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SYNTHESIS OF HEXA- AND OCTAHYDRO-PYRIDO[3'2':4,5]THIENO[3,2-*d*]PYRIMIDINES*

V. V. Dotsenko[1], S. G. Krivokolysko[1], and V. P. Litvinov[2]

The reaction of N-methylmorpholinium 4-(2-chlorophenyl)-5-cyano-2-oxo-1,2,3,4-tetrahydropyridine-6-thiolate with chloroacetamide in DMF in the presence of an excess of KOH gave 3-amino-2-carbamoyl-4-(2-chlorophenyl)-6-oxo-4,5,6,7-tetrahydrothieno[2,3-b]pyridine. Refluxing the latter with acyl chlorides in AcOH or heating in formic acid gave hexahydropyrido[3',2':4,5]thieno[3,2-d]pyrimidine derivatives and reaction with cyclohexanone gave a spiro-linked octahydropyrido[3',2':4,5]thieno-[3,2-d]pyrimidine.

Keywords: tetrahydropyridinethiolate, thienopyridine, partially hydrogenated pyridothienopyrimidines, cyclization.

Substituted 4,7-dihydrothieno[2,3-*b*]pyridines and their dehydrogenated analogs have been successfully used previously as starting reagents in the synthesis of polycondensed heterocycles, including pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidines [1-3]. Amongst compounds with a similar structure there have been discovered substances with antianaphylactic [4, 5] and antimicrobial [6] activity. With this in mind, the development of convenient methods for the synthesis of such compounds seems timely and promising.

In continuation of our study of the chemical properties of tetrahydropyridones [7, 8] and based on the tetrahydropyridinethiolate **1** we have carried out the synthesis of the substituted tetrahydrothieno[2,3-*b*]pyridine **2**. By further reaction it is transformed to the previously unknown partially hydrogenated pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidines.

Hence the reaction of salt **1** with chloroacetamide in the presence of an excess of 10% KOH solution in DMF gives a 91% yield of the target product **2**. The latter reacts with excess acetyl chloride or chloroacetyl chloride when refluxed in glacial AcOH to form the condensed structures **3a,b**. The reaction of compound **2** with cyclohexanone gives a 65.5% yield of octahydropyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine **4**. Reaction of the thienopyridone **2** with 99% formic acid leads to the formation of compound **3c** *via* a sequence of N-formylation and cyclization processes.

The IR spectra of the synthesized compounds show absorption bands for the stretching vibrations of the amino (for **2**) and imino groups (for **2-4**) in the range 3550-3150 cm^{-1}. The signals for the carbonyl groups are seen in the range 1655-1680 cm^{-1}. The ^1H NMR spectra of all of the synthesized samples show characteristic bands for the CH(Ar)–CH_2 fragment of the tetrahydropyridine ring [7, 9] as three double doublets for CH_2 (δ 2.59-2.64 and 3.05-3.17 ppm) and CH (δ 4.54-4.87 ppm). In a number of examples the signals for the

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[1] East-Ukrainian National University, Lugansk 91034, Ukraine; e-mail: ksg@lep.lg.ua. [2] N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Moscow 117913, Russia; e-mail: vpl@ioc.ac.ru.
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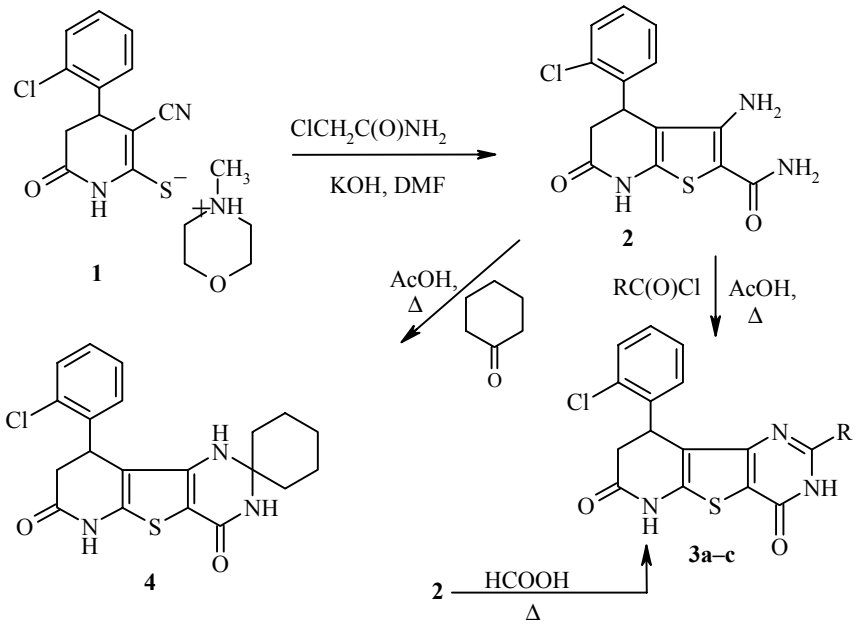
indicated protons appear as broadened pseudo doublets. From a number of signals confirming the pyridothienopyrimidine structure in compounds **3a-c** the most diagnostic are the singlet for the $N_{(3)}H$ group proton (δ 12.24-12.67 ppm) and the corresponding signals for the other substituents. The presence of the pyrimidine fragment in the structure of compound **4** is confirmed by the multiplet in the range δ 1.11-1.87 ppm ($(CH_2)_5$) and the singlets for the NH groups (δ 10.81, 7.15, and 6.16 ppm).



3 a R = Me; **b** R = CH_2Cl; **c** R = H

EXPERIMENTAL

^{1}H NMR spectra were taken on a Gemini 200 instrument (200 MHz) using DMSO-d_6 and TMS as internal standard. IR spectra were obtained on an IKS-29 spectrophotometer and elemental analysis was performed on a Perkin-Elmer C,H,N analyser. The course of the reaction and purity of the materials were monitored using TLC on Silufol UV-254 with acetone–heptane (1:1) as eluent. Melting points were measured on Koffler stage.

3-Amino-2-carbamoyl-4-(2-chlorophenyl)-6-oxo-4,5,6,7-tetrahydrothieno[2,3-*b*]pyridine (2). Aqueous KOH solution (10%, 23 ml, 41 mmol) was added to a solution of the thiolate **1** (15 g, 41 mmol) in DMF (60 ml). The mixture was taken to reflux and passed through filter paper into a solution of chloroacetamide (4 g, 43 mmol) in DMF (20 ml). The reaction mass was stirred for 12 h, a further 23 ml of the 10% KOH was added, the stirring was continued at reflux for 10 min, and after 48 h it was diluted with water to a volume of 230 ml and held for 7 days. The precipitate was filtered off and washed with water and ethanol. Yield 12 g (91%); mp 259-261°C (EtOH) as a white, finely crystalline powder. IR spectrum, ν, cm^{-1}: 1670 (C=O); 3450, 3265, 3150 (NH_2 and $CONH_2$). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.71 (1H, s, NH); 6.75-7.44 (4H, m, Ar); 6.47 (2H, br. s, $CONH_2$); 6.16 (2H, br. s, NH_2); 4.54 (1H, br. pseudo-d, $C_{(4)}H$); 3.07 (1H, m, $C_{(5)}H$); 2.64 (1H, br. pseudo-d, ^2J = 15.7, $C_{(5)}H$). Found, %: C 53.00; H 3.72; N 12.98. $C_{14}H_{12}ClN_3O_2S$. Calculated, %: C 52.26; H 3.76; N 13.06.

9-(2-Chlorophenyl)-2-methyl-4,7-dioxo-3,4,6,7,8,9-hexahydropyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine (3a). Acetyl chloride (0.44 ml, 6.2 mmol) was added to a suspension of the thienopyridine **2** (1 g, 3.1 mmol) in AcOH (10 ml) and the mixture was refluxed for 6 h. The precipitate formed was filtered off and washed with

ethanol. Yield 0.81 g (75%); mp >300°C as a white, finely crystalline powder. IR spectrum, ν, cm^{-1}: 1660, 1680 (2 C=O); 3420, 3465 (2 NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.24 (1H, br. s, $N_{(3)}H$); 11.03 (1H, s, $N_{(6)}H$); 6.64-7.46 (4H, m, Ar); 4.80 (1H, br. pseudo-d, $C_{(9)}H$); 3.15 (1H, m, $C_{(8)}H$); 2.59 (1H, br. pseudo-d, ^2J = 16.2, $C_{(8)}H$); 2.24 (3H, s, Me). Found, %: C 56.50; H 3.60; N 12.12. $C_{16}H_{12}ClN_3O_2S$. Calculated, %: C 55.57; H 3.58; N 12.15.

4,7-Dioxo-2-chloromethyl-9-(2-chlorophenyl)-3,4,6,7,8,9-hexahydropyrido[3',2':4,5]thieno[3,2-*d*]-pyrimidine (3b) was obtained similarly to product **3a** using chloroacetyl chloride (0.49 ml, 6.2 mmol). Yield 0.98 g (83%); mp >300°C as a white, finely crystalline powder. IR spectrum, ν, cm^{-1}: 1660, 1675 (2 C=O); 3390, 3470 (2 NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.67 (1H, br. s, $N_{(3)}H$); 11.12 (1H, s, $N_{(6)}H$); 6.68-7.48 (4H, m, Ar); 4.86 (1H, br. pseudo-d, $C_{(9)}H$); 4.38 (2H, s, CH_2Cl); 3.17 (1H, dd, ^2J = 16.3, ^3J = 8.1, $C_{(8)}H$); 2.59 (1H, br. pseudo-d, ^2J = 16.3, $C_{(8)}H$). Found, %: C 50.98; H 2.93; N 11.01. $C_{16}H_{11}Cl_2N_3O_2S$. Calculated, %: C 50.54; H 2.92; N 11.05.

4,7-Dioxo-9-(2-chlorophenyl)-3,4,6,7,8,9-hexahydropyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine (3c). A solution of the thienopyridine **2** (1 g, 3.1 mmol) in 99% formic acid (10 ml) was refluxed for 20 h and the mixture was then diluted with water (15 ml). The precipitate formed was filtered off and recrystallized from AcOH (50 ml). Yield 0.80 g (78%); mp >300°C as a white, finely crystalline powder. IR spectrum, ν, cm^{-1}: 1650, 1665 (2 C=O); 3425, 3480 (2 NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.67 (1H, br. s, $N_{(3)}H$); 11.07 (1H, br. s, $N_{(6)}H$); 7.86 (1H, br. s, $C_{(2)}H$); 6.67-7.45 (4H, m, Ar); 4.87 (1H, br. pseudo-d, $C_{(9)}H$); 3.10 (1H, m, $C_{(8)}H$); 2.61 (1H, br. pseudo-d, ^2J = 16.0, $C_{(8)}H$). Found, %: C 54.91; H 3.01; N 12.60. $C_{15}H_{10}ClN_3O_2S$. Calculated, %: C 54.30; H 3.04; N 12.66.

4,7-Dioxo-9-(2-chlorophenyl)-2-(1'-cyclohexanespiro)-1,2,3,4,6,7,8,9-octahydropyrido[3',2':4,5]-thieno[3,2-*d*]pyrimidine (4) was obtained similarly to pyrimidine **3a** using cyclohexanone (1.93 ml, 18.6 mmol) and reflux time of 12 h. Yield 0.78 g (65.5%); mp >300°C as colorless crystals. IR spectrum, ν, cm^{-1}: 1665, 1680 (2 C=O); 3465, 3435, 3400, 3250 (3 NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.81 (1H, s, $N_{(6)}H$); 6.71-7.48 (4H, m, Ar); 7.15 (1H, s, $N_{(3)}H$); 6.16 (1H, s, $N_{(1)}H$); 4.61 (1H, br. pseudo-d, $C_{(9)}H$); 3.05 (1H, dd, ^2J = 16.5, ^3J = 7.7, $C_{(8)}H$); 2.64 (1H, br. pseudo-d, ^2J = 16.5, $C_{(8)}H$); 1.11-1.87 (10H, m, $(CH_2)_5$). Found, %: C 60.09; H 4.97; N 10.41. $C_{20}H_{20}ClN_3O_2$. Calculated, %: C 59.77; H 5.02; N 10.45.

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