Significance of phase transfer catalysis in the selective reduction of acetophenones with sodium borohydride in organic solvents

Rajendran P.[1]**, Bashpa P.**[2] **and Bijudas K.**[2*]
1. Department of Chemistry, Government Victoria College, Palakkad, Kerala, 678001, INDIA
2. Department of Chemistry, N. S. S. College, Manjeri, Malappuram, Kerala 676122, INDIA
*bijudask@gmail.com

Abstract
The selective reduction of acetophenone and its para substituted derivatives was carried out in organic solvents like ethyl acetate and toluene using sodium borohydride as reducing agent under phase transfer catalysis conditions. Various phase transfer catalysts such as tetrabutylammonium bromide, tetrabutylammonium hydrogen sulphate, cetyltrimethylammonium bromide and tricaprylylmethylammonium chloride (Aliquat 336) were used. This reaction is also carried out in polar solvents like isopropyl alcohol so as to study the significance of phase transfer catalysis.

The reaction under polar solvent is found to be very slow with low yield on comparison with the reaction in organic solvents under phase transfer catalysis condition. The products, 1-phenyl ethanol and its para substituted derivatives were separated, purified, weighed and identified by infra-red spectral technique. The reaction was found to proceed with ease even under mild conditions with very high yield in organic solvents under phase transfer catalysis method without the formation of any byproducts. More over this method is found to follow green approach in organic synthesis.

Keywords: Selective reduction, acetophenone, para substituted acetophenones, phase transfer catalysis, phase transfer catalysts.

Introduction

Reduction of organic substrates is quite important from synthetic and technological view point where the reaction involves the addition of hydrogen and removal of oxygen[1-5]. Most of the industrially important compounds like alcohols, aldehydes, amines etc. can be prepared by the reduction of related substrates by using suitable reducing agents[6-10].

The common reducing agents used in organic synthesis are sodium amalgam, lithium aluminum hydride, sodium borohydride, aluminum isopropoxide etc. Use of such inorganic reductants in organic synthesis is limited to the reduction of organic substrates which are at least partially soluble in water. If the solubility of the substrate is too low, there cannot be proper interaction between the reductant in the aqueous phase and the organic substrate in the organic medium. The classical way of overcoming this problem is to use a dipolar organic solvent system that will dissolve both the reactants. But these solvents are highly toxic and expensive. All such problems were solved by the introduction of phase transfer catalysis (PTC) with the usage of crown ethers and quaternary onium salts as phase transfer catalysts (PT catalysts)[11-16].

Sodium borohydride is one of the most powerful inorganic reducing agents used in various reactions in polar media[17-19]. It is a nucleophile which reacts by the way of addition of hydride ion to the more positive end of the polarized bond. Even though there are lot of reports on oxidation reactions of various organic substrates under PTC, application of PTC in reduction reactions is scanty[20-23].

It is very difficult to prepare organic alcohols by the reduction of corresponding aldehydes and ketones using reducing agent alone. The use of dipolar aprotic solvents has to be discouraged due to the high cost and toxic nature.

Reduction of acetophenone and its para substituted derivatives was carried out by using sodium borohydride as the reductant under PTC conditions. The reaction was carried out in ethyl acetate and toluene using PT catalysts such as tetrabutylammonium bromide (TBAB), tetrabutylammonium hydrogen sulphate (TBAHS), cetyltrimethylammonium bromide (CTMAB) and tricaprylylmethylammonium chloride (TCMAC or Aliquat 336). The reaction was also carried in conventional manner to study the significance of PTC methods in such reactions. The products obtained were purified and characterization was done by recording the infra-red spectrum.

Material and Methods

Materials: Analar grade sodium borohydride (Merck, India) was used and its solution was prepared in double distilled water. Acetophenone (Merck, India, AR) was further purified by distillation under reduced pressure. The substituted acetophenones, 4-methoxyacetophenone, 4-chloroacetophenone, 4-nitroacetophenone and 4-methylacetophenone (Sisco Research Laboratories Pvt. Ltd., India) were used as such. Tetrabutylammonium bromide (TBAB), tetrabutylammonium hydrogen sulphate (TBAHS) and cetyltrimethylammonium bromide (CTMAB) and aliquat 336 (Sisco Research Laboratories Pvt. Ltd., India) were used as PT catalyst. The organic solvents toluene and ethyl acetate were purified according to the standard procedure[27]. The purified solvents were refluxed for 1-2 hours with a mixture of PT catalyst and sodium borohydride and then distilled.

Methods: The reduction of acetophenones was carried out in both conventional and PTC conditions. In conventional method, sodium borohydride solution is prepared by dissolving 3 g sodium borohydride in 15 mL 2 N sodium hydroxide and diluted to 50 mL in doubly distilled water. 5 g acetophenone is exactly weighed and dissolved in 50 mL isopropyl alcohol and is taken in a round bottom flask. Sodium borohydride solution is added to it at a rate of 0.5 mL per minute with occasional cooling.

This mixture was shaken well, fitted with a Liebig's condenser and refluxed for about three hours. After the completion of reaction, isopropyl alcohol was removed by distillation on a steam bath. The residue obtained is diluted with water and extracted with ether three times.

The ether layer was collected, washed with water and dried rapidly with anhydrous sodium sulphate. The ether content was removed by steam distillation and distilled under reduced pressure to obtain the pure product. Para substituted acetophenones were also subjected to the same reaction procedure as explained above and products were isolated after purification. The same procedure was repeated under PTC conditions using ethyl acetate and toluene as solvents by adding a pinch of PT catalysts. The reaction is further repeated with substituted acetophenones with all the four PT catalysts in ethyl acetate and toluene. The obtained products after each reaction were separated, purified and analyzed by infra-red spectral technique.

Results and Discussion

All the substrates (acetophenone and substituted acetophenones) on reduction with borohydride under PTC condition in non- polar solvents and under polar medium gave corresponding alcohols (1-phenyl ethanol and its derivatives) as the product. The yield was found to be very high (above 80 %) under the PTC experimental conditions. Product obtained under conventional method is also found to be corresponding secondary alcohol but the yield is found to very less (around 60 %). The weight and yield of products obtained in both methods are given in table 1.

From the results shown in table 1, it is evident that PTC method is far superior than the conventional method in terms of ease of reaction and yield.

Table 1
Wight and yield data of products on the reduction of acetophenones

S.N.	**Substrate**	**Weight of product (g) and yield (%)**				
		Polar solvent	**PTC condition**			
			TBAB	**TBAHS**	**CTMAB**	**TCMAC**
1	Acetophenone	3.216 (64.3)	3.964 (79.3)	4.148 (83.0)	3.868 (77.4)	4.212 (84.2)
2	p-methoxyacetophenone	3.124 (62.5)	3.842 (76.8)	4.024 (80.5)	3.743 (75.0)	4.012 (80.2)
3	p-methyl acetophenone	3.365 (67.3)	4.012 (80.2)	4.242 (84.8)	3.921 (78.4)	4.324 (86.5)
4	p-chloroacetophenone	3.372 (67.4)	4.112 (82.2)	4.248 (85.0)	4.048 (81.0)	4.423 (88.5)
5	p-nitroacetophenone	3.422 (68.4)	4.212 (84.2)	4.369 (87.4)	4.148 (83.0)	4.527 (90.5)

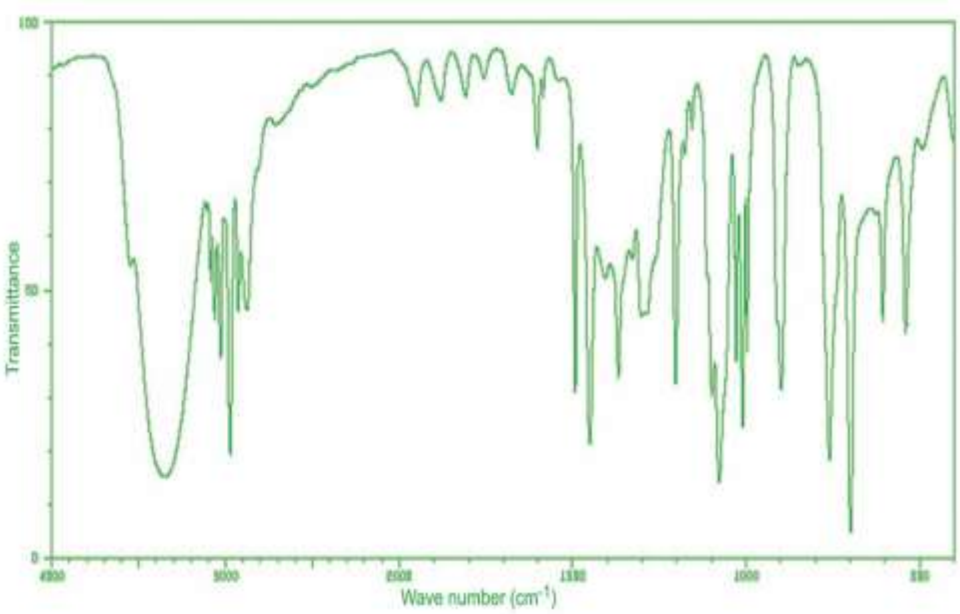


Figure 1: IR spectrum of product on reduction of acetophenone

We have refluxed the reaction mixture for three hours in conventional method where as in PTC method, only one-hour refluxing is enough for the completion of the reaction. This is quite significant in terms of increasing the rate of reaction at lower temperature with high yield. The yield is increased from 64.3 % to 84.2 % in case of reduction of acetophenone. Similar results were obtained for all other para substituted acetophenones. The yield of products based on the use of PT catalyst is in the order of TCMAC > TBAHS > TBAB > CTMAB. All the products obtained after purification were subjected to infra-red spectral studies for characterization.

The infra-red absorption spectra of the obtained products were recorded from KBr pellets using Jasco FT-IR 4100 spectrophotometer (Japan) and shown in figures 1, 2, 3, 4 and 5. The infra-red spectrum of figure 1 showed peaks at 3010 cm^{-1} (aromatic C-H stretching), 3720 cm^{-1} (O-H stretching), 2850 cm^{-1} (aliphatic C-H stretching), 1920 cm^{-1} (C=O stretching for secondary alcohol), 1360 cm^{-1} (aliphatic C-H stretching), 1410 cm^{-1} and 1690 cm^{-1} (C=C stretching in aromatic ring). Existence of these peaks leads to the conclusion that the product formed is 1-phenylethanol which is an aromatic secondary alcohol.

In figure 2, the peak for aromatic C-H stretching is shifted to 2910 cm^{-1} which shows the presence of a methoxy group where all other peaks are available as explained earlier which proved the formation of 4-methoxy-1-phenylethanol. The existence of a sharp peak at 2940 cm^{-1} in figure 3 shows the presence of a methyl group in addition to the other peaks present in figure 1.

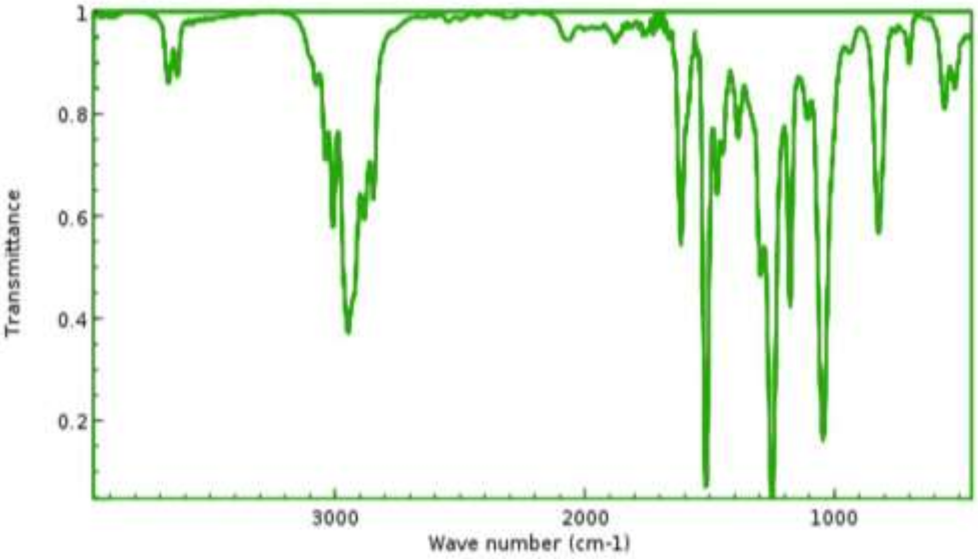


Figure 2: IR spectrum of product on reduction of p-methoxyacetophenone

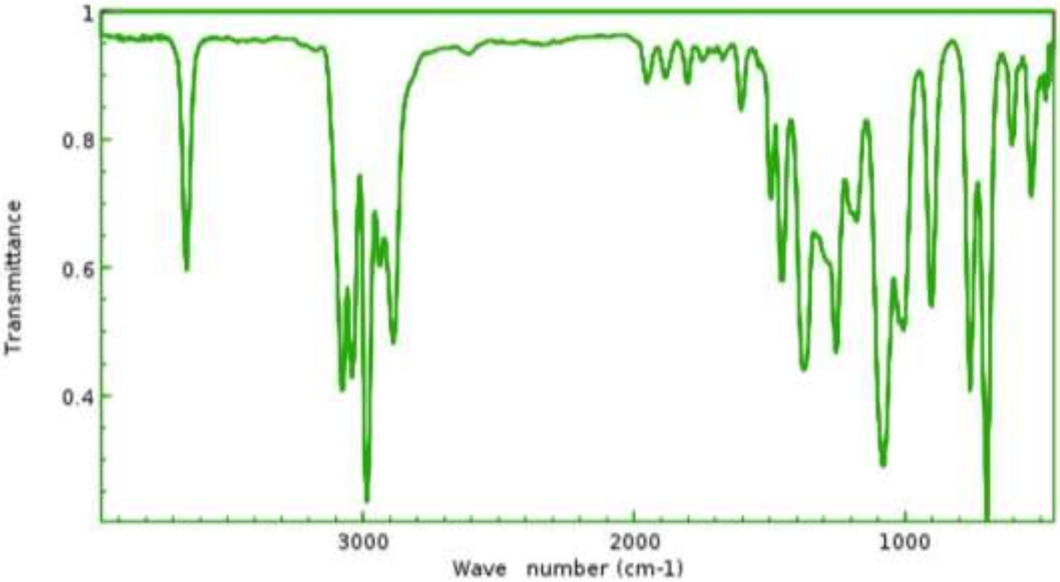


Figure 3: IR spectrum of product on reduction of p-methylacetophenone

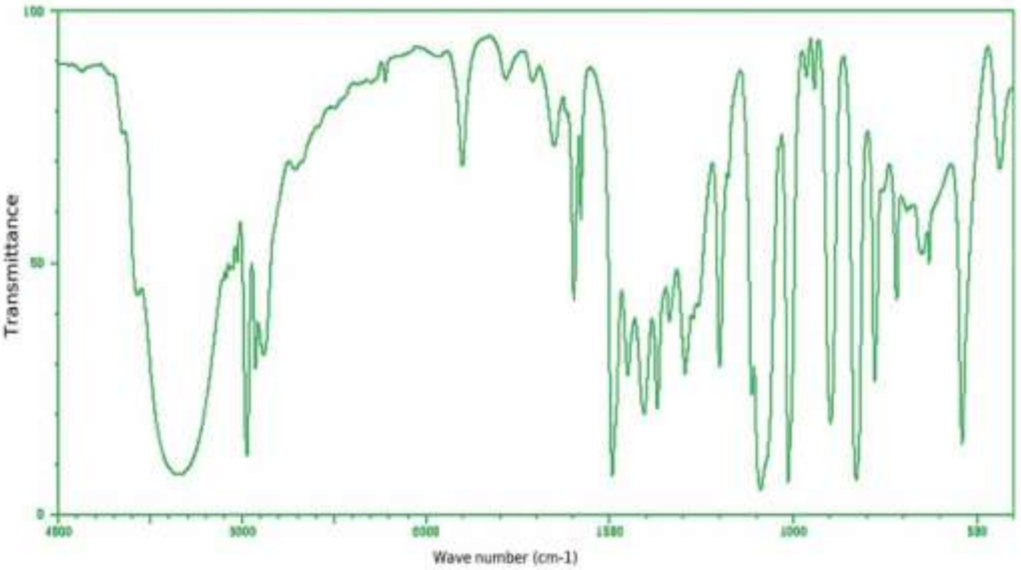


Figure 4: IR spectrum of product on reduction of p-chloroacetophenone

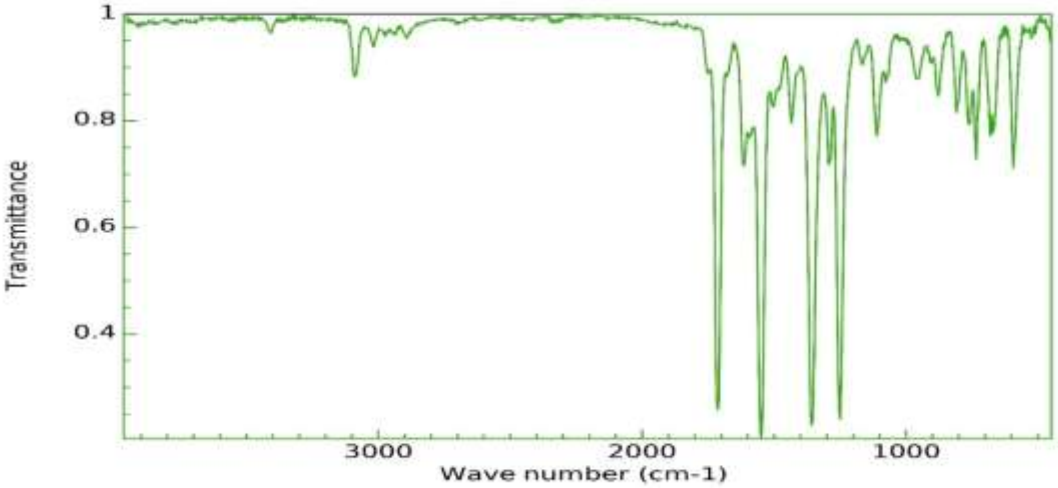


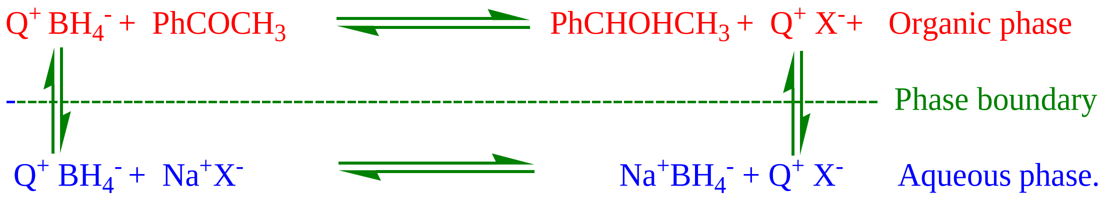
Figure 5: IR spectrum of product on reduction of p-nitroacetophenone

This proves that the product formed is 4-methyl-1-phenylethanol. The presence of a sharp peak at 780 cm^{-1} in figure 4 represents C-Cl stretching and aromatic C-H stretching shifts to higher wavelength of 3080 cm^{-1} in addition to other peaks available in parent compound which proves that product formed is p-chloro-1-phenylethanol. Presence of additional peaks at 1550 cm^{-1} and 1350 cm^{-1} in figure 5 represents N = O stretching of an aromatic nitro compound apart from the usual peaks which are already explained.

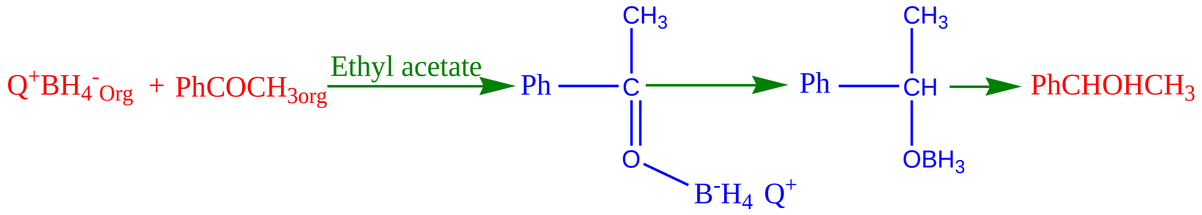
Therefore, the product obtained in this case may be p-nitro-1-phenylethanol. Furthermore, these spectra were compared with that original compounds available in literature and found excellent correlation. This further proves that the reduction of acetophenone and para substituted acetophenones by sodium borohydride under PTC conditions gives corresponding alcohols as product with very high yield.

Selective reduction of acetophenone and its para substituted derivatives by sodium borohydride under PTC condition gave excellent yield of 1-phenylethanol and para substituted 1-phenylethanols in ethyl acetate and toluene. There was no formation of any byproducts detected under the experimental conditions. But the yield is found to be more in ethyl acetate than in toluene due to the high polarity of ethyl acetate. PT catalysts can easily carry reductant as ion pair from aqueous phase to organic phase in solvents having high polarity due to high solubility and partitioning character.

All the PT catalysts used gave excellent yield of product but there is a slight increase in the order TCMAC > TBAHS > TBAB > CTMAB. This activity of PT catalysts is due to the difference in the combination of alkyl groups and anions present in it.



Scheme 1: Starks cycle for the reduction of acetophenones



Scheme 2: Mechanism for the reduction of acetophenones

The minimum requirement of a PT catalyst is that it should have sufficient organic structure for transferring the anion to the organic phase and should enjoy more solubility in it. Commonly PT catalysts having symmetrical structure with larger alkyl groups are more suitable for effecting the reaction.

TCMAC is having larger alkyl groups with symmetrical structure gave higher yield of the product followed by TBAHS in which hydrogen sulphate is a better anion. This is followed by TBAB which is a common and effective PT catalyst with sufficient symmetrical alkyl group than that of CTMAB which forms an emulsion in many reactions. The overall reaction under PTC condition can be represented as explained in Starks cycle in scheme 1 and the mechanism is explained in scheme 2.

Conclusion

Selective reduction of acetophenones and substituted acetophenones with sodium borohydride in aqueous medium and in organic medium under PTC conditions was reported. It was found that the reaction proceeds smoothly in organic medium under PTC method with very high yield and other benefits like high reaction rate, lower reaction temperature and ease without the formation of byproducts. Greener solvents like ethyl acetate and toluene were used in the entire reaction. All the four PT catalysts used gave excellent yield of the product in which TCMAC gave the best result.

This method proved the significance of PTC in organic synthesis especially in the green chemistry era by ensuring all the desired benefits. Therefore, PTC method can be adapted to other reaction systems also and even for reactions under solvent free conditions.

References

1. Marko I.E. and Donohoe T.J., Oxidation and reduction in organic synthesis, Oxford University Press, Oxford **(2000)**

2. Rinehart K.L., Oxidation and reduction of organic compounds, Prentice Hall, United States **(1973)**

3. Hudlicky M., Reductions in organic chemistry, American Chemical Society, United States **(1996)**

4. Andersson P.G. and Munslow I.J., Modern reduction methods, John Wiley & Sons, United States **(2008)**

5. Nishinaga T., Organic redox systems: Synthesis, properties and applications, John Wiley & Sons, United States **(2015)**

6. Shibley I.A., Amaral K.E., Aurentz D.J. and McCaully R.J., Oxidation and reduction reactions in organic chemistry, *J. Chem. Educ*., **87(12)**, 1351-1354 **(2010)**

7. Brown H.C., Kim S.C. and Krishnamurthy S., Selective reductions. 26. Lithium triethylborohydride as an exceptionally powerful and selective reducing agent in organic synthesis, Exploration of the reactions with selected organic compounds containing representative functional groups, *J. Org. Chem*., **45(1)**, 1-12 **(1980)**

8. Penne J.S., Reductions by the alumino and borohydrides in organic synthesis, Second ed., Wiley – VCH, New York **(1997)**

9. Di Cosimo J.I., Acosta A. and Apesteguia C.R., Allylic alcohol synthesis by gas-phase hydrogen transfer reduction of unsaturated ketones, *J. Mol. Catal. A-Chem*., **234(1-2)**, 111-120 **(2005)**

10. Johnson M.R. and Rickborn B., Sodium borohydride reduction of conjugated aldehydes and ketones, *J. Org. Chem*., **35(4)**, 1041-1045 **(1970)**

11. Starks C.M. and Liotta C., Phase transfer catalysis, principles and techniques, Academic Press, New York **(1978)**

12. Dehmlow E.V. and Dehmlow S.S., Phase transfer catalysis, VCH: Weinheim, Germany **(1993)**

13. Sasson Y. and Neumann R., Handbook of phase transfer catalysis, Kluwer Academic Publishers, Dordrecht **(1993)**

14. Weber P.W. and Gokel G.W., Phase transfer catalysis in organic synthesis, Springer Science & Business Media, Switzerland **(2012)**

15. Gordon J.E. and Kutina R.E., Theory of phase-transfer catalysis, *J. Am. Chem. Soc*., **99(12)**, 3903-3909 **(1997)**

16. Makosza M. and Fedorynsky M., Phase transfer catalysis, *Catal. Rev. Sci. Eng.*, **45(3-4)**, 321-367 **(2003)**

17. Brown H.C., Mead E.J. and Subba Rao B.C., A study of solvents for sodium borohydride and the effect of solvent and the metal ion on borohydride reductions, *J. Am. Chem. Soc.*, **77(23)**, 6209-6213 **(1955)**

18. Saeed A. and Ashraf Z., Sodium borohydride reduction of aromatic carboxylic acids via methyl esters, *J. Chem. Sci.*, **118(5)**, 419-423 **(2006)**

19. Azimzadeh M. and Setamdideh D., $NaBH_4$ /$Na_2C_2O_4$ /H_2O: An efficient System for Selective Reduction of Aldehydes in the presence of Ketones, *Orient. J. Chem.*, **31(2)**, 1085-1089 **(2015)**

20. Bijudas K. and Radhakrishnan Nair T.D., Selective oxidation of benzyl alcohol with monochromate in non – polar solvents, *Indian J. Chem. A.*, **43A**, 1216-1218 **(2004)**

21. Yadav G.D., Jadhav Y.B. and Sengupta S., Novelties of kinetics and mechanism of liquid–liquid phase transfer catalysed reduction of p-nitroanisole to p-anisidine, *Chem. Eng. Sci.*, **58(12)**, 2681-2689 **(2003)**

22. Jothimony K., Vancheesan S. and Kuriacose J.C., Phase transfer-catalysed transfer hydrogenation of ketones using iron carbonyls as catalysts, *J. Mol. Catal. A-Chem.,* **32(1)**, 11-16 **(1985)**

23. Bijudas K., Bashpa P., Bipin V. P., Nair L., Priya A.P., Aswathy M., Krishnendu C. and Lisha P., Selective synthesis of benzaldehydes by hypochlorite oxidation benzyl alcohols under phase transfer catalysis, *Bull. Chem. React. Engg. Catal.*, **10(1)**, 38-42 **(2015)**

24. Ning X.S., Dong S.J., Xiao Z.F., Yao C.Z. and Kang, Y.B., Ion-pair-catalyzed sodium borohydride reduction in aprotic organic solvents, *Asian J. Org. Chem.*, **4(4)**, 333-336 **(2015)**

25. Mahdavi H., Haghani E. and Malakian B., Cross-linked poly (diallyldimethylammonium chloride) as an efficient solid–liquid phase transfer catalyst in reduction of carbonyl compounds with sodium borohydride, *React. Funct. Polym.,* **66(10)**, 1033-1040 **(2006)**

26. Halimjani A.Z. and Saidi, M.R., Sodium borohydride–solid $LiClO_4$: An effective reagent for reducing aldehydes and ketones in aprotic solvent, *Synth. Commun.*, **35(17)**, 2271-2276 **(2006)**

27. Vogel A.I., Text book of practical organic chemistry, Longman, London **(1967)**.

(Received 06th April 2020, accepted 08th June 2020)