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Reduction of Carboxylic Acids to Alcohols Using Cyanuric Chloride and Borohydride Exchange Resin

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ABSTRACT

Reduction of carboxylic acid to corresponding alcohols were achieved by activating the carboxylic acids using cyanuric chloride and subsequently reduced by using borohydride exchange resin (BER) in excellent yields.

Key words: Reduction, cyanuric chloride, borohydride exchange resin, carboxylic acids, alcohols.

INTRODUCTION

Polymer supported borohydride exchange resin (BER) was synthesized first, by Gibson and Baily and was reported as a reducing agent for the reduction of benzaldehyde to benzyl alcohol.[1] BER is prepared from an anion exchange (chloride form) and aqueous sodium borohydride. As compared to sodium borohydride, BER is highly stable and easy to handle.[2] BER is a quaternary ammonium borohydride having stability greater in presence of transition metal salt than soluble quaternary ammonium borohydride, tetrabutyl ammonoim borohydride in methanol. BER is useful in solvent purification, generation of volatile metal hydrides and reduction of metal ions and some aldehydes.[3]

In organic synthesis, BER has number of advantages over other polymer supported reagents.[4] Various reagents[5] were developed for the selective reduction of α, β –unsaturated carbonyl compounds (aldehydes and ketones) to the corresponding unsaturated alcohols. But these reagents have several disadvantages like complex reaction work up, low yields etc. BER was extensively used in the reduction of carbonyl compounds in alcohol solvents.[6]

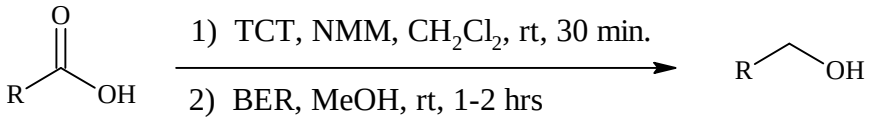
BER was used selectively in order to reduce aliphatic carboxylic acids to corresponding alcohols.[7] BER was found to be specific reagent for the reduction of aliphatic carboxylic acids at room temperature, low cost and simple isolation procedure and it is recyclable reagent

Several reducing systems were developed using BER in combination with LiCl,[8] transition metals,[9] $Ni(OAc)_2$,[10] $CuSO_4$,[11] Et_3NHCl,[12] phenyl disulfide,[13] $NiCl_2$ - $6H_2O$,[14] 2,4 Ionene.[15] BER reduces conjugated ethylenic linkage selectively.[16] BER was used as a reducing agents for the reduction of conjugated acid chlorides,[17] aryl and sulfonyl,[18] benzonitriles,[19] oximes,[10e] alkynes,[20] nitroso amines,[21] selenium.[22]

Cyanuric chloride (1,3,5, Trichloro 2,4,6, triazine/TCT) is the most important heterocyclic compound with three substituted chlorine atoms, which are coupled with the stable triazine ring. These chlorine atoms are more reactive towards the nucleophiles. Therefore, in organic synthesis, cyanuric chloride has been widely used as an important reagent. It is easily available and cheap reagent. In many chemical transformations, cyanuric chloride was extensively used for the activation of carboxylic acids,[23] an alternative to the other methods avoiding the use of toxic and expensive reagents.[24]

TCT [25] was used for the activation of carboxylic acid including N- protected amino acids followed by the reduction to corresponding alcohols using aq. sodium borohydride. Good yields were observed without racemization. However it reduces unsaturated bonds present in cinnamic and crotonic acids. Therefore yield of desired products were reduced by 15-20 %. Also when $NaBH_4$ is used, such reactions are vigorous and exothermic in nature, needs to cool to 0 ºC to avoid side reactions and control the evolution of gas during addition. To overcome some of these problems and to reduce carboxylic acids selectively, we utilized BER as reducing agent together with TCT as activator. The activation of carboxylic acid with TCT and subsequently reduction by BER as mild reducing agent could avoid above drawbacks. BER is having BH_4^- anion about 2.5 mmol per gram of resin and its very mild nature allows to use it in an excess amount. Reduction can be carried out simply by activation of carboxylic acid with TCT and subsequently by addition of BER in methanol.

In the present investigation, we report the activation of carboxylic acid with TCT followed by selective reduction of carboxylic acids to corresponding alcohols using BER as a reducing agent under mild conditions (Scheme I).



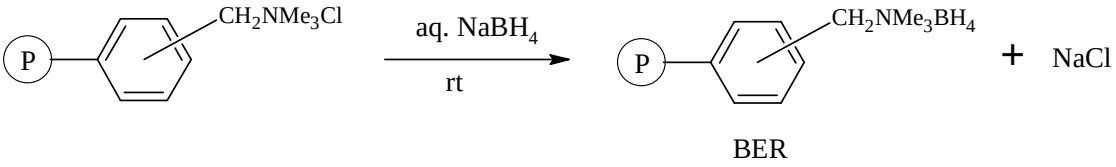
R = Alkyl

Scheme I

EXPERIMENTAL SECTION

1. Preparation of Borohydride Exchange Resin (BER)

An aq. solution of sodium borohydride (0.5 M, 100 ml) was stirred with 10 g wet chloride form resin (Amberlyst A- 26 anion exchange resin) for 1 hr. The resin formed, was washed thoroughly with distilled water until it was free from excess sodium borohydride. The resin was then dried in vacuum at 65 °C for 5 hrs. The dried resin was analyzed for borohydride content by hydrogen evolution on acidification with 0.05 N HCl, the average capacity of BER was found to be 2.5 mmole of BH_4^- per gram of resin. The dried resin was stored under nitrogen at room temperature.



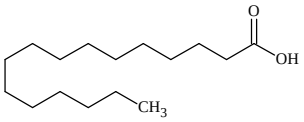
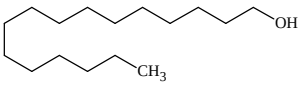
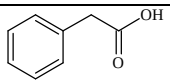
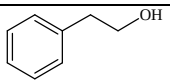
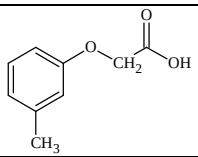
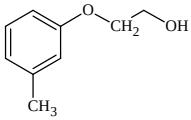
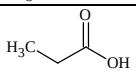
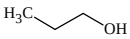
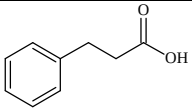
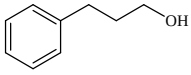
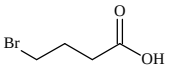
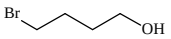
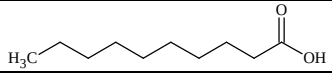
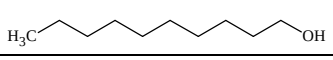
BER

2. Reduction of carboxylic acids to alcohols using TCT and BER

To a solution of TCT (92.2 mg, 0.5 mmol) in dichloromethane (30 ml) NMM (151mg, 1.5 mmol) was added at room temperature with stirring. A white suspension was formed. To this suspension, a solution of cinnamic acid (222 mg, 1.5 mmol) in dichloromethane (10 ml) was added. After 3 hrs., BER (1 gm) in methanol (15 ml) was added and continued the stirring of heterogeneous mixture for about 1-2 hours at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was filtered to separate BER. Dichloromethane and methanol was evaporated under reduced pressure and diethyl ether was added to the flask. The ether solution was acidified with 10 % HCl. The organic layer was separated, washed with sodium bicarbonate 10 % (2 x 10 ml), brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give pure product, cinnamyl alcohol.

The products were characterized by physical constants, spectroscopic analysis and by comparison with authentic samples. (IR, ^{1}H NMR, ^{13}C NMR and Mass).

Table 1: Reduction of carboxylic acids using TCT/BER

Entry	Carboxylic acids	Alcohols	Yield (%)	M.P./*B.P* [ºC] [Lit][7]
1			93	48-49 [49]
2			93	*217-219 [219]*
3			90	*145-146 [146]*
4			92	*96-97 [97-98]*
5			91	*233-235 [235]*
6			90	*57-58 [56-58]*
7			91	*229-231 [232]*

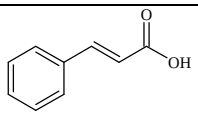
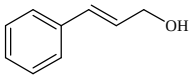
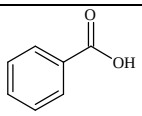
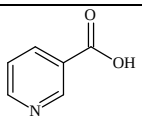
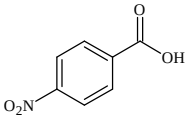
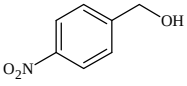
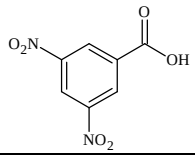
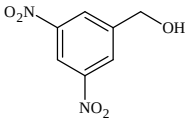
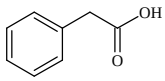
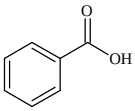
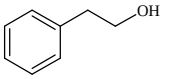
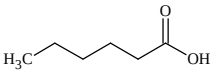
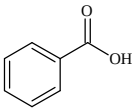
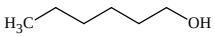
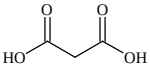
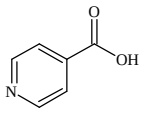
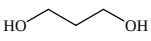
8			94	*248-249 [250]*
9		----	----	-----
10		-----	-----	-----
11			----	91 [92-94]

Table continued….

Entry	Carboxylic acids	Alcohols	Yield (%)	M.P./*B.P* [ºC] [Lit][7]
12			---	88 [88-91]
13	 + 		91	*217-218 [219]*
14	 + 		94	*156-157 [158]*
15	 + 		91	57-58 [59]

RESULTS AND DISCUSSION

The carboxylic acids were first activated with TCT in presence of NMM in dichloromethane and subsequently reduced to alcohols by using BER as mild reducing agent at room temperature in excellent yield (Table 1). Compared to TCT/$NaBH_4$ [25] TCT/BER system allows one pot reduction of carboxylic acid at room temperature avoiding unwanted side reactions and additional cost of cooling with improved yields. The system being mild in nature, also applicable for the selective reduction of conjugated acids. It reduces unsaturated carboxylic acids without affecting the olefinic group (entry 8).

The selectivity of this system amongst aliphatic and aromatic carboxylic acids was investigated. TCT/BER facilitates selective reduction of aliphatic carboxylic acids. When a mixture of aliphatic carboxylic acid and aromatic carboxylic acid were treated with TCT/BER, then it was observed that, only aliphatic carboxylic acids underwent reduction (entries 13, 14, 15). It could not reduce aromatic carboxylic acids even after longer reaction time (24 hours) (entries 9, 10). Importantly reductions were carried out at room temperature and simple work up procedure advances the existing methodologies. The isolation procedure is very simple; the reagent is separated only by filtration which expected to give boron free products.

CONCLUSION

A convenient one pot method is developed for the reduction of carboxylic acids to corresponding alcohols using TCT as acid activator and BER as reducing agent. BER is found to be mild and efficient reducing agent for the reduction of carboxylic acids at room temperature. Saturated as well as conjugated acids were reduced under mild conditions.

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