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NOTE

SYNTHESIS OF (2-METHYL-4-NITRO-1-[$^{15}N^{1}$]IMIDAZOLYL)ACETIC ACID

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SUMMARY

1,4-Dinitro-2-methylimidazole reacts under mild conditions with glycine to yield (2-methyl-4-nitro-1-imidazolyl)acetic acid. The use of [^{15}N]glycine gives a product having a labelled nitrogen in 1 position of 4-nitroimidazole.

Key words: ^{15}N-labelled 4-nitroimidazole, synthesis, ANRORC mechanism.

DISCUSSION AND RESULTS

In the reaction of 1,4-dinitroimidazole (and its 2- or 5-methyl derivatives) with aniline or its C-substituted derivatives, corresponding 1-aryl-(or 2- methyl or 5-methyl)-4-nitroimidazoles [1] have been obtained in high yields. The reactions were carried out in water-methanol solutions. The method of their execution consisted in introducing successively equimolar quantities of substrates into the solvent, stirring for a few hours, filtering off the product and crystallizing it from a suitable solvent. Similar methods, after small modifications, have made possible the synthesis of corresponding 1-substituted-4-nitroimidazoles by the reaction of 1,4-dinitroimidazoles with 2- and 3-aminopyridines [2], amino benzoic acids and their ethyl esters, as well as with methyl and ethyl esters of α-amino acids [3]. We now report the synthesis of (2-methyl-4-nitro-1-imidazolyl)acetic acid 3. This compound has been obtained by the reaction of 1,4-dinitro-2-methylimidazole 1 with glycine 2 in a water medium with controlled pH (Scheme 1).

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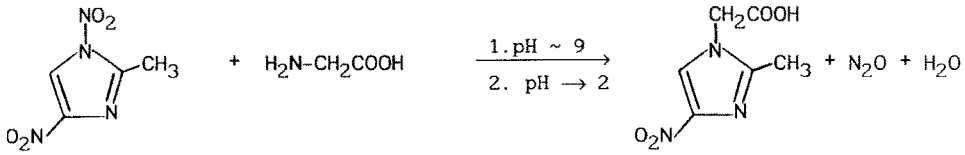
Scheme 1



1 2 3

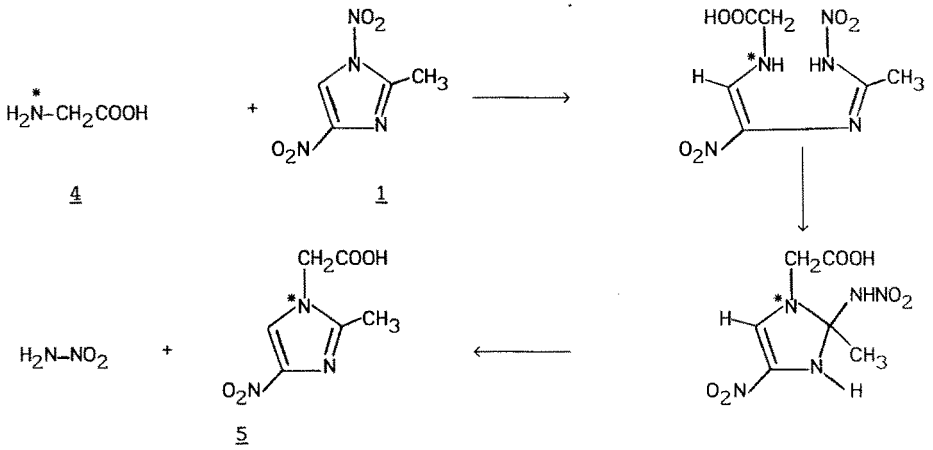
A condition for a rapid reaction is the maintenance of $H_2N\text{-}CH_2COO^{\ominus}$ ion concentration at a sufficiently high level. In order to achieve this, the reaction was carried out at pH = 9 (± 0.1) maintained by successive addition of potassium hydroxide solution throughout the progress of reaction. The separation of the product 3 consisted in concentration of the acidified post reaction solution under reduced pressure until the initiation of crystallization, the cooling of the suspension obtained to room temperature, and filtering off the crystals. To confirm the mechanism of the reaction, a parallel synthesis has been carried out using [^{15}N]glycine 4 as one of substrates. The physicochemical and spectroscopic characteristic of both products 3 and 5 were identical (within experimental error, Table).

Table: Yields and properties of (2-methyl-4-nitro-1-imidazolyl)acetic acids

Compd. No	3			5		
Yield %	71			70		
M.p. °C	246 dec.			246 dec.		
Elemental Analysis	% C	% H	% N	% C	% H	% N
Found	38.77	4.01	22.57	38.77	3.91	23.01
Calcd.	38.93	3.81	22.70	38.72	3.79	23.11
UV VIS (Water) $\lambda_{max}(\varepsilon_{max})$	314.6 (7200)			314.6 (7200)		
^{1}H NMR, δ, 80 MHz, DMSO-d_6, TMS	8.20(s,1H,Imid.), 4.91(s, 2H,CH_2), 2.23(s,3H,CH_3)			8.20(s,1H,Imid.), 4.91(s, 2H,CH_2), 2.23(s,3H,CH_3)		
MS m/e (%)	185(27), 86(5), 58(5), 43(100), 41(8), 27(6)			186(26), 87(5), 59(9), 43(100), 42(10), 30(5)		

The differences occurred in MS spectra. A molecular peak shift by a unit (185 for [^{14}N]glycine and 186 for [^{15}N]glycine) was observed. Similar shifts were present for certain fragmentation ions. According to the ANRORC (addition of nucleophile ,ring opening, ring closure) mechanism proposed by us for the reactions of 1,4-dinitroimidazoles with the compounds containing primary amino groups (Scheme 2), the product should contain ^{15}N in position 1 of the imidazole ring. The mass spectral analysis confirms this assumption and thus the mechanism proposed.

Scheme 2



Experimental:

To a 0.00132 mole of amino acetic acid (2 or 4), in 25 ccm of water at 20° - 25°C, 0.2N KOH solution was added to pH = 9.0. To the stirred solution 0.00132 mole of 1,4-dinitro-2-methylimidazole 1 was added in one portion and, to the suspension, 0.2N KOH was added dropwise to maintain the pH within the range 8.9 - 9.1. At the end of the reaction (stabilization of pH took place after about 35 min.) the solution obtained was acidified with 1N hydrochloric acid to pH ~ 2. The resulting solution was concentrated to about 5 ccm using a vacuum rotatory evaporator. The precipitate was collected and recrystallized from water, with addition of activated carbon, to yield 3 (71 %) or 5 (70 %) respectively.

4 - Product of the Sigma Chemical Company: [^{15}N]Glycine.

References:

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3. Suwiński J., Szczepankiewicz W.- Arch. Pharm.(Weinheim), in press.