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NEW ROUTES FOR THE SYNTHESIS OF 2,5-DISUBSTITUTED 4-FORMYLTHIAZOLES

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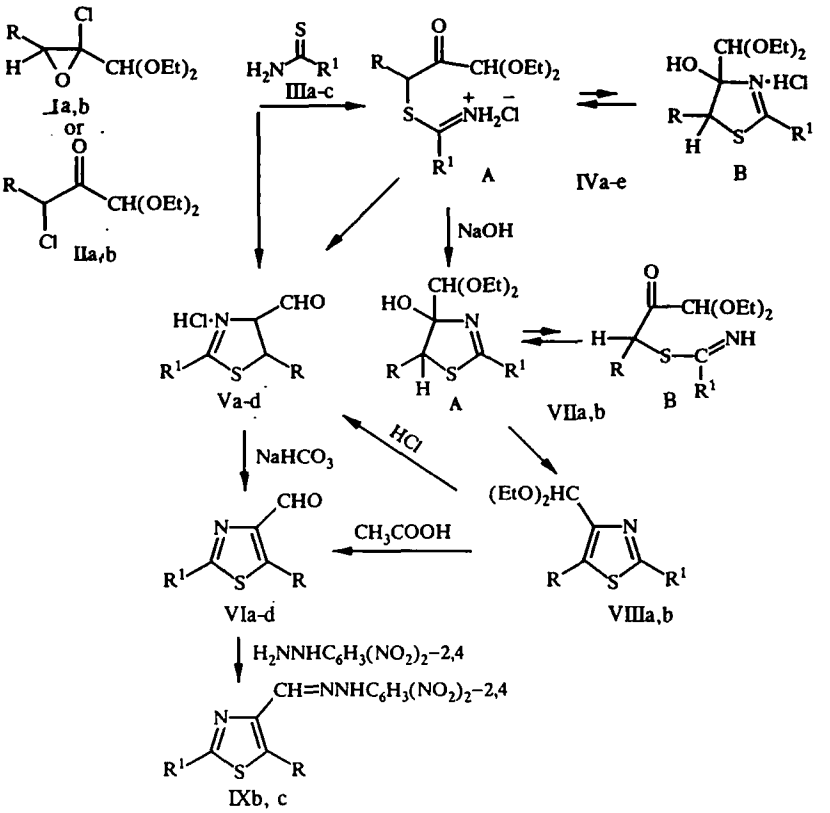
New 2,5-disubstituted 4-formylthiazoles have been obtained by the reaction of acetal-containing α-chloroxiranes or their rearrangement products, chloroketones, with thioamides and N-allylurea.

Previously we synthesized acetal-containing α-chloroxiranes I and suggested that these compounds and their rearrangement products, chloroketones II, might be useful synthons to construct various formyl-substituted heterocycles and their derivatives [1]. In this paper we show that reaction of compounds I and II with thioamides (IIIa and b) and N-allylthiourea (IIIc) occur in different ways, depending on the solvent and the temperature.



I, II a R = Me, b R = Ph; III a R^1 = Me, b R^1 = Ph, c R^1 = $NHCH_2CH{=}CH_2$; IV a R = Me, R^1 = Me, b R = Me, R^1 = $NHCH_2CH{=}CH_2$, c R = Ph, R^1 = Me, d R = Ph, R^1 = Ph, e R = Ph, R^1 = $NHCH_2CH{=}CH_2$; V, VI, IX a R = Me, R^1 = Me, b R = Ph, R^1 = Me, c R = Ph, d R = Ph, R^1 = $NHCH_2CH{=}CH_2$; VII, VIII a R = Ph, R^1 = Me, b R = Ph, R^1 = $NHCH_2CH{=}CH_2$

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TABLE 1. Characteristics of the Synthesized Compounds

Compound	Molecular formula	Found, % / Calculated, %		mp, °C	^{1}H NMR Spectra,* ppm (DMSO-D_6)	IR Spectra, cm^{-1}	Yield, %
		N	Cl				
1	2	3	4	5	6	7	8
IVa	$C_{10}H_{20}NO_3SCl$	5,45 / 5,19	13,75 / 13,17	127...130	1,125 (6H, t, $2CH_3$); 1,5 (3H,d, CH_3); 2,65 (3H, s, CH_3); 3,75 (4H, q, $2OCH_2$); 4,45 (1H,q, CH); 4,9 (1H,s, CH); 13 (2H, br. p NH_2^+)	1540 (C=N) 1670 (C=O) 2850...2970 (NH_2^+)	65
IVb	$C_{12}H_{25}N_2O_3SCl$	9,01 / 8,96	11,75 / 11,36	121...123	1,12 (6H,m, $2CH_3$); 1,55 (3H,d, CH_3); 3,7 (4H,m, $2OCH_2$); 3,85 (2H, m, CH_2); 4,53 (1H,q, CH); 4,95 (1H, s, CH); 5,3 (2H,m, CH_2); 5,85 (1H,m, CH); 10,5 (1H,br. p.NH); 10,95 (2H, br. p.NH_2^+)	—	65
IVc *	$C_{15}H_{22}NO_3SCl$	4,50 / 4,21	11,20 / 10,71	156...158	1,175 (6H,m, $2CH_3$); 2,3 (3H, s, CH_3); 3,675 (4H,m, $2OCH_2$); 5,0 (1H, s, CH); 5,67 (1H, s, CH); 7,37 (3H, m, Ph); 7,5 (2H, br. p NH_2^+); 7,75 (2H,m, Ph)	1619 (C=N) 1765 (C=O) 2850...2965 (NH_2^+)	75
IVd	$C_{20}H_{24}NO_3SCl$	3,86 / 3,55	10,11 / 9,02	167...169	1,075 (6H,m, $2CH_3$); 3,725 (4H, $2OCH_2$); 5,375 (1H, s, CH); 5,75 (1H, s, CH); 7,375 (3H,m, Ph); 7,625 (4H, Ph); 8,3 (3H, m, Ph)	1480 (C=N) 1610 (C=O) 2860...2965 (NH_2^+)	75
IVe	$C_{17}H_{25}N_2O_3SCl$	13,15 / 12,65	10,31 / 9,98	138...140	1,1 (6H,m, $2CH_3$); 3,6 (4H,m, $2OCH_2$); 3,85 (2H,m, CH_2); 4,65 (1H,s, CH); 5,3 (2H,m, CH_2); 5,45 (1H, s, CH); 7,3 (3H,m, Ph); 7,5 (2H, m, Ph); 10,45 (1H, br. p NH); 10,9 (2H, br.s, NH_2^+)	1172 (C–N) 1563 (C=N) 1650 (C=O) 2865...2970 (NH_2^+) 3110...3200 (NH)	70
Va	C_6H_8NOSCl	7,23 / 7,89	19,73 / 20,00	135...139	1,5 (3H, s, CH_3); 2,8 (3H, s, CH_3); 9,85 (1H, s, CHO)	—	55
Vb	$C_{11}H_{10}NOSCl$	5,97 / 5,80	14,95 / 14,80	163...165	2,75 (3H, s, CH_3); 7,45 (5H, s, Ph); 7,75 (1H, br. p NH^+); 9,95 (1H, s, CHO)	1598 (C=N) 1700 (CHO) 2875 (NH^+)	60
Vc	$C_{16}H_{12}NOSCl$	4,75 / 4,64	11,96 / 11,77	171...174	7,50 (8H,m, Ph); 8,63 (2H,m, Ph); 10,1 (1H, s, CHO)	—	70

TABLE 1 (continued)

1	2	3	4	5	6	7	8
Vd	$C_{13}H_{13}N_2OSCl$	10,15 / 9,98	13,07 / 12,65	140...142	4,10 (2H, m, CH_2); 5,37 (2H, m, CH_2); 5,92 (1H, m, CH); 7,56 (3H, m, Ph); 7,67 (2H, m, Ph); 8,9 (1H, br. p NH); 9,65 (1H, s, CHO)	1590 (C=N) 1686 (CHO) 2890 (NH^+) 3115 (NH)	75
VIa*†	C_6H_7NOS	9,74 / 9,93	–	130...133	1,53 (3H, s, CH_3); 2,85 (3H, s, CH_3); 9,8 (1H, s, CHO)	–	50
VIb	$C_{11}H_9NOS$	6,85 / 6,90	–	150...152	2,76 (3H, s, CH_3); 7,52 (5H, m, Ph); 9,75 (1H, s, CHO)	1580 (C=N) 1690 (CHO)	63
VIc	$C_{16}H_{11}NOS$	5,16 / 5,28	–	163...165	7,51 (8H, m, Ph); 8,1 (2H, m, Ph); 9,95 (1H, s, CHO)	1590 (C=N) 1693 (C=O)	71
VId	$C_{13}H_{12}N_2OS$	11,53 / 11,48	–	155...157	4,0 (2H, m, CH_2); 5,25 (2H, m, CH_2); 6,0 (1H, m, CH); 7,5 (5H, s, Ph); 8,1 (1H, br. p.NH); 9,61 (1H, s, CHO)	1540 (C=N) 1683 (C=O) 3110 (NH)	50
VIIa	$C_{15}H_{21}NO_3S$	5,03 / 4,74	–	131...133	1,17 (6H, m, $2CH_3$); 2,3 (3H, d, CH_3); 3,67 (4H, m, $2OCH_2$); 4,6 (1H, d, CH); 5,375 (1H, d, CH); 7,425 (3H, m, Ph); 7,55 (2H, m, Ph)	1630 (C=N) 3410 (OH)	50
VIIb	$C_{17}H_{24}N_2O_3S$	10,10 / 9,33	–	115...118	1,15 (6H, t, $2CH_3$); 3,575 (4H, m, $2OCH_2$); 3,95 (2H, m, CH_2); 5,225 (1H, s, CH); 5,3 (2H, m, CH_2); 5,8 (1H, m, CH); 7,375 (5H, m, Ph); 7,95 (1H, br.s , NH)	–	55
VIIIa	$C_{15}H_{19}NO_2S$	5,24 / 5,02	–	–	1,17 (6H, m, $2CH_3$); 2,37 (3H, s, CH_3); 3,75 (4H, m, $2OCH_2$); 5,47 (1H, s, CH); 7,49 (5H, m, Ph)	–	50
VIIIb	$C_{17}H_{22}N_2O_2S$	8,91 / 8,80	–	128...130	1,15 (3H, m, CH_3); 3,61 (4H, m, $2OCH_2$); 3,79 (2H, m, CH_2); 5,27 (1H, s, CH); 5,312 (2H, m, CH_2); 6,01 (1H, m, CH); 7,375 (5H, m, Ph); 8,15 (1H, br. p NH)	1583 (C=N) 3120...3200 (N–H)	50
IXc	$C_{22}H_{16}N_5O_4S$	15,51 / 15,7	–	169...171	7,61 (5H, m, Ph); 7,85 (1H, s, Ar); 8,13 (5H, m, Ph); 8,63 (1H, m, Ar); 8,79 (1H, s, CH=N); 8,95 (1H, d, Ar); 11,76 (1H, br. p.NH)	1585 (C=N) 3120...3185 (NH)	76
X	$C_{19}H_{17}N_6O_4SCl$	18,01 / 18,24	7,03 / 7,70	162...164	4,075 (2H, m, CH_2); 5,55 (2H, m, CH_2); 5,95 (1H, m, CH); 7,575 (5H, m, Ph); 7,95 (1H, s, H^3); 8,63 (1H, m, H^2); 8,85 (1H, s, CH=N); 9,125 (1H, d, H^1); 10,65 (1H, br. p NH); 11,5 (1H, s, N–NH)	1465...1480 (C=N) 2860...2895 (NH_2^+) 3250 (NH)	70

*^{1}H NMR spectra of compounds IVc and Vb were recorded in $CDCl_2$.

† ^{1}H NMR spectra of compounds VIa-d, VIIa and VIIb were recorded in $CO(CD_3)_2$.

TABLE 2. ^{13}C NMR Spectra of Compounds IV-VII in DMSO-D_6

Compound	Chemical shifts, ppm
IVc	15,01 q ($\underline{C}H_3CH_2$); 17,96 q (CH_3); 55,27 d ($\underline{C}H$—Ph); 55,76 t (OCH_2); 102,57 d (CH); 128,4, 128,6, 128,71, 129,36 (Ph); 164,93 s (C=N); 180,0 d (HC=O)
IVe	14,3 q ($\underline{C}H_3CH_2$); 47,9 d ($\underline{C}H$—Ph); 48,1 t (CH_2—N); 57,6 t (OCH_2); 90,7 d (CH); 119 t (CH_2=); 128,1, 128,53, 128,9, 129,54 (Ph); 138 d (CH=); 168 s (C=N); 181 s (CHO)
Va	19,0 q (CH_3); 130,1, 130,5, 130,9, 131,5 (Ph); 149,3 s ($C_{(5)}$); 153,2 s ($C_{(4)}$); 167,7 s ($C_{(2)}$); 184,9 d (CHO)
Vd	49,4 t (CH_2—N); 118 t (CH_2=); 130,5, 130,7, 130,9, 131,4 (Ph); 133 d (CH=); 136,1 s ($C_{(5)}$); 147,3 s ($C_{(4)}$); 171,1 s ($C_{(2)}$); 185 d (CHO)
VId	46,0 t (CH_2—N); 116 t (CH_2=); 128,4, 128,63, 128,8, 129,35 (Ph); 134 d (CH=); 141 s ($C_{(5)}$); 144 s ($C_{(4)}$); 166 s ($C_{(2)}$); 182 d (CHO)
VIIa	15,5 q ($\underline{C}H_3CH_2$); 20,54 q (CH_3); 57,64 d ($C_{(5)}$); 64,71 t (OCH_2); 105,57 d (4-CH); 108,53 s ($C_{(4)}$); 127,1, 127,8, 130,6, 137,1 (Ph); 166,7 s ($C_{(2)}$)

For example, when the reaction was carried out in ether at room temperature only the first step of the Hantzsch reaction [2] occurred, to give in high yield (75-90%) the S-alkyl polyfunctional compounds IVa-e, which exist in the acyclic form (Tables 1 and 2). The IR spectra of compounds IVa-c in the solid state contain the characteristic intense band of the C=O group at 1695 cm^{-1} together with $C=NH_2+$ absorption around 2965 cm^{-1}, while no absorption for the OH group was observed. The ^1H NMR spectra of compounds IVa-d contain, among others, signals for the methine group of the acetal unit in the range 5.0-5.4 ppm, and of 5-H at 5.4-5.7 ppm. The presence of a signal in the range 180-185 ppm, characteristic for a carbonyl carbon, in the ^{13}C NMR spectrum of compound IV confirms the existence of the acetal in the form of the acyclic tautomer A.

In polar solvents (acetonitrile, ethyl acetate) and at a temperature of 60-80°C, the reaction of chloroxiranes and chloroketones with nucleophiles leads directly to the formation of the hydrochlorides of substituted 4-formylthiazoles V in high yield. Compounds IV were also converted into the aldehydes V under these conditions. The presence of the aldehyde group in these compounds was confirmed by an intense absorption band at 1685-1700 cm^{-1}, characteristic of a conjugated carbonyl group, in the IR spectra of the thiazoles V. The aldehydic proton appears as a singlet in the 9.65-9.95 ppm range in the ^1H NMR spectra of compounds V. The signal of the aldehydic carbon atom is found in the 180-185 ppm region (J_{CH} 170 Hz) in the ^{13}C NMR spectra of the thiazolecarbaldehydes V.

Evidently the formation of the aldehydes V occurs via a series of consecutive conversions: dehydration and conversion of the acetal into an aldehyde. We have confirmed each of these stages experimentally. For example, reaction of compound IV with an equimolar amount of sodium hydroxide gave a stable acetal VII which exists in the cyclic form both in the crystalline state and in solution. In the IR spectrum of VII in the solid state there is no absorption in the 1675 cm^{-1} region, characteristic of a carbonyl group, and there are broad bands at 3340 cm^{-1} characteristic of a hydroxyl group. In the ^{13}C NMR spectra of solutions of these compounds there is no signal ascribable to a carbonyl carbon atom, whereas there is a signal of the hemiaminal carbon $C_{(4)}$. A characteristic peculiarity of both the ^1H and ^{13}C NMR spectra are the doubled signals corresponding to the ethoxy groups of the acetal.

Treatment of compounds IV with two moles of sodium hydroxide or treatment of the bases VII with two equivalents of alkali in ether gave the thiazolidine acetals VIII, the structures of which were confirmed by ^1H and ^{13}C NMR and IR spectroscopy and also by conversion to the thiazolecarbaldehydes V. Treatment of the acetals VIII with hydrochloric acid gave the aldehyde Va, the physical constants of which corresponded with the product of the conversion of IVa in polar solvents, which confirms the proposed scheme. It should be noted that aldehydes rather than acetals are used in many cases of syntheses designed for selective reactions. From this point of view, the acetals of thiazole-4-carbaldehydes are of considerable interest for preparative syntheses. Treatment of the hydrochlorides of thiazoles V with sodium hydrogen carbonate solution gave the corresponding formylthiazoles VI which can also be prepared by treatment of acetals VIII with acetic acid. The structures of the thiazolealdehydes VI, which are stable crystalline substances, were confirmed by ^1H and ^{13}C NMR and IR spectroscopy and elemental analysis (Tables 1 and 2). They were also characterized as hydrazones IX b and c.

In conclusion, it should be noted that the proposed new methods for the synthesis of 2,5-substituted 4-formylthiazoles differ significantly from the known methods [3-5] since in these reactions the formation of the thiazole ring and the formation of the aldehyde group occur in a single step.

EXPERIMENTAL

IR spectra of Nujol mulls were recorded with a UR-20 spectrometer. ^1H and ^{13}C NMR spectra were recorded with a Tesla BW-567 (100 MHz) spectrometer with HMDS as internal standard. Physicochemical characteristics of the compounds synthesized are given in Tables 1 and 2.

S-2-Oxo-1-methyl-3,3-diethoxypropylimidothionate Hydrochloride (IVa). A. A solution of α-chloroketone IIa (5.79 g, 29.6 mmol) in chloroform (10 cm^3) was added at room temperature to a mixture of thioacetamide (2.2 g, 29.6 mmol) in chloroform (50 cm^3). The reaction mixture was stirred under reflux for 5 h. The precipitated crystals were filtered off and recrystallized from acetone.

Compound IVb was obtained analogously.

Compounds IVc-e were obtained similarly but with ether as the solvent.

B. Compounds IVa-d were obtained by the same method starting from the corresponding chloroxiranes and thioamides. The physicochemical characteristics of compounds made by methods A and B were identical.

2,5-Dimethyl-4-formylthiazole Hydrochloride (Va). A. α-Chloroketone (IIa) (3.81 g, 19.5 mmol) in acetonitrile (10 cm^3) was added at room temperature to a mixture of thioacetamide (1.46 g, 19.5 mmol) in acetonitrile (45 cm^3). The mixture was boiled for 10 h, and the precipitate was filtered off and washed with acetone.

The formylthiazoles Vb-d were prepared analogously.

B. A mixture of compound IVa (2 g, 5.37 mmol) and ethyl acetate (30 cm^3) was boiled for 10 h. The crystals were filtered off and washed with acetone.

Compounds Vb-d were made analogously.

C. A mixture of compound VIIIa (1.5 g, 5.4 mmol) and 10% hydrochloric acid (20 cm^3) was stirred at room temperature for 3 h. The mixture was extracted twice with 20 cm^3 amounts of chloroform and the extract was dried over $MgSO_4$. After evaporation of the solvent, the crystals of Va were filtered off and washed with acetone.

The formylthiazoles Va-d made by methods A-C had identical physicochemical characteristics.

2-Methyl-4-oxo-5-phenyl-4,5-dihydrothiazol-4-carbaldehyde Diethyl Acetal (VIIa). Sodium hydroxide (0.18 g, 4.52 mmol) was added to a mixture of compound IVa (1.5 g, 4.52 mmol) and ether (25 cm^3) at −5°C. The reaction mixture was stirred with cooling for 2 h and then at room temperature for 1 h. The precipitate was filtered off and the filtrate was evaporated in vacuum. The crystals obtained were filtered off and washed with cold ether.

Compound VIIb was made similarly.

2-Methyl-5-phenylthiazol-4-carbaldehyde Diethyl Acetal (VIIIa). Sodium hydroxide (0.4 g, 8.02 mmol) was added to a mixture of compound IVa (1.5 g, 4.01 mmol) in ether (30 cm^3) cooled with cold water. The reaction mixture was stirred with cooling for 1 h and then at room temperature for 4 h. The precipitate was filtered off and the filtrate was evaporated in vacuum. The yellow crystals were filtered off and washed with a small amount of cold ether.

Thiazole VIIIb was made analogously.

2-Methyl-4-formyl-5-methylthiazole (VIa). A. Compound VIIIa (1.5 g, 5.4 mmol) was boiled for 5 h in a mixture of methylene chloride (15 cm^3) and acetic acid (15 cm^3). The reaction mixture was cooled, and the crystals formed were filtered off and washed with cold acetone.

B. A mixture of compound Va (1.5 g, 6.26 mmol) and 5% $NaHCO_3$ solution (30 cm^3) was boiled for 5 h and then extracted with chloroform. The extract was dried over magnesium sulfate, the chloroform evaporated in vacuum, and the crystals formed washed with cold acetone.

Compounds VIb-d were synthesized analogously from the corresponding thiazoles V. They all had physicochemical characteristics identical to compounds made by method A.

2,4-Dinitrophenylhydrazone of 2,5-Diphenylthiazol-4-carbaldehyde (IXc). Aldehyde VIc (1.5 g, 4.95 mmol) was added at 60°C to a mixture of 2,4-dinitrophenylhydrazine (0.98 g, 4.95 mmol) and ethyl acetate (20 cm^3). The reaction mixture was kept at room temperature for 1 h and the orange crystals of IXc were filtered off and washed with ethyl acetate.

Hydrochloride of 2-Methyl-5-phenylthiazol-4-carbaldehyde 2,4-Dinitrophenylhydrazone (IXb). Compound Vb (1.5 g, 5.35 mmol) was added to a mixture of 2,4-dinitrophenylhydrazine (1.06 g, 5.35 mmol) in ethyl acetate (20 cm^3). The mixture was stirred for 30 min at 60°C and then at room temperature for 3 h. The orange crystals formed were filtered off and washed with ethyl acetate.

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