Highly Efficient Conversion of Benzoates to Alcohols with Sodium Borohydride in DME-MeOH

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Abstract: Methoxybenzoates were quantitatively reduced to the corresponding alcohols with sodium borohydride in a mixed solvent (DME-MeOH). The described method was applicable to a large scale synthesis.

Key words: sodium borohydride, ester, benzoate, alcohol, reduction

Recently, it became necessary to prepare 3-methoxy-4methylbenzylalcohol (1b) in large quantities. Although various synthetic procedures for methoxy-benzylalcohols are known in the literature¹, there are few practical methods that are amenable to a large scale synthesis. The conceptually simple way to 1b uses the reduction of 3methoxy-4-methylbenzoate (1a) which is achieved with LiAlH₄ as the most common reductant on a laboratory scale.1a,b However, LiAlH4 involves several drawbacks from the standpoint of large scale manufacturability. For example, it presents significant pyrophoric hazards and involves large amounts of generated wastes. In addition, significant amounts of material are often absorbed on the surface of the insoluble materials in the reaction, making the workup procedure tedious. As an alternative reagent, NaBH₄ is especially attractive since this reagent is inexpensive and readily available in large quantities. Although esters are essentially inert to NaBH₄² except for those containing participating neighboring groups,³ the reduction reaction has been achieved by addition of reagents which enhance the reduction power. For example, Santaniello et al. reported a novel reduction of benzoates in polyethylene glycol under mild conditions.⁴ Though the method is efficient enough to give materials in gram quantities, control of evolution of hydrogen gas during heating the reaction mixture is problematic on a large scale. The reduction of esters into the corresponding alcohols was performed in the presence of metals such as LiBr⁵ or AlCl₃,⁶ a large amount of ethanedithiol (10 equiv)⁷ or with a large excess of NaBH₄ (20 equiv) in MeOH.⁸ More conveniently, the same reactions are possible with NaBH₄ in THF-MeOH or tert-BuOH-MeOH as a mixed solvent, as reported by Soai et al.⁹ However, when directly applying this method, significant starting material remained unreacted in the case of methoxybenzoates, presumably due to an electron donating effect reducing the reactivity of the ester group. Herein, we wish to report a modified procedure for quantitatively converting methoxy-benzoates to the corresponding alcohols in a rapid manner.

As pointed out in a previous paper, the reactivity is deeply affected by the solvent used.¹⁰ Thus, we firstly evaluated several mixed solvent systems at a temperature of 50°C with a view to developing an improved reduction system. As can be seen from Table 1, best results were obtained by using DME (dimethoxyethane)-MeOH or DGM (di-glyme)-MeOH as solvent. From the standpoint of efficient isolation of **1b** on large scale, DME (bp 85°C) is more favorable than DGM (bp 162°C), since it is easer to remove.



Scheme

Fable	1	Reduction	of	1:	a with	NaBH₄	in	mixed	sol	ve	enta	1

Entry ^a	Solvent	Yield ^{b,c}
1	THF-MeOH	61 (39)
2	1,4-dioxane-MeOH	55 (45)
3	iPE-MeOH	40 (60)
4	DME-MeOH	82 (18)
5	DGM-MeOH	82 (18)

^aReaction conducted in the presence of 5 equiv of NaBH₄ at 50°C and MeOH added dropwise over 1h. ^b Yield determined by quantitative HPLC. ^c Yields in parentheses refer to percent of recovered starting material.

Next, we investigated the optimized reaction conditions in DME-MeOH allowing complete starting material consumption and found that a higher reaction temperature in the presence of excess amounts of NaBH₄ was crucial for good conversion (Table 2). The reaction was also slightly improved by having the time of addition of methanol into the reaction mixture prolonged (entry 5, 6). As a result of these findings, **1a** was quantitatively reduced. Extractive workup followed by concentration provided **1b** in excellent yield and quality.

Finally, we have extended this method to the reduction of several methoxybenzoates.¹¹ As shown in Table 3, the DME-MeOH method has advantages over the THF-

Table 2 Reduction of 1 a with NaBH₄ in DME-MeOH^a

	equiv of	Time (h)	
Entry ^a	NaBH₄	$A^b + B^c$	Yield ^{d,e}
1	1	1+1	23 (77)
2	2	1+1	61 (39)
3	3	1+1	86 (14)
4	4	1+1	94 (6)
5	5	1+1	98 (2)
6	5	2+1	100
7	6	1+1	100
8	7	1+1	100

^aReaction conducted at reflux temperature. ^b Time for addition of MeOH. ^c Time for additional stirring. ^d Yield determined by quantitative HPLC.

^eYields in parentheses refer to percent of recovered starting material.

MeOH method,⁹ allowing complete consumption of starting material. Based on these optimized reaction conditions, *o*-methoxy- and *m*-methoxybenzoate were quantitatively reduced to the corresponding alcohols (entry 4, 6). On the other hand, methyl *p*-methoxybenzoate required somewhat harsher conditions presumably due to the stronger electron donating effect of the para methoxy group. This problem was overcome by further slow addition of methanol into the reaction mixture (entry 9). In agreement with results in previous reports,^{4,7} *p*-hydroxybenzoate was not reduced to any significant degree by changing reaction conditions (entry 14).

In summary, we could demonstrate a new method for quantitative reduction of methoxybenzoates into the corresponding alcohols. Slow addition of methanol in the presence of an optimized amount of NaBH₄ in DME as solvent, maintaining the reaction mixture at reflux, led to a significant improvement in the yield and is crucial to success. This procedure should expand the range of alcohols accessible from benzoates with NaBH₄. The described methods were successfully scaled up in a pilot plant to give >27 Kg of **1b**.

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^a Reaction was conducted in the presence of 5 equiv of NaBH₄

by addition of MeOH for 1 h at reflux temperature. ^c Yield was

determined by quantitative HPLC. ^d Yields in parentheses refer to percent of recovered starting material. ^e Addition of MeOH for

2h.

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Table 3	Reduction	of ester ((1a-8a)) in mixed	solvent
				,	

Entry ^a	Substrate	Solvent	Yield (%) ^{c,d}
	MeQ		
1	Me-CO ₂ Me	THF-MeOH	78 (22)
2	1a	DME-MeOH	98 (2)
3	MeO ₂ C MeO	THF-MeOH	98 (2)
4	3a	DME-MeOH	100
5	MeO (4a)	THF-MeOH	97 (3)
6	4a	DME-MeOH	100
7	MeO	THF-MeOH	67 (31)
8	5a	DME-MeOH	79 (21)
9 ^e	5a	DME-MeOH	98 (2)
10	MeO MeO (6a)	THF-MeOH	99 (1)
11	6a	DME-MeOH	100
12	MeO MeO MeO (7a)	THF-MeOH	95 (5)
13	7a	DME-MeOH	100
14	HO-CO ₂ Me (8a)	DME-MeOH	< 5 (> 95)

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 - (11) General procedure for conversion of benzoates to alcohols. To a mixture of methyl methoxybenzoate (14 mmol) and NaBH₄ (2.65 g, 70 mmol) in DME (25 mL) was added MeOH (12.5 mL) dropwise over a period of 1 h maintaining the temperature of >70°C. After stirring for an additional 1 h, the reaction mixture was quenched with water and extracted with toluene. The separated aqueous layer was reextracted with toluene. The combined organic layers were washed successively with water and 10% brine. Removal of the solvent under reduced pressure gave product as a colorless liquid which was homogeneous by HPLC analysis.
- (12) 4-methyl-3-methoxybenzylalcohol (**1b**); ¹H NMR (200 MHz, CDCl₃) δ = 2.20 (s, 3H), 3.81 (s, 3H), 4.60 (s, 2H), 6.80 (d, 2H, *J*=7.7), 6.82 (s, 1H), 7.08 (d, 1H, *J*=7.3); IR (neat) 3400, 1259 cm⁻¹; MS (EI) *m*/z 153 (M+H)⁺.

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