Nitration in the Thiazole Series

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Following the publication by Asato (1) of results dealing with the nitration of 2-methylthiazole by nitronium tetrafluoroborate, we present here, a summary of results that we obtained during the study of the nitration of some alkyl thiazoles, by nitric and sulfuric acids. Only a small part of these results have been published (2,3).

2,4-Dialkylthiazoles.

The 2,4-dialkylthiazoles are the more reactive of the the series (3). Nitration occurred at the 5 position which is also the position of greatest electronic density (4). The average reactivity of the 2,4-dialkylthiazoles will be referred to as 1, to give a comparison with the other alkylthiazoles. The yield of the nitration was 70%.

2,5-Dialkylthiazoles.

These compounds are nitrated at the 4 position. The reactivity has been determined by the competitive method, using 2,4-dimethylthiazole as the standard. The average reactivity is about 0.5. In the case of the 2-methyl-5-*tert*-butylthiazole, however, we must note that the yield in nitrated product is lower because of important oxidation of the substrate.

Monoalkylthiazoles.

(a) The 4-alkylthiazoles are nitrated at the 5 position. The reactivity is 0.066 when compared to 2,4-dimethylthiazole.

(b) Nitration of the 5-alkylthiazoles occurs at the 4 position. The reactivity is ~ 0.04.

(c) With regard to the 2-alkylthiazoles, the literature (6,7) claims for the 2-methylthiazole a yield of 2 to 3% when sulfuric acid and potassium nitrate are used at a temperature of 250°. The only product reported is the 2-methyl-5-nitrothiazole. Recently, Asato (1) described the nitration of the same compound using the nitronium tetrafluoroborate and borontrifluoride giving the products, 2-methyl-5-nitrothiazole and 2-methyl-4-nitrothiazole in the ratio of 3.6 to 1.

In our case, the yield of nitrated products was 12% with the 2-methylthiazole; with the 2-*n*-propylthiazole 14% of nitrated products were obtained together with 6% of oxidized products of unknown composition. The isomer ratios are indicated as follows:

2-Methylthiazole	5-nitro : 77%
	4-nitro : 23%
2-*n*-Propylthiazole	5-nitro : 71%
	4-nitro : 29%

These results were also confirmed by the nitration of 2-alkoxythiazoles where the two isomers in the reaction mixture were also found. We can point out that the average reactivity of the 2,4- and 2,5-dialkylthiazoles and that of the 4- and 5-alkylthiazoles allows us to ascertain the relative reactivities of the positions 4- and 5- of the 2-alkylthiazoles.

2,4-Dialkylthiazoles	reactivity : 1
2,5-Dialkylthiazoles	reactivity : 0.5

These results correspond go 66% for the 5 position and 34% for the 4 position.

4-Alkylthiazoles	reactivity : 0.066
5-Alkylthiazoles	reactivity : 0.04

These results correspond to 63% for the 5 position and 37% for the 4 position.

It is noteworthy that these figures are fairly close to those obtained experimentally during the nitration of the 2-alkylthiazoles.

EXPERIMENTAL

(a) The reaction mixtures were analysed by G.L.P.C. using a 10% SE 30 column.

(b) The position of the nitro group was easily deduced from the U.V. spectrum (λ are average values):

Substitution at the 5 position: λ_1 = 215 mμ; λ_2 = 285 mμ; with $\epsilon_1 < \epsilon_2$.

Substitution at the 4 position: λ_1 = 218 mμ; λ_2 = 280 mμ; with $\epsilon_1 > \epsilon_2$.

(c) The nuclear magnetic resonance showed (deuteriochloroform) the normal deshielding effect of the nitro group. Indicated below are the spectra of the 2-methyl-4- and 5-nitrothiazoles and

2-*n*-propyl-4- and 5-nitrothiazoles. For the *n*-propyl group, the middle of the coupling figures is indicated. Most of the other spectra of the nitrothiazoles are registered on the S.D.C. index: CFDA, CFDB, CFDD, CFDE, CFDF, CFDG, CFDI, CFBL, CFBN, CFCX, CFDC, CFDH, CFCZ, CRMB.

Compounds	Shifts of the Protons (ppm)				
	2 Position			4 Position	4 Position
	α	β	γ		
4-Nitro-2-methylthiazole	2.77				8.20
5-Nitro-2-methylthiazole	2.76			8.44	
5-Nitro-2-*n*-propylthiazole	3.12	1.91	1.06	8.48	
4-Nitro-2-*n*-propylthiazole	3.12	1.91	1.06		8.41

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