SYNTHESIS OF 2,5-DISUBSTITUTED 1,3,4-OXADIAZOLES CONTAINING BENZOTHIAZOLYLTHIOL GROUPING

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A series of 2,5-substituted 1,3,4-oxadiazoles containing 2-benzothiazolylthiomethyl grouping has been synthesized by condensing derivatives of (2-benzothiazolylthio)acetic acid with imino ester hydrochlorides and hydrazides of carboxylic acids, by the cyclodehydration of N-acetyl-N'(2-benzothiazolylthioacetyl)hydrazines under the action of POCl₃, and also by the reaction of 2-mercaptobenzothiazole with 2-chloromethyl-1,3,4-oxadiazoles in the presence of sodium methyolate.

Keywords: benzothiazole, carboxylic acid hydrazides, carboxylic acid imino ester hydrochlorides, 2-mercaptobenzothiazole, 1,3,4-oxadiazole, condensation.

N-Substituted 2-amino- and 2-alkylthio-1,3,4-oxadiazoles containing benzothiazole fragments in position 5 possess a wide spectrum of biological activity, including anti-inflammatory [1,2], antimicrobial [3], antibacterial [2], and hypotensive [4] activity. There is extremely limited information in the literature [5,6] regarding 2-alkyl(aryl)-5-substituted 1,3,4-oxadiazoles containing benzothiazole fragments.

In continuation of our investigations on the synthesis of heteryl-substituted 1,3,4-oxadiazoles, we give data in the present study on the preparation of 2,5-disubstituted 1,3,4-oxadiazoles containing 2-benzothiazolylthiomethyl grouping. Compounds of this type may be of interest as potentially biologically active substances and also as stabilizers and additives for polymeric material, hydrocarbon fuel, and lubricating oil [10].

Hydrochlorides of carboxylic acid imino esters may serve as convenient synths in the synthesis of 1,3,4-oxadiazoles [7,10,11]. In the present work the methyl imino ester hydrochlorides of the following acids were used as starting materials: butyric (1a), substituted acetic (1b-f), benzoic (1g), 4-nitro- (1h), and 4-hydroxy-3,5-di(tert-butyl)benzoic (1i), β-[4-hydroxy-3,5-di(tert-butyl)phenyl]propionic (1j), 5-nitro-2-furancarboxylic (1k), and 3-indolecarboxylic (1l) acids. 2-alkyl(aryl,heteryl)-5-(2-benzothiazolylthiomethyl)-1,3,4-oxadiazoles (3a-m) were formed as a result of the condensation of the imino ester hydrochlorides 1a-l with (2-benzothiazolylthiomethyl)acetic acid hydrazide (2a) (method A).

The best yields of compounds 3a-l (Table 1) were achieved on boiling the reactants in ethanol or dioxane at a molar ratio of 1 : 2a of 1.2 : 1. The duration of the process depends on the reactivity of the initial imino ester hydrochloride 1a-l. For example, the formation of compounds 3a-h,j,k is complete after boiling the reactants for 4-5 h in ethanol. When obtaining 1,3,4-oxadiazoles 3i,l from imino ester hydrochlorides 1i,l, which have reduced reactivity due to the effect of bonding of the electron-donating hydroxyaryl or indole substituent with the imino-ester group [11], it was necessary to boil in dioxane for 10-12 h.

We also used the condensation of (2-benzothiazolylthio)acetic acid imino ester dihydrochloride (1f) with hydrazides of various carboxylic acids (2b-f) in the synthesis of 1,3,4-oxadiazoles 3g,h,j-l (method B). The reaction was carried out by boiling the reactants (molar ratio of 1f : 2 = 1.25 : 1) in ethanol for several hours. The corresponding products 3g,h,j-l were formed in 65-76% yields. In addition, compounds 3g,h and 2-methyl-
1.3,4-oxadiazole 3i were obtained by cyclodehydration of the corresponding N-acyl-N'-[(2-benzothiazolylthioacetyl)hydrazines (4a-c) under the action of phosphorus oxychloride (method C) [7,9,12]. The latter were obtained by acylation of hydrazide 2a with acetic anhydride in an inert solvent at room temperature or with the acid chlorides in pyridine in 78-85% yield. However even brief heating with phosphorus oxychloride leads to strong resinification of the reaction mixture from which the desired products 3g,h,i were isolated in 38-47% yield. On boiling N,N'-diacylhydrazines 4a-c in an excess of acetic anhydride for several hours no cyclodehydration to the corresponding 1,3,4-oxadiazoles occurred.

2-Arylthiomethyl-5-R-1,3,4-oxadiazoles may be obtained by the interaction of 2-chloromethyl-5-R-1,3,4-oxadiazoles with arylthiols [13]. We have used this method in the present work for the synthesis of compounds 3f-h,l. As a result of the condensation of 2-chloromethyl-5-R-1,3,4-oxadiazoles 3b, 5a-c with 2-mercapto-benzothiazole in the presence of equimolar quantity of sodium methylate at 0-10°C (0.5 h), the corresponding 1,3,4-oxadiazoles 3f-h,l were formed in 78-87% yield (method D).

The characteristics of the disubstituted 1,3,4-oxadiazoles 3a-m synthesized are given in Table 1. The composition and structure of these compounds were confirmed by data of elemental analysis, IR and 1H NMR spectroscopy. In the IR spectra intense absorption maxima were observed in the ranges of 1600-1615, 1570-1585, and 1460-1490 cm⁻¹ characteristic of the stretching vibrations of the oxadiazole ring [14,15]. The presence of the latter was confirmed by occurrence of absorption bands at 1225-1250 and 1020-1050 cm⁻¹ assigned to the stretching vibrations of the =C-O-C= fragment in 1,3,4-oxadiazoles [16], and of an absorption maximum near 950 cm⁻¹ related to the breathing vibrations of the oxadiazole ring [14,15]. Absorption due to the benzothiazole fragment [14] was also observed for all the compounds considered at 1520-1530, 1430-1445 (stretching vibrations of the ring), 1060-1085, and 735-740 cm⁻¹.

In the 1H NMR spectra of the synthesized compounds the signals of the thiomethyl group protons were displayed as singlets in the range of 3.94-4.27 ppm. The multiplet signals at 7.14-8.14 ppm correspond to the protons of the benzothiazole fragments.