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Synthesis of 5-Amino-4-(4-aryl-2-thiazolyl)-2,3-Dihydro-2-Pyrrolones

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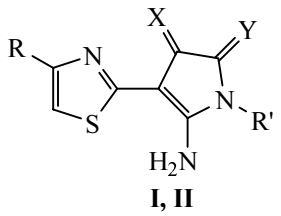
Abstract—A method was developed for preparation of 5-amino-4-(4-aryl-2-thiazolyl)-2,3-dihydro-2-pyrrolones by alkylation of 4-aryl-2-thiazolylacetonitriles by N-substituted chloroacetamides in the presence of K_2CO_3. In 1-(1-naphthyl)-substituted pyrrolones atropoisomerism was observed.

Recently an interest grew to the synthesis of 2-thiazolyl-substituted pyrrols. It is indicative that a half of approximately 20 articles concerning the chemistry of these compounds was published since 2000 [1–9]. This fact is due to discovery of highly efficient inhibitors of some enzymes among the 2-thiazolylpyrrols derivatives [10, 11]. Besides the thiazolyl-substituted pyrrols are important intermediates in the synthesis of antibiotics of the thiostrepton group [3, 12].

The majority of thiazolylpyrroles was obtained by Hantzsch reaction from various thioamides of pyrrole series [1, 3, 4, 9, 10, 13–15]. More seldom the pyrrole ring was built up from an acyclic precursor possessing a thiazole substituent [5–8, 11, 16–19]. Finally, specific approaches to the thiazolylpyrrole synthesis were described involving lithiated thiazole derivatives [2, 20], or recyclization of thiazolyl-substituted isoxazoles [21]. It should be noted that the synthesis of pyrrole derivatives with a thiazole substituent in position *3*(*4*) is considerably less documented [11, 14, 15] than that of their 2(5)-substituted analogs. We recently developed a preparation procedure for 4-(2-thiazolyl)-3-pyrrolones **I** based on the use of 2-thiazolylacetonitriles [6, 7, 18, 19]. In extension of research in this field we attempted a synthesis of isomeric pyrrolones aiming at further comparative study of the chemistry of compounds **I** and **II**.



I, II

I, X = O, Y = H_2; **II**, X = H_2, Y = O.

The reaction of methylene-active nitriles with N-substituted chloroacetamides **III** is known to give rise to 5-amino-2-pyrrolone derivatives [22–29]. Bringing 2-thiazolylacetonitriles **IV** and **V** into this reaction should result in the target thiazolylpyrrolones. However the reaction of nitriles **IV** and **V** with chloroacetamides **III** in anhydrous ethanol in the presence of K_2CO_3 in keeping with the previously described conditions [22–29] was unsuccessful. The reaction mixture suffered strong tarring, and compounds **VI** and **VII** were isolated in yields below 10% or were not isolable at all. The variation of reaction temperature, of character of the base used, and the application of iodide catalysts did not considerably improve the results. However we observed that the 2-propanol added to the reaction mixture reduced the tarring and increased the yield of pyrrolones **VI** and **VII.** Yet in the neat 2-propanol the reaction did not occur apparently due to low solubility of K_2CO_3 in this alcohol. We found experimentally that the best results gave the solvent containing 2-propanol–ethanol mixture, 3 : 2 (by volume). In this mixture tha tarring is minimal, and the yield of compounds **VI** and **VII** attains 50–60%.

The structure of prepared aminopyrrolones **VI** and **VII** was confirmed by IR and ^{1}H NMR spectra. The absorption band of the nitrile group lacked in the IR spectra of compounds **VI** and **VII** unambiguously indicating that it was consumed in building up the pyrrole ring. A strong band corresponding to the stretching vibrations of a

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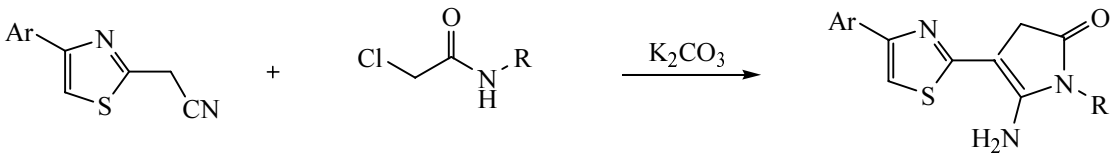

IV, V **IIIa–IIIg** **VIa–VIe, VIIa, VIIb, VIIf, VIIg**

Ar = 4-ClC_6H_4 (**IV, VI**), 4-BrC_6H_4 (**V, VII**); R = 4-(EtO)C_6H_4 (**a**), 1-$C_{10}H_7$ (**b**), 3-(MeO)C_6H_4 (**c**), 3,4-$Cl_2C_6H_3$ (**d**), 4-[*i*-PrN(Et)]C_6H_4 (**e**), *cyclo*-C_3H_5 (**f**), 4-(MeO)$C_6H_4CH_2CH_2$ (**g**).

carbonyl group was observed in the region 1700–1710 cm^{-1} typical of five-membered lactams [30]. In the ^1H NMR spectra of compounds **VI** and **VII** appeared a two-proton singlet of a methylene group at 3.2–3.5 ppm. The signal of amino group protons was observed in the 6.8–7.5 ppm as a broadened two-proton singlet that disappeared on adding D_2O. The protons of the thiazole fragmnt and of the substituent at position *1* gave rise to appropriate signals. In the ^1H NMR spectra of 1-(1-naphthyl)-pyrrolones (**VIb** and **VIIb**) the resonance of the methylene group protons was observed as two one-proton doublets at 3.69 and 3.54 ppm with a geminal coupling constant ~21.5 Hz. The magnetic nonequivalence of methylene protons is due to the lack of free rotation of the naphthyl substituent around the C–N bond imparting axial chirality to the molecule. Thus in the compounds **VIb** and **VIIb** an atropoisomerism was observed. Similar behavior was found also in other 1-(1-naphthyl)-2,5-disubstituted pyrroles [29]. However in isomeric derivatives of compound **I** no atropoisomerism was observed [7].

Hence we developed a convenient method for preparation of 5-amino-4-(4-aryl-2-thiazolyl)-2,3-dihydro-2-pyrrolones **VI** and **VII,** isomers of formerly obtained compounds **I** [6, 7, 18, 19]. The method is based on application of accessible initial compounds and simple experimental procedures and thus it is more attractive compared to more complex and labor-consuming ways of building up the pyrrole ring used in the syntheses of thiazolylpyrroles [5, 6, 16, 17]. The comparative study of the chemistry of compounds **I** and **VI, VII** is now in progress, and its results will be published elsewhere.

EXPERIMENTAL

Thiazolylacetonitriles **IV** and **V** [31, 32] and chloroacetamides **III** [33] were prepared by known methods. Ethanol and 2-propanol were dried first over CaO, and then with Na. IR spectra were recorded on Pye Unicam SP 3-300 instrument from samples pelletized with KBr. ^1H NMR spectra were registered on a spectrometer Varian VXR-300 at operating frequency 300 MHz from solutions in DMSO-d_6.

Table 1. Yields, melting points, and elemental analyses of 5-amino-4-(4-aryl-2-thiazolyl)-2,3-dihydro-2-pyrrolones **VIa–VIe, VIIa, VIIb, VIIf,** and **VIIg**

Compd. no.	Yield, %	mp, °C	Formula	Found (calculated), %			
				C	H	N	S
VIa	58	182	$C_{21}H_{18}ClN_3O_2S$	61.16 (61.23)	4.53 (4.40)	10.08 (10.20)	7.60 (7.78)
VIb	53	203	$C_{23}H_{16}ClN_3OS$	65.99 (66.10)	3.84 (3.86)	10.12 (10.05)	7.81 (7.67)
VIc	50	185	$C_{20}H_{16}ClN_3O_2S$	60.33 (60.37)	4.14 (4.05)	10.72 (10.56)	8.19 (8.06)
VId	60	148	$C_{19}H_{12}Cl_3N_3OS$	52.48 (52.25)	2.86 (2.77)	9.64 (9.62)	7.25 (7.34)
VIe	51	155	$C_{24}H_{25}ClN_4OS$	63.59 (63.63)	5.53 (5.56)	12.18 (12.37)	7.25 (7.08)
VIIa	59	206	$C_{21}H_{18}BrN_3O_2S$	55.33 (55.27)	3.81 (3.98)	9.01 (9.21)	7.21 (7.03)
VIIb	55	215	$C_{23}H_{16}BrN_3OS$	59.59 (59.75)	3.59 (3.49)	9.04 (9.09)	6.84 (6.93)
VIIf	56	187	$C_{16}H_{14}BrN_3OS$	51.09 (51.07)	3.87 (3.75)	11.15 (11.17)	8.43 (8.52)
VIIg	50	173	$C_{22}H_{20}BrN_3O_2S$	56.01 (56.18)	4.38 (4.29)	8.79 (8.93)	6.67 (6.82)

Table 2. ^{1}HNMR spectra of 5-amino-4-(4-aryl-2-thiazolyl)-2,3-dihydro-2-pyrrolones **VIa–VIe, VIIa, VIIb, VIIf**, and **VIIg**

Compd. no.	δ, ppm
VIa	1.36 t (3H, CH_3, *J* 6.6 Hz), 3.42 s (2H, CH_2), 4.08 q (2H, OCH_2, *J* 6.6 Hz), 6.92 s (2H, NH_2), 7.07 d (2H, H_R, *J* 8.0 Hz), 7.27 d (2H, H_R, *J* 8.0 Hz), 7.48 d (2H, H_{Ar}, *J* 8.4 Hz), 7.57 s (1H, SCH=), 7.93 d (2H, H_{Ar}, *J* 8.4 Hz)
VIb	3.54 d (1H, CH_2, *J* 21.2 Hz), 3.69 d (1H, CH_2, *J* 21.2 Hz), 6.91 s (2H, NH_2), 7.46 d (2H, H_{Ar}, *J* 8.0 Hz), 7.61 m (4H, SCH=, 2,6,7-H_R), 7.68 t (1H, H_R^3, *J* 7.6 Hz), 7.75 d (1H, H_R^8, *J* 8.0 Hz), 7.94 d (2H, H_{Ar}, *J* 8.0 Hz), 8.10 m (2H, $H_R^{4,5}$)
VIc	3.45 s (2H, CH_2), 3.81 s (3H, OCH_3), 6.94 m (2H, H_R), 6.99 s (2H, NH_2), 7.05 d (1H, H_R, *J* 9.2 Hz), 7.48 m (3H, H_R, H_{Ar}), 7.60 s (1H, SCH=), 7.94 d (2H, H_{Ar}, *J* 7.6 Hz)
VId	3.49 s (2H, CH_2), 7.14 s (2H, NH_2), 7.45 d.d (1H, H_R^6, J_3 8.4, J_4 2.4 Hz), 7.52 d (2H, H_{Ar}, *J* 8.4 Hz), 7.66 s (1H, SCH=), 7.77 d (1H, H_R^2, *J* 2.4 Hz), 7.86 d (1H, H_R^5, *J* 8.4 Hz), 7.99 d (2H, H_{Ar}, *J* 8.4 Hz)
VIe	1.15 m (9H, $3CH_3$), 3.28 q (2H, NCH_2, *J* 6.0 Hz), 3.38 C (2H, CH_2), 4.10 m (1H, NCH), 6.82 m (4H, NH_2, H_R), 7.09 d (2H, H_R, *J* 9.0 Hz), 7.48 d (2H, H_{Ar}, *J* 9.0 Hz), 7.55 s (1H, SCH=), 7.93 d (2H, H_{Ar}, *J* 9.0 Hz)
VIIa	1.41 t (3H, CH_3, *J* 7.2 Hz), 3.36 s (2H, CH_2), 4.08 q (2H, OCH_2, *J* 7.2 Hz), 6.83 s (2H, NH_2), 7.02 d (2H, H_R, *J* 8.8 Hz), 7.21 d (2H, H_R, *J* 8.8 Hz), 7.40 s (1H, SCH=), 7.53 d (2H, H_{Ar}, *J* 8.8 Hz), 7.82 d (2H, H_{Ar}, *J* 8.8 Hz)
VIIb	3.54 d (1H, CH_2, *J* 21.6 Hz), 3.69 d (1H, CH_2, *J* 21.6 Hz), 6.89 s (2H, NH_2), 7.62 m (7H, 2,3,6,7-H_R, H_{Ar}, SCH=), 7.75 d (1H, H_R^8, *J* 7.8 Hz), 7.87 d (2H, H_{Ar}, *J* 8.4 Hz), 8.11 m (2H, $H_R^{4,5}$)
VIIf	0.81 m (2H, H_R), 0.99 m (2H, H_R), 2.55 m (1H, H_R), 3.38 s (2H, CH_2), 7.25 s (2H, NH_2), 7.53 s (1H, SCH=), 7.62 d (2H, H_{Ar}, *J* 8.4 Hz), 7.90 d (2H, H_{Ar}, *J* 8.4 Hz)
VIIg	2.77 t (2H, CH_2, *J* 15.0 Hz), 3.21 s (2H, CH_2CO), 3.71 s (3H, OCH_3), 3.77 t (2H, NCH_2, *J* 15.0 Hz), 6.85 d (2H, H_R, *J* 9.0 Hz), 7.18 d (2H, H_R, *J* 9.0 Hz), 7.44 s (2H, NH_2), 7.52 s (1H, SCH=), 7.60 d (2H, H_{Ar}, *J* 9.0 Hz), 7.90 d (2H, H_{Ar}, *J* 9.0 Hz)

5-Amino-4-(4-aryl-2-thiazolyl)-2,3-dihydro-2-pyrrolones VIa–VIe, VIIa, VIIb, VIIf, and **VIIg**. To a solution of 0.0025 mol of nitrile **IV** or **V** and 0.0025 mol of chloroacetamide **III** in 5 ml of a mixture 2-propanol–ethanol (3:2 by volume) was added 0.42 g (0.003 mol) of finely crushed K_2CO_3. The mixture obtained was heated at reflux for 1 h, cooled, the separated precipitate was filtered off, thoroughly washed with water, and recrystallized from ethanol (**VIa, VIc, VIe, VIIa, VIIf**, and **VIIg**) or from dioxane (**VIb, VId**, and **VIIb**). Yields, analytic and spectral characteristics of pyrrolones **VI** and **VII** are given in Tables 1 and 2.

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