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Chemoselective Reduction of Aldehydes in the Presence of Ketones with $NaBH_4$ in Polyethylene Glycol Dimethyl Ethers

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Abstract: Aldehydes and ketones were treated with $NaBH_4$ in polyethylene glycol dimethyl ethers (PEGDME) to give the corresponding alcohols in good yields. Chemoselective reduction of aldehydes in the presence of ketones was described.

Keywords: Reduction, aldehydes, sodium borohydrate, phase transfer catalysts

Reduction of aldehydes and ketones with $NaBH_4$ is a process that is widely used in organic synthesis.[1] $NaBH_4$ is too reactive to reduce aldehydes selectively in the presence of ketones under normal conditions. Selective reduction of aldehydes with $NaBH_4$ has been achieved at $-78°C$[2] or in the presence of thiol,[3] but these methods require cooling to very low temperatures or the addition of the other reagents.

Polyethylene glycol dimethyl ethers (PEGDME) have been frequently used for phase-transfer catalysts in a two-phase system of organic-aqueous

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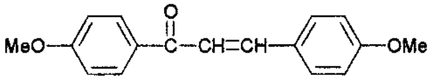
phase or organic-solid phase using organic solvents such as benzene or CH_2Cl_2,[4] however, there are few examples on the use of PEGDME as solvents for this purpose as far as we know.[5–7] We supposed that interesting reactivities might be expected in PEGDME.

In this article, we report that aldehydes and ketones react with $NaBH_4$ in PEGDME, which have an average molecular weight of 250 (PEG250DME), to give the corresponding alcohols in good to excellent yields. Furthermore, selective reduction of aldehydes in the presence of ketones at room temperature (rt) is described.

First, we examined the reactions of a variety of aldehydes with $NaBH_4$ in PEG250DME. The results are summarized in Table 1. In all cases, the reactions proceeded at room temperature within 0.5 h to give the corresponding alcohols in good yields (entries 1 and 3–6). On the other hand, reduction of ketones required heating at 60 or 100°C to afford the corresponding alcohols in good yields (entries 9–13). In the case of the reactive ketone, 4-*tert*-butylcyclohexanone (**6**), the longer reaction time (9 h) at room temperature was necessary (entry 7). The difference of reactivities between aldehydes and ketones makes chemoselective reduction of aldehydes possible. When this method was applied to the reduction of α,β-unsaturated ketones, small amounts of 1,4-addition products as well as 1,2-addition products were yielded at room temperature under high dilution conditions (entries 14, 16, and 17). When the reactions were conducted at normal concentrations (conditions of footnote *a* in Table 1), large amounts of polymeric materials were obtained together with the desired products. The ratios of 1,2- and 1,4-addition products were almost the same as those of the other reported methods.[8] When PEG500DME was employed as a solvent, the reactions proceeded more slowly and gave the same products in almost the same yields (entries 2, 8, and 15).

Next, we examined the chemoselective reduction of aldehydes in the presence of ketones in PEG250DME under high dilution conditions. The results are shown in Table 2. Indeed, aldehydes were reduced selectively in the presence of ketones in each case. The concentration of the solution is an important factor. When the reactions were conducted at normal concentrations, aldol-type dehydration products and small amounts of polymeric materials were obtained together with the reduced alcohols. For example, alcohols **18** (58%) and **25** (16%), α,β-unsaturated ketone **32** (14%), and small amounts of polymeric materials were obtained from the reaction of aldehyde **4** and ketone **11** with $NaBH_4$ in PEG250DME.



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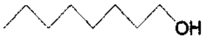
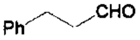
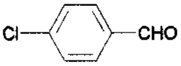
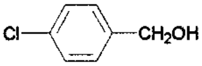
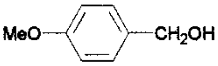
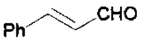
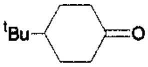
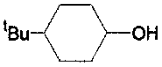
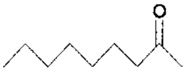
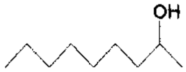
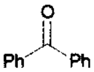
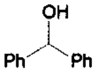
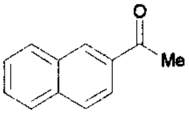
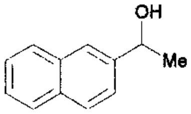
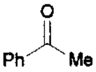
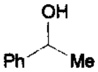
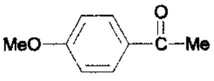
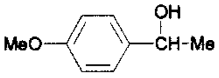
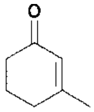
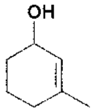
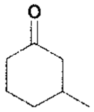
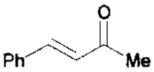
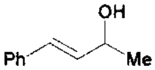
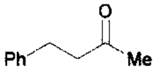
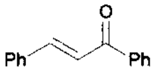
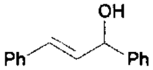
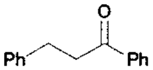
When the reduction with $NaBH_4$ was carried out in conventional protic solvents such as MeOH, EtOH, and H_2O, a large excess of the reducing

Table 1. Reduction of carbonyl compounds by $NaBH_4$ in PEGDME[a]

Entry	Substrate	T (°C)	Time (h)	Products (yield, %[b])
1	 **1**	rt	0.5	 **15** (98)
2[c]		rt	1.5	**15** (96)
3	 **2**	rt	0.25	 **16** (88)
4	 **3**	rt	0.25	 **17** (99)
5	 **4**	rt	0.5	 **18** (98)
6	 **5**	rt	0.5	 **19** (89)
7	 **6**	rt	9	 **20** (97) (cis:trans = 76:24)
8[c]		rt	18	**20** (97) (cis:trans = 76:26)
9	 **7**	60	8	 **21** (98)
10	 **8**	60	7	 **22** (95)
11	 **9**	60	5	 **23** (96)
12	 **10**	60	6	 **24** (90)

(*continued*)

Table 1. Continued

Entry	Substrate	T (°C)	Time (h)	Products (yield, %[b])	
13	 **11**	100	2	 **25** (93)	
14[d]	 **12**	rt	3	 **26** (71)	 **27** (18)
15[d]		rt	7	**26** (67)	**27** (21)
16[d]	 **13**	rt	3	 **28** (86)	 **29** (8)
17[d]	 **14**	rt	2	 **30** (88)	 **31** (8)

[a] Reagents and conditions: substrate 4.0 mmol, $NaBH_4$ 1.2 mmol, PEG250DME 1 mL.

[b] Isolated yields.

[c] PEG500DME was used.

[d] Solvent 20 mL.

Table 2. Reduction of aldehydes in the presence of ketones[a]

Entry	Aldehyde	Ketone	Time (h)	Products (yield/%[b])
1	**1**	**6**	2	**15** (94), **20** (6)
2	**1**	**7**	2	**15** (99), **21** (1)
3	**3**	**9**	1	**17** (88), **23** (4)
4	**3**	**10**	1	**17** (82), **24** (7)
5	**4**	**9**	2	**18** (77), **23** (10)
6	**4**	**11**	2	**18** (93), **25** (1)
7	**5**	**7**	2	**19** (89), **21** (2)
8	**5**	**8**	2	**19** (88), **22** (1)

[a] Reagents and conditions: aldehyde 4.0 mmol, ketone 4.0 mmol, $NaBH_4$ 1.2 mmol, PEG250DME 20 mL.

[b] Isolated yields.

agent was required because $NaBH_4$ gradually decomposes in these solvents. Under our conditions, 1.2 equiv. of $NaBH_4$ were sufficient to complete the reactions.

PEG250DME and PEG500DME can be readily removed by washing with water. If the products were solids, these can be isolated only by filtration (Table 1, entries 4, 5, 7, 8, 10, and 11). These PEG ethers possess high boiling points ($>300°C$), low chemical reactivities, high thermal stability at higher temperature, low vapor pressure (<0.01 hPa at 20°C), low toxicity (>2000 mg/kg), and low viscosity (PEG250DME, 7; PEG500DME, 25 mm^2/s at 20°C), which is much more lower than that of polyethylene glycol 400 (PEG400) (For some reactions including $NaBH_4$ reduction in PEG400 see[9]) (97–110 mm^2/s at 20°C).[10,11] PEGDME can dissolve most of polar and nonpolar substrates, especially for many inorganic salts to a large extent. Thus, PEGDME possesses many advantages as a solvent. PEG250DME and PEG500DME can be recovered quantitatively from the reaction mixture and used for the next experiment. Low vapor pressure and easy recovery of PEGDME indicate that PEGDME is also highly suitable as a solvent from an environmental point of view. In contrast, reactions using crown ethers or quaternary ammonium salts were conducted in highly volatile organic solvents such as benzene or CH_2Cl_2.[12]

In summary, we have demonstrated that PEG250DME was the efficient solvent for the reduction of carbonyl compounds with $NaBH_4$. Chemoselective reduction of aldehydes in the presence of ketones was achieved. Furthermore, PEGDME is inexpensive and possesses many attractive properties as a reaction medium.

EXPERIMENTAL

General

To a solution of **1** (512 mg, 4.0 mmol) in PEG250DME (1 mL) was added $NaBH_4$ (46 mg, 1.2 mmol). After stirring at room temperature for 0.5 h, a solution of 4 M NH_4Cl (10 mL) was added and the mixture was extracted with ether. The extracts were washed with water, dried over Na_2SO_4, and evaporated. The residue was chromatographed (hexane : acetone = 5 : 1) on silica gel to give **15** (511 mg, 98%) (Table 1, entry 1).

The combined aqueous layer was concentrated under reduced pressure to remove water. The residue was dissolved in ether and insoluble materials were removed by filtration. The filtrate was dried over Na_2SO_4 and evaporated to recover PEG250DME (97%), which was dried over MS4A before use. Recovered PEG250DME was used for the next experiment without further purification (**15**, 497 mg, 96%). It can be further purified by distillation under reduced pressure (123–215°C at 2 mmHg).

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