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MULTICOMPONENT SYNTHESIS OF 3-CYANO-2-METHYLTHIO-1,4,5,6,7-PENTAHYDROSPIRO-CYCLOHEXANE-1',4-PYRINDINE

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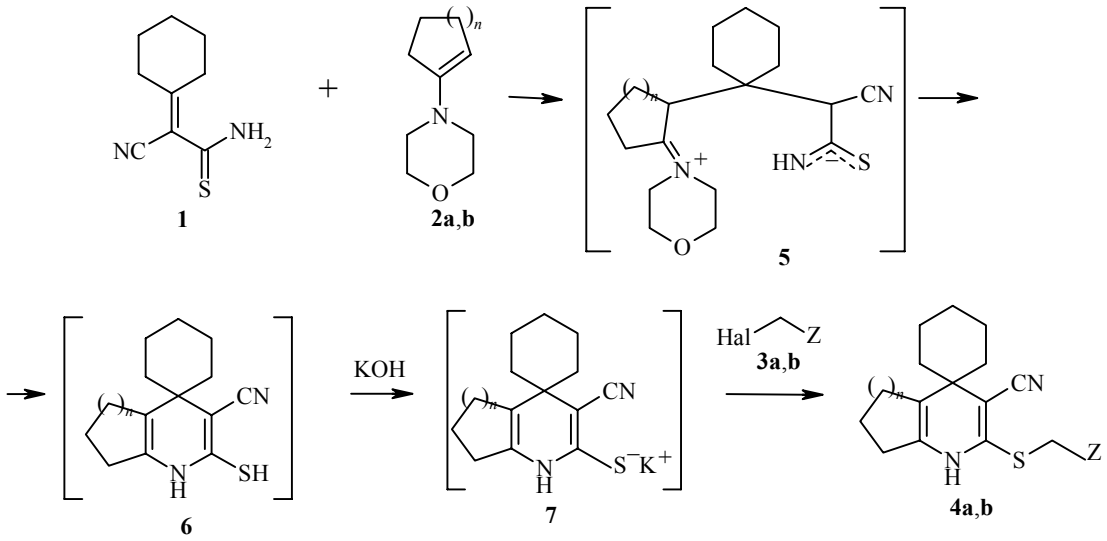
Pyrindine derivatives have found use as biologically active compounds, in particular, as anti-inflammatory agents [1, 2]. Spiro derivatives of these compounds have not been reported. In the development of a "self-assembly" method for condensed pyridines [3, 4], the reaction of cyclohexylidenecyanothioacetamide (**1**), cyclopentanone enamine **2a**, and methyl iodide (**3a**) in absolute ethanol at 20°C in the presence of aq. KOH gave the first reported pyrindine spiro derivative **4a**. This reaction probably proceeds through formation of intermediates **5-7**. The introduction of cyclopentanone enamine **2b** and alkylating agent **3b** instead of **2a** and **3a** into this multicomponent synthesis led to formation of substituted 5,6-pentamethylene-1,4-dihydropyridine **4b**, which confirms the feasibility of the preparation of other pyridine spiro derivatives through this pathway.



2 a *n* = 1, **b** *n* = 3; **3 a** Hal = I, Z = H; **b** Hal = Cl, Z = 2-MeC_6H_4NHCO,
4 a *n* = 1, Z = H; **b** *n* = 3, Z = 2-MeC_6H_4NHCO

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The ^{1}H NMR spectra were taken on a Bruker WP-100SY spectrometer at 100 MHz.

3-Cyano-2-methylthio-1,4,5,6,7-pentahydrospirocyclohexane-1',4-pyrindine (4a). A sample of enamine **2a** (1.53 g, 10 mmol) was added with stirring to a suspension of cyclohexylidenecyanothioacetamide (**1**) (1.8 g, 10 mmol) in absolute ethanol (25 ml) at 20°C and then left for 3 h. A sample of 10% aq. KOH (5.6 ml, 10 mmol) and methyl iodide (0.62 ml, 10 mmol) were then added consecutively and stirring was continued for an additional 2 h. The precipitate formed was filtered off and washed with ethanol and then hexane to give 1.45 g (56%) **4a**; mp 137-139°C (acetic acid). IR spectrum in vaseline mull, ν, cm^{-1}: 3335 (N–H), 2174 (CN). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 8.84 (1H, br.s, NH); 2.43 (3H, s, SCH_3); 1.33-2.55 (16H, m, $(CH_2)_8$). Found, %: C 68.97; H 7.62; N 10.89. $C_{15}H_{20}N_2S$. Calculated, %: C 69.19; H 7.74; N 10.76. Mass spectrum, *m/z* (I_{rel}, %): 260 (33) [M^+], 245 (18), 217 (100), 204 (22).

3-Cyano-2-(2-methylphenylcarbamoylmethylthio)-5,6-pentamethylene-1,4-dihydrospirocyclohexane-1',4-pyridine (4b) was obtained analogously to **4a** by replacing enamine **2a** and methyl iodide **3a** by N-(1-cycloheptenyl)morpholine (**2b**) (1.81 g, 10 mmol) and chloroaceto-*o*-toluidine (1.84 g) to give 3.1 g (73%) of **4b**; mp 205-207°C (acetic acid). IR spectrum in vaseline mull, ν, cm^{-1}: 3260 (N–H), 2190 (CN), 1670 (NHCO). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 9.93 (1H, br. s, NHCO); 8.57 (1H, br. s, NH); 7.07-7.45 (4H, m, C_6H_4); 3.95 (2H, s, SCH_3); 2.23 (3H, s, CH_3); 1.15-2.14 (20H, m, $(CH_2)_{10}$). Found, %: C 71.45; H 7.34; N 9.79. $C_{25}H_{31}N_3OS$. Calculated, %: C 71.22; H 7.41; N 9.97.

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