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ORIGINAL PAPER

Development of a novel protocol for chemoselective deprotection of *N*/*O*-benzyloxycarbonyl (Cbz) at ambient temperature

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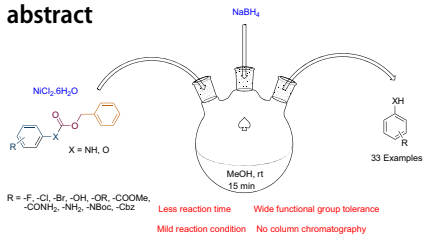
Abstract

A novel protocol for the deprotection of *N*-benzyloxycarbonyl and *O*-benzyloxycarbonyl groups by nickel boride generated in situ from $NaBH_4$ and $NiCl_2{\cdot}6H_2O$ in methanol at room temperature has been developed to give the corresponding amines and phenols. This protocol is chemoselective as groups like chloro, bromo, amide, ester, pyridine, and tert-butyloxycarbonyl moiety are unaffected under these conditions. The deprotection has also been validated in gram scale reactions, to establish the wider appropriateness of this protocol.

Graphical abstract



Keywords Hydrogenation · Deprotection · Heterogeneous catalysis

Introduction

Protection/deprotection approaches are often mandatory in synthetic sequences. Amino and phenolic groups are present in many starting materials and require protection/deprotection to achieve the desired goals [1–3]. They have application in organic synthesis, especially in the fields of pharmaceuticals [4, 5], peptides [6], nucleotides, and carbohydrates [7]. Benzyloxycarbonyl (Cbz) group is the most appropriate amine-protecting group and is stable in both mild acidic as well as in basic conditions. The *N*-benzyloxycarbonyl group can be easily introduced generally by reaction of benzyl chloroformate in presence of a mild base at room temperature [8]. It reduces the nucleophilic character of the heteroatom and can be deprotected when required. Several methods have been employed for the deprotection of Cbz, e.g., palladium-catalysed hydrogenolysis [9], Bu_4NF in THF [10], solvated electrons [11], BBr_3 [12], strong basic hydrolysis [13], zinc/iodine in methanol [14], catechol boron halides [15], and trimethylsilyl iodide [16]. Each of these methods has their own specific applications and there are certain drawbacks also such as harsh conditions, tedious workup, long reaction time, and expensive reagents.

Nickel boride can be readily prepared in situ from nickel(II) chloride and sodium borohydride in a variety of solvents and has been used as a reagent in a number of important reductions. In continuation of our efforts to

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broaden the scope of nickel boride as an efficient deprotection/reducing reagent [17–27], we have investigated the deprotection of *N*-benzyloxycarbonyl (Cbz) with nickel boride generated in situ.

Results and discussion

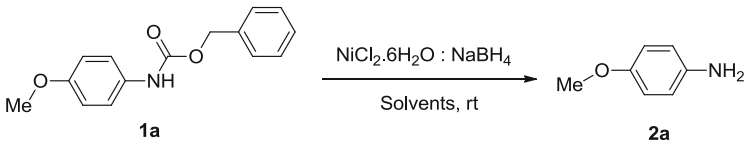
In this paper, we have reported a simple, efficient, and inexpensive procedure for the deprotection of benzyloxycarbonyl (Cbz) protected amines and phenols to the corresponding amines and phenols with nickel boride generated in situ from nickel chloride and sodium borohydride in methanol at ambient temperature. Benzyl 4-methoxyphenylcarbamate (**1a**) was chosen as the model reactant to investigate the appropriate conditions for deprotection of *N*-benzyloxy carbamates (Table 1). Initially, the reaction of **1a** was carried out with nickel boride using 1:5:15 molar ratio (reactant:$NiCl_2{\cdot}6H_2O$:$NaBH_4$) in different solvents such as dioxane, tetrahydrofuran, acetonitrile, and ethanol. The reactions were sluggish and resulted in mixture of products after 60 min (Table 1, entries 1–4). No reaction of **1a** was observed in dichloromethane (DCM) using same molar ratio of nickel boride (Table 1, entry 5). However the reaction of **1a** using 1:5:15 molar ratio of **1a**:$NiCl_2{\cdot}6H_2O$:$NaBH_4$ in methanol was complete in 15 min at room temperature and gave 88% of 4-anisidine (**2a**) after work up (Table 1, entry 6). Reaction of **1a** was then attempted with lower ratio using 1:4:12 molar ratio of **1a**:$NiCl_2{\cdot}6H_2O$:$NaBH_4$ in methanol but was incomplete even after 60 min and gave 56% of 4-anisidine after work up and separation (Table 1, entry 7). No deprotection of **1a** to 4-anisidine was observed when the reactions were performed with nickel chloride or sodium borohydride separately (Table 1, entries 8, 9). Reaction of **1a** was when attempted with equimolar ratio of $NiCl_2{\cdot}6H_2O$:$NaBH_4$ (1:5:5) in methanol but was incomplete even after 60 min and gave 18% of 4-anisidine (**2a**) after work up and separation (Table 1, entry 10).

Therefore, it can be inferred from above results that *N*-benzyloxycarbonyl group could be deprotected with nickel boride generated in situ using 1:5:15 molar ratio of reactant:$NiCl_2$:$NaBH_4$ in methanol at room temperature.

Subsequently, reactions of different Cbz-protected amines have been investigated with nickel boride in methanol at room temperature. All the compounds **1a**–**1x** underwent deprotection successfully using 1:5:15 molar ratio of reactant:nickel chloride:sodium borohydride. The reactions were complete in 15 min in methanol at ambient temperature and gave the corresponding amines **2a**–**2x** in high yields. All results are listed in Scheme 1.

It is inferred from the above results that the halo groups (**2d**–**2h**), amide group (**2v**), ester group (**2s**), methoxy and methylene dioxy groups (**2a**, **2r**), and pyridine rings (**2n**, **2o**) remained unaffected under these conditions making this reductive deprotection chemoselective. It can also be

Table 1 Deprotection of 4-methoxyphenyl carbamate (**1a**) using nickel boride at ambient temperature



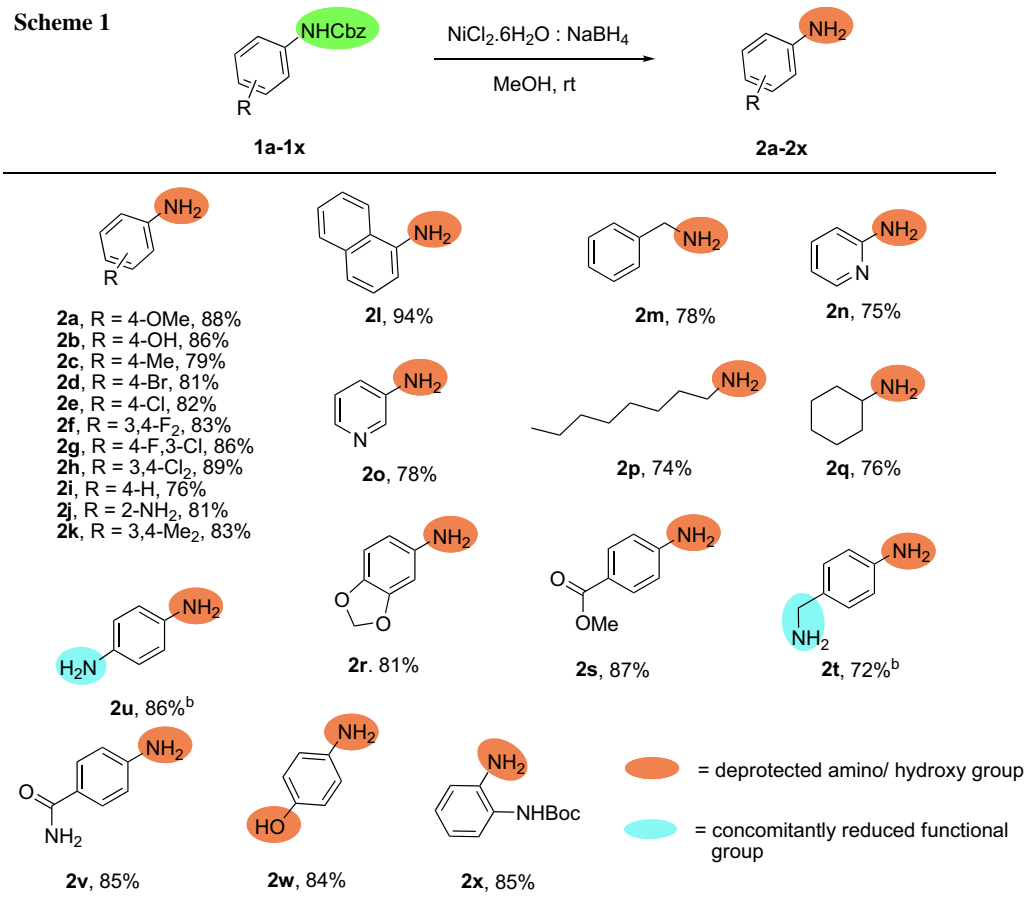
Entry	Molar ratio **1a**:$NiCl_2{\cdot}6H_2O$:$NaBH_4$	Solvent	Time/min	Isolated yield of **1a**/%
1	1:5:15	Dioxane	60	–[a]
2	1:5:15	THF	60	–[a]
3	1:5:15	CH_3CN	60	–[a]
4	1:5:15	EtOH	60	–[a]
5	1:5:15	DCM	60	–[b]
6	1:5:15	MeOH	15	88[c]
7	1:4:12	MeOH	60	56[c]
8	1:5:0	MeOH	60	–[b]
9	1:0:15	MeOH	60	–[b]
10	1:5:5	MeOH	60	18[c]

[a]Reaction incomplete and a mixture of products was obtained

[b]No reaction

[c]Yield of corresponding aniline

Scheme 1



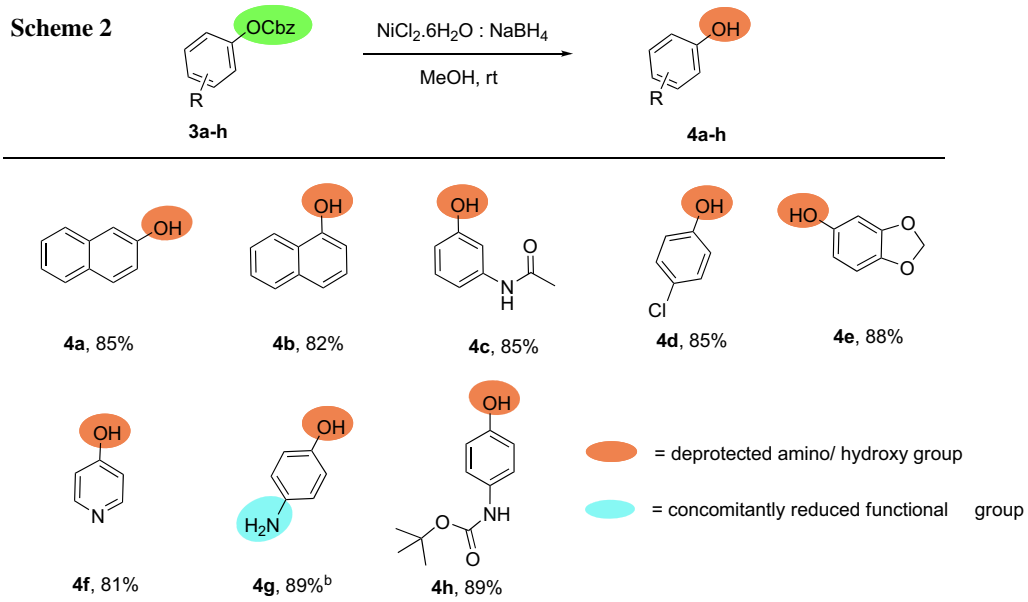
inferred that nickel boride chemoselectively deprotected only the −NCbz group in presence of *N-tert*-butyloxycarbonyl functional group (**2x**). However, nitro and cyano underwent concomitant reduction (**2t**, **2u**), and therefore, required higher molar ratios. Furthermore, the reaction proceeded very efficiently with aliphatic amines also (**2p**, **2q**) under similar condition and gave the desired amine in good yield. 4-Aminophenol having both N and O protected with −Cbz group underwent simultaneous deprotection of both −Cbz groups to give 4-aminophenol (**2w**). In case of benzylamine-Cbz, the isolated product was identified as benzylamine (**2m**) (Scheme 2).

Further, we investigated whether deprotection of phenols protected with Cbz could also be achieved under these conditions. Therefore, a reaction of benzyl oxycarbonylated 2-naphthol was attempted with nickel boride in 1:5:15 molar ratio (reactant:$NiCl_2$:$NaBH_4$) under identical conditions. The reaction was complete in 15 min and gave 85% of 2-naphthol (**4a**) after workup.

Subsequently, reactions of other phenols protected with −Cbz were also attempted under identical condition. All the −Cbz protected phenols underwent complete deprotection in 15 min to give the corresponding phenols in high yields. It can be inferred from the above results also that the chlorine (**4d**), acetamide (**4c**), and methylene dioxy group (**4e**) remained unaffected under these conditions. The −OCbz functional group underwent chemoselective deprotection in presence of *N-tert*-butyloxycarbonyl functional group (**4h**). The deprotection seemed to proceed via hydrogenolysis of benzyl C–O bond rather than a hydrolysis mechanism.

Conclusion

In conclusion, we have reported nickel boride as an efficient reagent for the reductive deprotection of amine-Cbz and *O*-Cbz to give the corresponding amines and phenols. The conditions are mild, neutral, and tolerate a wide range of functionalities, including methoxy, methylenedioxy, ester, amide, and halo group. The deprotection is believed to occur via hydrogenolysis.



Experimental

All the chemicals were commercial and purchased from Sigma-Aldrich or Merck and used as received. All the −NCbz and −OCbz compounds were prepared. Thin layer chromatography (GF254) was used to monitor reaction progress. Melting points were measured on Buchi M-560 melting point apparatus. IR (neat) and IR (DCM) spectra were recorded on a Shimadzu and Bruker FTIR spectrophotometer, respectively, and the values are expressed as cm^{-1}. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Jeol JNM ECX-400P at 400 and 100 MHz, respectively, using TMS as internal standard. The chemical shift values are recorded on δ scale and the coupling constants (J) are in Hz.

General procedure

In a typical experiment, benzyl 4-methoxyphenyl carbamate (**1a**, 1 mmol) and 10 cm^3 methanol were placed in a 100 cm^3 round-bottomed flask fitted with a water condenser and placed over a magnetic stirrer. Nickel(II) chloride hexahydrate (5 mmol) was added to the flask, followed by slow addition of sodium borohydride (15 mmol) with vigorous stirring. A vigorous reaction took place and the reaction mixture turned black due to in situ formation of nickel boride. The progress of the reaction was monitored by TLC (petroleum ether:ethyl acetate 80:20, v/v). After completion, the reaction mixture was filtered through a Celite pad ($\sim$ 2.5 cm) and washed with methanol (3 $\times$ 10 cm^3). The solution was concentrated on a rotavapor and diluted with water ($\sim$ 50 cm^3), followed by extraction with dichloromethane (3 $\times$ 10 cm^3). The combined dichloromethane extract was washed with water and dried over anhyd. K_2CO_3. The solvent was removed on a rotary evaporator and the product was dried. 4-Anisidine (**2a**) was obtained as colourless solid in 88% yield.

The products were identified by m.p., IR, and NMR spectra. The products Scheme 1, entry 24 and Scheme 2, entry 8 were purified by flash column chromatography on silica gel using petroleum ether:ethyl acetate (95:5, v/v) as eluent.

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