Synthesis of enantiomerically pure (d) – doxylamine using a novel chiral auxiliary

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ABSTRACT

It is known that the main mode of synthesis of doxylamine is a racemic mixture. However, the active enantiomers of the compound show superior activity to that of the racemate, thus the need to synthesize doxylamine as an enantiopure compound. This study aimed to synthesise an enantiopure (d)-doxylamine and it was achieved through the use of optically active diols synthesised from a novel chiral auxiliary. While most available methods employ Sharpless asymmetric dihydroxylation, this study reports a method that achieves superior enantiomeric excess with consequent better yields of 67% of end products not easily accessible by use of Sharpless Asymmetric Dihydroxylation.

Keywords: Antihistamine, chiral doxylamine, (R)-1-phenyl-1-(pyridin-2-yl) ethanol, chiral 1, 2-diols, enantiomeric excess, Sharpless asymmetric dihydroxylation.

INTRODUCTION

Doxylamine, chemically known as N,N-Dimethyl-1-2-[1-phenyl-1-(2-pyridinyl) ethoxy] ethanamine, is a highly sedative aminoalkylether and is used clinically in the short-term treatment of insomnia, symptomatic relief of allergic reactions, treatment of pruritic skin disorders and management of nausea and vomiting in pregnancy (Tadiboyina et al., 2015). This medicine is chiral and has a single chiral centre. Doxylamine, however, is most widely available and used as a racemic mixture in clinical settings. It has been reported in the patent filing documents that (d)-doxylamine is more efficient in arresting allergic reactions and improving sleep compared to its racemic form (Patti, 2011).

Currently, the main mode of synthesis of doxylamine is a racemic mixture. However, active enantiomers of a compound show a superior activity to that of the racemate. Additionally, any two possible enantiomers of
a chiral compound such as doxylamine usually possess variable biological activities. Therefore, the need to synthesize doxylamine as an enantiopure compound cannot be overemphasized (McConathy and Owens, 2003).

Most drugs are chiral, and their pharmacological activity depends mainly on their interaction with biological targets like proteins, nucleic acids, and biomembranes. Importantly, one enantiomer of a chiral drug may be a medicine useful for treating diseases while another may either be inactive or toxic (Reshma et al., 2018). Drug chirality influences both the interaction of these compounds with biological targets as well as the pharmacokinetics of drugs (Reshma et al., 2018).

Synthesis of doxylamine can be achieved by reacting a Grignard reagent generated by iodobenzene and magnesium with 2-acetylpyridine to generate 2-pyridyl phenyl methyl alcohol. 2-pyridyl phenyl methyl alcohol then reacts with sodium amide and 2-dimethylamino chloroethane sequentially (Jinyuan et al., 2013). Racemate doxylamine can also be synthesised using 2-acetylpyridine and bromobenzene with magnesium turning to generate in-situ Grignard reagent in the presence of anhydrous ether followed by reaction with 2-dimethylaminoethyl chloride using a strong base sodamine in xylene (Nilesh, 2016). However, chiral doxylamine succinate can be prepared by reacting 2-acetopyridine and phenylboronic acid in toluene solvent using chiral ligand, diethylzinc and Ti(iPO)₄ followed by reacting with 2-dimethyl aminoethyl chloride (Fukangren Biopharm-Sci R, 2013). This process is complicated to operate and requires costly chiral reagents and a longer reaction time with tedious workup (Nilesh, 2016). Thus, this study supports the synthesis of drugs as also reported in other studies (Bamba et al., 2021; Samuel and Adekunle, 2021; Kouamé et al., 2021; Chawe et al., 2021).

There is a need to develop new methods of asymmetric synthesis of Doxylamine. Therefore, this study was aimed at synthesising enantiopure (d)-doxylamine from optically active diols using a novel chiral auxiliary.

**MATERIALS AND METHODS**

**Experimental**

**General**

³H NMR and ¹³C NMR spectra were recorded on a Varian Inova 400 Spectrometer and chemical shifts were shown as values in parts per million relative to tetramethylsilane as an internal standard ( ). The melting points of all compounds were determined using a MEL-TEMP® apparatus while infrared (IR) spectra were recorded on a NICOLET IS5 FT/IR spectrometer. Column chromatography was conducted using the forced flow solvent on Merck Kieselgel 60(230–400 mesh). Thin-layer chromatography was carried out on 0.25 mm E. Merck precoated silica gel glass plates. All solvents were distilled with calcium hydride except tetrahydrofuran (THF) which was distilled from sodium benzenophene under a nitrogen atmosphere. Unless otherwise indicated, all chemicals were purchased from commercially available sources and used without additional purification.

**Synthesis of (R)-(R)-2,2-dimethyl-1,3-dioxolan-4-yl (4-methoxyphenyl) methanol(4)**

Copper iodide (2.05 g, 10.76 mmol) was added to a flask with THF: DMS (5:1) then cooled to (-78°C). Then 4-methoxyphenyl magnesium bromide (0.5 M solution in THF, 18 ml,9.22 mmol) was added to the mixture and stirred for 20 minutes followed by the addition of 2,3-O-isopropylidene-D-glyceraldehyde (1 g, 7.68 mmol) through a cannula in THF. The resulting mixture was stirred continually at -78°C while gradually increasing the temperature for an additional 2 hrs. The resulting product was checked by TLC to confirm its purity. The reaction was then quenched with NH₄Cl: NH₄OH (9:1) then stirred for 30 minutes. After which workup was done using NH₄Cl: NH₄OH (9:1), EtOAc, water, brine and dried over anhydrous Na₂SO₄. The resulting mixture was concentrated and purified using column chromatography (n-Hexane: EtOAc=5:1) to give title compound 4 as a solid (502 mg, 27%).
Synthesis of 2-((R)-(R)-2,2-dimethyl-1,3-dioxolan-4-yl) (4-methoxyphenyl) methoxy)-1-phenylethanol (5)

To a suspension of KH (84 mg, 30% in oil, 0.63 mmol) in THF (3 ml) was added a solution of alcohol 1 (100 mg, 0.42 mmol) in THF. The mixture was stirred for 30 minutes then cooled to RT. At RT, styrene oxide (75.7 μL, 0.63 mmol) and 18-crown-6 (5 mg) was added then refluxed at 55°C for 24 hrs. The reaction mixture was quenched with aq. NaHCl (5 mL) and diluted with ethyl acetate. The organic layer was washed with brine, copper sulfate solution, and water and dried over anhydrous Na2SO4, filtered and concentrated. The crude residue was purified by column chromatography (n-Hexane: EtOAc=5:1) to give compound 5 as a white solid (82 mg, 86%).

Synthesis of (R)-2-((R)-(R)-2,2-dimethyl-1,3-dioxolan-4-yl) (4-methoxyphenyl) methoxy)-1-phenyl-1-(pyridine-2-yl) ethanol (7)

2-bromopyridine (80 μL, 0.842 mmol) was added to a flask with 5 ml toluene and cooled to -78 °C. To the reaction mixture was added dropwise n-Butyl lithium (336.8 μL, 0.842 mmol, 2.5 M solution in Hexane) via a syringe then stirred for 30 minutes. 2-((R)-(R)-2, 2-dimethyl-1, 3-dioxolan-4-yl) (4methoxyphenyl) methoxy)-1-phenylethanolone (100 mg, 0.28 mmol) was added and stirred for another 2 hrs at -78 °C. The reaction mixture was quenched with water and diluted with ethyl acetate. The organic layer was washed with water, brine, dried over anhydrous Na2SO4, filtered and concentrated. The crude product was purified by column chromatography using (n-Hexane: EtOAc = 3:1) to give the compound as a pale-yellow oil (58.4 mg, 67%).

Synthesis of 1-phenyl-1-(pyridine-2-yl) ethane-1, 2-diol (8)

a) (R)-2-((R)-(R)-2,2-dimethyl-1,3-dioxolan-4-yl)(4methoxyphenyl) methoxy)-1-phenyl-1-(pyridine-2-yl)ethanol (26 mg, 0.06 mmol) was mixed with acetonitrile (3 ml), Tin(II) chloride (1.1 mg,0.006 mmol, 0.1 eq), chlorotrimethylsilane (23 μL,0.18 mmol, 3 eq) and sodium iodide (27 mg, 0.18 mmol, 3 eq) and stirred at -20°C for 1 hr. The reaction mixture was then quenched with NaHCO3 and diluted with ethyl acetate (50 ml). The organic layer was washed with water, brine then dried over anhydrous Na2SO4, filtered and concentrated. The crude product was then purified by column chromatography using (n-Hexane: EtOAc = 2:1) to give a white solid product (3 mg, 19%).

b) K3Fe(CN)6 (599 mg, 1.82 mmol), K2CO3 (251 mg, 1.82 mmol), K2OsO4,2H2O (cat) (DHQD)2PHAL (10.4 mg, 0.013 mmol)
and (R)-2-(2,2-dimethyl-1,3-dioxolane-4-yl)(4-methoxyphenyloxy)methoxy)-1-phenyl-1-(pyridine-2-yl)ethanol (110 mg, 0.607 mmol) were added to a flask containing 10 ml tert-Butanol:H2O (1:1) at 0°C. The reaction mixture was stirred at 0°C overnight, then added sodium sulfite (6 eq) and stirred for another 30 minutes. The mixture was then diluted with methylene chloride and washed with NaHCO3, H2O, brine followed by drying over anhydrous Na2SO4. The resulting crude product was purified by the use of column chromatography (n-Hexane: EtOAc =1:1) to give a white solid (49 mg, 38%).

Synthesis of a (R)-2-hydroxy-2-phenyl-2-(pyridine-2-yl) ethyl methane sulfonate (9)

To a solution of diol (65 mg, 0.30 mmol) in 4 ml pyridine was added methane sulfonyl chloride (116 µL, 1.50 mmol) and stirred at 0°C for 3 hrs. The reaction mixture was then quenched with water, diluted with methylene chloride, and then the organic layer was washed with brine and dried over anhydrous Na2SO4. The crude product was purified by column chromatography (n-Hexane: EtOAc =1:1) to give a white solid (49 mg, 38%).

Rf = 0.4(n-Hexane: EtOAc=1:1/ KMnO4)

Melting point= 66-68°C

1H NMR (400MHz, CDCl3): δ 8.54(d, J=4, 1H), 7.70(m, 1H) 7.47(m, 3H), 7.30(m, 4H), 5.55 (s, 1H), 4.92(d, J= 10.8, 1H), 4.75(d, J=10.8, 1H)

13C NMR (100MHz, CDCl3): δ 159.55, 147.85, 141.4, 137.3, 128.55, 128.03, 126.02, 123.0, 121.18, 77.33, 77.01, 76.82, 76.69, 74.51, 37.64

IR (Neat, cm⁻¹): 3466, 3039, 3011, 2988, 1612, 1514, 1469, 1253

Synthesis of (R)-1-phenyl-1-(pyridine-2-yl) ethanol (11)

To a solution of epoxide 10 (8 mg, 0.041 mmol) in 10 ml of THF was added lithium aluminium hydride (6.16 mg, 0.162 mmol, 4 eq) and stirred at RT overnight. The reaction mixture was then quenched with few drops of water and allowed to stir for an hour. The mixture was then glass filtered with EtOAc, dried over Na2SO4 then purified using (n-Hexane: EtOAc=10:1) to give (2.3 mg, 28%) syrup product.

RESULTS

Synthesis of Chiral auxiliary

Chiral auxiliary 4 (scheme 3) was prepared from (R) - glyceraldehyde diacetonide 3 giving the chemical yield of 27%. Rf = 0.60(n-Hexane: EtOAc=1:1/ anisaldehyde).

1H NMR (400MHz, CDCl3): δ 7.29(d, J=4.8Hz, 2H), 6.89(d, J=4.8Hz, 2H), 4.519(dd, J= 8.0, 2.0Hz, 1H), 4.22(q, J= 6.4Hz, 1H), 3.81(s, 3H), 3.78(dd, J= 8.4, 6.0Hz, 1H), 3.68(dd, J= 8.4, 6.0Hz, 1H), 2.73(s, 1H), 1.50(s, 3H), 1.38(s, 1H)

13C NMR (100MHz, CDCl3): δ 159.58, 131.73, 128.13(2c), 113.95(2c), 110.07, 80.25, 75.59, 66.00, 55.21, 26.93, 25.37

Melting point: 39–41°C

IR (KBr pellet, cm⁻¹): 3490, 3011, 2988, 1612,1514,1469,1253

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**Synthesis of Chiral auxiliary-conjugated α-alkoxy ketone**

Synthesis of compound 6 (scheme 4) was achieved through the synthesis of compound 5 from chiral auxiliary 4. \( R_f = 0.33 \) (n-Hexane: EtOAc=3:1/anisaldehyde)

Melting point: 67-69°C

\(^1\)H NMR (400MHz, CDCl$_3$): \( \delta \) 7.82(m, 2H), 7.39(m, 3H), 7.23(m, 2H), 6.85(m, 2H), 4.64(m, 2H), 4.45(m, 2H), 3.76(d, \( J=2.8 \), 3H), 3.62(m, 1H), 3.55(m, 1H), 1.38(d, \( J=2.4 \), 3H), 1.34(d, \( J=2.4 \), 3H)

\(^1\)C NMR (100MHz, CDCl$_3$):

\( \delta \) 196.27, 159.91, 147.73, 143.97, 136.54, 135.04, 133.30, 129.10, 128.71(2c), 127.99, 127.90, 114.05, 110.17, 83.43, 78.95, 77.31, 76.99, 76.67, 71.08, 66.09, 55.22, 26.57, 25.56

IR (Neat, cm$^{-1}$): 3018, 1591, 1570, 1367.

**Asymmetric nucleophilic 1, 2-addition**

Compounds 7a and 7b (Scheme 5) were prepared from the reaction of compound 6 with 2-bromopyridine in different solvents giving the following results.

\( R_f = 7a: 0.41 \) (n-Hexane: EtOAc= 1:1/ anisaldehyde). 7b: 0.39 (n-Hexane: EtOAc = 1:1/ anisaldehyde)

\(^1\)H NMR (400MHz, CDCl$_3$):

7a: \( \delta \) 8.47(m, 1H), 7.60(m, 4H), 7.15(m, 6H), 6.80(d, \( J=8.4 \), 2H), 4.93(s, 1H), 4.15(m, 4H), 3.76(m, 3H), 3.59(m, 1H), 3.34(m, 1H), 1.29(s, 6H)

7b: \( \delta \) 8.48(d, \( J=4.8 \), 1H), 7.61(t, 2H), 7.50(t, 2H), 7.15(m, 6H), 6.81(t, 2H), 5.09(s, 1H), 4.44(d, \( J=10 \), 1H), 4.22(d, \( J=7.2 \), 1H), 4.14(m, 1H), 3.77(s, 3H), 3.74(m, 1H), 3.59(m, 1H), 3.49(m, 1H), 1.31(s, 3H), 1.28(s, 3H)

\(^1\)C NMR (100MHz, CDCl$_3$):

7a: \( \delta \) 164.73, 147.39, 136.98, 128.20, 126.97, 125.87, 122.03, 120.28, 77.38, 77.07, 76.74, 75.06, 29.22

IR (Neat, cm$^{-1}$): 3009, 1591, 1570, 1367.

**Synthesis of optically active diol**

Optically active diols were synthesized from compound 7a by reacting it with trimethylsilyl chloride (TMSCl) and gave the following results.

\( R_f = 0.25 \) (n-Hexane: EtOAc= 1:1/ KMnO$_4$

Melting point: 88-90°C

\(^1\)H NMR (400MHz, CDCl$_3$): \( \delta \) 8.54(M, 1H), 7.69(m, 1H), 7.31(m, 7H), 5.25(s, 1H), 4.43(d, \( J=11.6 \), 1H), 3.97(d, 1H, \( J=11.2 \), 3.17(s, 1H)

\(^1\)C NMR (100, CDCl$_3$): \( \delta \) 195.18, 145.85, 135.04, 133.30, 129.10, 128.71(2c), 127.99, 127.90, 114.05, 110.17, 83.43, 78.95, 77.31, 76.99, 76.67, 71.08, 66.09, 55.22, 26.57, 25.56

IR (Neat, cm$^{-1}$): 3018, 1591, 1570, 1367.

**Synthesis of methyl alcohol from optically active diol**

Methyl alcohol 11 was prepared from optically active diols by formation of an epoxide 10 then reducing with Lithium aluminium hydride (scheme 7).

\( R_f = 0.34 \) (n-Hexane: EtOAc = 5:1/ KMnO$_4$

\(^1\)H NMR (400MHz, CDCl$_3$): \( \delta \) 8.50(m, 1H), 7.61(m, 1H), 7.49(m, 2H), 7.29(m, 3H), 7.14(m, 2H), 5.86(s, 1H), 1.92(s, 3H)

\(^1\)C NMR (100MHz, CDCl$_3$): \( \delta \) 164.73, 147.39, 136.98, 128.20, 126.97, 125.87, 122.03, 120.28, 77.38, 77.07, 76.74, 75.06, 29.22

IR (Neat, cm$^{-1}$): 3009, 1591, 1570, 1367.

**DISCUSSION**

Retrosynthetic analysis (scheme 1 and 2) of optically active doxylamine showed that it could be prepared from (R)-1-phenyl-1-(pyridine-2-yl) ethane-1, 2-diol (chiral diol). Presently, many studies have shown preparation of optically active diols through Sharpless Asymmetric Dihydroxylation, however, the main problem with this mode of preparation is poor enantiomeric excess. In a study conducted by Wang et al., (2000), the enantiomeric excess (ee) of diols was found to be 20-35% ee after 10 days. The use of a novel chiral auxiliary provides a superior method of preparing optically active diols with good enantiomeric excess. Hence, in this study, a retrosynthesis of doxylamine through a novel chiral auxiliary assisted diol formation was used with a better enantiomeric excess (scheme...
The synthesis of the target compound started with the preparation of chiral auxiliary conjugated α-alkoxy ketone as a substrate for the diastereoselective nucleophilic 1, 2 addition reaction. Chiral auxiliary 4 was prepared from (R) - glyceraldehyde diacetone 3 (Organic Synthesis, 1998) which was reacted with 4-methoxyphenyl magnesium bromide. 4-Methoxyphenylmagnesium bromide is a bulky compound, so its addition to compound 3 is through the less hindered convex side according to Cram’s chelation model (James Morrison, 2012) (Scheme 3). The chiral auxiliary 4 was then converted to its ether form by an o-alkylative epoxide ring-opening reaction. This was achieved by first converting alcohol 4 to its corresponding alkoxide with KH in tetrahydrofuran (THF), followed by O-alkylation styrene oxide in the presence of 18-crown-6 to make ether 5 in 36% yield. Thereafter, the resulting alcohol was oxidized by tetra propylammonium perruthenate (TPAP) in the presence of N-methylmorphine-N-oxide (NMO) to give a ketone 6 in 86% yield (Chang, 2008) (Scheme 4).

Ketone 6 was the main substrate and a short study was undertaken on it to determine the best conditions for asymmetric nucleophilic 1, 2- addition reaction. The condition included the use of different solvents THF, DCM and toluene. The optimum condition was observed with toluene at -78°C to give the desired major product 7a and its diastereomer 7b in 67% chemical yield, in a 3:1 ratio and (50% ee) of diastereomers (Table 1). The absolute configuration of the newly formed stereogenic centre of 7a could not be established at this stage but was assigned tentatively as (R) based on our proposed chelation model by Cram shown in Figure 1.

Alcohol 7a was then converted to chiral 1, 2 diol 8 by reacting with trimethylsilyl chloride (TMSCl) and sodium iodide (Chang, 2008). Chiral diols are generally readily prepared from an alkene by Sharpless asymmetric dihydroxylation. Compared to 20-35% enantiomeric excess of chiral diol found in Wang et al. (2000) study by use of Sharpless dihydroxylation, the use of chiral auxiliary assisted diol formation gave 50-67% enantiomeric excess which was better (scheme 5). Doxylamine preparation requires the use of chiral 1, 2 diols with high enantiomeric excess, therefore, the asymmetric nucleophilic 1, 2- addition (scheme 6) to an α-alkoxy ketone can provide an alternative to chiral diols not easily accessible through Sharpless asymmetric dihydroxylation method. Selective mesylation of a diol with methanesulfonyl chloride in pyridine produced a mesylate 9 in 83% yield which was then treated with sodium hydride in DMF to afford epoxide 10 in 47% yields. Finally, treatment of epoxide 10 with lithium aluminium hydride in THF at RT caused ring opening of epoxide to afford tertiary alcohol 11 (scheme 7) (Lee SY, 2015). The final chiral target compound can be prepared in a single reaction by reacting compound 11(tertiary alcohol) with N, N-dimethyl aminoethyl.

Scheme 1: Retrosynthetic analysis of chiral Doxylamine.
Scheme 2: Retrosynthetic analysis of chiral auxiliary assisted diol formation.

Scheme 3: Synthesis of Chiral auxiliary.

Scheme 4: Synthesis of Chiral auxiliary-conjugated \( \alpha \)-alkoxy ketone.

Table 1: Asymmetric nucleophilic 1, 2-addition.

| Entry | Solvent | Temp (°C) | Additive | Yield (%) | Ratio(7a:7b) | ee (%) |
|-------|---------|-----------|----------|-----------|--------------|--------|
| 1     | THF     | -78       | None     | 48        | 2:1          | 33     |
| 2     | Toluene | -78       | None     | 67        | 3:1          | 50     |
| 3     | DCM     | -78       | None     | 35        | 2:1          | 33     |
| 4     | DCM     | -78       | MgBr\(_2\)OEt\(_2\) | 11 | 5:1          | 67     |

The ratio(R/S) was determined by NMR and percentage yield (%).
Scheme 5: Asymmetric nucleophilic 1, 2-addition.

Figure 1: Proposed possible chelation model for asymmetric nucleophilic 1, 2-addition.

Scheme 6: Synthesis of optically active diol.

Scheme 7: Synthesis of methyl alcohol from optically active diol.
Conclusion

In summary, it has been established that (R)-1-phenyl-1-(pyridin-2-yl) ethanol 11 can be prepared better from chiral auxiliary through chelation-controlled diastereoselective nucleophilic 1,2-addition and reduction of primary protected alcohol. 1,4-asymmetric induction was also realized during the key alkylation step through a chelation-controlled mechanism. The synthetic method also provided an alternative way of preparing chiral 1,2-diols with the highest enantiomeric excess (ee) of 67% not easily accessible by use of Sharpless asymmetric dihydroxylation. We, therefore, advocate the use of a chiral auxiliary method as a better alternative way to synthesize Doxylamine.

COMPETING INTERESTS

The authors have not declared any competing interests.

AUTHORS’ CONTRIBUTIONS

CNH and HDK conceptualized the study and planned the experiments. CNH and HH wrote the initial manuscript. DM, ACK, CM, SM, RKM, and MK helped in analysing the results. All authors reviewed the intellectual content of the manuscript. All authors approved the final version of the manuscript.

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