J. Chem. Sci., Vol. 118, No. 5, September 2006, pp. 419–423.

Sodium borohydride reduction of aromatic carboxylic acids via methyl esters

AAMER SAEED* and ZAMAN ASHRAF
Department of Chemistry, Quaid-I-Azam University 45320, Islamabad, Pakistan
e-mail: aamersaeed@yahoo.com

MS received 7 July 2005; revised 25 January 2006

Abstract. A number of important aromatic carboxylic acids precursors, or intermediates in the syntheses of natural products, are converted into methyl esters and reduced to the corresponding primary alcohols using a sodium borohydride–THF–methanol system. The alcohols are obtained in 70–92% yields in 2–5 hours, in a pure state. This two-step procedure not only provides a better alternative to aluminum hydride reduction of acids but also allows the selective reduction of esters in presence of acids, amides, nitriles or nitro functions which are not affected under these conditions.

Keywords. Reduction; sodium borohydride; aromatic methyl esters.

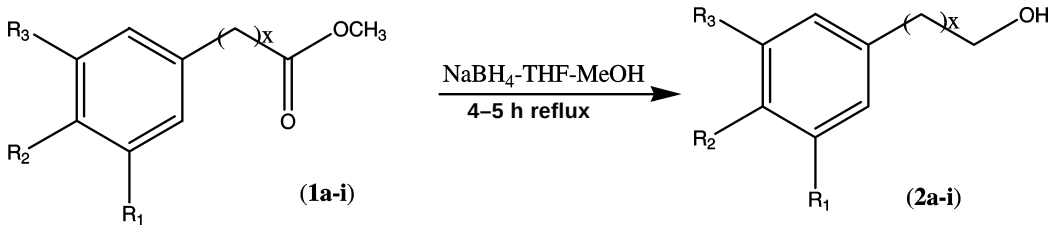
1. Introduction

The use of sodium borohydride in the simple chemoselective reductions of aldehydes and ketones to the corresponding alcohols is well known.[1] The reaction is normally carried out at ≈ 25°C or at reflux temperature using ethanol or methanol as solvent. Although, theoretically, one equivalent of sodium borohydride provides four equivalents of hydride, however, a slight excess of the reagent is typically used to counter consumption by reaction with the solvent. Under these conditions, carboxylic acids, esters, epoxides, lactones, nitro groups, imides, amides and nitriles are not reduced. Therefore, reduction of these functional groups is carried out using stronger reducing agents like lithium aluminum hydride.[2] Sodium borohydride can, however, be easily modified to a stronger or more selective reducing agent.[3] Examples include the borohydride reduction step in the industrial Sumitomo's synthesis of D-biotin (vitamin H)[4] and the selective hydroxy ester reduction in presence of non-substituted esters, employed in the synthesis of *R*-lipoic acid.[5] Sodium borohydride is versatile as a hydride reducing agent for both chemo- and diastereo-selectivity and thus has been used in the stereoselective reductions.[2,6] Hence a combination of sodium borohydride with organoborane has been developed for diastereoselective reduction of hydroxy ketone and of 'statin-type' molecules,[7] and stereoselective enamine ketone reductions.[8] The combination produces excellent diastereoselective yields, without requiring the transition metal separation necessary in case of catalytic hydrogenation. Sodium borohydride–cerium (III) chloride has been used in the selective reduction of a,b-unsaturated carbonyl compounds to the corresponding allylic alcohols (Luche Reduction).[9] The reactivity of sodium borohydride can also be enhanced in the presence of certain additives like iodine and zinc chloride.[10,11]

Sodium borohydride is a mild hydride donor and does not readily reduce acids or esters. However, since its discovery, there have been a number of attempts in this direction. Thus, esters, carboxylic acids and nitriles were reported to undergo reduction at room temperatures with sodium borohydride in diglyme in the presence of aluminum chloride[12] or sodium borohydride and ethane dithiol in THF at room or reflux temperature.[13]

The reduction of esters in non-polar solvents like THF has traditionally required long reaction times and forcing conditions. The addition of a precise amount of methanol to the reaction mixture enhances the reactivity of sodium borohydride-THF system.[14] In this article we wish to report the reduction of some aromatic methyl esters containing one, two, or more carbons or a,b-unsaturation in the side chain using sodium borohydride–THF system[15] (scheme 1). Thus, mono-, di-, or tri-methoxy substituted benzoic

*For correspondence



a; $R_1 = R_3 = OCH_3$, $R_2 = CH_3$, $x = 0$
b; $R_1 = R_3 = OCH_3$, $R_2 = CH_3$, $x = 1$
c; $R_1 = R_3 = OCH_3$, $R_2 = H$ $x = 1$
d; $R_1 = R_2 = R_3 = OCH_3$ $x = 2$
e; $R_1 = R_2 = OCH_3$, $R_3 = H$, $x = 1$
f; $R_1 = OCH_3$, $R_2 = R_3 = H$, $x = 1$
g; $R_1 = OCH_3$, $R_2 = R_3 = H$, $x = 1$
h; $R_1 = OCH_3$, $R_2 = R_3 = H$, $x = (CH=CH)$
i; $R_1 = R_3 = H$, $R_2 = NO_2$ $x = 0$
j; $R_1 = R_3 = H$, $R_2 = F$ $x = 0$
k; $R_1 = R_3 = H$, $R_2 = Cl$ $x = 0$
l; $R_1 = R_3 = H$, $R_2 = Br$ $x = 0$

Scheme 1. Boronhydride reduction of aromatic methyl esters.

Table 1. Physical and IR spectral data of compounds **2a–l**.

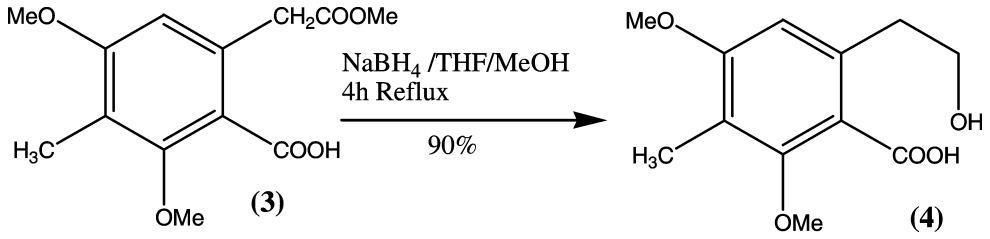
Compd.	m.p. (°C)	IR cm^{-1}		Reflux (h)	Yield (%)
		CO (ester)	–OH		
2a	55–57 (lit.[17] 62–65)	1729	3191	4.0	83
2b	42–45	1734	3328	4.0	81
2c	Oil	1740	3374	3.5	87
2d	Oil	1740	3414	3.30	90
2e	42–43 (lit.[20] 48)	1733	3422	4.30	70
2f	Oil	1737	3456	4.30	71
2g	Oil	1729	3462	4.30	70
2h	30–32	1718	3438	4.0	75
2i	98–99 (lit.[23] 94–95)	1720	3521	2.30	89
2j	Oil	1721	3512	3.0	91
2k	74–76 (lit.[24] 69–70)	1719	3520	2.50	92
2l	77–78 (lit.[25] 75–76)	1720	3521	2.0	91

acids, phenylacetic acids, phenylpropanoic acid and cinnamic acid, precursors or intermediates towards the synthesis of natural products were successfully reduced to corresponding alcohols via prior conversion into corresponding methyl esters. It may be mentioned that the previous report of reduction of *a*,*b*-unsaturated esters using a ten- to twenty-fold excess of reagent in water or alcohol, involved a concomitant reduction of the double bond, resulting in the corresponding saturated alcohol or a mixture of saturated and unsaturated alcohols.[16]

2. Results and discussion

3,5-Dimethoxy-4-methylbenzoic acid was prepared from 4-methylbenzoic acid according to the literature procedure[17] and was converted to 3,5-dimethoxy-4-methylphenylacetic acid by the standard homologation sequence.[18] These are the key starting materials for the synthesis of fungal metabolites of sclerotiorin and rotiorin groups.[19] 3-Methoxybenzoic acid, 3-methoxyphenylacetic acid, 3,4-dimethoxy phenylacetic acid, 3-methoxycinnamic acid and 3,4,5-trimethoxyphenylpropionic acid were commercial products from Aldrich. All these acids are important intermediates in the synthesis of natural products. 3,5-Dimethoxy-4-methylphenyl ethanol and 3,4-dimethoxyphenylethanol[20] are important precursors of 1-substitued isochromans.[21]

The acids were converted into corresponding methyl esters by the standard procedure. The reductions were completed in 2–4 h giving alcohols in 70–92% yields (table 1). The progress of reactions was monitored by analytical TLC. The alcohols were obtained as single pure products. The new compounds were initially characterized by the R_f values and IR spectra. Thus, there was complete absence of ester carbonyl stretching peaks, at 1718–1734 cm^{-1} and the appearance of broad peaks for the hydroxyl function at ≈ 3191–3462 cm^{-1} (table 1). Final characterization



Scheme 2.

was by use of ^{1}H NMR and mass spectra. Spectroscopic and physical data for known alcohols were in accordance with those reported in the literature. The selective reduction of the ester function in carboxy ester (**3**) to afford the corresponding hydroxy acid (**4)** has been used as a key step in our synthesis of the natural dihydroisocoumarin stellatin[22] (scheme 2).

That the method is not limited to activated substrates and nitro group is not affected under these conditions was shown by the smooth reduction of 4-nitrobenzoic acid to 4-nitrobenzyl alcohol[23] (**2i**). The generality of the method was further established by reduction of 4-fluoro-, 4-chloro- and 4-bromobenzoic acids to corresponding benzyl alcohols[24,25] (**2j–l**) and as expected, the attempted reduction of 3,5-dimethoxybenzonitrile to corresponding phenethyl amine was unsuccessful despite refluxing for 12 h. In general, the yields were higher and reflux time was shorter for benzoic acids as compared to the higher homologues.

The additional step involving the conversion into esters is justified and more than compensated for by the low cost, better yield, ease of workup and lack of mandatory anhydrous conditions necessary for a successful aluminum hydride reduction.

The mechanism of reduction probably involves the *in situ* generation of more reactive sodium methoxyborohydrides in presence of methanol. This is also supported by the fact that the use of more hindered alcohols like 2-propanol involving alkoxyborohydrides results in significantly longer reaction times.[14]

3. Experimental

Melting points were recorded using a MEL TEMP MP-D apparatus and are uncorrected. ^{1}H NMR spectra were determined as $CDCl_3$ solutions at 400 MHz using a Bruker AM-400 machine. FT IR spectra were recorded on an FTS 3000 MX spectrophotometer and mass spectra (EI, 70 eV) were recorded on a MAT 312 instrument. Commercial THF and methanol were distilled prior to reaction. A typical experimental procedure is described below.

3.1 *Synthesis of 2-(3,5-dimethoxy-4-methylphenyl) ethanol (***2b***)*

Sodium borohydride powder (1 g, 27·0 mmol) was added to a stirred solution of 2-(3,5-dimethoxy-4-methylphenyl)ethanoate **(1b)** (1 g, 4·46 mmol) in THF (16 ml). The resulting suspension was stirred at 65°C for 15 min. Methanol (16 ml) was then added dropwise and the reaction mixture was refluxed for 4 h. After cooling to room temperature the reaction mixture was quenched with 2N HCl (10 ml). The organic layer was separated and the aqueous phase extracted with ethyl acetate (3×20 ml). The combined organic phase was dried ($MgSO_4$) and concentrated to obtain a solid residue. Recrystallization from ethanol afforded the alcohol (**2b**) (0·7 g, 3·61 mmol, 81%) as colorless needles. m.p. 42–45°C; IR (KBr):= 3328, 2956, 1587, 1271, 1182, 1072, 741 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): d = 2·21 (3H, *s*, Ar-CH_3), 3·85 (*s*, 6H, MeO x2), 3·21 (2H, *t*, J = 5·60 Hz, Ar-$\underline{CH_2}$), 4·30 (2H, *t*, J = 5·60 Hz, $\underline{CH_2}$OH), 6·39 (2H, *s*, H-2, 6) ppm; MS (70 eV): *m*/*z* (%)= 196 (M^+, 100), 178 (31), 163 (19), 149 (36), 135 (25).

Alcohols **2a–l** were prepared in a similar manner. Physical and IR data are recorded in table 1.

3.2 *(3,5-Dimethoxy-4-methylphenyl)methanol (***2a***)*

IR (KBr):= 3191, 2937, 1600, 1271, 1185, 1072, 741 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): d = 2·21 (3H, *s*, Ar-CH_3), 4·92 (2H, *s*, Ar-$\underline{CH_2}$), 6·43 (2H, *s*, H-2, 6) ppm; MS (70 eV): *m*/*z* (%) = 182 (M^+, 37), 164 (100), 163 (19), 149 (36), 135 (23).

3.3 *2-(3,5-Dimethoxyphenyl)ethanol (***2c***)*

IR (KBr):= 3374, 2942, 1599, 1446, 1271, 1182, 1083, 691 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): d =

2·68 (2H, *t*, Ar-CH_2, *J* = 6·0 Hz), 3·81 (*s*, 6H, MeO x2), 4·1 (2H, *t*, *J* = 6·0 Hz, CH_2OH), 6·39 (1H, *s*, H-2), 6·47 (1H, *s*, H-6) ppm; MS (70 eV): *m*/*z* (%)= 196 (M^+, 41), 178 (31), 165 (43), 149 (36), 135 (21).

3.4 *3-(3,4,5-Trimethoxyphenyl) propan-1-ol (***2d***)*

IR (KBr):= 3414, 3208, 2932, 1596, 1271, 1182, 1072 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *d* = 1·83 (2H, *q*, *J* = 7·9 Hz, *J* = 6·48 Hz, CH_2-2), 2·60 (2H, *t*, *J* = 7·6 Hz, CH_2-3), 3·63 (2H, *t*, *J* = 6·2 Hz, CH_2-1), 3·77 (3H, *s*, MeO), 3·79 (6H, *s*, MeO x2), 6·37 (1H, *s*, Ar-H) ppm; MS (70 eV): *m*/*z* (%)= 226 (M^+, 24), 208 (41), 164 (100), 163 (19), 149 (36), 135 (23).

3.5 *2-(3,4-Dimethoxyphenyl)ethanol (***2e***)*

IR (KBr):= 3316, 3208, 2960, 1597, 1271, 1182, 1072, 941 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *d* = 2·80 (2H, *t*, *J* = 7·6 Hz, $ArCH_2$), 3·91 (2H, *t*, *J* = 6·2 Hz, CH_2OH), 3·70 (3H, *s*, MeO), 3·72 (6H, *s*, MeO x2), 6·57 (1H, *s*, Ar-H) ppm; MS (70 eV): *m*/*z* (%)= 182 (M^+, 27), 164 (43), 162 (19).

3.6 *(3-Methoxyphenyl)methanol (***2f***)*

IR (KBr):= 3462, 3220, 2945, 1602, 1271, 1182, 1072 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *d* = 1·83 (2H, *q*, *J* = 7·9 Hz, *J* = 6·48 Hz, CH_2-2), 2·60 (2H, *t*, *J* = 7·6 Hz, CH_2-3), 3·63 (2H, *t*, *J* = 6·2 Hz, CH_2-1), 3·77 (3H, *s*, MeO), 3·79 (6H, *s*, MeO x2), 6·37 (1H, *s*, Ar-H) ppm; MS (70 eV): *m*/*z* (%)= 138 (M^+, 37), 164 (100), 163 (19).

3.7 *2-(3-Methoxyphenyl)ethanol (***2g***)*

IR (KBr):= 3316, 3247, 2956, 1596, 1271, 1182, 1072, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *d* = 1·83 (2H, *q*, *J* = 7·9 Hz, *J* = 6·48 Hz, CH_2-2), 2·60 (2H, *t*, *J* = 7·6 Hz, CH_2-3), 3·63 (2H, *t*, *J* = 6·2 Hz, CH_2-1), 3·77 (3H, *s*, MeO), 3·79 (6H, *s*, MeO x2), 6·37 (1H, *s*, Ar-H) ppm; MS (70 eV): *m*/*z* (%)= 152 (M^+, 15), 164 (100), 163 (19).

3.8 *3-Methoxycinnamyl alcohol (***2h***)*

IR (KBr):= 3438, 2932, 1596, 1271, 1182, 1072 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *d* = 3·85 (*s*, 3H, MeO), 4·18 (*d*, *J* = 5·8 Hz, 2H), 6·53 (*d*, *J* = 15·84 Hz, 1H), 6·21 (*d*, *J* = 15·80 Hz, 1H), 6·68–6·80 (*m*, 3H, Ar-H), 6·84 (*s*, 1H, Ar-H) ppm; MS (70 eV): *m*/*z* (%)= 164 (M^+, 45), 146 (65), 137 (15).

4. Conclusion

In summary, the application of sodium borohydride–THF–methanol system for reduction of methyl esters is illustrated by several examples involving important methoxy acids. When compared to aluminum hydride reduction, it proves to be an efficient and selective procedure which allows selective reduction of esters in presence of acids, amides, nitriles or nitro functions.

References

1. Brown H C and Krishnamurthy R 1979 *Tetrahedron* **35** 567; Brown H C, Narasimhan S and Choi Y M 1982 *J. Org. Chem.* **47** 4702; Paquette L A, Burke S D and Danheiser R L 1999 In *Handbook of reagents for organic synthesis: Oxidizing and reducing reagents* (New York: John Wiley and Sons) pp 199–204
2. Seyden-Penne J 1997 *Reductions by alumino and borohydride in organic synthesis* 2nd edn (New York: Wiley–VCH)
3. Periasamy M and Tirumalaikumar M 2000 *J. Organomet. Chem*. **60** 9
4. Aoki Y, Suzuki H and Akano S 1975 US Pat. 3,876,656; 1974 *Chem. Abstr*. **80** 9595lz; Outten R A 1998 Biotin. In *Kirk-Othmer encyclopedia of chemical technology* **24** 3701
5. Balkenhohl F and Paust J 1996 US 5,530,143; *Chem. Abstr*. **124** 194262j
6. Nakata T, Tani Y, Hatozaki M and Oishi T 1984 *Chem. Pharm. Bull*. **32** 1411; Gensler W J, Johnson F and Slaon A D B 1960 *J. Am. Chem. Soc*. **82** 6074; Crabbe P, Garcia G A and Rius C 1973 *J. Chem. Soc., Perkin Trans. 1* 810
7. Chen K M, Hardtmann G E, Prasad K, Repic O and Shapiro M 1987 *Tetrahedron Lett.* **28** 155; Narasaka K and Pai F C 1984 *Tetrahedron* **40** 2233
8. Stoner E J, Cooper A J, Dickman D A, Kolaczkowski L, Lallaman J E, Liu J.-H, Oliver-Shaffer P A, Patel K M, Paterson J B Jr, Plata D J, Riley D A, Sham H L, Stengel P J and Tien J-H J 2000 *Org. Process Res. Dev*. **4** 264; Berakes D, Kolarovic A and Povazanec F 2000 *Tetrahedron Lett*. **41** 5257
9. Luche J-L 1978 *J. Am. Chem. Soc.* **100** 2226
10. Periasamy M and Thirumalaikumar M 2000 *J. Organometal. Chem*. **609** 137; Prasad A B S, Kanth J V B and Periasamy M 1992 *Tetrahedron* **48** 4623; Yamakawa T, Masaki M and Nohira H 1991 *Bull. Chem. Soc. Jpn.* **64** 2730; Chaikin S W and Brown W G 1949 *J. Am. Chem. Soc.* **71** 122
11. Brown H C and Krishnamurthy S 1979 *Tetrahedron* **35** 567; Aicher T D, Buszek K R, Fang F G, Forsyth

C J, Jung S H, Kishi Y, Matelich M C, Ireland R E, Armstrong J D III, Lebreton J, Meissner R S and Rizzacasa M A 1993 *J. Am. Chem. Soc.* **115** 7152
12. Brown H C and Subba Rao B C 1955 *J. Am. Chem. Soc.* **77** 3164
13. Guida W C, Entreken E E and Guida A R 1984 *J. Org. Chem.* **49** 3024
14. Daluge S M, Martin M T, Sickles R B and Livingstone D A 2000 *Nucleosides Nucleotides Nucleic Acids* **19** 297
15. Prasad A B S, Kanth J V B and Periasamy M 1992 *Tetrahedron* **48** 4623; Boechat N, Santos da Costa J C, de Souza Mendonc J, Santos M P, de Oliveira and De Souza M V N 2004 *Tetrahedron Lett*. **45** 6021
16. Brown M S and Rapoport H 1963 *J. Org. Chem.* **28** 3261
17. Manchand P S, Townsend J M, Belica P S and Wong H S 1980 *Synthesis* **5** 409
18. Saeed A, Rama N H and Arfan M 2003 *J. Heterocycl. Chem.* **40** 519; Saeed A 2003 *Helv. Chim. Acta* **86** 377
19. Saeed A and Rama N H 1994 *J. Sci. I.R. Iran* **5** 173; Dean F M, Staunton J and Whalley W B 1959 *J. Chem. Soc.* 3004
20. Barash M and Osbond J M 1959 *J. Chem. Soc.* 2157; Miyake A, Tada N and Oka Y 1982 *J. Takeda Res. Lab*. **4**1 14
21. Hunter J H and Hogg J A 1949 *J. Am. Chem. Soc.* **71** 1922
22. Saeed A and Ashraf Z 2005 *Nat. Prod. Res*. (in press)
23. Seitz L E, Suling W J and Reynolds R C 2002 *J. Med. Chem.* **45** 5604
24. Kawase M, Sinhababu A K and Borchardt R T 1990 *Chem. Pharm Bull.* **38** 2939
25. Mizuno M, Hamada M, Ida T, Suhara M and Hashimotoa M 2002 *Z. Naturforschung.* **A57** 388