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A CONVENIENT METHOD FOR THE SYNTHESIS OF SUBSTITUTED 2-ALKYLTHIO-3-CYANO-4,6-DIMETHYL-5-PHENYLCARBAMOYL-1,4-DIHYDROPYRIDINES

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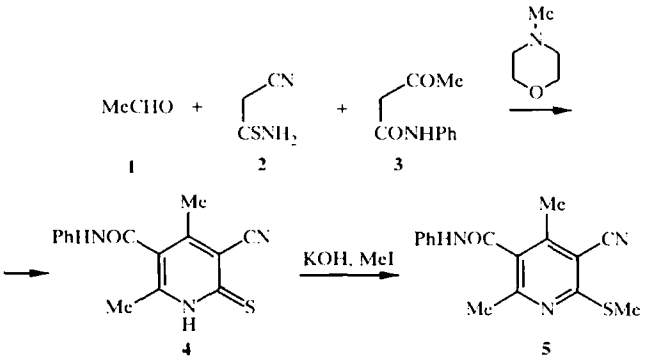
Substituted 2-alkylthio-3-cyano-4,6-dimethyl-5-phenylcarbamoyl-1,4-dihydropyridines were obtained by successive reaction of acetaldehyde with cyanothioacetamide and acetoacetanilide, α-chloroacetamide or phenacyl bromide in the presence of piperidine.

Keywords: acetaldehyde, acetoacetaldehyde, substituted 3-cyanopyridin-2(1H)-thione, thieno[2,3-*b*]-pyridine, 3-cyano-1,4-dihydropyridine, cyanothioacetamide, multicomponent condensation.

Condensation of the anilide of acetoacetic acid, propionyl aldehyde and cyanothioacetamide in the presence of N-methylmorpholine gave 3-cyano-4-ethyl-6-methyl-5-phenylcarbamoylpyridin-2(1H)-thione, which was alkylated in basic media to give the corresponding substituted 2-pyridyl sulfides [1]. The different effects of organic bases (N-methylmorpholine and piperidine) on the reaction of thienylmethylenecyanothioacetamide with 2-acetoacetotoluidine, which gives substituted di- or tetrahydro-3-cyanopyridon-2-thiolates, have been noted [2]. However there is no information in the literature on the preparation of hydrogenated 4-alkyl-3-cyanopyridin-2(1H)-thiones containing amide groups and their derivatives, which are potential biologically active compounds [3-5]. One variant of a solution to this problem is presented in this paper.

We have established that reaction of acetaldehyde (**1**) with cyanothioacetamide (**2**) and acetoacetanilide (**3**) in ethanol at 20°C in the presence of excess N-methylmorpholine occurs analogously to the reaction described above [1] to give thione **4**, alkylation of which with methyl iodide gave sulfide **5**.



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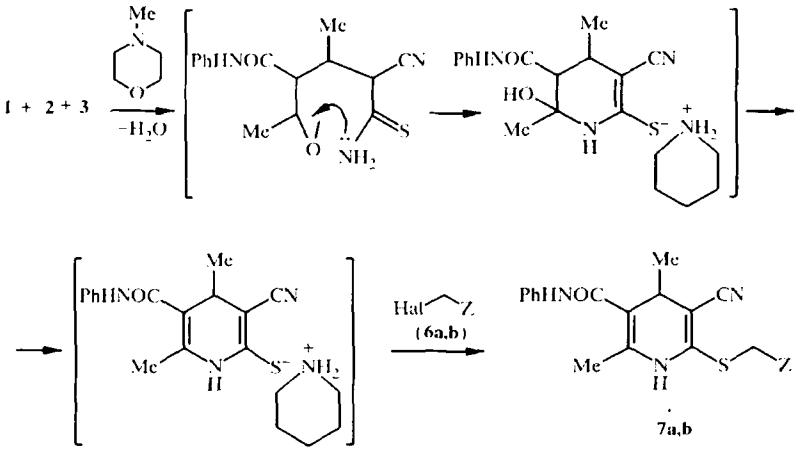
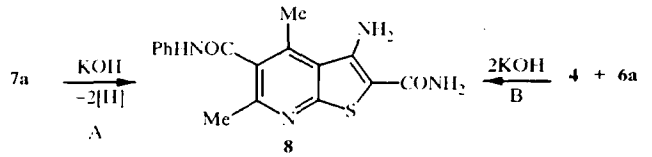
When the reaction was carried out under analogous conditions in the presence of piperidine with subsequent treatment of the reaction mixture with the halides **6**, the 3-cyano-1,4-dihydropyridines **7** were obtained in yields of up to 82%. The explanation may be that the intermediate piperidinium salt is more stable than the corresponding N-methylmorpholinium salt which is oxidized during the reaction to give the 3-cyanopyridine **5**.



6, **7** a Hal = Cl, Z = $CONH_2$, b Hal = Br, Z = COPh

The IR spectra of compounds **7** contain bands characteristic of the stretching vibrations of a conjugated cyano group at 2190-2197 cm^{-1}, while in the ^1H NMR spectra there are signals for dihydropyridine protons and the 4-Me group in the 8.87-9.0 (1H, s, NH), 3.51-3.57 (1H, q, C(4)H), and 1.05 ppm regions (3H, d, 4-Me), plus signals for PhNHCO, 6-Me, and SCH_2Z in the appropriate regions (see Experimental).

The dihydropyridyl sulfide **7a** cyclized in basic media to thieno[2,3-*b*]pyridine **8**, which was also obtained by an independent method from the thione **4** and α-chloroacetamide **6a** in the presence of a two fold excess of KOH.



EXPERIMENTAL

IR spectra of nujol mulls were recorded with an IKS-29 spectrophotometer. ^1H NMR Spectra of DMSO-d_6 solutions (TMS internal standard) were recorded with Bruker AC-300 (300.13 MHz) (compounds **4**, **5**, **7**) and Bruker WP-100 SY (100 MHz) instruments (compounds **7a** and **7b**). Progress of reactions and purity of products were monitored by TLC on Silufol UV-254 strips (eluent 3:5 acetone–hexane).

3-Cyano-4,6-dimethyl-5-phenylcarbamoylpyridin-2(1H)-thione (4). A mixture of acetaldehyde **1** (0.56 ml, 10 mmol), cyanothioacetamide **2** (1 g, 10 mmol), anilide **3** (1.17 g, 10 mmol), N-methylmorpholine (1.5 ml, 15 mmol) in ethanol (15 ml) was stirred at 20°C for 4 h and then left for 12 h. The precipitate was filtered off, and washed with ethanol and hexane to give thione **4** (2.24 g, 79%); mp 311-313°C (sublim.) (AcOH). IR spectrum: 3150-3200 (2NH), 2220 (CN), 1590, 1650 cm^{-1} (C=O). ^1H NMR spectrum: 2.40 (6H, s, 2Me); 7.18 t, 7.30 t, 7.64 d (5H, Ph); 10.38 (1H, s, CONH); 14.10 ppm (1H, br. s, NH). Found, %: C 63.40; H 4.73; N 15.01; S 11.15. $C_{15}H_{13}N_3OS$. Calculated, %: C 63.58; H 4.62; N 14.83; S 11.32.

3-Cyano-4,6-dimethyl-2-methylthio-5-phenylcarbamoylpyridine (5). 10% Aqueous KOH (2.8 ml, 5 mmol) was added to a stirred suspension of thione **4** (1.42 g, 5 mmol) in ethanol (15 ml), followed by methyl

iodide (0.3 ml, 5 mmol) over 1 min. After 1 h the precipitate was filtered off and washed with ethanol and hexane to give compound **5** (1.35 g, 91%); mp 187-188°C (ethanol). IR spectrum: 3165-3330 (NH), 2220 (CN), 1610, 1650 cm^{-1} (C=O). ^1H NMR spectrum: 2.45 s and 2.57 s (6H, 2 Me); 2.64 (3H, s, SMe); 7.10 t, 7.33 t, 7.68 d (5H, Ph); 10.37 ppm (1H, s, CONH). Found, %: C 64.44; H 5.20; N 13.95; S 10.61. $C_{16}H_{15}N_3OS$. Calculated, %: C 64.62; H 5.08; N 14.13; S 10.78.

2-Alkylthio-3-cyano-4,6-dimethyl-5-phenylcarbamoyl-1,4-dihydropyridines (7a,b). A mixture of aldehyde **1** (0.56 ml, 10 mmol), cyanothioacetamide **2** (1 g, 10 mmol), anilide **3** (1.17 g, 10 mmol), and piperidine (1.48 ml, 15 mmol) in ethanol (20 ml) was stirred at 20°C for 3 h, after which the respective halide **6a or 6b** (10 mmol) was added. After 1 h the precipitate was filtered off and washed with ethanol and hexane.

Compound 7a. Yield 2.64 g (77%); mp 235-237°C (ethanol). IR spectrum: 3150-3240, 3360 (2NH, NH_2), 2190 (CN), 1630, 1655, 1715 cm^{-1} (2C=O). ^1H NMR spectrum: 1.05 (3H, d, 4-Me); 1.97 (3H, s, 6-Me); 3.57 (1H, q, $C_{(4)}H$); 3.64 (2H, s, SCH_2); 7.02 t, 7.29 t, 7.58 d (5H, Ph); 7.55 s and 7.85 s (2H, $CONH_2$); 9.70 ppm (2H, s, NH and CONH). Found, %: C 59.44; H 5.46; N 16.22; S 9.28. $C_{17}H_{18}N_4O_2S$. Calculated, %: C 59.63; H 5.30; N 16.36; S 9.36.

Compound 7b: Yield 3.31 g (82%); mp 202-204°C (ethanol). IR spectrum: 3300-3375 (2NH), 2197 (CN), 1605, 1637, 1670 cm^{-1} (2C=O). ^1H NMR spectrum: 1.05 (3H, d, 4-Me); 1.94 (3H, s, 6-Me); 3.51 (1H, q, $C_{(4)}H$); 4.71 (2H, s, SCH_2); 70.2 t, 7.29 t, 7.62 m, 7.99 d (10H, 2Ph); 8.87 (1H, s, NH); 9.79 ppm (1H, s, CONH). Found, %: C 68.58; H 5.42; N 10.23; S 8.12. $C_{23}H_{21}N_3O_2S$. Calculated, %: C 68.46; H 5.25; N 10.41; S 7.95.

3-Amino-2-carbamoyl-4,6-dimethyl-5-phenylcarbamoylthieno[2,3-*b*]pyridine (8). A. 10% Aqueous KOH (2.8 ml, 5 mmol) was added with stirring to a solution of dihydropyridine **7a** (1.71 g, 5 mmol) in DMF (10 ml), stirring was continued for 3 h, then water (10 ml) was added and the precipitate was filtered off and washed with ethanol and hexane to give compound **8** (1.14 g, 67%); mp 259-261°C (DMF). IR spectrum: 315-3360 (NH, $2NH_2$), 1570, 1620, 1680 cm^{-1} (2C=O). ^1H NMR spectrum: 2.55 s and 2.73 s (6H, Me); 6.80 (2H, s, NH_2); 6.95 (2H, s, $CONH_2$); 7.09 t, 7.30 t, 7.70 d (5H, Ph); 10.38 ppm (1H, s, CONH). Found, %: C 59.81; H 4.55; N 16.68; S 9.54. $C_{17}H_{16}N_4O_2S$. Calculated, %: C 59.98; H 4.74; N 16.46; S 9.42.

B. α-Chloracetamide (2.8 ml, 5 mmol) was added with stirring to a suspension of thione **4** (1.42 g, 5 mmol) in DMF (10 ml). The reaction mixture was stirred for 3 h, then 10% aqueous KOH (2.8 ml) was added, stirring was continued for 1 h, and water (10 ml) was then added. The precipitate was filtered off and washed successively with water, ethanol, and hexane to give compound **8** (1.23 g, 72%), identical in melting point and IR spectrum with the product synthesized by method A.

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