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Synthesis and characterization of 4,4'-oxybis[N-ethyl-n-[1(RS)-2-(4-methoxy phenyl)-1-methylethyl]butan-1-amine]

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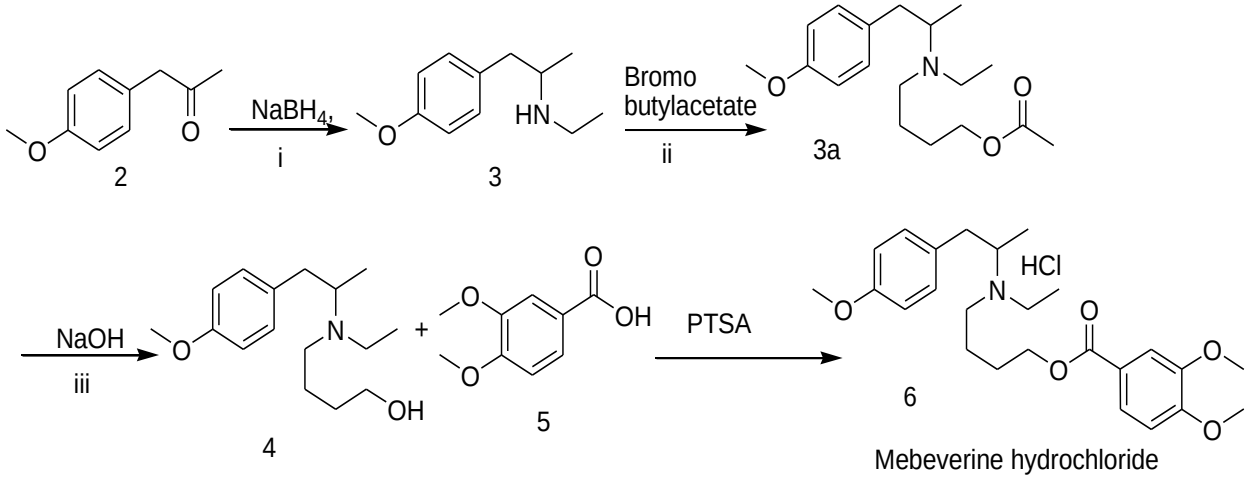
Abstract
The Proposed synthetic process of 4,4'-oxybis[N-ethyl-n-[1(RS)-2-(4-methoxy phenyl)-1-methylethyl]butan-1-amine] started with 4-methoxy phenyl acetone 2 was participated in reductive amination with aqueous ethylamine in presence of Sodium boro hydride obtained material 3 was reacted with bromo butanol we get 4 self coupling of compound No 4 in presence of *para* toluene sulphonic acid in toluene. we get target 1 and it was characterized by ^{1}HNMR and MASS

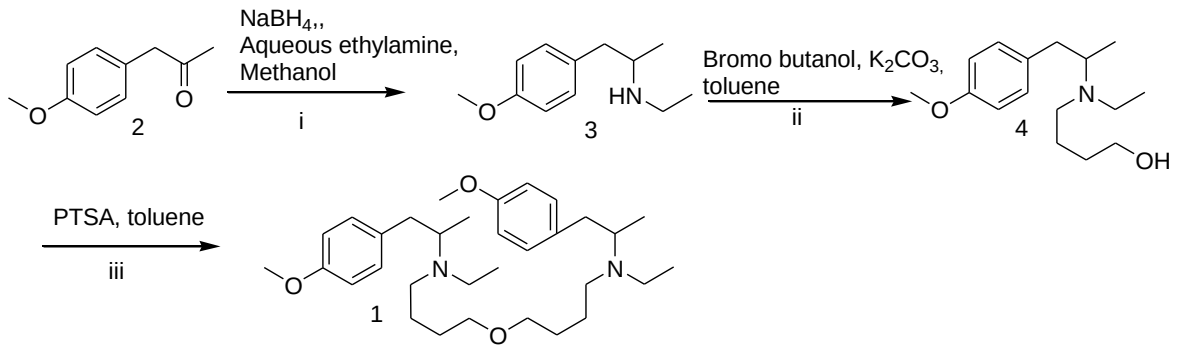
INTRODUCTION

The 4,4'-Oxybis[N-ethyl-n-[1(RS)-2-(4-methoxy phenyl)-1-methylethyl]butan-1-amine] 1 was reported impurity of Mebeverine hydrochloride (Drug) in European pharmacopoeia as a impurity J and we observed process impurity of Mebeverine hydrochloride in scheme-II during manufacturing ranging 0.1 to 0.2% were detected in HPLC. As of now no synthetic route was available. In this paper, new synthetic route for 1 was designed in scheme-I. All the reaction condition are well established very easy handling and used low cost reagents and key starting material

Scheme-II (Reported in **Indian patents: 201841023171(A))**



Scheme-1:



EXPERIMENTAL:

Preparation of N-Ethyl-1-(4-methoxyphenyl) propan-2-amine [1-4]:

10. 0 g of 4-methoxy phenyl acetone, 25 ml of aqueous ethyl amine and 60 ml of methanol was taken 250 ml RBF. Cool the reaction mixture -5 to 0 °C and slowly add sodium boro hydride 3.0 g at same temperature then the reaction mixture was maintained for1hr after maintenance check the 4-methoxy phenyl acetone content by HPLC or TLC (limit NMT 1.0 %).

Work up: Charge water and toluene into reaction mass, stir the reaction mass for 5 to 10 min and separated the organic layer and aqueous layer. Distilled the organic layer completely. After distillation required N-Ethyl-1-(4-methoxyphenyl) propan-2-amine was obtained .

^{1}H NMR (DMSO d_6, 400 MHz):7.08 (s, 2H), 6.84 (s, 2H), 2.99 (s, 3H), 2.76-2.36 (m, 5H), 0.99-0.90 (m, 6H)

Mass (M+H): 194.2

Weight : 8.0g Purity: NLT 95.0

Preparation of 4-(N-Ethyl-N-(1-(4-methoxyphenyl) propan-2-yl) amino)butan-1-ol

10.0 g of N-Ethyl-1-(4-methoxyphenyl) propan-2-amine was reacted with 22.0 g of 4-bromobutanol in presence of 30.0 mL toluene at 75-85°C for 24 to 30 hrs. After completion of reaction by HPLC or TLC (limit NMT 2.0%)

Work up: Cool the reaction mass to 25-35°C and charge 10.0 mL of Con HCl and maintained for 30 min then separated the toluene layer and aqueous layer (contains product). Aqueous layer basified and extracted with toluene followed by distillation to get the 4-(N-Ethyl-N-(1-(4-methoxyphenyl) propan-2-yl)amino)butan-1-ol.

^{1}H NMR (DMSO d_6, 400 MHz):7.08-7.06 (d, 2H), 6.82-6.80 (d,2H), 4.51-4.49 (m, 1H), 3.70 (s, 3H), 3.36 (t, 3H), 2.88-2.83 (m, 1H), 2.73-2.68 (m, 1H), 2.43-2.29 (m, 4H), 1.38-1.37 (m, 4H), 0.95(t, 3H), 0.83-0.82 (d, 3H)

Mass (M+H): 266.2

Preparation of 4,4'-oxybis[N-ethyl-n-[1(RS)-2-(4-methoxy phenyl)-1-methylethyl]butan-1-amine]

10.0 g of 4-(N-Ethyl-N-(1-(4-methoxyphenyl) propan-2-yl) amino)butan-1-ol, 100.0 ml of toluene and 13.0 g of Para toluene sulphonic acid was taken in 250.0 mL RBF along with azeotropic system for water collection resulting mixture was reflux for 10 hrs.

Workup: after completion reaction charge water 50 mL and slowly adjust the NLT pH 11at 25-35°C

and separated toluene layer and aqueous layer, distilled the toluene layer completely after distillation crude 4,4'-oxybis[N-ethyl-n-[1(RS)-2-(4-methoxy phenyl)-1-methylethyl]butan-1-amine] was obtained the above crude was purified in coloumn chromatography using with 100-200 silica and Ethyl acetate and Hexane.

^{1}HNMR (DMSO d_6): 0.83 (d, 6H), 0.94 (t, 6H), 1.43-1.31 (m, 6H), 1.90 (m, 8H), 2.42-2.37 (m, 4H),2.88-2.83 (m, 2H), 3.27 (t, 4 H), 3.69 (s, 6H), 6.80 (d, 4 H), 7.06 (d, 4H)

Mass (M=H):513.4

CONCLUSION:

Synthesis of 4,4'-oxybis[N-ethyl-n-[1(RS)-2-(4-methoxy phenyl)-1-methylethyl]butan-1-amine] was characterized by ^{1} HNMR and Mass along with supporting intermediates also characterized and all reaction condition are well optimized. Reported process was very use full for commercial manufacturing of Mebeverine hydrochloride as a impurity – J in European pharmacopoeia

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Conflict of interest

The authors do not have conflict of interest on the results disclosed in the publication of the present results of the study

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