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Synthesis and characterization of novel β-amino acid derivatives

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Abstract In the work discussed in this paper, novel β-amino acid derivatives were prepared by Michael addition between 3-substituted-2-propenic acid and hydrazine hydrate. The optimum reaction conditions were determined by analyzing the effects of the ratio of the starting materials, temperature, and reaction time. The conclusions were: reaction temperature 80 °C, reaction time 8 h, *n* (3-substituted-2-propenic acid)/*n* (hydrazine hydrate) = 1:15. Products were characterized by measurement of melting point, elemental analysis, and IR and ^{1}H NMR spectroscopy.

Keywords β-Amino acid derivatives · Synthesis · Characterization

Introduction

β-Amino acids are widely used in the synthesis of antibiotics [1]. β-Amino acids are the substrates of many antibiotics and are common intermediates in drug synthesis [2]. β-Amino acids are also the direct raw materials in the synthesis of β-amino alcohols [3]. β-Amino alcohols are important intermediates in the synthesis of peptides, which are important in asymmetric synthesis and medicinal chemistry [4, 5].

Structurally, β-amino acids are formed by addition of ammonia to acrylic acid and its derivatives, which is the simplest synthetic method [6]. Generally, β-amino acids are formed by addition of ammonia to acrylonitrile and acrylate, then hydrolysis to the corresponding amino acid under acidic or alkaline condition [7].

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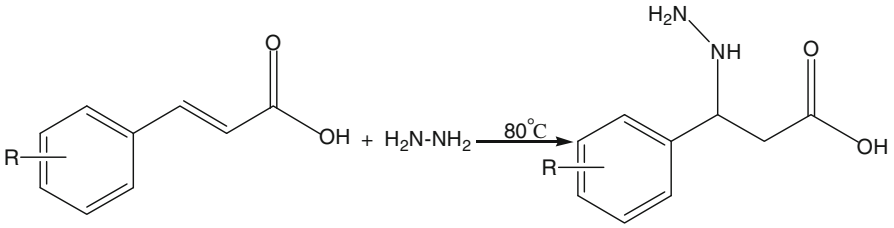

R=a, H; b, 4-CH_3; c, 4-C_2H_5; d, 4-C_3H_7; e, 4-OCH_3

Scheme 1 Synthesis of novel β-amino acid derivatives

β-Amino acids can be directly prepared by Michael addition reaction between ammonia and α,β-unsaturated acids. But the reaction can take a long time and must be in a closed tube or in the autoclave [8, 9]. β-Amino acids can be prepared by Michael addition reaction between hydrazine and α,β-unsaturated acids at normal pressure.

In the work discussed in this paper, novel β-amino acid derivatives were prepared by Michael addition between 3-substituted-2-propenic acid and hydrazine hydrate. The product is prone to cyclization. It has a heterocyclic intermediate, and has important significance in the study of organic reactions. β-Amino acids have been widely used in drug design because of their similarity to α-amino acids. α-Amino acids are the components of human proteins which are important materials in the body [10, 11]. The attention of medicinal and organic chemists is increasingly being devoted to methods of synthesis of these compounds. The medicinal nature of the β-amino acid derivatives synthesized in the work discussed in this paper has not yet been studied (Scheme 1).

Results and discussion

The effect of reaction conditions on yield

Effect of the molar ratio of reactants on yield

Under the conditions reaction temperature 80 °C and reaction time 8 h, the effect of molar ratio of reactants on yield was studied. The results are summarized in Table 1.

The results showed that the yield was maximum at *n* (3-phenyl-2-propenic acid):*n* (hydrazine hydrate) = 1:15.

Table 1 Effect of the molar ratio of reactants on yield

n (3-phenyl-2-propenic acid):*n* (hydrazine hydrate)	1:10	1:13	1:15	1:17	1:20
Yield (%)	50	53	71	51	45

Table 2 Effect of temperature on yield

Temperature (°C)	60	70	80	90	100
Yield (%)	55	57	71	56	53

Table 3 Effect of reaction time on yield

Reaction Time (h)	6	7	8	9	10
Yield (%)	55	68	71	69	66

Effect of temperature on yield

Under the reaction conditions *n* (3-phenyl-2-propenic acid):*n* (hydrazine hydrate) = 1:15 and reaction time 8 h, the effect of temperature on yield was studied. The results are summarized in Table 2.

The results showed that the yield was maximum when the reaction temperature was 80 °C. If the temperature was increased further, the yield decreased.

Effect of reaction time on yield

Under the reaction conditions *n* (3-phenyl-2-propenic acid):*n* (hydrazine hydrate) = 1:15 and reaction temperature 80 °C, the effect of reaction time on yield was studied. The results were summarized in Table 3.

The results showed that as reaction time increased the yield gradually increased. When the reaction time was 8 h the reaction was complete, so yield did not increase further.

Orthogonal experiments to determine the optimum conditions

The optimum reaction conditions were obtained by means of three factors : *n* (3-phenyl-2-propenic acid):*n* (hydrazine hydrate) (A), reaction temperature/°C (B), and reaction time/h (C) and a three-level orthogonal experiment L_9 (3^3). The levels and factors in the orthogonal experiments were designed as summarized in Table 4. The experimental results and analytical results are summarized in Table 5.

The results show that the effects of the three factors on the condensation reaction descending in the order: A > B > C, the optimum reaction conditions were: $A_2B_2C_2$, i.e. *n* (3-phenyl-2-propenic acid):*n* (hydrazine hydrate) = 1:15, reaction temperature 80 °C, and reaction time 8 h.

Table 4 L_9 (3^3) orthogonal experiment design of levels and factors

Level	A	B	C
1	1:13	70	7
2	1:15	80	8
3	1:17	90	9

Table 5 L_9 (3^3) orthogonal experimental design and results from analysis

	A	B	C	Yield (%)
1	1	1	1	49
2	1	2	2	56
3	1	3	3	53
4	2	1	3	57
5	2	2	2	71
6	2	3	1	55
7	3	1	3	51
8	3	2	1	52
9	3	3	2	54
K1	52.667	52.333	52.000	
K2	57.500	56.167	55.667	
K3	52.333	54.000	54.833	
R	5.167	3.834	3.667	

Replicate experiments

Under the optimum conditions, replicate experimental verification was conducted. The results are summarized in Table 6. The results (Tables 7, 8, and 9) show the repeatability of the experiment is good.

Conclusions

Novel β-amino acid derivatives were prepared by Michael addition of 3-substituted-2-propenic acid and hydrazine hydrate. The optimum experimental conditions for preparation of the target compounds were determined by means of single factor or orthogonal experiments: reaction temperature 80 °C, reaction time 8 h, *n* (3-substituted-2-propenic acid)/*n* (hydrazine hydrate) = 1:15. The novel β-amino acid derivatives were characterized by melting point, elemental analysis, and IR and ^{1}H NMR spectroscopy.

Experimental

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a Tensor 27 spectrometer as KBr pellet. ^{1}H NMR spectra was

Table 6 Repeatability experiments

Repetition	1	2	3	4	5	Average yield
Yield (%)	70.9	71	70.8	70.8	70.9	71

Table 7 Elemental analysis data for compounds a–e

Compound	Formula	M_r	w_i (calc.)/%			M.P. (°C)	Yield (%)
			w_i (found)/%				
			C	H	N		
a	$C_9H_{12}N_2O_2$	180.20	59.99	6.71	15.55	251–253	71
			59.86	6.69	15.51		
b	$C_{10}H_{14}N_2O_2$	194.23	61.84	7.27	14.42	245–247	73
			61.70	7.25	14.38		
c	$C_{11}H_{16}N_2O_2$	208.56	63.44	7.74	13.45	250–252	74
			63.30	7.72	13.41		
d	$C_{12}H_{18}N_2O_2$	222.28	64.84	8.16	12.60	247–248	76
			64.70	8.13	12.56		
e	$C_{10}H_{14}N_2O_3$	210.23	57.13	6.71	13.33	257–259	79
			57.00	6.69	13.30		

Table 8 Main IR data for compounds a–e

Compound	IR data for compounds
a	IR (KBr, ν/cm^{-1}): 3,450 cm^{-1}, 3,387 cm^{-1} (ν_{N-H}); 3,094 cm^{-1} (νPh_{C-H}); 3,030 cm^{-1} (ν_{COOH}); 2,920 cm^{-1}, 2855 cm^{-1} (ν_{C-H}); 1,598 cm^{-1}, 1,588 cm^{-1}, 1,495 cm^{-1}, 1,454 cm^{-1} (ν_{PhC-C}); 1,279 cm^{-1} (ν_{C-N}); 756 cm^{-1}
b	IR (KBr, ν/cm^{-1}): 3,455 cm^{-1}, 3,376 cm^{-1} (ν_{N-H}); 3,054 cm^{-1} (νPh_{C-H}); 3,020 cm^{-1} (ν_{COOH}); 2,921 cm^{-1}, 2,845 cm^{-1} (ν_{C-H}); 1,608 cm^{-1}, 1,589 cm^{-1}, 1,498 cm^{-1}, 1,450 cm^{-1} (ν_{PhC-C}); 1,381 cm^{-1}; 1,271 cm^{-1} (ν_{C-N}); 825 cm^{-1}
c	IR (KBr, ν/cm^{-1}): 3,465 cm^{-1}, 3,367 cm^{-1} (ν_{N-H}); 3,032 cm^{-1} (νPh_{C-H}); 3,034 cm^{-1} (ν_{COOH}); 2,931 cm^{-1}, 2,851 cm^{-1} (ν_{C-H}); 1,603 cm^{-1}, 1,587 cm^{-1}, 1,501 cm^{-1}, 1,449 cm^{-1} (ν_{PhC-C}); 1,451 cm^{-1}, 1,379 cm^{-1}; 1,272 cm^{-1}(ν_{C-N}); 836 cm^{-1}
d	IR (KBr, ν/cm^{-1}): 3,470 cm^{-1}, 3,359 cm^{-1} (ν_{N-H}); 3,024 cm^{-1} (νPh_{C-H}); 3,013 cm^{-1} (ν_{COOH}); 2,935 cm^{-1}, 2,848 cm^{-1}(ν_{C-H}); 1,599 cm^{-1}, 1,583 cm^{-1}, 1,499 cm^{-1}, 1,446 cm^{-1} (ν_{PhC-C}); 1,456 cm^{-1}, 1,379 cm^{-1}; 1,269 cm^{-1} (ν_{C-N}); 836 cm^{-1}
e	IR (KBr, ν/cm^{-1}): 3,480 cm^{-1}, 3,397 cm^{-1} (ν_{N-H}); 3,089 cm^{-1} (νPh_{C-H}); 2,999 cm^{-1} (ν_{COOH}); 2,929 cm^{-1}, 2,856 cm^{-1} (ν_{C-H}); 1,604 cm^{-1}, 1,576 cm^{-1}, 1,504 cm^{-1}, 1,447 cm^{-1} (ν_{PhC-C}); 1,449 cm^{-1}, 1,389 cm^{-1}; 1,274 cm^{-1} (ν_{C-N}); 838 cm^{-1}

obtained with an Inova-400 spectrometer, using DMSO-d_6 or $CDCl_3$ as solvents, and Me_4Si as internal standard. All reagents were analytically pure or chemically pure. 3-Substituted-2-propenic acid was laboratory prepared.

Synthesis of novel β-amino acid derivatives

3-Substituted-2-propenic acid (0.01 mol) and hydrazine hydrate solution 7.4 ml (0.15 mol) were well mixed in a dry flask (50 mL). The mixture was stirred at 80 °C for 8 h. After completion of the reaction (TLC), the mixture was cooled to room

Table 9 ^{1}H NMR data for compounds a–f

Compound	^{1}H NMR data for compounds
a	^{1}H NMR (DMSO-d_6),δ: 7.19–7.33 (m, 5H, Ar–H), 6.80 (d, 1H, –NH), 4.50 (t, 1H, –CH), 3.84 (d, 2H, –NH_2), 2.89 (d, 2H, –CH_2), 10.99 (hours, COOH)
b	^{1}H NMR (DMSO-d_6), δ: 6.89–7.21 (m, 5H, Ar–H), 6.79 (d, 1H, –NH), 4.49 (t, 1H, –CH), 3.78 (d, 2H, –NH_2), 2.69 (d, 2H, –CH_2), 10.84 (hours, COOH), 2.35 (s, 3H, –CH_3)
c	^{1}H NMR (DMSO-d_6), δ: 6.76–7.20 (m, 5H, Ar–H), 6.76 (d, 1H, –NH), 4.46 (t, 1H, –CH), 3.67 (d, 2H, –NH_2), 2.54 (d, 2H, –CH_2), 10.76 (hours, COOH), 2.63 (s, 2H, –CH_2), 1.21 (s, 3H, –CH_3)
d	^{1}H NMR (DMSO-d_6), δ: 6.69–7.23 (m, 5H, Ar–H), 6.79 (d, 1H, –NH), 4.47 (t, 1H, –CH), 3.69 (d, 2H, –NH_2), 2.56 (d, 2H, –CH_2), 10.80 (hours, COOH), 2.59 (s, 2H, –CH_2), 1.65 (s, 2H, –CH_2), 0.95 (s, 3H, –CH_3)
e	^{1}H NMR (DMSO-d_6), δ: 6.39–7.11 (m, 5H, Ar–H), 6.76 (d, 1H, –NH), 4.50 (t, 1H, –CH), 3.70 (d, 2H, –NH_2), 2.36 (d, 2H, –CH_2), 10.79 (hours, COOH), 3.73 (s, 3H, –CH_3)

temperature, and 10 % dilute hydrochloric acid was added until pH 7 (neutrality). The mixture was then filtered to give a white solid. Crude products were purified by recrystallization from ethanol–water (1:1) to yield the pure compounds.

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