MONTMORILLONITE SUPPORTED (-)N-DODECYL-N-METHYL EPHEDRENIUM BOROHYDRIDE : AN EFFICIENT REDUCING AGENT

A Sarkar* and B R Rao

Deptt. of Appl. Chemistry, Indian School of Mines, Dhanbad-826004(INDIA)

Abstract : The clay supported reagent reduces ketones under phase transfer conditions efficiently. A two fold activation of the carbonyl group – one by the Lewis acid sites on clay and the other by the β -hydroxy group of ephedrenium moiety, ensures facile reductions -maintaining a fair degree of stereoselectivity in reducing some of the cyclic ketones. Asymmetric inductions of 1-9.7% were observed in case of some prochiral ketones.

Recently¹ we have described the use of montmorillonite supported borohydride for reduction of ketones under phase transfer conditions. By exploiting two important properties of this clay, i.e., limited anion exchange capacity and expandable interlamellar space² - the reagent was prepared and utilised with a fair degree of success.

This paper reports the use of (-) N-dodecyl - N - methyl ephedrenium borohydride in enhancing the activation of carbonyl group by montmorillonite clay towards reduction.

(-) N-dodecyl - N - methyl ephedrenium salt has been used as specific catalyst for the borohydride reduction of carbonyl compounds under phase-transfer conditions³. It has also been used as supported catalyst after being immobilised on silica gel⁴. However, these procedures may have some distinct disadvantages in recovery of catalyst and immobilisation (use of expensive reagent). The reagent system prepared by us is advantageous for several reasons: (1) it has all the advantages of supported reactions⁵ (2) conservation of the expensive catalyst within the clay lattice (3) faster reaction rate of reductions (4) high degree of stereoselectivity in the reduction of some cyclic ketones and (5) possibility of activation by the clay support towards asymmetric induction in the reduction of prochiral ketones.

The reagent system was prepared by stirring sodium montmorillonite (10 g) with a solution of the substituted ephedrenium borohydride [prepared in situ from the quaternary bromide (2.575 g) and sodium borohydride (0.185 g)] in THF (25 ml) for 12 h. The absorbed salt was washed with THF (10 ml) and dried under vacuo. The borohydride equivalent, determined by hydrogen displacement on treatment of ca (0.3 g) of the dry reagent with dil. acid was found to be 0.36 meq/g. Three cyclic, namely 4-t-butylcyclohexanone, 3,3,5-trimethyl cyclohexanone, camphor and five acylic ketones - a few of them prochiral, were reduced using the above mentioned reagent in two different solvents namely benzene and dichloromethane. To check the role of polar protic solvent on the stereochemistry of reductions, the cyclic ketones were also reduced in ethanol.

To determine the effect of increased Lewis acid sites present in clay, on the stereochemical outcome of reductions of the hindered and unhindered cyclic ketones, the amount of clay used as support was varied keeping the amount of ammonium borohydride constant.

A perusal of table 1 reveals-the reductions of the ketones are quite facile, accompanied with a fair degree of stereoselectivity in some cases. The rates of reductions are quite fast, particularly in polar solvents like dichloromethane and ethanol. In non polar solvent like benzene, sodium borohydride normally reduces ketones either slowly or not at all⁶. However use of the present system increases the rate of reductions substantially. The faster rates of reductions may be attributed to the same reason as proposed by other workers³ i.e., a possible activation of the carbonyl group towards borohydride attack through hydrogen bonding with the β -hydroxy group present in the ephedrenium salt. However use of an inert support like montmorillonite (though advantageous for some reasons), introduces elements of heterogeneity in the interactions between the substrates for reductions and the reducing species. To some extent however this has been overcome by using quaternary salt with long chain hydrocarbon, thereby providing increased hydrocarbon solubility to the borohydride.

As far as the stereochemical outcome of reductions is concerned, the present reagent system, is quite stereoselective. The unhindered ketone $4-\underline{t}$ -butylcyclohexanone is reduced with a preponderance of $\underline{trans} - 4-\underline{t}$ -butylcyclohexanol over the cis. Thus 93.8, 92.4 and 89.9 percent of the trans alcohol are formed in reduction using benzene, dichloromethane and ethanol as solvents. In case of 3,3,5- trimethylcyclohexanone the percentages of cis isomer formed were 50.9 in benzene, 55.9 in dichloromethane and 45.7 in ethanol. Camphor was reduced with the exo isomer predominating over the endo. However, the percentages of endo isomer formed are higher than those obtained - in lithium aluminium/sodium borohydride reductions.

The preponderance of an axial attack by the BH_{4}^{-} ion is rationalised on the basis of cyclic transition state, where the carbonyl group is activated by an initial complexation with Lewis acid sites on clay¹. (+)



In our earlier communication¹, we have mentioned about this type of complexation. This was well substantiated by our observation that the \mathcal{V} CO's in I.R. shift to lower wavenumbers when the ketones are absorbed on montmorillonite clay. Similar observations have been made in the present investigations (note 8). Thus, the \mathcal{V} CO for 4-t-butyl-cyclohexanone was shifted from an initial 1728.9 (Free, uncomplexed in KBr) to 1639 cm⁻¹, when the ketone was absorbed on (-)N-dodecyl-N-methyl ephedrenium salt exchanged montmorillonite. Under similar condition, the shift was 130.6 cm⁻¹ with TEBAC

exchanged clay^{1} . The stereochemical course of reduction of 4-<u>t</u>-butylcyclohexanone is very nicely explained by these observations. Since the effective bulk of ephedrenium moiety with it's long dodecyl chain is enough to cause scrambling of the interlamellar space within the clay, two things can happen (a) complexation of the carbonyl group with the Lewis acid sites may be less strong (b) the number of Lewis acid sites available may be less.



This proposition is backed by another interesting observation-with increasing amount of clay used for preparing the reagent system the percentage of axial attack by BH_4 increased further in case of 4-t-butylcyclohexanone (from an initial value of 91.8 to 97.9%- table 1). However, the increase in the formation of equatorial alcohol became less prominent after addition of a fixed amount of clay. Moreover, exclusive formation of trans-alcohol (equatorial OH) never took place by increasing the amount of clay.

	Entry		Benzene			Ethanol	<u> </u>	Dichloromethane		
		Time (h)	Yield (%)	%7 Stable Alcohol	Time (h)	Yield (%)	% Stable 7 Alcohol	(h)	(%)	% Stable Alcohol
1.	4- <u>t</u> -butyl cyclohexa- none	4.5	95-98	97.9;97.3 97.2;94.2 93.8;92.5 91.8	1.5	90	89.9	2.5	97	92.4
2.	3,3,5 - trimethyl cyclohexa- none	16	95	50.9	6	80-86	50.8;50.2 50.0;48.7 45.7;44.8 43.2	8	94	55.9
3.	Camphor	72	50	21.2	72	45	14.5	72	48	18
4.	Ethyl methyl ketone	4	98	-	-	-	-	2.5	91.4	-
5.	Isobutyl methyl ketone	6	92	-	-	-	-	3,5	90	-
6.	Acetophenone	9	62	-	-	-	-	5	70	-
7.	Benzophenone	14	80	-	-	-	-	8	86	-
8.	Fluorenone	15	88	-	-	-	-	8.5	82	-
9.	Cyclohexa- none	2.5	95	-	-	-	-	1.5	90	-

Table - 1 : Reductions of Ketones with Reagent System

In case of 3,3,5-trimethylcyclohexanone and camphor which are highly hindered as far as axial attack by BH_4^- is concerned, there is a propensity of the species to attack from axial side. Thus in case of 3,3,5-trimethylcyclohexanone, the attack took place more from axial side (55.9,50.9) though the C-3 axial methyl impedes such an attack. In case of camphor, preponderance of endo isomer cannot be expected; however the amounts of endo alcohol formed is higher than those obtained with lithium aluminium hydride/sodium borohydride.

Another interesting observation is that the reductions of some of the ketones like acetophenone, isobutyl methyl ketone, were accompanied by small amounts of asymmetric induction (1.92% -9.07%). Under normal phase transfer condition of reduction using (-) N-dodecyl-N-methyl ephedrenium borohydride, no asymmetric induction was reported for acetophenone³. Use of clay as support probably imparts to the chiral catalyst an asymmetric environment. This is indicated by another interesting observation, i.e. asymmetric induction of 1.19% and 1.46% were observed when acetophenone and ethyl methyl ketone were reduced using sodium montmorillonite as support for the ketones (external addition of sodium borohydride). The observation is rather intriguing and investigations are presently underway in this laboratory to find out, whether the montmorillonite clay itself has some elements of asymmetry or not (possibly due to deformation of the clay lattice).

	Entry	Reagent System	[«] ^{28°}	Asymmetric Induction (%)	
1. 2.	Acetophenone	Sodium Clay Clay-ephedrenium borohydride	-0.46 +3.14	1.09 7.47	
3.	Ethyl methyl ketone	Sodium Clay	-0.19	1.46	
4.	U	Clay ephedrenium borohydride	+1.18	9.07	
5.	Isobutyl methyl ketone	Sodium Clay	-0.01	0.07	
6.	n	Clay-ephedrenium borohydride	+0.25	1.92	

Table - 2 : Asymmetric induction (%) in the reduction of prochirat	Table - 2	n of prochiral ketones
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References and Notes :

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7. The values correspond to the p.c. of stable alcohol obtained in reductions using reagents prepared by varying the amount of clay in the order 3.0,2.5,2.0,1.5,1.0,0.5 and 0.25 g respectively. The amount of borohydride, ephedrenium salt and ketones were 0.25 m mol in all the cases.

8. The shifts for v CO in IR for the ketones (adsorbed on clay ephedrenium borohydride) were(i) 89.9 (ii) 74.6 and 107.0 cm⁻¹ for entry 1,2,3 compared to the v CO for free ketones (KBr).

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