A Crystallization-Induced Asymmetric Transformation using Racemic Phenyl Alanine Methyl Ester Derivatives as Versatile Precursors to Prepare Amino Acids

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Abstract

L-Tyrosine and L-Dopa are the precursors in the biological synthesis of amine neurotransmitters. On the other hand, phenylalanine as an aromatic amino acid (AAA) is a precursor in the synthesis of L-Tyrosine and L-Dopa. For some substrates such as amino acids, resolution by the formation of diastereomers offers an attractive alternative. Among different methods in this case, crystallization-induced asymmetric transformation (CIAT) that is in situ racemization and selective crystallization of a reaction product can be a good choice. Using this method, preparation of L-Tyrosine and L-Dopa has been reported. In the synthetic route, racemic phenyl alanine methyl ester derivatives were prepared by reducing azlactone derivatives with Mg in methanol as a reducing reagent and then in the resolution step (S)-enantiomer of L-Dopa (3,4-dihydroxyphenylalanine) and L-Tyrosine (4-hydroxyphenylalanine) were achieved via salt formation with (2R,3R)-tartaric acid in the presence of 5-nitro salicylaldehyde in good yield and high optical purity.

Keywords: Azlactone; Racemic-phenylalanine methyl ester; Amino acids; Asymmetric transformation.

Introduction

Amino acids are essential building blocks of proteins and play very important roles in many metabolic pathways [1]. Except glycine, all proteineogenic amino acids occur in the L-configuration about the chiral carbon atom; this property of amino acids has created a complexity in function and even in chemical synthesis of these compounds [2]. One of the methods to categorize amino acids is to classify them based on their side chain group type (aliphatic, acyclic, aromatic, containing hydroxyl or sulfur, etc.). Amino acids containing an aromatic ring including phenylalanine, tryptophan, tyrosine and histidine are called aromatic amino acids (AAA) which play a vital role in the synthesis of many effective and regulatory molecules such as amine neurotransmitters in the body. Dopamine, serotonin, norepinephrine and epinephrine are important amine neurotransmitters involved in many physiological functions including sleep, sexual arousal, reinforcement and regulation of heart rate and blood pressure. For example, serotonin or 5-hydroxytryptamine (5-HT) is a
monoamine neurotransmitter which acts as the main factor regulating the sleep cycle, biochemically derived from tryptophan [3, 4]. Another example is phenylalanine that is the precursor in the synthesis of Tyrosine and L-Dopa. On the other hand L-Dopa is a precursor in the biological synthesis of melanin and all three catecholamines namely dopamine, norepinephrine and epinephrine [5, 6]. A synthetic route for the production of biological amines has been provided below, Scheme 1.

The amino acid levodopa which is orally administered for patients with Parkinson’s disease can easily penetrate the blood brain barrier (BBB) where it is then converted to dopamine [7]. Although, L-Dopa is an effective drug and standard therapy for Parkinson’s disease (PD), D-Dopa is biologically inactive [8]. The main source of L-Dopa for pharmaceutical approaches is provided either by biological source or chemical synthesis. Various biological sources such as enzymatic synthesis, fungal, bacterial and plant resources have been reported [9]. The well-known processes are nowadays being employed for the production of L-Dopa, are the Hoffmann La-Roche, the Monsanto, the Ajinomoto, and the Sankyo process. Most of the L-Dopa commercially sold is synthesized from vanillin, through hydantoin and azlactone by a chemical process which involves several reaction steps [10, 11]. L-Tyrosine is used as a dietary supplement with various pharmaceutical applications. In addition to the chemical production, various biotechnological strategies can be employed to produce L-Tyrosine [12].

Regarding the aim of our study to synthesis amine neurotransmitters such as L-Tyrosine and L-Dopa, azlactone derivatives were chosen as versatile intermediates in the synthesis of these compounds. As shown in scheme 2, the Erlenmeyer synthesis [13] of (2a-j) from benzaldehydes (1a-j) and N-acetylglycine or N-benzoylglycine were employed as the first step. Following the successful synthesis of azlactone derivatives (2a-j), a literature survey was done in order to find the ways for reduction and ring opening of them to provide racemic phenylalanine derivatives. Various
methods have been reported in this regard, among them, the usage of some reagents including P/HI, Zn amalgame, Zn/CH₃COOH, Zn/HCl and Na or Mg /MeOH could be taken into account [14, 15]. Some of these reagent effects were of evaluated (shown in Table 2) and finally Mg/MeOH reagent was used to reduce azlactone derivatives (2a-j). Mg/MeOH as a reducing reagent led to both reduction of olefinic bond and ring opening of azlactone derivatives (2a-j) to successfully produce racemic N-acetyl (benzoyl) phenylalanine methyl esters (3a-j). These compunds were then transferred to phenylalanine methyl ester derivatives (4a-j) via acid hydrolyzation .

In the following chemical synthesis of racemic phenyl alanine methyl esters (precursor for L-Tyrosine and L-Dopa), the resolution of D- and L-phenylalanine methyl esters (4a-j) has been studied as well to prepare L-Tyrosine and L-Dopa (Scheme 2). For some substrates such as amino acids, resolution by the formation of diastereomers, in help with other methods (asymmetric synthesis using chiral reagent, enzyme-based kinetic resolution), offers an attractive alternative [16, 17]. One of the earliest methods so-called Crystallization Induced Asymmetric Transformation (CIAT) was utilized in the preparation of optical active compounds. Crystallization is an efficient and cost-effective method to develop highly stereoselective processes for resolutions even when the yield of isolated product is less than the yield from a conventional workup using extraction before the crystallization. Asymmetric synthesis is frequently used in preparing a desired enantiomer especially in drugs. Under classic resolution conditions, such as the crystallization of desired amine enantiomer from a racemic mixture using a chiral acid, the maximum yield of the desired enantiomer is only 50%. Kinetic resolution is another practical approach to obtaining one enantiomer with high enantiomeric purity established by exploiting different reactivities of enantiomeric intermediates to enzymes or chiral reagents. Hence, in order to obtain products with high enantiomeric purification, processes may be stopped before 50% conversion, thus reducing the yield of the desired enantiomer to less than 50% of the moles of the initial carbon framework. Some researchers isolate and racemize the undesired enantiomer and recycle it by subjecting the racemic mixture to the resolution conditions. Although this racemization - recycling approach requires additional time and materials, the theoretical yield can be raised above 50%. It is interesting to consider that, under the CIAT right conditions; an extended crystallization may increase the theoretical yield of a resolution from 50% to 100% [18].

This method is very effective and popular and in some cases has been applied to resolve materials on large scales. Imines of aldehydes and ketones have also been resolved by a CIAT process. This method has been successful in the resolution of various derivatives of amino acids as well. By means of this method, both optical purity and yield of the obtained amino acids would be high. In line with this, there are some reports on the resolution of amino acids by this method. Shirawa et al. have reported the preparation of D-Histidine and D-Proline by asymmetric transformation [19, 20]. Villani et al. described CIAT of p-chlorophenylalanine methyl ester; the (R)-ester, crystallized as the salt with (S, S)-tartaric acid in the presence of salicylaldehyde [21]. In another example of CIAT, Wei et al. studied the possibility of preparation of D-phenylalanine by asymmetric transformation method in the presence of propionic acid [22].

Considering the ready synthetic availability of racemic phenyl alanine methyl ester by Mg/MeOH followed by acid catalyzed hydration [15] the main purpose of this paper was the resolution of enantiomers from this racemic mixture. So, we investigated the possibility of preparing L-Tyrosine and L-DOPA by asymmetric transformation method from racemic phenylalanine methyl ester derivatives. This is the first report on the resolution of L-Tyrosine and L-Dopa by this method (CIAT) in the presence of (2R, 3R)-tartaric acid with catalytic amount of salicylaldehyde derivatives.

Materials and Methods

General

All of the solvents and reagents used in this study, were procured from the Merck company and used without purification. Melting points were measured with a Kofler hot-stage apparatus and were uncorrected. 1H and 13C NMR spectra were run on Bruker 500, using TMS as an internal standard. IR spectra were recorded on a Shimadzu 470 spectrophotometer (KBr disks). Optical measurements were performed on a Perkin-Elmer 141 polarimeter.

General procedure for the preparation of 4-benzylidene-2-methyloxazol-5(4H)-one (azlactone) derivatives via Erlenmeyer synthesis (2a-j):

A mixture of aromatic aldehyde (100 mmole), N-acetyl glycine (120 mmole), acetic anhydride (500 mmole) and sodium acetate (130 mmole) was warmed on a steam bath until complete dissolution.

The resulting solution was boiled for 4 hours under reflux, upon cooling; it placed in a refrigerator...
overnight. The solid mass of yellow crystals was treated with 125 ml of cold water. The crystals was filtered and washed with cold water and 50% ethanol (3(25 mL)), then dried in vacuo to give the azlactone derivatives 2a-j in 60-90% yields. The product was sufficiently pure for preparative purposes.

**General procedure for the synthesis of N-acetyl (benzoyl)-(R,S)-phenylalanine methyl ester derivatives (3a-j):**

To a stirred solution of 70 mmol azlactone (2a-j) in 350 mL of dry methanol, was added 140 mmol of Mg turning. After 5 min induction period, mild exothermic reaction started with evolving hydrogen gas; stirring was continued another 45 min to dissolve Mg completely with maintaining the pot temperature at 10 °C in an ice bath. The reaction mixture was poured into 100 ml of ice-cooled 3N hydrochloric acid and stirred vigorously to make clear solution. The acidic solution was treated with 3N ammonium hydroxide to adjust its pH to 8.5-9.0. After usual work up, pure N-acetyl-(R,S)-phenylalanine methyl ester derivatives (3a-j) was obtained in 61-95% yields.

**General procedure for the synthesis of (R, S)-phenylalanine methyl ester derivatives (4a-j):**

N-acetyl(benzoyl)-(R, S)-phenylalanine methyl ester (3a-j) (60 mmol) was added to 10% hydrochloric acid (120 ml) and stirred at 120°C for 3 hours. Then, these steps were done in sequence: the 10% hydrochloric acid was distilled away under reduced pressure, the residue was added with water (150 ml), dried under reduced pressure, further added with water (150 ml), and dried under reduced pressure again to yield an amorphous. The amorphous was added with ethanol (200 ml) and dissolved in it, added dropwise with 25% aqueous ammonia under ice-cooling for pH adjustment to 6.5. The solution was allowed to stand in a refrigerator overnight. The precipitated crystals were filtered out, washed with ethanol and diethyl ether and then dried under reduced pressure to yield a residue. The powder was added to water (200ml) containing activated carbon and a trace amount of sodium bisulfite, heated to reflux and then decolorized. The filtrate was concentrated to yield (RS)-phenylalanine methyl ester (4a-j) as viscous oils in 60-90% yields.

**General procedure for the Crystallization-induced asymmetric transformation of 4a-e to give 5a-e:**

(RS)-phenylalanine methyl ester (4a-e) (40 mmol) was combined with (2R,3R)-(+)-tartaric acid (40 mmol), salicylaldehyde derivatives (1 mmol) and methanol (100 mL). The mixture was refluxed overnight and allowed to cool to ambient temperature. The resulting solid was filtered, washed with diethyl ether and air dried to give (L)-phenylalanine methyl ester (2R, 3R)-tartrate (5a-e) in 71-85% yields.

**General procedure for the synthesis of (L)-phenylalanine methyl ester derivatives (6a-e):**

To a solution of potassium carbonate (60 mmol) in distilled water (L)-phenylalanine methyl ester (2R, 3R)-tartrate (5a-e) (30 mmol) was added, followed by the addition of dichloroethane (100 mL). After string at room temperature for 1 h, the layers were separated and the aqueous layer was extracted with dichloroethane (3(25 mL)). The combined organic layer was dried over potassium carbonate, filtered and concentrated under reduced pressure to give (6a-e) of the free base, (L) - phenylalanine methyl ester in 83-95% yields.

**General procedure for the synthesis of (L)-hydroxy phenylalanine derivatives (7a-e):**

(L)-Phenylalanine methyl ester (6a-e) (10 mmol) was poured in hydrochloric acid 5 N (5 ml) and heated to reflux for 2-3 h. After completion of the reaction, the aqueous mixture is then concentrated to dryness in vacuo to yield a residue, which was refluxed with hydrobromic acid under an inert atmosphere for 8-10 h without further purification. The obtained mixture was concentrated under vacuum and then dissolved in hot acetone. After filtration, the pH of the remaining solution was adjusted to 8.4 with diethyl amine. After usual workup,7a-e was obtained as an oily product in 75-90% yields and 78-88% optical purities.

**Results and Discussion**

The ultimate goal of this study was to separate the S-enantiomer from the racemic mixture of phenyl alanine methyl ester derivatives to prepare L-Tyrosine and L-Dopa. Among the different methods described for resolution of commercially important compounds, a crystallization-induced asymmetric transformation of racemic amino acid methyl ester was developed to provide a convenient route to enantiomerically enriched (R)-or (S) methyl ester. Therefore, we envisaged an asymmetric transformation resolution of phenylalanine methyl ester derivatives.

In the first step, azlactone derivatives (2a-j) were prepared by Erlemeyer synthesis and characterized by melting point and 1H NMR, Table 1.

In the second step, the racemic mixture of N-acetyl (benzoyl) phenyl alanine methyl ester derivatives (3a-j) were obtained by reducing prepared azlactones (Scheme 2). There are numerous methods, employing reduction
and ring opening, for the conversion of azlactones to the corresponding N-acetyl (benzoyl) phenyl alanine. For example Roper et al. used high pressure catalytic hydrogenation for this goal. Under this condition, unexpected side reactions may also occur [23]. Although a few methods with relatively high yields have recently been reported for the reduction of the olefinic bonds present in various α, β-unsaturated compounds, they suffer from disadvantages such as high cost, harsh reaction conditions, the use of toxic solvents and lacking environmentally friendly procedures.

Considerable efforts have been made in order to optimize the reaction condition of reducing azlactone. We began our investigations by evaluating the effect of various reagents in different conditions for converting 2e to 3e. The results have been depicted in Table 2.

As indicated in table 2 (Entry 5), the best result among these reagents, was achieved with Mg/MeOH. Although the mechanistic details of this part are not fully understood, it seems that the reaction is initiated by the production of proton from methanol to produce intermediate, known as the methoxide ion. The carbonyl group of the azlactone ring will be then attacked by the methoxide resulting in breakage the bond and the opening the ring. Hydrogen gas production has also been reported. The double bond of alpha, beta-unsaturated ester are also simultaneously reduced. The yield of this reaction ranged from 61% to 95% (Table 1).

In the third step, the (R,S)-phenylalanine methyl ester (free base) was obtained from N-acetyl (benzoyl) phenyl alanine by hydrolysis with HCl [24] (Scheme 2). This compound (4a-j) was assigned based on spectral data. In the 1H NMR spectrum, loss of a signal displayed in range of 1.91-1.99 ppm showed that N-deacetylation occurred. The disappearance of the phenyl peaks related to the benzoyl groups is the reason for occurring N-debenzylation as well.

After these steps, crystallization induced asymmetric transformation (CIAT) was investigated for the resolution of prepared (R,S)-phenylalanine methyl esters under different solvents and catalytic conditions, Table 3.

Catalytic activity of salicylaldehyde derivatives was investigated in CIAT method for the resolution of (R,S)-...
phenylalanine methyl ester derivatives in various solvent at reflux condition. For this purpose, resolution of 4-(3-methoxy, 4-acetoxybenzylidene)-2-methylloxazol-5(4H)-one 4e with (2R, 3R)-tartaric acid was considered a model reaction to obtain optimum conditions (Table 3). In our initial investigations, the model reaction was conducted in the presence of different salicylaldehyde derivatives in methanol, as shown in Table 4. It was found that low yield of product was obtained whether in the absence of salicylaldehyde (Table 4, entry 1) or in the presence of 3-Methoxysalicylaldehyde (Table 4, entry 4) even after long reaction time. Conduction of reaction in the presence of salicylaldehyde and 3,5-Dichlorosalicylaldehyde gave a moderate yield (Table 4, entries 2,3). As shown in Table 4, using 5-Nitrosalicylaldehyde gave rise to much better yield of product indicating the efficacy of the catalyst. The model reaction was also tested in various solvent conditions in the presence of 5-Nitrosalicylaldehyde. Hence, it is conceivable that high yield of product was obtained thanks to the usage of methanol. Our results showed that 1 mmol of catalyst was enough to achieve the highest amount of product (Table 4, entry 5). In a higher amount (Table 4, entry 6), no change in the reaction yield occurred, and in lower amounts (Table 4, entry 7), yields were reduced.

The resolution by CIAT method consists of two steps, the first step is the formation of tartrate salts (5a-e) and crystallization of the L-enantiomers and the second step is the separation of tartrate from the pure enantiomers by basic hydrolysis (6a-e) (Scheme 3). Intermediate compounds 5a-e and 6a-e were assigned based on spectral (FT-IR and 1H NMR) data analysis. The IR spectrum of 5e showed bands at 3418.1 (O-H), 3072.3 (C-H), 1732.9 (COOH), 1688.1 (COOH), 1631.3 (NH), 1601.6 (COO-), and 1315.2 cm⁻¹ which proves the formation of these salts. In addition, the appearance

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**Table 3. Preparation of Compounds 5-7**

<table>
<thead>
<tr>
<th>Starting Material</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Starting Material</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Starting Material</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>5a</td>
<td>78</td>
<td>5a</td>
<td>6a</td>
<td>91</td>
<td>7a</td>
<td>87</td>
<td>-10°</td>
</tr>
<tr>
<td>4b</td>
<td>5b</td>
<td>71</td>
<td>5b</td>
<td>6b</td>
<td>85</td>
<td>6b</td>
<td>7b</td>
<td>-9°</td>
</tr>
<tr>
<td>4c</td>
<td>5c</td>
<td>64</td>
<td>5c</td>
<td>6c</td>
<td>83</td>
<td>6c</td>
<td>7c</td>
<td>-9.3°</td>
</tr>
<tr>
<td>4d</td>
<td>5d</td>
<td>69</td>
<td>5d</td>
<td>6d</td>
<td>80</td>
<td>6d</td>
<td>7d</td>
<td>75</td>
</tr>
<tr>
<td>4e</td>
<td>5e</td>
<td>85</td>
<td>5e</td>
<td>6e</td>
<td>95</td>
<td>6e</td>
<td>7e</td>
<td>-10°</td>
</tr>
</tbody>
</table>

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**Table 4. Investigation of different salicylaldehyde derivatives and various solvents for the preparation of 5e.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Catalyst</th>
<th>Catalyst amount (mol %)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOH</td>
<td>Without salicylaldehyde</td>
<td>0.001</td>
<td>(48%)</td>
</tr>
<tr>
<td>2</td>
<td>MeOH</td>
<td>Salicylaldehyde</td>
<td>0.001</td>
<td>(60%)</td>
</tr>
<tr>
<td>3</td>
<td>MeOH</td>
<td>3, 5-Dichlorosalicylaldehyde</td>
<td>0.001</td>
<td>(73%)</td>
</tr>
<tr>
<td>4</td>
<td>MeOH</td>
<td>3-Methoxysalicylaldehyde</td>
<td>0.001</td>
<td>(55%)</td>
</tr>
<tr>
<td>5</td>
<td>MeOH</td>
<td>5-Nitrosalicylaldehyde</td>
<td>0.001</td>
<td>(85%)</td>
</tr>
<tr>
<td>6</td>
<td>MeOH</td>
<td>5-Nitrosalicylaldehyde</td>
<td>0.002</td>
<td>(85%)</td>
</tr>
<tr>
<td>7</td>
<td>MeOH</td>
<td>5-Nitrosalicylaldehyde</td>
<td>0.0005</td>
<td>(70%)</td>
</tr>
<tr>
<td>8</td>
<td>EtOH</td>
<td>5-Nitrosalicylaldehyde</td>
<td>0.001</td>
<td>(78%)</td>
</tr>
<tr>
<td>9</td>
<td>n-PrOH</td>
<td>5-Nitrosalicylaldehyde</td>
<td>0.001</td>
<td>(70%)</td>
</tr>
<tr>
<td>10</td>
<td>n-BuOH</td>
<td>5-Nitrosalicylaldehyde</td>
<td>0.001</td>
<td>(65%)</td>
</tr>
</tbody>
</table>

*Isolated yields of the pure products*
of hydrogens related to tartrate in the $^1$H NMR spectrum is another proof of the formation of these salts. On the other hand, the absence of IR bands at 3418.1 (O-H) and 1688.1-1732.9 (COOH) cm$^{-1}$ corresponds to tartaric acid of $6e$ and also disappearance of the peaks related to tartrate in $^1$HNMR spectrum of $6e$ denotes the production of these compounds.

These products $6a$-$e$ underwent deprotection to achieve the final product (L-Tyrosine and L-Dopa ($7a$-$e$)). Spectral data ($^1$H-NMR) analysis confirmed the formation of L-Tyrosine and L-Dopa; the yield of the L-DOPA synthesis was in the range of 75-90% and in the case of L-Tyrosine this range was about 80-87%.

Optical purity for both (3,4-dihydroxy)-(L)-phenylalanine and (4-dihydroxy)-(L)-phenylalanine was determined in 1 M HCl using a polarimeter. $[\alpha] = -11.3 \pm 0.5$ (1, HCl 1 M) indicated for L-Dopa and $[\alpha] = -11.5 \pm 0.5(1$, HCl 1 M) for L-Tyrosine. The highest optical purities were 86 % and 88 % obtained from the derivatives for 6a and 6e, respectively.

Over 100 patents issued for CIAT processes dealing with the formation of imine (Schiff base) intermediates [25, 26]; as shown in Scheme 3, imine formation activated the methine proton and facilitated
racemization. Hence a variety of aldehydes can be used in CIAT processes, and racemization is generally more facile when electron-poor aldehydes are used. As the results show, 5-Nitrosalicylaldehyde as the epimerization catalyst provided the salt of the pure S or R enantiomer in high yield. The presence of (-)-tartaric acid or (+)-tartaric acid provides a crystalline salt which is essentially removed from the system owing to its insolubility nature, driving the equilibrium.

In conclusion, azlactone derivatives are considered good candidates for starting materials for the preparation of aromatic amino acids due to their easy and fast synthesis. On the other hand, magnesium in methanol catalyzes hydrogenation and ring opening of azlactones for the preparation of racemic phenylalanine methyl esters which are important intermediates for the synthesis of amino acids. This study examined crystallization induced asymmetric transformation of racemic phenylalanine methyl esters via (+)-tartaric acid in the presence of salicylaldehyde derivatives as a catalyst. The results indicated that electron poor salicylaldehydes are more effective. For rapid scale-up, resolution by diastereomers formation may be more reliable and easier. From the other point of view, in situ racemization and selective crystallization of a reaction product can lead to a crystallization-induced asymmetric transformation (CIAT) that can afford in principle a quantitative yield of chiral product through in situ resolution. Highly crystalline materials may be good candidates for CIAT process and may lead to the isolation in good yield of what is the minor product in solution. To efficiently develop CIAT process, it is necessary to optimize parameters for racemization and crystallization, as well as high-throughput screening and design of experiments. It is interesting to consider that, under the right conditions; an extended crystallization may increase the theoretical yield of a resolution from 50% to 100%. CIAT process will continue to be developed, due to their significant economic advantages. Nevertheless, many researchers have found that a product from CIAT process is unstable in solution which reflects the labile nature of CIAT products. If any resolving agent used in the CIAT process is unstable to the reaction conditions, additional considerations are necessary to develop a process that may already require controlling a number of parameters. In summary, CIAT processes will be continued to develop amino acid resolutions, due to their significant economic advantages. Thus from the results of the present study, it could be concluded that CIAT processes could be applied successfully to large-scale production of L-Tyrosine and L-Dopa.

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References
13.(a) El-Mekabaty A., Erlenmeyer Azlactones: Synthesis,


