Diastereoselective reduction of chiral N-tert-butanesulfinimines for the synthesis of (4S,6S)-5,6-dihydro-6-methyl-4H-thieno-[2,3-b] thiopyran-4-amine 7,7-dioxide: An important intermediate for dorzolamide

Chinnapillai Rajendiran1, Periyandi Nagarajan1*, A. Naidu2 and P. K. Dubey2

1Suven Life Sciences Ltd., R&D Center, Jeedimetla, Hyderabad, India
2Department of Chemistry, J. N. T. University, Hyderabad, Telangana, India

ABSTRACT

A new asymmetric synthesis of (4S,6S)-5,6-dihydro-6-methyl-4H-thieno-[2,3-b]thiopyran-4-amine 7,7-dioxide (9a) and (4S,6S)-5,6-dihydro-6-methyl-4H-thieno-[2,3-b]thiopyran-4-amine (19a), an important intermediate for the preparation of Dorzolamide (1) by diastereoselective reduction of chiral (R)-N-tert-butanesulfinimines (7&17)

Keywords: R(+-)tert-butanesulfimamide, S(-)-tert-butanesulfimamide, Borane, Sodium borohydride, Titanium tetraethoxide.

INTRODUCTION

Dorzolamide Hydrochloride [1] is known chemically as (4S,6S)-4-(Ethylamino)-5,6-dihydro-6-methyl-4H-thieno[2,3-b]thiopyran-2-sulfonamide 7,7-dioxide (1) used for antiglaucoma agent. Glaucoma is the pressure within eye can lead to damage to the optic nerve at the back of eye. If untreated, glaucoma may eventually lead to blindness. People with ocular hypertension have an increased risk glaucoma. Dorzolamide works by blocking the action of an enzyme carbonic anhydrase. Blocking this enzyme reduces the amount of fluid that make in the front part of eye, and this helps to lower the pressure within the eye [2-9].

Dorzolamide contains two chiral centre with four diastereisomeric forms. The trans- diastereomers having the configuration 4S,6S (1) and 4R,6R (2), cis-diastereomers having the configuration 4S,6R (3) and 4R,6S (4) as given in the Figure 1.
The diastereomer Trans-(4S,6S)-4-(Ethylamino)-5,6-dihydro-6-methyl-4H-thieno-[2,3-b]thiopyran-2-sulfonamide 7,7-dioxide (1) is marketed as Dorzolamide drug and the remaining three diastereomers (2,3&4) is unwanted and needs to be eliminated from the mixture of four isomers.

The (4S,6S)-5,6-dihydro-6-methyl-4H-thieno-[2,3-b]thiopyran-4-amine 7,7-dioxide (9a) and (4S,6S)-5,6-dihydro-6-methyl-4H-thieno-[2,3-b]thiopyran-4-amine (19a) is a critical intermediate for the synthesis of Dorzolamide (1).

![Figure-2](image.png)

Though there are several method have been reported for the preparation of Dorzolamide and its intermediates using classical resolution methods [10-15], enzymatic process [16-18] and asymmetric synthesis [19-27]. No reported process for the preparation of (4S,6S)-5,6-dihydro-6-methyl-4H-thieno-[2,3-b]thiopyran-4-amine 7,7-dioxide (9a) and (4S,6S)-5,6-dihydro-6-methyl-4H-thieno-[2,3-b]thiopyran-4-amine (19a) using (R)-N-tert-butanesulfinimines (7&17) as chiral amine source.

In recent year the asymmetric synthesis of chiral amines using chiral N-tert-butanesulfinimines plays a vital role in the synthetic organic chemistry. Ellman’s group has prepared many chiral amines using chiral N-tert-butanesulfinimine chemistry [28].

As part of our exploratory studies on the synthesis of chiral amines using chiral N-tert-butanesulfinimines chemistry [29-30], we prepared successfully the both important new intermediates 5,6-dihydro-6-methyl-4H-thieno-[2,3-b]thiopyran-4-amine 7,7-dioxide (9a) and 5,6-dihydro-6-methyl-4H-thieno-[2,3-b]thiopyran-4-amine (19a) through chiral (R)-N-tert-butane sulfinimines (7&17). We have also undertaken to study the effect of different reducing agent on both chiral (R)&(S)-N-tert-butanesulfinimines (7&12) derivatives to understand the effectiveness of our hypothesis. To our surprise we found that the Borane and DIBAL-H is more selective diastereoselective reducing agent for the preparation of chiral amines (9a&19a). We present here the investigation of different reducing agent for diastereoselective reduction on both (R)&(S)-N-tert-butanesulfinimines (7&12) and its results.

RESULTS AND DISCUSSION

We started our synthesis from known intermediate 5,6-dihydro-4H-6-methylthieno[2,3-b]thiopyran-4-one-7,7-dioxide (5) [31]. Condensation of Ketone (5) with R(+)-tert-butane sulfinamide (6) in the presence of using titanium tetraethoxide as water scavenger in 1,4-Dioxane solvent at reflux temperature gave 70% yield of (R)-N-tert-butanesulfinimine (7).

The use of Sodium borohydride as reducing agent for the reduction of (R)-N-tert-butanesulfinimine (7) in alcoholic solvent gave the sulfinylamine (8). Sulfinylamine (8) was hydrolysed with hydrochloric acid gave the the hitherto unknown intermediate 5,6-dihydro-4H-4-amino-6-methylthieno[2,3-b]thiopyran-7,7-dioxide (9). On acetylation of amine (9) with acetic anhydride in the presence of triethylamine in dichloromethane solvent gave 5,6-dihydro-4H-4-acetylamino-6-methylthieno[2,3-b]thiopyran-7,7-dioxide (10). To our surprise we found that, the product 5,6-dihydro-4H-4-acetylamino-6-methylthieno[2,3-b]thiopyran-7,7-dioxide (10) obtained from the sodium borohydride reduction gave only the unwanted cis-isomer (10b), which was confirmed by NMR and HPLC.

By encouraging above results, we have extended our investigation to understand further using different reducing agent for the reduction of (R)-N-tert-butanesulfinimine (7). When we used the borane and DIBAL-H as reducing agent gave predominately of required trans-isomer of 10a and was confirmed by NMR and HPLC. Exclusively the cis-isomer of 10b was formed by using Sodium borohydride+L-tartaric acid, Sodium borohydride+L-proline and...
Sodium triacetoxyborohydride as reducing agent. These reactions are summarized in the Scheme 1 and results are tabulated in Table 1.

![Scheme 1](image)

Table 1. Diastereoselective reduction on (R)-N-tert-butanesulfinimine (7) and its data

<table>
<thead>
<tr>
<th>No.</th>
<th>Reducing Agents</th>
<th>HPLC (%)</th>
<th>Trans (10a)</th>
<th>Cis (10b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Borane</td>
<td>70.44</td>
<td>29.30</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>DIBAL-H</td>
<td>74.00</td>
<td>25.74</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>NaBH₄</td>
<td>-</td>
<td>99.94</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>NaBH₄ + LiCl</td>
<td>-</td>
<td>99.03</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>NaBH₄ + L(+)-Tartaric acid</td>
<td>-</td>
<td>99.83</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Sodium triacetoxyborohydride</td>
<td>-</td>
<td>98.85</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Sodium cyanoborohydride</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Raney Nickel</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Palladium on carbon</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Rhodium on carbon</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

* NR – No reaction

Similarly, we have studied the diastereoselective reduction of opposite isomer (S)-N-tert-butanesulfinimine (12), prepared from Ketone (5) and S(-)-tert-butanesulfinamide (11). Using borane as reducing agent gave the mixture of trans & cis-isomers of 15 (15a & 15b), and sodium borohydride gave only cis-isomer of 15b. These reactions are summarized in the Scheme 2 and these results are tabulated in Table 2.

Table 2. Diastereoselective reduction on (S)-N-tert-butanesulfinimine (11) and its data

<table>
<thead>
<tr>
<th>No.</th>
<th>Reducing Agents</th>
<th>HPLC (%)</th>
<th>Trans - 15a</th>
<th>Cis - 15b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Borane</td>
<td>70.95</td>
<td>28.80</td>
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</tr>
<tr>
<td>2</td>
<td>NaBH₄</td>
<td>-</td>
<td>99.93</td>
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</table>

* NR – No reaction
Further we have also extended for studies on the synthesis of (4S,6S)-5,6-dihydro-6-methyl-4H-thieno-[2,3-b]thiopyran-4-amine (19a) by applying the same strategy of synthetic protocol to understand its effectiveness. The 5,6-dihydro-4H-6-methylthieno[2,3-b]thiopyran-4-one (16) [31] was condensed with R(+)-tert-butanesulfinamide (6) in the presence of using titanium tetraethoxide in 1,4-Dioxane solvent gave chiral (R)-N-tert-butanesulfinimine (17). Reduction of sulfinimines (17) with borane in THF solvent gave sulfynilamine (18). Sulfynilamine (18) was hydrolysed with IPA-HCl gave the chiral amine intermediate 5,6-dihydro-6-methyl-4H-thieno-[2,3-b]thiopyran-4-amine hydrochloride (19a&19b). The acylation of 19 in the presence of acetic anhydride and triethylamine gave the mixture of 5,6-dihydro-4H-4-acetylamino-6-methylthieno[2,3-b]thiopyran (20a&20b). Oxidation of 20 using hydrogen peroxide in the presence of sodium tungstate gave 70% of trans-5,6-dihydro-4H-4-acetylamino-6-methylthieno[2,3-b]thiopyran-7,7-dioxide (10a) and 30% of cis-5,6-dihydro-4H-4-acetylamino-6-methylthieno[2,3-b]thiopyran-7,7-dioxide (10b). These reactions are summarized in the Scheme 3.

Further the veracity and the usefulness of the compound 10 prepared from this method by converting in to final drug Dorzolamide (1) by the known method. The compound 10 obtained from (R)-N-tert-butanesulfinimines 7&17 gave the predominately the drug Dorzolamide (1) along with minor other isomers was removed by column purification.
The prepared Dorzolamide (1) was confirmed by comparing with the compound prepared from the reported method and by spectral data. These reactions are summarized in the Scheme 4.

Amide 15 obtained from (S)-N-tert-butanesulfinimine (12) gave the exclusively trans-isomer 4R,6R (2) and cis-isomer 4R,6S (4). These results are tabulated in Table 3.

<table>
<thead>
<tr>
<th>No.</th>
<th>Sulfinimine</th>
<th>Reducing Agents</th>
<th>Chiral HPLC (%)</th>
</tr>
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<td></td>
<td></td>
<td></td>
<td>Trans-4S,6S (1)</td>
</tr>
<tr>
<td>1</td>
<td>7</td>
<td>Borane</td>
<td>63.64</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>DBAL-H</td>
<td>61.11</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>NaBH₄</td>
<td>1.44</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>NaBH₄ – L(+)-Tartaric acid</td>
<td>0.23</td>
</tr>
<tr>
<td>5</td>
<td>7</td>
<td>NaBH₄ – L(+)-Proline</td>
<td>0.68</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>Sodiumtriacetoxyborohydride</td>
<td>1.19</td>
</tr>
<tr>
<td>7</td>
<td>12</td>
<td>Borane</td>
<td>61.90</td>
</tr>
<tr>
<td>8</td>
<td>12</td>
<td>NaBH₄</td>
<td>0.03</td>
</tr>
<tr>
<td>9</td>
<td>17</td>
<td>Borane</td>
<td>65.27</td>
</tr>
</tbody>
</table>

MATERIALS AND METHODS

Melting points were taken on a Branstead Melting point apparatus (Model - 9300) in open capillary tubes and are uncorrected. IR spectrum were recorded as Neat or KBr using Perkin-Elmer 2000 FT TR spectrometer. Both 1H-NMR(400 MHz) and 13C-NMR (100 MHz) spectra were recorded on a Bruker NMR spectrometer instrument. All mass spectra were recorded using electrospray ionization (ESI) technique on an API 2000, ABS triple quadrupole instrument. Chiral HPLC was done using Chiral AD-H 250 x 4.6mm,(SRC-906) column using n-hexane:Ethanol: Diethylamine(80:20:0.1) and Flow 0.5ml/min. at 254nm. Column chromatography was performed over silica gel (BDH 100-200 mesh) and TLC with silica gel GF 254. All reagents and solvents employed were of commercial grade and were used as such, unless otherwise specified.

I. General procedure for making N-tert-butanesulfinimines

Titanium tetraethoxide (2.0eq.) was added to a stirred solution of Ketone (5/16) and N-tert-butanesulfinamide (6/11) (1.1eq.) in 1,4-Dioxane at room temperature. The mixture was refluxed until completion (5-10 hr.), the reaction mass was cooled and saturated sodium chloride solution was added. The reaction mass was filtered through celite and the aqueous layer was extracted with ethyl acetate. The organic layer was concentrated and purified through column chromatography.
Preparation of 5,6-dihydro-4H-4-acetylamino-6-methylthieno[2,3-b]thiopyran-7,7-dioxide (10)

Prepared from the Ketone (5) and R(+)-tert-butanesulfinamide (6). Yield: 70.1%; 1H-NMR (CDCl3): δ 7.55-7.56(dd, 1HJ=2.81,4.97Hz), 7.42-7.45(t, 1HJ=5.5Hz), 3.32-4.26 (m, 3H), 1.42-1.50(d, 3H, J=6.77Hz), 1.29(s, 9H); 13C-NMR (DMSO-d6): 164.44, 163.78, 141.90, 141.64, 141.23, 130.23, 130.17, 125.85, 59.40, 58.93, 56.69, 56.65, 36.32, 35.75, 22.79(3C), 22.65(3C), 11.44, 11.38; IR (KBrt, cm⁻¹): 2926, 1736, 1570, 1506, 1453, 1422, 1388, 1268, 1180, 1070, 902, 750, 651; MS (m/z) = 288.2[M+1⁺]; SOR : +61.4° (c=1in Methanol at 25°C)

Preparation of 5,6-dihydro-4H-4-amino-6-methylthieno[2,3-b]thiopyran-7,7-dioxide (9)

Prepared from the Ketone (5) and 56.67, 56.64, 36.31, 35.74, 22.78(3C), 22.64(3C), 11.44, 11.37; IR (KBrt, cm⁻¹): 2964, 2926, 1736, 1570, 1506, 1453, 1422, 1388, 1268, 1180, 1070, 902, 750, 651; MS (m/z) = 320.3[M+1⁺]; SOR : -60.2° (c=1in Methanol at 25°C)

Preparation of R(-)-2-Methylpropane-2-sulfinic acid (5,6-dihydro-6-methyl-7,7-dioxo-thieno[2,3-b] thiopyran-4-ylidene)-amide (11)

Prepared from the Ketone (5) and S(-)-tert-butanesulfinamide (6). Yield: 65.7%; 1H-NMR (CDCl3): δ 7.53-7.55(dd, 1HJ=2.90,5.05Hz), 7.41-7.43(t, 1HJ=5.37Hz), 3.34-4.25 (m, 3H), 1.47-1.49(d, 3H, J=6.60Hz), 1.28(s, 9H); 13C-NMR (DMSO-d6): 164.39, 163.77, 141.86, 141.62, 141.22, 130.25, 130.19, 128.95, 59.37, 58.92, 56.67, 56.64, 36.31, 35.74, 22.78(3C), 22.64(3C), 11.44, 11.37; IR (KBrt, cm⁻¹): 2967, 2930, 1583, 1409, 1310, 1264, 1146, 1071, 767, 723; MS (m/z) = 320.3[M+1⁺]; SOR : +61.4° (c=1in Methanol at 25°C)

Preparation of 5,6-dihydro-4H-4-acetylamino-6-methylthieno[2,3-b]thiopyran-7,7-dioxide (10)

Prepared from the Ketone (5) and S(-)-tert-butanesulfinamine (7). Yield: 68.5%; 1H-NMR (CDCl3): δ 7.45-7.50(dd, 1HJ=5.40,11.00Hz), 7.00-7.01(t, 1HJ=5.52Hz), 3.60-3.87(m,2H), 2.78-3.12 (m, 1H), 1.44-1.47(d,3H), 1.28(s,9H); 13C-NMR (DMSO-d6): 81.164, 163.77, 141.86, 141.62, 141.22, 130.25, 130.19, 128.95, 59.37, 58.92, 56.67, 56.64, 36.31, 35.74, 22.78(3C), 22.64(3C), 11.44, 11.37; IR (KBrt,cm⁻¹): 2962, 2926, 1736, 1570, 1506, 1453, 1422, 1388, 1268, 1180, 1070, 902, 750, 651; MS (m/z) = 288.2[M+1⁺]; SOR : -75.1° (c=1in Methanol at 25°C)

II. Procedure for making 5,6-dihydro-4H-4-acetylamino-6-methylthieno[2,3-b]thiopyran-7,7-dioxide (10&15)

Preparation of Rs-2-Methylpropane-2-sulfinic acid (5,6-dihydro-6-methyl-7,7-dioxo-thieno[2,3-b] thiopyran-4-yl)-amide (8)

The Borane-DMS complex solution 2M in THF (0.1252moles) was added slowly to a stirred solution of N-tert-butanesulfinylamine (7/12) (20 gm, 0.0626 moles) and stirred for 18 hr. at room temperature. The mixture was stirred for 18 hr. at room temperature. Quenched the reaction by adding water and extracted in Dichloromethane. The organic extracts was washed with brine solution and concentrated. Purified through column chromatography to get 14.5 gm of Sulfinamide (8/13).

Preparation of 5,6-dihydro-4H-4-amino-6-methylthieno[2,3-b]thiopyran-7,7-dioxide (9)

The Sulfinamide (8) (14.0gm) is treated with 70.0 ml of IPA-HCl solution (~14%) and stirred for 5.0hr. at room temperature. After completion of reaction, the mass was concentrated, basified the sodium hydroxide solution and extracted in Ethyl acetate. Concentrated the organic layer to get 9.4 gm of amine (9a&9b). Isolated as free base. Yield: 85.0 %; IR (Neat,cm⁻¹): 3371, 2967, 2930, 1583, 1409, 1310, 1264, 1146, 1071, 767, 723; MS (m/z) = 322.2[M+1⁺]; SOR : +8.53° (c=1in Methanol at 25°C)

Preparation of 5,6-dihydro-4H-4-acetylamino-6-methylthieno[2,3-b]thiopyran-7,7-dioxide (10)

Triethylamine (17.96gm, 0.1775moles) was added slowly to a stirred solution amine hydrochloride (9) (9.0gm, 0.0354moles) in 90 ml of Dichloromethane at 0-5°C. Acetic anhydride (7.24gm, 0.071 moles) was added slowly at 0-5°C and stirred for 1.0hr. The reaction mass was quenched by adding water and separated. The organic layer was washed with 5% HCl solution, sat.NaHCO₃ and water. Concentrated the organic layer to get 5.6gm of acetalide (10a&10b).
Yield : 60.9% ; IR (KBr, cm⁻¹) : 3242, 3058, 1650, 1549, 1413, 1374, 1305, 1138, 1007, 752, 691 ; MS (m/z) = 260.4 [M+H]+ ; MR : 176.2-182.1°C.

Trans-10a : ¹H-NMR (DMSO-d₆) : δ 8.53-8.56(d,1H,J=8.40Hz), 7.94-7.96(d,1H,J=5.76Hz), 7.01-7.02(d,1H, J=4.88Hz), 5.15-5.18(m,1H), 3.76-3.80(m,1H), 2.37-2.41(m,1H), 2.18-2.25(m,1H), 1.83(s,3H), 1.32-1.34(d,3H), ¹³C-NMR (DMSO-d₆) : δ 8169.00, 144.88, 135.59, 131.94, 128.16, 53.02, 42.03, 35.56, 22.89, 10.79.

Cis-10b : ¹H-NMR (DMSO-d₆) : δ 8.49-8.51(d,1H,J=8.63Hz), 7.93-7.94(d,1H,J=6.36Hz), 6.93-6.95(d,1H, J=4.77Hz), 5.22-5.26(m,1H), 3.85-3.88(m,1H), 2.37-2.41(m,1H), 2.15-2.25(m,1H), 1.88(s,3H), 1.30-1.34(d,3H), ¹³C-NMR (DMSO-d₆) : δ 8169.36, 146.61, 135.15, 131.75, 127.44, 55.80, 45.11, 36.46, 22.91, 10.54.

III. Alternative synthesis of 5,6-dihydro-4H-4-acylamino-6-methylthieno[2,3-b]thiopyran hydrochloride (19)

Preparation of 5,6-dihydro-4H-4-acylamino-6-methylthieno[2,3-b]thiopyran hydrochloride (19)
The Borane-DMS complex solution 2M in THF (0.0696 moles) was added slowly to a stirred solution of N-tert-butylsulfinylimine (17) (10 gm, 0.0348 moles) in 100 ml of THF at room temperature. The mixture was stirred for 18 hr. at room temperature. Quenched the reaction by adding water and extracted in Dichloromethane. The organic extracts were washed with brine solution and concentrated get 8.5 gm of sulfonamide (18). The Sulfinamide (18) is treated with 50.0 ml of IPA-HCl solution (~14%) and stirred for 5.0hr. at room temperature. After completion of reaction, the mass was concentrated, stirred with Ethyl acetate and filtered to get 5.1 gm of amine hydrochloride (19a19b).

Yield : 66.1% ; ¹H-NMR (DMSO-d₆) : δ 8.45-8.61(br,3H), 7.40-7.42(t,1H,J=5.56Hz), 7.23-7.37(dd,1H,J= 5.32, 47.0Hz), 4.53(m,1H), 3.64(m,1H), 1.77-2.53(m,3H), 1.34-1.35(d,3H,J= 6.64Hz), ¹³C-NMR (DMSO-d₆) : δ 133.46, 132.17, 129.47, 128.89, 128.18, 127.23, 123.00, 122.65, 46.95, 44.42, 37.23, 37.13, 35.60, 35.56, 22.91, 10.54.

Preparation of 5,6-dihydro-4H-4-acetylarnino-6-methylthieno[2,3-b]thiopyran hydrochloride (20)

Triethylamine (8.2gm, 0.0811moles) was added slowly to a stirred solution of amine hydrochloride (19) (4.5gm, 0.0203moles) in 45 ml of Dichloromethane at 0-5°C. Acetic anhydride (3.2gm, 0.0406 moles) was added slowly at 0-5°C and stirred for 1.0hr. The reaction mass was quenched by adding water and separated. The organic layer was washed with 5% HCl solution, sat.NaHCO₃, and water. Concentrated the organic layer to get 4.0gm of 20a&20b.

Yield : 86.7% ; IR (KBr, cm⁻¹) : 3291, 3092, 3073, 2964, 2908, 1637, 1549, 1537, 1444, 1421, 1369, 1255, 1127, 995, 883, 730, 719 ; MS (m/z) = 228.1[M+H]+ ; MR : 194.2-195.9°C.

¹H-NMR (DMSO-d₆) : δ 8.26-8.28(d,1H), 7.24-7.27(d,1H), 6.80-6.88(d,1H), 5.00-5.05(m,1H), 3.28-3.65(m,1H), 1.64-2.27(m,3H), 1.29-1.37(d,3H), ¹³C-NMR (DMSO-d₆) : δ 169.20, 168.35, 134.42, 132.53, 130.57, 129.42, 128.82, 127.72, 122.07, 121.86, 45.55, 42.66, 39.34, 38.42, 38.07, 34.17, 22.97, 22.92, 20.77, 20.51;

Preparation of 5,6-dihydro-4H-4-acetylamino-6-methylthieno[2,3-b]thiopyran hydrochloride (20)

Amide (20) (3.5 gm, 0.0154moles) was dissolved in ethylacetate(35.0 ml) at room temperature. Sodium tungstate dihydrate (0.5gm, 0.0015moles) and Sulfuric acid(0.1ml) was added and cooled to 0-5°C. 30% hydrogen peroxide(0.054ml) was added dropwise at below 10°C. The reaction mixture was heated to reflux and maintained for 2.0hr. After completion, the reaction mass was cooled and separated the layer. The product organic layer was washed with 5% sodium sulfite solution and water. The organic layer was concentrated, hexane is added and stirred. The product was filtered and dried to get 2.5 gm of 10a&10b.

Yield : 62.6% ; IR (KBr, cm⁻¹) : 3244, 3060, 1649, 1547, 1448, 1414, 1372, 1304, 1138, 1007, 751, 714, 691, 682, 588, 510 ; MS (m/z) = 260.1[M+H]+ ; MR : 172.0-182.0°C.

Trans-10a : ¹H-NMR (DMSO-d₆) : δ 8.54-8.56(d,1H,J=8.40Hz), 7.94-7.96(d,1H,J=5.76Hz), 7.01-7.02(d,1H,J=4.88Hz), 5.15-5.18(m,1H), 3.76-3.80(m,1H), 2.37-2.41(m,1H), 2.18-2.25(m,1H), 1.83(s,3H), 1.32-1.34(d,3H), ¹³C-NMR (DMSO-d₆) : δ 8169.00, 144.88, 135.59, 131.94, 128.16, 53.02, 42.03, 35.56, 22.89, 10.79.
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Cis-10b: $^1$H-NMR (DMSO-d$_6$): $\delta$ 8.49-8.51(d,1H,J=8.64Hz), 7.93-7.94(d,1H,J=5.80Hz), 6.94-6.95(d,1H,J=4.84Hz), 5.19-5.26(m,1H), 3.85-3.89(m,1H), 2.37-2.41(m,1H), 2.18-2.25(m,1H), 1.88(s,3H), 1.30-1.32(d,3H); $^{13}$C-NMR (DMSO-d$_6$): $\delta$169.41, 146.59, 135.16, 131.71, 127.45, 55.83, 45.13, 36.46, 22.89, 10.54.

IV. Preparation of Dorzolamide (1)

Preparation of 5,6-dihydro-4H-4-acetylamino-6-methylthieno[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide (22)

Amide (10) (5.0gm, 0.0193moles) was added slowly to chlorosulfonic acid (10.0ml) at below 10°C. The reaction mixture was heated gradually to 50-55°C and stirred for 6.0 hr. The mass was cooled to room temperature and added Thionyl chloride (10.0ml). The mixture was heated again to 50-55°C and stirred for 4.0hr. The reaction was quenched in to ice water at 10°C. Filtered and washed with chilled water to get sulfonylchloride (21). The wet sulfonylchloride (21) was added slowly into to a solution of Acetone (40.0ml) and aqueous ammonia (20.0ml) at below 10°C and stirred. The reaction mixture was concentrate under vacuum and diluted with water. The pH was adjusted to 6-7 using con.hydrochloric acid and stirred. Filtered, washed with water and dried to get 4.5 gm of 22a&22b.

Yield : 68.9% ; IR (KBr,cm$^{-1}$) : 3337, 3248, 3056, 1653, 1527, 1447, 1354, 1296, 1166, 1137, 1030, 1005, 911, 696; MS (m/z) = 337.0[M+H]$^+$; MR : 222.0-238°C.

Trans-22a : $^1$H-NMR (DMSO-d$_6$): $\delta$ 8.68-8.70(d,1H,J=8.36Hz), 8.00(br,2H), 7.44(s,1H), 5.17-5.21(m,1H), 3.89-3.98(m,1H), 2.23-2.46 (m,2H), 1.87(s,3H), 1.37-1.38 (d,3H,J=6.71Hz); $^{13}$C-NMR (DMSO-d$_6$): $\delta$ 169.27, 150.13, 144.92, 138.46, 129.92, 53.46, 42.05, 35.01, 22.89, 10.78.

Cis-22b : $^1$H-NMR (DMSO-d$_6$): $\delta$ 8.62-8.64(d,1H,j=8.57Hz), 8.00(br,2H), 7.34(s,1H), 5.25-5.26(m,1H), 3.98(m,1H), 2.23-2.46 (m,2H), 1.92(s,3H), 1.34-1.3(d,3H); $^{13}$C-NMR (DMSO-d$_6$): $\delta$ 169.68, 149.95, 146.66, 138.10, 129.14, 56.15, 45.10, 35.93, 22.89, 10.43.

(4S,6S)-4-(Ethylamino)-5,6-dihydro-6-methyl-4H-thieno[2,3-b]thiopyran-2-sulfonamide7,7-dioxide hydrochloride (1)

Sodium borohydride (0.89 gm, 0.0236moles) was added slowly in to a stirred suspension of the compound 22 (4.0gm, 0.0118moles) in 40.0ml of THF at 0-10°C. Borontrifluoride-etherate (3.36gm, 0.0238moles) was added slowly at below 10°C. The reaction mixture was heated to 40-45°C and stirred for 8.0hr. After completion of reaction, the mass was cooled and acidified with con.hydrochloric acid and stirred for 10.0hr. at room temperature. Concentrated the mass and diluted with Water. The pH was adjusted to 7-7.5 using sodium hydroxide solution and stirred. The product was filtered and washed with water and dried to get 3.0 gm of trans and cis mixture.

In chiral HPLC Trans(4S,6S)-63.64% and Cis(4S,6R)-33.29% showed. Purified this mixture through column chromatography to get pure 1.3 gm of Trans-4S,6S and was treated with IPA-HCl in Ethyl acetate to get the hydrochloride salt of 1.3 gm of Trans-4S6S (1).

Yield : 30.5% ; $^1$H-NMR (DMSO-d$_6$): $\delta$ 9.94(br,1H), 9.66(br,1H), 8.18(s,2H), 8.02(s,1H), 4.69 (br,s,1H), 4.35-4.39(m,1H), 3.19(m,1H), 3.05(m,1H), 2.78-2.82(m,1H), 2.50-2.59(m,1H), 1.37-1.39(d,3H,J=6.68Hz), 1.27-1.31(t,3H,J=7.01Hz); $^{13}$C-NMR (DMSO-d$_6$): $\delta$49.96, 142.20, 137.61, 130.99, 51.84, 49.49, 41.04, 30.97, 11.40, 10.23; IR (KBr,cm$^{-1}$) :3371, 3117, 2989, 2936, 2688, 2452, 1589, 1545, 1447, 1418, 1344, 1305, 1290, 1158, 1132, 1077, 1022, 916, 741, 700, 643, 604, 561, 507, 474; MS (m/z) = 325.0[M+H]$^+$; SOR : -8.3(C=1in MeOH at 24°C); Chiral : 100%.

CONCLUSION

In summery, we have demonstrated a new asymmetric diasteroselective reduction protocol to get the different diastereoisomers from the same chiral source of N-tert-butanesulfinimines. This is highly useful for the synthetic organic chemist for the synthesis of chiral amines.

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