SYNTHESIS OF SUBSTITUTED THIOPHENES AND THIAZOLIDINES FROM 1-AMINO-2-BENZOYL-2-(1-PYRIDINIO)ETHYLENE-1-THIOLATES

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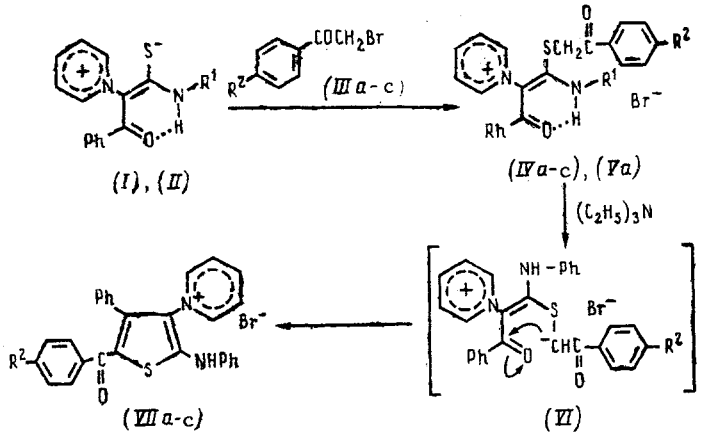
It was found that alkylation of Z-isomers of 1-amino-2-benzoyl-2-(1-pyridinio)-ethylene-1-thiolate with phenacyl bromides proceeds regioselectively with formation of Z-isomers of bromides of 1-amino-2-benzoyl-2-(1-pyridinio)-1-phenacylthioethylenes, which are used in the synthesis of not easily accessible thiophenes and thiazolidines.

In an earlier publication [1] we established that reaction of pyridinium ylides formed from 1-phenacylpyridinium salts with isothiocyanates proceeds stereoselectively with formation of substituted Z-isomers of 1-amino-2-benzoyl-2-(1-pyridinio)ethylene-1-thiolates. According to x-ray structural analysis, the sulfur atom in the molecules of substituted ethylene-1-thiolates is formally negatively charged. In this work we have studied the regio- and stereodirectivity of the reaction of Z-isomers of ethylene-1-thiolates with electrophilic reagents and we have shown the possibility of synthesizing not easily accessible substituted thiophenes and thiazoles.

Betaines (I) and (II) are regioselectively alkylated at the sulfur atom by compounds (III) in methanol solution with formation of bromides of 1-amino-2-benzoyl-2-(1-pyridinio)-1-phenacylthioethylenes (IV) and (V) (Tables 1 and 2). A similar regioselectivity was found earlier in alkylation reactions with alkyl halides of salts of 1,4-dihydropyridine-2-thiolates, in which the sulfur atom is also formally negatively charged [2] (Scheme 1).

Scheme 1



R^1 = Ph (I), (IV); $CH_2CH{=}CH_2$ (II), (V); (III)–(VII): R^2 = H (a), Cl (b), Br (c).

The structures of compounds (IV) and (V) were confirmed by spectral data. IR spectra are characterized by absorption bands of the CO and NH groups in the regions 1655-1658, 1677-1684, and 1628-1632, 3408-3438 cm^{-1}, respectively. In PMR spectra of salts (IV) and (V), in addition to characteristic signals of Py^+, CH_2, and Ph groups, a signal of an NH

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TABLE 1. Characteristics of the Prepared Compounds

Compound	Yield, %	Mp, °C	Empirical formula	Found / Calculated, %		
				C	H	N
(IVa)	68	208–209	$C_{28}H_{23}BrN_2O_2S$	63,31 / 63,28	4,27 / 4,36	5,19 / 5,27
(IVb)	59	177–178	$C_{28}H_{22}BrClN_2O_2S$	59,54 / 59,43	3,85 / 3,92	4,83 / 4,95
(IVc)	88	182–183	$C_{28}H_{22}Br_2N_2O_2S$	55,25 / 55,10	3,51 / 3,63	4,48 / 4,59
(Va)	64	233–235	$C_{25}H_{23}BrN_2O_2S$	60,53 / 60,61	4,63 / 4,68	5,72 / 5,65
(VIIa)	90	238–240	$C_{28}H_{21}BrN_2OS$	65,39 / 65,50	4,27 / 4,12	5,53 / 5,46
(VIIb)	80	142–144	$C_{28}H_{20}BrClN_2OS$	61,47 / 61,38	3,51 / 3,68	5,29 / 5,11
(VIIc)	89	145–146	$C_{28}H_{20}Br_2N_2OS$	56,62 / 56,78	3,52 / 3,40	4,84 / 4,73
(X)	83	225–226	$C_{17}H_{16}Br_2N_2OS$	44,62 / 44,76	3,41 / 3,54	6,29 / 6,14
(XIA)	82	211–212	$C_{18}H_{18}Br_2N_2OS$	45,81 / 45,98	3,74 / 3,86	6,20 / 5,96
(XII)	81	94–95	$C_{17}H_{16}BrClN_2O_3S$	42,83 / 42,92	3,47 / 3,39	5,78 / 5,89

TABLE 2. Spectral Characteristics of Compounds (IV)-(VII)

Compound	IR spectrum (ν, cm^{-1})		PMR spectrum (δ, ppm, ^3J, Hz)					
			protons of Py^+			NH	Ph(m)	CH_2(S)
	NH	CO	H^2, H^6(d	H^4(t)	H^3, H^5(t)			
(IVa)	1632 3433	1655 1670	9,28 J=5,3	8,64 J=8,5	8,11	8,01	7,04–7,72	6,75
(IVb)	1630 3418	1658 1677	9,28 J=5,2	8,66 J=8,1	8,14	8,02	6,95–7,64	**
(IVc)	1628 3408	1656 1678	9,28 J=5,1	8,64 J=8,2	8,16	8,02	6,97–7,53	**
(Va)	1628 3438	1658 1684	9,08* J=5,2	8,63 J=8,7	8,15	8,32	7,00–7,38	6,90
(VIIa)	1600 3410	1628	9,16 J=5,3	8,66 J=8,6	8,18	9,85	6,97–7,39	
(VIIb)	1607 3407	1629	9,11 J=5,2	8,63 J=8,4	8,18	9,88	6,98–7,37	
(VIIc)	1610 3412	1630	9,17 J=5,2	8,68 J=8,5	8,20	9,97	6,95–7,52	

*Signals of the protons of the allyl moiety, δ (ppm): 3.92 m (2H, CH_2), 5.27 d.d (1H, $CH_2{=}C_{cis}$, ^3J = 9.8 Hz), 5.40 d.d (1H, $CH_2{=}C_{trans}$, ^3J = 15.1 Hz), 5.88 m (1H, $CH{=}CH_2$).
**Superimposed by signals of the phenyl protons.

group is present in the region 8.01-8.32 ppm (Table 2). In comparison with betaines (I) and (II) the NH signal of salts (IV) and (V) is shifted to higher field (Δδ = 4.08-4.21 ppm). This is evidence of a decrease of the electronic conjugation in the S–C=C–C=O moiety of salts (IV) and (V), which, probably, leads to an increase in the covalency of the N–H bond in (IV) and (V). On the other hand, the stereoshielding effect of the phenacyl group bonded to the sulfur atom influences the high-field shift of the NH signal. It is known that as a result of the formation of intramolecular hydrogen bonds (IMHB) N–H...O=C the frequency of deformation vibrations of the N–H bond in the IR spectrum is increased [3]. For compounds (IV) and (V) it is found in the region 1628-1630 cm^{-1} (Table 2) and is com-

TABLE 3. Spectral Characteristics of Compounds (X)-(XII)

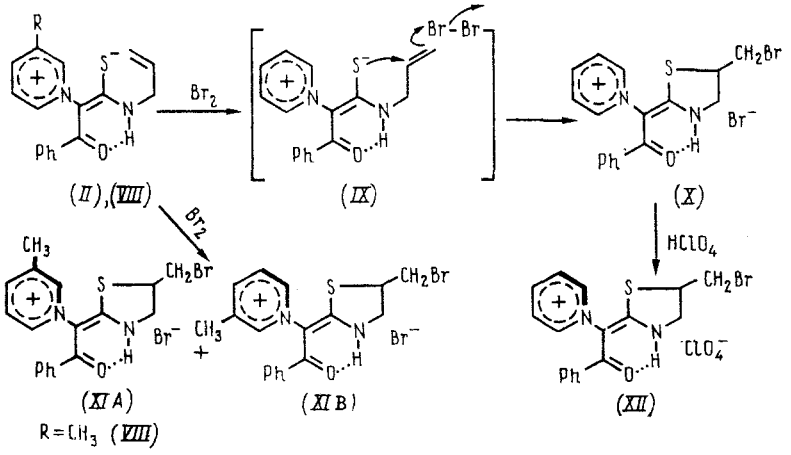
Compound	IR spectrum (ν, cm^{-1})		PMR spectrum (δ, ppm, ^3J, Hz)							
			protons of Py$^+$			NH (s)	Ph (m)	SCH (m)	CH_2Br	NCH_2
	NH	CO	H^2, H^6 (d)	H^4 (t)	H^3, H^5					
(X)	1630 3400	1637	9,00 9,27 J=5,2	8,62 J=8,2	8,05 t 8,16 t	10,49	7,03–7,34	4,15	3,80	3,90
(XIA)	1628 3397	1632	8,78 d J=5,3 8,97 d 9,03 s 9,19 s	8,44 d J=8,4	7,98 t 8,07 t	10,46	7,05–7,32	4,15	3,78*	3,85
(XII)	1627 3410	1630	8,97 9,22 J=5,3	8,61 J=8,4	8,14 m	10,50	7,04–7,23	4,18	3,54	3,80

*Chemical shift of the CH_3 protons (δ, ppm): 2.24 s and 2.32 s (3H, CH_3).

parable with the values of the same in spectra of 1-amino-2-benzoyl-2-(1-pyridinio)ethylene-1-thiolates (I) and (II) (νNH 1630-1632 cm^{-1}) in the molecules of which a strong IMHB N–H... O=C exists [1]. In contrast to compounds (VII) (Table 2) and 1-amino-2-(1-pyridinio)-2-cyanoethylene-1-thiolates [4], in which there is no IMHB, νNH in the spectra of compounds (II) and (V) is shifted by 30-32 cm^{-1} to the high-frequency region of the spectrum. Consequently, on conversion of compounds (I) and (II) to compounds (IV) and (V) the IMHB is preserved, which in the reaction probably adds a certain contribution to preservation of the Z-configuration that is characteristic of the starting compounds.

When heated in ethanol in the presence of Et_3N, compounds (IV) are cyclized in high yields to bromides of substituted 3-(1-pyridinio)thiophenes (Tables 1 and 2). When heated in the presence of Et_3N, compounds (IV) and (V) are isomerized to E-isomers (VI). Cis-position of the reaction centers in E-isomers (VI) creates the conditions for intramolecular condensation to substituted thiophenes (VII). Structures of compounds (VII) were confirmed by spectroscopic investigations (Table 2).

Scheme 2



Reaction of compounds (II) and (VIII) with bromine proceeds regioselectively with closure of only the thiazolidine ring and formation of salts (X) and (XI). Salt (X) gives an anion exchange reaction when it is heated with perchloric acid in acetic acid with formation of perchlorate (XII).

The regiodirectivity of these reactions has been confirmed by IR and PMR spectroscopy of compounds (X)-(XII). In the PMR spectra of compounds (X)-(XII) the signals of the pro-

tons of the NCH_2, CH_2Br, and SCH groups appear as multiplets in the regions 3.80-3.90, 3.54-3.80, and 4.14-4.18 ppm, respectively (Table 3) (Scheme 2).

The chemical shifts (CS) mentioned and the multiplicity of the protons are characteristic of hydrogenated salts of thiazolo[3,2-a]pyridine, which have an identical bromomethylthiazolidine moiety [5-7]. As a consequence of the preservation of the IMHB, the nature of the absorption CO and NH groups in the IR spectra is identical with the absorption of these groups in compounds (IV) and (V) (Table 2). Similar to salts (IV) and (V), in the PMR spectrum of compounds (X)-(XII) the proton signal of the NH group is shifted to higher field ($\Delta\delta$ = 2.06-2.10 ppm) as compared with betaines (I), (II), and (VIII) [1]. Thus, the electrophilic heterocyclization reaction of betaines (II) and (VIII) proceeds with preservation of the Z-configuration. Obviously, the regioselectivity of the electrophilic heterocyclization reaction is governed by synchronous action on the π-bond of the allyl fragment of donor (thiolate sulfur atom) and acceptor (bromine molecule) in transition state (IX). A similar interaction of the p-electrons of the endocyclic nitrogen atom with the π-bond of the allyl fragment was found in the series of 2-allyl(cyclohexenyl)thiopyridines by x-ray structural investigations [5]. Subsequent ruptures and formations of new bonds in transition state (IX) obviously proceed synchronously, just as in electrophilic heterocyclization reactions studied earlier [5-9].

In contrast to betaines (II) and (VIII), in salts (X)-(XII) α- and β-protons of the pyridinium ring are differently shielded sterically by the nonplanar part of the thiazolidine ring. The nonequivalent stereoshielding leads to double signals of the α- and β-protons of the pyridinium ring in the PMR spectra of compounds (X) and (XII). Half of the α- and β-protons of the pyridinium are under the stereoshielding effect (XI, Scheme 2, bold lines) of the thiazolidine moiety and their signals are shifted to high field, the other part of the protons under a deshielding effect and their signals are shifted to the lower field of the spectrum. Electrophilic heterocyclization of compound (VIII) proceeds with formation of a mixture of invertomers (XIA) and (XIB) in the ratio of 1.6:1 with predominance of stereoshielded invertomer (XIA). In the PMR spectrum of compound (XI) the protons of the methyl group and the α- and β-protons of the picolinium are also doubled (Table 3). Invertomers (XIA) and (XIB) are stable and in DMSO-d_6 solution they do not undergo inversion on heating to 100°C. However, in the PMR spectrum a slight broadening of the α- and β-protons of the picolinium takes place. The doublet signal of the γ-proton remains unchanged. That points to the fact that the picolinium cation performs hindered rotations around the C–N bond. Complete inversion of the picolinium ring is prevented by fixed hydrogen and double bonds with adjacent benzene and thiazolidine substituents.

EXPERIMENTAL

IR spectra were taken on a Perkin-Elmer 577 spectrometer from KBr disks. PMR spectra were recorded on a Bruker WM-250 spectrometer (250 MHz) in DMSO-d_6 relative to TMS.

Bromides of (Z)-1-Amino-2-benzoyl-2-(1-pyridinio)-1-phenacylthioethylenes (IVa-c), (Va). A mixture of 10 mmoles of compound (I) or (II) and 10 mmoles of the appropriate phenacyl bromide (IIIa-c) in 30 ml of methanol is stirred at 20°C for 10-12 h. The solvent is evaporated and the residue is crystallized from nitromethane (Tables 1 and 2).

Bromides of 5-Benzoyl-4-phenyl-2-phenylamino-3-(1-pyridinio)thiophene (VIIIa-c). A solution of 10 mmoles of corresponding salt (IV) and 0.1 ml of Et_3N in 20 ml of ethanol is refluxed for 10-15 min. The solvent is evaporated and the residue is crystallized from isopropanol (Tables 1 and 2).

Bromides of 2-[Benzoyl-(1-pyridinio)methylene]-5-bromomethylthiazolidine (X) and 2-[Benzoyl-(3-methyl-1-pyridinio)methylene]-5-bromomethylthiazolidine (XI). To a suspension of 10 mmoles of betaine (II) or (VIII) in 15 ml of chloroform is added dropwise with stirring at 20°C in 5 min a solution of 10 mmoles of bromine in 5 ml of chloroform. The reaction mixture is stirred at 20°C for 5 h, the precipitate is filtered off, washed with chloroform and hexane, and crystallized from isopropanol (Tables 1 and 3).

Perchlorate of 2-[Benzoyl-(1-pyridinio)methylene]-5-bromomethylthiazolidine (XII). A solution of 5 mmoles of salt (X) and 5 ml of 70% perchloric acid in 12 ml of acetic acid is heated to the reflux temperature. The reaction mixture is cooled to 5°C and 20 ml of ether is added. The precipitate is filtered off and crystallized from ethanol (Tables 1 and 3).

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CYCLIZATION REACTIONS OF NITRILES

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The interaction of 2-thienylidene derivatives of malononitrile and cyanothioacetamide with methylene active nitriles gives 2,6-diamino-3,5-dicyano-4-(2-thienyl)-4H-thiopyran which is smoothly recrystallized into 6-amino-3,5-dicyano-4-(2-thienyl)-2(1H)-pyridinethione. The latter is easily alkylated at the sulfur atom by α-halocarbonyl compounds. This reaction was used in the synthesis of 3,6-diamino-4-(2-thienyl)thieno[2,3-b]pyridines.

In a recent review [1] the synthesis and properties of substituted 3-cyano-2(1H)-pyridinethiones, including those obtained from nitriles, are presented. However, there was no mention in this report of thienylidene derivatives of malononitrile, and the report [2] of the isolation of 4,6-diamino-5-(2-thienylidene)-2-thioxo-3-cyano-2,5-dihydropyridine upon reaction of 2-thienylidene derivatives of malononitrile (I) with cyanothioacetamide (II) in boiling ethanol in the presence of catalytic traces of piperidine, is in our opinion erroneous. We have examined various approaches to a synthesis of 2,6-diamino-3,5-dicyano-4-(2-thienyl)-4H-thiopyran and its recyclization to 6-amino-3,5-dicyano-4-(2-thienyl)-2(1H)-pyridinethione.

It was shown that reaction of 2-thienylidene derivatives of malononitrile (I) and cyanothioacetamide (III) with cyanothioacetamide (II) and malononitrile (IV), respectively, in alcohol under the action of organic bases at 20°C leads to formation of 4H-thiopyran (V). Upon heating an isopropanol or ethanol 4H-thiopyran (V) is recyclized into 6-amino-3,5-dicyano-4-(2-thienyl)-2(1H)-pyridinethione (VII), isolated as the 4-methylmorpholinium salt (VI). Thione (VII) was obtained upon acidifying of salt (VI) with dilute hydrochloric acid. Moreover, thione (VII) is formed from compounds (I) and (II), (III), (IV), respectively, in boiling ethanol under the action of catalytic amounts of 4-methylmorpholine. It turned out that synthesis of pyran (V) and thione (VII) can be significantly simplified using 2-thiophenaldehyde and nitriles (II) and (IV) as starting reagents. The structures of isolated thiopyran (V), thione (VII), and salt (VI) were confirmed by their spectral characteristics (see experimental part) and chemical conversions.

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