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Synthesis and characterization of several valinamide derivatives

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ABSTRACT

Azalactone peptide synthesis is a classical method for the synthesis of dipeptides. Successful synthesis and high yield of dipeptides are the main aim of our study. Valine is an important essential aminoacid of human body, different dipeptide derivative of valine have been synthesized using azalactone peptide synthesis. The UV-Vis, IR, PNMR and Mass spectral studies showed the successful synthesis of dipeptide.

Keywords: Amino acids, dipeptides, oxazolones, valine, amide

INTRODUCTION

Dipeptides are the group of compounds, two amino acid units joined together by a peptide bond. In compare to amino acids, dipeptides are absorbed more rapidly and come to systemic circulation [1]. Different methods have been developed for synthesizing dipeptides, among them azalactone peptide synthesis is one of the classical synthetic methods for the preparation of dipeptides [2]. In this method oxazolones and substituent at position 4 of oxazolone are typically encountered as intermediates during chemical synthesis of dipeptides. There are several examples of important dipeptides involved in the proper functioning of human body i.e. Carnosine, Anserine, Homoanserine, Kyotorphin, Balenine, Aspartame Glorin, Barettin, Pseudoproline. Valine is a branched-chain amino acid that works with the other two branched chain amino acids, isoleucine and leucine to promote normal growth, repair tissues, regulate blood sugar, and provide the body with energy. Valine helps stimulate the central nervous

system, and is needed for proper mental functioning [1,3,4]. So present study it is our endeavor to synthesizing dipeptides of valine and characterizes them using spectral data.

EXPERIMENTAL SECTION

Melting point was determined in open capillary method on tempo apparatus and was uncorrected. UV spectra were recorded on SYSTRONIC UV VISIBLE SPECTROPHOTO METER-117 from. FTIR spectra were recorded using Thermo Nicolet Nexus 670 spectrometer, H^1 NMR is obtained using GEMINI -300 MHz. Mass spectra obtained by using SHIMADZU QP 5000 mass spectrometer (70 eV). Aldehydes, valine, other chemicals and solvents are LR grade procured from SD-fine and Sigma-Aldrich Pvt. Ltd. Purity of chemicals was checked by single spot in TLC using glass plate coated with silica gel-G and iodine vapor as detecting agent.

1) Synthesis of benzoyl glycine (1) [5]

A solution of 25 g (0.33 mol) of glycine in 250 ml of 10% NaoH was prepared and 45.0 ml (0.385 mol) benzoyl chloride was added to the above solution in 5 portions. The mixture was shaken vigorously after each addition until all the chlorides have been reacted. The mixture was cooled by adding few grams of crushed ice and was acidified by adding conc. HCl slowly with constant stirring. The resulting crystalline precipitate of benzoyl glycine was filtered and washed with cold water and dried. The solid was treated with 100ml of hot CCl_4 in order to remove benzoic acid. The dried product was recrystalised with boiling water. Colour: creamy white, Yield: 21.08g (84.32%), m.p=179^0 C.

2) Synthesis of 4-benzylidine-2-phenyl oxazolone-5-one (2a-e) [5,6]

Place 8.6g (0.0476mmol), of **1,** 5ml (0.0476mmol) benzaldehyde, 14ml (0.146mmol) acetic anhydride and 3.9g (0.0476mmol) anhydrous sodium acetate in a 250 ml conical flask. Heat the flask on electric hot plate with constant shaking until the mixture liquefies completely, reflux the contents for 2h on water bath. To the contents of flask add 10ml ethanol slowly and allowed the mixture to stand overnight. The crystalline precipitate was filtered with suction and washed with 2 portions of ice-cold alcohol (6ml) and finally with 2 portions of boiling water. The product was dried and recrystallized using benzene. The procedure was repeated by using different other aldehydes to get other derivatives. Physical characteristic data of the compounds 2a-e given in Table 1.

Table 1: Physical data of 4-benzylidine-2-phenyl oxazolone-5-one (2a-e)

Code	Colour	Mol. Formula	Mol. Weight	Melting point (□C)	Yield (%)
2a	Light yellow	$C_{16}H_{11}NO_2$	251	154-156	72
2b	Dark yellow	$C_{17}H_{13}NO_3$	281	177-179	82
2c	Red	$C_{18}H_{16}N_2O_2$	294	176-178	64
2d	Greenish yellow	$C_{16}H_{10}NO_2Cl$	285	165-168	52
2e	Bright yellow	$C_{16}H_{10}N_2O_4$	296	192-194	72

3) Synthesis of N-(1-(3-amino-2-methyl butanoyl)-2-[(substituted phenyl) vinyl] benzamide (3a-e)

A mixture of 4 ml 1N NaOH and 10ml of acetone, 100 mg (0.01mmol) valine was added and the mixture was stirred with 250 mg (0.01mmol) of **2**. After 2-3 h, the resulting clear solution was acidified by addition of excess of 1N Hydrochloric acid. The solid thus separate out was filtered and washed thoroughly with cold water. The product was dissolved in acetone and crystallized on addition of water. Same procedure was carried out by using other compounds. Physical characteristic data of 3a-e given in Table 2.

3a: λ_{max}: 310nm (methanol); IR (KBr): 3705cm^{-1} (OHstr), 3295.7 cm^{-1} (NHstr), 3009 cm^{-1} (ArHstr), 1639 cm^{-1} (COstr), 1681 cm^{-1} (C=Cstr); MS: m/e 365(M^+), 115 (100%): ^{1}HNMR: 6.791-7.533(m, 10H, ArH), 7.905-7.922 (d, 1H, peptide NH); 7.549 (s, 1H, amide NH), 1.252 (s, 1H, CH), 0.845-0.876 (t, 1H, CH), 8.1 (s, 1H, COOH), 0.002-0.068(m, 1H, CH), 3.750-3.792 (d, 6H, 2CH_3).

3b: λ_{max}: 230nm (methanol); IR (KBr): 3716 cm^{-1}(COOHstr), 3234 cm^{-1}(NHstr), 2836 cm^{-1}(Ar-CH), 1688 cm^{-1}(C=Ostr), 1506 cm^{-1}(C=Cstr); MS: m/e 397(M^+), 359 (100%); ^{1}HNMR: 7.048-7.342(m, 9H, ArH), 7.728-7.746 (d, 1H, peptide NH), 7.342 (s, 1H, amide NH), 2.340 (s, 1H, CH), 1.921-1.931 (t, 1H, CH), 8.877 (s, 1H, COOH), 0.162-0.242 (m, 1H, CH), 2.344-2.340 (d, 6H, 2CH_3), 1.234 (s, 3H, OCH_3).

3c: λ_{max}: 400nm (methanol); IR: 3279 cm^{-1} (NHstr), 2993 cm^{-1} (Ar-CHstr), 1651 cm^{-1} (C=Ostr), 1596 cm^{-1} (C=Cstr); MS: m/e 409 (M^+), 280 (100%); ^{1}HNMR: 7.326- 7.703 (m, 9H, ArH), 7.832 (d,1H, peptide NH), 7.280 (s,1H,Peptide NH), 2.266 (s, 1H, CH), 1.327-1.462 (t, 1H, CH), 8.624 (s, 1H, COOH), 0.172-0.217 (m, 1H, CH), 2.722-2-932 (d, 6H, 2CH_3). 3.436 (s, 6H, N(CH_3)$_3$).

3d: λ_{max}: 210nm (methanol); IR: 3232 cm^{-1} (NHstr), 2851 cm^{-1} (Ar-Hstr), 1696 cm^{-1} (C=Ostr), 1644 cm^{-1} (C=Cstr), 1208 (C-Nbend); MS: m/e 400(M^+), 116(100%); ^{1}HNMR: 7.154-7.426(m, 9H, ArH), 7.631-7.666 (d, 1H, peptide NH), 7.523 (s, 1H, amide NH), 2.219 (s, 1H, CH), 1.862-1.871 (t, 1H, CH), 8.735 (s, 1H, COOH), 0.153-0.202 (m, 1H, CH), 2.437-2.542 (d, 6H, 2CH_3), 1.224 (s, 3H, OCH_3).

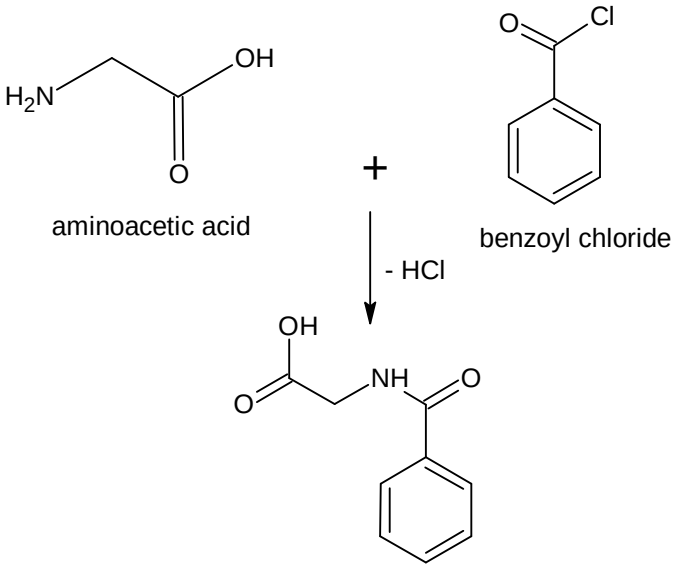
4e: λ_{max}: 220nm (methanol); IR: 3214 cm^{-1} (NHstr), 2966 cm^{-1} (Ar-Hstr), 1647 cm^{-1} (C=Ostr), 1430 cm^{-1} (COOHbend), 1153 cm^{-1} (C-Nstr); MS: 412(M+1), 398 (398); ^{1}HNMR:6.762-7.227(m, 9H, ArH), 7.723-7.741 (d, 1H, peptide NH); 7.323 (s, 1H, amide NH), 0.893 (s, 1H, CH), 0.846-0.869 (t, 1H, CH), 8.382 (s, 1H, COOH), 0.325-0.336(m, 1H, CH), 3.568-3.602 (d, 6H, 2CH_3).

Table 2: Physical data and yields of N-(1-(3-amino-2-methyl butanoyl)-2-[(substituted phenyl) vinyl] benzamide (3a-e)

Code	Colour	Mol. Formula	Mol. Weight	Melting point (◦C)	Yield (%)	R_f value
3a	Creamy White	$C_{21}H_{22}N_2O_4$	366	185-188	60	0.59*
3b	Off white	$C_{22}H_{24}N_2O_5$	396	195-197	73	0.67*
3c	Shiny yellow	$C_{23}H_{27}N_3O_4$	409	154-156	33	0.72*
3d	Puffy white	$C_{21}H_{21}N_2O_4Cl$	400	166-168	76	0.26$^\#$
3e	Yellow	$C_{21}H_{21}N_3O_6$	411	170-172	64	0.47$^\$$

Solvent system for TLC; $CHCl_3$: CH_3OH = *7:3, $^\#$8:2, $^\$$5:5

SCHEME I

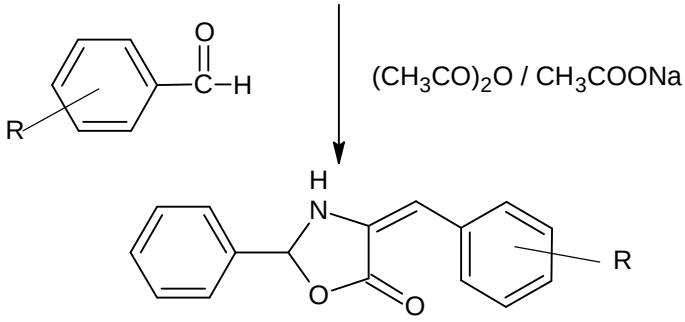


aminoacetic acid

benzoyl chloride

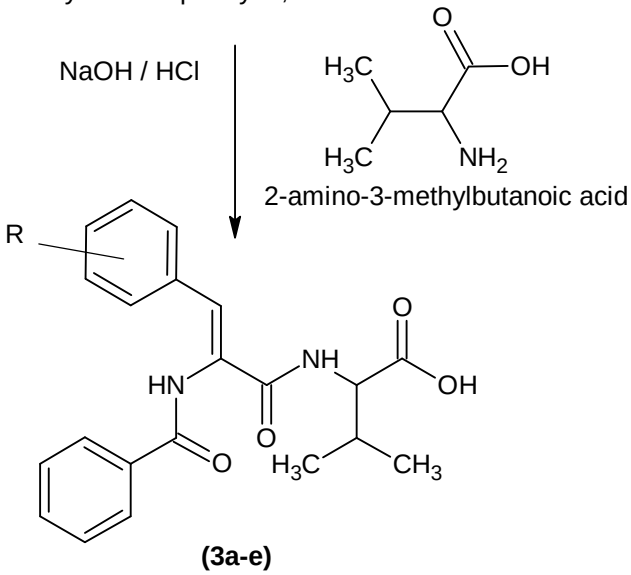
(1)

(benzoylamino)acetic acid



(2a-e)

(4*E*)-4-benzylidene-2-phenyl-1,3-oxazolidin-5-one derrivative



2-amino-3-methylbutanoic acid

(3a-e)

2-{[(2*Z*)-2-(benzoylamino)-3-phenylprop-2-enoyl]amino}-3-methylbutanoic acid derrivative

R: a) H, b) 4-OCH_3, c) 4-$N(CH_3)_2$, d) 4-Cl, e)4-NO_2

RESULTS AND DISCUSSION

The action of acetic anhydride on an alpha-acylamino acid in aqueous solution yields an azalactone in presence of a basic catalyst, such as sodium acetate. Various 4-substituted benzylidine-2-phenyl-oxazole-5-one which were required as starting materials for the synthesis of dipeptide, were prepared by condensing aromatic aldehydes with benzoyl glycine in the presence of acetic anhydride and anhydrous sodium acetate. The yields of oxazolones were uniformly good ranging from 60 to 90%.

The oxazolones were condensed with valine in aqueous acetone containg sodium hydroxide to obtain the title compound. The presence of alkali is essential to open the oxazolone ring. Five compounds were synthesized and the yields were generally moderate. Highest yield was obtained with 4-Cl derivative and lowest for 4-$N(CH_3)_2$ derivative. All the physical data was tabulated in Table: 1, 2. All the compounds showed sharp melting point and showed single spot in TLC which confirms the purity of the compounds. UV-Vis, IR, Mass, PNMR data confirms the successful synthesis of dipeptide compounds. From the above study we can conclude that azalactone peptide synthesis is a classical method for the synthesis of dipeptides, the yield was good between 60-90%. By using this method we can synthesize different derivatives of dipeptides with good yield. Biological activity of those derivatives are yet to evaluate and considering our future plan.

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