurizations are taking place by the hydrogenation of $>C=S$ group to give $>CH-SH$ which undergoes rapid hydrogenolysis by loss of H_2S to give the corresponding hexahydropyrimidine-4,6-diones.

Reductive desulfurization of 3-aryl-2-thioxo-4(3H)-quinazolinones with nickel boride¹⁴

Quinazolinones form the largest group of known quinazoline derivatives. This abundance is attributed to the ease of their preparation from accessible intermediates and so they have often been used as the source of other quinazolines. Quinazolinones have a variety of pharmaceutical applications. In view of the importance of quinazolinones, we decided to explore the application of nickel boride to achieve reductive desulfurization of 2-thioxo-4(3H)-quinazolinones which would provide a new route for the syntheses of various dihydroquinazolinones and tetrahydroquinazolinones in high yields.

Reductive desulfurization of 3-phenyl-2-thioxo-4(3H)-quinazolinone (**29a**) as a model substrate could be achieved with nickel boride in dry methanol at ambient temperature to give 3-phenyl-1,2,3,4-tetrahydro-4-quinazolinone (**30a**) in high yield. In general, 3-aryl-2-thioxo-4(3H)-quinazolinones (**29**) could be reductively desulfurized with nickel boride, prepared *in situ*, in dry methanol at ambient temperature, to give 3-aryl-1,2,3,4-tetrahydro-4-quinazolinones (**30**) or 3-aryl-4(3H)-quinazolinones (**31**) in high yields (eq. (14)).

The product selectivity (final product) is dependent on the molar ratio of substrate to nickel chloride to sodium borohydride. In the reaction of **29e**, concomitant debromination was also observed leading to the formation of **30a**. The unsubstituted quinazolinone **29f**, could also be selectively converted to tetrahydro (**30f**) or dihydro (**31f**)

quinazolinone. In the reaction of *N*-1-methyl substituted quinazolinone **29g**, the formation of dihydro-product is not anticipated and the product isolated was identified to be corresponding tetrahydroquinazolinone (**30g**). It has been shown that the initial reductive desulfurization results in the formation of dihydro analogues (**29**) which undergo subsequent reduction to afford tetrahydro analogues (**30**). Reduction of dihydroquinazolinones to tetrahydroquinazolinones by nickel boride has also been observed. The desulfurization is believed to be proceeding by hydrogenolysis of the initially formed $>CH-SH$ bond.

Chemoselective reduction of α,β -unsaturated aldehydes, ketones, carboxylic acid and esters¹⁵

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. Therefore 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. With our experience in handling nickel boride, we decided to investigate the conjugate reduction under appropriate conditions.

Chalcone and 4-methylchalcone were chosen as model substrates to investigate the appropriate conditions for selective conjugate reduction. The molar ratio of substrate to nickel chloride to sodium borohydride was varied and different solvents/cosolvents were tried. The regioselective reduction of these substrates could be achieved using 1 : 5 : 2 molar ratio of substrate to nickel chloride hexahydrate to sodium borohydride in methanol-water. Subsequently a variety of chalcones (**32**) could be regioselectively reduced to dihydrochalcones (**33**) under these conditions (eq. (15)). 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 **32** with sodium borohydride in a 1 : 2 molar ratio resulted in the complete reduction of chalcone to tetrahydrochalcone.

The amount of water plays a crucial role in the selective reductions.

Chemoselective carbon-carbon double bond reductions were also observed in α,β -unsaturated aldehydes, ketones, carboxylic acids and esters, and labile functionalities like aldehyde, ketone, acid and ester were unaffected (eq. (16)).

It was inferred that disubstituted α,β -unsaturated aldehydes are reduced faster and in lower molar ratios than the di- and tri-substituted α,β -unsaturated ketones. Dibenzylidenel acetone and cinnamylideneacetophenone underwent selective reduction of both double bonds. 4-(2-Furyl)-3-buten-2-one was reduced selectively to 4-(2-furyl)butan-2-one without interference from the sensitive furan nucleus. α,β -Unsaturated amides and nitriles could not be selectively reduced. Chromones could also be selectively reduced with nickel boride in methanol- H_2O to give the corresponding chromanones. Flavones were more difficult to reduce selectively to give flavanones e.g. flavone and 6-methyl flavone were reduced selectively in low yields after long reaction times. 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.

We conclude that nickel boride is not merely a catalyst but an extremely useful reagent for a variety of organic transformations. Further work on reductive coupling, desulfurization of thiono esters, thioamides and synthesis of new heterocycles is under progress.

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