



Research Article

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A facile and low solvent preparation of HBA's with absence of formaldehyde impurity by the reduction of aldehydes

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ABSTRACT

Hydroxyl benzyl alcohols (abbreviated customarily as HBA's) are the biological relevant molecules due to their excellent neuroprotective effect and free radical scavenging ability. In addition, 4-HBA exhibits inhibitory effect on tyrosinase activity and melanogenesis and warrantee a potential agent for skin lightening to be used in cosmetic products. An efficient, high purity method amenable to the industrial scale manufacture of HBA's is reported. The present work deals with preparation of HBA's with absence of formaldehyde impurity required in pharmaceutical application by the reduction of aldehydes to the corresponding alcohols using sodium borohydride and ammonium carbonate as simple reducing system.

Keywords. Reduction, formaldehyde free, Benzaldehyde, Sodium borohydride-ammonium carbonate, Hydroxyl benzyl alcohols.

INTRODUCTION

Aromatic compounds, with preferred functional groups are key in chemical industries, as they are intermediates for the manufacture of dye stuffs, pharmaceutical, agricultural and photographic chemicals, additives, surfactants textile auxiliaries, chelating agents, and polymers[1,2]. Among these, hydroxyl benzyl alcohols (HBA's) are biologically important molecules as they exhibit excellent neuroprotective effect [3,4,5] and are good free radical scavengers[6,7]. In this regard, 4-Hydroxybenzyl alcohol (4-HBA) is one of the well-known phenolic compounds in diverse plants, displaying a significant inhibition in the chick chorioallantoic membrane (CAM) angiogenesis assay. 4-HBA possesses anti-angiogenic, anti-inflammatory and anti-nociceptive activity possibly via its down-regulating activity on NO production, which may be partly responsible for the pharmacological efficacy of several folkloric medicines [8]. In addition, 4-HBA exhibits inhibitory effect on tyrosinase activity and melanogenesis and warrantee a potential agent for skin lightening to be used in cosmetic products [9, 10].

An important goal in the preparation of relevant organic compounds is the improvement of synthetic efficiency [11]. Moreover, other essential issues such as economical advantages, preservation of our resources, and care of environment, have generated a need for paradigm shift to perform chemical reactions by using ecological safe, inexpensive reagents. A general way to improve synthetic efficiency and also to address the other criteria is the development of multicomponent reactions [12].

HBA's are generally synthesized by reduction of corresponding aromatic aldehydes and variety of reducing agents has been introduced for this achievement [13]. Sodium borohydride (NaBH_4) is a remarkable reducing agent for this purpose as it is safe, inexpensive and milder reagent, which reduces only aldehydes and ketones in protic solvents [14]. Literature survey reveals the extensive use of NaBH_4 in reduction of carbonyl compound to alcohols [15]. The

main limitations of earlier reports were the need of large amount of solvent, low purity and problem in extraction. To circumvent such problems recently rapid, more selective and solvent free reduction methods of synthesis of 4-HBA and 2-HBA were developed [1,16-17]. But the use of expensive catalysts in reduction restricts their industrial application.

The main objective of this work is to describe a facile synthetic procedure of HBA's using sodium borohydride-ammonium carbonate as an effective reducing system. This reaction is mild, environmentally benign, and has been of interest in process chemistry exhibiting the potential of scaling up.

EXPERIMENTAL SECTION

The chemicals and solvents were obtained from the commercial sources and used as received unless otherwise stated. Melting points were measured on Viggo Scientific (I) apparatus. Elemental analysis data were obtained from the Elementar Analysensysteme GmbH vario EL-III instrument. NMR measurements were done using an Avance Bruker 300 MHz instrument at 25°C and were referenced to external SiMe₄ ($\delta=0.00$). Infrared spectra (as KBr pellet) were recorded using Perkin-Elmer FTIR-2000 spectrometer. GC analyses were performed using a GC-2014AF chromatograph equipped with a RTX-624 (0.32mm x 1.8 μ m x 30m) column.

2.1 Typical procedure for the preparation of 3-Hydroxybenzyl alcohol (3-HBA)

A 2 lit. round bottomed flask equipped with a condenser and magnetic stirrer, was charged with 3-hydroxy benzaldehyde (100 g, 0.82 mol) in 1.2 lit ethanol and cooled up to 20°C. Slowly within 15 min, sodium borohydride (31 g, 0.82 mol) and ammonium carbonate (78 g, 0.82 mol) were added to the above solution. The reaction mixture was stirred at room temperature for half an hour. Reaction progress was monitored by TLC. After completion of the reaction the mixture was filtered through a pad of celite and the filtrate was concentrated at atmospheric pressure. The remainder thus obtained was extracted twice with diethyl ether. The combined ether solution was dried over magnesium sulphate. Afterwards most of the solvent was evaporated and the concentrated material was kept in deep freezer for cooling which afforded a solid product. The solid was filtered, dried at 45°C under vacuum to give pure desired.

The compounds 2-HBA and 4-HBA were synthesized using similar procedure as described for compound 3-HBA.

3-Hydroxybenzyl alcohol (3-HBA): 85%. m.p 69-71°C, Anal. Calcd. for C₇H₈O₂; C 67.66, H 6.44, O 25.77, found: C 67.62, H 6.44, O 25.75. IR (as KBr pellet): 3369 ν (aromatic O-H), 1270 ν (C₇-OH), 2932 ν (CH₂), 3060 ν (O-H), 1410, 1458, 1484, 1590 ν (four C=C), 787, 862, 922, 989 γ (C-H), ¹HNMR (300 MHz, D₂O): 4.353 (s, 2H¹, -CH₂), 6.628 (m, 1H²) 6.676 (m, 1H³), 6.740 (m, 1H⁴), 7.106 (t, J = 7.5 Hz, 1H⁵).

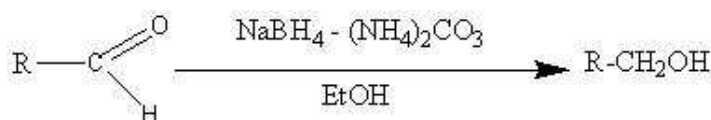
2-Hydroxybenzyl alcohol (2-HBA): 65%. m.p 84-85°C, Anal. Calcd. for C₇H₈O₂; C 67.66, H 6.44, O 25.77, found: C 67.62, H 6.44, O 25.75. IR (as KBr pellet): 3447 ν (aromatic O-H), 1267 ν (C₇-OH), 2963 ν (CH₂), 3163 ν (O-H), 1458, 1482, 1596, 1615 ν (four C=C), 751, 851, 938, 994 γ (C-H), ¹HNMR (300 MHz, D₂O): 4.500 (s, 2H¹-CH₂), 6.762 (m, 1H²) 6.842 (m, 1H³), 7.106 (m, 1H⁴), 7.175 (m, 1H⁵).

4-Hydroxybenzyl alcohol (4-HBA): 72%, m.p 114-116°C, Anal. Calcd. for C₇H₈O₂; C 67.66, H 6.44, O 25.77, found: C 67.62, H 6.44, O 25.75. IR (as KBr pellet): 3388 ν (aromatic O-H), 1290 ν (C₇-OH), 2966 ν (CH₂), 3109 ν (O-H), 1458, 1519, 1560, 1612 ν (four C=C), 716, 836, 941, 994 γ (C-H), ¹HNMR (300 MHz, D₂O): 4.403 (s, 2H¹-CH₂), 6.776 (m, 2H^{2/2'}), 7.153 (m, 2H^{3/3'}).

RESULTS AND DISCUSSION

The selective reduction of aldehydes and other substituted moieties is a fascinating area of research, particularly when other potentially reducible moieties are present in the molecule. Furthermore, the choice of inexpensive and efficient systems of reduction is important criterion to be fulfilled for a potential use in industrial process. As our aim was to develop an industrial production process, we restricted ourselves to the kinds of reduction reactions that were generally applicable to ordinary chemical plants. Therefore, for detailed study we decided to concentrate on the reaction reported by F. Mohananzadeh et al [18]. They achieved the reduction of carbonyl compounds by sodium borohydride and ammonium carbonate system in protic solvent.

While installing the synthetic experiments for a representative reaction of 3-hydroxy benzaldehyde to 3-hydroxy benzyl alcohol, we process developed synthetic and extraction procedures for 3-HBA. We worked to modify the reaction parameters such as amount of solvent and reaction time etc. so that the protocol becomes more feasible for large scale production of 3-HBA. The applicability of this reducing system was further explored on the analogous reduction of 4-hydroxy benzaldehyde and 2-hydroxy benzaldehyde (Scheme 1).



R=2/3/4-hydroxy aryl derivatives

Scheme1. General Synthetic scheme for HBA's

These reductions were also efficient with excellent purity. The purity of all the HBA's by GC is very high more than 99%. However, the yields are not as good as in case of 3-HBA. The results are summarized in Table 1.

The most striking feature of this synthetic procedure is the absence of formaldehyde impurity, which was detected when 4-HBA was synthesized with other synthetic strategies. Many bulk drug manufacturing companies especially require 4-HBA with negative test of formaldehyde for using it as starting materials in the production of various API's.

Firstly, the amount of ethanol used in the reduction of 3-hydroxy benzaldehyde was reduced by 10 times. Since on the large scale, a far greater amount of solvent and larger reaction vessel are required for this, which would lead to higher manufacturing cost and inconvenience in handling. The same reduction in the amount of solvent for 4-HBA and 2-HBA were attempted, but this resulted in reduces yields. Therefore, 8 times solvent reduction conditions were applied for 4-HBA and 2-HBA. Furthermore, many significant changes were made in the extraction process which was explained in the synthetic procedure of experimental section.

The separation of HBA's in the present protocol is straightforward comparable to column chromatography required in other synthetic procedures which, makes our protocol more applicable for large scale production.

Table 1 Reduction of Benzaldehydes with NaBH₄/(NH₄)₂CO₃ System^a

S. No.	Substrate	Product	Time (h)	Yield (%) ^b	Purity (GC)
1	2-hydroxy benzaldehyde	2-HBA	0.6	65	99.4
2	3-hydroxy benzaldehyde	3-HBA	0.5	85	99.8
3	4-hydroxy benzaldehyde	4-HBA	0.8	72	99.6

^aAll reactions were performed in C₂H₅OH at room temperature; ^bYields referred to isolated pure products

3.1 HBA's characterization

The structures of HBA's were deduced from their elemental analysis, IR and ¹HNMR spectra. The IR spectrum of 3-HBA showed characteristic band at 3369 cm⁻¹ ascribed to ν(O–H) of aromatic alcohol. A broad and intense band in the region 3000-3270 cm⁻¹ assigned to ν (O–H) stretching mode in bonded form. These assignments are in agreement with Sing et al [19]. The CH₂ stretching vibrations in 3-HBA are attributed to the group of bands in the range 2950-2865 cm⁻¹ which is in agreement with the assignment of methylene stretching in cyclohexane and other alkanes [20,21]. Additionally, signals observed in the region 1400-1620 cm⁻¹ were attributed to the characteristic skeletal stretching modes of C–C bond of aromatic ring [22]. The ¹HNMR spectrum of 3-HBA in D₂O exhibited a sharp singlet at 4.35 ppm due to –CH₂ group proton. Signals in the range 6.62-7.10 ppm arise due to aromatic protons [23]. Partial assignments of these resonances are given in experimental section. The IR and ¹H NMR spectra of 2-HBA and 4-HBA are similar to those of 3-HBA and exhibited characteristic signals (see Experimental Section).

CONCLUSION

A scalable process for the synthesis of 3-HBA from readily available 3-hydroxy benzaldehyde using sodium borohydride-ammonium carbonate as reducing system has been process developed by judicious changes in the synthetic and extraction process. The use of expensive catalysts, column chromatographic purification were not required which, established the usefulness of this protocol in a large scale laboratory. Furthermore, this synthetic method has shown its applicability to the preparation of 2-HBA and 4-HBA's with absence of formaldehyde impurity. Thus considering the high efficiency, low solvent, isolation method change, simple working up procedure

and use of inexpensive chemicals, and this protocol can be attractive for a synthetically useful addition to the present methodologies.

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