REACTION OF 4-IMINOTHIAZOLIDINONE-2 WITH ACETOACETIC ESTER

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The reaction of 4-iminothiazolidinone-2 with acetoacetic ester and its alkyl and aralkyl derivatives gives derivatives of thiazolo-[4,5-b]pyridine, which form salts with alkalis and are acylated.

4-Iminothiazolidinone-2 (I) reacts with acetylacetone or benzoylpyruvic acid to form the respective thiazolo[4,5-b]pyridines [1].

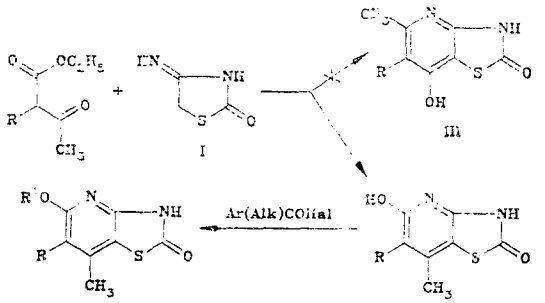
We have studied the reaction of compound (I) with acetoacetic ester and its derivatives. Best yields of reaction product (II) are obtained by carrying out the reaction in absolute methanol on the presence of sodium methylate at room temperature. Methyl, propyl, and benzyl derivatives of acetoacetic ester react similarly.

In the reaction with ylidene- and isonitrosoacetoacetic esters the corresponding derivatives could not be separated.

An attempt to carry out the reverse synthesis of derivative (IIa) from 5-(1-carbethoxy-isopropylidene)isorhodanine and ammonia unexpectedly gve thiazolidinone (I).

We also studied the reaction of isorhodanine with ethyl β-aminocrotonate, for the purpose of obtaining the cyclization product (III) which is an isomer of (II). But in that case only thiazolidinone (I) was isolated. This indicates indirectly that the union of acetoacetic ester with compound (I) takes place only by the ketone group of acetoacetic ester joining the methylene in position 5 of the thiazolidine ring In the opposite case unstable compounds might be formed that would be converted to thiazolidinone (I) under the reaction conditions.

Compounds (II) form salts with alkali alcoholates or hydroxides, and are also acylated at the oxygen at position 5 to form thiazolopyridinone (IV); this agrees with the data on the acylation of pyridinones-2 [2].



IVa-j IIa-d

IIa R=H; b R=CH_3; c R=C_3H_7; d R=$C_6H_5CH_2$; IVa R=H, R^1=CH_3CO; b R=H, R^1=C_2H_5CO; c R=H, R^1=C_6H_5CO; d R=H, R^1=$CH_3(CH_2)_2CO$; e R=$CH_3CH_2CH_2$, R^1=CH_3CO; f R=$C_6H_5CH_2$, R^1=CH_3CO; g R=$CH_3CH_2CH_2$, R^1=C_2H_5CO; h R=$CH_3CH_2CH_2$, R^1=$CH_3(CH_2)_2CO$; i R=$CH_3CH_2CH_2$, R^1=C_6H_5CO; j R=CH_3, R^1=CH_3CO

EXPERIMENTAL

IR spectra were obtained with a IKS-29 spectrophotometer in KBr tablets; UV spectra, with a Spektromom 203 spectrophotometer; PMR spectra, with a Bruker WP-200 spectrometer (200 MHz) in DMSO-D_6 with HMDS internal standard. Chromatography was carried out on Silufol UV-254 plates in 10:1:1 isopropyl alcohol–25% ammonia–water.

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TABLE 1. Properties of Synthesized Compounds

Compound	R	R'	Empirical formula	mp, °C*	UV spectrum in ethanol, λ_{max}, nm (log ε)	Yield, %
IIa	H	H	$C_7H_6N_2O_2S$	277-...278	302 (3,82), 351,5 (3,84)	88
IIb	CH_3	H	$C_8H_8N_2O_2S$	>270	306 (3,86), 356 (3,72)	79
IIc	$-C_3H_7$	H	$C_{10}H_{12}N_2O_2S$	249...250	307 (3,94), 356 (3,65)	100
IId	$C_6H_5CH_2$	H	$C_{14}H_{12}N_2O_2S$	277	246 (3,50), 307 (3,84), 359 (3,58)	86
IVa	H	CH_3CO	$C_9H_8N_2O_3S$	240...241	296 (3,68), 352 (3,68)	92
IVb	H	C_2H_5CO	$C_{10}H_{10}N_2O_3S$	181	293 (4,18), 352 (3,94)	92
IVc	H	C_6H_5CO	$C_{14}H_{10}N_2O_3S$	203	228 (4,35), 293 (4,01), 353 (3,59)	74
IVd	H	C_3H_7CO	$C_{11}H_{12}N_2O_3S$	164	243 (3,61), 297 (4,03), 353 (4,00)	56
IVe	C_3H_7	CH_3CO	$C_{12}H_{14}N_2O_3S$	212	299 (4,20), 355 (3,79)	91
IVf	$C_6H_5CH_2$	CH_3CO	$C_{16}H_{14}N_2O_3S$	216	246 (3,34), 305 (3,67), 358 (3,73)	90
IVg	$-C_3H_7$	C_2H_5CO	$C_{13}H_{16}N_2O_3S$	195	300 (4,11), 357 (3,97)	89
IVh	$-C_5H_7$	C_3H_7CO	$C_{14}H_{18}N_2O_3S$	183	297 (4,15), 356 (3,83)	88
IVi	$-C_5H_7$	C_6H_5CO	$C_{17}H_{16}N_2O_3S$	208	227 (4,22), 300 (3,97), 356 (3,48)	76
IVj	CH_3	CH_3CO	$C_{10}H_{10}N_2O_3S$	265...267	212 (4,42), 295 (4,16), 355 (2,92)	81

*Crystallization: (IIa), from 1:2 acetic acid–water; (IIb), from acetic acid; (IIc, IVa, b, d, e, g-i), from ethanol; (IId), from 3:1 acetic acid–water; (IVc), from isopropanol; (IVf, j) from methanol.

The elemental composition of compounds (IIa-d) and (IVa-j) (C, H, N, S) agrees with the calculated composition. The properties of the synthesized compounds are given in Table 1.

5-Hydroxy-7-methyl-2,3-dihydrothiazo[4,5-b]pyridin-2-one (IIa, $C_7H_6N_2O_2S$). To a solution of 2.5 g sodium in 125 ml of absolute methanol was added at 20°C 6.8 g (50 mmoles) of 4-iminothiazolidinone-2 and 10 ml of acetoacetic ester. The mixture was let stand for 3 days with occasional mixing. It was then acidified to pH ~5 with acetic acid and diluted fivefold with water. The precipitate was filtered off, washed with water, and dried. R_f 0.72. IR spectrum: 3400, 3170 (OH, NH), 3090 (CH arom.), 2940, 2830 (CH in CH_3), 2370 ($\overset{+}{N}H$), 1720, 1635 (C=O), 1560 cm^{-1} (amide II). PMR spectrum: 2.16 (3H, 6.24 (1H), 11.45 ppm (1H).

Compounds (IIb-d) were obtained similarly. These are white crystalline substances, soluble in DMFA, pyridine, and alkali solutions.

Sodium Salt of 5-Hydroxy-7-methyl-2,3-dihydrothiazolo[4,5-b]pyridin-2-one ($C_7H_5N_2NaO_2S$). To a solution of sodium methylate prepared from 30 ml of methanol and 0.34 g (15 mmoles) of sodium was added 2.73 g (15 mmoles) of 5-hydroxy-7-methyl-2,3-dihydrothiazolo[4,5-b]pyridin-2-one (IIa). The mixture was boiled for 1 h, then cooled. The precipitate was filtered off, washed with a small amount of methanol, and dried. Yield, 2.65 g (87%). Mp 280°C (from 1:2 methanol–water). R_f 0.87. White crystalline powder, soluble in water, poorly soluble in organic solvents. IR spectrum: 3465 (NH), 3045 (CH arom.), 2955, 2865 (CH in CH_3), 1648 (C=O), 1565 cm^{-1} (amide II). UV spectrum in water, λ_{max} (log ε); 207 (4.01), 219 (3.97), 264 (3.08), 344 nm (4.09).

5-Acetoxy-7-methyl-2,3-dihydrothiazolo[4,5-b]pyridin-2-one (IVa, $C_9H_8N_2O_3S$). A mixture of 5.5 g (30 mmoles) of (IIa) and 50 ml of acetic anhydride was boiled for 20 min. The precipitate that formed in the cold was filtered off, washed with acetic acid and water, and dried. R_f 0.75. IR spectrum: 3460 (NH), 3060 (CH), 2985, 2945, 2895 (CH_3), 1780, 1740 (C=O), 1180 cm^{-1} (COC).

The identical compound was obtained in 70% yield by Schotten–Baumann acetylation. Equimolar amounts of (IIa) and acetyl chloride in pyridine were let stand for 6 h; the product was precipitated by water.

Compounds (IVb-j) were obtained similarly. These white crystalline substances have good solubility in DMSO, DMFA, and pyridine.

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2-ARYL-1,2,3-THIADIAZOLIUM SALTS

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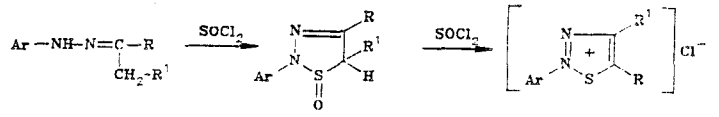
When arylhydrazones of α-methyleneketones are treated with thionyl chloride they form 2-aryl-1,2,3-thiadiazolium chlorides in high yield, via the intermediate 1,2,3-thiadiazol-3-ine 1-oxides. The effect of substituents on the course of the cyclization was investigated.

The reaction of acyl- and arenesulfonylhydrazones of α-methyleneketones with thionyl chloride gives 1,2,3-thiadiazoles; at the same time acyl- or arenesulfonyl groups are split off [1]. The final products are formed via the intermediate 1-oxides [2].

We have found that α-methyleneketone arylhydrazones containing electron-acceptor substituents in the aromatic nucleus of the hydrazine segment form 2-aryl-1,2,3-thiadiazolium (III) salts when boiled with thionyl chloride. When such groups are not present, as, e.g., in the case of acetophenone phenylhydrazone the reaction is extremely vigorous even at low temperature and produces a resinous reaction mass.



Ia-k IIh,k IIIa-j

a-e, h-k Ar = 4-$NO_2C_6H_4$, f Ar = 2-$NO_2C_6H_4$, g Ar = 2,4-$(NO_2)_2C_6H_3$; a,e-g R = C_6H_5, b R = 4-$CH_3OC_6H_4$, c R = $CH_2C_6H_5$, d R = 4-CH_3(3-NO_2)C_6H_3, h R = 2,5-$Br_2C_6H_3$, j R = C_2H_5, k R = 4-$NO_2C_6H_4$; i R—R¹ = $(CH_2)_4$; a $R^1 = C_2H_5$, b-h,j,k R^1 = H

In the case of p-nitrophenyl methyl ketone p-nitrophenylhydrazone (Ik) the reaction stops at the formation of 1,2,3-thiadiazol-3-ine 1-oxide (IIk), which is not converted to a salt even after boiling for many hours in thionyl chloride. Probably the electron-acceptor substituents in the aromatic nucleus of the ketone segment hinder the conversion of the intermediate 1-oxide to a 1,2,3-thiadiazolium salt. In the case of 2,5-dibromophenyl ketone p-nitrophenylhydrazone (Ih), reaction in thionyl chloride without heating gives the respective 1-oxide (IIh), which is converted to salt (IIIh) when boiled in thionyl chloride. Increasing the donor capability of substituent R accelerates cyclization and salt formation, so that in the case of hydrazones Ii,j the reactions proceed without heating.

In the IR spectra of the 1,2,3-thiadiazolium salts the NO_2 bands are very strong. Although it is known that 4-aryl-1,2,3-thiadiazoles have characteristic bands in the form of a doublet at 1470-1480 cm^{-1}, assigned to the vibrations of the five-membered heterocyclic ring [3], in this case they are overlapped by the nitro absorption. The IR spectra of 1,2,3-thiadiazol-3-ine 1-oxides (IIh, k) lack NH bands; this repudiates the 1,2,3-thiadiazol-4-ine structure assigned by Hurd and Mori [1] to the products of the reaction of ketone acylhydrazones and thionyl chloride. The intense C=N band at 1670-1660 cm^{-1} confirms the structure of 1,2,3-thiadiazol-3-ine 1-oxide.

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