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SYNTHESIS OF FURO[2,3-d]PYRIMIDINES CONDENSED WITH A TETRAHYDROTHIOPYRAN

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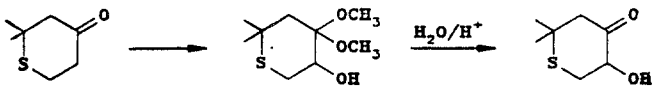
UDC 547.859'818.1'728.2.07

Using o-iodobenzoic acid we synthesized 5-hydroxy-2,2-dimethyltetrahydrothiopyran-4-one. From the latter we synthesized 2-amino-5,5-dimethyl-3-cyano-4,5-dihydro-7H-furo[2,3-c]thiopyran; this is a starting material for the preparation of furo[2,3-d]pyrimidine condensed with tetrahydrothiopyran and triazole rings.

In a number of condensed derivatives of 2,2-dimethyltetrahydrothiopyran-4-one we wished to find new biologically active compounds. We therefore attempted to obtain thiopyran condensed with a 2-amino-3-cyanofuran ring, and also furo[2,3-d]pyrimidines condensed with a thiopyran or triazole ring.

Data have been published on the synthesis of thiopyranes condensed with a 2-amino-3-cyanothiophene ring [1], and on their further conversions [2]. Thiopyran synthesis proceeds smoothly in one step when powdered sulfur is used [3]. For the synthesis of condensed furan derivatives ketol (III), a 5-hydroxy derivative of ketone (I), is necessary. There are efficient methods for the α-hydroxylation of ketones that use "hypervalent iodine," [iodosobenzene, o-iodosobenzoic acid (o-IBA), and idosobenzene diacetate] [4-6]. We used o-IBA to oxidize the starting ketone to ketal (II), which was then hydrolyzed to (III) in good yield.



I II III

According to the PMR spectra the hydroxy group in (II) has axial orientation.

Condensation of acyl ion (III) with malonodinitrile in the presence of an equimolar amount of diethylamine forms furo[2,3-c]thiopyran (IV). Attempts to condense o-aminonitrile (IV) with formamide and then to cyclize to furo[2,3-d]pyrimidine (VII) were unsuccessful even with boiling. To obtain (VII), 2-amino-3-cyanofuran (IV) was first converted to 2-ethoxymethyleneamino-3-cyanofuran (V). Treatment of (V) with cooled 25% ammonia in ethanol gave 2-aminomethyleneamino-3-cyanofuran (VI); boiling of (VI) in ethanolic sodium hydroxide formed furo-[2,3-d]pyrimidine (VII), which represents a new condensed heterocyclic system (see scheme on page 1171).

A. L. Mndzhoyan Institute of Fine Organic Chemistry, Academy of Sciences of the Armenian SSR. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1403-1405, October, 1990. Original article submitted May 31, 1988; revision submitted December 12, 1989.

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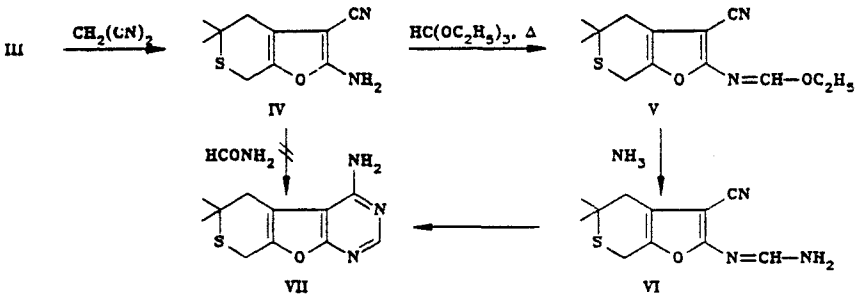
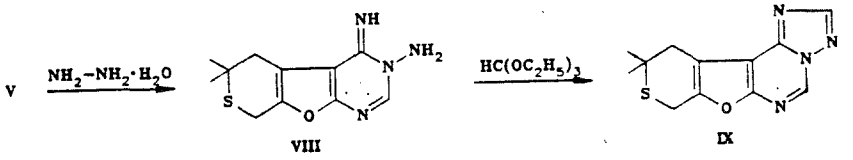


It is known that 4,5-di(2-furyl)-3-cyano-2-ethoxymethyleneaminofuran reacts with hydrazine hydrate to form the corresponding 3-amino-4-iminofuro[2,3-d]pyrimidine, which upon boiling in aqueous solution undergoes a Dimroth rearrangement to 4-hydrazinefuro[2,3-d]pyrimidine [7]. Ethoxymethyleneamino-substituted furan (V) also reacts with hydrazine hydrate to form the substituted pyrimidine (VIII), which, however, could not be made to undergo the Dimroth rearrangement. Either basic or acidic catalysts caused only slow decomposition of iminoamine (VIII). Cyclization of (VIII) with orthoformate also gives a new condensed heterocyclic system, viz., 10,10-dimethyl-10,11-dihydro-8H-thiopyrano[4',3':4,5]furo[3,2-e](1,2,4)triazolo[2,3-c]pyrimidine (IX).



EXPERIMENTAL

IR spectra were obtained with a UR-20 instrument in mineral oil; PMR spectra, with a Varian T-60 instrument (60 MHz); mass spectra, with a MKh-1303 instrument with 70 eV ionization voltage. GLC analysis was carried out on a KhROM 5 apparatus [glass column 2.5 m long and 3 mm inside diameter, filled with 5% KhE-60 on NAW Chromatone (PID) 1.6-2.0 mm, N_2 flow rate 40 ml/min]. TLC monitoring was carried out on Silufol UV-254 plates with development by UV light or iodine vapor. Compound (I) was obtained by the procedure of [8].

2,2-Diemthyl-4,4-dimethoxytetrahydrothiopyran-5-ol (II, $C_9H_{18}O_3S$). To a solution of 26.3 g (0.47 mole) of potassium hydroxide in 250 ml of methanol at 0°C was added over 1 h a solution of 20.0 g (0.13 mole) of ketone (I) in 60 ml of methanol dropwise with stirring. Then over 1 h 60.0 g (0.23 mole) of powdered o-IBA was added so that the reaction temperature did not exceed 25°C, and stirring was continued for 6 h. Methanol was then evaporated in vacuum. To the residue was added 200 ml of water, and the product was extracted with chloroform. The extract was dried over $MgSO_4$ and evaporated in vacuum, and the residue was distilled. Yield 17.5 g (61%), bp 77°C at 1 mm Hg, n_D^{20} 1.4992, R_t 9.1 min (T_{evap} 250°C, T_{therm} 96°C). IR spectrum: 3480 cm^{-1} (OH). PMR spectrum (methanol-D_4, TMS): 1.18 (3H, s, 2-CH_3); 1.20 (3H, s, 2-CH_3); 1.80 (2H, s, 3-CH_2); 2.60 (1H, d.d, J_{gem} = 14.5, J_{6a5e} = 5 Hz, 6-H_a); 3.10 (1H, d.d, J_{gem} = 14.5, J_{6e5e} = 2 Hz, 6-H_e); 3.15 (3H, s, OCH_3); 3.20 (3H, s, OCH_3); 3.80 ppm (1H, d.d, J_{6a5e} = 5, J_{6e5e} = 2 Hz, 5-H_e).

5-Hydroxy-2,2-dimethyltetrahydrothiopyran-4-one (III, $C_7H_{12}O_2S$). To a solution of 15.0 g (0.08 mole) of ketal (II) in 50 ml of chloroform was added 40 ml of 5% H_2SO_4, and the reaction mixture was stirred vigorously for 5 h at room temperature. The chloroform layer was separated and the water layer was extracted with chloroform. The combined extracts were dried over $MgSO_4$ and evaporated in vacuum and the residue was distilled. Yield 10.5 g (90%), bp 65°C at 1 mm Hg, n_D^{20} 1.5122, R_t 6.6 min (T_{evap} 250°C, T_{therm} 96°C). IR spectrum: 1725 (C=O), 3450 cm^{-1} (OH). PMR spectrum (CCl_4, TMS): 1.33 (3H, s, 2-CH_3), 1.40 (3H, s, 2-CH_3), 2.43-3.30 (4H, m, 3-CH_2 and 6-CH_2), 3.86-4.40 ppm (2H, m, 5-CH and OH).

2-Amino-5,5-dimethyl-3-cyano-4,5-dihydro-7H-furo[2,3-c]thiopyran (IV, $C_{10}H_{12}N_2OS$). To a solution of 16.0 g (0.1 mole) of (III) and 6.6 g (0.1 mole) of malonitrile in 150 ml of ethanol was added 7.3 g (0.1 mole) of diethylamine dropwise at room temperature, and the reaction mixture was stirred for 6 h. Ethanol was removed in vacuum, and 200 ml of water was added to the residue. The crystalline precipitate was filtered off, washed with hot water, and dried. Yield 15.7 g (75%), mp 135°C (from water), R_f 0.42 (1:3 acetone–pentane). IR spectrum: 2230 (C≡N), 3200, 3300, 3375

cm^{-1} (NH_2). PMR spectrum ($CDCl_3$, TMS): 1.41 [6H, s, 5-$(CH_3)_2$], 2.83 (2H, t, 4-CH_2), 3.40 (2H, t, 7-CH_3), 5.75 ppm (2H, br.s, NH_2). Mass spectrum, m/z (%): M^+ 208 (100), 193 (22), 175 (80), 134 (99).

5,5-Dimethyl-3-cyano-2-ethoxymethyleneamino-4,5-dihydro-7H-furo[2,3-c]thiopyran (V, $C_{13}H_{16}N_2O_2S$). A mixture of 10.0 g (0.05 mole) of (IV), 30 ml of triethyl orthoformate, and 1 ml of acetic anhydride was boiled for 8 h. Excess orthoformate was distilled off in vacuum and the dark residue was recrystallized from hexane. Yield 9.0 g (71%), mp 71°C (from hexane). R_f 0.60 (1:1 ether–hexane). IR spectrum: 2235 cm^{-1} (C≡N). PMR spectrum ($CDCl_3$, TMS): 1.40 (3H, t) and 4.45 (2H, q, OCH_2CH_3), 1.43 [6H, s, 5-$(CH_3)_2$] 2.66 (2H, t, 4-CH_2), 3.61 (2H, t, 7-CH_2), 8.41 ppm (1H, s, –N=CH–).

2-Aminomethyleneamino-5,5-dimethyl-3-cyano-4,5-dihydro-7H-furo[2,3-c]thiopyran (VI, $C_{11}H_{13}N_3OS$). To a solution of 2.5 g (0.01 mole) of (V) in 20 ml of ethanol was added 20 ml of 25% ammonia in ethanol cooled to –10°C; the mixture was stirred at room temperature for 2 h. The crystalline precipitate was filtered off, washed with water and ethanol, and dried. Yield 2.0 g (86%), mp 205-206°C (from ethanol), R_f 0.75 (1:2 pyridine–methanol). IR spectrum: 2235 (C≡N), 3340, 3380 cm^{-1} (NH_2). PMR spectrum (DMSO-D_6, HMDS): 1.46 [6H, s, 5-$(CH_3)_2$], 2.63 (2H, t, 4-CH_2), 3.60 (2H, t, 7-CH_2), 7.43 (2H, br.s, NH_2), 8.13 ppm (1H, br.s, –N=CH–).

4-Amino-6,6-dimethyl-5,6-dihydro-8H-thiopyrano[4',3':4,5]furo[2,3-d]pyrimidine (VII, $C_{11}H_{13}N_3OS$). To 2.4 g (0.01 mole) of (VI) is added a solution of 0.4 g (0.01 mole) of sodium hydroxide in 30 ml of ethanol. The mixture is boiled for 3 h, and the crystalline precipitate is filtered off, washed with water and ethanol, and dried. Yield 2.0 g (85%), mp 236-238°C (from ethanol). R_f 0.68 (1:2 pyridine–methanol). IR spectrum: 1570, 1595, 1680 (C=C, C=N), 3320 cm^{-1} (NH_2). PMR spectrum (DMSO-D_6, HMDS): 1.40 [6H, s, 6-$(CH_3)_2$], 3.0 (2H, t, 5-CH_2), 3.86 (2H, t, 8-CH_2), 7.80 (2H, br.s, NH_2), 8.4 ppm (1H, s, 2-CH). Mass spectrum, m/z (%): M^+ 235 (100), 220 (6), 202 (19), 161 (100).

3-Amino-4-imino-6,6-dimethyl-5,6-dihydro-8H-thiopyrano[4',3':4,5]furo[2,3-d]pyrimidine (VIII, $C_{11}H_{14}N_4OS$). To a solution of 2.6 g (0.01 mole) of (V) in 20 ml of ethanol is added 5 ml of hydrazine hydrate. The mixture is stirred for 2 h at room temperature. The crystalline precipitate is filtered off, washed with water and alcohol, and dried. Yield 2.0 g (81%), R_f 0.69 (5:1 butanol–pyridine). IR spectrum: 1610, 1630, 1660 (C=C, C=N), 3260, 3305 cm^{-1} (NH_2). PMR spectrum (DMSO-D_6, HMDS): 1.38 [6H, s, 6-$(CH_3)_2$], 2.90 (2H, t, 5-CH_2), 3.71 (2H, t, 8-CH_2), 5.55 (2H, s, 3-NH_2), 7.86 ppm (1H, s, 2-CH).

10,10-Dimethyl-10,11-dihydro-8H-thiopyrano[4',3':4,5]furo[3,2-e](1,2,4)triazolo[2,3-c]pyrimidine (IX, $C_{12}H_{12}N_4OS$). A mixture of 2.5 g (0.01 mole) of (VIII) and 15 ml of triethyl orthoformate was boiled for 4 h. The crystalline precipitate was filtered off, washed with ether, and dried. Yield 2.3 g (87%), R_f 0.61 (5:1 butanol–pyridine). IR spectrum: 1550, 1630, 1660 cm^{-1} (C=C, C=N). PMR spectrum ($CDCl_3$, TMS): 1.53 [6H, s, 10-$(CH_3)_2$]; 3.10 (2H, t, 11-ch_3), 3.90 (2H, t, 8-CH_2), 8.33 (1H, s, 5-CH), 8.80 ppm (1H, s, 2-CH). Mass spectrum, m/z (%): M^+ 260 (57), 245 (11), 227 (50), 186 (100).

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