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REGARDING THE INTRAMOLECULAR CYCLIZATION OF ETHYL (*E*)- 2-CYANO-3-(S-METHYLISOTHIOUREIDO)-2-PROPENOATE

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Keywords: ethyl 4-amino-2-methylsulfanyl-5-pyrimidine carboxylate, 5-cyano-2-methylsulfanyl-4(3H)-pyrimidinone, ethyl (*E*)-2-cyano-3-(S-methylisothioureido)-2-propenoate, ethyl (*E*)-2-cyano-3-ethoxy-2-propenoate, ethyl (*E*)- and (*Z*)-2-cyano-3-ureido-2-propenoates, intramolecular cyclization.

It is known that, depending on the substituent in the ureido fragment, the intramolecular cyclization of esters of 2-cyano-3-(S-alkylisothioureido)-2-propenooic acid in basic catalysis conditions occurs by two routes to form a mixture of the corresponding 2-alkylsulfanyl-5-cyano-4(3H)-pyrimidinone salts and ethyl 2-alkylsulfanyl-4-amino-5-pyrimidine carboxylates [1-4]. At the same time, from our data, the cyclization reaction of 3-(S-alkyl-isothioureido)-2-cyano-2-propenoates in acid conditions has hardly been studied.

We have found that, in contrast to the 3-benzamidino derivative [4], refluxing ethyl (*E*)-2-cyano-3-(S-methylisothioureido)- 2-propenoate (**2**) in glacial acetic acid shows a selective formation of just the ethyl 4-amino-2-methylsulfanyl-5-pyrimidine carboxylate (**3**). The interest in the synthetic method for the latter is due to its potential use as a precursor of the antibiotic bacimethrin and the thiamine antimetabolites 5-hydroxymethyluracil, metioprim, and toxopyrimidine [1, 3, 5-7]. Reaction of compound **2** in aqueous alkaline medium gives a complex mixture of cyclization and hydrolysis products, i.e. 5-cyano-2-methylsulfanyl-4(3H)-pyrimidinone (**4**, the main product) and as minor products the 4-amino derivative **3** and the (*E*)- and (*Z*)-isomers of ethyl 2-cyano-3-ureido-2-propenoate **5a,b**. Compounds **4, 5** are of interest as precursors in the synthesis of biologically active pyrimidines [8-12].

Elemental analysis, IR, and ^{1}H and ^{13}C NMR spectra are fully in agreement with the structure of the cyclization and hydrolysis products. Compound **1**, existing as the individual thermodynamically more stable (*E*)-isomer [13], undergoes a vinyl nucleophilic substitution (S_NVin) with S-methylisothiuronium sulfate to give the 3-(S-methylisothioureido) derivative **2** with retention of configuration [14]. The ^{1}H NMR spectra (DMSO-d_6) of the (*E*)-isomers **1, 2, 5a** show characteristic signals for the H-3 protons at 8.42, 8.51, and 8.41 ppm respectively (8.45 ppm [10]). An analogous signal for the H-3 proton in the (*Z*)-isomer **5b** separated by us is seen at higher field at 8.11 ppm (8.15 ppm [10]). Additional important information in identifying the isomer pair **5a,b** comes from the position of the signals and the spin-spin coupling for the NH proton doublets. For the

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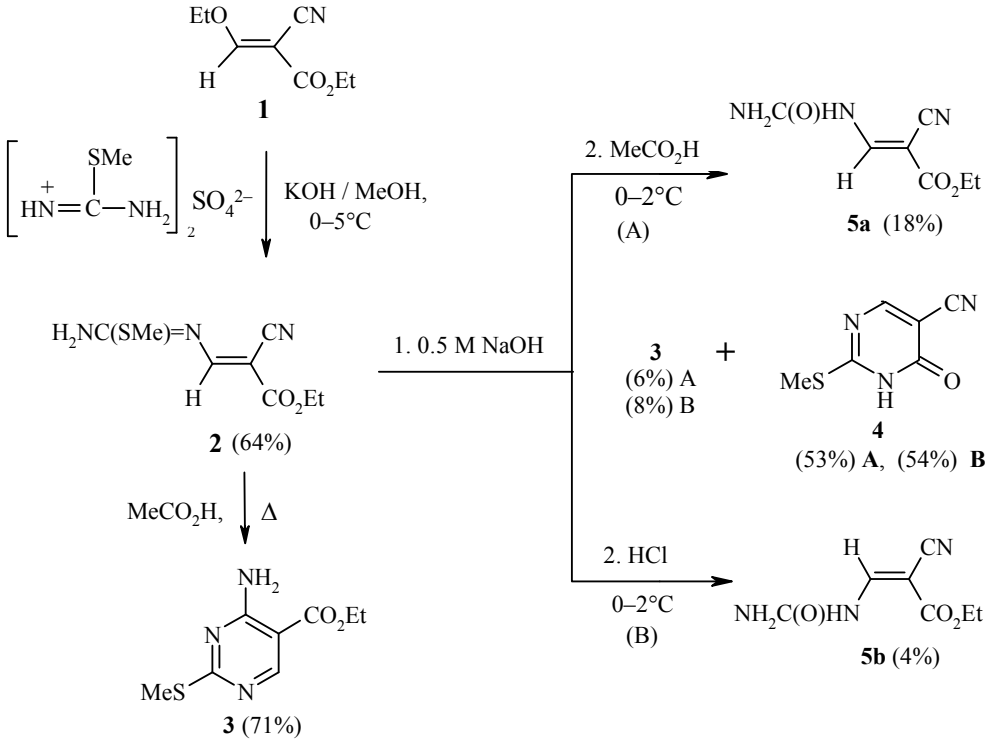
(*E*)-isomer **5a** δ_{NH} is seen at 10.34 ppm with J = 13.2 Hz (10.35 ppm, J = 13 Hz [10]) whereas for the (*Z*)-isomer **5**b (which forms an intramolecular hydrogen bond) it is seen at 10.58 ppm with = 12.6 ppm (10.60 ppm, J = 13 Hz [10]).

IR spectra (KBr) were taken on a Perkin-Elmer BX II FT-IR Fourier spectrophotometer and ^{1}H and ^{13}C NMR spectra on a Varian INOVA spectrometer (300 and 75 MHz) respectively using DMSO-d_6 and with the residual DMSO signals (2.52 and 40.21 ppm for ^{1}H and ^{13}C respectively) used as the internal standard. Monitoring of the course of the reaction and the purity of the compounds obtained was carried out by TLC on silica gel 60 F254 glass plates (Sigma-Aldrich) and revealed using UV light.



The starting ethyl (*E*)-2-cyano-3-ethoxy- and (*E*)-2-cyano-3-(S-methylisothioureido)- 2-propenoates (**1, 2**) were prepared by methods [15] and [2] respectively.

Ethyl (*E*)-2-cyano-3-ethoxy-2-propenoate (1). Yield 57%; mp 51-53ºC (hexane) (mp 51ºC, bp 128-132ºC (2 mm Hg) [15]), R_f 0.79 ($CHCl_3$–ethyl acetate, 4: 1). IR spectrum, ν, cm^{-1}: 2228 (CN), 1712 (CO). ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.25 (3H, t, J = 7.2, $COOCH_2C\underline{H}_3$); 1.33 (3H, t, J = 7.2, $=C–OCH_2C\underline{H}_3$); 4.21 (2H, q, J = 7.2, $COOC\underline{H}_2CH_3$); 4.48 (2H, q, J = 7.2, $=COC\underline{H}_2CH_3$); 8.42 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm: 14.80, 15.75, 61.77, 74.52, 84.98, 114.07, 163.32, 175.92.

Ethyl (E)-2-cyano-3-(S-methylisothioureido)- 2-propenoate (2). Yield 64%; mp 127-128ºC (128-129ºC [2]), R_f 0.10 ($CHCl_3$–ethyl acetate, 4:1). IR spectrum, ν, cm^{-1}: 3440 (NH_2), 2209 (CN), 1703 (CO), 1661 (C=N). ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.23 (3H, t, J = 7.2, CH_3); 2.54 (3H, s, SCH_3); 4.16 (2H, q, J = 7.2, CH_2); 8.51 (1H, s, H-3); 8.75 (1H, br. s, NH); 9.16 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 14.57, 15.01, 60.90, 86.00, 117.39, 162.23, 165.57, 174.85.

Cyclization in Glacial Acetic Acid. A solution of compound **2** (1.0 g, 4.7 mmol) in glacial acetic acid (5 ml) was refluxed for 1 h. The reaction mixture was cooled to room temperature, poured into iced water (20 ml), and the precipitate formed was filtered off, washed with water (2×10 ml), and recrystallized to give compound **3** (0.71 g, 71%) with mp 130-132ºC (ethanol) (mp 130-131ºC [1]), R_f 0.71 ($CHCl_3$–ethyl acetate, 4:1). IR spectrum,

ν, cm^{-1}: 3415, 3270, 3136 (NH_2), 1692 (CO). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.31 (3H, t, *J* = 7.2, CH_3); 2.48 (3H, s, SCH_3); 4.29 (2H, q, *J* = 7.2, CH_2); 7.67 (1H, br. s, NH); 8.04 (1H, br. s, NH); 8.59 (1H, s, H-6). ^{13}C NMR spectrum, δ, ppm: 14.13, 14.78, 61.29, 101.12, 159.18, 162.05, 166.34, 175.50.

Cyclization in aqueous alkaline medium. A. Compound **2** (1.0 g, 4.7 mmol) was added to an aqueous solution of NaOH (0.5 M, 10 ml) and stirred at room temperature for 1 h. The reaction mixture was then cooled to 10ºC, the insoluble precipitate filtered off and washed with water (2×30 ml) to give compound **3** (0.04 g, 6%); mp 129-131ºC, R_f 0.71 ($CHCl_3$–ethyl acetate, 4:1). The filtrate cooled to 0-2ºC was acidified with glacial acetic acid to pH 2-3 and the precipitate formed was filtered off and recrystallized from 2-propanol to give the pyrimidinone **4** (0.29 g, 53%); mp 220-224ºC (mp 220-222ºC [2]) and R_f 0.16 ($CHCl_3$–ethyl acetate, 4:1). IR spectrum, ν, cm^{-1}: 2229 (CN), 1666 (CO). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.56 (3H, s, SCH_3); 8.53 (1H, s, H-6); 13.80 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 14.00, 97.46, 115.81, 160.37, 160.80, 169.19. The filtrate was held for 96 h at 0ºC and the precipitate formed was filtered off to give the (*E*)-isomer **5a** (0.11 g, 18%); mp 198-203ºC (2-propanol), R_f 0.08 ($CHCl_3$–ethyl acetate, 4:1). IR spectrum, ν, cm^{-1}: 3432, 3338, 3256, 3183 (NH_2), 2222 (CN), 1740 (sh, CO ester), 1699 (CO amide). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.24 (3H, t, *J* = 7.2, CH_3); 4.20 (2H, q, *J* = 7.2, CH_2); 6.67 (1H, br. s, NH); 7.47 (1H, br. s, NH), 8.41 (1H, d, *J* = 13.2, H-3); 10.34 (1H, d, *J* = 13.2, NH). ^{13}C NMR spectrum, δ, ppm: 14.85, 61.67, 79.12, 115.48, 151.80, 152.84, 164.08. Found, %: C 46.04; H 4.97. $C_7H_9N_3O_3$. Calculated, %: C 45.90; H 4.95.

B. Compound **2** (21.3 g, 100 mmol) was added to an aqueous solution of NaOH (0.5 M, 213 ml) and stirred for 10 min at 50ºC. The reaction mixture was cooled to 15ºC and the insoluble precipitate was filtered off and washed with water (2×30 ml) to give compound **3** (1.66 g, 8%); mp 130-132ºC, R_f 0.71 ($CHCl_3$–ethyl acetate, 4:1). The filtrate cooled to 0-2ºC was acidified with 1M HCl to pH 2 and the precipitate formed was filtered off and washed with water (2×30 ml) to give the pyrimidinone **4** (9.14 g, 54%); mp 222-224ºC (2-propanol). The filtrate was held for 12 h at 0ºC and the insoluble precipitate was filtered off to give the (*Z*)-isomer **5b** (0.9 g, 4%); mp 213-216ºC (2-propanol), R_f 0.18 ($CHCl_3$–ethyl acetate, 4:1). IR spectrum, ν, cm^{-1}: 3366, 3312, 3236, 3196 (NH_2), 2233 (CN), 1755 (CO ester), 1687 (CO amide). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.28 (3H, t, *J* = 7.2, CH_3); 4.25 (2H, q, *J* = 7.2, CH_2); 7.40 (1H, br. s, NH); 7.63 (1H, br. s, NH); 8.11 (1H, d, *J* = 12.6, H-3); 10.58 (1H, d, *J* = 12.6, NH). ^{13}C NMR Spectrum, δ, ppm: 14.78, 61.71, 78.24, 117.83, 152.46, 152.58, 165.44. Found, %: C 46.10; H 4.80. $C_7H_9N_3O_3$. Calculated, %: C 45.90; H 4.95.

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