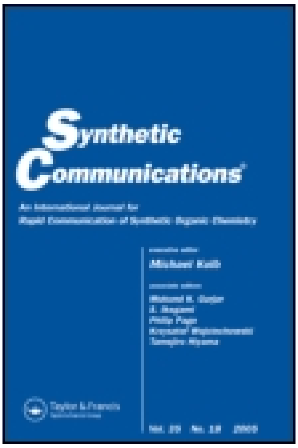


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

$CeCl_3$-Catalyzed Reduction of Methyl Esters of Carboxylic Acids to Corresponding Alcohols with Sodium Borohydride

Yinan Xu [a] & Yunyang Wei [a]

[a] School of Chemical Engineering, Nanjing University of Science and Technology, Nanjing, China

Version of record first published: 15 Oct 2010.

To cite this article: Yinan Xu & Yunyang Wei (2010): $CeCl_3$-Catalyzed Reduction of Methyl Esters of Carboxylic Acids to Corresponding Alcohols with Sodium Borohydride, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 40:22, 3423-3429

To link to this article: http://dx.doi.org/10.1080/00397910903457233

Synthetic Communications®, 40: 3423–3429, 2010

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910903457233

$CeCl_3$-CATALYZED REDUCTION OF METHYL ESTERS OF CARBOXYLIC ACIDS TO CORRESPONDING ALCOHOLS WITH SODIUM BOROHYDRIDE

Yinan Xu and Yunyang Wei
School of Chemical Engineering, Nanjing University of Science and Technology, Nanjing, China

A wide range of methyl esters, including esters of aromatic carboxylic acids, alkenyl carboxylic acids, aliphatic carboxylic acids, and protected amino acids, were reduced to the corresponding alcohols with $NaBH_4$ in ethanol in the presence of a catalytic amount of $CeCl_3$. The reaction was completed within 24 h at ambient temperature and showed high functional group compatibility and chemoselectivity. With esters containing nitro, methoxyl, halogen, alkenyl, and protected amino functionalities, only the ester group was reduced. The alcohols were isolated after evaporation of the solvent and routine aqueous workup in good yields (75–95%).

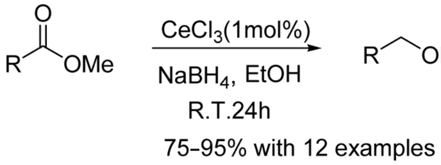
Keywords: Catalytic reduction; $CeCl_3$; $NaBH_4$

INTRODUCTION

Reduction is a fundamental transformation in synthetic and industrial organic chemistry. Sodium borohydride has received considerable attention as a selective, mild, yet effective reducing reagent since its discovery by Schlesinger and coworkers,[1] especially in the reduction of aldehydes and ketones to corresponding alcohols. The reduction of carboxylic acids or esters using sodium borohydride is relatively difficult because of the low reactivity of sodium borohydride. The $NaBH_4$–MeOH system was reported to reduce methyl esters of aromatic carboxylic acids to corresponding alcohols.[2] The reaction needs 6 equivalents of $NaBH_4$ for the reduction of 1 equivalent of the methyl ester. The reactivity of sodium borohydride can be enhanced by carrying out the reaction in the presence of certain additives, such as iodine,[3] lithium,[4] aluminum,[5] calcium,[6] cobalt,[7] copper,[8] nickel,[9] and magnesium chloride.[10] Addition of iodine to $NaBH_4$ in tetrahydrofuran (THF) provides H_3B–THF, which is useful for hydroborations, reduction of esters, and various others functional groups.[11] The $ZnCl_2$–$NaBH_4$ reagent system also exhibits powerful reducing properties toward esters.[12]

Received April 21, 2009.

Address correspondence to Yunyang Wei, School of Chemical Engineering, Nanjing University of Science and Technology, Nanjing 210094, China. E-mail: ywei@mail.njust.edu.cn



Scheme 1. Reduction of methyl esters catalyzed by $CeCl_3$ with $NaBH_4$.

However, these methods suffer from limitations such as lack of generality, incompatibility with other functionalities in the substrates, and high equivalents of sodium borohydride and additives.

To achieve functional group compatibility and efficient reduction, an alternative approach is to transform the carboxylic acid into an activated derivative such as hydroxybenzotriazoly (HOBt) esters,[13] phenyl esters,[14,15] cyclic acyloxyboron intermediate,[16] and cyanurates[17] followed by reduction with $NaBH_4$. Although these procedures give satisfactory results, use of expensive and hazardous reagents limits their applications.

In this article, we report a simple procedure for the chemoselective reduction of methyl esters of carboxylic acids to corresponding alcohols in good yields with 2 equivalents of $NaBH_4$ in the presence of a catalytic amount of $CeCl_3 \cdot 7H_2O$ (1 mol%) in ethanol within 24 h at ambient temperature (Scheme 1).

EXPERIMENTAL

All chemicals were obtained from commercial sources with more than 99% purity and used without prior purification. Purity of products was analyzed by high-performance liquid chromatography (HPLC). Products are all known compounds and were identified by comparing of their physical and spectral data with those reported in the literature.

General Experimental Procedure for Reduction of Esters

$NaBH_4$ (40 mg, 2 mmol) was added to a stirred solution of methyl 4-nitrobenzoate (181 mg, 1 mmol) and $CeCl_3 \cdot 7H_2O$ (4 mg, 0.01 mmol) in 5 mL of EtOH at room temperature. The resulting suspension was stirred for 24 h. The solvent was evaporated, and the residue was treated with 1 N HCl (20 mL). The aqueous solution was extracted with ethyl acetate (3 × 20 mL). The organic layer was separated and subsequently washed with saturated $NaHCO_3$ and brine. After drying over anhydrous Na_2SO_4, ethyl acetate was evaporated to give 4-nitrobenzyl alcohol (137 mg, 90%).

RESULTS AND DISCUSSION

Effects of Different Metal Salts

In our recent work on metal-catalyzed reduction of methyl esters with $NaBH_4$, we use methyl 4-nitrobenzoate as a probe substrate and various metal salts as

Table 1. Reduction of methyl 4-nitrobenzoate with $NaBH_4$ in the presence of metallic salts[a]

Salt	Solvent	Time (h)	Yield[b] (%)
—	EtOH	24	63
LiCl	Ether	24	54
$CaCl_2$	THF	24	12
$ZnCl_2$	THF	24	—
$AlCl_3$	THF	24	25
$BiCl_3$	EtOH	15	—
$NiCl_2 \cdot 6H_2O$	EtOH	15	—
$CoCl_2 \cdot 6H_2O$	EtOH	24	41
$CuSO_4 \cdot 5H_2O$	EtOH	15	50
$CeCl_3 \cdot 7H_2O$	EtOH	24	90

[a] Reaction conditions: methyl p-nitrobenzoate (1 mmol), $NaBH_4$ (2 mmol), metallic salts (1 mol%), solvent (5 mL), at room temperature (20–30 °C).

[b] Based on HPLC analysis with cinnamyl alcohol as an internal standard.

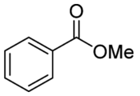
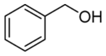
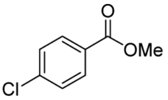
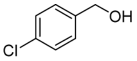
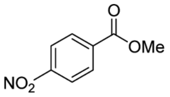
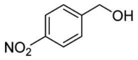
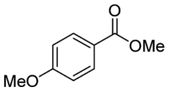
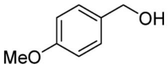
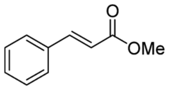
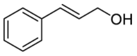
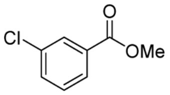
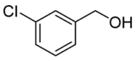
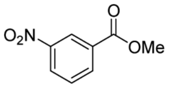
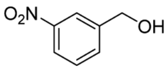
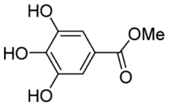
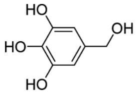
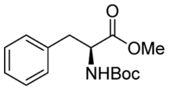
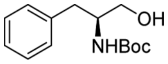
coreducing agents to form reducing systems with $NaBH_4$. It was found that among the metal salts we used, $CeCl_3$ catalyzed the reduction of the probe substrate to the corresponding alcohol effectively. Reduction of methyl 4-nitrobenzoate with 2 equivalents of $NaBH_4$ in the presence of 1 mol% of $CeCl_3 \cdot 7H_2O$ in ethanol within 24 h at ambient temperature gave (4-nitrophenyl)-methanol in 90% yield (Table 1).

Reduction of Esters Catalyzed by $CeCl_3$

We then studied the scope of the reaction and found that a wide range of substrates, including esters of aromatic carboxylic acids, alkenyl carboxylic acids, aliphatic carboxylic acids, and protected amino acids, can be reduced to the corresponding alcohols in good yield with a $NaBH_4$–$CeCl_3$ system (Table 2). The reactions proceeded smoothly at room temperature. Evaporation of the solvent and routine aqueous workup gave the alcohol without further purification.

As shown in Table 2, methyl esters bearing functionalities such as halogen, nitro, methoxyl, and hydroxyl groups (Table 2, entries b, c, d, and h), underwent clean reduction of the ester functionality. In the case of methyl cinnamate (Table 2, entry e), the product was the expected allylic alcohol and no 3-phenylpropanol was detected. An N-protected methyl ester of amino acid (Table 2, entry i) was also successfully transformed into the corresponding N-protected amino alcohol. Electron-deficient methyl benzoate was more reactive than electron-rich esters. Methyl benzoates substituted by Cl and NO_2 groups in *meta* and *para* positions were totally converted. Electron-donating methoxyl group inhibit the reduction when in *para* position (Table 2, entry d), while hydroxyl groups in *meta* and *para* positions gave a considerably good yield without detection of ester (Table 2, entry h). It was evident that both the substitution pattern and positon of the aromatic ring affected the reaction.

Table 2. $CeCl_3$-catalyzed chemoselective reduction of methyl esters with $NaBH_4$[a]

Entry	Ester **1a–j**	Product **2a–j**	Yield[b] (%)
a			90
b			86
c			90
d			75
e			95
f			88
g			91
h			92
i			85
j	$CH_3(CH_2)_{16}COOMe$	$CH_3(CH_2)_{17}OH$	85
k	$CH_3(CH_2)_{10}COOMe$	$CH_3(CH_2)_{11}OH$	91
l	$MeOOC(CH_2)_8COOMe$	$HO(CH_2)_{10}OH$	93

[a] Reaction conditions: ester (1 mmol), $NaBH_4$ (2 mmol), $CeCl_3 \cdot 7H_2O$ (1 mol%), EtOH (5 mL), 20–30 °C, 24 h.

[b] Isolated yields.

To probe the applicability of the same reaction conditions to other alkyl esters, we tried the reduction of ethyl benzoate and ethyl 1*H*-imidazole-5-carboxylate: the latter is a key intermediate in the synthesis of cimetidine. It was found that reduction of ethyl benzoate under the same conditions for 48 h gave 30% yield of phenyl methanol with 36% conversion of ethyl benzoate. Reduction of 1*H*-imidazole-5-carboxylate under the same conditions for 24 h led to quantitative recovery of the starting material. These results suggest that the present procedure is best applied to the reduction of methyl esters.

Mechanistic Aspects

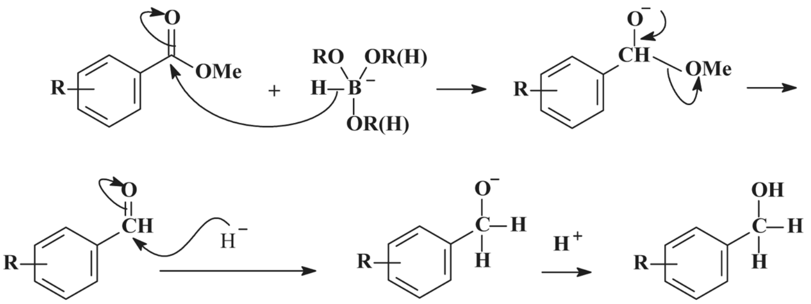
$NaBH_4$–$CeCl_3$ has been used in the selective reduction of α,β-unsaturated ketones to the corresponding allylic alcohols.[18] The authors attributed the 1,2-selectivity in the reduction of α, β-unsaturated ketones to the in situ formation of alkoxyborohydrides because of the lanthanoid-catalyzed decomposition of BH_4^- in hydroxylic solvents. $CeCl_3$-catalyzed reduction of esters with $NaBH_4$ in ethanol has seldom or never been reported, according to our knowledge.

The reducing reactivity of $NaBH_4$ can be increased by either the catalysts or protic solvents. Brown and coworkers concluded that $LiBH_4$ in ethyl ether is the preferred system for the reduction of esters.[19] Alcoholic solvents are less useful for this application because of the competitive solvolysis. $NaBH_4$ appears always to be the least reactive. In the presence of metal salts, the reducing agent could be the metal borohydride formed in situ. The reduction of esters in alcoholic solvent involves loss of hydride, forming sodium alkoxyborohydrides, which are capable of reducing esters.

In our procedure, 2 molar equivalents of $NaBH_4$ were required for complete reduction of the esters. An obvious hydrogen evolution occurred upon mixing $NaBH_4$ with the ethanol solution of $CeCl_3 \cdot 7H_2O$. Obviously, Ce^{3+} can catalyze the decomposition of BH_4^- in hydroxylic solvent to afford alkoxyborohydrides. Therefore, it is highly probable that the actual reducing species is not BH_4^- but the in situ–derived alkoxyborohydrides (Scheme 2). As shown in Table 1, without the presence of any catalyst, yield of the reduction product decreased from 90% to 63%. The nature of the metallic ion was found to be an important factor for the chemoselectivity. When Ce^{3+} was replaced by Cu^{2+}, Bi^{3+}, or Ni^{2+}, reduction of

$$Cl_3Ce\text{--}^{-}BH_{4-n}(OR)_n + ROH \longrightarrow {}^{-}BH_{4-p}(OR)_p + H_2 + CeCl_3$$

$n=0,\ 1,\ 2;\ p=n+1$



Scheme 2. Possible mechanism for reduction of esters catalyzed by $CeCl_3$.

methyl 4-nitrobenzoate gave (4-nitrophenyl)methanol in a rather poor yield because of the competitive reduction of the nitro group.

CONCLUSION

In conclusion, we have developed an efficient, chemoselective, and general protocol for the reduction of esters of aromatic carboxylic acids, alkenyl carboxylic acids, aliphatic carboxylic acids, and protected amino acids to the corresponding alcohols with good potential for industrial process.

REFERENCES

1. Schlesinger, H. I.; Brown, H. C.; Hoekstra, H. R.; Rapp, L. R. Reaction of diborane with alkali metal hydrides and their addtional compounds: New Synthesis of borohydrides: Sodium and potassium borohydrides. *J. Am. Chem. Soc.* **1953**, *75*, 199–204.
2. Boechat, N.; Costa, J. C. S.; Mendonc, J. S.; Oliveira, P. S. M.; Souza, V. N. A simple reduction of methyl aromatic esters to alcohols using sodium borohydride–methanol system. *Tetrahedron Lett.* **2004**, *45*, 6021–6022.
3. Prasad, A. S. B.; Kanth, J. V. B.; Periasamy, M. Convenient methods for the reduction of amides, nitriles, carboxylic esters, acids, and hydroboration of alkenes using $NaBH_4/I_2$ system. *Tetrahedron* **1992**, *48*, 4623–4628.
4. Zhu, H. J.; Charles, U. P. J. Reductions of carboylic acids and esters with $NaBH_4$ in diglyme at 162 °C. *Synth. Commun.* **2003**, *33*, 1733–1750.
5. Brown, H. C.; Subba, R. B. C. A new powerful reducing agent, sodium borohydride, in the presence of aluminum chloride and other polyvalent metal halides. *J. Am. Chem. Soc.* **1956**, *78*, 2582–2588.
6. Banerji, J.; Das, B. Synthesis of (±)-gaddain, a new lignan from *Jatropha gossypifolia* linn (Euphorbiaceae). *Heterocycles* **1985**, *23*, 661–665.
7. Chung, S. K. Selective reduction of mono- and disubtituted olefins by sodium borohydride and cobalt(II). *J. Org. Chem.* **1979**, *44*, 1014–1016.
8. Sung-eun, Y.; Sang-hee, L. Reduction of organic compounds with sodium borohydride-copper(II) sulfate system. *Synlett* **1990**, 419–420.
9. Lin, S. T.; Roth, J. A. Nikel(0)-catalyzed sodium borohydride hydrogenolysis of aromatic boromides. *J. Org. Chem.* **1979**, *44*, 309–310.
10. Brown, H. C.; Mead, E. J.; Subba, R. B. C. A study of solvents for sodium borohydride and the effect of solvent and the metal ion on borohydride reductions. *J. Am. Chem. Soc.* **1955**, *77*, 6209–6213.
11. Periasamy, M.; Thirumalaikumar, M. Methods of enhancement of reactivity and selectivity of sodium borohydride for applications in organic synthesis. *J. Organometal. Chem.* **2000**, *609*, 137–151.
12. Yamakawa, T.; Masaki, M.; Nohira, H. A new reduction of some carboxylic esters with sodium borohydride and zinc chloride in the presence of a tertiary amine. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2730–2734.
13. McGory, R. P. Facile and chemoselective reduction of carboxylic acids to alcohols using BOP reagent and sodium borohydride. *Tetrahedron Lett.* **1998**, *39*, 3319–3322.
14. Eleni, P.; Petros, C.; Despina, T.; Panagiota, M.-M. Reduction of pentafluorophenyl esters to the corresponding primary alcohols using sodium borohydride. *Tetrahedron Lett.* **2007**, *48*, 8323–8325.

15. Jagdale, A. R.; Sudalai, A. Co-catalyzed mild and chemoselective reduction of phenyl esters with $NaBH_4$: A practical synthesis of (R)-tolterodine. *Tetrahedron Lett.* **2008**, *49*, 3790–3793.
16. Tale, R. T.; Patil, K. M.; Dapurkar, S. E. An extremely simple, convenient, and mild one-pot reduction of carboxylic acids to alcohols using 3,4,5-trifluorophenylboronic acid and sodium borohydride. *Tetrahedron Lett.* **2003**, *44*, 3427–3428.
17. Falorni, M.; Porcheddu, A.; Teddei, M. Mild reduction of carboxylic acids to alcohols using cyanuric chloride and sodium borohydide. *Tetrahedron Lett.* **1999**, *40*, 4395–4396.
18. Gemal, A. L.; Luche, J.-L. The reduction of α-enones by sodium borohydride in the presence of lanthanoid chlorides: Synthetic and mechanistic aspects. *J. Am. Chem. Soc.* **1981**, *103*, 5454–5459.
19. Brown, H. C.; Narasimhan, S.; Choi, Y. M. Effect of cation and solvent on the reactivity of saline borohydride for reductions of carboxylic esters: Improved procedures for the conversion of esters to alcohols by metal borohydride. *J. Org. Chem.* **1982**, *47*, 4702–4708.