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SYNTHETIC APPLICATION OF 4-HYDROXY BENZYL ALCOHOL FOR ENANTIOMERICALLY PURE BETA AMINO ALCOHOLS

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ABSTRACT

An ecofriendly and cost-effective ultrasonication procedure was adapted for the synthesis of different beta amino alcohol derivatives. An enantiomerically pure isomers were synthesized using pure R-epichlorohydrin. These products were isolated and characterized with spectral techniques.

KEYWORDS: Ecofriendly Catalysts, Amberlyst 15, Ultrasonication, Enantiomeric pure, R-epichlorohydrin, S-epichlorohydrin, Bisphenol, N-methyl piperazine, Drug release, Chiral HPLC purity, Amberlyst A21.

INTRODUCTION

4-hydroxybenzyl alcohol derivatives have their own importance in pharmaceutical applications. Some natural products were metabolized into 4-hydrobenzyl alcohol[1] in the human body. It can be used as a standard marker compound or precursor compound with additional advanced strucutre modifications and introducing novel side chains. Its derivatives are considered to be more effective, potent sedatives and hypnotic reagents.[2-6]Epoxy resins and polymers have huge applications in circuit boards, aerospace industries, and electric insulators. They have good thermostability.[7] Direct chemical reactions generate both desired and side products as well. And hence from research to practice, we need to implement safe act along with ecofriendly, greener approach. Use of corrosive chemicals and solvent reagents to find alternatives for them with respect to cost and health will be the always part of development for scientists.

Generally catalyzed reactions minimize and eliminate hazardous wastes, time and cost. Biocatalyzed eg enzyme, metal catalyzed reactions generate less side products. Here in this research topic, we have tried to approach well known green reagents, recovery of solvents, recycling of reagent and solvents wherever possible.

EXPERIMENTAL

Synthesis of compound 1 (4-hydroxy benzyl alcohol) (KSM II):

To a stirred solution of the commercially available 4-hydroxy benzaldehyde (KSM I) 100g in 500mL methanol, 0.5 mol eq of NaBH4 was added portion wise at cooled condition (5°C to 10°C). Complete conversion of reactant to product was verified with the help of TLC. Then added little ice-cold water (approx. 10ml) and excess methanol solvent was evaporated under reduced pressure. Then an additional quantity of water 100mL was added and the solid was filtered, dried, characterized by Mass and IR. [Fig.1]. Yield 95%, mp: 110.1°C. IR (cm^{-1}): 3377(OH), 1560, 1270(C-OC),991.

Synthesis of 4-[(2-Isopropoxy ethoxy)methyl]phenol (A1-A3):

To a solution of above compound KSM II, 5g (1 mole eq), excess of respective substituted ethanol (2-isopropoxy ethanol, A4) (25mL) and Amberlyst A21 catalysts in suitable round bottom flask were kept in ultra sonication water batch at room temperature. The reaction completion was monitored by TLC. After completion of the reaction 100mL water was added and extracted with ether (100mL x2). Collective organic layer dried over sodium sulfate and was allowed dry under vacuum. The oil compound was obtained and characterized by mass and HNMR. Yield: 65%. MS ESI (m/z) 209.9. HNMR (400MHz, CDCl3): 7.20(d,2H,phenyl-H),7.0(s,1H,hydroxy),6.89(d,2H,phenyl-H),4.50(s,2H,methylene),3.80(s,1H, methyleneCH),3.50(d,4H,CH2), 1.10(d,6H). IR(cm-1): 3420(OH), 2917(CH), 1120(C-OC).

Synthesis of (S)-2-((4-((2-isopropoxy ethoxy)methyl)phenoxy)methyl)oxirane (B1-B3): To a stirred solution of above compound A1-A3, 4g (1 mole eq), excess of R-epichlorohydrin

(20mL) and Amberlyst 15 2mole eq was kept under 50°C heating conditions in ultrasonication bath. The reaction completion was monitored by TLC. After completion of the reaction 100mL water was added and extracted with ethyl acetate (100mL x2). Collective organic layer dried over sodium sulfate and was allowed dry under vacuum. The oil compound obtained was subjected to flash column chromatography purification. After purification in hexane: ethyl acetate solvent, oil compound was obtained. It was verified by mass and HNMR. Yield: 70%. Oxirane: MS ESI 266.0. ^{1}HNMR (400MegaHz, CDCl3):7.40(d,2H, phenyl-H),7.91(d,2H, phenyl-H),4.50(s,2H,methylene),4.20(d,1H,methylene),3.80(d,1H,methylene),3.51(m,7H,methylene),3.20(d,1H),1.10(d,6H). IR (cm-1): 2970, 2927(CH),1612,1511(C-OC), 1222,771.

Synthesis of (S)-1-Isopropylamino-3- [4-(2-methoxyethoxy)methyl]-phenoxy-2- propanol (C1): To a stirred solution of above synthesized compound B1-B3, 1g (1 mol eq.) and excess of isopropyl amine and aqueous ethanol was kept under stirring for 1-2 hrs. Reaction completion was checked by performing lab TLC. After complete consumption of the starting material added 50mL additional water and extracted with (100mlx2) ethyl acetate. The combined organic layer was dried over sodium sulfate and evaporated to dryness to get crude compound (C1-C3). It was subjected for flash column purification to get pure enantiomerically S-isomer of respective beta amino alcohols C1-C3. Sticky compounds. Yield: 67-82%. Ms ESI 298.3; ^{1}HNMR(400MegaHz,$CDCl_3$):7.40(d,2H,phenyl-H),6.90(d,2H,phenyl-H),4.60(s,2H,methylene),4.10-3.90(m,3H),3.60(m,7H,methylene),2.90(m,3H,CH),1.10(s,6H). IR (cm^{-1}): 3450(OH), 2927, 1513(C-OC), 1244, 1095, 1028(CH).

(S)-1-(4-((2-ethoxyethoxy)methyl)phenoxy)-3-(isopropylamino)propan-2-ol (C2): MS-ESI312.1. ^{1}HNMR(400MHz CDCl3):7.40(d,1H,phenyl-H), 7.20(d,1H,phenyl-H), 6.90(d,2H,phenyl-H),4.60(s,2H,methylene),4.10-3.90(m,3H),3.60(m,6H,methylene),2.80(m,3H,CH),1.20(t,3H,methyl),1.10(s,6H).IR(cm^{-1});3356(NH),2931,1513(C-OC),1244,1095,1028(CH). Yield: 67%.

(S)-1-Isopropylamino-3-[4-(2-propoxy ethoxymethyl) phenoxy]propan-2-ol (C3):MS-ESI:326.3;^{1}HNMR(CDCl3):7.40(d,2H,phenyl-H),6.90(d,2H,phenyl-H),4.60(s,2H,CH

$_2$),4.10-3.90(m,3H,methylene),3.60(m,6H,methylene),2.90(m,3H,CH),2.40(q,2H,CH),1.10(s,6H).0.90(t,3H,methyl). IR (cm^{-1}): 3450(OH), 2927, 1513 (C-OC),1244,1095,1028(CH).

Synthesis of N-benzyl-N-methyl -2-((4-(2-(4-methylpiperazin-1-yl)ethoxy)benzyl) oxy)ethan-1-amine (E): To a stirred solution of 1g (1 mol eq.) 4-hydroxy benzaldehyde (KSM I), 20mL solvent DMF, 0.45g (1.1 mol eq.) potassium carbonate and 2-chloroethyl-N-methyl piperazine 0.5g (1 mol eq.) was added and reaction completion was monitored by TLC**.** After the complete conversion of KSM I, 100mL water was added into it and extracted with ethyl acetate. Collective organic layer was dried over sodium sulfate and evaporated under reduced pressure. The intermediate compound D was processed further as such for next step of NaBH4 reduction in methanol solvent. The alcohol product was isolated from the reaction mass and used for the next step coupling reaction with 2-Chloroethyl-N-methylbenzyl amine in presence of potassium carbonate base and DMF solvent. Reaction progress was monitored by TLC. After complete conversion of the starting material, an additional quantity of 100mL water was added and extracted with ethyl acetate. The combined organic layer was dried over sodium sulfate and evaporated under vacuum to get crude compound E. It was purified using flash chromatography to get pure compound. Overall Yield 58%. Oil compound. Direct MS ESI 396, 438(M+39). ^{1}HNMR (400MegaHz, CDCl3); 7.42-7.01(m,9H,phenyl-H), 4.51(m,2H, methylene),4.01(m,4H,methylene),3.52(m,4H,methylene),3.2(m,6H),2.81(m,4H),1.2(s,6H,methyl).

Synthesis of methyl (S)-4-(2-hydroxy-3-(isopropyl-amino)propoxy)-benzoate (4a):

To a stirred mixture of 4-hydroxy methyl benzoate 2g (1 mole eq) was subjected for treatment with R-epichlorohydrin and isopropyl amine step as mentioned in C1 compound step to get desired S-isomer of compound 4a. It was purified by flash chromatography to get oil compound. [Fig. 2]. Yield 90%. Ms ESI 268.0; ^{1}HNMR ($CDCl_3$): 8.10(d,2H,phenyl-H),6.90(d,2H,phenyl-H),4.20(s,3H,methylene),3.80(s,3H,methoxy),2.90(m,3H,methylene),1.10(s,6H,isopropyl). IR (cm^{-1}): 3387(OH), 3370(NH), 2925, 1715(ester), 1513 (C-OC),1244,1195,1128(CH).

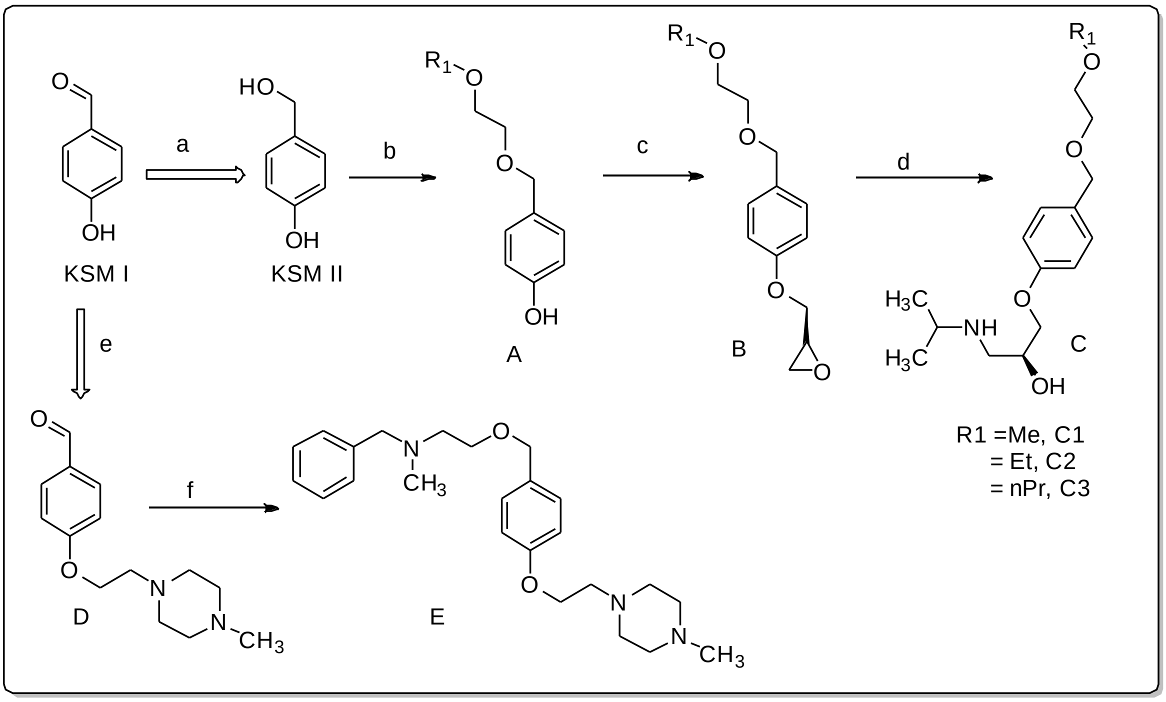

Fig 1: Synthetic scheme for compound C1 to C3 and E.

Reaction condition: a) methanol, NaBH4 b) R1O(CH2)-OH, Amberlyst A21, ultrasonication c) R-epichlorohydrin, Amberlyst A21 d)aq ethanol, isopropanol e) 2-chloroethyl-N-methyl piperazine, K2CO3, DMF f)K2CO3, DMF, 2-Chloroethyl-N-methylbenzyl

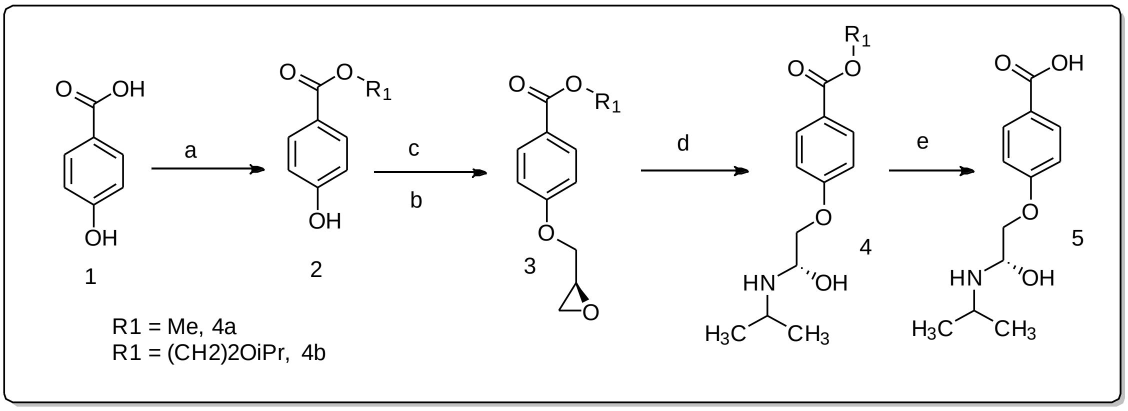

Fig. 2 Synthetic scheme for compound 4a,4b and 5.

Reaction conditions: a)Cat. H2SO4, MeOH, b) KHPO4, Toluene, isopropoxy ethanol, dean stark, heat c)R-epichlorohydrin, Amberlyst A21,ultrasonication d) isopropyl amine, aq ethanol e) aq NaOH, ethanol

Synthesis of (S)-4-(2-hydroxy-3- (isopropyl-amino)-propoxy) benzoic acid (5): Above compound 4a was subjected to basic hydrolysis (ethanol and aq. NaOH at 95°C) till complete conversion of ester and pH of reaction mixture made acidic to get the respective white solid acid compound. Yield 90%. MS ESI 254.0; ^{1}HNMR

($CDCl_3$):12.01(bs,1H,Acid),9.20(s,1H,hydroxy),7.90(d,2H,phenyl-H),7.10(d,2H,phenyl-H),6.0(s,1H),4.20(s,3H,methylene),3.10(s,3H,CH),1.10(s,6H,isopropyl). IR (cm^{-1}): 3398(OH), 2964, 1685(acid), 1170 (C-OC),850(CH). Melting point: 239.3°C.

Synthesis of 2-isopropoxyethyl (S)-4-(2-hydroxy-3-(isopropyl-amino)-propoxy) -benzoate(4b): In a suitable round bottom flask 2g (1 mol eq) 4-hydroxy methyl benzoate was mixed with KHPO4 (1 mol eq), toluene 50mL and 2-isoproxy ethanol (1 mole eq) and kept under reflux condition in as dean stark apparatus. The trans esterification reaction was verified with TLC and after complete conversion into product it was allowed to cool at room temperature. Then the organic layer was washed with water (100mlx2) and collective organic layer was evaporated under reduced pressure. The crude product was purified using flash chromatography using hexane and ethyl acetate solvent. It was further treated with chiral R-epichlorohydrin and then isopropyl amine as per procedure mentioned in C1 compound. From isopropyl amine step the desired 4b compound was obtained.

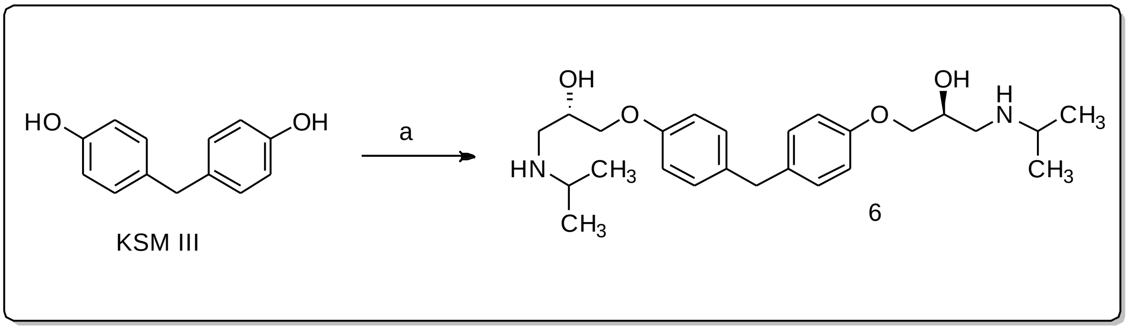

Fig:3 Synthetic scheme for compound 6

Reaction condition: a) R-epichlorohydrin, Amberlyst A21 cat, ultrasonication.

It was purified by column chromatography to oil compound. Yield: 78%. MS ESI 340.1; ^{1}HNMR(400MHz$CDCl_3$):7.90(d,2H,phenyl-H),7.10(d,2H,phenyl-H),4.40(s,2H,methylene), 4.0 (m,3H),3.80(s,3H,methylene),3.20-2.90(s,3H),1.10(d,12H,isopropyl). IR (cm^{-1}): 3282(NH), 2968, 1708(ester), 1606, 1255 (C-OC),844(CH).

Synthesis of (S)-1-(4-(4-((S)-2- hydroxy-3-(isopropylamino)- propoxy) benzyl)phenoxy)-3-(isopropylamino)propan-2-ol (6): Compound 6 was prepared from KSM III bisphenol, R-epichlorohydrin and followed by isopropyl amine stage as mentioned in similar compound preparation in B1 to C1. The crude compound 6 was purified by column chromatography and using DCM: MeOH to get pure bis beta amino alcohol compound 6. Sicky liquid compound. [Fig.3].Yield 83%. MS ESI 431.2; ^{1}HNMR(400MHz $CDCl_3$): 7.41(d,4H,phenyl-H),6.90(d,4H,phenyl-H),4.60(s,2H,methylene),4.10(m,2H,CH),4.0(d,4H,methylene),3.0(d,4H,methylene,2.90(d,2H,CH),2.67(m,2H,methylene),1.20(d,12H,isopropyl). IR (cm-1): 3298(hydroxy), 2922(CH), 1512, 1242(C-OC), 1026.

MATERIALS AND METHODS

Lab grade and commercial grade chemicals were used. Also, products isolation was done with the help of flash chromatography. Isolated products were identified by NMR and Mass spectra, HPLC purity verified with Shimadzu liquid chromatography. The reactions were monitored with standard TLC image reader technique. Thin-layer chromatography (TLC) was run on silica gel 60 F254 pre-coated plates (0.25 mm, Merck, Art. 5554) and spots were visualized inside an UV cabinet under short UV. Infrared spectra were recorded on IR Affinity-1, Shimadzu. 1H-NMR spectra were recorded on Bruker Advance III, 400 MHz with TMS as an internal standard. Mass spectra were obtained using LC-MS API-2000, ABSciex. Yields mentioned are from unoptimized reaction condition, of isolated pure product.

RESULTS AND DISCUSSION.

4-hydroxy benzyl alcohol with acid and amine substituents have versatile applications and have a vital role in the medicinal applications. They have reported for sedative properties an agent for insomnia therapy. Beta amino alcohols and protected compounds are converted into secondary amino alcohols. These are known as the good precursor for pharmaceutical and agrochemical compounds.[7] The asymmetric ring-opening (ARO) reaction of epoxides with amines is the most straightforward route to prepare β-amino alcohols. In recent years, several catalysts have been studied for such type of research. These compounds are useful for the synthesis of bioactive compounds like cardiovascular, antihypertensive, beta blockers, antimalarial drugs.[8]

Here 4-hydroxy benzyl alcohol derivatives were synthesized and confirmed with mass, HNMR and IR spectroscopy. Chiral HPLC purity is performed to check enantiomeric purity. R-epichlorohydrin gives S-isomer of the beta amino alcohol after epoxide ring opening and S-epichlorohydrin gives R-isomer of it. It was verified by specific optical rotation in ADL lab.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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