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Original Article

An efficient and safe process for synthesis of doxylamine succinate

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ABSTRACT

Described herein is an improved synthesis of N,N-dimethyl-2-[1-phenyl-1-(pyridine -2-yl)ethoxy]ethanamine succinate **(1)**. The synthesis comprises steps i) reacting compound of 2-acetylpyridine and bromobenzene in presence of magnesium turning, tetrahydrofuran and toluene solvents to obtained 2-pyridylphenylmethyl carbinol HCl **(4)** ii) reacting compound **4** with 2-dimethylaminoethyl chloride hydrochloride in presence of potassium hydroxide and toluene solvent to obtained N,N-dimethyl-2-[1-phenyl-1-(pyridine-2-yl)ethoxy]ethanamine **(6)** and iii) treatment of compound **6** with succinic acid in acetone solvent to obtain **1**. The present work provides safe, robust and commercial viable manufacturing process for the synthesis of **1** having purity ≥ 99.5%.

Keywords: Doxylamine, Doxylamine succinate, anthistamine, potassium hydroxide, 2-acetylpyridine

INTRODUCTION

Doxylamine succinate having chemical name N,N-dimethyl-2-[1-phenyl-1-(pyridine -2-yl)ethoxy] ethanamine succinate is an antihistamine of the ethanolamine class [1], used as sleep inducing drug and in the therapeutic formulation of Bendectinem as an anti-nausea agent taken by pregnant women [2]. Literature review revealed that Nathan et al [3] developed method for synthesis of Doxylamine using 2-acetylpyridine and bromobenzene with magnesium turning to generate insitu Grignard reagent in presence of anhydrous ether followed by reaction with 2-dimethylaminoethyl chloride using sodamide as strong base in xylene. Charles et al [4] reported preparation of Doxylamine succinate salt by treating doxylaminen base with succinic acid in isopropyl alcohol. Chiral Doxylamine succinate is prepared by reacting acetopheneone and phenylboric acid using chiral ligand, diethylzin and $Ti(iPO)_4$ in toluene solvent followed by reacting with 2-dimethylaminoethyl chloride and further preparation of its succinate salt [5]. The process is complicated to operate with use of large amount of solvent and costly chiral reagent which increases overall cost of production. Also reported process for preparation of **1** using key intermediates **2**, **3** and **4** suffers major drawbacks [5-8]. Like its required longer reaction time with tedious work up procedures, low yields, involves high vacuum distillation for isolation of pure intermediate 2-pyridylphenylmethyl carbinol and use of pyrophoric base such as sodamide, sodium hydride [6-8]. In view of above literature data, there is need of development for high efficient process with safer base which can be easy handle in large scale production. Thus, the present work we used potassium hydroxide as a safer base which replaced the pyrophoric bases like Na metal, sodium hydride and sodamide. Also present process has high process efficiency, simple post-treatment process, higher product yield and quality with low cost technology for industrial production of Doxylamine succinate.

MATERIAL AND METHODS

Melting point of the synthesized Doxylamine succinate was determined in open capillary tubes and uncorrected. The progress of reaction was monitored on TLC using hexane:ethyl acetate (9:1) as eluent. IR spectra were recorded on Shimadzu FTIR 8400 spectrophotometer. ^{1}H NMR spectra were recorded on Bruker spectrometer 400MHz (chemical shifts in δ ppm). The solvents for NMR spectra were deuterochloroform ($CDCl_3$) and deuterodimethylsufloxide (DMSO-d6) unless otherwise stated. Mass spectra was recorded on a mass spectrometer at an iononizing voltage of 70

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eV. All the chemicals used were of analytical grade.

Synthesis of 2-pyridylphenylmethyl carbinol HCl (4): To (13.2 g, 0.540 mol) of magnesium turning in 50 ml THF, 0.1 ml dibromoethane was added and heated reaction mass to 60°C. To stirred mixture, solution of bromobenzene (**2,** 84.3 g, 0.536 mol) in 50 ml THF was added dropwise at a rate which produce rapid reflux. After complete addition the suspension was stirred at reflux temperature for an additional 1.5 hrs. To the grey reaction mixture added 75 ml toluene and raised temperature to 90-95°C and added solution of 2-acetylpyridine (**3,** 50.0 g, 0.412 mol) in 75 ml toluene and stirred for additional 10 hrs. After completion of reaction, (monitored on TLC) quench reaction mass with cold dilute hydrochloric acid to pH 6-7 and extracted with toluene. The toluene layer washed with water and dried over sodium sulfate. Organic layer then acidified with IPA-HCl to give pale yellow solid **4** as 2-pyridylphenylmethyl carbinol HCl. Yield-78 % Purity-99% .

Mass-200.2 [M+H]+
^{1}H-NMR:(400MHz, DMSO-d_6): δ2.09 (s, 3H, CH_3), 5.5-9.8 (bs, D_2O exchangable proton, 2H), 7.25-7.29 (m, Ar-H, 1H), 7.33-7.37 (m, Ar-H, 2H), 7.51-7.53 (m, Ar-H, 2H), 788-7.92 (m, Ar-H, 1H), 8.07-8.09 (m, Ar-H, 1H), 8.48-8.52 (m, Ar-H, 1H), 8.69-8.71 (m, Ar-H, 1H)

N,N-dimethyl-2-[1-phenyl-1-(pyridin-2-yl)ethoxy]ethanamine (6): 2-Pyridylphenylmethyl carbinol HCl (50g, 0.212 mol) dissolved in 400 ml water, basified with 20% NaOH solution and extracted in toluene. To organic layer added KOH pellets (53.5g, 0.954 mol) and stirred for 30 minute (as solution A). During this period, a toluene solution of dimethylaminoethyl chloride was prepared (as solution B): To a solution of dimethylaminoethyl chloride hydrochloride (**5**, 53.5 g, 0.371 mol) in about 25 ml water and 135 ml toluene added. The mixture cooled to 0-5°C and basified with NaOH solution. Organic layer separated & aqueous layer re-extracted with 135 ml toluene to obtained solution B. This solution B added to solution A over a period of 45 minutes and reaction mixture refluxed for 12 hours. After completion of reaction (monitored on TLC), cool reaction mixture and washed with water. Organic layer subjected to acid base treatment to remove impurities which on distillation gave **6** as *N,N*-dimethyl- 2-[1-phenyl-1-(pyridin-2-yl)ethoxy] ethanamine. Yield- 91%. Purity-99% Mass: 271 [M+H]+ . ^{1}H-NMR: (400MHz, $CDCl_3$): δ2.0 (s, 3H, CH_3), 2.28 (m, 6H, -N(CH_3)$_2$), 2.59-2.62 (m, 2H), 3.40-3.45 (m, 2H), 7.09-7.12 (m, Ar-H, 1H), 7.20-7.22 (m, Ar-H, 1H), 7.27-7.31 (m, Ar-H, 2H), 7.41-7.43 (m, Ar-H, 2H), 7.61-7.63 (m, Ar-H, 2H), 8.52-8.54 (m, Ar-H, 1H).

Doxylamine succinate (1): A solution of doxylamine (**6**, 35g, 0.129 mol) and succinic acid (15.3g, 0.129 mol) was added 105 ml of acetone was heated at reflux until the solid dissolved, stirring continued for 1 hour, cooled reaction mass to room temperature and stirred for 1 hour, solid precipitates out filtered to give **1** doxylamine succinate. Yield-80%, GC Purity-99.7%. Mass: 271 [M+H]+, ^{1}H-NMR (400MHz, $CDCl_3$): δ1.99 (s, 3H, CH_3), 2.53 (s, 4H), 2.78 (s, 6H), 3.16-3.18 (m, 2H), 3.59-3.65 (m, 2H), 7.15-7.16 (m,Ar-H, 1H), 7.20-7.24 (m, Ar-H, 1H), 7.28-7.35 (m, Ar-H, 4H), 7.53-7.55 (m, Ar-H, 1H), 7.65-7.69 (m, Ar-H, 1H), 8.53-8.54 (m, Ar-H, 1H), 11.38 (s, 2H).

RESULTS AND DISCUSSION

Synthesis of 1 was explored from a basic key starting materials i.e. 2-acetylpyridine, bromobenzene and 2-dimethylaminoethyl chloride hydrochloride by systematic understanding of reaction parameters contributing to the yield and quality and then systematic optimization study was conducted to establish the scalable, economic and production friendly process (Scheme 1).

Grignard reaction on 2-acetylpyridine using bromobenzene was explored with different solvents and temperatures like diethyl ether, tetrahydrofuran, toluene and mixture of tetrahydrofuran-toluene. Among the explored combination of solvent and temperature, use of tetrahydrofuran-toluene as a solvent and 90-95°C temperature furnished desired yield of 78% with GC purity > 99%. Further, volume of tetrahydrofuran-toluene, mole ratio of 2-acetylpyridine: bromobenzen: magnesium and temperature for reaction optimized and as per the optimized process 8 volumes of tetrahydrofuran-toluene and 1:1.3:1.31 moles of acetylpyridne: bromobenzene: magnesium and 90-95°C temperature were found to be optimum for the reaction. Since the purity of the isolated material was over 99%, we proceeded to next step without further purification.

Next stage was explored using 2-dimethylethyl chloride and different bases like sodium hydride, sodium hydroxide, potassium hydroxide, sodium carbonate and potassium carbonate and solvents like toluene and xylene. Among the explored combination potassium hydroxide and sodium hydride furnished desired yield 90-92% but potassium hydroxide gave the better quality having GC purity > 98%. Further, volume of toluene, mole

ratio of potassium hydroxide: 2-dimethylethyl chloride hydrochloride and temperature for reaction were optimized and as per the optimized process 8 volumes of toluene, 4.5 moles of potassium hydroxide and 1.75 moles of 2-dimethylethyl chloride hydrochloride were found to be optimum for reaction. Also we found that at pH 4 all the impurities were washed out in organic solvent and then aqueous layer was extracted at 9-10 pH in toluene to get > 98% purity of doxylamine base.

Finally salt was prepared using succinic acid in different solvents like ethyl acetate, acetone and isopropyl alcohol and different temperatures. Among the explored combinations of solvent and temperature, use of acetone gave purity ≥ 99.5% and desired yield 80% at 20-25ºC. Further volume of acetone and temperature for reaction were optimized and as per optimized process 3 volumes of acetone and 20-25ºC were found to be optimum.

CONCLUSION

In conclusion, the present work provides safer and an efficient manufacturing process for synthesis of **1**. The work describes purification process for intermediate 4 and 6 which is additional advantage of process. Also in preference potassium hydroxide is a safer option in large scale production of **1**. Thus this process provide better scope and practical alternative by overcoming limitation of the reported methods for synthesis of **1.**

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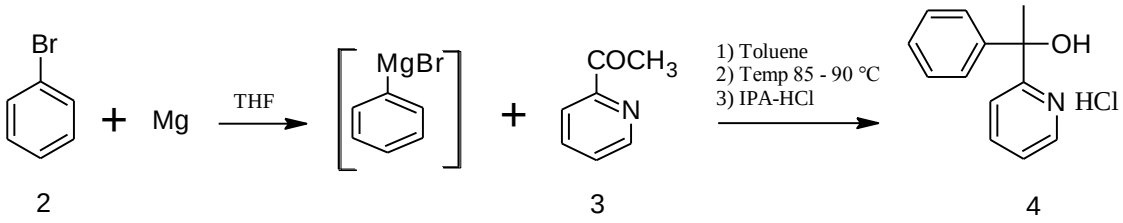
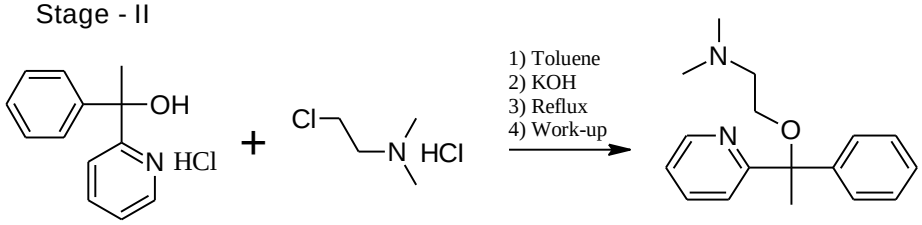
Reaction Scheme

Step - I



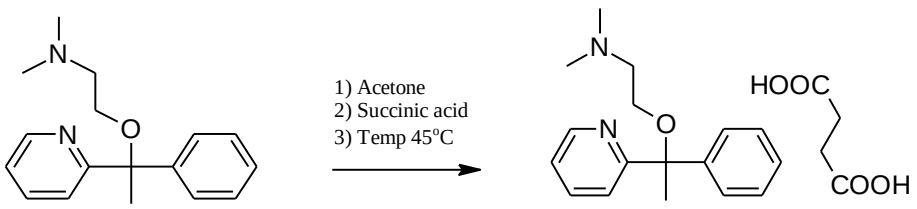
2 3 4

Stage - II



4 5 6

Stage - III



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