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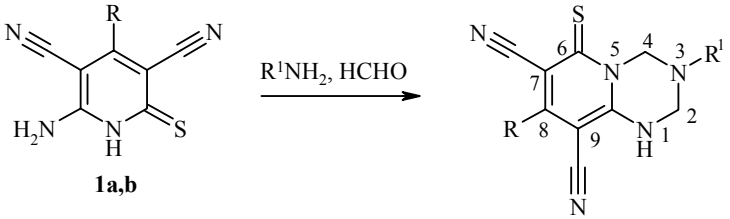
SYNTHESIS OF NEW DERIVATIVES OF PYRIDO[1,2-*a*]TRIAZINE

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

Keywords: 6-amino-4-(het)aryl-2-thioxopyridine-3,5-dicarbonitriles, 1,3,4,6-tetrahydro-2H-pyrido[1,2-*a*]-[1,3,5]triazines, the Mannich reaction.

One of the most useful methods for the annelation of the 1,3,5-thiadiazine ring is the double Mannich aminomethylation of 2-mercaptoazoles and -azines. This reaction is of a general nature and has been used successfully for the synthesis of derivatives of *sym*-triazolo[3,4-*b*][1,3,5]thiadiazine [1], thiazolo-[3',4':1,5][1,2,4]triazolo[3,4-*b*][1,3,5]thiadiazine [2], imidazo[2,1-*b*][1,3,5]thiadiazine [3,4], 1,2,4-triazino[3,2-*b*]-[1,3,5]thiadiazine [4], and 1,3,5-thiadiazino[3,2-*a*]benzimidazole [5]. In the case of derivatives of pyridine-2-thiolate the Mannich reaction does not proceed uniquely but leads to derivatives of pyrido[2,1-*b*]-[1,3,5]thiadiazine [6], 3,7-diazabicyclo[3.3.1]nonane (bispidine) [7], or 3,5,7,11-tetraazatricyclo-[7.3.1.$0^{2.7}$]tridec-2-ene [8] depending on the structure of the aminomethyl substrate. We have studied the behavior of 6-amino-4-(het)aryl-2-thioxopyridine-3,5-dicarbonitriles **1** which are readily accessible by the reaction arylmethylenemalonitriles with cyanothioacetamide under Mannich reaction conditions. It was established that thione **1** readily and under mild conditions underwent aminomethylation with primary amines and HCHO to give pyrido[1,2-*a*]triazines **2**. Thus the presence of an amino group in position 6 is region-directing , and the thione **1** behaves as an N,N-binucleophile rather than an N,S-binucleophile under Mannich conditions. The structures of compounds **2** were confirmed spectroscopically. Characteristic signals in the ^{1}H NMR spectra are the broad peak of the N(1)H proton at 9.61-9.16 ppm and the signals of protons H-4 (6.04-5.36) and H-2 (5.06-4.44 ppm) which are resolved at 200 MHz as a pair of broadened pseudosinglets.

Antihelminthics, fungicides [9], and antagonists of 5-hydroxytryptamine receptors [10] are found among the pyrido[1,2-*a*][1,3,5]triazines, but only a limited number of methods for the synthesis of derivatives of these heterocyclic systems is known.



1a,b **2a,b**

1, 2 a R = 4-ClC6H4, R1 = 4-MeC6H4; b R = fur-2-yl, R1 = CH2Ph

^{1}H NMR spectra of DMSO-d_6 solutions with TMS as internal standard were recorded on a Varian Mercury VX-200 (200 MHz) spectrometer. IR spectra of nujol mulls were recorded with an IKS-29 spectrometer and elemental analyses were carried out with a Perkin-Elmer CHN analyzer.

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[1]"ChemEx" Laboratory, Vladimir Dal' 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; e-mail: vpl@mail.ioc.ac.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No.4, 621-622, April, 2007. Original article submitted September 28, 2006.

Pyrido[1,2-*a*][1,3,5-triazines 2. A suspension of a thione, **1a,b**, (2 mmol) in EtOH (20 ml) was heated until solution was complete, filtered through paper, and a primary amine (2 mmol) and an excess of 37% CH_2O (3.5 ml) were added to the filtrate. The mixture was boiled for 2-3 min with intense stirring. The precipitate was separated and recrystallized from a suitable solvent.

8-(4-Chlorophenyl)-3-(4-methylphenyl)-6-thioxo-1,3,4,6-tetrahydro-2H-pyrido[1,2-*a*][1,3,5]triazine-7,9-dicarbonitrile (2a). Yellow crystals, yield 48%; mp 238-240°C (dec) (from DMF–EtOH, 1 : 1). IR spectrum, ν, cm^{-1}: 2206, 2225 (2C≡N), 3200 (NH). ^{1}H NMR spectrum, δ, ppm (*J* , Hz): 9.61 (1H, br. s, NH); 7.56 (4H, q, ^3J = 8.4, 4-ClC_6H_4); 7.05 (4H, q, ^3J = 8.3, 4-MeC_6H_4); 6.04 (2H, br. pseudo s, H-4); 5.06 (2H, br. pseudo-s, H-2); 2.21 (3H, s, CH_3). Found, %: C 62.94; H 3.87; N 16.80. $C_{22}H_{16}ClN_5S$. Calculated, %: C 63.23; H 3.86; N 16.76.

3-Benzyl-8-(2-furyl)-6-thioxo-1,3,4,6-tetrahydro-2H-pyrido[1,2-*a*][1,3,5-triazin-7,9-dicarbaldehyde (2b). Yellow crystals, 64% yield; mp 300°C (from DMF-EtOH, 1 : 1). IR spectrum, ν, cm^{-1}: 2203, 2215(2 C≡N), 3210 (NH). ^{1}H NMR spectrum, δ, ppm: 9.16 (1H, br. s, NH); 8.10 (1H, m, H-5_{furyl}); 7.38 (1H, m, H-3_{furyl}); 7.32 (5H, m, C_6H_5); 6.82 (1H, m H-1_{furyl}); 5.36 (2H, br. pseudo s, H-4); 4.44 (2H, br. pseudo s, H-2); 3.85 (2H, br. s, $C\underline{H_2}C_6H_5$). Found, %: C 63.89; H 4.06; N 18.80. $C_{20}H_{15}N_5OS$. Calculated, %: C 64.43; H 4.05; N 18.75.

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