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BOROHYDRIDE REDUCTION OF $\Delta^{1,9}$ 2-OCTALONE : CATION INFLUENCE AND AMINE ADDITION EFFECTS

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Abstract:

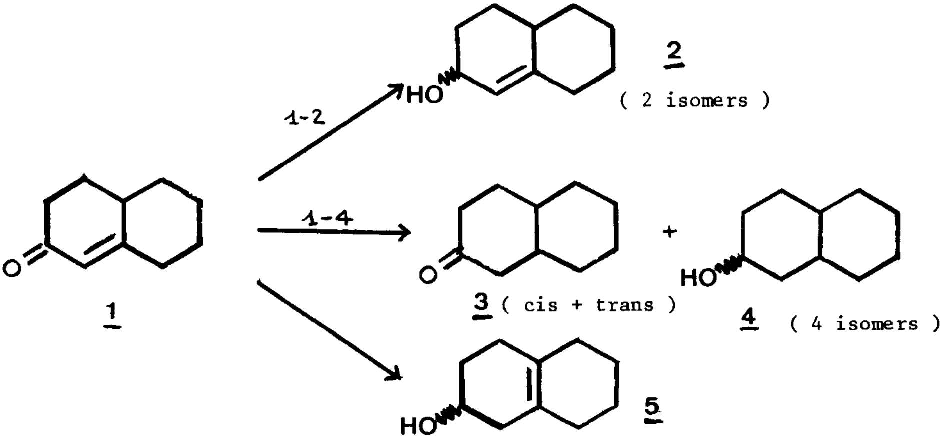
Proton removal of $\Delta^{1,9}$ 2-octalone occurs when reacted with NBu_4BH_4 in aprotic solvents while 1-2 reduction is important with $NaBH_4$ in THF. Both are inhibited when $NaBH_4$ reduction is performed in the presence of amines, leading thus to highly selective formation of saturated alcohols.

While $LiBH_4$ or $NaBH_4$ reduction of cyclic α-enones in ethereal or alcoholic solvents generally leads to a mixture of allylic and saturated alcohols (1-5),we have shown that NBu_4BH_4 reduction of 2- cyclohexenone or isophorone in toluene or T.H.F. induces a very selective formation of saturated alcohols(6). In order to generalize this study, we intend to report the reduction of a bicyclic α-enone such as $\Delta^{1,9}$ 2 octalone 1 in similar conditions.

RESULTS :

-NBu_4BH_4 reduction

Besides saturated alcohols 4 (7), occasionally accompanied by ketones 3 [1-4 reduction products] and by small amounts of allylic alcohols 2 [1-2 reduction products] , we detected noticeable amounts of alcohols 5 in the reaction mixture.



The most significant results are given in Table I

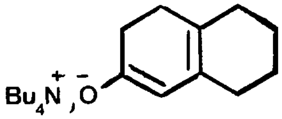
- TABLE I -

NBu_4BH_4 reductions of enone 1 at 50°C in 0.05M solutions (NBu_4BH_4/enone = 1:1)[a)]

solvent	% 2	% 4	% 5	$t_{1/2}$ (mn)
Toluene	2	48	50	45
THF	2	60	38	75
HMPA	2	55	43	120

a) analysis are carried out by glpc and ^1H NMR

Alcohol 5 formation can be interpreted by a prior proton removal of enone 1 leading to enolate 6 (8) which can be further reduced (11). Up to our knowledge, α-enone enolization induced by BH_4^- was not yet described in the literature.



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The competition between enolization and nucleophilic addition is known to be strongly affected by the nature of the associated counterion (14,15,16) : small cations, according to their strong complexing power towards carbonyl compounds, lead essentially to nucleophilic addition whereas larger ones lead rather to enolization. Consequently,we intended to suppress the formation of unsaturated alcohol 5 [due to the basic behaviour of BH_4^- in NBu_4BH_4] by performing the reduction with $NaBH_4$, as $LiBH_4$ is known to give mainly 1-2 reduction products - i.e. allylic alcohols 2 (4,5).

- $NaBH_4$ reduction (table II)

- TABLE II -

$NaBH_4$ reduction of enone 1 at 50°C in 0.05M solutions ($NaBH_4$ / enone = 1:1)

	%2	%4	%5	yield %	time (mn)
THF	58	42	0	30	30
DME	55	45	0	95	30
Tetraglyme	41	59	0	98	60
HMPA	6	51	43	98	180

We notice that the formation of 5 is effectively suppressed when the reduction of 1 is performed with $NaBH_4$ (except in HMPA where $NaBH_4$ or NBu_4BH_4 give very close results) ;

however, the amount of allylic alcohols 2 is greatly increased in line with previous results (6).

The large amount of allylic alcohols 2 is connected to a noticeable interaction between the α-enone and Na^+ (17) ; in order to improve the yield in saturated alcohols 4 [1-4 reduction], it is necessary to weaken this interaction. For this purpose, we tested the influence of the addition of various Na^+ complexing agents. They had to complex Na^+ in such an extend that the Na^+-enone interaction will be weak enough in order to minimize the 1-2 reduction, but still strong enough escape enolization.

- Na^+ complexing agents addition effect :

The reduction of 2-octalone 1 was performed with solutions of $NaBH_4$ in THF after addition of various Na^+ complexing agents. Results are given in table III as well as those of two experiments performed in the same conditions with NBu_4BH_4.

- TABLE III -

Effect of the addition of cation complexing agents to 0.05M $M^+BH_4^-$ solutions in THF at 50°C.

Run N°			eq.	%2	%4	%5	reaction time(h)	yield[a)] %
1	$NaBH_4$	–		58	42	0	5	⩾ 98
2		tetraglyme	2,5	52	48	0	1	93
3		crown ether[b)]	1,2	34	66	0	1	⩾ 98
4		cryptand [2,2,1]	1,2	3	72	25	2	⩾ 98
5			1,2	<1	>99	0	4	86
6		TMEDA	2,5	<1	>99	0	4	75
7		NEt_3	1 or 5	7	87	6	4	92
8		pyridine	1	4	91	5	3	82
9	NBu_4BH_4	–		2	60	38	3	⩾ 98
10		NEt_3	1	1	85	14	1	76

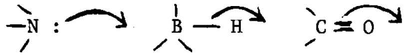
a) yields are quantitative when extending the reaction time.

b) dicyclohexyl-18 crown-6.

The oxygenated complexing agents are not strong enough and their addition does not hinder the formation of a great amount of allylic alcohols 2 (runs 2,3). As cryptand [2,2,1] is a too strong complexing agent of the cation, it leads to a noticeable proton removal (25% alcohol 5, run 4). On the other hand, amines addition in $NaBH_4$ reduction (runs 5 to 8), especially TMEDA (run 6), leads very selectively to the formation of saturated alcohols 4. This effect of amines addition on the regioselectivity of α-enones reduction has already been noticed (1) ; in our case, it is accompanied by a suppression of the enolization process.

The effect of amines addition is twofold :

1) BH_4^- nucleophilicity enhancement, previously shown by BROWN and al (18) and by JONES and WISE (19) : effectively, NEt_3 addition increases the rate of 1 reduction by NBu_4BH_4 ; this effect is coupled with a decrease of the enolization process (runs 9,10).



2) Na^+ complexation, the consequence of which being a decrease of 1-2 reduction process ; this effect is coupled with a decrease of the electrophilic reactivity of the carbonyl compound.

The total rate decrease induced by amines addition (runs 1,5 to 8) in $NaBH_4$ reduction points out that the dominant kinetic effect is the weakening of Na^+ electrophilic assistance which prevails over BH_4^- nucleophilicity enhancement.

In conclusion, TMEDA addition in $NaBH_4$ reduction of $\Delta^{1,9}$ 2 octalone in THF allows the selective obtention of saturated alcohols 4 at the expense of unsaturated alcohols 2 or 5.

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(8) Proton abstraction on the cycle junction has been described in proton removal of enone 1 by strong bases ; the so-formed enolate is the thermodynamically stable one (9,10).

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