A Novel Synthesis of (4aS,7aS)-Octahydro-1$H$-pyrrolo[3,4-b]pyridine: An Intermediate of Moxifloxacin Hydrochloride

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A novel synthesis of (4aS,7aS)-octahydro-1$H$-pyrrolo[3,4-b]pyridine (1) is demonstrated along with recovery and reuse of chiral auxiliary naproxen. Further to this alternative stereoselective reduction procedures on 6-benzyl-5$H$-pyrrolo[3,4-b]pyridine-5,7(6$H$)-dione 3 enabling the desired chirality in the nonane 1 is demonstrated.

Key Words: None, Racemization, Naproxen, Naphroamide, L-Proline.

INTRODUCTION

(4aS,7aS)-Octahydro-1$H$-pyrrolo[3,4-b]pyridine 1, is an important intermediate in the manufacture of moxifloxacin and commonly known as “nonane”. For the past few decades, enormous amount of research has been carried out and several processes are reported.$^{1-8}$

Literature$^{1-8}$ illustrated that the majority of manufacturers follow the resolution process (Scheme-I), which involves coupling of 2,3-pyridine dicarboxylic acid 2 with benzylamine to obtain 3 followed by pyridine ring reduction to afford intermediate 4 which upon reduction of carbonyl groups afforded N-benzyl nonane intermediate 5. There after intermediate 5 was subjected to resolution with D(-) tartaric acid in ethanol followed by deprotection to afford nonane 1.

Herein, we report alternative stereoselective reduction procedures on dione 3 as a source of chirality in the nonane 1.

EXPERIMENTAL

General: Solvents and reagents were used for all the reactions as received. The$^1$H and$^{13}$C NMR spectra were recorded in CDCl$_3$/DMSO-$d_6$ on Varian Gemini 400 MHz or 500 MHz FT NMR spectrometer; the chemical shifts were reported in $\delta$ ppm relative to tetramethylsilane TMS (0 ppm). The FT-IR spectra were recorded in the solid state KBr/neat dispersion using Shimadzu IR Prestige-21 spectrophotometer. The mass spectra were recorded on SSMS PESCIEX, API-3000 machine in electron spray mode. The melting points were determined by using Polmon (Model No.: MP96) melting point apparatus. The specific optical rotation was recorded on Jasco P-2000 polarimeter and at 589 nm. The chiral HPLC was recorded on Agilent Model 1260 by using Chiral AGP, 150 × 4.0 mm, 5 µ.

6-Benzyltetrahydro-1$H$-pyrrolo[3,4-b]pyridine-5,7(6$H$,7a$H$)-dione (4): 50 g, (0.21 mol, 1.0 eq) of 6-benzyl-5$H$-pyrrolo[3,4-b]pyridine-5,7(6$H$)-dione 3 was added to 250 mL of toluene in hydrogen vessel, 29 g, (0.252, 1.2 eq) of L-proline was added and continued the stirring for 10 min, 3.5 g, (7 %) of palladium charcoal on carbon was added. Stirring was continued for 15-30 min and warmed to 70 ºC with 7-8 kg/cm$^2$ hydrogen pressure for 5-6 h and further warmed the reaction mass to 80-85 ºC with 8 kg/cm$^2$ hydrogen pressure for 9-10 h, after completion of the reaction cooled to room temperature and catalyst was separated and washed with 100 mL of toluene. The clear filtrate was concentrated under reduced pressure at below 70 ºC to furnish 49.5 g, (0.20 mol, 97.05 %) of 6-benzyltetrahydro-1$H$-pyrrolo[3,4-b]pyridine-5,7(6$H$,7a$H$)-dione 4 with 15 % ee. IR (KBr, v$_{max}$, cm$^{-1}$): 3382.49 (NH), 3034.40 (aromatic CH), 2957.04 (aliphatic CH), 178.20, 177.09, 174.77, 174.45, 163.13, 159.52, 154.68, 149.22, 147.61, 128.52, 124.32, 117.41, 114.63, 111.04, 100.70, 78.69, 69.76, 60.39, 33.26, 28.82; MS (ESI): m/z calculated for C$_{17}$H$_{14}$N$_2$O$_3$ (M + H): 338.12, 336.12, 254.12, 252.12, 244.12, 242.12; found: (M + H$^+$) 345.5.

2,3-Bis[chloromethyl]pyridine (7): 25 g, (0.142 mol, 1 eq) of pyridine-2,3-diyldimethanol hydrochloride was dissolved in 51.3 g, (0.431 mol, 2.4 eq) of thionyl chloride
with stirring at 0-10 °C and temperature increased to 15-20 °C for 1 h, 60 mL of MTBE was added and continued stirring for 30-60 min. Reaction mass was cooled to 0-5 °C for 1 h, filtered the precipitated material and washed with 20 mL of MTBE to furnish 27 g of dichloro compound in the form of hydrochloride salt as a white solid. This material was added to 150 mL of DCM with stirring, 100 mL of water also added and pH of the reaction mass was adjusted to 7.5-8.0 with 5 % sodium carbonate solution. Organic layer was separated and extracted aqueous layer with 50 mL of DCM. Combined extracts were concentrated under reduced pressure at below 50 °C and diluted with 500 mL of DCM and 1 mL of DMF with stirring and cooled to 0-5 °C. After completion of the reaction, water (400 mL) was added at below 25 °C and maintained for 2 h at 25-35 °C. After completion of the reaction water (400 mL) was added and stirred for 15 min. Organic layer was separated and extracted aq. layer with dichloromethane (2 × 200 mL), combined organic layer was washed with 10 % sodium carbonate solution. Final organic layer was dried with sodium sulphate and solvent was evaporated under reduced pressure at below 50 °C to afford 22 g, (0.094 mol, 74 %) of (S)-2-(6-methoxy-naphthalen-2-yl)-1-(5-chloro-2-yl)propanamide 8 as a off-white powder. IR (KBr, νmax, cm⁻¹): 3350.04 (NH), 3195.34 (aromatic CH), 2983.51 (aliphatic CH), 1612.04 (aromatic C=C); 1H NMR (400 MHz, DMSO-d6): δ (ppm) 7.70-7.78 (m, 3H), 7.43 (q, 1H, J = 2 Hz), 7.40 (s, 1H), 7.26 (s, 1H), 7.12 (d, 1H, J = 2.4 Hz), 6.83 (s, 1H), 3.85 (s, 1H), 3.70 (q, 1H, J = 6.8 Hz), 1.37 (d, 3H, J = 6.8 Hz); 13C NMR (400 MHz, DMSO-d6): δ (ppm) 176.47, 157.42, 137.76, 133.58, 129.27, 128.79, 127.12, 126.86, 125.75, 119.03, 106.12, 55.59, 45.21, 18.67; MS (ESI): m/z calculated for C₁₇H₁₅NO₂ (M + H): 229.27; found: (M + H⁺) 230.4.

(S)-2(6-Methoxynaphthalen-2-yl)propanamide (8): A mixture of 6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-6(7H)-yl)propan-1-one (9); (S)-2-(6-Methoxynaphthalen-2-yl)-1-(5H-pyrrolo[3,4-b]pyridin-6(7H)-yl)propan-1-one (9): A mixture of 6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-6(7H)-yl)propan-1-one 9 as a light brown coloured liquid. IR (KBr,

(4aS,7aS)-Octahydro-1H-pyrrolo[3,4-b]pyridine (1): 5 g (0.014 mol, 1 eq) of (S)-1-((4aS,7aS)-hexahydro-1H-pyrrolo[3,4-b]pyridine-6(2H)-yl)-2-(6-methoxynaphthalen-2-yl)propan-1-one 10 was added into round bottom flask. To this 30 mL of 20 %aq. methanol and 8.2 g, (0.14 mol, 10 eq) of KOH was added with stirring at room temperature. Warmed the reaction mass to reflux for 72 h, after completion of the reaction, methanol was evaporated under reduced pressure at below 60 ºC. 25 mL of water was added, extracted aqueous layer with 3 × 25 mL of CHCl3; combined organic layer was dried over Na2SO4, clear filtrate was concentrated under reduced pressure at below 50 ºC to furnish 1.8 g, (0.014 mol, 96 %) of (4aS, 7aS)-octahydro-1H-pyrrolo[3,4-b]pyridine 1 as a light brown coloured liquid.

Aqueous layer was taken and adjusted the pH to 2 with aqueous HCl and extracted into toluene; isolated racemic naproxen 14 from toluene at 0-5 ºC after charcoal treatment as half white coloured powder (3.23 g, 95 % yield with 97 % purity).

(4aS,7aS)-Octahydro-1H-pyrrolo[3,4-b]pyridine (2): Purity by HPLC: 96.7 %; chiral purity by HPLC: 98.93 %; 1H NMR (400 MHz, DMSO-d6): δ (ppm): 2.95-2.98 (m, 2H), 2.63-2.82 (m, 4H), 2.54 (dd, 1H, J = 1.6 Hz, J = 1.2 Hz), 3.29-3.45 (m, 1H), 1.96-2.08 (m, 1H); 13C NMR (400 MHz, DMSO-d6): δ (ppm) 178.59, 138.25, 129.13, 128.81, 127.8, 127.2, 126.1, 125.0, 119.87, 109.27, 46.6, 32.1; MS (ESI): m/z calcd. (%) for C17H24NO3 (M+H): 321.17, found 321.16; MS (ESI): m/z: 320.16; MS (ESI): m/z calcd. (%) for C17H24NO3 (M+H): 321.17, found 321.16; MS (ESI): m/z: 320.16; MS (ESI): m/z calcd. (%) for C17H24NO3 (M+H): 321.17, found 321.16; MS (ESI): m/z: 320.16.  

RESULTS AND DISCUSSION

In our endeavor, we attempted to improve the enantio-selectivity during the reduction of 6-benzyl-5H-pyrrolo[3,4-b]pyridine-5,7(6H)-dione (3) involving the reduction of pyridine ring using L-proline as a chelating agent and 5 % palladium
on carbon as reducing agent. The required amide 3 for employed in the reduction was synthesized using known procedure. Present studies involve varying the mole ratio of L-proline by using Pd/C and Pd-Cu/C as a reducing agents were conducted and the results are summarized in Table-1. When the reaction was performed with the catalytic quantity of L-proline there was no enhancement in the ee and it was similar to racemic mixture (entry 2 in Table-1). Increasing the quantity of additive (L-proline) to stoichiometric amount brought about a marginal increase in ee in favour of the desired isomer (entry 3 in Table-1).

In the next step, various solvents were screened to find out the impact on selectivity. It can be observed that there was no big impact on enantioselectivity with various solvents screened except toluene as shown in Table-1 (entry 3).

![Scheme-II: Reduction of 3](image)

While the possible hydrogen bonding effect of L-proline was demonstrated to achieve the selectivity up to 15 % ee further study focused on the reducing agent. Copper-palladium couple on carbon catalyst was used as a reducing agent. However selectivity could not be improved (Table-1; entry 7).

It was observed that there was no remarkable effect of solvent and additive L-proline on the selective hydrogenation of the pyridine ring. In continuation with the studies, we shifted our focus to find an alternative route that could furnish the enantiotomerically pure nonane.

At first bis(chloromethyl)pyridine 7 was synthesized following the known procedure. Our attempts to cyclize the chloro intermediate 7 by using benzamide was not successful. In addition to this, various other bases screened to couple the benzamide and chloro intermediate and attempts were unsuccessful.

In order to increase the reactivity of amide component, (S)-2-(6-methoxynaphthalen-2-yl)propanamide 8 was selected for condensation assuming that it is more reactive than the benzamide and being chiral it might help in getting selectivity during the reduction. Substantial improvement was observed in reaction time and yield. Unprecedented reaction conditions employed for condensation involved reaction temperature of 80-90 ºC using 5 mol equivalents of sodium hydride in 10 volume toluene. The results are summarized in Table-2.

![TABLE-1](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Reducing agent</th>
<th>L-Proline qty (eq)</th>
<th>Yield (%)</th>
<th>*Chiral HPLC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene</td>
<td>Pd/C</td>
<td>0.00</td>
<td>94</td>
<td>50.5 (49.4)</td>
</tr>
<tr>
<td>2</td>
<td>Toluene</td>
<td>Pd/C</td>
<td>0.10</td>
<td>96</td>
<td>50.2 (49.8)</td>
</tr>
<tr>
<td>3</td>
<td>Toluene</td>
<td>Pd/C</td>
<td>1.2</td>
<td>96</td>
<td>57.4 (42.6)</td>
</tr>
<tr>
<td>4</td>
<td>Methanol</td>
<td>Pd/C</td>
<td>1.2</td>
<td>96</td>
<td>53.6 (46.4)</td>
</tr>
<tr>
<td>5</td>
<td>AcOH</td>
<td>Pd/C</td>
<td>1.2</td>
<td>90</td>
<td>54.1 (45.9)</td>
</tr>
<tr>
<td>6</td>
<td>Ethanol</td>
<td>Pd/C</td>
<td>1.2</td>
<td>92</td>
<td>53.5 (46.5)</td>
</tr>
<tr>
<td>7</td>
<td>Toluene</td>
<td>Pd-Cu/C</td>
<td>0.00</td>
<td>90</td>
<td>51.5 (48.5)</td>
</tr>
<tr>
<td>8</td>
<td>Toluene</td>
<td>Pd-Cu/C</td>
<td>1.2</td>
<td>91</td>
<td>57.5 (42.5)</td>
</tr>
</tbody>
</table>

*Intermediate 4 was further converted to 1 and analyzed for chiral HPLC.

Thereafter (S)-2-(6-methoxynaphthalen-2-yl)-1-(5H-pyrrole-3,4-b)pyridin-6(7H)-yl)propan-1-one 9 was subjected to hydrogenation with 5 % palladium catalyst followed by deprotection with HBr in acetic acid to afford the target nonane 1 (Scheme-III). The resulted nonane was analyzed for chiral purity and it was found to be a racemic. However, the reaction time was reduced along with the improvement in the yield.

In order to understand whether the zero enantioselectivity was due to non-selective hydrogenation or early on racemization of chiral centre present in naproxen amide 8 under basic conditions or not, we performed control experiment by employing similar reaction condition i.e., NaH/toluene. Chiral HPLC analysis of the product showed the complete racemization (Scheme-IV). Results are summarized in Table-3.

![TABLE-2](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base Qty (Eq)</th>
<th>Solvent</th>
<th>Base Qty (Eq)</th>
<th>Temp. (ºC)</th>
<th>9 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaH</td>
<td>Toluene</td>
<td>3</td>
<td>80-90</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>NaH</td>
<td>Toluene</td>
<td>4</td>
<td>80-90</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>NaH</td>
<td>Toluene</td>
<td>5</td>
<td>80-90</td>
<td>90</td>
</tr>
</tbody>
</table>

*Confirmed by TLC.

Since the reaction conditions employed for di-alkylation was leading to racemization of the (S)-2-(6-methoxynaphthalen-2-yl)propanamide 8, we adopted another approach featuring the preparation of 6,7-dihydro-5H-pyrralo[3,4-b]pyridine 12 following the known procedure. Alkylation of the 6,7-dihydro-5H-pyrralo[3,4-b]pyridine 12 with (S)-naproxen 13 was carried out in presence of phenyl boronic acid as catalyst in o-xylene at 145 ºC. The intermediate obtained after 2-(6-methoxynaphthalen-2-yl)-1-(5H-pyrrol-3,4-b)pyridin-6(7H)-yl)propan-
a) (S)-Naproxamide (8), toluene, NaH, 80 - 90°C, 5h, AcOH, EA, H₂O, n-heptane; b) 5% Pd/C, toluene, 80°C, 8 kg/cm², 24h; c) 48% HBr, propionic acid, phenol, reflux, 6 - 7h, MTBE, EA, NaOH, H₂O, NaCl, CHCl₃.

**Scheme-III:** Novel approach for 1

1-one 9 was subjected to reduction of pyridine ring using 5% palladium on carbon catalyst in toluene to afford the 1-(hexahydro-1H-pyrrolo[3,4-b]pyridin-6(2H)-yl)-2-(6-methoxynaphthalen-2-yl)propan-1-one 10, which was subjected to de-coupling to yield the target intermediate nonane 1 (Scheme-V).

To our surprise, we once again encountered with racemization. The reason for ending up with racemic compound was found to be due to racemization of the (S)-naproxen 13 during the coupling with 6,7-dihydro-5H-pyrrolo[3,4-b]pyridine 12. This was confirmed by chiral HPLC analysis of (S)-naproxen 13 before and after reflux in o-xylene in presence of phenyl boronic acid as a catalyst and in absence of intermediate 12, respectively. Chiral HPLC results are summarized in Table-4 (Scheme-VI).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Initial</th>
<th>S-Isomer (%)</th>
<th>R-Isomer (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>99.8</td>
<td>0.2</td>
</tr>
<tr>
<td>2</td>
<td>After 10 h, maintenance at 145 °C</td>
<td>51.5</td>
<td>48.5</td>
</tr>
</tbody>
</table>

Hence, we concluded that the racemization of the coupling agent was not only due to presence of strong base, but also due to the reaction temperature in the presence of acidic catalyst.

Keeping in view of the extreme reaction conditions leading to racemization of the coupling agent, the coupling agent was primarily activated by making its acid chloride and then coupled with the 6,7-dihydro-5H-pyrrolo[3,4-b]pyridine 12 using DIPEA as a HCl scavenger at 0-5 °C. The coupled intermediate 9 was further reduced with 5% palladium on carbon to get the reduced intermediate 10 followed by de-coupling with HBr to afford the target intermediate nonane 1. The obtained nonane was analyzed for chiral purity and the enantioselectivity was found to be much improved (20% ee) but still it is extremely poor proposition from synthesis standpoint (Scheme-VII).
Having gained intellectual control over reaction sequence, we decided to develop a simple method for purification and hydrolysis of 10 to obtain the nonane 1 and naproxen 13. At first the required isomer was isolated by making the HCl salt in IPA thereafter various bases were screened to hydrolyze 10. Among all the bases KOH and KtOBU were afforded the best results (Table-5, entry-1 and 2).

Based on the results and observations from the experiments conducted to attain enantioselectivity of nonane, the following process was finalized. The cyclic amine intermediate 10 was coupled with the acid chloride of (S)-naproxen 13 in presence of DIPEA at 0-5 °C. The crude material obtained after workup was purified through column chromatography to afford the coupled intermediate 9. The pyridine ring of the intermediate 9 was reduced using palladium on carbon as catalyst in toluene solvent. The catalyst was filtered off and the target diastereomeric intermediate was obtained as a crude. Diasteriomers were separated by making the hydrochloride salt in isopropyl alcohol. After separation, intermediate 10 converted to nonane by hydrolyzing with KOH in aqueous methanol to afford nonane 1 and racemic naproxen 14 with an excellent yield (95 and 90 %) was recovered (Scheme-VIII).

**Scheme-VI:** Racemization of 13

- a) o-xylene, phenyl boronic acid, reflux, 10h.

**Scheme-VII:** Modified novel approach for 1

- a) (S)-Naproxen acid chloride, toluene, DIEPA, Na$_2$CO$_3$, H$_2$O, 0 - 5°C, 2h; b) 5% Pd/C, toluene, 80°C, 8 kg/cm$^2$, 24h; c) HBr in AcOH, phenol, propionic acid, reflux, 6 - 7h, NaCl, NaOH, CHCl$_3$.

**Scheme-VIII:** Optimized Final novel scheme for 1

- a) (S)-Naproxen acid chloride, DIEPA, MDC, Na$_2$CO$_3$, H$_2$O, 0 - 5°C, 1h; b) 5% Pd/C, toluene, 80°C, 8 kg/cm$^2$, 24h; c) IPA, dry HCl, d) KOH, Aq. methanol, reflux, 72h, NaCl, CHCl$_3$, Aq. HCl, toluene.

**TABLE-5 SCREENING OF BASES**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Temp. (°C)</th>
<th>% of 1</th>
<th>% of 32</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KOH</td>
<td>80</td>
<td>92</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>KOBU</td>
<td>80</td>
<td>90</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>LiOH</td>
<td>80</td>
<td>Reaction incomplete</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>NaOMe</td>
<td>80</td>
<td>Reaction incomplete</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>NaOCH$_3$</td>
<td>80</td>
<td>Reaction incomplete</td>
<td></td>
</tr>
</tbody>
</table>

*Reactions carried out in aq. methanol.*
Conclusion

An efficient process for pyridine ring reduction with 15-20% ee has been developed by using L-proline or naproxene as a chiral auxiliary. Enantiomerically enriched novel process has been developed for (4aS,7aS)-octahydro-1H-pyrrolo[3,4-b]pyridine by investigating three different approaches. We demonstrated coupling between 2,3-bis(chloromethyl)pyridine 7 and (S)-2-(6-methoxynapthalen-2-yl)propanamide 8 for the first time in presence of sodium hydride in toluene with 70% of yield and recovery process for racemic naproxen 14 by hydrolyzing of 10 with KOH in aq. methanol was also established.

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