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Sodium Borohydride-Amberlyst-15 (H^+): An Effective Reductor for Hindered and Unreactive Ketones in Aprotic Solvent.

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Abstract: The combination of sodium borohydride and amberlyst-15(H+) in tetrahydrofurane is a powerful reductor for unreactive ketones. The reduction is fast, high-yielding and the work-up is extremely simple. Ketals, silyl ethers and other organic functions are not disturbed during the reduction.
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As a part of a project addressed toward the synthesis of artificial receptors for nucleic bases we needed to reduce ketone **1** to alcohol **2** (Table 1). Attempts to undergo this reduction using $NaBH_4$ in methanol were fruitless even when a large excess of hydride was used. The pair $NaBH_4$-Amberlyst-15 (H^+) in THF proved to be an exceptionally active reductor system, able to undergo this transformation smoothly and in high yield. Although borohydride exchanged-ion resin (BER)[1] and acid-sodium borohydride systems[2] have been used for the reduction of a variety of organic functions, this is the first use of an exchanged-acid resin in the reduction of ketones by sodium borohydride in an aprotic solvent.

Here we report that this pair effects the reduction of unreactive and hindered ketones to the corresponding alcohols in THF rapidly, in excellent yield and with an extremely simple work-up, which makes it a reagent of practical synthetic value for use in aprotic solvents.

Table 1 shows a set of different ketones which were reduced with this reagent to the corresponding alcohols. Entries 1-4 are examples of unreactive ketones which are reduced in a time period between 10 min and $3^{1/2}$ h for the least reactive one. Entries 5-7 are examples of reactive ketones which are fully reduced within a few minutes. Ketals, silyl ethers, acetates, allylic acetates, allylic γ-lactones, carboxylic esters, halides and isolated double bonds are not disturbed during the reduction (entries 4-7). Cyclic ketones are reduced with a high level of stereoselectivity. The preference for axial attack of the hydride is observed in the case of unhindered ketones (entries 5, 6 and 8) whereas in the case of camphor the *endo* isomer is produced in a ratio of 3:1 with regard to the *exo* isomer. The extremely stable ketone **3** needs 10h to be reduced to the alcohol **4** in very low yield, which undergoes a slow acid-catalysed cyclization to give the ether **5**.[3]

Table 1.

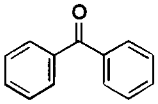
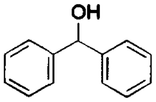
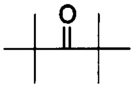
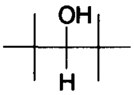
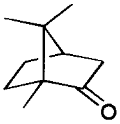
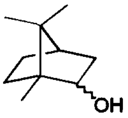
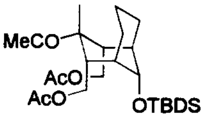
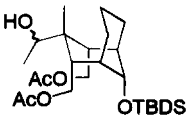
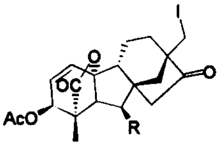
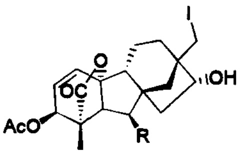
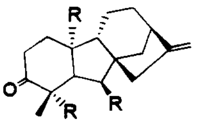
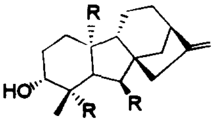
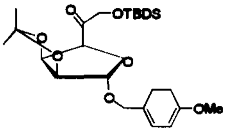
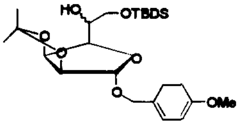
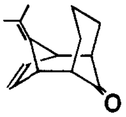
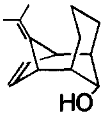
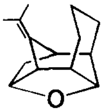
Entry	*Ketone*	*Alcohol*[a] (*% yield*)[b]	*Ketone mmol/ml*	*Amberlyst-15 g/mmol ketone*	*NaBH*$_4$ *eq*	*Time*
1		 (98)	0.1	1	5	10 min
2		 (98)	0.2	6	40	7 min
3		 endo/exo: 3/1 (80)	0.1	6	40	$3^{1/2}$ h
4	 **1**	 **2** (95)	0.02	3	20	30 min
5		 (95)	0.05	3	5	3 min
6	 R = CO$_2$Me	 R = CO$_2$Me (98)	0.05	3	5	4 min

Table 1 (Cont.)

Entry	*Ketone*	*Alcohol*	*Ketone mmol/ml*	*Amberlyst-15 g/mmol ketone*	*NaBH4 eq*	*Time*
7		 (98)	0.02	3	5	8 min
8		 ax/eq: 7/93 (80)	0.05	1	5	4 min
9	 3	  4 (10) 5 (20)	0.05	6	40	10 h

[a] All new compounds showed spectroscopic and analytical data consistent with the assigned structures. [b]Yields of isolated product.

The time of reduction strongly depends on the amount of resin used, 6g/mmol of ketone being the best proportion to achieve fast reductions in the case of the most reluctant ketones. The number of equivalents of $NaBH_4$ varies with regard to the ketone reactivity and a large excess has to be used with the most resistant ketones to complete the reduction before all the borohydride is destroyed by the resin. Table 2 shows the variations of the time of reduction of benzophenone under different combinations of the two reagents.

Table 2. [Benzophenone] = 0.1 M

Amberlyst-15 (gr/mmol ketone)	$NaBH_4$ (eq)	Time	Amberlyst-15 (gr/mmol ketone)	$NaBH_4$ (eq)	Time
0.2	2	18 h	0.7	3	50 min
"	16	18 h	0.9	"	30 min
0.4	2	4 h	1	"	20 min
"	20	4h	0.7	4	50 min
0.6	2	$2^{1/2}$ h	0.9	"	30 min
"	20	$2^{1/2}$ h	1	"	20 min
0.7	4	50 min	0.7	5	55 min
"	20	50 min	0.9	"	30 min
			1	"	20 min

Representative procedure: Ketone **1** (10 mg, 0.022 mmol) in dry tetrahydrofurane (1 ml) is stirred with amberlyst-15 (H^+) (66mg) and sodium borohydride (4,2 mg; 20 meq)) for 30 minutes. The reaction mixture is filtered through a pad of celite and the filtrate concentrated and flash chromatographed (hexanes - ethyl acetate: 7/3 v/v) to give the pure alcohol **2** (8,3 mg; 0.018 mmol).

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3. For the base-catalysed version in a very related system see: G. M. R. Tambo, R.A. Pfünd, C. Ganter, *Helv. Chim. Acta*, **1981**, 64, 813.

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