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2,N-DICYANOACETAMIDINE IN THE REGIOSELECTIVE SYNTHESIS OF PYRIDO[2,3-D]URACILS

V. L. Ivanov, V. A. Artemov, A. M. Shestopalov, and V. P. Litvinov

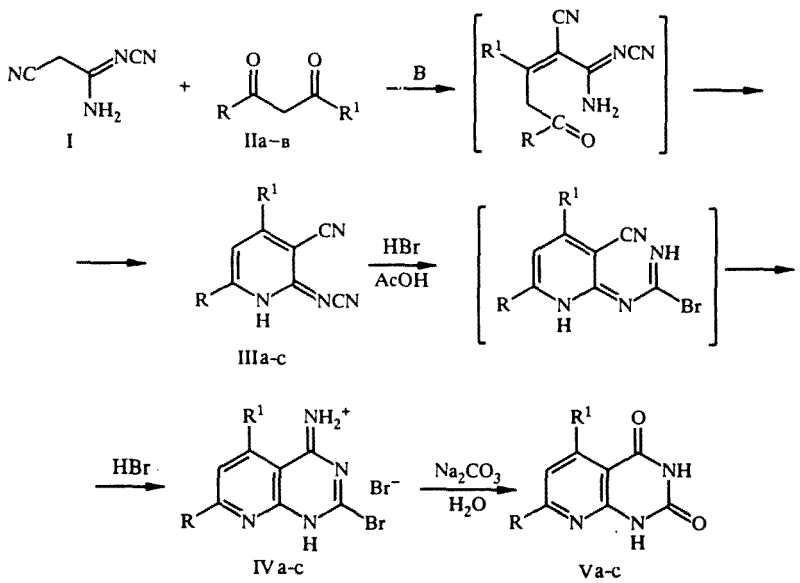
A new regioselective method of synthesizing functionally substituted pyrido[2,3-d]uracils from 2,N-dicyanoacetamidine is proposed. 3-Cyanopyridinecyanoimidines and 4-amino-2-bromopyrido[2,3-d]pyrimidine hydrobromides were obtained as intermediate compounds. The structures of the compounds obtained were established by data of elemental analysis, NMR, IR, and mass spectra.

Functionally substituted pyrido[2,3-d]pyrimidines are of great interest as compounds displaying a wide spectrum of biological activity, such as antiviral, diuretic, antibacterial, etc. However, the known methods of obtaining such compounds, based on closing the pyridine or pyrimidine ring, are characterized by low yields and require forcing conditions [1-7]. We propose a new convenient method for the regioselective synthesis of functionally substituted pyrido[2,3-d]pyrimidines based on 2,N-dicyanoacetamidine (I) which was obtained previously [8-10].

The acetamidine (I) reacts with the β-dicarbonyl compounds (IIa-c) in alcohol in the presence of base leading to the 3-cyanopyridine-2-cyanoimines (IIIa-c) in 42-93% yield (see Table 1).

The formation of pyrimidines (III) probably occurs by a Knoevenagel condensation with the participation of the acidic CH_2 group of compound (I) and a carbonyl group of diketone (II) with subsequent closure of the pyridine ring.

Scheme 1



II–V a R = R^1 = Me; b R = Ph, R^1 = Me; c R = Ph, R^1 = CF_3

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TABLE 1. Yields and Characteristics of Compounds (III), (IV), and (V)

Compound	Empirical formula	Data of elemental analysis, % found/ calculated			mp, °C	IR spectrum, ν, cm^{-1}	PMR spectrum, δ, ppm	Mass spectrum, m/z (I_{rel}, %)	Yield*, %
		C	H	N					
IIIa*2	$C_9H_8N_4$	63.46 62,78	4.51 4,68	33.13 32,54	210...212 (sublimes)	3440, 3352, 3400(NH), 2213, 2184, 2135 (CN)	2.38 (6H, s, $2CH_3$), 6.65 (1H, s, 5-H)	172 (100, M^+), 131 (15), 130 (17)	56; 82
IIIb*2	$C_{14}H_{10}N_4$	71.65 71,78	4.61 4,30	24.20 23,92	>280	3350, 3180 (NH), 2228, 2182, 2120 (CN)	2.52 (3H, S, CH_3), 7.54 (3H, (3H, m, H_{ph}), 7.78 (1H, s, 5-H), 8.13 (2H, m, H_{ph})	234 (100, M^+), 293 (11), 292 (8)	42; 58
IIIc*2	$C_{14}H_7F_3N_4$	57.34 58,34	2.52 2,45	20.63 19,44	165...167 (sublimes)	3380, 3120 (NH), 2280, 2254, 2230 (CN)	7.56 (3H, m, H_{ph}), 7.92 (1H, s, 5-H), 8.25 (2H, m, H_{ph}) 8.25 (2H, m, H_{ph})	288 (100, M^+), 247 (8), 246 (3)	80; 79
IVa*3	$C_9H_9BrN_4 \cdot HBr$	–	–	–	>280	3400... 3200, 2420 (NH), 1710 (C=N)	2.72 (3H, s, 7-CH_3), 2.92 (3H, s, 5-CH_3), 7.05 (1H, s, 6-H), 8.45 and 9.61 (2H, s.s, 12.30 (1H, s, 1-H)	252, 254 (24, M^+), 173 (31), 80,82 (100)	93
IVb*3	$C_{14}H_{11}BrN_4 \cdot HBr$	–	–	–	>280	3400...3200, 2440 (NH), 1705 (C=N)	2.83 (3H, s, CH_3), 7.58 (3H, m, H_{ph}), 7.92 (1H, s, 6-H), 8.20 (2H, m, H_{ph}), 8.95 and 9.48 (2H, s.s, NH_2), 12.55 (1H, s, 1-H)	316, 314 (18, M^+), 235 (22), 80,82 (100)	58
Va*2	$C_9H_9N_3O_2$	56.33 56,54	4.82 4,74	22.40 21,98	>280	3516, 3076 (NH), 1636, 1590 (C=O)	2.50 (3H, s, 7-CH_3), 2.82 (3H, s, 5-CH_3), 7.19 (1H, s, 6-H), 11.5 (2H, br.s, NH)	191 (20, M^+), 190 (100), 148 (81)	67
Vb*2	$C_{14}H_{11}N_3O_2$	66.31 66,40	4.35 4,38	16.44 16,59	>280	3495, 3298, 3207 (NH), 1630, 1580 (C=O)	2.87 (3H, s, CH_3), 7.55 (3H, m, H_{ph}) 7.99 (1H, s, 6-H), 8.23 (2H, m, H_{ph}), 11.5 (2H, br. s, NH)	253 (31, M^+), 252 (100), 210 (90)	51
Vc*2	$C_{14}H_8F_3N_3O_2$	54.12 54,73	2.48 2,62	15.07 13,68	>280	3540, 3256 (NH), 1680, 1592 (C=O)	7.55 (3H, m, H_{ph}), 8.00 (1H, s, 6-H), 8.19 (2H, m, H_{ph}), 11.5 (2H, br. s, NH)	307 (27, M^+), 306 (100), 264 (92)	65

*For compounds (IIIa-c) the first yield is from method A and the second from method B.

*2The signal intensity from the NH group proton is reduced due to exchange with D_2O contained in the DMSO-D_6.

*3Isolation of compounds (IVa, b) in a pure state was unsuccessful.

The process occurs strictly regioselectively for unsymmetrical diketones. Thus only the product with a methyl group in position 4 was obtained from benzoylacetone. This was established by comparing the PMR spectrum of compound (IIIb) with the spectrum of 3-cyano-4-methyl-6-phenylpyridine-2(1H)-thione, the structure of which has been established unambiguously by x-ray crystallographic analysis [11]. Such regioselectivity may be explained by the fact that the initial condensation occurs selectively at the most reactive carbonyl group.

Piperidine was used as base when carrying out the condensation. Good yields were obtained with a catalytic quantity of piperidine (method A) only for benzoyltrifluoro-acetone (IIc) which possesses the most reactive carbonyl group. The yields were significantly increased for the other β-diketones on using an equimolar quantity of piperidine (method B).

Compounds (IIIa-c) were yellow crystalline compounds luminescing in UV light. Their structures were confirmed by data of elemental analysis, PMR, IR, and mass spectra (see Table 1).

Three absorption bands appear in the IR spectra of compounds (III) at 2100-2250 cm^{-1}. The band near 2220 cm^{-1} was assigned to the 3-cyano group. The two bands at 2180 and 2140 cm^{-1} are characteristic of a cyanoimidine fragment [12, 13] and consequently the compounds (III), like their N-nitro analog [14], exist in the imino form.

The cyanopyridocyanoimines (IIIa-c) proved to be convenient starting materials for constructing the pyrido[2,3-d]pyrimidine system. The salts (IVa, b) were obtained in 93 and 58% yield respectively on treating compounds (IIIa, b) with dry HBr in glacial acid. The pyrimidine ring closure reaction occurs regioselectively, which was confirmed by data of IR and PMR spectra (see Table 1). The presence in the PMR spectra of compounds (IVa, b) of two strongly differing single-proton signals at 8.4-8.9 and 9.5-9.6 ppm and also the sharp singlet for the NH group at 12.3-12.5 ppm suggests a structure of 2-bromo-4-imino-1,4-dihydropyrido[2,3-d]pyrimidines as indicated in Scheme 1. The corresponding salt (IVc) is probably also formed from pyridinecyanoimine (IIIc) under analogous conditions. However isolation of (IVc) was unsuccessful, possibly linked with its high solubility (see below).

The regioselectivity of forming these salts is probably caused by the high basicity of the nitrogen atom of the =NCN group compared with a nitrile group linked to carbon.

Compounds (IVa, b) were white crystalline compounds, soluble in water and subliming on heating. Instantaneous hydrolysis occurs on neutralizing them with aqueous sodium carbonate solution with the formation of the pyrido[2,3-d]pyrimidine-2,3-diones (Va, b). Since we were unsuccessful in isolating salt (IVc) from the reaction mixture, as mentioned above, the latter was treated directly with Na_2CO_3 solution and compound (Vc) was isolated. Such ease of nucleophilic substitution in a pyrimidine ring is probably explained by the acceptor influence of the annelated pyridine ring, which is strengthened even more on introducing an electron-accepting group such as CF_3 into the pyridine ring. The yields of the products (V) were 51-67%.

The structures of compounds (Va-c) were confirmed by data of elemental analysis, PMR, IR, and mass spectra (see Table 1). There were two absorption bands for carbonyl groups in the IR spectra of pyridopyrimidinediones (Va-c) near 1630 and 1580 cm^{-1} which are characteristic of condensed uracils [15]. The main direction of fragmentation in the mass spectra was fission of HNCO, which is also characteristic of pyrimidinediones and is in agreement with the structure proposed.

We have developed a new regioselective method of synthesis of pyridouracils from 2,N-dicyanoacetamidine and β-dicarbonyl compounds. The products potentially possess a wide spectrum of biological activity. In addition, the facile nucleophilic substitution in the pyrimidine nucleus of the salt (IVb) may enable the preparation of various functionally substituted 5-deazapteridines, which are also of interest as biologically active compounds.

EXPERIMENTAL

Melting points were determined on a Kofler stage. The IR spectra were taken on a Specord M-80 instrument in KBr disks, PMR spectra on a Bruker WM 250 instrument in DMSO-D_6 solution, and mass spectra on a Varian MAT CH-6 instrument (70 eV). Elemental analysis for C, H, and N was conducted on a Perkin-Elmer C, H, N analyzer. The yields and characteristics of compounds (IIIa-c), (IVa, b), and (Va-c) are given in Table 1.

2,4-Dicyanoacetamidine (I) was obtained according to the method proposed in [8].

3-Cyano-4-R-6-R^1-pyridine-2(1H)-cyanoimidines (IIIa-c). A. A solution of the acetamidine (I) (10 mmole), diketone (II) (10 mmole), and piperidine (2-3 drops) in ethanol (10 ml) was left for 24 h at room temperature. Dilute hydrochloric acid

was then added to the reaction mixture to pH 7. The crystals of product (III) which precipitated were filtered off, washed with ethanol, and air-dried.

B. The products (IIIa-c) were synthesized as described above but using piperidine (10 mmole).

The identity of the compounds obtained by methods A and B was established by IR spectral data.

2-Bromo-4-imino-7-R-5-R^1-1,4-dihydropyrido[2,3-d]pyrimidine Hydrobromides (IVa, b). Dry HBr gas was passed into a suspension of the cyanoimine (III) in glacial acetic acid (50 ml) with stirring and cooling until complete solution of the starting material and the appearance of crystals of product. The reaction mixture was then left overnight in the refrigerator, the crystals of (IV) hydrobromide were filtered off, washed with ether, and air-dried.

7-R-5-R^1-Pyrido[2,3-d]pyrimidine-2,4-diones (Va, b). An aqueous solution of Na_2CO_3 was added to a solution of (IVa, b) hydrobromide (10 mmole) in water (10 ml) until a weakly alkaline reaction was given. The crystals of product (IVa, b) were filtered off, washed with water and with acetone, and air-dried.

7-Phenyl-5-trifluoromethylpyrido[2,3-d]pyrimidine-2,4-dione (Vc). Dry HBr gas was passed into a suspension of cyanoimine (IIIc) (10 mmole) in glacial acetic acid (50 ml) with stirring and cooling until complete solution of the starting material. After maintaining at room temperature for 3 h the reaction mixture was poured into water and neutralized with sodium carbonate. The precipitated crystals were filtered off, washed with water and with acetone, and air-dried.

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