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SYNTHESIS OF METHYL ESTERS OF (2S OR 2R) 2-(4-NITRO-1-IMIDAZOLYL) ALKANECARBOXYLIC ACIDS

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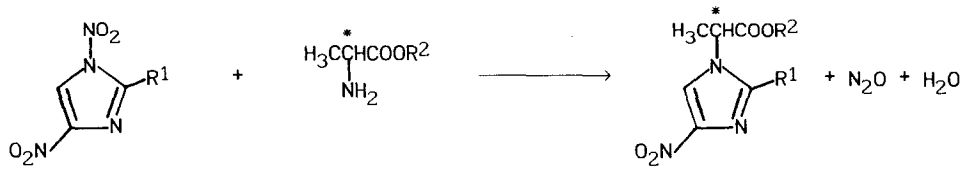
Abstract: 1,4-Dinitroimidazole (or its 2-methyl derivative) reacts with chiral α-amino esters and yields chiral esters of 2-(4-nitro-1-imidazolyl)alkanecarboxylic acids.

Recently[1], we proved that 1,4-dinitroimidazole and its 2- or 5-methyl derivatives react with a number of different compounds containing primary amino groups and yield 1-substituted-4-nitroimidazoles. From hitherto observations, it can be assumed that a nitrogen atom in reaction products at the position 1 of imidazole ring originates from amino substrate. Therefore, the use of enantiomeric amino compounds containing chiral carbon atom linked to amino group should yield enantiomeric 1-substituted nitroimidazole derivatives. These compounds may find potential applications in tumor radiotherapy[2].

In this work, 1,4-dinitroimidazole (or 1,4-dinitro-2-methylimidazole), R and S-alanine methyl esters hydrochlorides, S-alanine and some other optically active α-amino acids or their esters[3] were used for synthesis. The reaction of the dinitroimidazoles with the ester hydrochlorides and with α-amino acids was performed in a slightly different way considering generation of a free amino group in reaction medium[4,5]. During reaction, the approximately equimolar quantities of the product (by weight) and nitrous oxide (by volume) were determined. Reaction results using the mentioned substrates are presented in a scheme and table below.

The products obtained from S and R-alanine esters exhibit practically equal but opposite optical rotation . This result may prove that an amine nitrogen - chiral carbon bond present in amino substrate is not subject to a cleavage during reaction.

Scheme



R^1 = H, CH_3 R^2 = H, CH_3

Table

Substrates			Products		
			Yield	Melting point	Rotation
R^1	R^2	*	%	°C	$[\alpha]^{25}_{546}$
H	CH_3	S	70	85-86	+34.00[6a]
H	CH_3	R	76	84-86	-34.00[6a]
CH_3	CH_3	S	68	104-106	+17.16[6b]
CH_3	CH_3	R	71	103-105	-17.11[6b]
CH_3	H	S	86	98-100	+39.00[6c]

Considering the results we propose a stage reaction mechanism. It consists of a nucleophilic addition of amino compound to dinitroimidazole, ring opening, ring closure, its rearomatization with nitroamide elimination and decomposition of the latter to nitrous oxide and water.

Experiments with amine substrates containing an isotope ^{15}N are currently performed. A preliminary report has been sent for publication.

References and notes

1. Suwiński J., Llempen H., Salwińska E., Szczepankiewicz W., 8-th Int. IUPAC Conf. Org. Synth., Helsinki, July 1990. Abstract no 1,348.

2. Widel M., Watras J., Suwiński J., Salwińska E., Neoplasma, 34, 241(1987).

3. Data concerning reactions not described here and spectroscopic characteristics of all the compounds obtained will be published in a paper sent to "Archiv der Pharmazie" (Weinheim) and are available from the authors.

4. Procedure: Solid sodium bicarbonate (0.01 mole) was added to a solution of α-amino acid ester hydrochloride (0.01 mole) in 15 ccm of water - methanol (1:1) mixture cooled to a temperature of -10°C. The reaction mixture was stirred until carbon dioxide evolution was completed (5 to 10 minutes). 1,4-Dinitroimidazole (or its 2-methyl derivative) (0.01 mole) was added in one portion to the obtained solution with continuous stirring. The formed suspension was left for 1 hour at room temperature. Then, water (10 ccm) was added and the reaction mixture was kept at 4°C for several hours. The obtained precipitate was filtered off and crystallized from methanol or water - methanol mixture with addition of active carbon.

5. Procedure: 0.1M potassium hydroxide was added to α-amino acid (0.01 mole) dissolved (or suspended) in 60 ccm of water at 20° to 25°C until pH = 9.0 was reached. 1,4-Dinitro-2-methylimidazole (0.01 mole) was added in one portion to the mixture under stirrng. Then, 0.1M KOH was added gradually to the reaction mixture to keep pH within 8.7 to 9.0. After completion of the reaction (for alanine, pH becomes stable after about 40 minutes), a concentrated hydrochloric acid was added to the obtained solution to reach pH = 2. The obtained precipitate was filtered off, rinsed and recrystallized from water. Additional quantities of the product were obtained by concentration of the filtrate to 25 ccm .

6. a) c = 1.25, MeOH; b) c = 1, MeCN; c) c = 1, DMF.