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SYNTHESIS OF α-SUBSTITUTED α-AMINO ACIDS BY THE ALKYLATION OF 5-OXAZOLINONE DERIVATIVES

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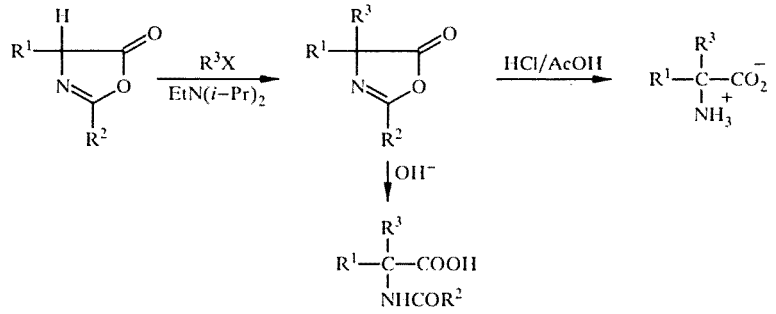
Methods have been developed for the alkylation of 5-oxazolinone derivatives in DMF in the presence of K_2CO_3, KOH, or diisopropylethylamine and a phase transfer catalyst as well as for the preparation of α-methylphenylalanine, α-methylalanine, α-methylalanine, and the methyl ester of N-benzoyl-α-methylalanine. Increasing the initial concentration of the starting 5-oxazolinone in the reaction mixture leads to a sharp drop in the yield of reaction products due to side condensation reactions. The reaction of 2-phenyl-4-benzyl-5- oxazolinone with ethyl iodide gave a dimer, namely, 3-(benzoylamino)-3,5-dibenzylpyrrolidine-2,4-dione.

α-Methylamino acids are valuable intermediates, which are stable toward the enzymatic cleavage of peptides [1]. Furthermore, this amino acids and their derivatives have a unique spectrum of biological activity and are used in medicine [2]. Thus, significant work has been undertaken on the development of convenient methods for the preparation of these compounds, most of which involve the use of not readily available reagents [3]. A number of monographs and reviews have been devoted to the chemical and biological properties of α-methylamino acids [2-6]. The synthesis of α-amino acids through the formation of 5-oxazolinone derivatives is convenient in light of the availability of these reagents [2, 7, 8]. The 4,4-disubstituted 5-oxazolinones obtained in the presence of diisopropylethylamine in aprotic solvents undergo hydrolysis to give the corresponding α-amino acids [7].



R^1 = *i*-C_3H_7, $C_6H_5CH_2$; R^2 = C_6H_5; R^3 = CH_3, $C_6H_5CH_2$, HO_2CCH_2, *p*-$NO_2C_6H_5CH_2$, CH_3COCH_2

This method gives low or medium yields of α-substituted α-amino acids. The reasons for such yields are not clear. There is no information on the use of this method in the synthesis of achiral α-substituted amino acids such as α-methylalanine and α-benzylphenylalanine although the oxazolinone method holds the greatest promise for the synthesis of such acids since racemization of a chiral amino acid would be likely.

In the present work, we studied the alkylation of 2-phenyl-4-methyl-5-oxazolinone and 2-phenyl-4-benzyl-5-oxazolinone by methyl iodide, ethyl iodide, or benzyl bromide in the presence of potassium carbonate and tetrabutylammonium iodide as a phase transfer catalyst in DMF. KOH and diisopropylethylamine were also used as the base (Table 1). The yield of

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TABLE 1. Alkylation of 5-Oxazolinone Derivatives

Experiment	Starting compound	Reaction conditions					Reaction product after acid hydrolysis	Yield, %
		starting concentration moles/liter	alkylating agent	molar reagent (moles)	reaction temperature, °C	reaction time		
1	2-phenyl-4-methyl-5-oxazolinone	1,1	$C_6H_5CH_2Br$	1 : 1,7	Room	12 days	α-Me—Phe	43,2
2		1,7		1 : 1,8	80...90	8,5 h		45,7
3		1,6		1 : 1,7	Room	12 days		43,2
4		2,4	CH_3I	1 : 3,6	Room	12 days	α-Me—Ala	21,3*
5	2-phenyl-4-benzyl-5-oxazolinone	1,0	CH_3I	1 : 1,7	90...95	5,5 h	α-Me—Phe	31,9*[2]
6		0,9		1 : 1,7	90...95	6 h		25,5*[2]
7		0,63		1 : 3,2	Room	13 days		49,2
8		1,08		1 : 3,8	Room	13 days		39,4
9		1,98		1 : 3,1	Room	13 days		26,9
10		1,1		1 : 1,7	Room	12 days		30,1
11		1,7	$C_6H_5CH_2Br$	1 : 3,1	Room	10 days	α-Bzl—Phe	40,7
12		2,5		1 : 2,3	Room	10 days		28,7
13		2,2		1 : 3,2	Room	10 days		17,3
14		1,8		1 : 5,1	Room	12 days		17,6
15		2,1		1 : 5,4	70...75	21 h		18,1

*Potassium hydroxide was used in the methylation (the 2-phenyl-4-methyl-5-oxazolinone:KOH mole ratio was 1:2.4).

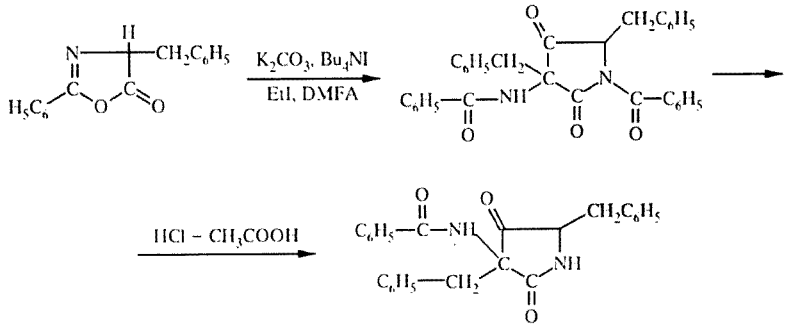
*[2]Diisopropylethylamine was used in the methylation (the 2-phenyl-4-benzyl-5-oxazolinone:diisopropylethylamine mole ratio was 1:1.84).

α-methylphenylalanine was found to be higher in the alkylation of 2-phenyl-4-methyl-5-oxazolinone by benzyl bromide than in the alkylation of 2-phenyl-4-benzyl-5-oxazolinone by methyl iodide (Table 1, experiments 1 and 10). Raising the alkylation temperature from room temperature to 90°C did not lead to a marked change in the yield of α-methylphenylalanine (experiments 2 and 3). Increasing the excess of the alkylating agent does not have a positive effect on the reaction course, while decreasing the initial concentration of the oxazolinone leads to a considerable increase in the yield of the desired product (experiments 7 and 9). These findings indicate inhibition by the reaction products or the existence of side condensation reactions. Thus, the reaction should be carried out at relative high dilution with initial concentration of the starting reagent below 1 mole/liter in order to achieve a higher yield of the desired products.

2-Phenyl-4,4-dibenzyl-5-oxazolinone was obtained in the alkylation of 2-phenyl-4-benzyl-5-oxazolinone by benzyl bromide and subsequent acid hydrolysis gave α-benzylphenylalanine. The yield of this product did not exceed 41%. Even lower yields (19-21%) were obtained in the alkylation of 2-phenyl-4-methyl-5-oxazolinone by methyl iodide and subsequent hydrolysis. This may be related to greater losses in the isolation of α-methylalanine due to its high solubility in water and in most organic solvents.

The methyl ester of N-benzoyl-α-methylalanine, which is formed in the reaction of the amino acid in the presence of methyl iodide, was obtained upon hydrolysis of the reaction mixture with water and evaporation. An attempt to alkylate 2-phenyl-4-(4-benzyloxybenzyl)-5-oxazolinone by methyl iodide to give the product of methylation and hydrolysis, namely, O-benzyl-α-methyltyrosine, was unsuccessful.

We studied the condensation reactions accompanying the alkylation of 5-oxazolinone derivatives. We were unable to isolate side-products from the reaction mixture after alkylation of the corresponding 5-oxazolinone derivatives by methyl iodide and benzyl bromide. The formation of 1-benzoyl-3-(benzoylamino)-3,5-dibenzylpyrrolidine-2,4-dione was established in the alkylation of 2-phenyl-4-phenyl-5-oxazolinone. Acid hydrolysis of this dione gives 3-(benzoylamino)- 3,5-dibenzylpyrrolidine-2,4-dione in 25% yield:



The rate of dimerization of the azalactone increases with decreasing reactivity of the alkylating agent. The ethylation of 2-phenyl-4-benzyl-5-oxazolinone by ethyl iodide gives only slight amounts of product. The dimerization and polymerization of 5-oxazolinones have not been studied extensively [8]. Organic bases such as sodium methylate, butyllithium, lithium diisopropylamide, and triethylamine are used as the dimerization catalysts [9]. Potassium hydroxide and potassium carbonate also probably facilitate the dimerization of 5-oxazolinones. Our studies indicate that the alkylation of 5-oxazolinone derivatives is accompanied by the formation of derivatives of pyrrolidine-2,4-diones. In order to suppress the side-reactions, this reaction should be carried out with relatively low concentrations of the starting reagents and a reactive alkylating agent.

EXPERIMENTAL

The PMR spectra were taken on a Bruker WH-90 DS spectrometer with 2,2-dimethyl-5-silapentane-5-sulfonic acid or TMS as the internal standard. The mass spectra were taken on an AEI MS-50 mass spectrometer. The ionizing voltage was 70 eV.

The elemental analysis data for C, H, and N for the previously unreported compounds are in accord with the calculated values.

Samples of N-benzoylalanine, N-benzoyl-O-benzyltyrosine, and N-benzoylphenylalanine were synthesized according to Taylor et al. [10]. The dehydrocyclization of N-benzoylamino acids was carried out in acetic anhydride with 88-99% yields of 5-oxazolinone derivative. The major product accounted for 93-94% of the product mixture as indicated by high-efficiency liquid chromatography. The amounts of 5-oxazolinone and α-methylamino acid derivatives were determined by high-efficiency liquid chromatography on a Dupont liquid-phase chromatograph using a Zorbax ODS column. The eluent was 3% acetonitrile and 97% 0.1 M KH_2PO_4, H_3PO_4.

α-Methylalanine. A sample of 4.9 g KOH was added with stirring to a solution of 6.34 g (36.2 mmoles) 2-phenyl-4-methyl-5-oxazolinone and 19.26 g (138.8 mmoles) methyl iodide in 15 ml DMF. The reaction was stirred at room temperature for 13 days. Inorganic products were filtered off at the end of the reaction and washed with three 40-ml toluene portions. The solvent was evaporated off. The precipitate was dissolved in water and extracted with three 40-ml ethyl acetate portions. The ethyl acetate solution was dried over anhydrous sodium sulfate. The filtrate was evaporated to give a dark oil. A sample of 45 ml concentrated hydrochloric acid and 90 ml glacial acetic acid were added to the oil obtained and stirred vigorously for 6 h at 95 ± 2°C. After hydrolysis, the reaction mixture was evaporated and the dry residue was dissolved in 75 ml water. The unreacted starting reagent and side-products were extracted from water with three 40-ml ethyl acetate portions. The aqueous solution was evaporated to 20-30 ml and neutralized with AV 17 × 8 ion exchange resin. The resin was filtered off and the filtrate was evaporated. The dry residue was recrystallized from 2-propanol to give 0.792 g (21.3%) α-methylalanine, mp 315°C (dec.) [mp 316°C (dec.) [11]].

α-Methylphenylalanine ($C_{10}H_{13}NO_2$). A. A sample of 0.8 g K_2CO_3 was added with stirring to a solution of 1.6 g (6.3 mmoles) 2-phenyl-4-benzyl-5-oxazolinone, 2.84 g (20 mmoles) methyl iodide, and 0.23 g (0.63 mmole) tetrabutylammonium iodide in 10 ml DMF and stirred at room temperature for 12 days. The inorganic salts were filtered off and washed with 5 ml DMF. The solvent was evaporated. The dry residue was dissolved in 35 ml water and the desired product was extracted with five 30-ml methylene chloride portions. Methylene chloride was evaporated. Then, 10 ml concentrated hydrochloric acid and 20 ml glacial acetic acid were added to the oil obtained. The mixture was stirred for 5.5 h at 95 ± 1°C and evaporated. The dry residue was dissolved in 40 ml water. The unreacted starting reagent and side-products were extracted from water with three 30-ml portions of ethyl acetate. The aqueous solution was evaporated to 2 ml and neutralized with

6 N NaOH to pH 8. The precipitate formed was recrystallized from water to give 0.56 g (49.2%) α-methylphenylalanine, mp 228-230°C (subl.) (mp 230°C (subl.) [12]). PMR spectrum in D_2O: 7.15-7.44 (5H, *m*-C_6H_5), 3.31, 2.98 (1H, d, 1H, d, ^2J = 14.0 Hz, CH_2), 1.55 ppm (3H, s, $-CH_3$).

B. A sample of 8.2 g K_2CO_3 was added with stirring to a solution of 11.4 g (65.16 mmoles) 2-phenyl-4-methyl-5-oxazolinone, 20.9 g (122.5 mmoles) benzyl bromide, and 2.37 g tetrabutylammonium iodide in 40 ml DMF and stirred vigorously for 8.5 h at 75-80°C. The inorganic salts were filtered off at the end of the reaction. DMF was evaporated and the dry residue was dissolved in water. The desired product was extracted from water with three 40-ml methylene chloride portions. Methylene chloride was evaporated. Then, 66 ml concentrated hydrochloric acid and 130 ml glacial acetic acid were added to the oil obtained and stirred for 6 h at 95±3°C. The solution was evaporated and the dry residue was dissolved in 100 ml water. The unreacted starting reagent and side-products were extracted from water with three ethyl acetate portions. The aqueous solution was evaporated to ~22 ml and neutralized with 6 N NaOH to pH 8. The precipitate formed was filtered off and recrystallized from water. The yield of α-methylphenylalanine was 5.03 g (43.2%), mp 229°C.

α-Benzylphenylalanine. A sample of 1.6 g K_2CO_3 was added with stirring to a solution of 2.18 g (8.67 mmoles) 2-phenyl-4-benzyl-5-oxazolinone, 4.65 g (27.18 mmoles) benzyl bromide, and 0.31 g (0.87 mmole) tetrabutylammonium iodide in 5 ml DMF and stirred at room temperature for 10 days. At the end of the reaction, the inorganic salt precipitate was filtered off and washed with toluene. The toluene extract and filtrate were evaporated. Then, 28 ml concentrated hydrochloric acid and 55 ml glacial acetic acid were added to the oil obtained and stirred vigorously for 6 h at 95 ± 2°C. The solution was evaporated. The dry residue was dissolved in 60 ml water. The unreacted starting reagent and side-products were extracted with three 20-ml portions of ethyl acetate. The aqueous solution was evaporated to 3-4 ml and a precipitate began to form. The precipitate was filtered off and the solution was neutralized by adding 6 N NaOH to pH 8. A precipitate formed and was combined with the previous precipitate. The yield of α-benzylphenylalanine was 0.90 g (40.7%), mp 280°C. Mass spectrum: *m/z* (*I*, %): 255 (0) $M^{+\cdot}$, 210 (19) $(M - COO_2H)^+$, 164 (11) $(M - CH_2C_6H_5)^+$, 118 (54) $(C_6H_5C{\equiv}NH)^+$, 91 (100) $(CH_2C_6H_5)^+$. PMR spectrum in D_2O: 3.20 (d, CH_2, ^2J = 14.4 Hz), 3.61 (d, CH_2), 7.37 ppm (m, C_6H_5).

Methyl ester of N-Benzoyl-α-methylalanine. A sample of 5.11 g K_2CO_3 was added with stirring to a solution of 7.25 g (41.4 mmoles) 2-phenyl-4-methyl-5-oxazolinone, 9.39 g (66.1 mmoles) methyl iodide, and 1.52 g (4.1 mmoles) tetrabutylammonium iodide in 5 ml DMF and stirred at room temperature for 11 days. The inorganic salts were filtered off and carefully washed with toluene. The toluene solution and filtrate were evaporated. The precipitate obtained was dissolved in 200 ml water and left for 24 h. Then, water was evaporated to give a thick oil, which was recrystallized twice from 25% aqueous ethanol. The yield of the methyl ester of N-benzoyl-α-methylalanine was 2.32 g (25.3%), mp 119°C (mp 120°C [13]).

3-(Benzoylamino)-3,5-dibenzylpyrrolidine-2,4-dione ($C_{22}H_{22}N_2O_3$). A sample of 5 g K_2CO_3 was added with stirring to a solution of 3.64 g (14.5 mmoles) 2-phenyl-4-benzyl-5-oxazolinone, 0.53 g (1.44 mmole) tetrabutylammonium iodide, and 8.69 g (55.7 mmoles) ethyl iodide in 5 ml DMF and stirred vigorously for 6.5 h at 55-60°C. At the end of the reaction, the inorganic salts were filtered off and washed with 5 ml DMF. The filtrate was washed until it became oily. Then, 10 ml concentrated hydrochloric acid and 20 ml glacial acetic acid were added. The mixture was heated for 2 h at 90-95°C. A white precipitate formed after 1 h and was filtered off at the end of the reaction. The precipitate was washed with ethyl acetate to give 1.44 g (25%) dione, mp 270°C. PMR spectrum in DMSO: 1.11 d.d (1H, 5-CH, ^3J = 9.4, ^2J = 14 Hz), 2.10 d.d (1H, 5-CH, ^3J = 5.0, ^2J = 14 Hz), 2.97 d (1H, 3-CH, ^2J = 12.4 Hz), 3.31 d (1H, 3-CH, ^2J = 12.4 Hz), 4.20 m (1H, 5-CH), 6.9-7.9 m (15H, C_6H_5), 8.49 d (1H, 1-NH, ^3J < 1 Hz), 9.32 ppm (s, 1H, 3-NH). ^{13}C NMR spectrum in DMSO-d_6: 35.76 (3-CH_2), 38.39 (5-CH_2), 62.72 ($C_{(5)}$), 63.28 ($C_{(3)}$), 126.36 (1C), 127.61 (1C), 127.80 (2C), 128.29 (2C), 128.40 (2C), 128.47 (2C), 128.96 (2C), 130.98 (2C), 131.73 (1C), 132.10 (1C), 133.38 (1C), 136.98 (1C) aromatic protons of the three phenyl groups, 166.15 (2-NC=O), 171.68 ($C_{(2)}$), 207.91 ($C_{(4)}$).

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