



Effect of Reaction Conditions in the Reduction of Carbonyl Group using Polymer Anchored Ethylenediamine–Borane Reducing Agent

K Rajasree, EP Aparna and KS Devaky*

School of Chemical Sciences, Mahatma Gandhi University, Kottayam, Kerala, India

ABSTRACT

Polymer bound ethylenediamine-borane (EDA-borane) reagent was prepared from 2% crosslinked chloromethylpolystyrene resins with polar flexible 1,6-hexanediol diacrylate (HDODA) and nonpolar rigid divinylbenzene (DVB) cross links. A number of aldehydes and ketones were reduced under mild conditions. Investigations on the effect of reaction conditions such as presence of acid catalyst, temperature and solvent medium on the rate of reduction using the polymer bound reducing reagent were carried out. Reduction reactions of various aldehydes and ketones using the polymer bound EDA-borane reagent in the presence of acetic acid exhibited significant rate enhancement. The effect of temperature was also studied and increased reaction rates were observed at elevated temperatures. The nature of solvent was also found to play a significant role on the reactivity of the polymer-anchored amine-borane functionality. Chlorinated solvents like DCM and chloroform were found to be most compatible solvents for the reduction reactions using the polymer-bound reducing agent. The reduction of 2-nitrobenzaldehyde was taken as the model reaction for the present studies and the reaction was followed quantitatively by spectrophotometry.

Keywords: Polymer-bound amine-borane reagent; Reduction; Acid catalyst; Temperature; solvent

INTRODUCTION

Polymer supported reagents find immense applications in the fields of synthetic organic chemistry and catalysis [1-3]. Even though there are many reports on polymer bound oxidizing reagents, only very few polymer supported reducing agents have been reported [4,5]. Preparation of polymer supported ethylenediamine-borane reagent and its application reduction of carbonyl compounds have been reported earlier [6]. The polymeric reducing agent was found to be efficient in the reduction of aldehydes under very mild reaction conditions. Further the reagent selectively reduces aldehydes in the presence of other carbonyl compounds like ketones. As a continuation to the preliminary studies, investigations were carried out to optimize the polymeric characteristics and reaction conditions to enhance the efficiency of the polymeric reagent. The present paper focuses on the influence of reaction conditions like acid catalyst, temperature and solvent on the reactivity of polymer supported ethylenediamine-borane reagent.

EXPERIMENTAL SECTION

Styrene was purchased from Fluka, AG (Buchs, Switzerland). Poly(vinyl alcohol) (PVA, molecular weight 70,000-1,00,000) and 1,6-hexanediol diacrylate (HDODA) were supplied by the Aldrich Chemical Co.(Milwaukee, WI). Ethylenediamine (EDA) (Merck), sodium borohydride (Spectrochem), benzaldehyde, acetophenone, benzophenone, 2-nitrobenzaldehyde, 4-cyanobenzaldehyde, and 4-methoxybenzaldehyde (Qualigens, Mumbai) were used as received. Analar grade solvents were purified according to literature procedures. Spectrophotometric analyses were done by Shimadzu UV-160A spectrophotometer.

Preparation of polymer bound EDA-borane reagent: General procedure

Polystyrene crosslinked with 2% HDODA was prepared by suspension polymerization using benzoyl peroxide as the initiator and 1% aqueous solution of polyvinyl alcohol as the stabilizing agent. The mixture containing styrene, HDODA, diluent toluene, benzoyl peroxide was suspended in 1% aqueous solution of PVA and the suspension was stirred mechanically at a temperature of 85^oC. The dry resin was swollen in dichloromethane and refluxed with chloromethyl methyl ether in the presence of 1M ZnCl₂ in dry THF at 50^o C. The chloromethylated resin was treated with excess ethylenediamine in the presence of pyridine. The aminated resin was shaken with HCl for 6 h and the amine hydrochloride resin was shaken with 2 molar excess of sodium borohydride for 5 h. The polymer bound EDA-borane (**P1**) formed was filtered and dried. Following the same procedure EDA-borane (**P2**) was prepared using 2% DVB crosslinked polystyrene resin. The polymer-bound borane reagents were characterized by IR spectroscopy. The IR spectra showed B-H stretching at 2390 cm⁻¹ and B-N stretching at 1170 cm⁻¹.

Reduction reactions using polymer bound EDA-borane reagent: General procedure

In a typical reaction 2-nitrobenzaldehyde (20 mg) dissolved in DCM (2mL) was added to polymer bound EDA-borane reagent (100 mg), swollen in DCM (10mL). To this mixture was added glacial acetic acid (0.1 mL) in drops and the reaction mixture was stirred. The progress of the reaction was monitored by TLC and the time for complete reduction was noted as 50 min. After completion of the reaction, the spent polymer was filtered off, washed and the combined filtrate and washings were evaporated. The product 2-nitrobenzylalcohol obtained was characterized by comparing with authentic sample. Benzaldehyde, 4-methoxybenzaldehyde, 4-cyanobenzaldehyde, acetophenone and benzophenone were reduced with the polymeric EDA-borane reagents. The reduction reactions were carried out in the absence of acetic acid and the time for complete reduction was noted in each case. The results are summarized in Table 1.

Temperature studies

Polymer bound reagent (P1, 100 mg) was swelled in toluene in (10 mL) and 2-nitrobenzaldehyde (20 mg) added to the swollen polymer. The mixture was shaken at room temperature (27^oC) and the reaction was followed by TLC. Time for complete reduction was noted as 3h. The reaction was repeated at temperatures 37, 47, 57 and 67^oC and time for complete reduction was noted in each case by TLC.

Solvent studies

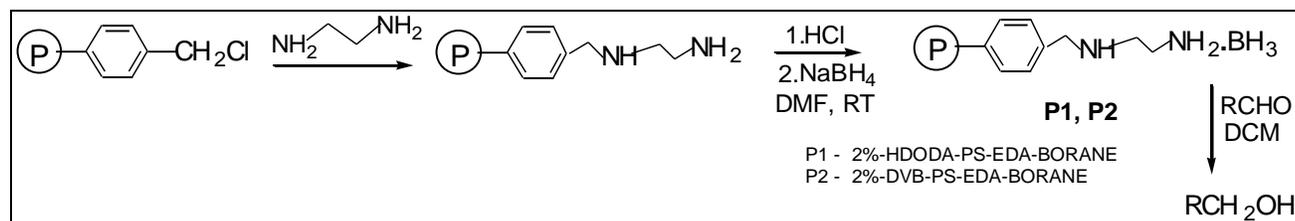
Polymer bound EDA-borane reagent (2a, 100 mg) was suspended in DCM (5 mL). To the suspension, a solution of 2-nitrobenzaldehyde (20 mg) in DCM was added and the reaction mixture was shaken at room temperature (27^oC). After 3h, 0.1 mL of the solution was withdrawn and diluted to 5 mL with methanol. The absorbance at 253 nm was noted. The percentage conversion of 2-nitrobenzaldehyde to 2-nitrobenzyl alcohol was calculated from the standard curve. The reaction was repeated in different solvents such as toluene, THF, chloroform, DMF and NMP under identical conditions.

RESULTS AND DISCUSSION**Preparation of polymer-bound EDA-borane reagent**

Polymer bound ethylenediamine-borane reagents P1 and P2 were prepared from 2% cross linked polystyrene resins with polar flexible 1,6-hexanediol diacrylate (HDODA) and nonpolar rigid divinylbenzene (DVB) crosslinks by suspension polymerization technique[6]. The resins were chloromethylated using chloromethyl methyl ether following Friedel-Crafts method [7]. The polymer bound EDA-borane reagent was prepared from the chloromethyl resin using a series of polymer analogous reactions- amination, conversion to amine hydrochloride and reaction with sodium borohydride (Scheme 1). The reagents were characterized by IR spectroscopic method. The capacity of the polymeric reagents P1 and P2 were found to be 3.70 and 2.85 mmol/g respectively.

Reduction reactions

Various aldehydes and ketones were reduced by the reagents. The reaction was carried out in DCM at room temperature and two molar excess of the reagent was used. The progress of the reaction was followed by TLC. The kinetics of the reduction reaction was monitored spectrophotometrically.



Scheme 1: Preparation of polymer-bound EDA-Borane reagent and reduction of aldehydes using the reagent

Effect of acid catalyst

In the reduction of carbonyl compounds with low molecular weight amine-borane reagents, increased reaction rate in the presence of Lewis acid has been reported [8]. Significant rate enhancement was reported in the reduction of carbonyl compounds with polyvinylpyridine-borane in the presence of Lewis acid catalyst BF_3 -ether is also reported [9]. Brown *et al* have reported that the reduction of cyclohexanone with low molecular weight amine-borane reagent in the presence of acetic acid proceeded at faster rates [10].

The amine-borane reagents were found to be stable and less sensitive to acetic acid. The effect of acid catalyst on the reduction of aldehydes and ketones with polymer bound EDA-borane reagent was investigated by carrying out the reaction in the presence of acetic acid after swelling the polymeric reagent in dichloromethane. The progress of the reaction was monitored by TLC. In the presence of acetic acid, the reduction of 2-nitrobenzaldehyde was completed within 50 min. whereas in the absence of acid catalyst time for complete reduction was found to be 3 h. Similar results were observed in the reduction of other aldehydes in the presence of acetic acid. The reduction of ketones with polymer bound EDA-borane reagent was carried out under the same reaction conditions. Ketones were reduced with increased rate in the presence of acid catalyst but at lower rates when compared to aldehydes, which is probably due to the higher electrophilic nature of aldehydes. In the reduction of acetophenone with PS-HDODA bound EDA-borane (P1), only 30% of the substrate was reduced after 20 h in the absence of catalyst. But 55% conversion was found after 20 h in the presence of acid catalyst and complete reduction was not observed even after 30 h. In the reduction of benzophenone 10% conversion was obtained after 30 h in the absence of acid and 20% reduction was observed in the presence of acid. With PS-DVB bound EDA-borane (P2) the reaction periods were found to be increased.

Table 1: Comparison of reduction in the presence and absence of acid with HDODA-PS bound ethylenediamine-borane reagent (P1) and DVB-PS bound EDA-borane reagent (P2)

Substrates	P1		P2	
	reaction time in the presence of catalyst (h)	reaction time in the absence of catalyst (h)	reaction time in the presence of acid catalyst (h)	reaction time in the absence of acid catalyst (h)
Benzaldehyde	3.5	6	8	10
2-Nitrobenzaldehyde	< 1 (50 min)	3	4	6.5
4-Cyanobenzaldehyde	2	4	4.5	8
4-Methoxybenzaldehyde	7	13	14	18
Acetophenone*	20 (55 %)	20 (30%)	20(25%)	20(15%)
Benzophenone*	30 (20 %)	30 (10 %)	48(25%)	48(10%)

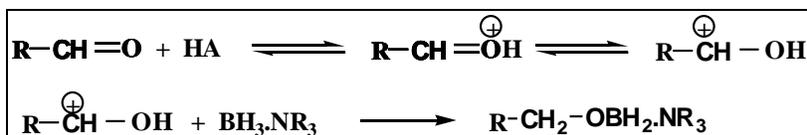
*complete reduction was not observed

Complete reduction of 2-nitrobenzaldehyde was observed after 4 h. In the case of ketones the percentage reduction was very low. Even in the presence of acid catalyst. PS-DVB polymer backbone is rigid and imparts steric hindrance at the reactive groups making them less accessible to the substrate molecules in the solution phase. The results are given Table 1.

Several mechanisms have been put forward to explain the increased rate of reduction with low molecular weight amine-borane reagent in the presence of acid [11,12].

a) Activation of reducible group by protonation

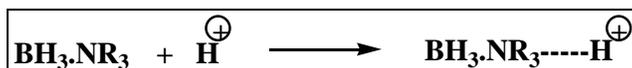
The carbonyl group of aldehydes can be activated by co-ordination with protic acid or Lewis acid, decreasing the electron density of carbonyl carbon, making it more electrophilic towards the reducing agent (Scheme 2).



Scheme 2

b) Activation of borane-amine complex by protonation

Reduction reactions of substituted benzaldehydes were also carried out with polymer bound EDA-borane reagent and it was observed that the substrates with electron withdrawing substituents were reduced at faster rates. These results support the former mechanism that protonation of aldehydes make them more reactive leading to increased reduction rates (Scheme 3).



Scheme 3

Effect of temperature

The effect of temperature on the reduction of aldehydes with the polymer supported EDA-borane reagent was studied by carrying out the reduction of 2-nitrobenzaldehyde in toluene at different temperatures 27 (RT), 37, 47, 57 and 67 °C. The reaction was carried out with 2 molar excess of the polymeric reagent and time taken for complete reduction of 2-nitrobenzaldehyde was noted by TLC. The effect of temperature on the reduction of 2-nitrobenzaldehyde with polymer supported EDA-borane was depicted in Figure 1.

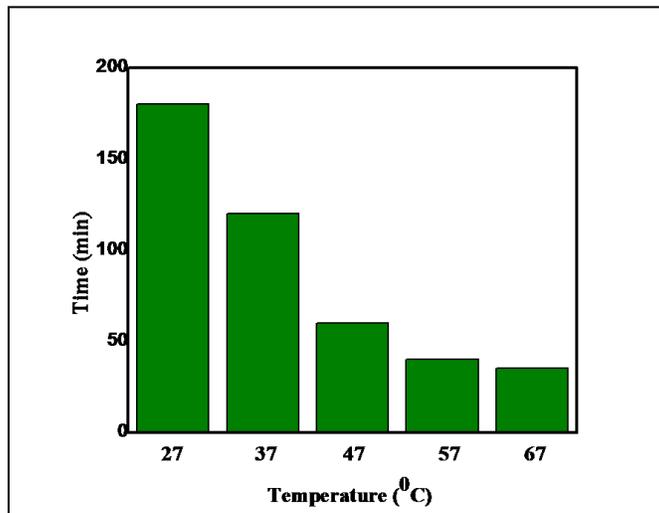


Figure 1: Effect of temperature on the reduction of 2-nitrobenzaldehyde with polymer bound EDA-borane

The reaction rate is increased as the temperature is increased. The time taken for complete reduction was 3 h at room temperature. As the temperature was increased to 37 °C, the reduction time was decreased to 2 h. At 47 °C complete reduction of 2-nitrobenzaldehyde was achieved within 1h. The time for 100% conversion was 35min. at 67 °C. Further increase in temperature has no significant influence in the reaction rate.

Effect of solvent

Solvent plays an important role in the reactivity of polymeric reagents. In the case of reactions with insoluble polymer bound reagents the compatibility of the polymeric reagent with solvent is very crucial [13]. The extent of solvation of polymer bound EDA-borane in different solvents were determined by swelling studies. The solvation characteristics of crosslinked polymer bound reagents were studied by determining the swelling capacities in different solvents. Swelling capacity of the polymeric reagent in a given solvent was determined by equilibrating a known amount of the resin, in the solvent for 24 h and then determining the weight of the swollen polymer.

$$\text{Swelling capacity} = \frac{\text{Weight of the swollen polymer}}{\text{Weight of the dry polymer}}$$

The swelling capacities of the 2% HDODA-PS and DVB-PS bound EDA-borane reagents (**P1** and **P2**) are given in Table 2.

Table 2: Swelling capacities of 2% HDODA-PS and DVB-PS bound EDA-borane reagents

Solvents	Swelling capacity of EDA-borane reagent (P1) (mL/g)	Swelling capacity EDA-borane reagent (P2) mL/g
DCM	5.87	4.05
Toluene	4.99	4.99
NMP	4.91	4.91
DMF	3.89	2.73
CHCl ₃	5.98	4.13
THF	3.73	3.37

To study the influence of the solvent on the reactivity of polymer supported EDA-borane the reaction was carried out in various solvents commonly used in organic reactions. The reduction of 2-nitrobenzaldehyde with polymer bound EDA-borane reagents derived from 2% HDODA-PS and DVB-PS resins were carried out in solvents like dichloromethane, toluene, tetrahydrofuran, N-methylpyrrolidone and dimethylformamide at RT. The reactions were monitored by TLC and spectrophotometric analysis. The time taken for complete reduction of 2-nitrobenzaldehyde with polymer supported EDA-borane reagent derived from HDODA-PS (P1) and DVB-PS (P2) resins in different solvents were noted by TLC and given in Table 3.

Table 3: Time for complete reduction of 2-nitrobenzaldehyde by polymer bound EDA-borane reagents in different solvents

Solvents	Time for 100% reduction with P1 (h)	Time for 100% reduction P2 (h)
DCM	3	5.5
CHCl ₃	3	6
Toluene	5	5
THF	5	10
NMP	6	11
DMF	9	12

The order of solvents in the increasing order of reaction rates in the case of HDODA-PS resins was DCM=CHCl₃>toluene>THF>NMP>DMF and in the case of DVB-PS resin the order was toluene>DCM>CHCl₃>THF>NMP>DMF. Swelling studies showed that both DVB-PS and HDODA-PS resins exhibit better swelling in DCM, toluene and THF than in NMP and DMF. The reactivity of a reagent function attached to a crosslinked polymer is very much influenced by solvation of the polymer backbone. If the polymer has good compatibility with solvent, the swelling of polymer matrix will be high. In good solvents the polymer chains expand to a larger extent and the functional groups are more exposed to substrate molecules in the solution [14,15]. In poor swelling solvents the polymer chains get collapsed and the reactive sites are buried inside and are not readily available. Here DCM and toluene are more compatible with the polymeric EDA-borane reagent and hence show greater reactivity in these solvents.

The extent of reduction of 2-nitrobenzaldehyde in different solvents with polymer bound EDA-borane reagents (P1 & P2) after 3 h was determined spectrophotometrically. The percentage conversions of 2-nitrobenzaldehyde in different solvents were noted after 3 h. The results are shown in Figure 2.

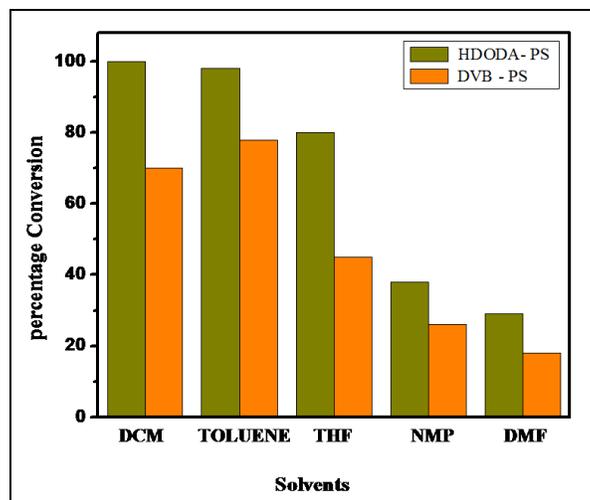


Figure 2: Effect of solvents in the reduction of 2-nitrobenzaldehyde with EDA-borane reagents derived from HDODA & DVB crosslinked resins

In dichloromethane 100% reduction of 2-nitrobenzaldehyde to 2-nitrobenzyl alcohol with reagent resin **a** was observed after 3h. The percentage of reduction after 3 h in toluene, THF, NMP and DMF were 98%, 80%, 38% and 29% respectively. In the case of DVB-PS supported EDA-borane reagent the highest percentage of conversion after 3 h was 78% in toluene (78%). The extent of reduction in DCM was 70% and the lowest percentage of conversion (18%) was observed in DMF. Further, DCM was found to be the ideal solvent for reduction owing to the easy removal of solvent during product isolation.

Kinetics of reduction of 2-nitrobenzaldehyde with polymer EDA-borane reagents P1 and P2

The studies of reduction of aldehyde with polymer bound EDA-borane reagent was done in a quantitative way by following the reduction of 2-nitrobenzaldehyde spectrophotometrically. The kinetics of reduction of 2-nitrobenzaldehyde with polymer bound EDA-borane reagent was followed by sampling the reaction mixture at different intervals of time and estimating the quantity of unreacted aldehyde by measuring the absorbance of diluted solutions of reaction mixture at λ_{\max} 253 nm. The concentration of the solution corresponding to the absorbance was noted from the standard curve and the percentage of reduction was calculated at each time interval. The course of reduction of 2-nitrobenzaldehyde with polymer bound EDA-borane reagents (P1 & P2) with time is given in Figure 3.

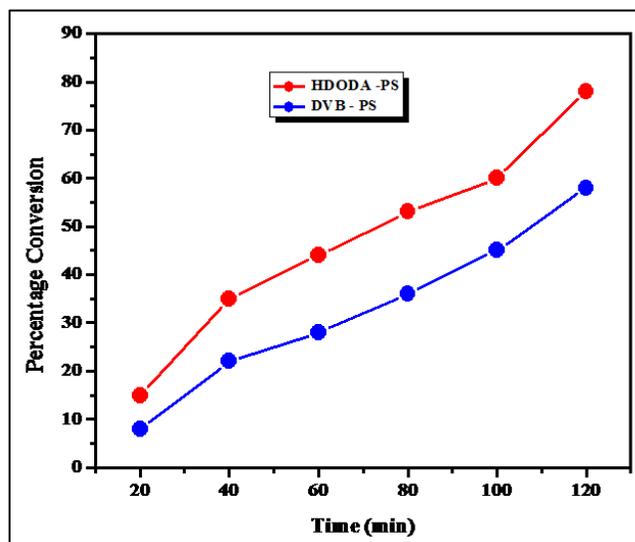


Figure 3: Kinetics of reduction of 2-nitrobenzaldehyde with reagents P1 and P2

CONCLUSION

The influence of acid catalyst, temperature and solvent in promoting the efficiency of polymer bound ethylenediamine-borane reagent was studied. Various aldehydes and ketones were reduced with polymeric EDA-borane reagent in the presence of acetic acid catalyst and considerable increase in the rate of reduction was observed. The effect of temperature on the reduction of 2-nitrobenzaldehyde using polymer supported EDA-borane was studied and the rate of reduction was found to increase with increase in temperature. The role of solvent on the reactivity of polymer bound EDA-borane reagent was investigated and DCM and toluene were found to be ideal solvents.

ACKNOWLEDGEMENTS

The authors thank Mahatma Gandhi University, Kottayam, Kerala, India for providing junior and senior research fellowships to K. Rajasree.

REFERENCES

- [1] J Lu; PH Toy. *Chem. Rev* **2009**, 109: 815-838.
- [2] P Hodge; *Curr. Opin. in Chem. Biol*, **2003**, 7: 362-373.
- [3] S Bhattacharya. *Ind J Chem*, **2001**, 40B: 878-890.
- [4] S Bhattacharya; S Rana; OW Gooding; J Labadie. *Tetrahedron Lett.*, **2003**, 44: 4957-4960.
- [5] KS Devaky ; PN Leelamma. *J Chem Pharm Res*, **2016**, 8: 704-713.
- [6] K Rajasree; KS Devaky. *J Appl Polym Sci*. **2001**, 82: 593-600.
- [7] RS Feinberg; RB Merrifield. *Tetrahedron*, **1974**, 30: 3209-3212.
- [8] JBL Taumalin; M Baboulene. *Tetrahedron Asymmetry*, **1997**,8: 1259-1265.
- [9] FM Menger; M Shinozaky; HC Lee. *J Org Chem*,**1980**, 45: 2724-2725.
- [10] HC Brown; LT Murray. *Inorg Chem*, **1984**, 23: 2746-2753.
- [11] SS White; HC Kelley. *J Am Chem Soc*, **1970**, 92: 4203-4209.
- [12] TC Wolfe; HC Kelley. *J Chem Soc Perkin Trans II*, **1973**, 1948-1950.
- [13] R Arshady. *Adv Mater*, **1991**, 3 (4): 182-190.
- [14] P Hodge. *Polymer Supported Chemical Reactions*, Pergamon press, **1992**; 3-103.
- [15] DC Sherrington. *Chem. Commun*, **1998**, 21: 2275-2286