REACTION OF 2-THIOBENZAZOLES WITH THIONYL CHLORIDE

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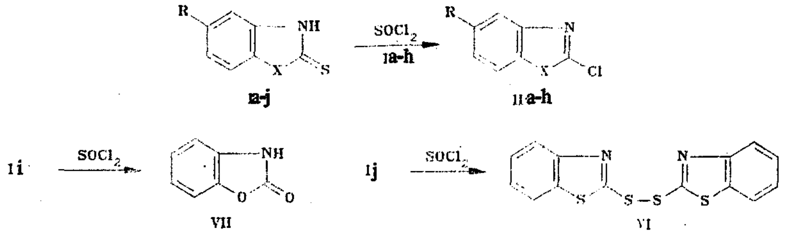
A new reaction in the benzimidazole series, viz., replacement of the mercapto group by chlorine by the action of thionyl chloride on 2-thiobenzimidazoles, was discovered. Benzoxazolone is formed by treatment of 2-thiobenzoxazole with thionyl chloride, and 2,2'-dithiobis(2-benzothiazole) is formed from 2-thiobenzothiazole.

2-Chloro derivatives of benzimidazole are obtained from benzimidazolones and phosphorus oxychloride in sealed ampuls at 160-170°C [1, 2]. In an attempt to obtain 1-benzyl(methyl, ethyl)-2-thiobenzimidazole-5-carboxylic acid chlorides we observed that in the reaction of thiones Ia, g, h with thionyl chloride, in addition to the formation of acid chlorides, the mercapto group is replaced by chlorine, and 1-benzyl(methyl, ethyl)-2-chloro-benzimidazole-5-carboxylic acid chlorides (IIa, g, h) are formed in 60-70% yields.



I, II a–f $X=NCH_2C_6H_5$, g $X=NCH_3$, h $X=NC_2H_5$; I i $X=O$,& $X=S$; Ia, g, h $R=COOH$; II a, g, h $R=COCl$; I, II b $R=COOCH_3$, c $R=COOC_2H_5$, d $R=NO_2$, e $R=Cl$, f $R=Br$; Ii,j $R=H$

The structures of acid chlorides IIa, g, h were proved by hydrolysis to the corresponding acids, which, with respect to their melting points and IR spectra, were identical to samples obtained from benzimidazolones and phosphorus oxychloride by the method in [3].

It should be noted that the conditions under which the reaction is carried out depend on the substituent in the 1 position. Thus to obtain IIa, h the reaction is carried out in a solvent (benzene, toluene, or chloroform) with a 1:(7-10) molar excess of $SOCl_2$, whereas prolonged refluxing of thione Ig in a large excess of $SOCl_2$ without a solvent is necessary for the preparation of IIg; this is evidently associated with the solubility of the resulting acid chlorides.

Replacement of the mercapto group by chlorine was studied in greater detail in the case of 1-benzyl-2-thiobenzimidazole-5-carboxylic acid (Ia): the effects of the solvent and the reagent ratio on the reaction pathway and the yields of the final products were studied. Starting thione Ia was isolated in the case of an equimolar reagent ratio in benzene or chloroform even upon prolonged refluxing. An increase in the amount of thionyl chloride to 2-5 moles leads to the formation of two products, viz., 1-benzyl-2-thiobenzimidazole-5-carboxylic acid chloride (III) and 1-benzyl-2-chlorobenzimidazole-5-carboxylic acid chloride (IIa).

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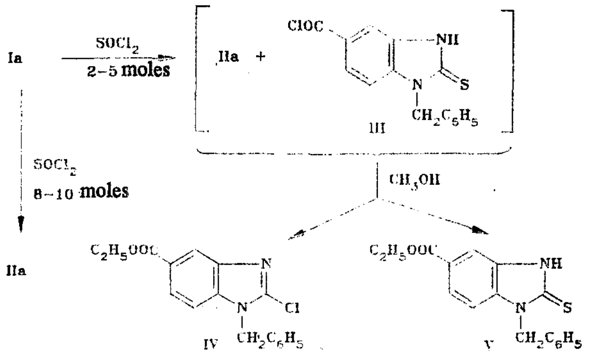
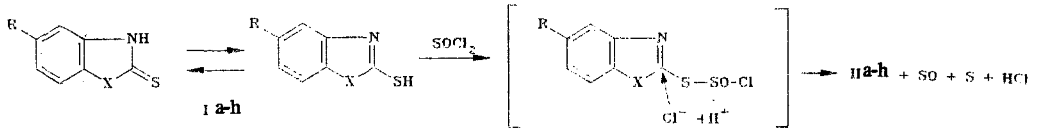


It is not possible to separate IIa and III, but the corresponding esters IV and V were obtained in 30-35% yields after treatment of the mixture with methanol. Acid chloride IIa is formed in 70-75% yield when the reaction is carried out with a 1:(8-10) molar excess of $SOCl_2$ in benzene or chloroform. Thiones that contain chloro, bromo, carbomethoxy, carbethoxy, and nitro substituents in the 5 position of the benzimidazole system, as well as 1,5,6-trimethyl-2-thiobenzimidazole and unsubstituted 2-thiobenzimidazole, were used to ascertain the effect of substituents on the pathway of the reaction of 2-thiobenzimidazoles with thionyl chloride. Replacement of the mercapto group by chlorine proceeded in high yields (60-80%) in compounds with electron-acceptor substituents (nitro, chloro, bromo, carbomethoxy, and carbethoxy groups) in the 5 position. The starting compound was isolated when 1,5,6-trimethyl-2-thiobenzimidazole was refluxed in excess thionyl chloride. Replacement of the SH group by chlorine also did not take place in 2-thiobenzimidazole.

The reaction of heterocyclic thiones with thionyl chloride has not been described in the literature. However, the reaction of 2-mercaptobenzothiazole with sulfuryl chloride to give 2-chlorobenzothiazole was described in [4], and a reaction scheme was proposed. A similar scheme can be proposed for the reaction of 2-thiobenzimidazoles Ia-h with thionyl chloride:



The formation of elementary sulfur during the reaction was confirmed experimentally.

Refluxing 2-thiobenzothiazole (Ij) with a 1:(2-10) molar excess of thionyl chloride in benzene gives disulfide VI (in 75% yield), which is identical to the compound obtained by oxidation of Ij with $K_3Fe(CN)_6$. 2-Benzoxazolone (VII) was isolated in 80% yield under similar conditions in the reaction of 2-thiobenzoxazole (Ii) with $SOCl_2$.

Thus the new reactions in the benzimidazole series, viz., replacement of the mercapto group by chlorine by the action of thionyl chloride, is general only for thiones of the benzimidazole series with acceptor substituents in the benzene ring. The mild conditions under which the reaction is carried out and the high yields of the corresponding 2-chloro derivatives make these compounds readily accessible.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. Monitoring of the course of the reactions and determination of the R_f values were realized by means of thin-layer chromatography (TLC) on Silufol UV-254 plates in chloroform—ethyl acetate (10:3) (A) and chloroform—ethanol (10:1) (B) systems.

Reaction of 1-Benzyl-2-thiobenzimidazole-5-carboxylic Acid (Ia) with Thionyl Chloride. A) A 2.8-g (10 mmole) sample of thione Ia and 1.5 ml (20 mmole) of thionyl chloride were refluxed in 30 ml of benzene for 5 h, after which the reaction solution was evaporated to dryness, and the residue was refluxed in 20 ml of methanol for 2-3 min. According to TLC data, a mixture of 1-benzyl-5-carbomethoxy-2-chlorobenzimidazole (IV) and 1-benzyl-5-

carbomethoxy-2-thiobenzimidazole (V) was obtained. Cooling precipitated V, which was crystallized from 50% aqueous ethanol to give 1.5 g (35%) of a product with mp 217-218°C and R_f 0.68 (A). IR spectrum: 1668 (C=O), 1617, 1588, 1470, 1415, 1375, 1357, 1330, 1306, 1290, 1232, 1220, 1158, 1125, 1111, 1080, 1038, 957, 947, and 867 cm^{-1}. Found: C 64.6; H 4.8; N 9.8%. $C_{16}H_{14}N_2O_2S$. Calculated: C 64.4; H 4.7; N 9.7%. With respect to its IR spectrum, the substance was identical to the substance obtained by esterification of thione Ia. 1-Benzyl-5-carbomethoxy-2-chlorobenzimidazole, with mp 165-166°C (from ethanol) and R_f 0.65 (B), was obtained from the mother liquor after evaporation to dryness. Found: C 63.6; H 4.5; Cl 12.0; N 9.2%. $C_{16}H_{13}ClN_2O_2$. Calculated: C 63.9; H 4.4; Cl 11.8; N 9.3%.

B) A 2.8-g (10 mmole) sample of thione Ia and 7.5 ml (100 mmole) of thionyl chloride were refluxed in 30 ml of benzene, after which the reaction solution was evaporated to dryness, and the residue was crystallized from benzene to give 1.9 g (63%) of 1-benzyl-2-chlorobenzimidazole-5-carboxylic acid chloride with mp 110-112°C. Found: C 58.9; H 3.4; N 9.2%. $C_{15}H_{10}Cl_2N_2O$. Calculated: C 59.0; H 3.3; N 9.2%.

1-Methyl-2-chlorobenzimidazole-5-carboxylic Acid Chloride (IIg). A 10.4-g (50 mmole) sample of 1-methyl-2-thiobenzimidazole-5-carboxylic acid was refluxed in 50 ml of thionyl chloride until the solid material dissolved (4-5 h), after which the thionyl chloride was removed by distillation to dryness, and the residue was crystallized from toluene to give 6.5 g (59%) of acid chloride IIg with mp 175-178°C. Found: C 47.8; H 2.8; Cl 30.6; N 12.0%. $C_9H_6Cl_2N_2O$. Calculated: C 47.2; H 2.6; Cl 30.9; N 12.2%.

1-Ethyl-2-chlorobenzimidazole-5-carboxylic Acid Chloride (IIh). A 20-g (90 mmole) sample of 1-ethyl-2-thiobenzimidazole-5-carboxylic acid and 32 ml (270 mmole) of thionyl chloride were refluxed in 200 ml of toluene for 4 h, after which the mixture was evaporated to dryness, and the residue was crystallized from benzene to give 16.2 g (74%) of a product with mp 125-126°C. Found: C 49.4; H 3.4; Cl 29.1; N 11.6%. $C_{10}H_8Cl_2N_2O$. Calculated: C 49.4; H 3.3; Cl 29.5; N 11.5%.

Hydrolysis of 1-Methyl-2-chlorobenzimidazole-5-carboxylic Acid Chloride. A 2.3-g (10 mmole) sample of acid chloride IIg was refluxed in 30 ml of water for 20 min, after which the precipitate was removed by filtration and crystallized from ethanol. The resulting 1-methyl-5-carboxy-2-chlorobenzimidazole was identical to the compound obtained by the method in [3] with respect to its melting point and IR spectrum.

Reaction of 1-Benzyl-5-nitro-2-thiobenzimidazole (Id) with Thionyl Chloride. A 2.85-g (10 mmole) sample of thione Id and 3.8 ml (50 mmole) of $SOCl_2$ were refluxed in 30 ml of benzene for 1 h, after which the solution was evaporated to dryness, and the 1-benzyl-5-nitro-2-chlorobenzimidazole (IId) was crystallized from ethanol to give 2.3 g (80%) of a product with mp 151-152°C (mp 150-152°C [5]) and R_f 0.58 (B). Found: C 58.4; H 3.5; Cl 12.5%. $C_{14}H_{10}ClN_3O_2$. Calculated: C 58.4; H 3.5; Cl 12.3%.

The reaction of 1-benzyl-5-chloro(bromo, carbomethoxy, carbethoxy)-2-thiobenzimidazoles with thionyl chloride was carried out similarly. 1-Benzyl-2,5-dichlorobenzimidazole (IIe) had mp 139-140°C (from isopropyl alcohol) and R_f 0.84 (B). Found: C 60.6; H 3.8; Cl 25.5%. C H Cl N . Calculated: C 60.7; H 3.5; Cl 25.6%. 1-Benzyl-5-bromo-2-chlorobenzimidazole (IIf) had mp 145°C (from petroleum ether) and R_f 0.74 (B). Found: C 52.0; H 3.2; N 8.6%. $C_{14}H_{10}BrClN_2$. Calculated: C 52.3; H 3.2; N 8.7%. 1-Benzyl-5-carbethoxy-2-chlorobenzimidazole (IIb) had mp 119-120°C (from ethanol) and R_f 0.65 (B). Found: C 64.9; H 5.0; Cl 11.3; N 8.8%. $C_{17}H_{15}ClN_2O_2$. Calculated C 64.8; H 4.8; Cl 11.3; N 8.9%.

Reaction of 2-Thiobenzothiazole with Thionyl Chloride. A 1.67-g (10 mmole) sample of 2-thiobenzothiazole and 1.5 ml (20 mmole) of thionyl chloride were refluxed in 30 ml of benzene for 1 h, after which the reaction solution was evaporated to dryness, and the residue was crystallized from benzene or dimethylformamide to give 1.3 g (75%) of disulfide VI with mp 179-180°C. The product was identical to the compound obtained by oxidation of thione Ij by the method in [6] according to its melting point and IR spectrum.

The reaction of 2-thiobenzoxazole with thionyl chloride was carried out similarly. Evaporation of the reaction solution gave 1.2 g (90%) of 2-benzoxazolone with mp 138°C (from benzene) (mp 138-139°C [7]). Found: C 62.3; H 3.7; N 10.3%. $C_7H_5NO_2$. Calculated: C 62.2; H 3.7; N 10.4%.

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RELATIONSHIP BETWEEN THE CONSTANTS OF GEMINAL SPIN-SPIN COUPLING OF PHOSPHORUS AND HYDROGEN ATOMS AND THE CHANGES IN THE CHROMOPHORE LINK IN AZOLO[4,5-d]OXAPHOSPHOLENES AND THEIR PROTONATION PRODUCTS

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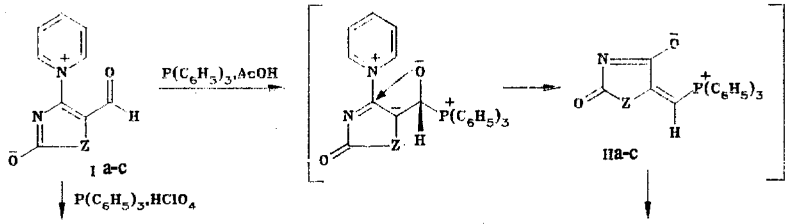
Data on the linear dependence of the constants of geminal spin-spin coupling of the phosphorus and hydrogen atoms on the long-wave absorption maxima in the electronic spectra for azolo[4,5-d]oxaphospholenes and their acyclic isomeric salts were obtained. The effect of the substituents and conformational factors on the indicated dependence was studied.

The spin-spin coupling constants (SSCC) of the phosphorus and hydrogen nuclei constitute an important characteristic in the determination of the structures of organophosphorus compounds. The tendency for the SSCC to change is not always fixed as a function of the number of bonds between the nuclei and is due to their electronic environment and structural factors. According to [1], in triethyl phosphate the SSCC decrease as the distance from the hydrogen atoms increases, so that $J_{CH_2-P} = 8.38$ Hz and $J_{CH_3-P} = 0.76$ Hz, whereas in compounds with an alkyl group bonded directly to the phosphorus atom the SSCC are greater for the β protons than for the α protons ($J_{H_\alpha-P} = 14.2$ Hz; $J_{H_\beta-P} = 30.0$ Hz) [2]. In connection with the synthesis of new two-ring systems of the types oxaphospholeno[4,5-d]azolinones (III) and acyclic trans-E (IV) and cis-Z (VII) conformers of 1-aryl-5-triphenylphoniamethylidene-imidazolidine-2,4-dione, uracil betaines VIII, and azoles V with phosphonium cations it seemed possible to follow the effect of changes in the chromophore link that bears the terminal coupling nuclei on the SSCC (J_{HP}). As we have previously reported [3], the reactions of betaines I with triphenylphosphine proceed, depending on the character of the acid used, either as a result of attack on the carbon atom of the formyl group with subsequent sigmatropic rearrangement of the oxygen atom in the 4 position of the azole ring or as a result of direct exchange of the pyridinium cation for a phosphonium group.



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