SHORT PAPER

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Mild and efficient method for reduction of aldehydes and ketones with $NaBH_4$ in the presence of Dowex1-x8†

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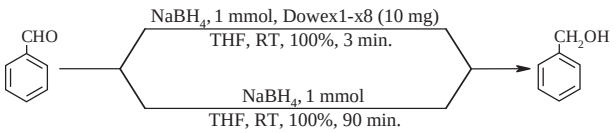
Various aldehydes and ketones are reduced efficiently to alcohols with $NaBH_4$/ Dowex1-x8.

Keywords: reduction, $NaBH_4$, aldehyde, ketone, Dowex1-x8

Reduction is one of the most fundamental and useful reactions in organic synthesis. Hydride transferring agents are the most versatile reagents used for this purposes.[1] Lithium aluminum hydride and sodium borohydride are commonly used providing simple and convenient routes for the reduction of many organic functional groups.[2,3] However, the use of these reducing agents has certain limitations. Lithium aluminum hydride is an exceedingly powerful reducing agent capable of reducing practically all-organic functional groups. Consequently, it is quite difficult to apply this reagent for the selective reduction of multifunctional molecules.[2] On the other hand, sodium borohydride is a milder reducing agent, primarily used for the reduction of reactive functional groups in protic solvents.[1,3]

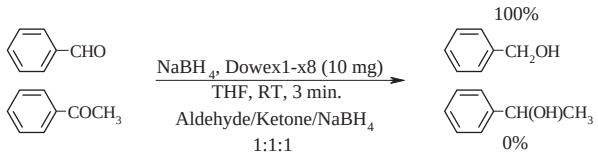
It is desirable to develop means for controlling the reducing power of such reagents. In fact, this has been achieved by different modifications, including hydride exchange,[4-6] cation exchange,[7-10] cation and anion exchange,[11-14] use of a combination of borohydrides with metal halides,[18] Lewis acids,[16] solid supports,[17] and mixed solvent systems.[18]

In continuation of our studies on the applications of Dowex1-x8, a highly basic anion exchange resin,[19] we decided to prepare a new polymeric reducing agent by replacing chlorine anions in Dowex1-x8 with BH_4^-. Unfortunately all attempts to achieve this failed. We have, however, found that the presence of Dowex1-x8 in the reaction mixture enhances the reducing power of $NaBH_4$ (Scheme 1). Herein we report the efficient reduction of aldehydes and ketones with $NaBH_4$ in the presence of Dowex1-x8.



Scheme 1

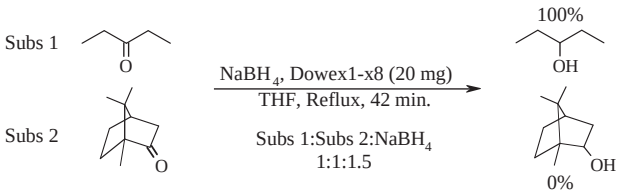
The $NaBH_4$/Dowex1-x8 system can reduce aldehydes and ketones in THF, in good to high yields (Tables 1 and 2). The selectivity of the reduction is temperature dependent. Aldehydes are reduced at room temperature in high yields (Table 1). In order to show the chemoselectivity of the system towards various carbonyl groups we performed the reduction of acetophenone in the presence of an equimolar amount of benzaldehyde with $NaBH_4$/Dowex1-x8 at room temperature. The selectivity ratio for the reduction of aldehyde with respect to ketone is 100% (Scheme 2). This is a general trend for the reduction of various aldehydes in the presence of ketones (Table 3).



Scheme 2

Investigation into the reduction of ketones with this system shows that their reductions can be carried out in refluxing THF (Table 2). These reactions need a higher molar ratio of $NaBH_4$ (1.5–8 mmols) and higher amounts of Dowex1-x8 (20 mg) in comparison with those required for the reduction of aldehydes ($NaBH_4$, 1–1.5 mmols; Dowex1-x8, 10 mg).

As shown in Table 2, less hindered ketones are reduced faster than those with steric hindrance. The actual role of Dowex1-x8 is not clear but it can be attributed to the bulk and polymeric nature of the resin, which induces a special steric selectivity in the reduction of ketones. This effect is also demonstrated by a competitive reaction between two ketones, which is indicated by the following reactions (Scheme 3). This is also a general trend for the reduction of ketones with this system (Table 3).



Scheme 3

In conclusion, we have shown that $NaBH_4$ in the presence of Dowex1-x8 easily and efficiently reduces aldehydes and ketones to their corresponding alcohols. Ease of procedure, mild reaction conditions, high yields of the products, chemoselectivity and ease of work-up make this system attractive and a useful addition to the present methods.

Experimental

General: Yields referred to isolated products. Reactions proceeded in THF at room temperature or at reflux. The products were characterised by a comparison with authentic samples (m.p. or b.p.), their ^{1}H-NMR, IR, MS spectra and elemental analysis.

Reduction of 4-chlorobenzaldehyde with $NaBH_4$ in the presence of Dowex1-x8: a typical procedure: To a solution of 4-chloro-benzaldehyde (0.14 g, l mmol) in THF (8 ml), Dowex1-x8 (10 mg) and $NaBH_4$, (0.037 g, 1 mmol) were added and the resulting mixture was stirred magnetically at room temperature for 9 min. The progress of the reaction was monitored by TLC. After completion of the reaction, methanol (3 ml) was added and the reaction mixture stirred for 15 min. The solvent was evaporated and the resulting crude material was purified by a silica gel column chromatography using CCl_4/Et_2O: 5/2 as eluent. Evaporation of the solvent afforded pure crystals of 4-chloro-benzyl alcohol (0.14 g, 99% yield, Table 1)(m.p.: 70–71°C; Lit.[20a] 70–72 °C).

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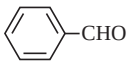
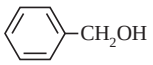
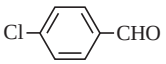
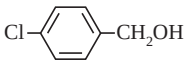
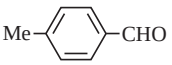
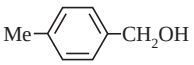
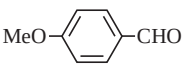
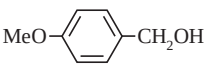
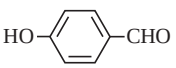
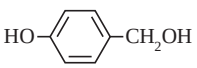
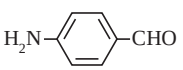
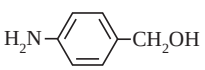
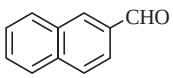
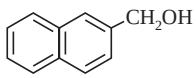
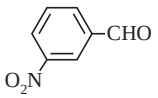
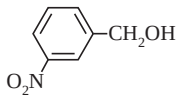
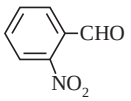
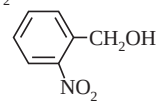
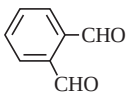
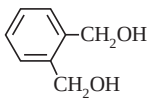
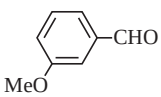
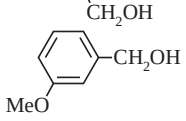
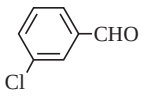
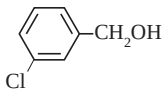
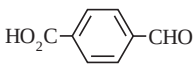
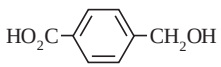
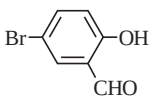
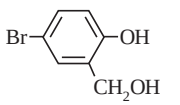
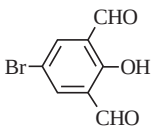
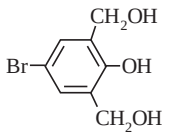
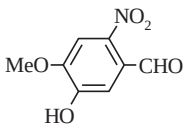
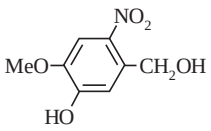
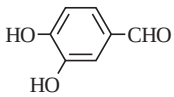
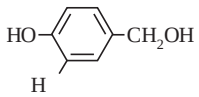
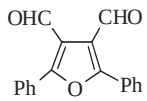
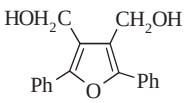
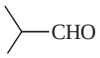
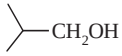
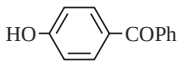
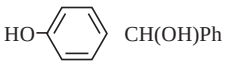
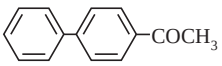
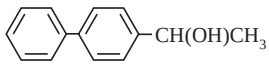
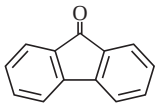
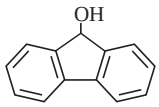
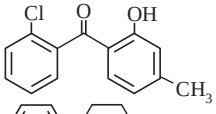
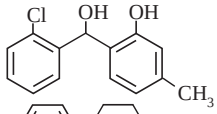
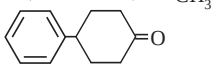
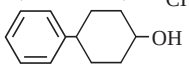
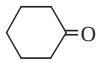
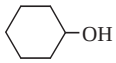
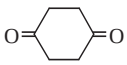
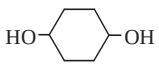
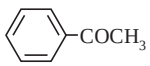
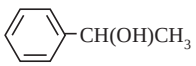
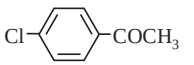
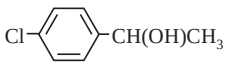
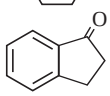
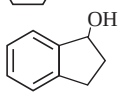
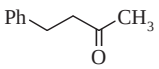
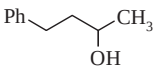
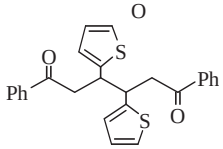
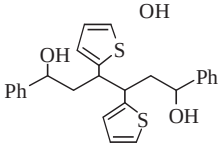
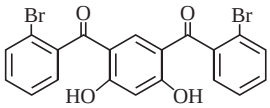
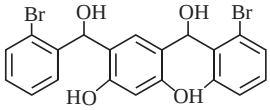
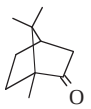
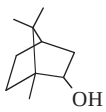
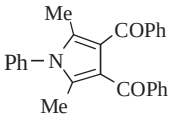
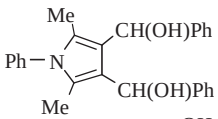
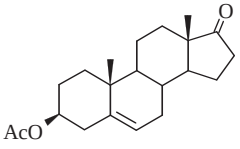
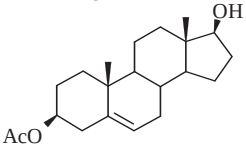
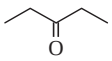
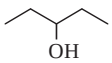
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1 Reduction of aldehydes to their alcohols with $NaBH_4$ in the presence of Dowex1-x8[a,b]

Entry	Substrate	Product (**a**)	Molar Ratio Subs./$NaBH_4$	Time/h	Yield/%[c]	M.p. or B.p./°C	
						Found	Reported
1			1:1	0.05	96	204–205	205[20a]
2			1:1	0.15	99	70–71	70–72[20a]
3			1:1.5	1.3	97	60–61	59–61[20a]
4			1:1.5	3	99	23–25	23–25[20a]
5			1:1.5	0.5	92	119–121	118-122[20a]
6			1:1	0.7	91	63–65	60–65[20a]
7			1:1	1	98	79–81	79–81[20a]
8			1:1	0.1	94	30–31	30–32[20a]
9			1:1	0.03	96	70–71	70–72[20a]
10			1:1	0.17	92	64–65	63–65[20a]
11			1:1	0.5	99	250/723	250/723[20a]
12			1:1	0.1	97	236	237[20a]
13			1:1	0.15	96	184–185	183–185[20a]
14			1:1	0.01	98	109–111	110–112[20a]
15			1:1	0.01	94	—	—
16			1:1	0.1	99	—	—
17			1:1	0.25	91	115–116	114–115[20b]
18			1:1.2	0.1	97	—	—
19			1:1	0.3	90	107–108	108[20a]

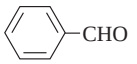
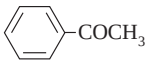
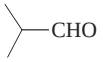
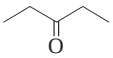
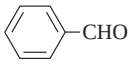
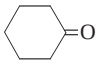
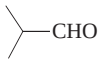
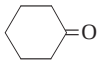
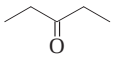
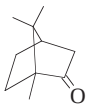
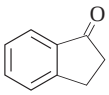
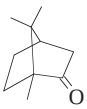
[a]All reactions were performed with 10mg of Dowex1-x8 in THF at room temperature. [b]Dowex1-x8 which was used as powdered form.
[c]Yields referred to isolated products.

Table 2 Reduction of ketones to their alcohols with $NaBH_4$ in the presence of Dowex1-x8[a,b]

Entry	Substrate	Product (**a**)	Molar Ratio Subs./$NaBH_4$	Time/h	Yield/%[c]	M.p. or B.p./°C	
						Found	Reported
1			1:3	3.2	98	66–67	65–67[20a]
2			1:3	5.5	96	—	—
3			1:3	2.8	99	—	—
4			1:2	1.8	94	154–155	153–154[20a]
5			1:2	0.1	91	—	—
6[d]			1:2	0.17	96	116–118	118–119[20b,c]
7			1:1.5	1.25	90	161	160–161[20a]
8			1:2	0.34	90	98–99	98–100[20a]
9			1:4	20	50	203/745	204/745[20a]
10			1:1.5	5	98	119/10	119/10[20a]
11			1:4	20	60	51–53	50–54[20a]
12			1:2	4.3	97	129/16	128–130/16[20d]
13			1:8	6	96	—	—
14			1:2	0.3	93	—	—
15[e]			1:4	20	60	205–207	206–208[20b,e]
16			1:4	5	98	—	—
17			1:4	7.5	97	148–149	147–148[20f]
18			1:1.5	0.7	90	114/749	115/749[20a]

[a]All reactions were performed with 20 mg of Dowex1-x8 in THF under reflux condition. [b]Dowex1-8 which was used as powdered form. [c]Yields referred to isolated products. [d]Ratio of *trans/cis* alcohols is 90:10 (by GLC analysis). [e]Ratio of exo/endo alcohols is 95:5 (by GLC analysis).

Table 3 Competitive reduction of aldehydes and ketones with $NaBH_4$ in the presence of Dowex1-x8[a]

Entry	Substrate 1	Substrate 2	Condition	Molar ratio Sub 1/Sub 2/ $NaBH_4$	Dowex1-x8 /mg	Time /min	Conv.1(%)[b]	Conv.2(%)[b]
1			RT	1:1:1	10	3	100	0
2			RT	1:1:1	10	15	100	5
3			RT	1:1:1	10	3	100	5
4			RT	1:1:1	10	18	100	4
5			Reflux	1:1:1	20	42	100	0
6			Reflux	1:1:1	20	20 hrs	50	10

[a]Dowex1-x8 which was used as powdered form. [b]Conversions referred to GLC or TLC monitoring.

Reduction of benzophenone with $NaBH_4$ in the presence of Dowex1-x8: a typical procedure: To a solution of benzophenone (0.182 g, l mmol) in THF (8 ml) was added $NaBH_4$ (0.075 g, 2 mmol) and Dowex1-x8 (20 mg). The reaction mixture was heated at reflux with stirring for 3.2 h. The progress of the reaction was monitored by TLC. After completion of the reaction, methanol (3 ml) was added and the reaction mixture stirred for 15 min. The solvent was evaporated and the resulting crude material was purified by a silica gel column chromatography using CCl_4/Et_2O: 5/2 as eluent. Evaporation of the solvent afforded pure crystals of diphenylmethanol (0.18 g, 98% yield, Table 2)(m.p.: 66–67 °C; Lit.[20a] 65–67 °C). Spectral data of some of the products are as follows:

15a: 4-Bromo-2,6-bis(hydroxymethyl) phenol: δ_H (60 MHz, $CDCl_3$): 7.3 (2H, s), 6.1 (1H, broad), 4.70 (4H, s), 2.6 (2H, broad). MS: *m/e* (70 eV), 234 (M^+). Elemental analysis for $C_8H_9BrO_3$, found: C, 41.26; H, 3.91; Br, 34.22; calculated: C, 41.23; H, 3.89; Br, 34.28%.

16a: 5-Hydroxy-4-methoxy-2-nitrobenzyl alcohol: δ_H (60 MHz, $CDCl_3$): 7.6 (1H, s), 7.1 (2H, broad), 4.8 (2H, s), 3.65 (3H, s), 2.7 (1H, broad). MS: *m/e* (70 eV): 199 (M^+). Elemental analysis for $C_8H_9NO_5$, found: C, 48.22; H, 4.58; N, 7.08; calculated: C, 48.25; H, 4.55; N, 7.03%.

18a: 3,4-Bis(hydroxymethyl)-2,5-diphenylfurane: δ_H (60 MHz, $CDCl_3$): 7.45–7.0 (10H, m), 4.45 (4H, s), 2.4 (2H, broad). MS: *m/e* (70 eV): 280 (M^+). Elemental analysis for $C_{18}H_{16}O_3$; found: C, 77.10; H, 5.72; calculated: C, 77.12; H, 5.75%.

2b: (4-Hydroxyphenyl)phenyl methanol: δ_H (60 MHz, $CDCl_3$): 7.15–6.7 (4H, m), 7.2 (5H, s), 5.7 (2H, broad), 2.50 (1H, broad). MS: *m/e* (70 eV): 200 (M^+). Elemental analysis for $C_{13}H_{12}O_2$, found: C, 77.92; H, 6.10; calculated: C, 77.98; H, 6.04%.

3b: 1-[(4-Phenyl)phenyl] ethanol: δ_H (60 MHz, $CDCl_3$): 7.6–7.25 (9H, m), 4.65 (1H, q), 2.4 (1H, s), 1.45 (3H, d). MS: *m/e* (70 eV): 198.10 (M^+). Elemental analysis for $C_{14}H_{14}O$; found: C, 84.85; H, 7.10; calculated: C, 84.81; H, 7.12%.

5b: (2-Chlorophenyl)(2-hydroxy-3-methylphenyl) methanol: δ_H (60 MHz, $CDCl_3$): 7.2–6.7 (7H, m), 5.65 (2H, broad), 2.45 (1H, broad), 2.3 (3H, s). MS: *m/e* (70 eV): 248 (M^+). Elemental analysis for $C_{14}H_{13}ClO_2$; found: C, 67.64; H, 5.24; Cl, 14.22; calculated: C, 67.61; H, 5.27; Cl, 14.26%.

13b: 1,6-Diphenyl-3,4-dithiophen-2-yl-hexane-1,6-diol: δ_H (60 MHz, $CDCl_3$): 7.1 (10H, s), 6.8–6.4 (6H, m), 4.6 (2H, t), 3.15 (2H, t), 2.9 (2H, broad), 2.15 (4H, m). MS: *m/e* (70 eV): 434 (M^+). Elemental analysis for $C_{26}H_{26}O_2S_2$; found: C, 71.86; H, 6.05; S, 14.76; calculated: C, 71.85; H, 6.03; S, 14.76%.

14b: 4,6-Bis[(2-bromophenyl)hydroxymethyl]benzene-1,3-diol: δ_H (60 MHz, $CDCl_3$): 7.4–7 (8H, m), 6.6 (1H, s), 6.1 (1H, s), 5.5 (2H, s), 5.1 (2H, broad), 2.8 (2H, broad). MS: *m/e* (70 eV): 481 (M^+). Elemental analysis for $C_{20}H_{16}Br_2O_4$; found: C, 50.07; H, 3.37; Br, 33.22; calculated: C, 50.03; H, 3.36; Br, 33.28%.

16b: 3,4-Bis(hydroxyphenylmethyl)-2,5-dimethyl-1-phenyl pyrrole: δ_H (60 MHz, $CDCl_3$): 7.35 (5H, s), 7.2 (10H, s), 5.65 (2H, s), 2.8 (2H, broad), 1.9 (6H, s). MS: *m/e* (70 eV): 383 (M^+). Elemental analysis for $C_{26}H_{25}NO_2$; found: C, 81.40; H, 6.59; N, 3.68; calculated: C, 81.43; H, 6.57; N, 3.65%.

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