Chemistry of Heterocyclic Compounds, Vol. 37, No. 3, 2001

SYNTHESIS OF ALKYL 5,6-DIALKYL-2-AMINO-3-CYANOPYRIDINE-4-CARBOXYLATES

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An unusual route has been found for the hydrolysis of 3-amino-1,1-dialkoxy-6,7-dialkyl-4-aryl-3a,4,5,7a-tetrahydro-1H-pyrrolo[3,4-c]pyridine-3a,7a-dicarbonitriles in acidic medium which leads to the formation of alkyl 5,6-dialkyl-2-amino-3-cyanopyridine-4-carboxylates.

Keywords: 3-amino-1,1-dialkoxy-6,7-dialkyl-4-aryl-3a,4,5,7a-tetrahydro-1H-pyrrolo[3,4-*c*]pyridine-3a,7a-dicarbonitriles, alkyl 2-amino-5,6-dialkyl-3-cyanopyridine-4-carboxylates.

By studying the addition reaction of nucleophiles at the cyano group of 1,1,2,2-tetracyano-substituted cyclic systems it has been shown that the process occurs selectively at one of the cyano groups with subsequent cyclization and formation of 2-amino-5,5-dialkoxypyrroline or 2-aminopyrrolin-5-one fragment [1-4]. The hydrolysis reaction of compounds containing these fragments has been studied for many substances. In the majority of cases the hydrolysis in the presence of mineral acids occurs without affecting the remaining cyano groups and leads to the formation of imides [4, 5]. Examples are also known where the hydrolysis reaction occurs more extensively, but in these cases it has been proposed that imides are formed in the intermediate stages [5, 6].

For 1,1-dialkoxy-6,7-dialkyl-3-amino-4-aryl-3a,4,5,7a-tetrahydro-1H-pyrrolo[3,4-*c*]pyridine-3a,7-dicarbonitriles **1a-i** [7] we have discovered an unusual route for the hydrolysis using dilute sulfuric acid in which alkyl 5,6-dialkyl-2-amino-3-cyanopyridine-4-carboxylates (**9**) are formed instead of the expected imides **2**. Their structures are based on a series of experimental facts and on their physico-chemical analytical data. Hence compounds **1a** and **1f**, which differ only in their alkoxy groups give different compounds in the course of the reaction and hence the alkoxy groups are wholly or partially retained in the structure. Among the reaction products aromatic aldehydes are found. The hydrolysis of compounds **1a** and **1e**, which have different aryl substituents, leads to one and the same compound **9a**, i.e. in the hydrolysis process elimination of fragment containing the aromatic substituent occurs and this is converted to the aldehyde under the reaction conditions.

Absorption bands at 3300-3200 and 1660 cm^{-1} corresponding to the stretching and bending vibrations of the NH_2 group and strong absorption bands of the conjugated cyano group at 2230-2240 cm^{-1} are observed in the IR spectra of the compounds obtained (Table 1).

The nature of the absorption bands of the cyano and amino groups allows one to suppose the presence of enaminonitrile fragment in the hydrolysis product molecule. The presence of a strong absorption band in the region of 1705-1725 cm^{-1} points to the occurrence of carbonyl group in the synthesized compounds. The mass

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TABLE 1. IR Spectral Characteristics (cm^{-1}) of Compounds **9a-h**

Compound	νNH	δNH	νC=N	νC=O
9a	3190, 3315, 3400, 3420	1635	2227	1705
9b	3190, 3323, 3387, 3412	1640	2232	1723
9c	3170, 3250, 3330, 3380	1640	2230	1705
9d	3165, 3250, 3320, 3383	1639	2223	1698
9e	3150, 3240, 3335, 3410	1640	2229	1722
9f	3120, 3220, 3330, 3400	1662	2232	1715
9g	3160, 3330, 3387, 3405	1649	2230	1710
9h	3175, 3315, 3369, 3415	1645	2227	1707

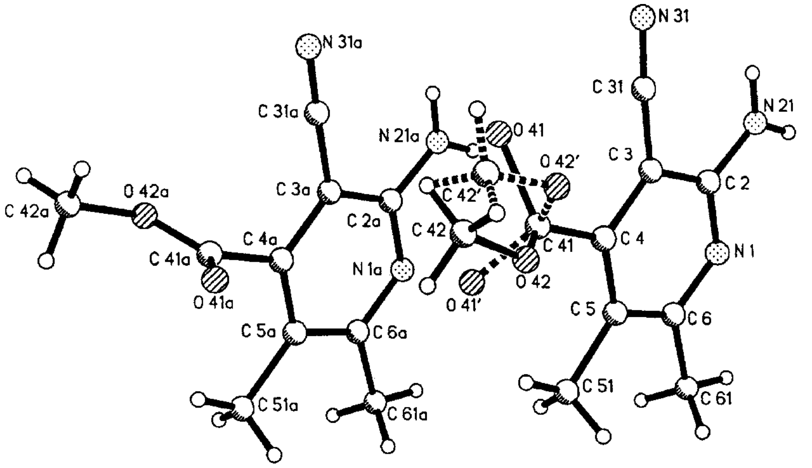
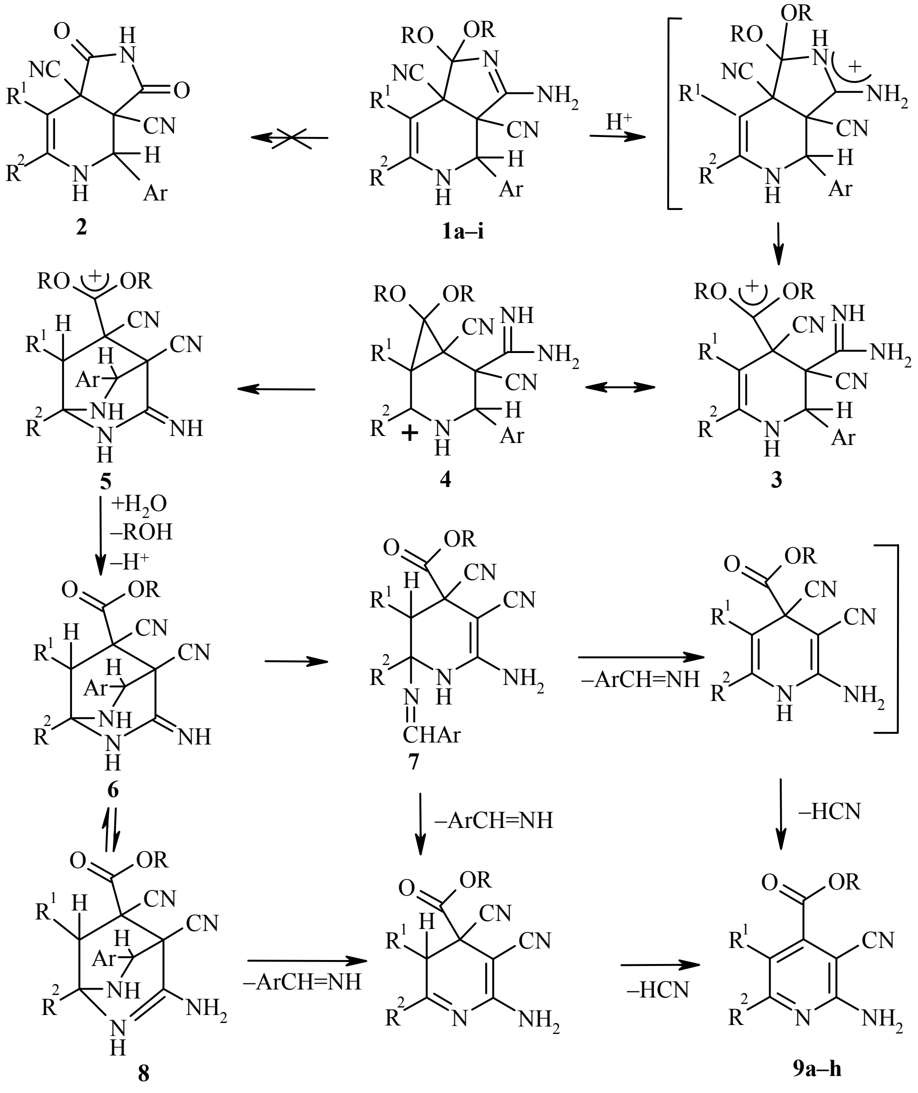


Fig. 1. Molecular structure of
methyl 2-amino-3-cyano-5,6-dimethylpyridine-4-carboxylate **9b**.

spectroscopic data for the product of hydrolysis of compound **1a** allow to suppose that the starting compound adds a molecule of water in the course of the reaction but also eliminates molecules of benzaldimine, methanol, and hydrogen cyanide. X-ray structural investigation of the single crystal of compound **9b** was carried out to provide an unambiguous proof of the structure of the reaction products (see Fig. 1).

A comparative analysis of compounds containing 5,5-dialkoxy-2-amino-3,4-dicyanopyrroline fragment (hydrolysis of which gives the corresponding imides) and pyrrolo[3,4-*c*]pyridines **1** discussed here has shown that one of the significant differences in the latter is the presence of the multiple bond (having an enamine character) in direct proximity to the pyrroline fragment. Thanks to this disposition of the multiple bond it is able to provide anchimeric assistance to the fission of the pyrroline ring [8]. On the other hand, addition of the amidine group formed in this way to the electrophilic carbon atom of the enamine provides the possibility of subsequent stabilization to give the aromatic system of the end product. In our view, these factors predetermine the reaction course and are the most likely reason for its anomalous character. Hence we propose the following scheme for the reaction.



1 **a** $R^1,R^2 = (CH_2)_4$, $R = CH_3$, Ar = Ph; **b** $R^1 = R^2 = CH_3$, $R = CH_3$, Ar = Ph;
c $R^1 = CH_3$, $R^2 = H$, $R = CH_3$, Ar = Ph; **d** $R^1,R^2 = (CH_2)_3$, $R = CH_3$, Ar = Ph;
e $R^1,R^2 = (CH_2)_4$, $R = CH_3$, Ar = 4-MeOC_6H_4; **f** $R^1,R^2 = (CH_2)_4$, $R,R = (CH_2)_2$, Ar = Ph**;**
g $R^1 = R^2 = CH_3$, $R,R = (CH_2)_2$, Ar = Ph; **h** $R^1 = CH_3$, $R^2 = H$, $R,R = (CH_2)_2$, Ar = Ph;
i $R^1,R^2 = (CH_2)_4$, $R = C_2H_5$, Ar = Ph; **9** **a** $R = CH_3$, $R^1,R^2 = (CH_2)_4$; **b** $R = R^1 = R^2 = CH_3$;
c $R = R^1 = CH_3$, $R^2 = H$; **d** $R = CH_3$, $R^1,R^2 = (CH_2)_3$; **e** $R = HOCH_2CH_2$, $R^1,R^2 = (CH_2)_4$;
f $R = HOCH_2CH_2$, $R^1 = R^2 = CH_3$; **g** $R = HOCH_2CH_2$, $R^1 = CH_3$, $R^2 = H$;
h $R = C_2H_5$, $R^1,R^2 = (CH_2)_4$

Initially the protonated substrate undergoes fission of the pyrroline fragment to form intermediate **3**. Evidently in the latter, an additional stabilization is possible due to the interaction of the carbocationic center with a π-orbital of the double bond and this can be represented by the Lewis structure **4**. This must result in an increase in the partial positive charge on atom $C_{(6)}$ of the tetrahydropyridine ring which favors the intramolecular addition of the amidine group. The carbocation **5** formed as a result of these reactions is further stabilized by the formation of the ester group and subsequent fission of aldimine and hydrogen cyanide. For the intermediate **6** two routes can be proposed for the elimination of aldimine, i.e. staged fission *via* the intermediate **7** or an simultaneous cycloelimination *via* the tautomeric form **8**.

TABLE 2. The Characteristics of the Synthesized Compounds **9a-h**

Com-pound	Empirical formula	Found, % Calculated, % C	 H	 N	mp, °C	Yield, %
9a	$C_{12}H_{13}N_3O_2$	62.30 62.33	5.71 5.66	18.15 18.17	195-196	56
9b	$C_{10}H_{11}N_3O_2$	58.55 58.59	5.43 5.40	20.45 20.41	171-172	78
9c	$C_9H_9N_3O_2$	56.51 56.54	4.77 4.74	21.95 21.98	188-189	51
9d	$C_{11}H_{11}N_3O_2$	60.78 60.82	5.15 5.11	19.31 19.34	219-220	58
9e	$C_{13}H_{15}N_3O_3$	59.79 59.77	5.76 5.74	16.15 16.09	143-144	42
9f	$C_{11}H_{13}N_3O_3$	56.17 56.17	5.53 5.56	17.85 17.88	225-226	57
9g	$C_{10}H_{11}N_3O_3$	54.27 54.29	4.96 4.97	19.05 19.00	185-186	82
9h	$C_{13}H_{15}N_3O_2$	68.15 68.12	6.56 6.55	18.32 18.34	155-156	75

TABLE 3. Bond Lengths (*d*) and Bond Angles (ω) in the Molecule **9b**

Bond	*d*, Å	Angle	ω, deg.
O(41)–C(41)	1.190(5)	C(41)–O(42)–C(42)	115.5(4)
O(42)–C(42)	1.458(5)	N(21)–C(2)–N(1)	116.6(3)
N(l)–C(2)	1.348(4)	N(1)–C(2)–C(3)	120.6(3)
N(31)–C(31)	1.148(5)	C(4)–C(3)–C(31)	122.4(3)
C(3)–C(4)	1.402(5)	N(31)–C(31)–C(3)	178.0(4)
C(4)–C(5)	1.372(5)	C(5)–C(4)–C(41)	120.5(3)
C(5)–C(6)	1.419(5)	O(41)–C(41)–O(42)	125.2(4)
C(6)–C(61)	1.496(5)	O(42)–C(41)–C(4)	111.8(3)
O(42)–C(41)	1.310(5)	C(4)–C(5)–C(51)	122.4(3)
N(1)–C(6)	1.340(4)	N(1)–C(6)–C(5)	123.0(3)
N(21)–C(2)	1.339(5)	C(5)–C(6)–C(61)	120.8(3)
C(2)–C(3)	1.415(5)	C(6)–N(1)–C(2)	120.0(3)
C(3)–C(31)	1.435(5)	N(21)–C(2)–C(3)	122.8(3)
C(4)–C(41)	1.514(5)	C(4)–C(3)–C(2)	118.4(3)
C(5)–C(51)	1.518(5)	C(2)–C(3)–C(31)	119.2(3)
		C(5)–C(4)–C(3)	121.2(3)
		C(3)–C(4)–C(41)	118.3(3)
		O(41)–C(41)–C(4)	123.0(4)
		C(4)–C(5)–C(6)	116.8(3)
		C(6)–C(5)–C(51)	120.8(4)
		N(1)–C(6)–C(61)	116.2(3)

EXPERIMENTAL

Monitoring of the reaction course and the purity of the synthesized compounds was carried out by TLC on Silufol UV-254 plates with UV or iodine vapor visualization. IR spectra were obtained for thin layers (suspensions in vaseline oil) on UR-20 instrument. High- and low-resolution mass spectra were recorded on a Varian MAT-212 instrument with an ionization energy of 70 eV.

TABLE 4. Coordinates of Non-hydrogen Atoms ($\times 10^4$) and Coefficients of Equivalent Isotropic Shift ($Å^2 \times 10^3$) for Compound **9b**

Atom	*x*	*y*	*z*	$U_{(eq)}$
O(41)	463(4)	8142(4)	-68(4)	83(1)
O(42)	2788(3)	8795(3)	-701(2)	43(1)
N(l)	4301(3)	5558(3)	1727(2)	26(1)
N(21)	5245(5)	7537(4)	2935(3)	53(1)
N(31)	3863(5)	10577(4)	2075(3)	45(1)
C(2)	4392(4)	6989(4)	2035(3)	27(1)
C(3)	3629(4)	7847(4)	1417(3)	25(1)
C(31)	3740(5)	9366(4)	1771(3)	30(1)
C(4)	2750(4)	7168(4)	493(3)	27(1)
C(41)	1848(5)	8074(4)	-130(3)	32(1)
C(42)	2028(8)	9739(7)	-1298(5)	52(1)
C(5)	2645(4)	5711(4)	180(3)	26(1)
C(51)	1738(5)	4950(5)	-830(3)	38(1)
C(6)	3472(4)	4934(4)	834(3)	23(1)
C(61)	3425(5)	3340(4)	560(3)	28(1)
O(4lA)	1010(6)	6368(5)	2650(3)	23(1)
O(42A)	569(6)	7849(5)	4102(3)	18(1)
O(41')	2281(8)	8466(7)	3759(5)	60(2)
O(42')	71(9)	6924(7)	3389(6)	60(2)
N(IA)	3314(4)	4346(3)	5679(2)	27(1)
N(21A)	4279(4)	6345(4)	6883(3)	37(1)
N(31A)	3364(5)	9373(4)	5999(4)	59(1)
C(2A)	3484(4)	5786(4)	5957(3)	26(1)
C(3A)	2814(5)	6656(4)	5297(3)	34(1)
C(31A)	3086(5)	8183(5)	5659(4)	43(1)
C(4A)	1949(5)	6001(5)	4366(3)	39(1)
C(41A)	1240(7)	6928(8)	3679(4)	76(2)
C(42A)	-161(13)	8734(12)	3440(9)	32(2)
C(42')	-627(16)	8021(14)	2889(11)	47(3)
C(5A)	1787(5)	4519(5)	4083(3)	45(1)
C(51A)	858(9)	3691(9)	3099(4)	83(2)
C(6A)	2507(5)	3733(5)	4775(3)	34(1)
C(61A)	2419(7)	2135(5)	4524(4)	49(1)

Alkyl 5,6-Dialkyl-2-amino-3-cyanopyridine-4-carboxylates (9a-h). (General Method). Compound **1** (0.01 mol) was suspended in mixture of water and 2-propanol (1:1, 5 ml) and sulfuric acid (1.1 g, 0.011 mol) was added as 15% aqueous solution. A large excess of acid led to some difficulties in the separation of the final material. The mixture obtained was brought to boiling and then cooled. It was neutralized with sodium bicarbonate to neutral reaction and the precipitate formed was filtered, washed with 2-propanol, and purified by recrystallization from ethyl acetate or sublimation in vacuo. The melting point, yield, and elemental analysis data are given in Table 2. The mass spectrum of compound **9a** showed the following *m/z* (I_{rel}, %): 231 (42), 216 (100), 200 (14), 188 (7), 172 (10), 170 (22), 157 (9), 143 (8), 77 (14), 63 (9), 43 (10) (the molecular ion peak and 10 strongest fragment ions are referred).

X-ray Diffraction Investigation of Compound 9b. Crystals of **9b** ($C_{10}H_{11}N_3O_2$, M = 205.22) at 20°C are triclinic; the space group *P*1; *a* = 8.479 (2), *b* = 9.491 (2), *c* = 12.939 (3) Å; α = 98.62 (2), β = 92.64 (3), γ = 97.37 (3)°; V = 1018.7 (4) $Å^3$; *Z* = 4 (two crystallographically independent molecules), d_{calc} = 1.338 g/cm^3. The unit cell parameters and intensities of 4780 reflections were measured on a Siemens P3/PC automatic four-circle diffractometer (293 K, λMoKα, graphite monochromator, $\theta/2\theta$ scanning, θ_{max} = 27°) (Table 3). The structure was solved by direct method and refined by full-matrix, least-squares analysis in the anisotropic approximation for non-hydrogen atoms (Table 4). The hydrogen atoms were localized directly by Fourier difference synthesis and refined in the isotropic approximation. A disordering of the methoxycarbonyl group in one of the crystallographically independent molecules was observed. The final divergence factors were $R_1 = 0.083$ for 4412 independent reflections with $I > 2\sigma(I)$ and $wR_2 = 0.264$ for all 4473 independent reflections. Calculations were performed using the SHELXTL PLUS; SHELXL-93 programs.

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