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Ecofriendly Synthesis and Characterization of Halo Substituted Benzylalcohols

Chemistry

KEYWORDS : Benzyl alcohol, Biocatalyst, Baker's yeast, Immobilization

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ABSTRACT

The synthesis and characterization of some aromatic alcohols such as 2, 4-Dichloro benzyl alcohol, 2-Chloro-6-fluorobenzyl alcohol and 2-Bromobenzyl alcohol employing biotransformation (using whole cells of Baker's Yeast in their free as well as immobilized form in mixtures of glycerol and water) is reported. The products obtained were purified and then characterized by spectroscopic techniques.

INTRODUCTION

Chiral alcohols are very useful materials in pharmaceutical industries and in preparation of single enantiomer drugs or building blocks[1] therefore asymmetric reduction of ketones mediated by biocatalysts becomes one of the most important, fundamental and practical reactions for producing chiral alcohols, to synthesize industrially important chemicals such as pharmaceuticals, agrochemicals and natural products. Biocatalysts have Very high enantio-, regio- and chemoselectivities [2]. Using biocatalysis in some chemical synthesis steps, higher product selectivity can be achieved under ambient process conditions. The potential advantages of a biocatalytic process over traditional chemistry include stereo- and regioselectivity, the use of milder, green reaction conditions [3-4], to deliver greener chemical syntheses, design synthetic routes which are environmentally compatible as well as to fulfil the demands of process economics and product specification, reduction of development times [5], generating optically pure compounds & developing synthetic routes to target compounds[6]**.** Among the various possible biocatalysts, Baker's Yeast (BY, *Saccharomyces cerevisiae*) mediated reduction of synthetic substrate is a useful method for preparing chiral intermediate in synthetic chemistry because it is emerged as one of the most frequently employed microorganisms in whole cell conditions due to its high bioavailability, easiness of treatment inexpensive and mild reaction conditions [7].

Benzyl alcohol derivatives are found to be potential bioactive material against the pathogenic microorganism. 2, 4-Dichlorobenzyl alcohol is a mild antiseptic, able to kill bacteria and viruses associated with mouth and throat infections. It is a common ingredient in throat lozenges such as Strepsils. A low-pH throat lozenge containing dichloro benzyl alcohol (1.2 mg) and amylmetacresol (600μg) has been found to inactivate respiratory syncytial virus and SARS-Cov, but not adenovirus or rhinovirus [8]. 2, 4-Dichlorobenzyl alcohol throat lozenges ((Strepsils) relieve acute sore throat caused by upper respiratory tract infection [9]. A dentifrice containing 10% sodium benzoate and 0.3% Dichlorobenzyl alcohol maintains antimicrobial activity for 5–10 minutes after brushing [10]. 2, 4-dichlorobenzyl alcohol is used in the preparation of a medicament for the treatment or prevention of HIV viral infections [11]. 2-chloro-6-fluoro benzyl alcohol is useful as synthesis intermediates for pharmaceutical drugs and agricultural chemicals.

EXPERIMENTAL

All chemicals used in the present investigation were of analytical grade. All the solvents were distilled out. Doubly distilled water was used to prepare the required solutions. ^{1}H NMR spectra were recorded using Jeol (Japan) 300MHZ spectrophotometer. FT-IR spectra were recorded from Nicolet (USA) FT-IR spectrophotometer. Mass spectral analysis has been done from Central Drug Research Institute (CDRI), Lucknow.

Biocatalytic reduction

Immobilization of Baker's Yeast in 5% polyacrylamide gel has been carried out by preparing following solutions.

Solution A: - 10g Acryl amide and 2.5g N, N-methylene bis acrylamide in 100 ml doubled distilled water.

Solution B: - 5.98g Trihydroxy methyl amino methane, 0.46ml N, N, N', N"-tetramethyl ethylenediamine and 48ml 1N Hcl solution to 100 ml solution.

Solution C: - 560mg Ammonium per sulphate in 100 ml doubled distilled water.

Solution D: - 34.2 g Sucrose in 100 ml doubled distilled water.

The solutions were mixed then deareated and allowed to polymerize for nearly 1hr. The resulting gel was cut into small pieces.

Asymmetric Reduction

In a 500 ml flat bottom flask, a mixture of water and glycerol (50:50), fresh Baker's Yeast (free or immobilized) 10 g, sucrose (10 g) was placed and the suspension was stirred for 30 minutes. Chosen Carbonyl Compound (2mM) dissolved in minimum amount of absolute alcohol was then poured into the suspension. The resulting mixture was magnetically stirred for appropriate time (Table 1). After completion of the reaction, the product was filtered using celite (filter aid powder), extraction was done with diethyl ether (30ml) and the procedure was repeated three times. The ether was first evaporated from ether extract and then dried over calcium chloride to yield the product which was then characterized by melting point determination and spectral techniques viz. IR, ^{1}H NMR & Mass (Table-1).

RESULTS AND DISCUSSION

Asymmetric reduction of carbonyl compounds using whole cells of Baker's Yeast as biocatalysts involve two enzyme systems. One of them is the enzyme catalyzing the asymmetric reduction and other is the cofactor regeneration system, which supplies NADPH from $NADP^+$ through the oxidation of the energy source such as sucrose. *Saccharomyces cerevisiae* cells has an extra cellular invertase (β-D-fructosidase), that hydrolyzes sucrose into glucose and fructose, which are transported into the cell by hexose transporters and metabolized through glycolysis. Addition of sucrose to the reaction mixture increases the bioreduction. It is due to enhanced regeneration of the co-factor in Baker's Yeast in the presence of glucose that is used as electron donor.

Although water is the most suitable, natural and neutral solvent for biocatalysis from the viability and activity point of view, glycerol is an alternative green solvent. It has the advantage with respect to substrate solubility and product separation. Therefore asymmetric reduction in a mixture of water and glycerol has

advantages of both the solvents while carrying out the reduction using either free or immobilized whole cells. The reduction carried out using whole cells of immobilized Baker's yeast give high yield as compared to free whole cells due to enhanced operational stability of free Baker's Yeast. Isolation of the products and the facility of repeated reused are extra advantages with this type of Baker's Yeast.

Table: 1 Physical data from free and immobilized Baker's Yeast mediated Reduction

Name of Product	Reaction time (hrs)		Melting point (^{0}C)	Yield (%)	
	FBY	**IBY**		**FBY**	**IBY**
2,4-Dichloro benzyl alcohol	72	96	55	80	82
2-Chloro-6-fluoro benzyl alcohol	72	96	44	78	80
2-Bromo benzyl alcohol	72	96	80	82	83

Spectral data from free and immobilized Baker's Yeast mediated Reduction

2,4-Dichloro benzyl alcohol : IR Data (cm^{-1}):- 3350(OH), 3010 (Ar C-H str),2965(CH-str),1605,1495,1465(C=C ringstr), 1200&1390(C-OstrPh), 1100(C-O str primary alcohol) **^{1}H NMR Data (δ):-** 2.1(O**H**), 4.75(-C**H$_2$**-OH), 7.2(ortho-C**H**), 7.4(meta-C**H**), **Mass Data m/e (M$^+$):-** 177.04

2-Chloro-6-fluoro benzyl alcohol IR Data (cm^{-1}):- 3360(OH), 3010(Ar C-H str), 2970(CH-str), 1605,1525,1470(C=C ring str), 1200&1375(C-O str Ph), 1100(C-Ostr primary alcohol**^{1}H NMR Data (δ):-** 2.1(O**H**), 4.75(-C**H$_2$**-OH) 6.9(meta-C**H**), 7.1(para-C**H**) **Mass Data m/e (M$^+$):-** 160.56

2-Bromo benzyl alcohol IR Data (cm^{-1}):-3355(OH), 3020(Ar C-H str), 2960(CH-str), 1600,1525,1465(C=C ring str), 1200&1385(C-O str Ph), **^{1}H NMR Data (δ):-** 2.0(O**H**), 4.79(-C**H$_2$**-OH),7.3(meta -C**H**), 7.1(para-C**H**) **Mass Data m/e (M$^+$) :-** 187.07

CONCLUSION

The present work is an attempt to apply alternative synthetic routes via Biocatalytic reduction and has merits like specificity and cost effectiveness. This procedure follow green methodology over conventional chemical methods in terms of effectiveness, safety, economy, ecofriendly nature, easy to handle and provide new and improved synthetic routes to many valuable compounds in fields of pharmaceutical, flavor and perfume industry.

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