

Rapid Chemoselective Deprotection of Benzyl Esters by Nickel Boride

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Abstract: Benzyl esters of a variety of acids can be chemoselectively cleaved on treatment with nickel boride in methanol at ambient temperature to give the parent carboxylic acids in high yields. Other protecting functionalities such as methyl, ethyl, *tert*-butyl, and trityl esters as well as benzyl ethers, *tert*-butyl ethers, and *N*-benzylamides are unaffected under these conditions.

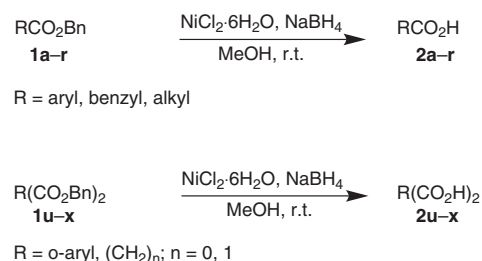
Key words: benzyl esters, chemoselectivity, carboxylic acids, cleavage, nickel boride

Protection and deprotection are unavoidable sequences in the synthesis of complex synthetic targets. Benzyl esters are frequently used as carboxylic acid protecting groups¹ because of their ready accessibility by various classical methods. The common deprotection protocols for benzyl esters include catalytic hydrogenolysis,² catalytic transfer hydrogenation,³ application of strong Lewis acids⁴ like aluminum trichloride or boron trichloride, bis(tributyltin) oxide,⁵ aluminum trichloride/*N,N*-dimethylaniline,⁶ rhenium carbonyl complexes/iron(III) chloride,⁷ BS2 esterase/CAL-A lipase enzymes⁸ etc. The limitations of some of the reported methods are the use of expensive reagents, long reaction times, high temperatures, and other side reactions. In recent years, we have developed new synthetic strategies using nickel boride as the reagent.⁹ Therefore, we decided to investigate the versatility of nickel boride for O–C bond cleavage in different esters and ethers.

We report herein a novel, mild, and chemoselective approach to the cleavage of benzyl esters with nickel boride in methanol at ambient temperature to give the corresponding parent carboxylic acids in high yields. Nickel boride was generated in situ from nickel(II) chloride hexahydrate and sodium borohydride. Methyl, ethyl, *tert*-butyl, and trityl esters are unaffected under these conditions. Benzyl ethers and *N*-benzylamides are also unaffected, thus enhancing its chemoselectivity. The deprotection of benzyl 3-chlorobenzoate (**1a**) to give 3-chlorobenzoic acid (**2a**) was chosen as the standard reaction. The optimal reaction conditions were identified by performing reactions of benzyl 3-chlorobenzoate (**1a**) in different solvents (THF, CH₂Cl₂, EtOH, DMF, MeCN, and MeOH) and by varying molar ratios of nickel(II) chloride hexahydrate and sodium borohydride. Methanol is the solvent of choice to bring the unmasking reactions

to completion as reactions in other solvents were predominantly incomplete and in some cases resulted in a mixture of products. Cleavage of **1a** with nickel boride in 1:3:9 ratio (**1a**/NiCl₂·6 H₂O/NaBH₄) in methanol was rapid (5 min), as monitored by TLC, and 3-chlorobenzoic acid (**2a**) was obtained in 89% yield. The reaction was incomplete even after two hours when a lower molar ratio of nickel boride (1:2:6) was used. Cleavage was undoubtedly proceeding due to the involvement of nickel boride generated in situ as no deprotection was observed in the reactions of **1a** with nickel(II) chloride hexahydrate and sodium borohydride alone.

Subsequently, a variety of differently substituted aromatic as well as aliphatic benzyl esters **1b–r** were subjected to identical deprotection conditions. The reactions were complete in 5–60 minutes at ambient temperature. The reactions were clean and high yields of the corresponding acids **2b–r** were obtained (Scheme 1). Benzyl 4-nitrobenzoate (**1s**) and benzyl 4-hydroxybenzoate (**1t**) resulted in a mixture of products under these conditions (Table 1, entries 19 and 20). The deprotection of dibenzyl esters **1u–x** was also equally efficient and rapid, but required higher molar ratios of the reagent (Scheme 1, Table 1, entries 21–24). These results are summarized in Table 1.



Scheme 1

Reactions of methyl, ethyl, *tert*-butyl, and trityl esters of substituted benzoic acids were also attempted with nickel boride, even in high molar ratios, but none of these showed any reaction and the starting esters were recovered. Similarly, *N*-benzylbenzamide, benzyl 2-naphthyl ether, and benzyl 4-tolyl ether were also stubbornly resistant to the action of nickel boride under different conditions.

The drastic difference between the reactivity of benzyl esters and the above mentioned protecting groups towards nickel boride prompted us to investigate the selective de-blocking of benzyl esters. A reaction of equimolar mixture of benzyl benzoate (**1g**) and methyl benzoate (1:1)

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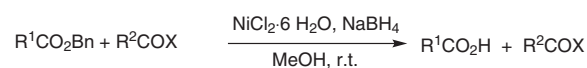
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with molar 3:9 equivalents of nickel(II) chloride hexahydrate and sodium borohydride in methanol at ambient temperature yielded benzoic acid (**2a**, 87%) besides the quantitative recovery of unreacted methyl benzoate. Also, the reaction of an equimolar mixture of benzyl 3-chlorobenzoate (**1a**) and *N*-benzylbenzamide (1:1) with nickel boride under these conditions showed complete disappearance of benzyl 3-chlorobenzoate in ten minutes, but *N*-benzylbenzamide was found inert to nickel boride mediated cleavage. 3-Chlorobenzoic acid (**2a**) (89%) and

N-benzylbenzamide (86%) were obtained after separation (Scheme 2).



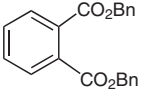
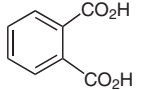
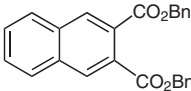
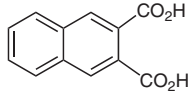
1g, 2g R¹ = R² = Ph, X = OMe
1a, 2a R¹ = 3-ClC₆H₄, R² = Ph, X = NHBn

Scheme 2

Table 1 Deprotection of Benzyl Esters with Nickel Boride in Methanol at Ambient Temperature

Entry	Substrate	Ratio ^a	Time (min)	Product	Yield (%)
1	3-ClC ₆ H ₄ CO ₂ Bn 1a	1:3:9	5	3-ClC ₆ H ₄ CO ₂ H 2a	89
2	3-BrC ₆ H ₄ CO ₂ Bn 1b	1:3:9	10	3-BrC ₆ H ₄ CO ₂ H 2b	90
3	2-ClC ₆ H ₄ CO ₂ Bn 1c	1:3:9	5	2-ClC ₆ H ₄ CO ₂ H 2c	83
4	4-ClC ₆ H ₄ CO ₂ Bn 1d	1:3:9	5	4-ClC ₆ H ₄ CO ₂ H 2d	87
5	4-MeC ₆ H ₄ CO ₂ Bn 1e	1:3:9	10	4-MeC ₆ H ₄ CO ₂ H 2e	92
6	4-BrC ₆ H ₄ CO ₂ Bn 1f	1:3:9	15	4-BrC ₆ H ₄ CO ₂ H 2f	87
7	PhCO ₂ Bn 1g	1:3:9	20	PhCO ₂ H 2g	87
8	4-MeOC ₆ H ₄ CO ₂ Bn 1h	1:3:9	20	4-MeOC ₆ H ₄ CO ₂ H 2h	88
9	PhCH ₂ CO ₂ Bn 1i	1:3:9	10	PhCH ₂ CO ₂ H 2i	83
10	Ph ₂ CHCO ₂ Bn 1j	1:3:9	15	Ph ₂ CHCO ₂ H 2j	86
11	2,4,6-Me ₃ C ₆ H ₂ CO ₂ Bn 1k	1:3:9	15	2,4,6-Me ₃ C ₆ H ₂ CO ₂ H 2k	85
12	2-furylCO ₂ Bn 1l	1:3:9	10	2-furylCO ₂ H 2l	86
13	1-naphthylCO ₂ Bn 1m	1:6:18	10	1-naphthylCO ₂ H 2m	84
14	2-HO ₂ CC ₆ H ₄ CO ₂ Bn 1n	1:3:9	30	2-HO ₂ CC ₆ H ₄ CO ₂ H 2n	85
15	2-MeO ₂ CC ₆ H ₄ CO ₂ Bn 1o	1:3:9	10	2-MeO ₂ CC ₆ H ₄ CO ₂ H 2o	83
16	4-BnOC ₆ H ₄ CO ₂ Bn 1p	1:3:9	60	4-BnOC ₆ H ₄ CO ₂ H 2p	84
17	Me ₂ CHCH ₂ CO ₂ Bn 1q	1:3:9	15	Me ₂ CHCH ₂ CO ₂ H 2q	93 ^b
18	Me ₂ CHCO ₂ Bn 1r	1:3:9	20	Me ₂ CHCO ₂ H 2r	95 ^b

Table 1 Deprotection of Benzyl Esters with Nickel Boride in Methanol at Ambient Temperature

Entry	Substrate	Ratio ^a	Time (min)	Product	Yield (%)
19	4-O ₂ NC ₆ H ₄ CO ₂ Bn 1s	1:3:9	20	4-O ₂ NC ₆ H ₄ CO ₂ H 2s	— ^c
20	4-HOC ₆ H ₄ CO ₂ Bn 1t	1:3:9	30	4-HOC ₆ H ₄ CO ₂ H 2t	— ^d
21	 1u	1:5:15	10	 2u	84
22	 1v	1:7:21	10	 2v	87
23	(CO ₂ Bn) ₂ 1w	1:5:15	10	(CO ₂ H) ₂ 2w	90 ^b
24	CH ₂ (CO ₂ Bn) ₂ 1x	1:5:15	15	CH ₂ (CO ₂ H) ₂ 2x	85 ^b

^a **1a**/NiCl₂·6H₂O/NaBH₄.

^b The acids were obtained as their corresponding *S*-benzyl derivatives.

^c Reaction complete, but a mixture of products observed on TLC.

^d Reaction incomplete and a mixture of products observed on TLC.

A testament to the chemoselectivity of our deprotection protocol is also reflected in the selective cleavage of benzyl ester group in preference to other protecting groups present in the same molecular skeleton. Thus benzyl methyl phthalate (**1o**), when treated with nickel boride in 1:3:9 molar ratio in methanol, resulted in the formation of monomethyl phthalate (**2o**) in high yield (83%) (entry 15). Likewise, 4-(benzyloxy)benzoic acid (**2p**) was isolated in 84% yield after selective cleavage of the benzyl ester group with nickel boride in benzyl 4-(benzyloxy)benzoate (**1p**) (entry 16).

We conclude that deprotection of benzyl esters by nickel boride offers an inexpensive and rapid alternative to existing methodologies in view of its chemoselectivity, high yields, short reaction times and easy workup procedure. Methyl esters, *tert*-butyl esters, trityl esters, benzyl ethers, and *N*-benzylamides are completely tolerated.

All the melting points were recorded on Tropical Labequip apparatus and are uncorrected. IR spectra were recorded on Perkin Elmer FT-IR spectrum-2000. NMR spectra were recorded on a FT-NMR model R-600 Hitachi (60 MHz) with TMS as internal standard. All products are known and were identified by co-TLC, mp, IR, and NMR spectra.

3-Chlorobenzoic Acid (**2a**); Typical Procedure

A 50 mL round-bottomed flask was fitted with a reflux condenser and mounted over a magnetic stirrer. Benzyl 3-chlorobenzoate (**1a**, 0.15 g, 0.61 mmol) dissolved in MeOH (7 mL) was placed in the flask and NiCl₂·6H₂O (0.23 g, 1.825 mmol) was added to the mixture. NaBH₄ (0.21 g, 5.475 mmol) was added cautiously to the flask with continuous stirring. Onset of the reaction was manifested by the formation of a black precipitate typical of nickel boride. The mixture was stirred at r.t. and the progress of the reaction was mon-

itored by TLC (petroleum ether–EtOAc, 95:5), which showed complete disappearance of the starting material after 5 min. The reaction was quenched by addition of MeOH (10 mL), filtered through a Celite pad (~2.5 cm), and washed with MeOH (20 mL). H₂O (~5 mL) was added to the combined filtrates, which were then extracted with EtOAc (3 × 10 mL). The combined extracts were dried (anhyd MgSO₄), decanted through a cotton pad, and concentrated on a rotary evaporator. The colorless solid product obtained was characterized as 3-chlorobenzoic acid (**2a**, 0.095 g, 89%) by mp and superimposable IR and ¹H NMR spectra.

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