REACTIONS OF 1-VINYLBENZIMIDAZOLE-2-THIONE WITH ALCOHOLS AND PHENOL

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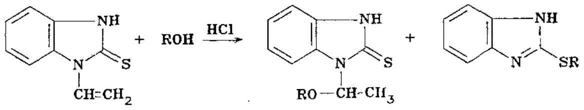
1-(α-Alkoxyethyl)- and 1-(α-phenoxyethyl)benzimidazole-2-thiones were obtained in the reaction of 1-vinylbenzimidazole-2-thione with alcohols and phenol in the presence of gaseous hydrogen chloride. It was established that partial hydrolysis of the 1-(α-alkoxyethyl)benzimidazole-2-thiones to benzimidazole-2-thione with subsequent alkylation with excess alcohol at the exocyclic sulfur atom occurs under the conditions of the investigated reaction. A convenient method for the alkylation of thiones was proposed, and a number of 2-alkylthiobenzimidazoles were synthesized.

We have previously shown [1] that thiols readily add to the vinyl group of 1-vinylbenzimidazole-2-thione (I) in the presence of ionic catalysts. In the present research we studied the electrophilic addition of alcohols to vinyl thione I in order to synthesize new alkoxy derivatives of benzimidazole-2-thione as potentially biologically active substances. The presence of ethyl groups with different lengths of the alkyl chain and the presence of a strongly polarized C=S group in such compounds constitute evidence for their possible plasticizing capacity. Methyl, ethyl, propyl, isopropyl, and butyl alcohols and phenol were used as hydroxy-containing compounds.

We found that vinyl thione I in the presence of catalytic amounts of concentrated hydrochloric acid adds alcohols in accordance with Markownikoff's rule to give 1-(α-alkoxyethyl)-benzimidazole-2-thiones (IIa-d). However, the yields of the latter are low (~15%). When an equimolar amount of concentrated HCl is added, the process is accompanied by heating up of the reaction mixture and complete hydrolysis of the starting compound to benzimidazole-2-thione (III). The hydrolysis of vinyl thione I can be eliminated to a considerable extent if the reaction is carried out in absolute alcohol saturated with gaseous hydrogen chloride at the boiling point of the alcohol.



I IIa-e IVa-d

II,IV a R=CH_3; b R=C_2H_5; c R=C_3H_7; d R=C_4H_9; e R=C_6H_5

In this case the yields of alkoxy derivatives IIa-d amount to 40 to 64%. The characteristics of the synthesized compounds are presented in Table 1.

The presence of a quartet at 6.40 ppm (CH) and a doublet at 1.59 ppm (CH_3) in the PMR spectrum of 1-(α-ethoxyethyl)benzimidazole-2-thione (IIb) demonstrates that the addition of alcohol to the C=C bond proceeds in accordance with Markownikoff's rule. The ethyl group forms a triplet at 1.08 ppm (CH_3) and a multiplet at 3.40 ppm (CH_2) as a consequence of the anisochronicity of the diastereotopic methylene protons. This phenomenon is characteristic for acetals and hemiacetals [2]. It should be noted that hemiacetals IIa-d do not undergo disproportionation under the conditions of the investigated reaction.

A comparison of the reactivities of the alcohols in the reaction with vinyl thione I under identical conditions (50-60°C, HCl) shows that their activities decrease in the order MeOH ≈ EtOH > PrOH > BuOH.

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TABLE 1. 1-(α-R-Oxyethyl)benzimidazole-2-thiones (IIa-e) and 2-Alkylthiobenzimidazoles (IVa-d)

Compound	mp, °C	Found, %				Empirical formula	Calc., %				Yield, %
		C	H	N	S		C	H	N	S	
IIa	114—115	57,5	5,8	13,8	15,3	$C_{10}H_{12}N_2OS$	57,7	5,8	13,5	15,4	63
IIb	92—93	59,3	6,4	12,8	14,5	$C_{11}H_{14}N_2OS$	59,4	6,3	12,6	14,4	64
IIc*	—	61,0	6,7	11,8	13,7	$C_{12}H_{16}N_2OS$	61,0	6,8	11,9	13,6	46
IId*	—	62,4	7,4	10,9	12,7	$C_{13}H_{18}N_2OS$	62,4	7,4	11,2	12,8	40
IIe	183—185	66,8	5,3	10,3	11,9	$C_{15}H_{14}N_2OS$	66,6	5,2	10,4	11,9	40
IVa	205—206	58,5	4,9	16,8	19,6	$C_8H_8N_2S$	58,5	4,9	17,0	19,5	95
IVb	172—173	60,7	5,6	15,8	18,2	$C_9H_{10}N_2S$	60,6	5,6	15,7	18,0	85
IVc	162—163	62,5	6,2	14,8	16,7	$C_{10}H_{12}N_2S$	62,5	6,3	14,6	16,7	78
IVd	134—135	64,0	6,9	13,8	15,6	$C_{11}H_{14}N_2S$	64,0	6,8	13,6	15,5	80

*Compounds IIc and IId were oils.

Phenol adds smoothly to vinyl thione I. The resulting 1-(α-phenoxyethyl)benzimidazole-2-thione (IIe) is distinguished by high hydrolytic stability. We were unable to obtain a product of addition of isopropyl alcohol. We assume that the absence of 1-(α-isopropoxyethyl)-benzimidazole-2-thione in the reaction products is due to its complete hydrolysis to thione III under the investigated conditions.

We found that alkoxy derivatives IIa-d undergo partial hydrolysis under the conditions of their syntheiss. It is interesting that the reaction does not stop at the step involving the formation of thione III but is accompanied by subsequent alkylation at the exocyclic sulfur atom. The isolation of 2-alkylthiobenzimidazoles (IVa-d) from the reaction mixtures constitutes evidence for this. The yields of alkylation products IVa-d depend substantially on the presence of water in the alcohol and the degree of saturation with gaseous hydrogen chloride. Thus the hydrolytic stabilities of hemiacetals IIa-d decrease when the HCl concentration is increased and nonabsolutized alcohols are used, and the yields of alkylthiobenzimidazoles IVa-d reach 40%.

To confirm the proposed scheme of the synthesis of alkyl derivatives IVa-d we carried out the reaction of thione III with various alcohols in the presence of gaseous hydrogen chloride under the conditions of the preparation of the hemiacetals. We isolated 2-alkylthiobenzimidazoles IVa-d with a high degree of purity in 78-95% yields. We demonstrated that thione III does not react with the alcohols in the presence of aqueous solutions of HCl.

The alkylation with alcohols is sensitive to the substituent in the 1 position of the heteroring, since alkylation of alkoxy derivatives IIa-d was not observed. This is probably due to steric hindrance created by the substituent attached to the nitrogen atom.

Thus as a result of an investigation of 1-vinylbenzimidazole-2-thione (I) with alcohols and phenol we have accomplished the synthesis of new alkoxy derivatives of benzimidazole-2-thione and have developed a convenient method for the alkylation of heterocyclic thiones with alcohols. Vinyl thione I was found to be highly active in reactions involving the electrophilic addition of alcohols as compared with 1-vinylbenzimidazole, which forms stable salts with gaseous hydrogen chloride [3], whereas the lack of an ability to form salts with an acidic catalyst is characteristic for thione I, which has low basicity. The double bond of the vinyl group of vinyl thione I is distinguished by high nucleophilicity because of the absence of conjugation of it with the imidazole ring as a consequence of disruption of the aromatic character of the latter when a sulfur atom is introduced into the meso position.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of solutions of the compounds in $(CD_3)_2CO$ were recorded with a Tesla BS 487B spectrometer with hexamethyldisiloxane as the internal standard.

1-Vinylbenzimidazole-2-thione (I) was obtained by the method in [1].

1-(α-Methoxyethyl)benzimidazole-2-thione (IIa). A stream of dry hydrogen chloride was passed into 15 ml of absolute methanol for 2-5 min at room temperature, 1.76 g (0.01 mole) of vinyl thione I was added, and the mixture was refluxed for 2 h. The excess alcohol was removed by vacuum distillation, and the residue was chromatographed with a column packed with Al_2O_3 [chloroform—benzene—ethanol (20:4:1)] to give 1.31 g (63%) of IIa (Table 1).

Compounds IIb-d were similarly obtained. An intense absorption band at 1125 cm^{-1} (C–O–C) appeared in the IR spectra of alkoxy derivatives IIa-d. Thioamide bands were found at 1235 and 1505 cm^{-1}.

1-(α-Phenoxyethyl)benzimidazole-2-thione (IIe). A 1.88-g (0.02 mole) sample of phenol and 1.76 g (0.01 mole) of vinyl thione I were added at room temperature in the course of 5 min to 20 ml of benzene saturated with HCl, and the mixture was refluxed for 3 h. The benzene was removed by vacuum distillation, and the solid residue was recrystallized from hot benzene to give 1.08 g (40%) of white crystalline IIe.

2-Methylthiobenzimidazole (IVa). A stream of dry hydrogen chloride was passed for 5-10 min at room temperature into 10 ml of methanol, 1.5 g (0.01 mole) of benzimidazole-2-thione (III) was added, and the mixture was refluxed for 2 h. The excess alcohol was removed *in vacuo*, and the residue was dissolved in 10 ml of water. The solution was made alkaline to pH 8 with concentrated KOH solution, and the resulting white precipitate was removed by filtration, washed with water, and dried to give 1.56 g (95%) of IVa with mp 205-206°C (mp 201°C [4]). IR spectrum: 1370 (CH$_3$); 1450-1620 (ring C=C, C=N); 1600, 3430 (NH); 3100 cm^{-1} (associated NH). The PMR spectrum contained a singlet of methyl protons at 2.71 ppm and a multiplet of aromatic protons at 7.30 ppm.

Compounds IVb-d were similarly obtained.

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FRIEDEL–CRAFTS ACYLATION OF BENZIMIDAZOLIN-2-ONES WITH ALIPHATIC ACID CHLORIDES

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The acylation of benzimidazolin-2-one and its 5,6-disubstituted derivatives with aliphatic acid chlorides in the presence of anhydrous aluminum chloride was studied. The corresponding 5(6)-acyl-, 5-R-6-acyl-, and 5,6-dimethyl-4-acylbenzimidazolin-2-ones, the structures of which were confirmed by the results of elementary analysis and IR, PMR, and mass spectroscopy, were obtained. The yields of the acylation products depend on the electronic effects of the substituents in the benzene ring of the benzimidazolin-2-one and on steric factors.

Many benzimidazole derivatives are highly effective pesticides [1]. The purposeful synthesis of new benzimidazolin-2-one derivatives — analogs of compounds with antibiotic activity [2] — therefore seems promising. In the present research we studied the acylation of benzimidazolin-2-one (I) and its 5-methyl, 5-chloro, 5,6-dimethyl, and 5-(β-carboxypropyl) derivatives (II-V) with aliphatic carboxylic acid chlorides in the presence of anhydrous aluminum chloride in order to ascertain the effect of substituents in the benzene ring of benzimidazolin-2-one, the reactivities of the acyl chlorides themselves with respect to benzimidazolin-2-ones, and steric factors in the 5-R^1-6-R^2-benzimidazolin-2-one series on the yields of the acylation products.

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