Cyclization of *N*-Cyanovinyl-lactam Imines to Condensed 4-Aminopyridines or Substituted Aminopyrazole

Michael Pätzel, Alexej Ushmajev and Jürgen Liebscher*

Institut für Organische Chemie, Fachbereich Chemie, Humboldt-Universität Berlin, Hessische Str. 1-2, D-1040 Berlin, Germany

Vladimir Granik, Sofia Grisik and Mikhail Polievktov

Chemical-Pharmaceutical All-Union Research Institute VNICHPHI, Zubowskaja Street 7, Moscow 119815, USSR

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N-Cyanovinyl-lactam imines **2** react with hydrazine giving aminopyrazole **4a** while lactam imine **3** is split off. Treatment of **2** with strong bases gives intramolecular cyclization to condensed 4-aminopyridines **5**. The progress of reaction was observed by polarographic method.

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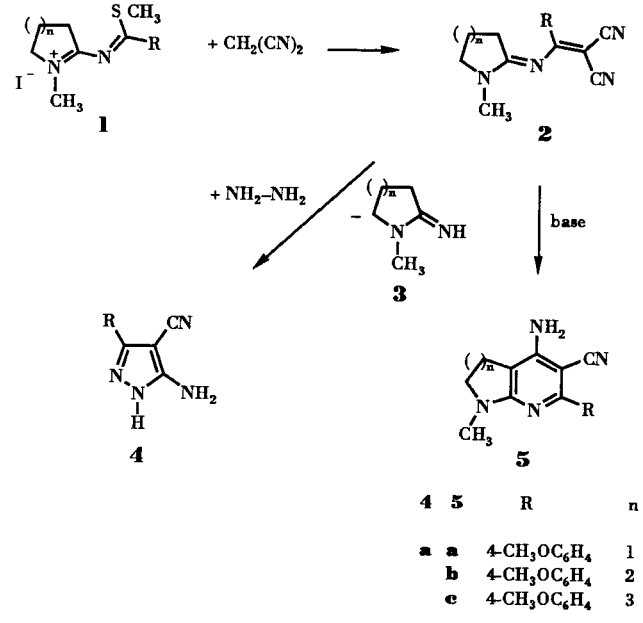
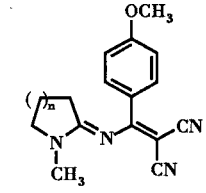
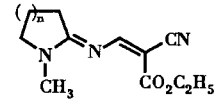
Recently we reported on the ring chain transformation of semicyclic 3-methylthio-2-aza-2-propeniminium salts **1** with malonodinitrile giving aminoalkylpyrimidines [1]. *N*-Cyanovinyl-lactam imines **2** were isolated as primary condensation products cyclizing by the subsequent influence of hydrogen bromide. We were further interested to investigate the chemical behavior of these *N*-cyanovinyl-lactam derivatives **2**. Approaches to open the lactam imine ring by primary amines in order to obtain 3-amidinoacrylonitrile compounds which should be suitable for cyclization to pyrimidines [2] failed. The unchanged starting material **2** was recovered. Further attempts to adopt the known reaction of 1-amino-4-cyanobutadienes with hydrazine hydrate giving 1-aminopyridin-2-imines [3] to *N*-cyanovinyl-lactam derivatives **2** gave an unforeseen result. Instead of the expected 1-amino-6-iminopyrimidines deriving from attack of the hydrazine at the amidine as well as at the cyano carbon atom of **2** 3-amino-4-cyano-5-(4-methoxyphenyl)pyrazole **4a** was obtained. The formation of this



4	5	R	n
a	a	4-$CH_3OC_6H_4$	1
	b	4-$CH_3OC_6H_4$	2
	c	4-$CH_3OC_6H_4$	3

Table 1

Half-wave Potentials of *N*-Cyanovinyl-lactam Imines **2**

No.	Formula	n	$E_{1/2}$ [V]
2a		1	-1.67
2b		2	-1.68
2c		3	-1.70
6a		1	-1.97 [6]
6b		2	-1.96 [6]
6c		3	-1.95 [6]

compound **4a** can be explained by attack of the hydrazine at both, position 1 and 3 of the acrylonitrile fragment. The lactam imino group acts as a leaving group. Similar synthesis of aminopyrazoles are known with acrylonitriles having other amino substituents at position 3 [4].

Like other lactam imines *N*-cyanovinyl-lactam imines **2** should be relatively acidic at the CH_2 group in position 3 of the lactam imine ring. This property was exploited in intramolecular cyclizations of *N*-ethoxycarbonylvinyl-lactam imines affording condensed 4-pyridones by attack of the carbon atom found in position 3 of the lactam imine ring at the ester carbonyl carbon atom [5]. This cyclization was brought about either by mere heating or in the presence of 4-toluenesulfonic acid. Analogous investigations with the corresponding nitriles **2** gave no reaction. In the presence of strong bases such as sodium hydride in DMF (Method A) however a smooth reaction took place by heating giving the expected condensed 4-aminopyridines **5** in high yields. The structure of the new compounds **5** is confirmed by spectroscopic and analytical data. It can be assumed that the reaction is initiated by deprotonation of position 3 of the lactam imine ring following by Thorpe-analogous addition to the cyano group. The progress of

the reaction can be observed by polarography (see below). Running the reaction in a polarographic cell showed that all starting material **2** disappeared within 30 seconds even at room temperature. Therefore we elaborated a second method (Method B) for the synthesis of condensed 4-aminopyridines **5** operating under more mild conditions that is at 28° in the presence of sodium ethoxide, giving comparable yields. Half wave reduction potentials of **2** are found in the range from 1.67 to 1.70 V (see Table 1). They are hardly influenced by the size of the lactam imine ring. The relative ease of the reduction of **2** in comparison to previously known *N*-cyanovinyl-lactam imines **6** is worth mentioning [6].

EXPERIMENTAL

The melting points were measured with a "Boetius" hot-stage apparatus and are uncorrected. The ^{1}H-nmr spectra were recorded with a Varian XL 200 (200 MHz). Mass specta were taken with a Varian MAT-112 (70 eV) spectrometer and the ir spectra with a Perkin-Elmer 457. Polarography: Polarografic curves were registered on polarograph OH-105 (Hungary). The capillary used had the following characteristic: m = 1.3 mg/sec, t = 0.26 sec (with strip for forced drop brake off). Reference electrode was Ag rode emerged in stock solution (0.05 *M* Bu_4NI in DMF). The half wave potentials are given against saturated calomel electrode by using standard potassium seale. Polarografic cell was thermostated at 25°.

3-Amino-4-cyano-5-(4-methoxyphenyl)pyrazole **4a**.

Hydrazine hydrate (80%, 1.0 g, 30 mmoles) is dropped under stirring to a solution of *N*-cyanovinyl-lactam imine **2** (n = 1, R = 4-Meo-Ph) (2.8 g, 10 mmoles) in 2-propanol (20 ml). The mixture is slowly heated to 125° in distillation set up while the solvent is distilled off. The residue is kept at this temperature for 5 minutes. After cooling to room temperature the obtained product is recrystallized from ethanol/water (10:1) to give **4a** (1.2 g, 55%), mp 184-185° (ethanol/water); ir (potassium bromide): 2210 cm^{-1} ms: (m/z) 214 (M^+, 49), 199 (14), 116 (19), 28 (16), 15 (100); ^{1}H-nmr: δ 3.77 (s, 3H, OCH_3), 6.41 (br, 2H, NH_2), 7.02 (d, J = 8 Hz, 2H, C_6H_5), 7.72 (d, J = 8 Hz, 2H, C_6H_5), 12.01 (br, 1H, NH).

Anal. Calcd. for $C_{11}H_{10}N_4O$ (214.23): C, 61.67; H, 4.71; N, 26.15. Found: C, 61.86; H, 4.89; N, 25.92.

4-Amino-5-cyano-6-(4-methoxyphenyl)-1-methyl-2,3-dihydropyrrolo[2,3-*b*]pyridine **5a**.

Method A.

N-Cyanovinyl-iminopyrrolidine **2** (R = 4-$CH_3OC_6H_4$, n = 1) (1.38 g, 5 mmoles) is added to a suspension of sodium hydride (0.12 g, 5 mmoles) in dry DMF (30 ml). The mixture is refluxed for 1 hour. After cooling to room temperature absolute ethanol (10 ml) is added. The solvent is evaporated in vacuum and the remaining material is poured into water. The colorless crystalline product is filtered and dried, yield 1.20 g (86%), mp 164-165° (ethyl acetate); ^{1}H-nmr (DMF-d_7): δ 2.93 (t, J = 8.8 Hz, 2H, CH_2), 2.93 (s, 3H, NCH_3), 3.56 (t, J = 8.8 Hz, 2H, CH_2), 3.88 (s, 3H, OCH_3), 6.09 (br, 2H, NH_2), 7.05 (d, J = 9 Hz, 2H, C_6H_4), 7.81 (d, J = 9 Hz, 2H, C_6H_4); ir (nujol): ν = 2190 (CN), 3220, 3350, 3460 cm^{-1} (NH_2); ms: (m/z) 280 (M^+, 95), 279 (100), 252 (12).

Anal. Calcd. for $C_{16}H_{16}N_4O$ (280.3): C, 68.57; H, 5.71; N, 20.00. Found: C, 68.54; H, 5.85; N, 20.21.

Method B.

Sodium hydride (0.034 g, 1.43 mmoles) is added to a solution of *N*-cyanovinyliminopyrrolidine **2** (R = 4-$CH_3OC_6H_4$, n = 1) (0.4 g, 1.43 mmoles) in dry DMF (10 ml). The mixture is stirred at 28° for 1 hour. After the addition of water (20 ml) the precipitate is filtered and washed with water, yield 0.30 g (75%).

Method C.

Ethanolic sodium ethoxide (14.8%, 1.7 ml, 3.6 mmoles) is added to a solution of *N*-cyanovinyliminopyrrolidine **2** (R = 4-$CH_3OC_6H_4$, n = 1) (0.1 g, 0.36 mmole) in dry DMF (5 ml). The mixture is stirred for 2 hours and water (20 ml) is added. The precipitate is filtered off and is washed with water until *p*H reaches 7, yield 0.8 g (80%).

5-Amino-6-cyano-7-(4-methoxyphenyl)-1-methyl-1,2,3,4-tetrahydro-1,8-naphthiridine **5b**.

Sodium hydride (0.08 g, 3.4 mmoles) is added to a solution of *N*-cyanovinyliminopiperidine **2** (R = 4-$CH_3OC_6H_4$, n = 2) (1.0 g, 3.4 mmoles) in 10 ml of dry DMF. The mixture is refluxed for 1 hour. After cooling to room temperature water (30 ml) is added. The precipitating product is filtered and is washed with water, yield 0.85 g (85%), mp 156-157° (ethyl acetate); ^{1}H-nmr (DMF-d_7): δ 1.94 (m, 2H, CH_2), 2.59 (t, J = 6.6 Hz, 2H, CH_2), 3.15 (s, 3H, CH_3), 3.37 (t, J = 5.5 Hz, 2H, CH_2), 3.87 (s, 3H, OCH_3), 5.92 (br, 2H, NH_2), 7.07 (d, J = 8.8 Hz, 2H, C_6H_4), 7.84 (d, J = 8.8 Hz, 2H, C_6H_4); ir (nujol): ν = 2200 (CN), 3220, 3340, 3480 cm^{-1} (NH_2); ms: (m/z) 294 (M^+, 100), 279 (26), 239 (18).

Anal. Calcd. for $C_{17}H_{18}N_4O$ (294.4): C, 69.39; H, 6.12; N, 19.05. Found: C, 69.49; H, 6.10; N, 18.90.

6-Amino-7-cyano-8-(4-methoxyphenyl)-1-methyl-2,3,4,5-tetrahydropyrido[2,3-*b*]azepine **5c**.

N-Cyanovinyliminohexahydroazepine **2** (R = 4-$CH_3OC_6H_4$, n = 3) (1.0 g, 3.25 mmoles) is reacted with sodium hydride in DMF following the forstanding procedure, yield 0.87 g (87%), mp 164-166° (ethyl acetate); ^{1}H-nmr (DMF-d_7): δ 1.85 (m, 2H, CH_2), 2.69 (t, J = 5.2 Hz, 2H, CH_2), 3.10 (s, 3H, NCH_3), 3.43 (t, J = 5.3 Hz, 2H, CH_2), 3.87 (s, 3H, OCH_3), 6.04 (br, 2H, NH_2), 7.08 (d, J = 8.7 Hz, 2H, C_6H_4), 7.86 (d, J = 8.7 Hz, 2H, C_6H_4); ir (nujol): ν = 2200 (CN), 3220, 3340, 3480 cm^{-1} (NH_2); ms: (m/z) 308 (M^+, 92), 293 (54), 279 (100), 239 (23).

Anal. Calcd. for $C_{18}H_{20}N_4O$ (308.4): C, 70.13; H, 6.49; N, 18.18. C, 69.86; H, 6.54; N, 18.02.

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