Brief Communications

Synthesis of 3-cyano-5-ethoxycarbonyl-6-hydroxypyridine-2-thiol derivatives

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Ethyl ethoxymethylenemalonate reacts with cyanothioacetamide and *N*-methylmorpholine to give *N*-methylmorpholinium 3-cyano-5-ethoxycarbonyl-6-oxopyridine-2-thiolate. Alkylation of the latter yields *S*-alkyl derivatives.

Key words: ethyl ethoxymethylenemalonate, cyanothioacetamide, *N*-methylmorpholine, alkylation.

It is known that 4-unsubstituted 3-cyanopyridin-2-one[1,2] and -selenone[3] derivatives are pharmacologically valuable substances. They can be obtained by the reaction of ethoxymethylenemalononitrile with cyanoacetamide or cyanoselenoacetamide, respectively.

We carried out the reaction of ethyl ethoxymethylenemalonate (**1**) with cyanothioacetamide (**2**) in the presence of a 1.5 excess of *N*-methylmorpholine in dehydrated ethanol at 25 °C, which resulted in *N*-methylmorpholinium 3-cyano-5-ethoxycarbonyl-6-oxo-1*H*-pyridine-2-thiolate (**3**), another representative of this class of biologically active compounds. Apparently, the condensation proceeds through intermediate adduct **4**, which is transformed into salt **3** in 52% yield (Scheme 1).

The structure of salt **3** was confirmed by spectroscopic data. Thus, its IR spectrum exhibits characteristic absorption bands of the =NH (3255 cm^{-1}), C=O (1725 cm^{-1}), and conjugated C≡N (2200 cm^{-1}) stretching vibrations. The high-intensity band of the last suggests that the negative charge is delocalized over the N≡C—C=C—S^- fragment. In the ^1H NMR spectrum of compound **3**, one can observe signals for the protons of the *N*-methylmorpholinium cation, a triplet and a quadruplet for the protons of the ethoxycarbonyl group, and singlets for the protons at the N(1) and C(4) atoms of the pyridine ring at δ 11.15 and 7.83, respectively.

Reaction of salt **3** with alkyl halides **5a—c**, benzyl chloride (**5d**), and allyl bromide (**5e**) (see Scheme 1) in boiling ethanol (in the case of **5d**, stirring with short-term heating) proceeds regioselectively to give the corresponding substituted pyridines (**6a—e**).

The structures of the sulfides **6a—e** thus obtained were confirmed by ^1H NMR and IR spectroscopic data (see Experimental).

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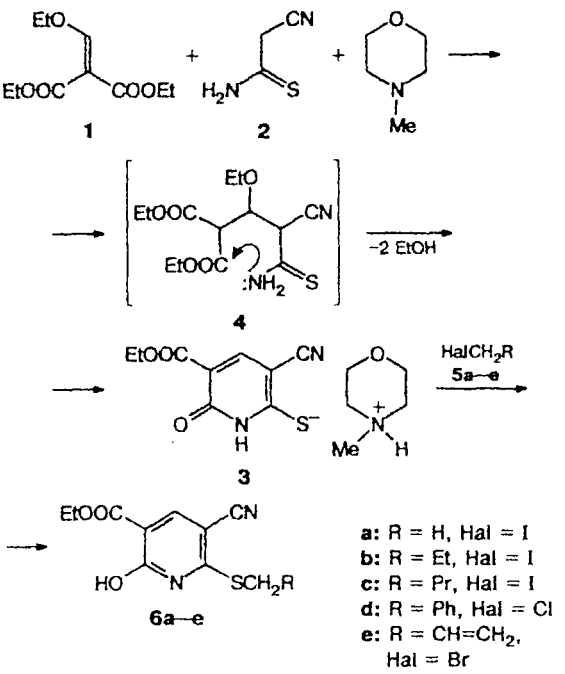
Scheme 1



Experimental

IR spectra of the compounds synthesized were recorded on a IKS-29 instrument (Vaseline oil). ^{1}H NMR spectra were recorded on a Bruker WP-100 SY instrument (100 MHz) in DMSO-d_6 with Me_4Si as the internal standard. The course of the reaction and the individuality of the compounds obtained were monitored by TLC on Silufol UV-254 plates in an acetone—heptane (3 : 5) system. Spots were visualized with iodine vapors.

***N*-Methylmorpholinium 3-cyano-5-ethoxycarbonyl-6-oxo-1*H*-pyridine-2-thiolate (3).** *N*-Methylmorpholine (15 mL, 0.14 mol) was added with stirring to a mixture of ethyl ethoxymethylenemalonate **1** (20 g, 92 mmol) and cyanothioacetamide **2** (9.2 g, 92 mmol) in 20 mL of dehydrated EtOH at 25 °C. The initial compounds being completely dissolved, the reaction mixture was filtered through a folded paper filter. The filtrate was stirred for 5 h and kept for additional 12 h. The precipitate that formed was filtered off and washed with acetone to give compound **3** (52%), m.p. 126—128 °C. Found (%): C, 51.57; H, 5.96; N, 12.85; S, 9.79. $C_{14}H_{19}N_3O_4S$. Calculated (%): C, 51.68; H, 5.89; N, 12.91; S, 9.85. IR, ν/cm^{-1}: 3255 (NH); 2200 sh (CN); 1725 (CO). ^{1}H NMR, δ: 11.15 (s, 1 H, N(1)H); 7.83 (s, 1 H, C(4)H); 4.08 (q, 2 H, CH_2O); 3.80 (br.s, 4 H, CH_2OCH_2); 3.22 (br.s, 4 H, CH_2NCH_2); 2.82 (s, 3 H, CH_3); 1.22 (t, 3 H, CH_3CH_2O).

2-Alkylthio- and 2-benzylthio-3-cyano-5-ethoxycarbonyl-6-hydroxypyridines (6a—d). The corresponding alkyl or benzyl halide **5a—d** (6 mmol) was added to salt **3** (1 g, 3 mmol) in 20 mL of EtOH and refluxed for 1 h. The precipitate that formed upon cooling of the reaction mixture was filtered off and washed with ethanol.

Compound 6a. Yield 72%, m.p. 141—142 °C. Found (%): C, 50.33; H, 4.28; N, 11.64; S, 13.52. $C_{10}H_{10}N_2O_3S$. Calculated (%): C, 50.41; H, 4.23; N, 11.76; S, 13.46. IR, ν/cm^{-1}: 2218 (CN); 1680 (CO). ^{1}H NMR, δ: 8.38 (s, 1 H, C(4)H); 4.27 (q, 2 H, CH_2O); 2.64 (s, 3 H, CH_3S); 1.30 (t, 3 H, CH_3CH_2O).

Compound 6b. Yield 50%, m.p. 80—82 °C. Found (%): C, 54.09; H, 5.40; N, 10.68; S, 12.13. $C_{12}H_{14}N_2O_3S$. Calculated (%): C, 54.12; H, 5.30; N, 10.52; S, 12.04. IR, ν/cm^{-1}: 2217 (CN); 1686 (CO). ^{1}H NMR, δ: 8.38 (s, 1 H, C(4)H); 4.24 (q, 2 H, CH_2O); 3.26 (t, 2 H, CH_2S); 1.69 (q, 2 H, CH_2); 1.30 (t, 3 H, CH_3CH_2O); 0.99 (t, 3 H, $CH_3(CH_2)_2S$).

Compound 6c. Yield 74%, m.p. 83—85 °C. Found (%): C, 55.58; H, 5.83; N, 9.78; S, 11.29. $C_{13}H_{16}N_2O_3S$. Calculated (%): C, 55.70; H, 5.75; N, 9.99; S, 11.44. IR, ν/cm^{-1}: 2218 (CN); 1690 (CO). ^{1}H NMR, δ: 8.37 (s, 1 H, C(4)H); 4.27 (q, 2 H, CH_2O); 3.28 (t, 2 H, CH_2S); 1.56 (m, 4 H, $(CH_2)_2$); 1.29 (t, 3 H, CH_3CH_2O); 0.90 (t, 3 H, CH_3).

Compound 6d. Yield 79%, m.p. 132—134 °C. Found (%): C, 61.06; H, 4.58; N, 8.79; S, 10.00. $C_{16}H_{14}N_2O_3S$. Calculated (%): C, 61.13; H, 4.49; N, 8.91; S, 10.20. IR, ν/cm^{-1}: 2215 (CN); 3180 (OH). ^{1}H NMR, δ: 8.40 (s, 1 H, C(4)H); 7.31 (m, 5 H, Ph); 4.57 (s, 2 H, SCH_2); 4.27 (q, 2 H, CH_2O); 1.30 (t, 3 H, $CH_3CH_2O_2$).

2-Allylthio-3-cyano-5-ethoxycarbonyl-6-hydroxypyridine (6e). Allyl bromide (0.32 mL) was added to salt **3** (0.6 g, 1.8 mmol) in 6 mL of EtOH and refluxed with stirring until the initial compounds were dissolved. The heating was stopped, and the reaction mixture was stirred for additional 4 h. The precipitate that formed was filtered off and washed with ethanol. Yield 52%, m.p. 111—113 °C. Found (%): C, 54.33; H, 4.71; N, 10.49; S, 12.05. $C_{12}H_{12}N_2O_3S$. Calculated (%): C, 54.53; H, 4.58; N, 10.60; S, 12.13. IR, ν/cm^{-1}: 2200 (CN); 1690 (CO). ^{1}H NMR, δ: 7.99 (s, 1 H, C(4)H); 5.89 (m, 1 H, =CH); 5.25, 5.14 (both d, each 1 H, CH_2=); 4.14 (q, 2 H, CH_2O); 3.79 (d, 2 H, CH_2S); 1.23 (t, 3 H, CH_3).

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