APPLIED ORGANOMETALLIC CHEMISTRY
Appl. Organometal. Chem. 2006; **20**: 798–810
Published online 17 August 2006 in Wiley InterScience
(www.interscience.wiley.com) DOI:10.1002/aoc.1137

Recent methodologies mediated by sodium borohydride in the reduction of different classes of compounds

Marcus Vinícius Nora de Souza* and Thatyana Rocha Alves Vasconcelos

FioCruz-Fundação Oswaldo Cruz, Instituto de Tecnologia em Fármacos-Far Manguinhos. Rua Sizenando Nabuco, 100, Manguinhos, 21041-250 Rio de Janeiro, RJ, Brazil

Received 22 March 2006; Revised 6 April 2006; Accepted 17 June 2006

Reduction is a fundamental transformation in organic synthesis. Since its discovery by Brown and co-workers, sodium borohydride is the most frequently hydride used in reduction processes. Owing to the importance of this reagent in modern organic synthesis, the aim of this review is to highlight recent methodologies (2000–2006) mediated by sodium borohydride in the reduction of different classes of compounds. Copyright © 2006 John Wiley & Sons, Ltd.

KEYWORDS: sodium borohydride; reduction; functional groups

INTRODUCTION

During World War II, Brown and co-workers discovered a method for producing sodium borohydride ($NaBH_4$), which allowed the production of boranes and hydrogen.[1,2] This reagent brought a new era for the reduction of functional groups in organic synthesis with several advantages: it is the least expensive metal hydride commercially available, and is safe with regards to use, storage and handling. Additionally, it can be used in different solvents, allows an easy work-up and it is useful for reducing different functional groups with chemo-, regio- and diastereoselectivities[3–10] (Table 1).

Owing to the importance of this reagent in modern organic synthesis, the aim of this review is to highlight recent methodologies (2000–2006) mediated by sodium borohydride in the reduction of different classes of compounds.

REDUCTION OF ALDEHYDES AND KETONES

Chadha and Kumar have developed a simple and efficient one-pot reaction for reduction and transesterification of β-keto esters, **1**, under mild conditions to produce the corresponding β-hydroxy esters, **2** (Scheme 1).[32] This procedure allows the preparation of β-hydroxy esters from β-keto esters after reduction and transesterification in 12–18 h with 25–72% yield by using sodium borohydride and different alcohols at 0 °C to room temperature. The kinetic study made by the authors demonstrated that reduction precedes transesterification (Scheme 2). The explanation given was that, when sodium borohydride is dissolved in an alcohol, it forms a complex, $Na^+[BH_m(OR'')4\text{-}m$ with hydride and alkoxy moieties. As the reduction proceeds, the number of active hydrides in the borohydride complex decreases, and consequently the number of alkoxy groups increases (Scheme 2).

Benedetti and co-workers have shown that the reduction of β-diketones, **3**, and further reduction of β-hydroxyketones, **4–5**, with $NaBH_4$ in the presence of albumins induced high levels of stereoselectivity and produced the corresponding *anti*-diols, **6**, with up to 96% d.e. (Scheme 3).[33] This method was monitored by HPLC and, in the absence of albumins, the reduction of β-diketones was found not to be chemoselective. Additionally, a small or no diastereoselectivity was observed in the overall reduction to the *anti* and *syn* diols **6** and **7**.

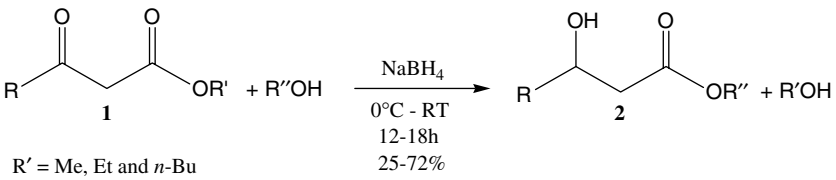
A practical diastereoselective synthesis of α-hydroxy-β-amino carboxylates has been reported by Chung and co-workers from β-amino-α-keto esters using $NaBH_4$ (Scheme 4).[34] The diastereoselectivity in the reduction of α-keto esters was examined using different reaction conditions. In this context, by using $NaBH_4$ in the presence of methanol at −20 °C, the *anti*-α-hydroxy-β-amino carboxylates, **9**, were obtained in high d.e., and were efficiently converted to the

*Correspondence to: Marcus Vinícius Nora de Souza, FioCruz-Fundacao Oswaldo Cruz, Instituto de Tecnologia em Farmacos-Far Manguinhos, Rua Sizenando Nabuco, 100, Manguinhos, 21041-250 Rio de Janeiro, RJ, Brazil.
E-mail: marcos_souza@far.fiocruz.br

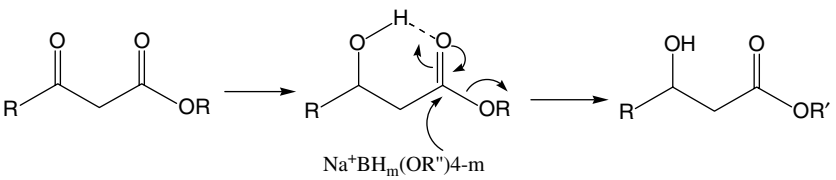
Table 1. Examples of the wide use of $NaBH_4$ as reduction reagent in different classes of compounds

Organic functions	Conditions	Reduction product
Alkenes and alkynes	$NaBH_4/BF_3$/diglyme[11]	Alcohols
	$NaBH_4/I_2$/THF[12,13]	
	$NaBH_4/Bu_3N^+Cl^-/CHCl_3$[14]	
Aldehydes and ketones	$NaBH_4/AlCl_3$/THF[15]	Alcohols
	$NaBH_4/ZrCl_4$/THF[16]	
	$NaBH_4$/Amberlyst[17]	
Carboxylic acids	$NaBH_4/ZnCl_2$/THF[18]	Alcohols
	$NaBH_4/ZrCl_4$/THF[19]	
	$NaBH_4/I_2$/THF[20]	
Esters	$NaBH_4/ZnCl_2$/THF/tertiary amine[21]	Alcohols
	$NaBH_4/I_2$/THF[22]	
Amides	$NaBH_4/CoCl_2$[23]	Amines
	$NaBH_4/I_2$/THF[24]	
Nitriles	$NaBH_4/CoCl_2$[a]	Amines
	$NaBH_4/ZrCl_4$/THF[25,26]	
Acid chlorides	$NaBH_4/ZnCl_2$/TMEDA[27]	Alcohols
Nitro compounds	$NaBH_4/CuSO_4$/EtOH[28]	Amines
	$NaBH_4/BiCl_3$/THF[29,30]	
Amino acids and derivatives	$NaBH_4/I_2$/THF[31]	Amino alcohols

[a] Thirumalaikumar M, Periasamy M. unpublished results.



Scheme 1.



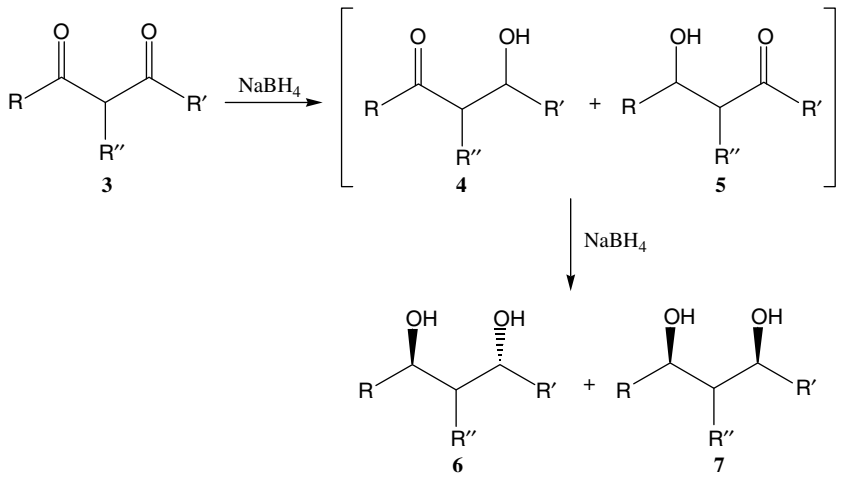
Scheme 2.

corresponding syn-β-amino-α-hydroxy carboxylates, **14**, via oxazolidine ring formation, **13** (Scheme 5).

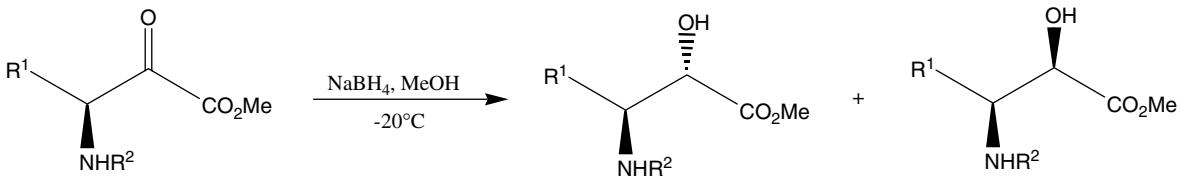
Zeynizadeh and Behyar have reported an important study on the influence of the solvent THF in the reduction of carbonyl compounds with $NaBH_4$.[35] They demonstrated that $NaBH_4$ in wet THF provides the easy reduction of different carbonyl compounds, such as aldehydes, ketones, conjugated enones, acyloins and α-diketones in good to excellent yields. In the optimization of reaction conditions, the authors found that the presence of a small amount of water in THF greatly accelerates the rates of reduction of carbonyl compounds with $NaBH_4$ (Table 2).

Another important observation in this system was that chemoselective reduction of aldehydes over ketones is successfully achieved (Table 3).[35] The chemo- and regioselectivity were demonstrated in conjugated carbonyl compounds, such as in the competitive reduction of cinnamaldehyde over benzalacetone (Scheme 6).[35]

DOI: 10.1002/aoc

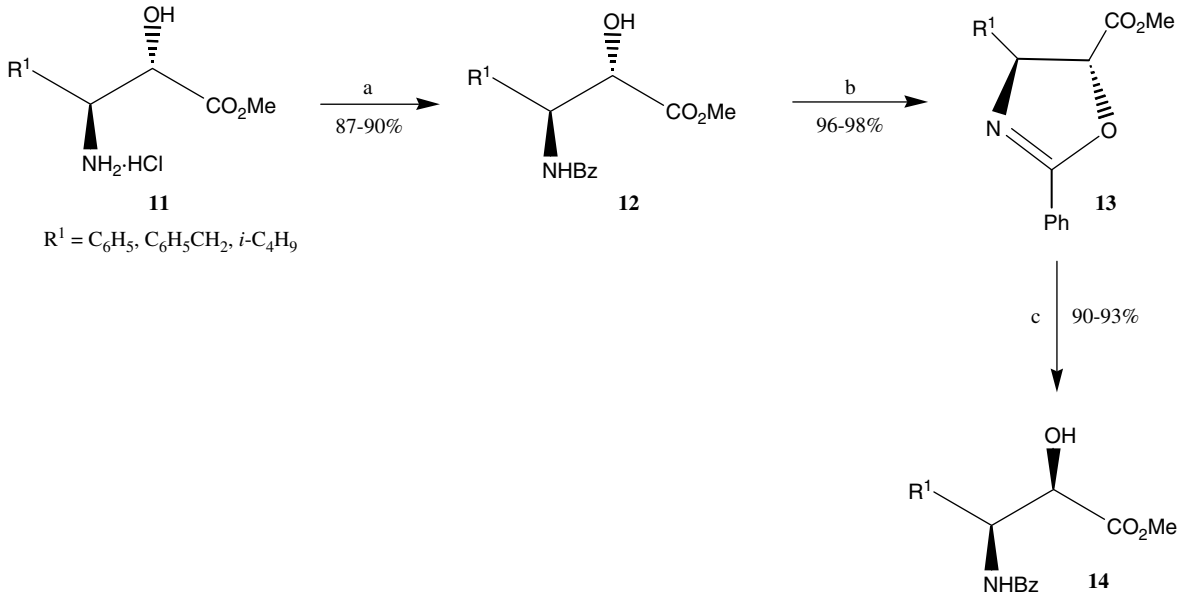


Scheme 3.



R^1	R^2	*anti:syn*	de,%	yield,%
C_6H_5	H.HCl	99:1	98	73
$C_6H_5CH_2$	H.HCl	99:1	98	77
i-C_4H_9	H.HCl	18:6:1	98	75

Scheme 4.



$R^1 = C_6H_5, C_6H_5CH_2, i\text{-}C_4H_9$

Scheme 5. (a) BzCl, $NaHCO_3$, MeOH. 0 °C; (b) $SOCl_2$, CH_2Cl_2, reflux; (c) 1N HCl, MeOH, reflux, followed by saturated $NaHCO_3$, 50 °C.

DOI: 10.1002/aoc

Table 2. Reaction condition for optimization in the reduction of benzaldehyde with benzophenone with $NaBH_4$

Condition	Reaction components (molar ratio)	Solvent (ml)	Temperature	Time (min)	Conversion (%)
1	PhCHO/$NaBH_4$ (1 : 1)	Dry THF (3 ml)	RT	80	100
2	PhCHO/$NaBH_4$ (1 : 1)	Dry CH_3CN (3 ml)	RT	90	100
3	PhCHO/$NaBH_4$ (1 : 0.5)	THF-H_2O (3 : 0.05 ml)	RT	20	100
4	PhCHO/$NaBH_4$ (1 : 0.5)	THF-H_2O (3 : 0.1 ml)	RT	5	100
5	PhCHO/$NaBH_4$ (1 : 0.5)	THF-H_2O (3 : 0.2 ml)	RT	4	100
6	PhCHO/$NaBH_4$ (1 : 0.5)	THF-H_2O (3 : 1 ml)	RT	2	100
7	PhCHO/$NaBH_4$ (1 : 0.4)	THF-H_2O (3 : 0.1 ml)	RT	15	100
8	PhCHO/$NaBH_4$ (1 : 0.25)	THF-H_2O (3 : 0.05 ml)	RT	180	90
9	PhCHO/$NaBH_4$ (1 : 0.5)	CH_3CN-H_2O (3 : 0.1 ml)	RT	10	100
10	PhCHO/$NaBH_4$ (1 : 2)	THF-H_2O (3 : 0.1 ml)	Reflux	50	100

Table 3. Chemoselective reduction of aldehydes versus ketones to their respective alcohols with $NaBH_4$ in wet THF

Condition	Compound **1**	Compound **2**	Molar ratio (1 : 2:$NaBH_4$)	Temperature	Time (min)	Conversion **1** (%)	Conversion **2** (%)
1	PhCHO	$PhCOCH_3$	0.5 : 1:1	RT	5	100	0
2	PhCHO	PhCOPh	0.5 : 1:1	RT	5	100	0
3	PhCHO	Cyclohexanone	0.5 : 1:1	RT	6	100	10
4	9-fluorenone	PhCHO	2 : 1:1	RT	15	100	12
5	$Ph(CH_2)_2COCH_3$	PhCHO	2 : 1:1	RT	10	100	8

The same authors also reported the reduction of different carbonyl compounds such as aldehydes, ketones, α,β-unsaturated enals and enones, α-diketones and acyloins with $NaBH_4$ in the presence of wet SiO_2 (30% m/m) under solvent-free conditions. This methodology also demonstrated the chemoselective reduction of aldehydes over ketones, by the selective reduction of benzaldehyde over acetophenone using 0.5 molar equivalent of $NaBH_4$ at room temperature (Scheme 7 and Table 4). They also applied this protocol for the reduction of two ketones, 9-fluorenone and 4-phenyl-2-butanone vs acetophenone, and observed that the first ones were reduced with high chemoselectivity (Table 4).[36]

Yadav and co-workers reported a study of kinetics and mechanisms of the chemoselective reduction of citronellal to citronellol by sodium borohydride under liquid–liquid phase transfer catalysis (L-L PTC), using tetrabutylammonium bromide (TBAB) as a catalyst[37] (Scheme 8). The reaction was found to be 100% selective towards the formation of the desired product. Different parameters were considered such as speed of agitation, phase : volume ratio, catalyst concentration, sodium borohydride concentration, citronellal concentration and temperature.

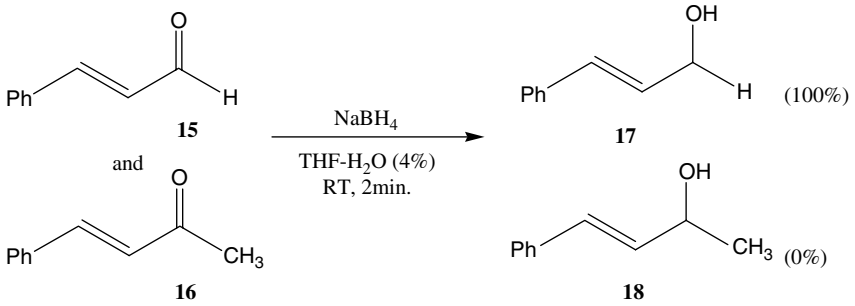
REDUCTION OF CARBOXYLIC ACIDS AND ESTERS

Tale and co-workers have described an one-pot reduction of carboxylic acids to alcohols using catalytic amounts of 3,4,5-trifluorophenylboronic acid and sodium borohydride (Scheme 9).[38] This methodology can be easily applied in the reduction of carboxylic acids to alcohols bearing easily reducible functional groups, such as halogeno, cyano, nitro, hydroxy and even azido. The process is inexpensive, uses mild conditions, gives good yields and is also efficiently used to reduce *N*-protected amino acids to the corresponding *N*-protected amino alcohol. The proposed mechanism is based on the *in situ* formation of acyloxyboron intermediates between carboxylic acid and 3,4,5-trifluorophenylboronic acid, which is reduced in the presence of $NaBH_4$ to give the corresponding alcohols (Scheme 10).

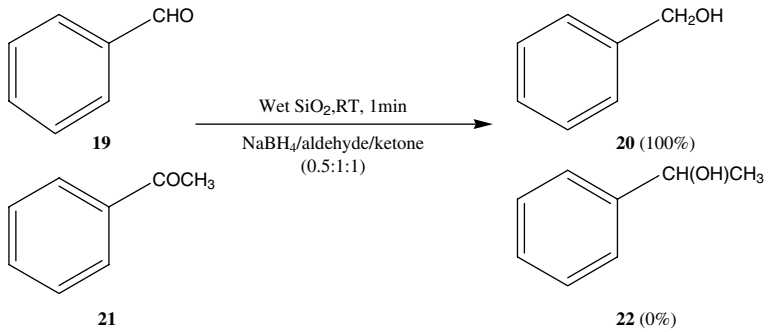
Pittman Jr and co-workers have described important studies using $NaBH_4$ at high temperatures (120–290 °C) in glyme solvents, which led successfully to the reduction of esters, carboxylic acids, nitriles, benzamide, 4-chlorobiphenyl and pentachlorophenol. More recently, the same authors have developed a method for the reduction of aromatic carboxylic acids and esters using $NaBH_4$ in diglyme at 162 °C, including sterically hindered ester, such as *t*-amyl 2-chlorobenzoate (Scheme 11).[39] This method produces the corresponding benzyl alcohols after 1–5 h in 64–95% yield with 96–97% purity.

Our group has reported a general one-pot procedure for the reduction of different aromatic and heteroaromatic esters into the corresponding alcohols using the $NaBH_4$–MeOH reagent system (Scheme 12).[40–42] The general procedure described is simple, safe, inexpensive and the reduction of different

DOI: 10.1002/aoc



Scheme 6.

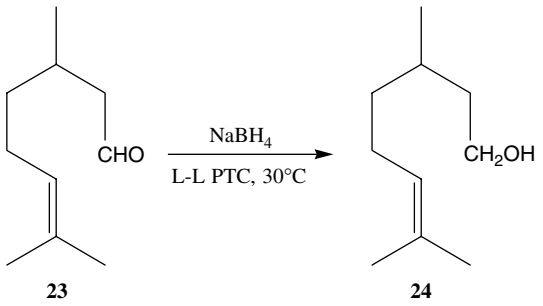


Scheme 7.

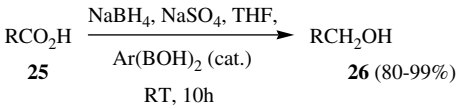
Table 4. Competitive reduction of aldehydes and ketones with $NaBH_4$ in the presence of wet SiO_2

Entry	Compound **1**	Compound **2**	Molar ratio[a]	Condition[b]	Time (min)	Conversion **1** (%)	Conversion **2** (%)
1	PhCHO	$PhCOCH_3$	0.5 : 1 : 1	RT	1	100	0
2	PhCHO	PhCOPh	0.5 : 1 : 1	RT	1	100	0
3	9-fluorenone	$PhCOCH_3$	2 : 1 : 1	Oil bath	10	92	15
4	$Ph(CH_2)_2COCH_3$	$PhCOCH_3$	2 : 1 : 1	Oil bath	7	98	3

[a] $NaBH_4$/substrate **1**/substrate **2**. [b] Temperature of oil bath was 75–80 °C.



Scheme 8.

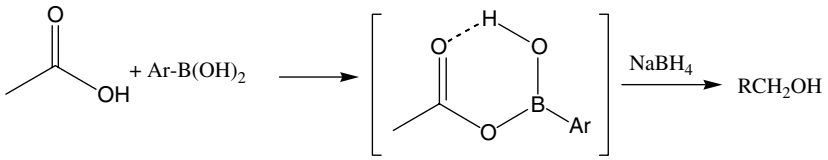


Scheme 9.

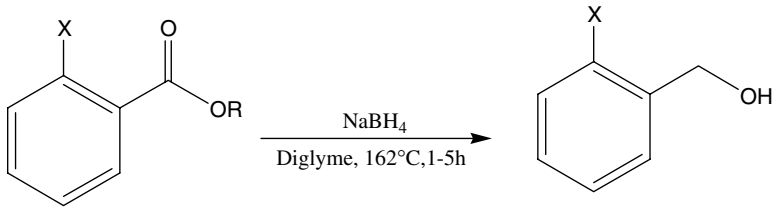
aromatic and heteroaromatic esters was completed within 0.15–4.0 h after refluxing in THF. The respective alcohols were isolated in moderate to excellent yields (48–100%) after aqueous workup. This method could be a good one to employ in an industry process also.

The one-pot synthesis of *N*-protected chiral *β*-amino alcohols has been reported by Somlai and co-workers from the corresponding *N*-protected *α*-amino acids via their methyl esters using $NaBH_4$ (Scheme 13).[43] The direct esterification was done by dissolving the amino acids in methanol followed by adding an ethereal solution of diazomethane. After that, $NaBH_4$ was added in small portions to produce the respective *N*-protected *β*-chiral amino alcohols in 85–93% yield (Scheme 13). The enantiopurity of the *N*-protected chiral *β*-amino alcohols was evaluated by a chiral HPLC method, which found less than 1% of racemization in all cases.

DOI: 10.1002/aoc



Scheme 10.



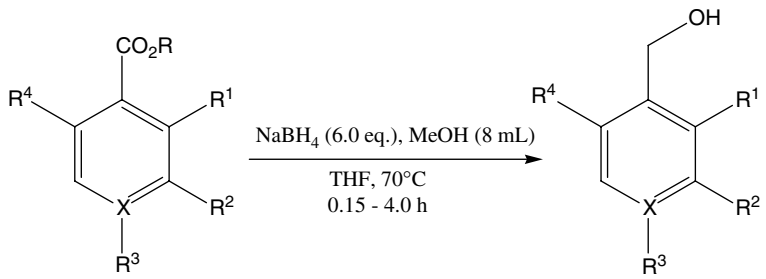
27

X,R: H,H; Cl,H; Cl,Me;
Cl,*i*-Pr; Cl,*t*-amyl

28 (96-97%)

(X: H,Cl)

Scheme 11.



29

R = Me, Et, i-Pr, n-Bu, Bn

R^{1-4} = halogen

X = C or N

30 (48-100%)

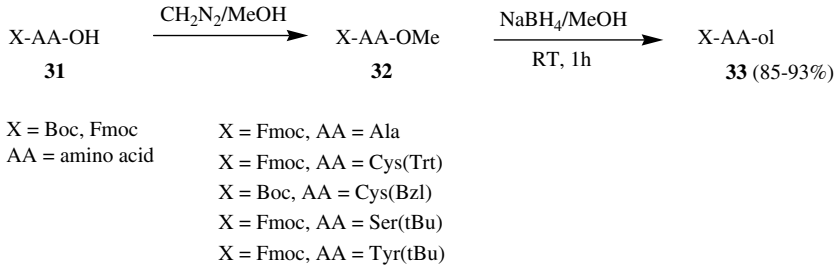
Scheme 12.

REDUCTION OF AMIDES, NITRILES, AZIDES AND IMINES

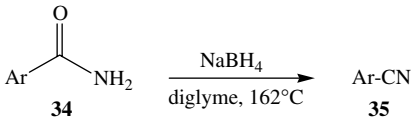
Pittman Jr and co-workers have described the reduction of primary aromatic amides in the presence of $NaBH_4$ in diglyme at 162 °C, which furnished the corresponding nitrile, followed by reduction to amines (Scheme 14).[44] However, the addition of LiCl to the $NaBH_4$-diglyme system increases the rate of primary aromatic amide and aromatic nitrile conversion to both the nitrile first, and the amine. The mechanism proposed by Pittman Jr and co-workers for the reduction of primary aromatic amides was based on the initial evolution of one mole equivalent of hydrogen and formation of the nitrile, followed by reduction to the amine (Scheme 15). Another important observation was that, when primary aromatic amides were heated to 162 °C in diglyme for 1 h, in the absence of $NaBH_4$, no reaction was observed. In this context, the borohydride must be involved in the mechanism, which gives the azenolate borohydride **40** via **38**–**39**, followed by elimination via transition state **41**, which produced **42** (Scheme 15).

Khurana and Kukreja have reduced several aromatic niriles to their corresponding primary amines using nickel boride, which was generated *in situ* from dry nickel (II) chloride and sodium borohydride, in the presence of dry ethanol at room temperature (Scheme 16).[45] This method can be efficiently used for the rapid reduction of robust aromatic nitriles compounds in their corresponding aromatic amines, **43**, in high yields (64–86%). Another advantage of this method is that the reductions are chemoselective in the presence of several groups, such as methoxy, halo (chloro and bromo), dimethylamino, olefinic and naphthyl groups.

DOI: 10.1002/aoc



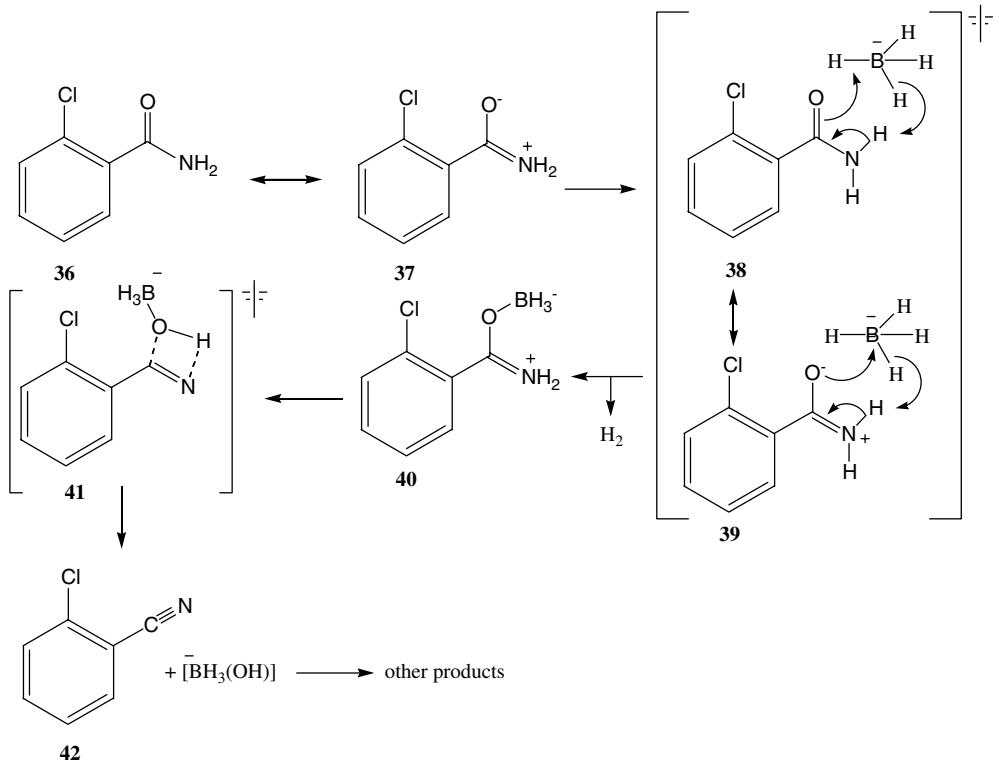
Scheme 13.



Scheme 14.

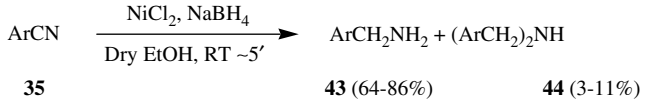
Cho and Kang have developed an efficient chemoselective reduction of imines to amines using boric acid-activated sodium borohydride under solvent-free conditions (Scheme 17).[46] This chemoselective methodology was able to reduce imines to amines bearing easily reducible functional groups, such as ketone, carboxylic acid, ester, nitrile, amide, nitro, furyl and alkenyl groups and it was a clean, rapid and very simple procedure to prepare substituted amines in practically quantitative yields.[46] In order to demonstrate the efficacy of this procedure, Cho and Kang have compared the reduction of 4-acetylbenzaldehyde-*N*-phenylimine, **47**, with metal hydrides, such as $NaBH_3CN$, $NaBH(OAc)_3$, $Zn(BH_4)_2$, pyridine-borane and PMHS-Ti(Oi-Pr)$_4$ (Table 5). However, when compared with these metal hydrides, boric acid-activated sodium borohydride under solvent-free conditions was by far the best condition.

Paraskar and Sudalai reported a new synthetic procedure for the reductive cyclization of azido- and cyano-substituted α,β-unsaturated esters with $NaBH_4$ catalyzed by cobalt chloride, which led to synthesis of γ- and δ-lactams (Table 6). The methodology has been successfully applied to an efficient enantioselective synthesis of (*R*)-baclofen, (*R*)-rolipran and (*R*)-4-fluorophenylpiperidinone, a key intermediate for (–) -paroxetine.[47]

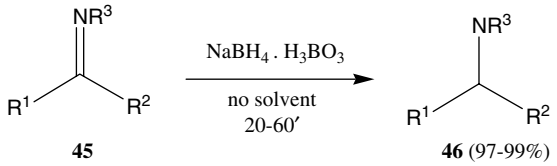


Scheme 15.

DOI: 10.1002/aoc



Scheme 16.



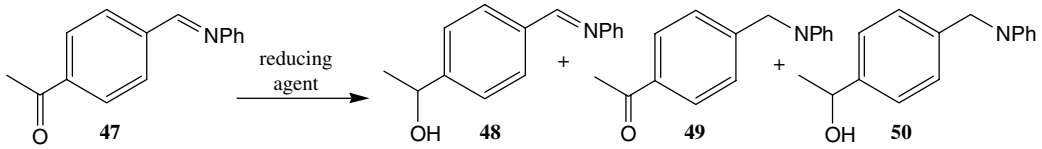
Scheme 17.

REDUCTION OF DOUBLE AND TRIPLE BONDS

A novel one-pot method for the preparation of γ-butyrolactones have been developed by Iyengar and co-workers,[48] This simple one-step reaction was based on α-methylene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolides, **57**, which were converted to the corresponding γ-butyrolactones, **58**, in methyl alcohol with $NaBH_4$ in the presence of triethylamine (Scheme 18). The general procedure of this method consisted in a solution of α-methylene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolides, **57** (1 mmol), in methyl alcohol (25 ml) and triethylamine (1 mmol), which were stirred at room temperature (28 °C) for 0.5 h. Then, $NaBH_4$ (1.5 mmol) was added to the solution and the reaction mixture was stirred at room temperature for an additional 0.5 h and finally, refluxed for 1 h. After extraction and purification using column chromatography, the γ-butyrolactones, **58**, were obtained in 92–98% yield.

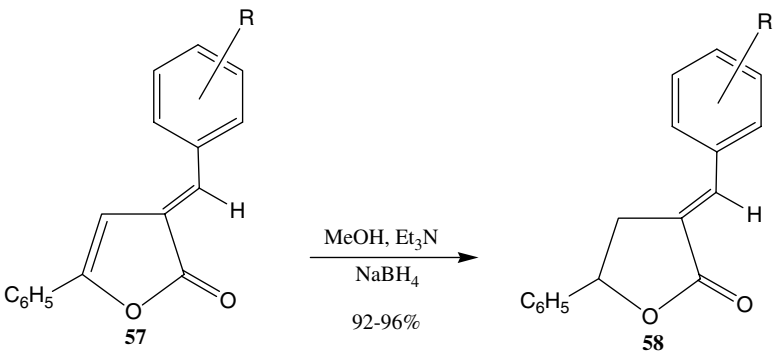
Koide and Naka have reported a simple and original methodology for *trans* conversion of γ-hydroxy-$\alpha,\beta(E)$-alkenoic esters, **60**, from γ-keto-alkynoic esters, **59**, in the presence of $NaBH_4$ in methanol (Scheme 19).[49,50] The alkenoic esters are important synthetic intermediates, which are included and present in many natural products and drugs. Hence, this methodology should be useful for the preparation of a wide variety of γ-hydroxy-$\alpha,\beta(E)$-alkenoic esters.

Table 5. Chemoselective reduction of **47** with various reducing agents



Entry	Reducing agent	Solvent	Time (h)	47	48	49	50
1	$NaBH_4/H_3BO_3$ (1 : 1)	None	0.5	0	100(98)[a]	0	0
2	$NaBH_3CN$	MeOH	16	0	97(94)[a]	3	0
3	$NaBH(OAc)_3$	DCE	19	6	94	0	0
4	$NaBH_4$	None	2	87(84)[a]	13(11)[a]		
5	PMHS/Ti(O*i*-Pr)$_4$	THF	39	65	0	28	7
6	BH_3. Pyridine	Petroleum ether	15	4	80	0	16
7	$Zn(BH_4)_2$	DME	38	89	6	3	2

[a] The numbers in parentheses indicate isolated yield.

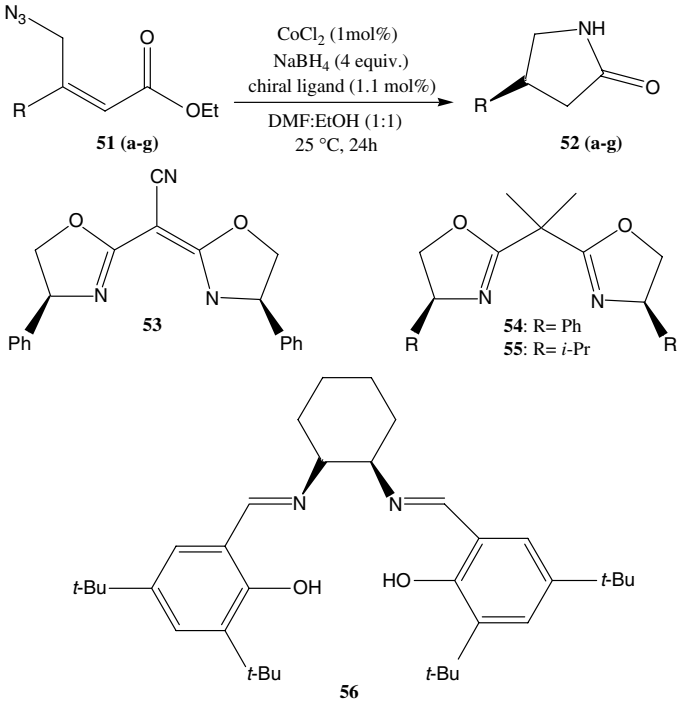


R = H; 2,6-Cl; *p*-F; *p*-CH_3; *m*-OPh; *p*-OCH_3; *p*-OH

Scheme 18.

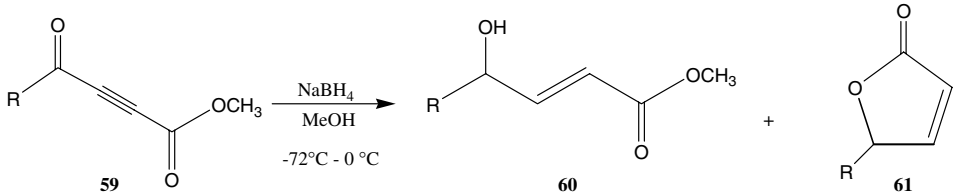
DOI: 10.1002/aoc

Table 6. $CoCl_2$-catalyzed reductive cyclization of γ-azido-α,β-unsaturated esters with $NaBH_4$ in the presence of chiral ligands **53–56**



Entry	R	Chiral ligand	Yield of **52** (%)	% ee[a] (configuration)
a	Ph	**53**	86	51 (*R*)
b	4-ClPh	**53**	82	89 (*R*)
	4-ClPh	**54**	86	05
	4-ClPh	**55**	80	12
	4-ClPh	**56**	73	05
c	4-FPh	**53**	80	ND[b]
d	2-MeOPh	**53**	91	ND
e	4-MeOPh	**53**	93	98 (*R*)
f	3-CpO-4-MeOPh	**53**	92	92 (*R*)
g	*t*-C_4H_9	**53**	77	ND

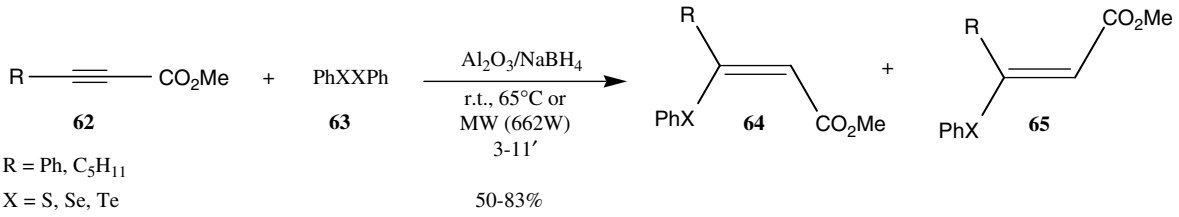
[a] Determined by comparison of $[\alpha]_D$ with the reported values as well as by chiral HPLC analysis.
[b] % ee not determined.
Cp = cyclopentyl.



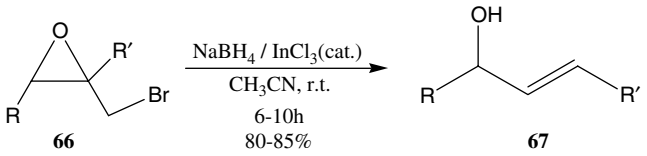
R	**60**	**61**
	Yield (%)	
Methyl	70	Not detected
Cyclohexyl	63	12
t-Butyl	47	9
Phenyl	60	Not detected

Scheme 19.

DOI: 10.1002/aoc



Scheme 20.



Scheme 21.

An efficient and general procedure has been developed by Lenardão and co-workers for preparation of β-phenylchalcogeno-α,β-unsaturated esters **64** and **65** from hydrochalcogenation of acetylenes, **62** (Scheme 20).[51,52] This solvent-free methodology was based on hydrochalcogenation of acetylenes, **62**, in the presence of the phenylchalcogenolate anion generated *in situ* from the corresponding diphenyl dichalcogenide (S, Se, Te), **63**, using alumina supported $NaBH_4$, under MW irradiation, which accelerates the reaction.

REDUCTION OF EPOXY COMPOUNDS

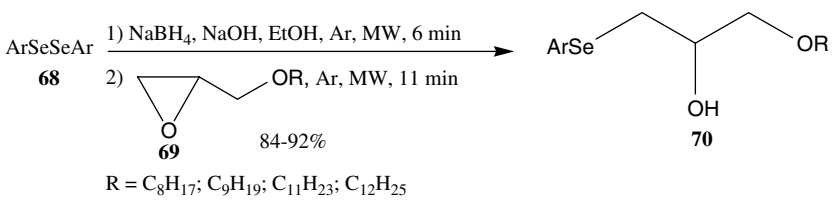
Rave and co-workers have prepared allylic alcohols, **67**, from their corresponding 2,3-epoxybromides, **66**, by combining $NaBH_4$ with catalytic amounts of indium(III) chloride (Scheme 21).[53] This method was based on the reduction of the bromide moiety followed by selective C–O bond cleavage through a radical process. The experimental procedure of this method is very simple: a solution of $NaBH_4$ and a catalytic amount of indium(III) chloride were added to a solution of the corresponding 2,3-epoxybromides, **66**, in anhydrous acetonitrile. After 6–10 h the reaction mixture was purified by column chromatography and the respective allylic alcohols were obtained in 80–85% yield.

Wang and co-workers have reported a simple method for the preparation of 1-arylseleno-3-alkoxy-2-propanol (Scheme 22).[54] The synthetic methodology was based on diaryl diselenides, **68**, as starting material which, in the presence of NaOH and $NaBH_4$ under microwave irradiation, generates arylselenide ions. These ions, in the presence of epoxypropoxyalkoxyls, **69**, under microwave irradiation, furnished the 1-arylseleno-3-alkoxy-2-propanol, **70**, in 84–92% yield.

MISCELLANEOUS

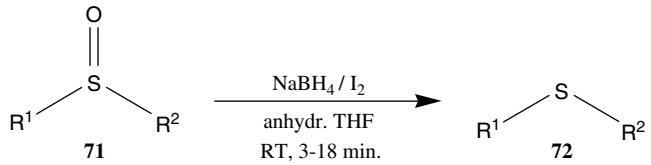
An efficient and chemoselective deoxygenation of sulfoxides, **71**, to thioethers, **72**, was achieved by Karimi and Zareyee by using $NaBH_4/I_2$ in anhydrous THF (Scheme 23).[55] This method was efficient in attaining chemoselectivity in the conversion of a wide range of structurally different sulfoxides, **71**, to their respective thioethers, **72**, in the presence of other reducible functional groups, such as nitro, esters, nitriles and double bonds. Other advantages, such as inexpensive methodology, fast reaction (3–18 min) and good yields (57–98%), can be cited (Scheme 23).

Traumer and co-workers have reported a new stereoselective synthesis of different glycosylamines based on the reductive cyclization of δ-hydroxy nitriles using $NaBH_4$ (Scheme 24).[56] For example, the synthesis of β-tetra-*O*-benzylglucosylamine, **76**, was achieved using 2,3,4,6-tetra-*O*-benzylglucose, **73**, as starting material, which after transformation to the respective oxime, **74**, and dehydration, furnished the key intermediate, **75**. This intermediate, in the presence of $NaBH_4$ in ethanol, furnishes the glycosylamine, **76**, as the single β-anomer in 70% yield (Scheme 24). According to the authors, the reaction probably involves a base-catalyzed cyclization of the δ-hydroxy nitrile, **77**, to the respective imidate, **78**, followed by reduction and solvolysis (Scheme 25). The stereoselective course of this reaction can be



Scheme 22.

DOI: 10.1002/aoc



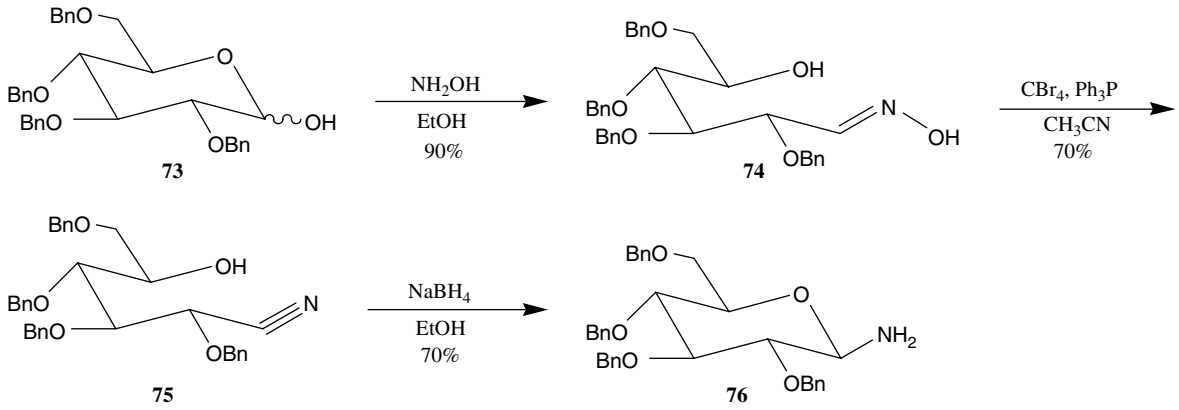
Scheme 23.

rationalized by a preferential axial attack of the hydride onto the imidate.

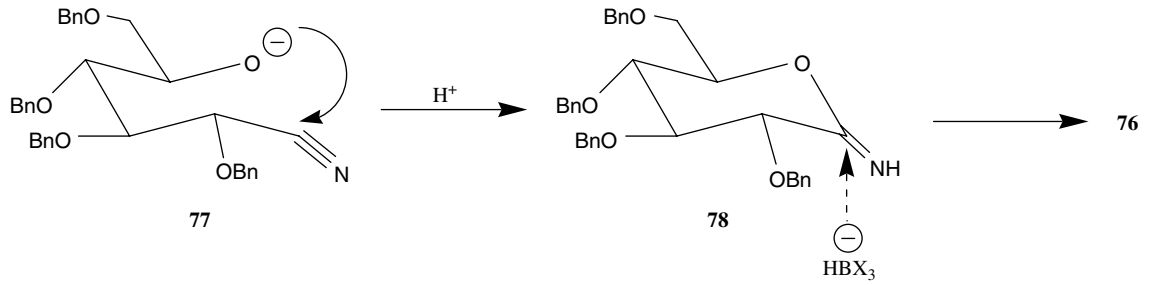
Sodium borohydride has also been successfully applied by Chiriac and co-workers in a new direct synthesis of cinnamic acids from aromatic and aliphatic carboxylic acids.[57] This method furnished different cinnamic acids in 59–86% yield in the presence of $NaBH_4$ and *N*-methyl-2-pyrrolidinone as the solvent, at reflux (185–190 °C) for 9–12 h. It is important to mention that the reaction does not proceed without the presence of $NaBH_4$ (Scheme 26).

Ray and co-workers have reported a simple method of preparation of different *N*-aryl-1-formylpyrroles, which have been synthesized after reduction of γ-lactam carboxylic acids using $NaBH_4/I_2$, followed by reaction with DDQ, which is responsible to mediate oxidative aromatisation[58] (Scheme 27).

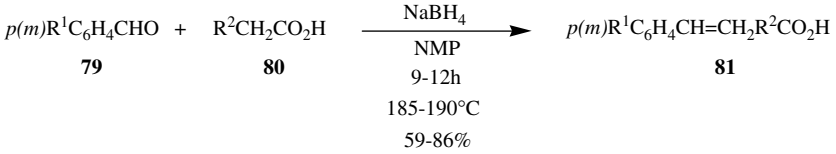
Rao and co-workers have reported an interesting method for removing copper from amino acid–copper complexes using $NaBH_4$.[59] The literature describes many different reagents used for this purpose, such as hydrogen sulfide, potassium cyanide, HCl, HBr, thioacetamide, 8-quinolinol, metal ion exchange resins and EDTA, which is the most widely used. However, the use of $NaBH_4$ is an important contribution because it is simple, nontoxic, inexpensive, the amino acids are furnished in high yield, purity and without racemization.[59] This new method was based on reducing the amino acid–copper complexes into the insoluble copper(I), which was filtered and washed with water, releasing the free amino acid.



Scheme 24.

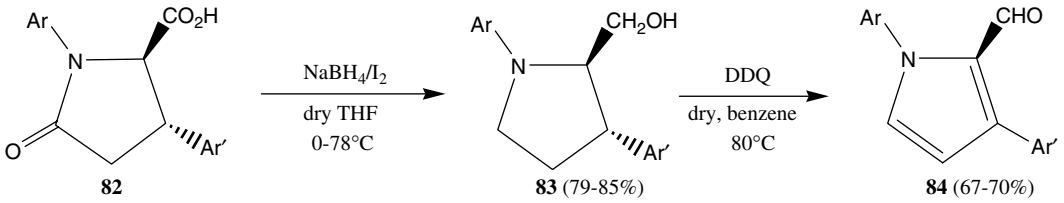


Scheme 25.



Scheme 26.

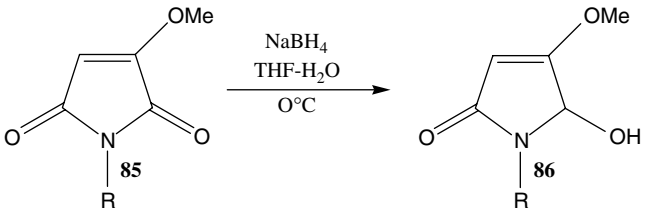
DOI: 10.1002/aoc



Ar,Ar′: 4-ClC_6H_4, 2-thienyl
4-MeC_6H_4, C_6H_5
4-ClC_6H_4, C_6H_5
$C_6H_3F_2$-3,4; C_6H_5
C_6H_3-3-Cl,4-F; C_6H_5

Scheme 27.

Table 7. Synthesis of methyl 5-hydroxytetramates from reduction of 3-methoxymaleimide using $NaBH_4$ in THF-H_2O at 0 °C



Entry	R	Time (min)	Yields (%)
1	H	30	87
2	Me	45	87
3	Et	90	84
4	Allyl	30	85
5	Bn	100	83
6	PMB	180	76
7	Ph	60	70

Coster and co-workers have described the regioselective reduction of 3-methoxymaleimide and *N*-alkyl 3-methoxymaleimides derivatives using $NaBH_4$ in THF-H_2O at 0 °C (Table 7).[60] The resultant methyl 5-hydroxytetramates are useful intermediates in the synthesis of a variety of tetramates derivatives.

They explained that the delocalization of a lone pair on the methoxy oxygen of the substrates would significantly decrease the reactivity of the C_5 carbonyl group toward nucleophilic attack by hydride reducing reagents.

CONCLUSION

Nowadays, modern organic synthesis still requires more efficient reducing reagents. In this context, reduction carried out by sodium borohydride and additives is an important synthetic method to obtain different classes of compounds in high yield, mild conditions and with easy purification.

REFERENCES

1. Schlesinger HI, Brown HC, Hoekstra HR, Rapp LR. *J. Am. Chem. Soc.* 1953; **75**: 199.
2. Brown HC, Subba RBC. *J. Am. Chem. Soc.* 1955; **77**: 3164.
3. Brown HC. *Boranes in Organic Chemistry*. Cornell University Press: Ithaca, NY, 1972.
4. Brown HC, Krishnamurthy R. *Tetrahedron* 1979; **35**: 567.
5. Grilble GW, Nutaitis CF. *Org. Prep. Proced. Int.* 1985; **17**: 317.
6. Guerrier L, Royer J, Grierson D, Husson HP. *J. Am. Chem. Soc.* 1983; **105**: 7754.
7. Marco JL, Royer J, Husson HP. *Synth. Commun.* 1987; **17**: 669.
8. Banfi EN, Riva R. *Reagents for Organic Synthesis*. Wiley: New York, 1995.
9. Brown HC. *Tetrahedron*. 1979; **35**: 567.
10. Periasamy M, Thirumalaikumar M. *J. Organomet. Chem.* 2000; **609**: 137.
11. Rice B, Livasy JA, Schaeffer GW. *J. Am. Chem. Soc.* 1950; **77**: 2750.
12. Leutenegger U, Madin A, Pfaltz A. *Angew. Chem. Int. Edn Engl.* 1989; **77**: 60.
13. Von Matt P, Pfaltz A. *Tetrahedron Asymm.* 1991; **2**: 691.
14. Narasimhan S, Swarnalakshmi S, Balakumar R. *Indian J. Chem.* 1998; **37B**: 1189.
15. Prasad ASB, Kanth JVB, Periasamy M. *Tetrahedron* 1992; **48**: 4623.
16. Kabalka GW, Wadgaonkar PP, Narayana C. *J. Chem. Edn* 1990; **67**: 975.
17. Narasimhan S, Madhavan S, Prasad KG. *J. Org. Chem.* 1995; **60**: 5314.
18. Itsuno S, Sakurai Y, Ito K. *Synthesis* 1988; 995.
19. Kanth JVB, Periasamy M. *J. Org. Chem.* 1991; **56**: 5964.
20. Wu S, Takeya R, Eto M, Tomizawa C. *J. Pestic. Sci.* 1979; **12**: 221.
21. Karrer P, Suter M. *Helv. Chim. Acta.* 1948; **32**: 1156.
22. McKennon MJ, Meyers AI, Drauz K, Schwarm M. *J. Org. Chem.* 1993; **58**: 3568.
23. Abiko A, Masamune S. *Tetrahedron Lett.* 1992; **33**: 5517.
24. Yamakawa T, Masaki M, Nohira H. *Bull. Chem. Soc. Jpn.* 1991; **64**: 2730.
25. Akabori S, Takanohashi Y. *Chem. Lett*. 1990; 251.
26. Akabori S, Takanohashi Y. *J. Chem. Soc. Perkin Trans.* 1991; **1**: 479.
27. Brown WG. *Organic Reactions*. Wiley: New York, 1952.
28. Ren P, Dong T, Wu S. *Synth. Commun.* 1997; **27**: 1547.
29. Gribble GW. *Eastman Org. Chem. Bull.* 1979; **51**: 1.
30. Cho BT, Yoon NM. *Synth. Commun.* 1985; **15**: 917.
31. Molander GA. *Chem Rev.* 1992; **92**: 29.
32. Kumar S, Chadha A. *Synthesis.* 2003; **5**: 639.
33. Benedetti F, Beti F, Donati I, Fregonese M. *Chem. Commun.* 2002; 828.
34. Lee JM, Lim HS, Seo KC, Chung SK. *Tetrahedron Asymm.* 2003; **14**: 3639.

35. Zeynizadeh B, Behyar T. *Bull. Chem. Soc. Jpn.* 2005; **78**: 307.
36. Zeynizadeh B, Behyar T. *J. Braz. Chem. Soc.* 2005; **16**: 1200.
37. Yadav GD, Lande SV. *J. Mol. Cat. A: Chem.* 2006; **247**: 253.
38. Tale RH, Patil KM, Dapukar SE. *Tetrahedron Lett.* 2003; **44**: 3427.
39. Zhu HJ, Pittman Jr. CU. *Synth. Commun.* 2003; **10**: 1733.
40. Souza MVN, Oliveira PSM, Boechat N, Mendonça JS, Costa JCS. *Tetrahedron Lett.* 2004; **45**: 6021.
41. Souza MVN, Boechat N, Mello PSM, Costa JCS, Mendonça JS, Fernandes EL, Pais KC, Vasconcelos TRA. *Synth. Commun.* 2005; **35**: 3187.
42. Souza MVN, Boechat N, Mendonça JS, Fernandes EL, Pais KC, Costa JCS, Vasconcelos TRA. *Arkivoc.* 2006; 128.
43. Somlai C, Peter A, Forgó P, Penke B. *Synth. Commun.* 2003; **11**: 1815.
44. Zhu HJ, Lu KT, Sun GR, He JB, Li HQ, Pittman Jr CU. *New J. Chem.* 2003; **27**: 409.
45. Khurana J, Kukreja G. *Synth. Commun.* 2002; **8**: 1265.
46. Chao B, Kang SK. *Synlett.* 2004; **9**: 1484.
47. Paraskar AS, Sudalai A. *Tetrahedron* 2006; **62**: 4907.
48. Reddy GS, Neelakantan P, Iyengar DS. *Synth. Commun.* 2002; **17**: 2601.
49. Naka T, Koide K. *Tetrahedron Lett.* 2003; **44**: 443.
50. Meta CT, Koide K. *Organic Letters.* 2004; **6**: 3237.
51. Perin G, Jacob RG, De Azambuja F, Botteselle GV, Siqueira GM, Freitag RA, Lenardão EJ. *Tetrahedron Lett.* 2005; **46**: 1679.
52. Zeni G, Barros OSR, Moro AV, Braga AL, Peppe C. *Chem. Commun.* 2003; 1258.
53. Ranu BC, Baneyee S, Das A. *Tetrahedron Lett.* 2004; **45**: 8579.
54. Wang JX, Wu X, Huang D, Hu Y. *Synth. Commun.* 2002; **12**: 1903.
55. Karimi B, Zareyee D. *Synthesis* 2003; 335.
56. Dorsey AD, Barbarow JE, Trauner D. *Organic Letters.* 2003; **5**: 3237.
57. Chiriac CI, Tanasa F, Orciu M. *Tetrahedron Lett.* 2003; **44**: 3579.
58. Haldar P, Guin J, Ray JK. *Tetrahedron Lett.* 2005; **46**: 1071.
59. Sailaja G, Nowshuddin S, Rao MNA. *Tetrahedron Lett.* 2004; **45**: 9297.
60. Issa F, Fischer J, Turner P, Coster MJ. *J. Org. Chem.* 2006; **71**: 4703–4705.

DOI: 10.1002/aoc