



Synthesis and Characterization of *S*(-)-1-Phenyl-1,2,3,4-Tetrahydro Isoquinoline Acetamide Analogues

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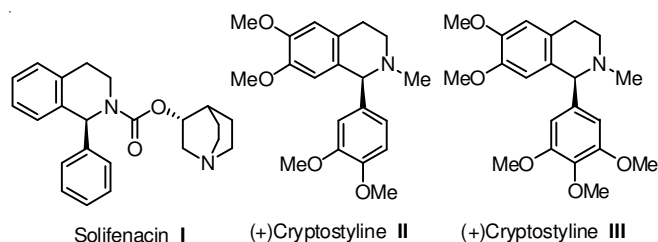
S(-)-1-Phenyl-1,2,3,4-tetrahydro isoquinoline acetamide analogues are prepared by sequence of reactions which involve a metal hydride reduction of 3,4-dihydroisoquinoline followed by separation of *S*-form with mandelic acid (chiral reagent) by resolution. The product *S*(-)-1-phenyl-1,2,3,4-tetrahydro isoquinoline is treated with halosubstituted acetyl chlorides to obtain tetrahydro isoquinoline acetyl chloride which is further employed to synthesize acetamide derivatives of tetrahydro isoquinoline using various substituted aryl amines. The products were characterized by advanced spectroscopic techniques.

Keywords: 1-Phenyl-3,4-dihydro isoquinoline, Resolution, Aryl amines, Acetamide analogues of tetrahydro isoquinoline.

INTRODUCTION

Tetrahydro isoquinolines are heterocyclic fused ring systems, which contain hetero atom 'N', positioned at 2 in the fused ring molecule. These isoquinolines are the most important intermediates in the drug development molecules. These are also an important class in alkaloid compounds and they exhibit wide biological properties. The various natural products possess tetrahydro isoquinolines and its derivatives such as cactus alkaloids (peyoruvic acid) [1], mammalian alkaloids (salsoline carboxylic acid) [2-4], the esteinascidine family (ET743) [5-8] and spiro-benzo quinoline alkaloids (parfumine) [9,10].

Many pharmaceutical drug molecules are made up of tetrahydro isoquinoline and its derivatives such as solifenacin (**I**), (+) cryptostyline (**II**) and (+) cryptostyline (**III**).



1-Phenyl-3,4-dihydro isoquinoline is widely used in the industrial production of this particular tetrahydro isoquinoline

which depends on the optical resolution of the *racemic* mixture using a chiral molecule such as mandelic acid.

The Pictet-Spengler reaction was the most suitable method for the synthesis of substituted 1,2,3,4-tetrahydro isoquinoline. The highly substituted, optically pure tetrahydro isoquinoline having a quaternary carbon as stereo center was synthesized by Kaluza and co-workers [11]. A catalytic enantioselective quaternary carbon prepared a similar to Reissert reaction with quinolines by Funabashi *et al.* [12]. 1-Substituted isoquinolines (or) 3,4-dihydro isoquinolines were used as starting materials for the synthesis of Reissert compounds [13-17]. Kubota *et al.* [18] also synthesized various *N*-acetyl-1,2,3,4-tetrahydro isoquinoline derivatives and also studied the pharmacological activity which are potent molecules.

EXPERIMENTAL

Melting points of the products were measured using MR-VIS visual melting range apparatus and are uncorrected. IR spectra were recorded on a Shimadzu-IR Affinity. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker DRX 400 MHz spectrometer and 100 MHz respectively. NMR spectra were obtained in the solution using CDCl₃ as solvent using TMS as an internal standard. Elemental (C, H, N) analysis was done using FLASH EA analyzer.

Thin layer chromatography was carried out to check the progress of the reaction. Spots were visualized using iodine

and exposing to UV light. Characterization of the products primarily conformed by NMR technique.

General procedure for synthesis of *S*(-)-1-phenyl-1,2,3,4-tetrahydro isoquinoline acetyl amide derivatives (8a-8h): *S*(-)-1-Phenyl-1,2,3,4-tetrahydro isoquinoline acetyl chloride (1.0 equiv) and substituted aryl amine (a-h) (1.2 equiv) were dissolved in dichloromethane. To this triethylamine (2.0 equiv) was added at room temperature. Then reaction mixture was heated to reflux temperature with constant stirring. Reaction was monitored by TLC and after completion of the reaction, the mixture was diluted with dichloromethane and water was added. Both the layers were separated and dichloromethane fraction was washed with brine solution, dried over anhydrous Na_2SO_4 . The concentrated crude was loaded on silica gel column for purification. By eluting the column with hexane and ethyl acetate mixture, pure *S*(-)-1-phenyl-1,2,3,4-tetrahydro isoquinoline acetyl amide derivatives (8a-8h) were obtained in good to excellent yields.

Synthesis of *N*-(2-phenyl ethyl)-benzamide (3): To the suspension of benzoic acid (1, 1.2 equiv) in dichloromethane, phenylethylamine (2, 1.0 equiv) followed by carbonyldiimidazole (CDI) (1.2 equiv). Then the reaction mixture was heated to reflux. The reaction mixture was washed with saturated brine solution, dried over anhydrous Na_2SO_4 and concentrated to get crude product. Pure product **3** was obtained in 95 % yield after column chromatography (silica gel; hexanes and ethyl acetate).

***N*-Phenylethylbenzamide:** ^1H NMR (400 MHz, CDCl_3) δ : 7.70 (d, J = 8.4 Hz, 2H), 7.49-7.30 (m, 5H), 7.25-7.22 (m, 3H), 6.32 (br s, 1H), 3.68-3.73 (m, 2H), 2.93 (t, J = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ : 167.6, 139.0, 134.7, 131.4, 128.8, 128.7, 128.6, 126.9, 126.6, 41.2, 35.7. LCMS (m/z): 226.21. m.f.: $\text{C}_{15}\text{H}_{15}\text{NO}$, Elemental analysis (%): Calculated: C-79.97, H-6.71, N-6.22. Obtained: C-79.98, H-6.69, N-6.20.

Synthesis of 1-phenyl-3,4-dihydroisoquinoline (4): Compound **3** was dissolved in xylene and P_2O_5 (1.2 equiv) followed by POCl_3 (3.0 equiv) were added at room temperature. The reaction mixture was then refluxed. Reaction was monitored by thin layer chromatography and after completion of the reaction, hot reaction solution was poured into ice and carefully the pH of solution was adjusted to 12 using 20 % NaOH. Later, water was added to dissolve precipitated phosphates. Then toluene was added to extract using 1 N HCl. The aqueous fraction was made alkaline using 20 % NaOH under ice-cooling condition. Again the product was extracted using toluene, dried over anhydrous Na_2SO_4 , solvent was evaporated under vacuum, which yielded the desired product **4** in 92 % as yellow colored viscous liquid.

1-Phenyl-3,4-dihydroisoquinoline: ^1H NMR (400 MHz, CDCl_3) δ : 7.62-7.52 (m, 2H), 7.39-7.30 (m, 4H), 7.22-7.18 (m, 3H), 3.80 (t, J = 6.8 Hz, 2H), 2.74 (t, J = 6.4 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ : 165.11, 141.18, 139.00, 138.69, 131.02, 130.50, 129.16, 129.04, 128.06, 127.19, 126.03, 45.84, 27.33. LCMS (m/z): 206.18. m.f.: $\text{C}_{15}\text{H}_{13}\text{N}$. Elemental analysis Calculated: C-86.92, H-6.32, N-6.76, Obtained: C-86.93, H-6.30, N-6.75.

Reduction of 1-phenyl-3,4-dihydroisoquinoline (5): 1-Phenyl-3,4-dihydroisoquinoline in methanol (**4**, 1.0 equiv)

was taken in round bottom flask and then cooled to 0 °C. Sodium borohydride (1.5 equiv.) was added in portions at 0 °C and then slowly warmed to room temperature. After 3 h stirring, methanol was evaporated and the residue was taken in dichloromethane. Water was added in fractions and washed twice with dichloromethane. All the dichloromethane fractions were combined, dried over anhydrous Na_2SO_4 , solvent was removed, purified by column chromatography using silica gel as stationary phase and mixture of ethyl acetate and hexanes as eluent to obtain pure *racemic* 1-phenyl-1,2,3,4-tetrahydro-isoquinoline **5** in 88 % yield as white solid.

***rac*-1-Phenyl-1,2,3,4-tetrahydroisoquinoline:** ^1H NMR (400 MHz, CD_3OD) δ : 7.30-7.18 (m, 5H), 7.12-7.07 (m, 2H), 6.99-6.95 (m, 1H), 6.65 (d, J = 8.0 Hz, 1H), 5.02 (s, 1H), 3.08-2.92 (m, 3H), 2.75-2.84 (m, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ : 142.4, 136.0, 133.4, 127.3, 127.1, 126.5, 126.2, 125.6, 124.6, 123.83, 59.9, 39.6, 27.0. LCMS (m/z): 210.16. m.f.: $\text{C}_{15}\text{H}_{15}\text{N}$. Elemental analysis (%): Calculated: C-86.08, H-7.22, N-6.69, Obtained: C-86.10, H-7.21, N-6.68.

Resolution of *rac*-1-phenyl-1, 2,3,4-tetrahydroisoquinoline for *S*-isomer (6): Optically active (*S*)-mandelic acid (0.5 equiv) was added to the solution of *racemic* compound **5** (1.0 equiv) in mixture of toluene and methanol solvents at room temperature. The resulting suspension was stirred at 80 °C to make homogeneous reaction mixture. The stirring was continued with heating at 80 °C until completion of reaction. It was found that after 30 min the reaction was completed. The solution was allowed to cool to room temperature. Mandelic acid resolves diastereomeric mixture to *S*-form of **5**, which was filtered from the solution. The filter cake was washed once with toluene and air-dried to yield compound **6** (*S*-form) as a white solid in 47 % yield. Compound **6** was treated with 2 M Sodium hydroxide solution and the toluene was added. Two layers were separated. Toluene fraction was dried over anhydrous Na_2SO_4 , concentrated and purified on silica gel column (eluted using mixture of hexane and ethyl acetate) to obtain pure *S*-isomer.

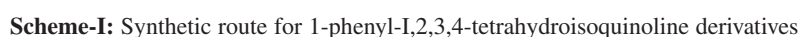
***S*-1-Phenyl-1,2,3,4-tetrahydroisoquinoline:** ^1H NMR (400 MHz, Acetone- D_6) δ : 7.31-7.20 (m, 5H), 7.10-7.08 (m, 2H), 7.00-6.96 (m, 1H), 6.66 (d, J = 7.6 Hz, 1H), 5.03 (s, 1H), 3.23-3.19 (m, 1H), 3.03-2.96 (m, 2H), 2.78-2.68 (m, 1H), 2.36 (br s, 1H). ^{13}C NMR (100 MHz, Acetone- D_6) δ : 145.7, 139.1, 135.7, 129.0, 128.9, 128.0, 127.8, 127.0, 125.9, 125.3, 62.1, 42.3, 30.0. LCMS (m/z): 210.16. m.f.: $\text{C}_{15}\text{H}_{15}\text{N}$. Elemental analysis (%): Calculated: C-86.08, H-7.22, N-6.69, Obtained: C-86.10, H-7.21, N-6.68.

Synthesis of *S*(-)-1-phenyl-1,2,3,4-tetrahydro isoquinoline acetyl chloride (7): Potassium carbonate was added to the solution of *S*-1-phenyl-1,2,3,4-tetrahydro isoquinoline (compound **6**) in acetone at room temperature. After stirring for 30 min, chloroacetyl chloride was added and then reaction mixture was allowed to stir at reflux temperature. Reaction was monitored by TLC and found completed in 4 h. Reaction mixture was filtered acetone was evaporated and was purified by column chromatography using silica gel as stationary phase and mixture of hexanes and ethyl acetate as eluent to get pure acetyl chloride derivative **7** as white solid in 95 % yield.

^1H NMR (400 MHz, CDCl_3) δ : 7.35-7.98 (m, 7H), 6.86 (br s, 1H), 6.64-6.58 (m, 2H), 4.73 (s, 2H), 4.50 (s, 1H), 3.31-

(S)-2-(1-Phenyl-1,2,3,4-tetrahydroisoquinolin-2(1H)-yl)-N-(pyridin-2-yl)acetamide (8f): ¹H NMR (400 MHz, CDCl₃) δ: 8.04 (d, *J* = 4.4 Hz, 1H), 7.44-7.40 (m, 1H), 7.34-

(S)-N-(1*H*-Imidazol-2-yl)-2-(1-phenyl-1,2,3,4-tetrahydroisoquinolin-2(1*H*)-yl)acetamide (8h): ¹H NMR (400 MHz, CDCl₃) δ: 7.33-04 (m, 3H), 6.97 (d, *J* = 8.0 Hz, 2H), 6.87 (br s, 1H), 6.61 (d, *J* = 8.0 Hz, 2H), 4.61 (s, 2H), 4.48 (s, 1H), 3.10-2.55 (m, 4H). ¹³C NMR (100 MHz, CDCl₃) δ: 169.1, 143.0, 138.1, 134.7, 130.0, 129.9, 128.22, 128.20, 128.1, 127.8, 127.3, 125.73, 125.69, 122.4, 58.4, 55.2, 48.8, 28.7. LCMS (*m/z*): 331.40, m.f.: C₂₀H₂₀O, Elemental analysis (%): Calculated: C-72.27, H-6.06, N-16.86, Obtained: C-72.29, H-6.05, N-16.83.



Scheme-I: Synthetic route for 1-phenyl-1,2,3,4-tetrahydroisoquinoline derivatives

RESULTS AND DISCUSSION

The biological activity reported for *S*(-)-1-phenyl-1,2,3,4-tetrahydro isoquinoline has provided a great deal of interest and has influenced for the synthesis of a new tetrahydro isoquinoline acetamide derivatives with the various aryl amines.

The *S*(-)-1-phenyl-1,2,3,4-tetrahydro isoquinoline acetamide derivatives can be prepared by a sequence of reaction has shown in **Scheme-I**. Initially, the direct condensation of benzoic acid (**1**) and 2-phenyl ethylamine (**2**) leads to the formation of *N*-(2-phenyl ethyl)-benzamide (**3**) in excellent yield. Compound **3** was cyclised by Bischler-Napieralski method to yield 1-phenyl, 3,4-dihydro isoquinoline (imine) (**4**) using $P_2O_5/POCl_3$ in xylene under reflux conditions. Reduction of imine **4** resulted in *racemic* 1-phenyl-1,2,3,4-tetrahydro isoquinoline (**5**), which undergo classical resolution using mandelic acid to separate **6** (*S*-form) which is treated with chloroacetyl chloride to form tetrahydro isoquinoline acetyl chloride **7**. Compound **7** was treated with different substituted aryl amine in the presence of triethyl amine/dichloromethane resulting in the formation of acetamide analogues (**8a-8h**).

We further studied the substrate scope for the final step of the above sequence, by taking several aryl amines. Aryl amines having both electron donating groups such as -Me, -OH and electron withdrawing groups such as -NO₂, -Br on phenyl ring are used in this reactions, which leads to various acetamide derivatives (**8a-8h**).

Conclusion

We reported for the first time tetrahydro isoquinoline acetamide analogues employing mandelic acid (as chiral reagent) for separation of *S* form in the synthesis, which was further treated with substituted aryl amines to obtain the target molecule.

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