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CONVENIENT METHODS FOR SYNTHESIS OF PARTIALLY HYDROGENATED BENZO-THIAZOL-2-YLPYRIDINES

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By condensation of 2-chlorobenzaldehyde, cyanothioacetamide, and 2-phenacylbenzothiazole in the presence of piperidine, we have synthesized piperidinium 5-(benzothiazol-2-yl)-4-(2-chlorophenyl)-3-cyano-6-hydroxy-6-phenyl-1,4,5,6-tetrahydropyridine-2-thiolate, based on which the corresponding partially hydrogenated 2-alkylthiopyridines have been obtained.

Keywords: benzothiazol-2-ylpyridines.

Recently the number of studies devoted to synthesis of thiazolyl-containing pyridones has been growing considerably [1], since many of these compounds display high physiological activity. The basic method for obtaining these heterocyclic compounds is the reaction of substituted 5-bromoacetylpyridin-2-ones with various reagents containing thiocarbamoyl moiety. However, there are no convenient methods for synthesis of pyridinethiones containing thiazole substituent. The synthesis of some 5-(benzothiazol-2-yl)pyridine-2-thiones using a novel reagent: benzothiazol-2-ylthioacetamide is noteworthy from this standpoint [2].

We have established that condensation of 2-chlorobenzaldehyde (**1**) with cyanothioacetamide (**2**) and 2-phenacylbenzothiazole (**3**) in ethanol (~20°C) in the presence of piperidine occurs nonstereoselectively with formation of a mixture of *trans* and *cis* isomers of piperidinium tetrahydropyridine-2(1H)-thiolate (**4**) in 2:1 ratio. The regioselectivity of this reaction is probably determined in intermediate **5**, where as a result of reaction of the thiocarbamoyl moiety with the benzoyl group, closure of the pyridine ring and formation of salt **4** occur.

At alkylation of salt **4** by methyl iodide (**6**) or 4-bromo-α-chloroacetanilide (**7a**) in the presence of KOH, the ratio of *trans* and *cis* isomers in the reaction products **8** is preserved.

In the ^{1}H NMR spectra of sulfides **4** and **8** obtained, there are signals from protons of Ar, Het, OH, NH groups and the piperidinium cation in the characteristic regions (Table 2). The signals from protons $C_{(4)}H$ and $C_{(5)}H$ of these compounds have the form of two pairs of doublets in the regions of 4.83-4.96 ppm and 3.89-4.15 ppm (*trans* isomer), 4.12-4.42 ppm and 4.07-4.43 ppm (*cis* isomer), with spin–spin coupling constants of 10.8-12.7 Hz and 4.6-5.4 Hz respectively, where the indicated signals for the *cis* isomer in sulfide **8a** are superimposed to form a broad singlet.

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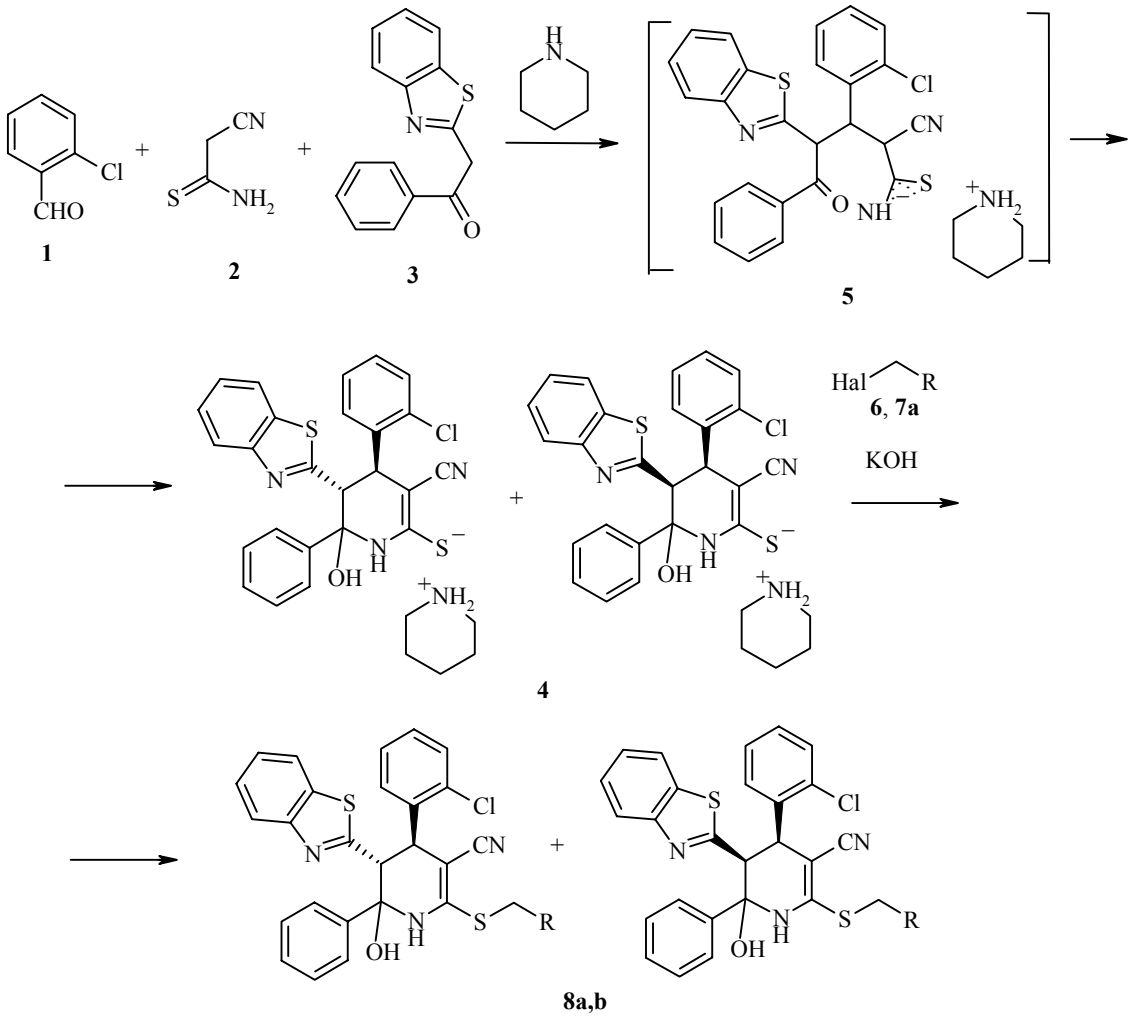
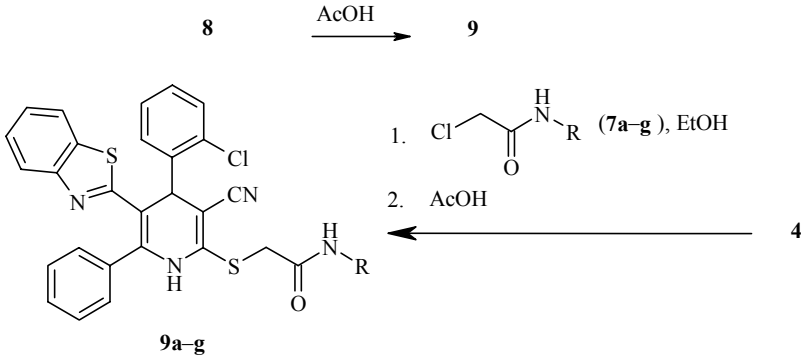


6 Hal = I, R = H; **7a** Hal = Cl, R = 4-BrC_6H_4NHCO; **8a** R = H, **b** R = 4-BrC_6H_4NHCO

We observed that brief boiling of compound **8b** in glacial acetic acid leads to its dehydration with formation of 1,4-dihydropyridine **9a**. Accordingly, we have developed a convenient method for obtaining sulfides **9**, involving alkylation of salt **4** by chlorides **6** upon heating in ethanol, followed by recrystallization of the products formed from acetic acid.



7, **9** **a** R = 4-BrC_6H_4, **b** R = 2-MeC_6H_4, **c** R = 2,5-$Me_2C_6H_3$,
d R = 2,4-$Me_2C_6H_3$, **e** R = 3-ClC_6H_4, **f** R = 4-$EtOC_6H_4$, **g** R = H

TABLE 1. Characteristics of Synthesized Compounds **4, 8, 9**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	IR spectra, ν, cm^{-1}	Yield, %
		C	H	N	S			
4	$C_{30}H_{29}ClN_4OS_2$	64.32 / 64.21	5.04 / 5.21	10.07 / 9.98	11.59 / 11.43	129-132	3240-3390 (NH, N^+H_2, OH), 2170 (CN)	93
8a	$C_{26}H_{20}ClN_3OS_2$	63.55 / 63.73	4.25 / 4.11	8.41 / 8.57	13.22 / 13.09	191-193	3240-3395 (NH, OH), 2187 (CN)	77
8b	$C_{33}H_{24}BrClN_4O_2S_2$	57.44 / 57.61	3.59 / 3.52	8.25 / 8.14	9.12 / 9.32	235-237	3120-3210 (2NH, OH), 2190 (CN), 1620, 1680 (CO)	84
9a	$C_{33}H_{22}BrClN_4OS_2$	59.11 / 59.15	3.52 / 3.31	8.52 / 8.36	9.33 / 9.57	273-275	3180-3210 (2NH), 2190 (CN), 1618, 1645 (CO)	73 (A) 66 (B)
9b	$C_{34}H_{25}ClN_4OS_2$	67.31 / 67.48	4.32 / 4.16	9.02 / 9.26	10.58 / 10.60	254-256	3175-3206 (2NH), 2190 (CN), 1645, 1680 (CO)	64
9c	$C_{35}H_{27}ClN_4OS_2$	67.71 / 67.89	4.57 / 4.40	9.13 / 9.05	10.11 / 10.36	282-285	3270, 3420 (2NH), 2192 (CN), 1684, 1740 (CO)	58
9d	$C_{35}H_{27}ClN_4OS_2$	67.63 / 67.89	4.15 / 4.40	9.18 / 9.05	10.31 / 10.36	254-256	3214-3305 (2NH), 2185 (CN), 1670, 1710 (CO)	49
9e	$C_{33}H_{22}Cl_2N_4OS_2$	63.08 / 63.36	3.66 / 3.54	9.15 / 8.96	10.34 / 10.25	255-257	3225-3316 (2NH), 2203 (CN), 1620, 1680 (CO)	67
9f	$C_{35}H_{27}ClN_4O_2S_2$	66.29 / 66.18	4.26 / 4.28	8.62 / 8.82	9.91 / 10.10	258-260	3115, 3415 (2NH), 2200 (CN), 1647, 1680 (CO)	74
9g	$C_{27}H_{19}ClN_4OS_2$	62.71 / 62.96	3.82 / 3.72	11.06 / 10.88	12.12 / 12.45	261-263	3270-3390 (NH, NH_2), 2187 (CN), 1680 (CO)	63

TABLE 2. ^{1}H NMR Spectral Characteristics of Synthesized Compounds **4, 8, 9**

Com-pound	Chemical shifts, δ, ppm, *J* (Hz)
4	1.63 (6H, m, $(CH_2)_3$); 2.98 (4H, m, $N(CH_2)_2$); 3.89 (1H, d, ^3J = 12.7, $C_{(5)}H$ *trans*-isomer); 4.07 (1H, d, ^3J = 4.6, $C_{(5)}H$ *cis* -isomer); 4.12 (1H, d, ^3J = 3.9, $C_{(4)}H$ *cis*-isomer); 4.83 (1H, d, ^3J = 12.7, $C_{(4)}H$ *trans*-isomer); 6.59 (1H, br. s, OH); 7.02-7.18, 7.47 and 7.83 (14H, three m, H_{arom} and NH) (2:1)*
8a	2.54 (3H, s, SMe); 4.12 (1H, d, ^3J = 10.8, $C_{(5)}H$ *trans*-isomer); 4.43 (2H, br. s, $C_{(5)}H$ and $C_{(4)}H$ *cis*-isomer); 4.96 (1H, d, ^3J = 10.8, $C_{(4)}H$ *trans*-isomer); 6.96, 7.17, 7.52 and 7.85 (13H, four m, H_{arom}); 7.37 (1H, s, OH *trans*-isomer); 7,71 (1H, s, OH *cis*-isomer); 8.04 (1H, s, NH *trans*-isomer); 8.29 (1H, s, NH *cis*-isomer) (2:1)*
8b	3.85 and 3.99 (2H, both d, ^2J = 16, SCH_2); 4.15 (1H, d, ^3J = 11.4, $C_{(5)}H$ *trans*-isomer); 4.37 (1H, d, ^3J = 5.4, $C_{(5)}H$ *cis*-isomer); 4.42 (1H, d, ^3J = 5.4, $C_{(4)}H$ *cis*-isomer); 4.94 (1H, d, ^3J = 11.4, $C_{(4)}H$ *trans*-isomer); 6.97, 7.18, 7.54 and 7.85 (18H, four m, H_{arom} and OH); 8.50 (1H, s, NH *cis*-isomer); 8.59 (1H, s, NH *trans*-isomer); 10.51 (1H, s, CONH) (2:1)*
9a	3.89 and 4.04 (2H, both d, ^2J = 15.2, SCH_2); 5.78 (1H, s, $C_{(4)}H$); 7.13-7.67 (17H, m, H_{arom}); 10.22 (1H, s, NH); 10.39 (1H, s, CONH)
9b	2.19 (3H, s, Me); 4.01 and 4.15 (2H, both d, ^2J = 16.2, SCH_2); 5.79 (1H, s, $C_{(4)}H$); 7.15-7.63 (17H, m, H_{arom}); 9.83 (1H, s, NH); 10.51 (1H, s, CONH)
9c	2.13 and 2.22 (6H, both s, 2Me); 3.97 and 4.21 (2H, both d, ^2J = 14.8, SCH_2); 5.78 (1H, s, $C_{(4)}H$); 6.91-7.62 (16H, m, H_{arom}); 9.77 (1H, s, NH); 10.53 (1H, s, CONH)
9d	2.13 and 2.23 (6H, both s, 2Me); 3.99 and 4.21 (2H, both d, ^2J = 17.5, SCH_2); 5.78 (1H, s, $C_{(4)}H$); 6.85 d (^3J = 8.2 Hz), 7.05 s, 7.35-7.72 m, (16H, H_{arom}); 9.78 (1H, s, NH); 10.56 (1H, s, CONH)
9e	3.96 and 4.12 (2H, both d, ^2J = 14.2, SCH_2); 5,78 (1H, s, $C_{(4)}H$); 7.36-7.78 (17H, m, H_{arom}); 10.29 (1H, s, NH); 10.54 (1H, s, CONH)
9f	1.3 (3H, t, ^3J = 5.8, Me); 3.81 and 4.14 (2H, both d, ^2J = 17.4, SCH_2); 3.98 (2H, q, ^3J = 5.8, OCH_2); 5.78 (1H, s, $C_{(4)}H$); 6.81 d (^3J = 8.1); 7.25-7.71 m (17H, H_{arom}); 10.27 (1H, s, NH); 10.52 (1H, s, CONH)
9g	3.68 and 3.93 (2H, both d, ^2J = 14.5, SCH_2); 5.77 (1H, s, $C_{(4)}H$); 7.25-7.77 m and 7.95 br. s (15H, H_{arom} and NH_2); 10.99 (1H, s, NH)

* Ratio of *cis* and *trans* isomers.

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Bruker AM-300 (300 MHz) in DMSO-d_6 (internal standard TMS). The IR spectra were recorded on an IKS-29 spectrophotometer (in vaseline oil). The course of the reaction and the purity of the compounds were monitored by TLC (Silufol UV-254), 3:5 acetone–hexane.

Piperidinium 5-(Benzothiazol-2-yl)-4-(2-chlorophenyl)-3-cyano-6-hydroxy-6-phenyl-1,4,5,6-tetrahydropyridine-2-thiolate (4). 2-Phenacylbenzothiazole **3** (10.12 g, 40 mmol) and piperidine (4.94 ml, 50 mmol) were added to a stirred mixture of 2-chlorobenzaldehyde **1** (4.5 ml, 40 mmol), cyanothioacetamide **2** (4 g, 40 mmol), and piperidine (3 drops) in ethanol (40 ml) at ~20°C. After 1 h, the precipitate formed was filtered off and washed with acetone.

5-(Benzothiazol-2-yl)-4-(2-chlorophenyl)-3-cyano-6-hydroxy-2-methylthio-6-phenyl-1,4,5,6-tetrahydropyridine (8a) and 5-(Benzothiazol-2-yl)-2-(4-bromophenyl)carbamoylmethylthio-4-(2-chlorophenyl)-3-cyano-6-hydroxy-6-phenyl-1,4,5,6-tetrahydropyridine (8b). 10% Aqueous KOH solution (2.8 ml, 5 mmol) was added with stirring to suspension of salt **4** (2.81 g, 5 mmol) in 80% ethanol (25 ml), and then the corresponding halide **6** or **7a** (5 mmol) was added after 5 minutes. The precipitate formed after 3 h was filtered off and washed with water, ethanol, and hexane.

5-(Benzothiazol-2-yl)-2-(4-bromophenyl)carbamoylmethylthio-4-(2-chlorophenyl)-3-cyano-6-phenyl-1,4-dihydropyridine (9a), 5-(Benzothiazol-2-yl)-4-(2-chlorophenyl)-3-cyano-2-(2-methylphenyl)-carbamoylmethylthio-6-phenyl-1,4-dihydropyridine (9b), 5-(Benzothiazol-2-yl)-4-(2-chlorophenyl)-3-cyano-2-(2,5-dimethylphenyl)carbamoylmethylthio-6-phenyl-1,4-dihydropyridine (9c), 5-(Benzothiazol-2-yl)-4-(2-chlorophenyl)-3-cyano-2-(2,4-dimethylphenyl)carbamoylmethylthio-6-phenyl-1,4-dihydropyridine (9d), 5-(Benzothiazol-2-yl)-4-(2-chlorophenyl)-2-(3-chlorophenyl)carbamoylmethylthio-3-cyano-6-phenyl-1,4-dihydropyridine (9e), 5-(Benzothiazol-2-yl)-4-(2-chlorophenyl)-3-cyano-2-(4-ethoxyphenyl)carbamoylmethylthio-6-phenyl-1,4-dihydropyridine (9f), 5-(Benzothiazol-2-yl)-2-carbamoylmethylthio-4-(2-chlorophenyl)-3-cyano-6-phenyl-1,4-dihydropyridine (9g). A. Sulfide **8b** (3.44 g, 5 mmol) was recrystallized from of glacial acetic acid (40 ml).

B. Mixture of salt **4** (2.81 g, 5 mmol) and the corresponding chloride **7a-g** (5 mmol) in 80% ethanol (35 ml) was heated to boiling, and after the starting reagents dissolved, the mixture was filtered through a paper filter. The precipitate formed after 12 h was separated, washed with ethanol and hexane, and recrystallized from glacial acetic acid (30 ml).

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