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Solvent-Mediated Chemoselective Reduction of Aldehydes by Using Tributyltin Hydride in Methanol, Aqueous Organic Solvents, or Water : An Environmentally Benign Process

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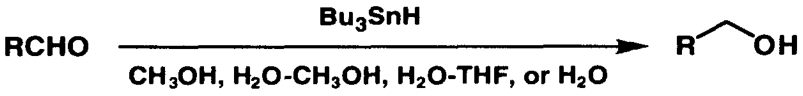
Abstract: Aldehydes are reduced chemoselectively by using tributyltin hydride in methanol, aqueous organic solvents, or water to provide the corresponding alcohols in high yields. No additional catalyst is required.

Key-words Reduction; Aldehydes; Tin and compounds; Solvents and solvent effects;

Trialkyltin hydrides are widely used in organic synthesis,[1] and although the reducing ability of the most commonly used tri-n-butyltin hydride (Bu_3SnH) is low, it acts as a reducing agent of organic halides in organic solvents under radical conditions using radical initiators such as AIBN and UV irradiation.[2] On the other hand, it is well-known that trialkyltin hydrides will only reduce aldehydes and ketones under condition of high pressure, or in the presence of Lewis acids or transition metal catalysts.[3] Shibata and Baba reported the reduction of aldehydes and ketones by Bu_3SnH-HMPA or Bu_3SnH-Bu_4NF combined system, where the combination with HMPA or Bu_4NF increased the reducing ability of Bu_3SnH toward the carbonyl group.[4] However, needless to say, a reduction of aldehydes and ketones by Bu_3SnH without an additive in protic solvent, aqeous organic solvents, or water is hitherto unknown, although a water soluble tin hydride reagent reduces alkyl halides in water under radical conditions.[5] The use of protic solvents, aqueous solvents, or water for organic reactions offers considerable advantages.[6] There is the practical convenience of not having to handle inflammable and anhydrous organic solvents. The tedious protection-deprotection processes for certain acidic-hydrogen containing functional groups can be simplified, which contributes to the overall synthetic efficiency. Water-soluble compounds, such as carbohydrates, can be used directly without the need for derivatization. Such processes greatly reduce the burden of solvent disposal and its impact upon the environment. Finally, the reaction conditions may be environmentally benign.

Herein, we wish to report the reduction of various aldehydes by using Bu_3SnH in CH_3OH, H_2O-CH_3OH, H_2O-THF, or H_2O without additional catalysts under mild conditions.[7]



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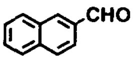
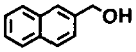
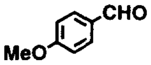
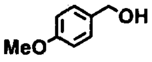
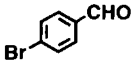
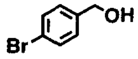
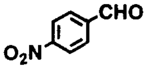
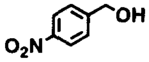
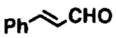
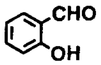
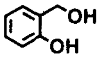
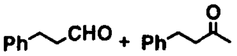
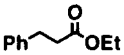
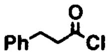
In the course of our continuous investigations on reactions carried out in protic solvents, aqueous organic solvents, or water,[8] first, we tried mixing Bu_3SnH with CH_3OH and confirmed that Bu_3SnH does not react with CH_3OH.[9]

Table 1 shows that 3-phenylpropanol is obtained in 99% yield at room temperature in CH_3OH (Entry 3), although Bu_3SnH hardly reduces 3-phenylpropanal in THF at 65 °C(Entry 2). Heating was effective in shortening the reaction time (Entry 4). Selected results with another various aldehydes by using CH_3OH as a solvent are also shown in Table 1. Not only aliphatic aldehydes but also aromatic aldehydes reacted smoothly to afford the corresponding alcohols in good yields. In the case of cinnamaldehyde, the 1,2-reduction proceeded preferentially to give cinnamyl alcohol (Entry 15). It is noteworthy that salicyl aldehyde was reduced in a quantitative yield without the protection of the hydroxyl group (Entry 16). The reduction of aldehydes took place cleanly even in the case of the substrate bearing another reducible functional group such as halogen and nitro groups (Entries 13 and 14), although it is known that organotin hydrides can also act as dehalogenating agents.[2] Although the reduction of 4-phenyl-2-butanone took place in 39 % yield in CH_3OH at reflux temperature, the selective reduction of 3-phenylpropanal was achieved in good yield even in the presence of 4-phenyl-2-butanone, where the ketone was recovered quantitatively (Entry 18). No reaction occurred with ethyl 3-phenylpropionate and 3-phenylpropionyl chloride (Entries 19 and 20). Noteworthy are the facts that reduction of 3-phenylpropanal took place cleanly even in H_2O-THF (4:1) or H_2O-CH_3OH (4:1) (Entries 5 and 6) and aliphatic and aromatic aldehydes reacted with Bu_3SnH in good yields even in water although the reaction mixture was heterogeneous (Entries 7, 9, 11, and 17).

It is interesting to note that CH_3OH and H_2O promote the reduction of aldehydes with Bu_3SnH. There was no IR[9] nor NMR spectroscopic evidence for a signaificant change of Bu_3SnH in refluxing CH_3OH and boiling H_2O. This observation suggests that the primary influence of the solvent is not to activate Bu_3SnH. The reduction of 3-phenylpropanal was performed in CD_3OD and monitored by ^1H NMR spectroscopy. This spectroscopic study revealed that 3-phenylpropanal existed primarily as the hemiacetal in CH_3OH.[10] We suggest that hydrogen bonding between the carbonyl group and CH_3OH or H_2O is the predominant activating effect, and a six-membered transition state involving CH_3OH or H_2O coordination to tin and hydrogen bonding to the carbonyl group can be invoked.[11] From a synthetic perspective, however, it is clear that the use of Bu_3SnH in CH_3OH, aqueous organic solvents, or H_2O provides an extremely mild, clean, convenient, and environmentally benign procedure for the chemoselective reduction of aldehydes.

A typical procedure for the reduction of 3-phenylpropanal in CH_3OH is described as follows: 3-phenylpropanal (0.134g, 1.1mmol) and Bu_3SnH (0.320g, 1.1mmol) were dissolved in CH_3OH (6ml). The mixture was stirred at room temperature for 23h, and quenched with aqueous 1M hydrochloric acid (10ml, M=mol/dm^3). The organic materials were extracted with diethyl ether (30ml × 3) and the combined organic layer was dried over $MgSO_4$. After evaporation of the solvents, the residue was purified by thin layer chromatography on silica gel (hexane:ethyl acetate = 4:1) followed by filtration through a short bed of silica gel (dichloromethane) to give 3-phenylpropanol (0.134g, 99% yield).

Table 1. Reduction of several aldehydes by using Bu_3SnH

Entry	RCHO	Solvent	Reaction Conditions	Product	Yield / %
1		neat	65 °C, 4 h		18
2	"	THF	65 °C, 4 h	"	9
3	"	CH_3OH	r.t., 23 h	"	99
4	"	CH_3OH	reflux, 4 h	"	100
5	"	H_2O-THF[a]	65 °C, 6 h	"	87
6	"	H_2O-CH_3OH[b]	65 °C, 6 h	"	84
7	"	H_2O	65 °C, 6 h	"	71
8	$CH_3(CH_2)_7CHO$	CH_3OH	reflux, 4 h	$CH_3(CH_2)_8OH$	100
9	"	H_2O	65 °C, 6 h	"	64
10		CH_3OH	reflux, 4 h		93
11	"	H_2O	65 °C, 6 h	"	85
12		CH_3OH	reflux, 4 h		76
13		CH_3OH	reflux, 4 h		100
14		CH_3OH	reflux, 4 h		100
15		CH_3OH	reflux, 4 h		90
16		CH_3OH	reflux, 4 h		100
17	"	H_2O	65 °C, 6 h	"	81
18		CH_3OH	reflux, 4 h		80
19		CH_3OH	65 °C, 5 h	—	0
20		CH_3OH	65 °C, 5 h	—	0

a) H_2O : THF = 4 : 1 (6 ml); b) H_2O : CH_3OH = 4 : 1 (6 ml)

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