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ACID CYCLIZATION OF AMINO-SUBSTITUTED HETEROCYCLES. SYNTHESIS OF 1,3-DIOXO-PYRROLO[3,4-*c*]- AND THIENO[3,4-*c*]ISOQUINOLINES AND CINNOLINES

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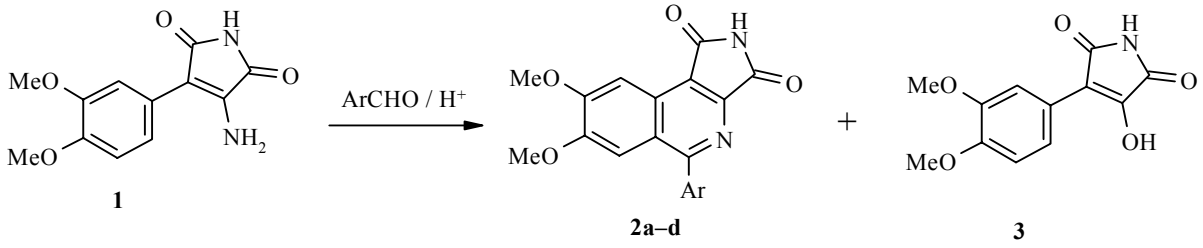
The reaction of 3-amino-4-(3,4-dimethoxyphenyl)maleimide and the methyl esters of 3-amino-4-(3,4-dimethoxyphenyl)-5-R-thiophene-2-carboxylic acids with carbonyl compounds and nitrous acid has been investigated. Dioxopyrrolo[3,4-c]- and thieno[3,4-c]isoquinolines and cinnolines were obtained.

Keywords: aminomaleimide, 3-aminothiophene, carbonyl compounds, cyclization.

We have shown in previous studies that 5-amino-4-arylpyrazoles may readily be converted into pyrazolo[3,4-*c*]isoquinolines on interaction with benzaldehydes and certain other carbonyl compounds under acid catalysis conditions [1, 2]. Possibilities have been investigated in the present study for obtaining polyannelated heterocycles from 4-aryl-substituted 3-aminomaleimides and 3-aminothiophenes.

The formation of imides of isoquinoline-3,4-dicarboxylic acids on acylation of 3-amino-4-(3,4-dimethoxyphenyl)maleimide (**1**) with acyl perchlorates is known [3]. Investigation of the reactions of compound **1** with carbonyl compounds showed that on interaction with benzaldehydes in strong organic acids 5-aryl-7,8-dimethoxy-1,3(2H)-dioxopyrrolo[3,4-*c*]isoquinolines (**2**) may be obtained in 40-60% yield.



1 **2a–d** **3**

2 a Ar = 3,4-$(MeO)_2C_6H_3$, **b** Ar = 2-$MeOC_6H_4$, **c** Ar = 3-ClC_6H_4; **d** Ar = 2-Br-4,5-$(MeO)_2C_6H_2$

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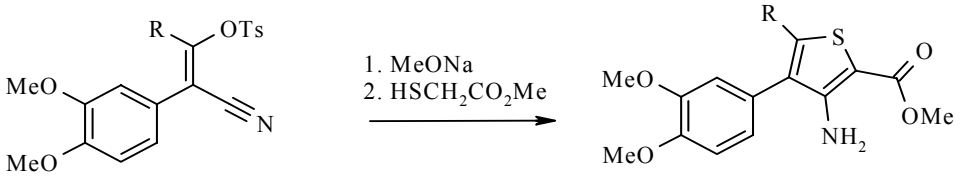
The lower yields of final products in comparison with pyrazoloisoquinolines, are caused by the partial hydrolysis of the initial compound to the corresponding hydroxymaleimide **3** (5-10% yield) with the participation of water eliminated in the course of the reaction [3]. On using aliphatic aldehydes and ketones only the starting materials were isolated from the reaction.

Among heterocyclic structures containing an annelated thiophene ring only single examples of obtaining thieno[*c*]isoquinolines have been reported in the literature. The strategy of their synthesis comprizes interaction of 2-formylaryl borates with 3-amino-2-halothiophenes in the presence of palladium catalysts [4]. The low availability of reactants for assembling the thienoisoquinoline system and the low yields of reaction products did not make this method preparative. We investigated the possibility of obtaining polyannelated heterocycles from derivatives of 3-amino-4-arylthiophene. Methyl esters of 3-amino-4-(3,4-dimethoxyphenyl)-5-R-thiophene-2-carboxylic acids **4a,b** were used as starting materials. These were obtained from tosylates of β-keto nitriles analogous to the procedure of [5].

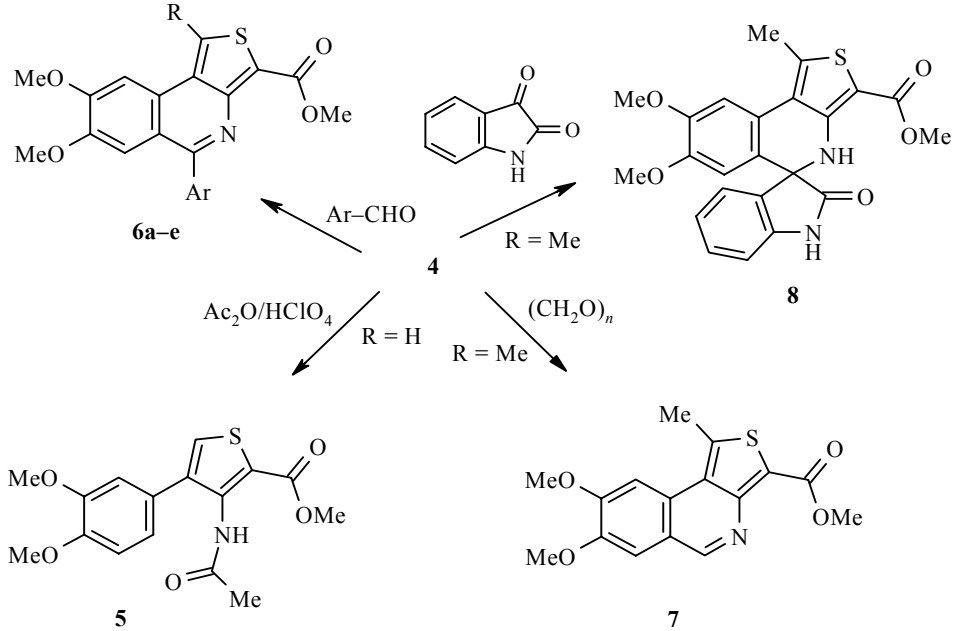


4a,b

4 a R = H, **b** R = Me

Reactions of aminothiophenes **4** with acyl perchlorates (mixtures of carboxylic acid anhydrides with perchloric acid) and various carbonyl compounds have been studied.

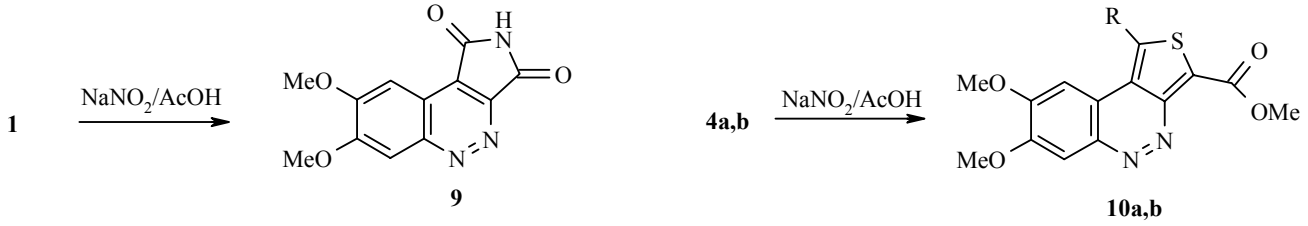
It was established that only acylation of the amino group without cyclization of acylamide **5** occurred on the action of acetyl perchlorate on aminothiophenes **4** in the temperature range 20-100°C. On the other hand heating compounds **4a,b** with various benzaldehydes in trifluoroacetic acid leads to the methyl esters of 1-R-5-aryl-7,8-dimethoxythieno[3,4-*c*]isoquinoline-3-carboxylic acids **6** in 50-75% yield.



6 a R = H, Ar = 4-ClC_6H_4; **b** R = H, Ar = 3-MeO-4-OH-C_6H_3; **c** R = Me, Ar = 4-ClC_6H_4; **d** R = Me, Ar = 3-EtO-4-OH-C_6H_3; **e** R = Me, Ar = 4-$MeOC_6H_4$

Like aminopyrazoles [1], aminothiophenes **4** did not react with acetophenones, aldehydes, and ketones of the aliphatic series with the exception of paraformaldehyde and isatin. In the reaction of compound **4b** with paraformaldehyde the methyl ester of 1-methyl-7,8-dimethoxythieno[3,4-*c*]isoquinoline-3-carboxylic acid (**7**) was obtained, and on interaction with isatin – 3-methoxycarbonyl-7,8-dimethoxy-1-methyl-4,5-dihydrothieno-[3,4-*c*]isoquinoline-5-spiro-3'-(2-oxoindoline) (**8**).

Recently we reported that aryl-substituted 5-aminopyrazoles and isoxazoles are successfully cyclized into derivatives of pyrazolo- and isoxazolo[3,4-*c*]cinnoline by the action of sodium nitrite in glacial acetic acid [6]. Under the same conditions 7,8-dimethoxy-1,3(2H)-dioxopyrrolo[3,4-*c*]cinnoline (**9**) was obtained in high yield from aminomaleimide **1**. Diazotization of aminothiophenes **4a,b** enabled us to obtain derivatives of a new heterocyclic system, thieno[3,4-*c*]cinnoline **10**.



10 a R = H, **b** R = Me

TABLE 1. Physicochemical Characteristics of the Obtained Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
2a	$C_{21}H_{18}N_2O_6$	63.89 / 63.96	4.42 / 4.60	7.05 / 7.10	293-295	68
2b	$C_{20}H_{16}N_2O_5$	65.87 / 65.93	4.32 / 4.43	7.60 / 7.69	287-289	64
2c	$C_{19}H_{13}ClN_2O_4$	61.82 / 61.88	3.40 / 3.55	7.62 / 7.66	294-296	66
2d	$C_{21}H_{17}BrN_2O_6$	53.25 / 53.29	3.35 / 3.62	5.87 / 5.92	288-290	65
4a	$C_{14}H_{17}NO_4S$	57.29 / 57.32	4.90 / 5.15	4.70 / 4.77	141-143	63
4b	$C_{15}H_{19}NO_4S$	58.57 / 58.62	5.20 / 5.57	4.49 / 4.56	151-153	68
5	$C_{16}H_{17}NO_5S$	56.65 / 57.30	4.80 / 5.11	4.12 / 4.18	180-182	50
6a	$C_{21}H_{16}ClNO_4S$	60.89 / 60.94	3.78 / 3.90	3.19 / 3.38	264-266	52
6b	$C_{22}H_{19}NO_6S$	62.05 / 62.11	4.30 / 4.50	3.25 / 3.29	260-262	63
6c	$C_{22}H_{18}ClNO_4S$	61.70 / 61.75	4.00 / 4.24	3.12 / 3.27	250-252	51
6d	$C_{24}H_{23}NO_6S$	63.45 / 63.56	4.90 / 5.11	3.00 / 3.09	257-260	68
6e	$C_{23}H_{21}NO_5S$	65.15 / 65.23	4.85 / 5.00	3.28 / 3.31	237-239	75
7	$C_{16}H_{15}NO_4S$	60.48 / 60.55	4.55 / 4.76	4.35 / 4.41	241-243	90
8	$C_{23}H_{20}N_2O_5S$	63.18 / 63.29	4.52 / 4.62	6.38 / 6.42	262-264	71
9	$C_{12}H_9N_3O_4$	55.51 / 55.60	3.38 / 3.50	16.14 / 16.21	381-383	66
10a	$C_{14}H_{12}N_2O_4S$	55.20 / 55.26	3.75 / 3.97	9.12 / 9.21	240-242	96
10b	$C_{15}H_{14}N_2O_4S$	56.61 / 56.59	4.20 / 4.43	8.74 / 8.80	239-241	94

The investigated directions of cyclization of derivatives of aminomaleimide and of 3-aminothiophene may be a basis of preparative methods for obtaining polyannelated heterocycles, including new heterocyclic systems with fragments of isoquinoline and cinnoline.

TABLE 2. Spectral Characteristics of Compounds

Compound	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, δ, ppm (*J*, Hz)
2a	3200, 1760, 1725, 1685	3.81 (3H, s, CH_3O); 3.83 (3H, s, CH_3O); 4.02 (3H, s, CH_3O); 4.05 (3H, s, CH_3O); 7.10 (1H, s, H arom.); 7.14-7.47 (4H, m, H arom.); 7.91 (1H, s, H arom.); 11.25 (1H, s, NH)
2b	3210, 1760, 1720, 1690	3.70 (3H, s, CH_3O); 3.72 (3H, s, CH_3O); 4.02 (3H, s, CH_3O); 6.95 (1H, s, H arom.); 7.10-7.65 (4H, m, H arom.); 7.98 (1H, s, H arom.); 11.36 (1H, s, NH)
2c	3200, 1760, 1725, 1685	3.85 (3H, s, CH_3O); 4.04 (3H, s, CH_3O); 7.37 (1H, s, H arom.); 7.60-7.75 (4H, m, H arom.); 8.01 (1H, s, H arom.); 11.35 (1H, s, NH)
2d	3205, 1765, 1720, 1695	3.77 (3H, s, CH_3O); 3.80 (3H, s, CH_3O); 3.90 (3H, s, CH_3O); 4.05 (3H, s, CH_3O); 6.95 (1H, s, H arom.); 7 .98 (1H, s, H arom.); 7.15 (1H, s, H arom.); 7.35 (1H, s, H arom.); 11.42 (1H, s, NH)
4a	3460, 3350, 1660	3.75 (3H, s, CH_3O); 3.78 (3H, s, CH_3O); 3.79 (3H, s, CH_3O); 6.30 (2H, s, NH_2); 6.95-7.06 (3H, m, H arom.); 7.61 (1H, s, H arom.)
4b	3450, 3350, 1660	2.23 (3H, s, CH_3); 3.72 (3H, s, CH_3O); 3.76 (3H, s, CH_3O); 3.82 (3H, s, CH_3O); 6.04 (2H, s, NH_2); 6.75-7.10 (3H, m, H arom.)
5	3360, 1750, 1630	1.94 (3H, s, CH_3); 3.75 (3H, s, OCH_3); 3.76 (3H, s, OCH_3); 3.77 (3H, s, OCH_3); 6.98 (1H, s, NH); 7.00 (2H, d, *J* = 8, H arom.); 7.86 (1H, s, H arom.); 9.61 (1H, s, H arom.)
6a	1700, 1610, 1230	3.74 (3H, s, CH_3O); 3.84 (3H, s, CH_3O); 4.03 (3H, s, CH_3O); 7.22 (1H, s, H arom.); 8.06 (1H, s, H arom.); 7.64 (2H, d, *J* = 8, H arom.); 7.77 (2H, d, *J* = 8, H arom.); 9.04 (1H, s, H arom.)
6b	3200, 1700, 1610, 1240	3.78 (3H, s, CH_3O); 3.85 (3H, s, CH_3O); 3.86 (3H, s, CH_3O); 4.04 (3H, s, CH_3O); 6.98 (1H, d, *J* = 8, H arom.); 7.18 (1H, d, *J* = 8, H arom.); 7.35 (1H, s, H arom.); 7.46 (1H, s, H arom.); 8.03 (1H, s, H arom.); 9.00 (1H, s, H arom.); 9.48 (1H, s, OH)
6c	1720, 1610, 1220	3.10 (3H, s, CH_3); 3.75 (3H, s, CH_3O); 3.82 (3H, s, CH_3O); 4.08 (3H, s, CH_3O); 7.30 (1H, s, H arom.); 7.62 (2H, d, *J* = 8.5, H arom.); 7.78 (2H, d, *J* = 8.2, H arom.); 7.90 (1H, s, H arom.)
6d	3350, 1700, 1610, 1220	1.37 (3H, t, *J* = 9, CH_3); 2.98 (3H, s, CH_3); 3.70 (3H, s, CH_3O); 3.81 (3H, s, CH_3O); 4.00 (3H, s, CH_3O); 4.10 (2H, q, *J* = 9, CH_2); 6.95 (1H, d, *J* = 9, H arom.); 7.15 (1H, d, *J* = 8, H arom.); 7.30 (1H, s, H arom.); 7.43 (1H, s, H arom.); 7.75 (1H, s, H arom.)
6e	1700, 1610, 1220	3.05 (3H, s, CH_3); 3.71 (3H, s, CH_3O); 3.77 (3H, s, CH_3O); 3.85 (3H, s, CH_3O); 7.10 (2H, d, *J* = 8.8, H arom.); 7.40 (1H, s, H arom.); 7.72 (2H, d, *J* = 8.5, H arom.); 8.83 (1H, s, H arom.)
7	1700, 1620, 1210	3.10 (3H, s, CH_3); 3.85 (3H, s, CH_3O); 3.94 (3H, s, CH_3O); 4.04 (3H, s, CH_3O); 7.68 (1H, s, H arom.); 7.80 (1H, s, H arom.); 9.05 (1H, s, H arom.)
8	3350, 1730, 1620, 1230	2.75 (3H, s, CH_3); 3.45 (3H, s, CH_3O); 3.68 (3H, s, CH_3O); 3.86 (3H, s, CH_3O); 6.00 (1H, s, NH); 6.93-7.20 (4H, m, H arom.); 7.05 (1H, s, H arom.); 7.34 (1H, s, H arom.); 10.40 (1H, s, NH)
9	3200, 1760, 1730	4.10 (3H, s, OCH_3); 4.17 (3H, s, OCH_3); 7.67 (1H, s, H arom.); 8.05 (1H, s, H arom.); 11.25 (1H, s, NH)
10a	1695, 1620, 1240	3.99 (3H, s, CH_3O); 4.03 (3H, s, CH_3O); 4.05 (3H, s, CH_3O); 7.95 (1H, s, H arom.); 7.98 (1H, s, H arom.); 9.07 (1H, s, H arom.)
10b	1690, 1620, 1230	2.42 (3H, s, H arom.); 3.97 (3H, s, CH_3O); 4.01 (3H, s, CH_3O); 4.03 (3H, s, CH_3O); 7.90 (1H, s, H arom.); 7.95 (1H, s, H arom.)

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian Geminy (200 MHz) spectrometer in DMSO-d_6, internal standard was TMS. Melting points were determined on a Boetius apparatus and are not corrected. The IR spectra were recorded on a Perkin-Elmer 881 spectrometer in nujol. Aminomaleimide **1** was obtained by the method described by us previously in [3]. Analytical characteristics, melting points, and spectral data of the synthesized compounds are given in Tables 1 and 2.

5-Aryl-7,8-dimethoxy-1,3(2H)-dioxopyrrolo[3,4-*c*]isoquinolines 2 and Methyl Esters of 1-R-5-aryl-7,8-dimethoxythieno[3,4-*c*]isoquinoline-3-carboxylic Acids 6 (General Method). An equimolar amount of aldehyde was added with cooling to a solution of maleimide **1** (5 mmol) or aminothiophene **4a,b** (5 mmol) in trifluoroacetic acid (50 ml) and the mixture heated for 7-10 h. The solvent was evaporated in vacuum, and the residue triturated with 5% aqueous ammonia solution. The solid was filtered off, washed with water, dried, and crystallized from ethanol or acetonitrile.

7,8-Dimethoxy-1-methylthieno[3,4-*c*]isoquinoline-3-carboxylic Acid Methyl Ester (7). Paraformaldehyde (0.6 g, 10 mmol) was added with cooling to a solution of aminothiophene **4b** (5 mmol) in trifluoroacetic acid (50 ml) and the mixture heated for 10 h. The solvent was evaporated in vacuum, and the residue neutralized with 5% aqueous ammonia solution. The solid was filtered off, washed with water, dried, and crystallized from acetonitrile.

3-Acetylamino-4-(3,4-dimethoxyphenyl)-5-R-thiophene-2-carboxylic Acid Methyl Ester (5). Aminothiophene **4a** (1 g, 3.4 mmol) was added to a mixture of acetic anhydride (4 ml, 40 mmol) and 70% perchloric acid (0.68 ml, 6.8 mmol). The reaction mixture was heated for 2 h at 90-100^{o}C, then evaporated in vacuum at a temperature not exceeding 50^{o}C. The residue was treated with 5% aqueous ammonia solution, the solid filtered off, washed with water, and crystallized from ethanol.

7,8-Dimethoxy-1,3(2H)-dioxopyrrolo[3,4-*c*]cinnoline (9) and 1-R-7,8-dimethoxythieno[3,4-*c*]cinnoline-3-carboxylic Acid Methyl Ester (10). Sodium nitrite (0.4 g, 6 mmol) was added with stirring to a suspension of aminomaleimide **1** (3 mmol) or aminothiophene **4a,b** (3 mmol) in acetic acid (10 ml). Stirring was continued until precipitation began, and the mixture was left for 2-3 h to complete the reaction. Water (50 ml) was poured onto the reaction mass, the precipitated solid was filtered off, washed with water, and dried.

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