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SYNTHESIS OF NEW NICOTINOYL AMINO ACID DERIVATIVES

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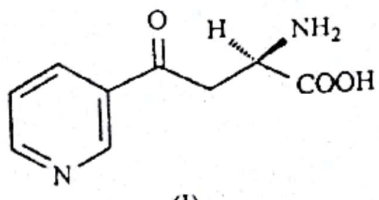
ABSTRACT

(S)-and/or (R)-(2-methyl-3-benzyloxycarbonyl-5-oxo-4-oxazolidinyl)-acetyl chloride, prepared from S-aspartic acid, which was reacted with 3-trimethyl stannylpyridine to give the corresponding pyridyl-ketone, then converted into enantiomeric (S)-and (R)-α-methylnicotinylalanine by hydrolysis with hydrochloric acid. Analogously, α-nicotinylalanine III was prepared from L-glutamic acid.

INTRODUCTION

In the course of the programme directed towards the synthesis of the enantiomers of nicotinylalanine derivatives[1,2] as neuroprotecting agent, our was focused on the synthesis and reactivity of the parent compound and its substitution products which arise from promise shown as inhibitor of Kynureninase and Kynurenine hydroxylase in vivo and vitro[3]. More recently, the anticonvulsant activity of nicotinylalanine has also been discovered[1]. All this prompted the synthesize of α-methylnicotinylalanine II and γ-nicotinylalanine III. We report a synthesis of α-methylnicotinylalanine similar to that L-Dopa[4], according to scheme 1. S-aspartic acid **1** was esterified with methanol in acid medium when the corresponding methyl ester **2** was obtained as hydrochloride salt which was neutralized to give compound **3.** Benzaldimine **4** was obtained by treating **3** with benzaldehyde in basic medium, and methylated by treating with diisopropylamine and methyllithium followed by reaction with methyl iodide to give **5.** The enantiomeric (S)-and (R)-α-methylaspartic ester **6** was obtained from **4** via mild acid hydrolysis (1N hydrochloric acid).



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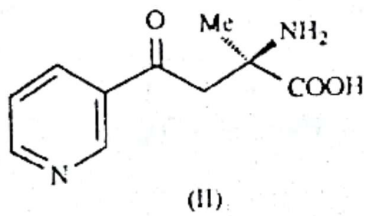

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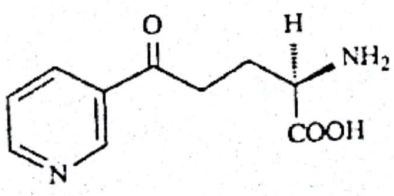

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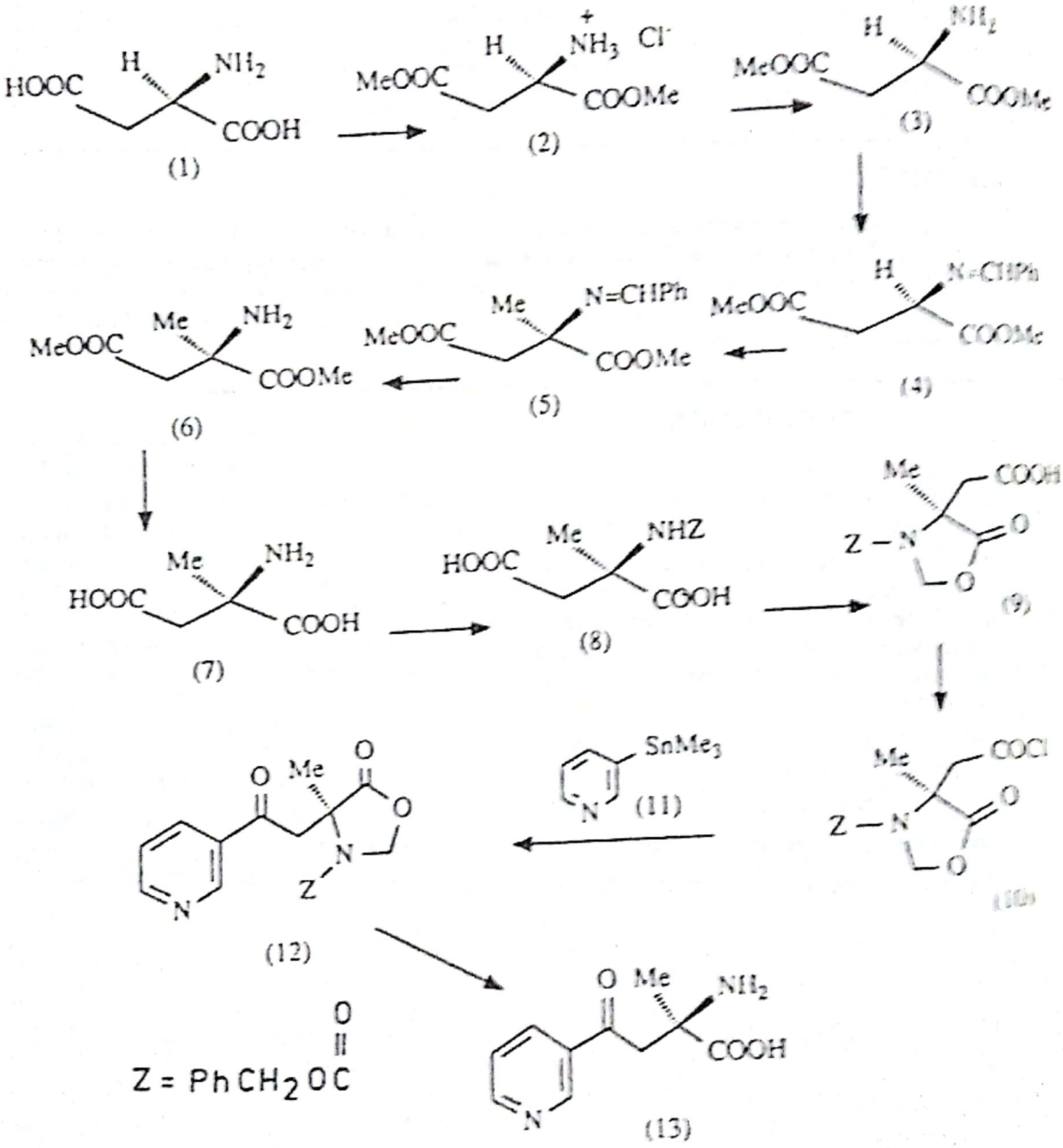
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H
NH2
COOH
(1)
MeOOC
H
NH3 Cl
COOMe
(2)
MeOOC
H
NH2
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(3)
MeOOC
H
N=CHPh
COOMe
(4)
MeOOC
Me
N=CHPh
COOMe
(5)
MeOOC
Me
NH2
COOMe
(6)
HOOC
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NH2
COOH
(7)
HOOC
Me
NHZ
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(8)
Me
COOH
Z – N
O
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(9)
Me
COCl
Z – N
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O
SnMe3
N
(11)
O
Me
O
O
N
Z
(12)
O
Z = PhCH2OC
O
Me
NH2
COOH
N
(13)

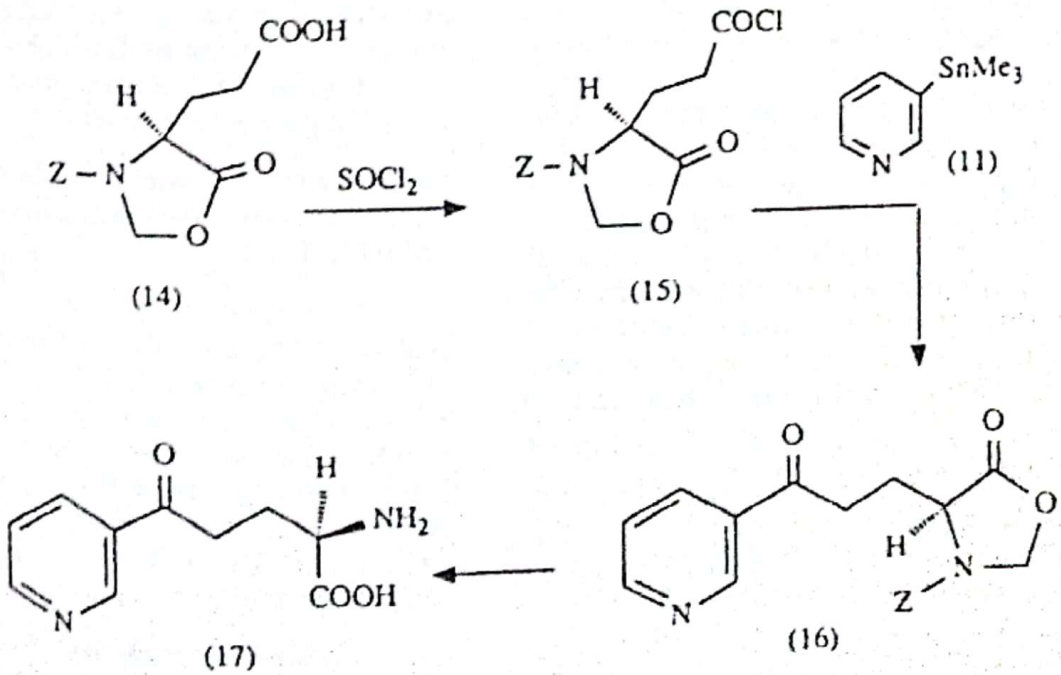
Scheme 1

Deprotection of **6** was achieved by shaking for 4 h in 1N LiOH in THF giving the enantiomeric (S)-and (R)-α-methylaspartic acid **7**. Direct protection of the amino group in **7** with benzyl chloroformate afforded α-methyl-N- benzyloxycarbonyl - aspartic acid **8** which was reacted with paraformaldehyde and a catalytic amount of p-toluenesulfonic acid with azeotropic removal of water[5], to yield (s)-or (R)-4-methyl - 3 - benzyloxycarbonyl-5-oxo-4-oxazolidineacetic acid **9** which was converted to the corresponding ß-acid chloride **10**. Then, a mixture of **10** and 3-trimethylstannyl pyridine[6] **11** was refluxed for 6 h in dry toluene to give the corresponding pyridyl-ketone **12** which was converted into enantiomeric (S)-and (R)-α-methylnicotinylalanine **13** in good yield by hydrolysis with hydrochloric acid followed by Dowex ion exchange resin chromatography. This method provides a possible starting point for the synthesis of other α-alkylated nicotinylalanine.

Analogously, a mixture of **11** and S- (3 - benzyloxycarbonyl - 5 - oxo - 4 - oxazolidinyl)-propionyl chloride **15**[5], prepared from L-glutamic acid, was refluxed for 12 h in dry toluene in the presence of $PdCl_2$ $(PPh_3)_2$ to give the corresponding pyridyl-ketone **16** which was converted to compound **17** by hydrolysis with acid followed by Dowex ion exchange resin chromatography.

EXPERI MENTAL

Melting points are uncorrected. IR spectra were determined in KBr discs or nujol with a Perkin-Elmer 577 spectrophotometer; absorptions (ν, cm^{-1}) are given only for the main bands. ^1H and ^{13}C NMR spectra were obtained on a Varian 200 gemini spectrometer with TMS as an internal standard. Elemental analyses were performed at the Instituto de Chimica Farmaceutica, Perugia University, Italy. Most of the commercial chemicals were purified and dried by standard procedures.



Scheme 2

(S)-and(R)-α-methylaspartic ester 6 :

(i) HCl (gas) passed on a suspension of L-aspartic acid (13.31 g, 0.1 mol) in methanol (100 ml) till the solution become clear, then it was boiled under reflux for 5 h. The solvent was evaporated in vacuo and the residue (colourless syrup 98% yield) was neutralized by $NaHCO_3$ solution, then extracted with ethyl acetate (three times, 40 ml each), dried over Na_2SO_4 and evaporated at reduced pressure to get pure **3** as colourless semisolid (90% yield). (ii) A mixture of **3** (16.10 g, 0.1 mol), benzaldehyde (12.72 g, 0.12 mol) and triethylamine (100 ml) was stirred for 6 h at room temperature. The excess of benzaldehyde and TEA were removed in vacuo to afford oily residue **4** (95% yield) was used without further purification. (iii) A solution of diisopropylamine (11.20 ml) in THF (40 ml) was stirred at -78°C for 20 min in a nitrogen atmosphere and n-BuLi (35.18 ml) was added directly with contineous stirring for 30 min. Then a solution of compound 4 (20.00 g) in THF (60 ml) was added dropwise and stirring was continued for an additional 0.5 h. Methyl iodine (5.00 g) was added dropwise and the mixture was stirred for 2 h at -78°C. Then it was left overnight at room temperature. The lithium iodide which formed was removed by filtration and the solvent was evaporated in vacuo. The resulting oil was treated with 1N hydrochloric acid (25 ml) for 1 h at room temperature. The reaction mixture was washed with ethyl ether (3 x 30 ml) and the aqueous phase was made basic with $NaHCO_3$, extracted with ethyl acetate (4 x 40 ml) and dried with anhydrous Na_2SO_4. Evaporation of the solvent and the residue (75% yield) was submitted to flash chromatography, elution with $CHCl_3$/MeOH (9.5 : 0.5) afforded pure **6** (69% yield).

α-Methyl-N-benzyloxycarbonyl-aspartic acid 8:

A solution of 1N LiOH (100 ml) was added to solution of **6** (5.00 g) in THF (100 ml). The reaction mixture was shaked at 50°C for 4 h, neutralized with 10 N HCl and then $NaHCO_3$ (8.00 g) was added at room temperature, under vigorous magnetic stirring. Benzyl chloroformate (5.5 ml) was added dropwise (15 min) to the reaction mixture. Stirring was continued for 3 h, the resulting solution was washed with ether (2 x 25 ml) then, acidified with 6N HCl and extracted by ethyl acetate (4 x 30 ml) and dried over Na_2SO_4 anhydrous. The solvent was evaporated in vacuo to afford **8** (82% yield).

(S)-and(R)-4-methyl-3-benzyloxycarbonyl-5-oxo-4-oxazolidineacetic acid 9.

A mixture of compound **8** (8.00 g), paraformaldehyde (2.00 g), and PTSA (0.40 g) in benzene (400 ml) was boiled under reflux for 1 h, with removal of water with a Dean-Stark trap. Ethyl acetate (40 ml) was added and the solution was washed with 0.3 M K_2CO_3 (10 ml) and water (3 x 10 ml), then dried over $MgSO_4$ anhydrous. The solvent was evaporated in vacuo to afford colourless syrup. Purification by flash chromatography ethyl acetate/petroleum ether (7:3) afforded pure **9** (58% yield).

(S)-and/or(R)-(2-methyl-3-benzyloxycarbonyl-5-oxo-4-oxazolidinyl)-acetyl chloride 10.

Compound **9** (2.93 g, 0.01 mol) was added to a solution of thionyl chloride in toluene (8 ml, 1:1, v:v) and the resulting mixture was stirred at room temperature for 4 h in argon atmosphere. After evaporation of the solvent, the residue was dried in high vacum to afford pure **10** (99% yield). It was used without further purification.

3[S-(3-benzyloxycarbonyl-5-oxo-4-oxazolidinyl)] propionyl chloride 15.

Analogously, 3 [(S)-3-benzyloxycarbonyl-5-oxo-4-oxazolidine propanic

Table (1): Selected IR and NMR data for the compunds prepared.

Compound	Mol. Formula[a]	IR (CCl_4), υ(cm^{-1})	^{1}H-NMR ($CDCl_3$ / TMS); δ	^{13}C-NMR ($CDCl_3$ / TMS), δ
4	$C_{13}H_{15}NO_4$ (249.3)	1750 - 1720, 1625, 1580	2.85 m, 2 H (CH_2); 3.5 s, 3 H (OCH_3); 3.6 s, 3 H (OCH_3); 4.35 t, 1 H (CHCO); 7.2 - 7.7 m, 5 H (Ph); 8.25 s, 1 H (N=CH)	-----
6	$C_7H_{13}NO_4$ (175.2)	3420 - 3340, 1740, 1725, 1420	1.3 s, 3 H (CH_3); 2.3 br., 2 H (NH_2); 2.5-2.6 and 2.85-2.95 dd, 2 H (CH_2); 3.65 s, 3 H (OCH_3); 3.75 s, 3 H (OCH_3)	25.8, 50.2, 51.3, 54.9, 76.3, 76.9, 77.6, 170.8, 176.2
8	$C_{13}H_{15}NO_6$ (281.3)	3370, 2600, 1720, 1700, 1600, 1480	1.6 s, 3 H (CH_3); 2.8 - 3.2 dd, 2 H (CH_2CO); 5.0 s, 2 H (OCH_2); 6.1 br., 1 H (NH); 7.3 s, 5 H (Ph); 9.6 s, 2 H (COOH)	-----
9	$C_{14}H_{15}NO_6$ (293.3)	3015, 2600, 1800, 1710, 1580, 1450	1.6 s, 3 H (CH_3); 2.9 and 3.6 dd, 2 H (CH_2CO); 5.1 s, 2 H ($C\underline{H}_2Ph$); 5.3 - 5.4 m, 2 H (CH_2O); 7.3 s, 5 H (Ph); 10.1 s, 1 H (COOH)	23.1, 46.2, 51.6, 68.4, 78.4, 128.3, 128.6, 135.1, 152.6, 171.6, 175.0
12	$C_{19}H_{18}N_2O_5$ (354.4)	3020, 2985, 1805, 1680,1620, 1560	1.6 s, 3 H (CH_3); 3.4 and 4.0 dd, 2 H (CH_2CO); 5.1 s, 2 H (CH_2Ph); 7.3-7.4 m, 1 H (Py); 8.15 m, 1 H (Py); 8.75 dd, 1 H (Py); 9.1 s, 1 H (Py)	22.6, 43.7, 56.7, 66.8, 76.9, 123.3, 127.4, 127.9, 128.2, 130.7, 135.1, 149.1, 153.6, 174.3, 195.7
13	$C_{10}H_{12}N_2O_3$ (208.2)	3500 - 3340, 2850, 1720, 1685, 1625[b]	1.4 s, 3 H (CH_3); 3.3-3.4 dd, 1 H (H-2); 3.7-3.8 dd, 1 H (H-2); 7.4 m, 1 H (Py); 8.2 m, 1 H (Py); 8.5 dd, 1 H (Py); 8.9 s, 1 H (Py)[c]	23.0, 44.5, 57.4, 124.6, 132.6, 142.4, 148.7, 153.5, 175.2, 200.7[c]
15	$C_{14}H_{14}ClNO_5$ (311.7)	3010, 2973, 1805, 1735, 1510, 1460	2.5 m, 2 H (CH_2CO); 2.8 m, 2 H (CH_2); 4.6 dd, 1 H (H-4); 5.15 s, 2 H ($C\underline{H}_2Ph$); 5.25 and 5.5 dd, 2 H (CH_2O)(7.35 s, 5 H (Ph)	26.0, 30.3, 53.6, 68.2, 77.9, 128.3, 128.6, 135.1, 153.2, 171.7, 175.1
16	$C_{19}H_{18}N_2O_5$ (354.4)	3025, 2990, 1805, 1683, 1615, 1580	2.4 m, 2 H (CH_2); 3.1 br, 2 H (CH_2CO); 4.4 m, 1 H (H-4); 5.1 s, 2 H ($C\underline{H}_2Ph$); 5.2 dd, 1 H (H-2); 5.5 br, 1 H (H-2); 7.3 s, 5 H (Ph); 7.4 m, 1 H (Py); 8.1 dd, 1 H (Py); 8.7 m, 1 H (Py); 9.1 s, 1 H (Py)	25.0, 33.8, 53.9, 68.1, 77.6, 123.6, 127.4, 128.3, 128.7, 135.2, 149.5, 152.1, 153.6, 171.7, 196.5
17	$C_{10}H_{12}N_2O_3$ (208.2)	3400 - 3210, 3015, 2600, 1725, 1685, 1630, 1575[b]	2.4 m, 2 H (CH_2); 3.5 m, 2 H (CH_2CO); 4.2 m, 1 H (H-1); 7.4 m, 1 H (Py); 8.2 m, 1 H (Py); 8.5 dd, 1 H (Py); 8.9 dd, 1 H (Py)[c]	32.6, 44.6, 61.3, 124.7, 131.5, 137.5, 149.1, 153.4, 173.3, 201.3[c]

a : Satisfactory microanalyses obtained C ± 0.40%, H ± 0.44%, N ± 0.33%.
b : KBr c: D_2O.

acid[5] (1.20 g, 0.01 mol) in a 1:1 mixture of thionyl chloride and toluene afforded **15** (98% yield).

Preparation of pyridyl-ketone 12 and/or 16.

Dichloro-bis (triphenylphosphine) palladium (II) (0.123 g) was added to a solution of compound **10** (3.11 g, 0.01 mol) or **15** (3.11 g, 0.01 mol) and trimethylstannylpyridine (2.42 g, 0.01 mol) in dry toluene (25 ml). The mixture was boiled under reflux with stirring, (t.l.c. showed the reaction to be complete: 18 h for compound **10** and 6 for compound **15**). Filtraction which using celite and evaporation of the solvent in vacuo gave a residue which was dissolved in ethyl acetate (30 ml), washed with $NaHCO_3$ solution (5 ml) and water (5 ml). The organic layer was separated, washed with conc. solution of NaCl (20 ml), dried over $MgSO_4$ anhydrous, evaporation of the solvent and the residue obtained was purified by flash chromatography using a mixture of ethyl acetate and pet. ether (7:3) to afford the pure **12** or **16**.

Hydrolysis of pyridyl-ketone 12 and/or 16.

A suspension of **12** and/or **16** (0.75 mmol) in 6N hydrochloric acid (25 ml) was refluxed for 6 h. The resulting solution was then washed with ether (8 ml) and the aqueous phase was evaporated. The residue was neutralized with NH_4OH. The neutral solution was passed through an ion exchange resin column (Dowex 1 x 8, AcO^- form), elution with 0.3N acetic acid gave pure **13** (yield 95%), mp 148-150°C, $[\alpha]_D^{25} = +21.5$ (c = 0.6, H_2O) and/or **17**, respectively (yield 42%), mp 180-181°C, $[\alpha]_D^{25} = +12.2$ (c = 0.8, H_2O).

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تحضير مشتقات جديدة من حامض نيكوتينويل مع الأحماض الأمينية

عاطف محمد عامر

قسم الكيمياء - كلية العلوم - جامعة الزقازيق

تم تحضير المشتابهات S,R ٢-ميثيل-٣-بنزيل أوكسي كربونيل-٥-أوكسو-٤-أوكسازلدينيل-كلوريد الأستيل من تفاعل S- حامض الأسبرتيك والذي بدوره تفاعل مع ٣-ميثيل ترای استايل بيريدين لبعطى الكيتونات المقابلة. التحلل المائي لتركيب ١٢ أعطى المشتابهات R,S ألفا ميثيل نيكوتينيل اللأنين مستخدماً حامض الهيدروكلوريك. وبالمثل تم تحضير ألفا-نيكوتينيل الأنين من L- حمض الجلبكتاميك.