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Synthesis of *L*-3, 4-Dihydroxyphenylalanie Derivative from L-Tyrosine by Microwave Irradiation

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ABSTRACT

A range of amide derivatives of *L*-dopa were synthesized and investigated for their enormous pharmacological activity and their capability to be converted into others natural and unnatural products of great biological interest. Herein, a microwave assisted rearrangement has been developed in the final step to produce much improved yield of *L*-DOPA derivative without any racemization with minimal byproducts and reduce the processing time also.

Keywords : *L*-Tyrosine, *L*-DOPA, Parkinson's disease, Microwave Antitumor.

I. INTRODUCTION

L-3,4-Dihydroxyphenylalanine (*L*-DOPA) was just known as an intermediate in the biological synthesis of Malanine[1] and Epinefrine[2] until the middle of the 20th century. Over a past few decades *L*-DOPA (Figure 1) has been established to the chemist, as it has excellent natural remedy for neurological disorder[3] like Perkinson's disease[4]. The administration of *L*-DOPA was the way to re-establish cerebral concentration of dopamine, which made great advance in the treatment of the disease[5] and increasing demand for this optically pure substance. *L*-DOPA is also precursor of other very important neurotransmitter like norepinephrine (noradrenaline) and epinephrine (adriline) which are also released by the brain and central nervous system (CNS) Activity of *L*-Tyrosine in human body or in microorganism is very weak in general. Both *L*-Tyrosine and *L*-DOPA are rapidly decomposed to other metabolites. Hence design and synthesis and extended biological evaluation of *L*-DOPA derivatives in vivo as well as in vitro could be a potential prodrugs for not only the treatment of Parkinson's disease but also others variety of diseases. Even some derivatives of *L*-dopa was found are more active[6,7] than *L*-DOPA, so they could be used as prodrugs. In addition to that *L*-dopa derivatives are also used to synthesize a number of natural products[8] such as O.F-4949s, K-13 etc. which have confirmed immune potentiating and antitumor properties. Hence these generate great biological importance to treat a range of disease, even treatment of fatal cancer in human beings.

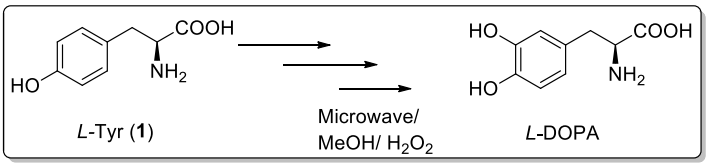


Figure 1. General synthesis of *L*-DOPA.

The first synthesis of optically pure *L*-DOPA was presented by Washer and Lewandowski[9], which was based on "chiral pool". After that, many methods has been developed[10] for the preparation of *L*-DOPA using either chiral pool materials or chiral catalyst. More recently, chiral phase transfer agent[11], an ammonium quaternary salt with a C2 symmetry has been introduced.

Therefore, an urgent need of sortable cheap process to produce the optically pure chiral amino acids due to their intensive use as active pharmaceutical intermediates[12].

Because of technological advantages of recent years, microwave induced synthesis[13] in solid phase or in solvent has been attracted synthetic chemist for their better yield, atom economy and time economy also. However, synthesis of *L*-DOPA using microwave has been so far restricted. In the present work, I tried to develop a simple tricks of synthesis of *L*-DOPA derivative from *L*-Tyrosine using microwave irradiation and changing solvent polarity to improve the yield in the final step of the very old Boger's procedure.[14]

II. METHODS AND MATERIAL

Preparation of (*S*)-Methyl3-(4-(benzyloxy)-3-hydrox phenyl)-2-(benzyloxycarbonylamino) Propanoate (**8**):

A solution of alcohol **6** (1 g, 2.15 mmol), 30% H_2O_2 (2.2 mL, 21.5 mmol, 10 equi.), p-TsOH.H_2O (0.123 g, 0.64 mmol, 30 mol%) and THF (4 mL) was taken in 20 mL glass tubes sealed with Teflon septum and placed in microwave cavity. The reaction mixture was then irradiated at operating frequency 2.45 GHz with continuous irradiation power 0 to 300 W at the required set temperature (here 60 ˚C) for 60 min. The reaction was monitored by TLC on silica gel using combination of hexane and ethyl acetate as eluents. It was then cooled and diluted with half-saturated $NaHCO_3$ (5 ml) before being extracted with ethyl acetate (2 × 20 ml). The combine organic extracts were washed with brine (1 × 15 ml), and then dried over Na_2SO_4. It was then filtered and the filtrate was concentrated in vacuum to leave a pale yellow crude product which on purification by flash chromatography over silica using 20% ethyl acetate in hexane gave **7** as colourless oil.

Yield: 810 mg (86%).

[α]D: – 14.9 (*c* = 1.1, MeOH). [Lit [14][α]D for **ent-7:** -15.15 (*c* = 1.0, MeOH).

IR: (KBr): 3409, 3064, 3033, 2953, 2924, 2852, 1738, 1721, 1610, 1499, 1454, 1379, 1352, 1288, 1245, 1214, 1178, 1138, 1978, 1062, 1026, 812, 797, 773, 738, 697 cm^{-1}.

^{1}H NMR: ($CDCl_3$, 500 MHz): δ 7.42-7.38 (5H, m, Ar-*H*), 7.37-7.29 (5H, m, Ar-*H*), 6.81(1H, d, *J* = 8.2 Hz, C_5-Ar-*H*), 6.99 (1H, d, *J* = 2 Hz, C_2-Ar-*H*), 6.55 (1H, dd, *J* = 8.2, 2 Hz, C_6-Ar-*H*), 5.61 (1H, br s, O*H*), 5.20 (1H, d, *J* = 8 Hz, N*H*), 5.09 (2H, s, PhCH_2OAr), 5.06 (2H, s, PhCH_2O_2C), 4.61 (1 H, q, *J* = 8 Hz, CH_2CHNH), 3.73 (3H, s, OCH_3), 3.04 (1H, dd, *J* = 16 Hz, CH_2CHNH), 2.90(1H, dd, *J* = 8 Hz, CH_2CHNH).

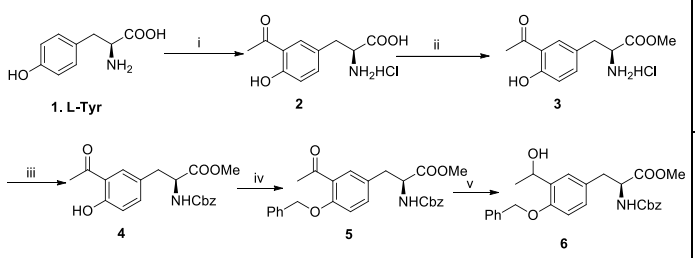
^{13}C NMR: ($CDCl_3$, 160.1 MHz): δ 153.9, 136.7, 136.1, 131.9, 128.9, 128.7, 127.1, 127.6, 126.9, 111.9, 66.8, 66.1, 58.2, 51.2, 37.0, 23.1.

HRMS: (TOF MS ES+): *m/z* 458.1583 (M + Na) ($C_{25}H_{25}NaNO_6$); Calcd 458.1580

III. RESULTS AND DISCUSSION

The compound **2** was synthesized from commercially available starting material *L*-Tyrosine **1** by Friedel-Crafts acylation using acetyl chloride, anhydrous

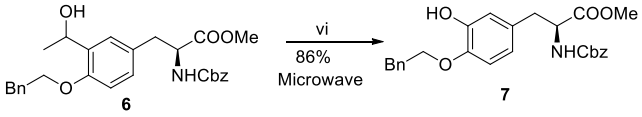
$AlCl_3$ in nitrobenzene in very good yield (78%). Esterification of the acid functionality in the latter with CH_3COCl in dry MeOH at rt delivered **3** in excellent yield (91%). Subsequent protection of free amine in **3** with Cbz-group using benzylchloroformate, sodium carbonate in diethyl ether-water, afforded **4** also in high yield (90%). Protection of free phenol in **4** as its benzyl ether using benzyl bromide, K_2CO_3 and tetra-n-butyl-ammonium iodide as catalyst in DMF furnished **5** in quantitative yield again. Reduction of acetyl functionality of **5** by $NaBH_4$ in methanol led to corresponding secondary benzylic alcohol **6** in 99% yield (Scheme-1). All compounds including **6** were characterized by IR, rotation, NMR and Mass-spectrum.



Scheme 1. *Reagents and conditions:* (i) $AlCl_3$, CH_3COCl, $PhNO_2$, 100 °C, 6 h, 76%; (ii) CH_3COCl, MeOH, rt, 2 h, 98%; (iii) Benzylchloroformate, Na_2CO_3, Et_2O-H_2O (1:1), rt, 3 h, 90%; (iv) benzyl bromide, K_2CO_3, tetra-n-butyl ammonium iodide (cat), DMF, rt, 6 h, 94%; (v) $NaBH_4$, MeOH, rt, 1 h, 99%.

In previous work, the compound **6** is converted to *L*-DOPA derivative **7** by an acid catalysed benzylic-peroxide rearrangement[15] in the presence of H_2O_2 (30%) and catalytic *p*-TsOH.H_2O in THF in 61% yield[14].

Microwave irradiated synthesis of *L*-DOPA derivative had hardly been tried to the best of my knowledge. With the key precursor **6** in hand, I next focused on improve the yield of **7** by microwave assisted condition. A number of solvent and acids have been used for the intramolecular rearrangement in microwave chamber. Notable among those are TsOH, camphoric acid, citric acid, acetic acid, *p*-nitro benzoic acid, 2,4 dinitro benzoic acid, Picric acid etc. We opted to evaluate these conditions by changing solvent polarity[16] as well as the acid catalyst to absorb microwave energy. The results are summarized in Table 1.



Scheme 2. (vi) 30% aq. H_2O_2, p-Tolune sulphonic acid (10 mol %), THF, Microwave, 1 h, 86%.

Table 1. Attempted microwave induced synthesis of 7 to 8 with varying conditions with 30% H_2O_2.

Entry	Acid	Solvent	Temp/ Time (Min)	[yield]	S.M (%)
1	*p*-Toluene Sulphonic acid	H_2O	100 °C, 30 min	23	63
2	Acetic Acid	THF	50 °C, 20 min	43	33
3	*p*-Nitrobenzoic acid	DME	50 °C, 25 min	47	31
4	2,4-dinitro benzoiacid	MeOH	35 °C, 30 min	20	71
5	Picric acid	THF	35 °C, 60 min	64	23
6	Camphoric acid	THF	50 °C, 30 min	43	40
7	Camphoric acid	MeOH	50 °C, 35 min	53	25
8	Oxalic acid	THF	50 °C, 25 min	26	61
9	*p*-Toluene Sulphonic acid	EtOH	50 °C, 35 min	76	5
10	*p*-Toluene Sulphonic	THF	60 °C, 60 min	86	7

	acid				
11	*p*-Toluene Sulphonic acid	Neat	25 °C, 10 min	13	71
12	Camphoric acid	Neat	25 °C, 10 min	16	66

Reaction condition: Alcohol **6** (1gm, 2.15 mmol), 30% H_2O_2 (2.2ml, 21.5 mmol), *p*-Toluenesulphonic acid, monohydrate (123mg, 0.64 mmol, 30 mol%) under microwave irradiation
(300 μ, closed vessel).

The use of aqueous medium in organic synthesis is also well known[17] in microwave. But active investigation with compound **6** in water gives very poor yield of **7** under varying temperature and different acid catalysts. Others solvents are also tried, but could not provide satisfactory yield of **7**. Even the reaction was carried out in open-vessel solvent free microwave condition[18], no change in the poor yield of **7** was observed.

Pleasingly, when the compound **6** is taken in a THF and catalytic amount *p*-Toluenesulphonic acid, monohydrate and 30% H_2O_2 and irradiated in a microwave at 60 °C in a closed vessel, conversion to the desired *L*-DOPA derivative **7** took place in an very good yield of 86%.(Scheme-2). The picric acid in THF also provides **7** in satisfied yield (Table-1), but lower than former.

The *L*-DOPA derivative **7** was obtained after purification by flash column chromatography over silica using 20% ethyl acetate in hexane as a colourless oil. The all characteristic ^{1}H-NMR, ^{13}C-NMR, I.R and mass spectrum confirmed its formation. Measurement of optical rotation ([α]D = -15.4, c = 1.1, MeOH) of **7** compared to its exact value ([α]D = -15.1, c = 1.0, MeOH) suggest that no racemisation took place during the whole reaction sequences above (Scheme 1,2).

IV. CONCLUSION

In conclusion, microwave induced *L*-DOPA derivatives has been reported, which is providing much better yield and less time consuming procedure. The methodology described here, may find application in the synthesis of other biologically impotent molecules. *L*-DOPA derivatives is also a valuable scaffold to provide verities of natural and synthetic compounds of immense biologically important. Work will be continued along this direction in my laboratory.

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