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Formation of Oxopyridine Ring from Two Cyanoacetanilide Molecules via Preliminary Transformation of One of Them into Ethoxymethylidene Derivative

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Abstract—Cyanoacetanilides reacted with their ethoxymethylidene derivatives to produce two regioisomeric products from the same linear intermediate, the isomer ratio depending on the substituents in the aromatic rings of the initial cyanoacetanilides.

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Studies on mechanisms of chemical reactions constitute an important field of synthetic organic chemistry. We were interested in nucleophilic vinylic substitution in ethoxymethylidene derivatives of nitriles having an activated methylene group [1]. We previously studied reactions of diethyl ethoxymethylidenemalonate with cyanoacetanilides, which afforded 2-amino-5-cyano-6-oxo-*N*,1-diaryl-1,6-dihydropyridine-3-carboxamides as the major products [2]. The same compounds were synthesized via an alternative route, by reaction of ethoxymethylidene derivatives of CH acids with cyanoacetanilides having similar substituents in the aryl rings. When the reaction was carried out in the presence of 0.5 equiv of a base, we succeeded in isolating intermediate S_NVin product. Heating of the latter in the presence of excess base gave the expected cyclic structure.

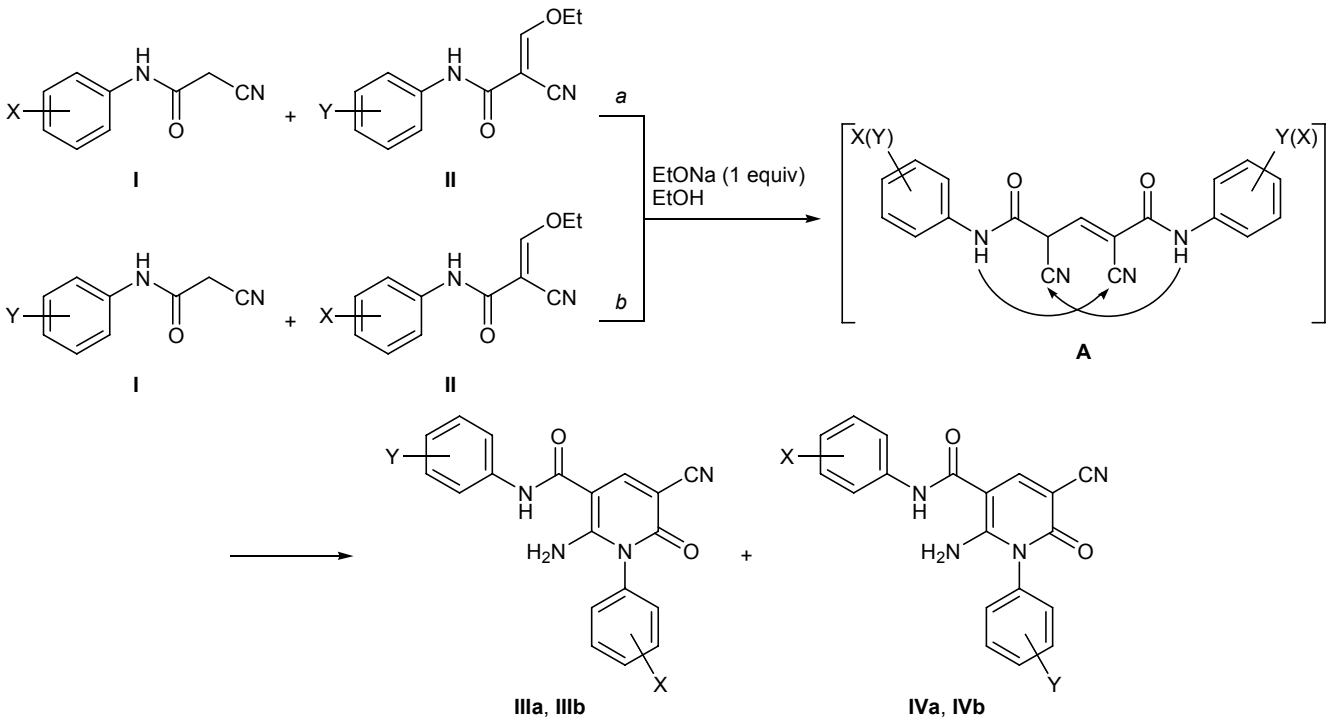
In the present work we tried to elucidate the effect of substituents in the aromatic rings of initial cyanoacetanilides on the direction of intramolecular cyclization of linear intermediate **A**. For this purpose we performed a series of reactions with compounds **I** and **II** having different substituents in the benzene rings (Scheme 1). As expected, these reactions led to the formation of two regioisomers **III** and **IV** at different ratios.

The ratio of isomers **IIIa** and **IVa** obtained according to paths *a* and *b* was ~70:30% (Scheme 1). It was estimated by analysis of the ^{1}H NMR spectra of crude isomer mixtures **IIIa**/**IVa**. This means that the isomer ratio is determined by the structure of linear intermediate product rather than of initial compounds. Presumably, conjugation of lone electron pair on the chlorine atom with the benzene ring weakens conjugation of the latter with lone electron pair on the nitrogen atom which becomes more accessible for subsequent cyclization; as a result, compound **IIIa** is formed as the major product. Here, it does not matter whether the substituent is present in the aromatic ring of cyanoacetanilide **I** or ethoxymethylidene derivative **II**; in both cases the isomer ratio **IIIa**:**IVa** depends on the nucleophilicities of the nitrogen atoms in linear intermediate **A**.

The results of analogous condensations of cyanoacetanilides with ethoxymethylidene derivatives having *o*-methoxy- and *p*-chlorophenyl substituents (Scheme 1) confirmed our assumption that the S_NVin reaction is governed exclusively by the substituent nature. The ratio of isomers **IIIb** and **IVb** was 91:9 (*a*) and 83:17 (*b*). Obviously, the effect of the chlorine atom is the same as above.

In the reaction of *o*-methoxy-substituted cyanoacetanilide **Ia** with *o*-ethyl-substituted ethoxymethylidene derivative **IIa** we succeeded in isolating intermediate linear condensation product **V** (Scheme 2). The NH signals in the ^{1}H NMR spectrum of **V** were observed at δ 8.22 ppm, whereas the cyclic structures were characterized by NH chemical shifts δ of 9.45–9.67 ppm. The

Scheme 1.



III, **IV**, X = 4-Cl, Y = H (**a**), 2-MeO (**b**).

Path	X	Y	Products (ratio, %)
a	4-Cl	H	**IIIa**, **IVa** (71 : 29)
	4-Cl	2-OMe	**IIIb**, **IVb** (91 : 9)
b	4-Cl	H	**IIIa**, **IVa** (68 : 32)
	4-Cl	2-OMe	**IIIb**, **IVb** (83 : 17)

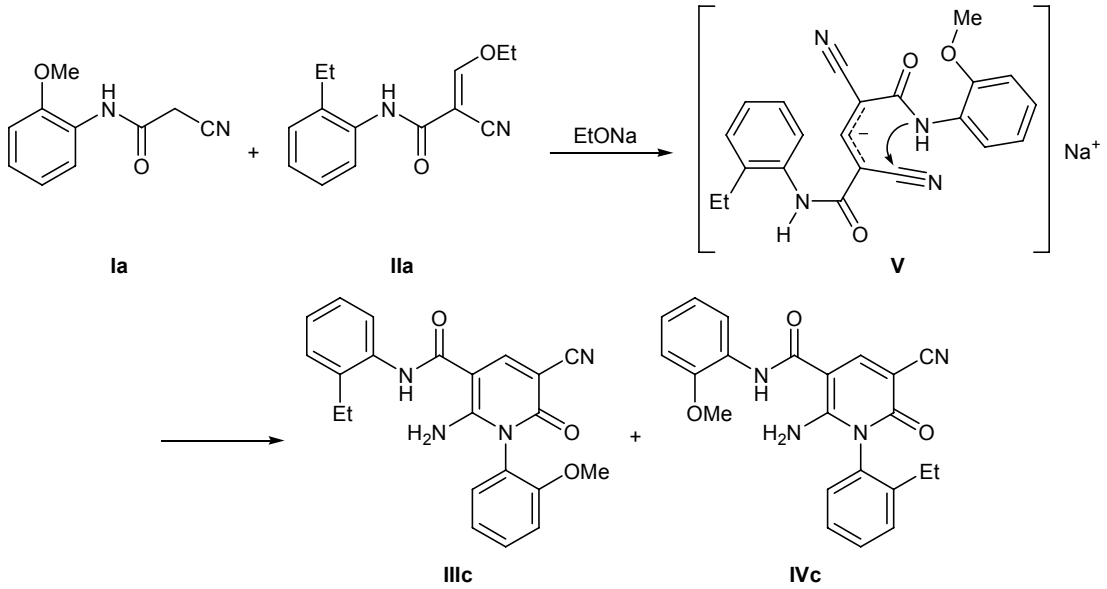
IR spectrum of **V** contained absorption bands at 2210 and 2190 cm^{-1} due to stretching vibrations of the cyano groups [3], and the carbonyl stretching vibration bands were observed at 1635 cm^{-1}, which is typical of such compounds [3].

The structure of **V** can be represented as anion generated as a result of elimination of proton and distribution of the negative charge over all functional groups. The COSY spectrum of **V** showed coupling between protons in the ethyl group and CH proton. This indicates that the cyano group is neighboring to the amide nitrogen atom linked to the *o*-methoxyphenyl substituent. Such spatial orientation of the substituents in molecule **V** implies preferential formation of cyclic structure **IIIc** with *o*-methoxyphenyl group on the nitrogen atom in the pyridine ring. The formation of isomer **IVc** requires an alternative structure of linear intermediate **V**, where the cyano group appears in the vicinity of the anilide fragment with *o*-ethylphenyl substituent. In fact, heating of compound **V** in alcoholic sodium ethoxide gave a mixture of isomers **IIIc** and **IVc** at a ratio of 92 : 8.

Thus we presumed that only one linear intermediate product is formed, which gives rise to two isomeric cyclic structures.

Linear structure can be detected by ^{1}H NMR spectroscopy only when both initial compounds contain a substituent in the *ortho* position of the benzene ring. Intermediate product could not be isolated in reactions with unsubstituted or *para*-substituted derivatives. The reaction gives two isomeric pyridinones with different positions of substituted aryl groups, and their ratio depends on the substituent nature. Reactions with *ortho*-substituted compounds are also affected by steric factor which is likely to slightly hamper cyclization of linear intermediate, so that the latter can be isolated in some cases. We ought to refrain from estimating the effect of *ortho* substituents because of the lack of definite relations in the formation of final products.

Scheme 2.



To conclude, cyano(ethoxymethylidene)acetanilides **II** act as three-carbon synthons in the formation pyridine ring. The position of differently substituted aryl groups in the resulting compounds depends on the substituent nature. The cyclization to pyridin-2-one is facilitated by increase in nucleophilicity of the anilide nitrogen atom.

EXPERIMENTAL

The melting points were determined on a Kofler hot stage. The IR spectrum of compound **V** (in mineral oil) was recorded on an IKS-29 spectrometer. The ^{1}H and ^{13}C NMR spectra were measured on a Bruker Avance DRX-500 spectrometer from solutions in DMSO-d_6 using tetramethylsilane as internal reference. The mass spectrum of **V** was obtained on a Hewlett–Packard HP 5890/5972 GC/MS system (HP-5MS column; electron impact, 70 eV). The progress of reactions and the purity of products were monitored by thin-layer chromatography on Silufol UV-254 plates using acetone–hexane (3:5) as eluent; spots were developed by treatment with iodine vapor or under UV light.

2-Amino-*N*,1-diaryl-5-cyano-6-oxo-1,6-dihydropyridine-3-carboxamides IIIa, IIIb, IVa, and IVb (*general procedure*). Metallic sodium, 0.23 g (10 mmol), was dissolved in 20 ml of anhydrous ethanol, 10 mmol of the corresponding cyanoacetanilide **I** added, and the mixture was stirred for 5 min (it became homogeneous). Compound **II**, 10 mmol, was then added, and the mixture was stirred for 10 min (a solid separated from the solution). The mixture was left to stand for 2 h, the precipitate was filtered off and washed with ethanol and hexane, and ^{1}H NMR spectrum of the crude product was recorded. The isomer ratio was calculated from the intensities of 4-H and NH signals. Isomer **IIIa** or **IIIb** was isolated by recrystallization of the crude product from acetone–ethanol (4:1).

Isomer mixture IIIa/IVa. ^{1}H NMR spectrum, δ, ppm: 7.11 t (major), 7.34 t (major), 7.39–7.42 m (minor) (3H, C_6H_5, J = 7.3 Hz); 7.43 d (major), 7.58–7.59 m (major), 7.65 d (minor), 7.67 d (major) (4H, 4-ClC_6H_4, J = 8.5 Hz); 7.57–7.58 m (minor), 7.61 d (major) (2H, C_6H_5, J = 7.9 Hz); 8.69 s (minor), 8.70 s (major) (1H, 4-H); 9.93 br.s (major), 10.02 br.s (minor) (1H, NH).

2-Amino-1-(4-chlorophenyl)-5-cyano-6-oxo-*N*-phenyl-1,6-dihydropyridine-3-carboxamide (IIIa). Yield 68–72%, colorless plates, mp 278–280°C (from acetone–EtOH, 4:1). ^{1}H NMR spectrum, δ, ppm: 7.11 t (1H, C_6H_5, J = 7.3 Hz), 7.34 t (2H, C_6H_5, J = 7.3 Hz), 7.43 d (2H, C_6H_4, J = 8.5 Hz), 7.61 d (2H, C_6H_5, J = 7.9 Hz), 7.67 d (2H, C_6H_4, J = 8.5 Hz), 8.70 s (1H, 4-H), 9.93 br.s (1H, NH); signals from the NH_2 group were not observed, presumably because of fast exchange. ^{13}C NMR spectrum, δ_C, ppm: 30.64, 84.93, 93.40, 117.73, 120.93, 123.77, 128.54, 130.47, 130.77, 132.93, 134.56, 138.50, 146.28, 157.23, 159.55, 164.84. Found, %: C 62.41; H 3.42; N 15.11. $C_{19}H_{13}ClN_4O_2$. Calculated, %: C 62.56; H 3.59; N 15.36.

Isomer mixture IIIb/IVb. ^{1}H NMR spectrum, δ, ppm: 3.72 s (major), 3.73 s (min) (3H, MeO); 6.83–6.88 m, 6.95–7.00 m (1H, H_{arom}); 6.92–6.49 m (major), 7.10–7.11 m (minor) (2H, H_{arom}); 7.23 d (major), 7.28 d (minor), 7.45–7.48 m (minor), 7.62 d (major) (4H, ClC_6H_4, J = 8.5 Hz); 8.11 s (minor), 8.13 s (major) (1H, 4-H); 8.51 d (major), 8.52 d (minor) (1H, H_{arom}, J = 7.7 Hz); 13.33 br.s (major), 13.84 br.s (minor) (1H, NH).

2-Amino-1-(4-chlorophenyl)-5-cyano-*N*-(2-methoxyphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (IIIb). Yield 83–91%, white powder, mp 262–264°C (from acetone–EtOH, 4:1). ^{1}H NMR spectrum, δ, ppm: 3.72 s (3H, MeO), 6.83 t (1H, H_{arom}, J = 8.5 Hz), 6.92–6.94 m (2H, H_{arom}), 7.23 d (2H, ClC_6H_4, J = 8.5 Hz), 7.62 d (2H, ClC_6H_4, J = 8.5 Hz), 8.13 s (1H, 4-H), 8.51 d (1H, H_{arom}, J = 7.7 Hz), 13.33 br.s (1H, NH); signals from the NH_2 group were not observed, presumably because of fast exchange. Found, %: C 60.72; H 3.77; N 14.02. $C_{20}H_{15}ClN_4O_3$. Calculated, %: C 60.84; H 3.83; N 14.19.

Compounds IIIc, IVc, and V. Compound **V** was synthesized according to the procedure described above for **IIIa/IVa** and **IIIb/IVb**. Recrystallization of the crude product from acetone–ethanol (4:1) gave compound **V**. Heating of the latter in ethanolic sodium ethoxide [0.23 g (10 mmol) of metallic sodium was dissolved in 20 ml of anhydrous ethanol] gave isomer mixture **IIIc/IVc**.

Isomer mixture IIIc/IVc. ^{1}H NMR spectrum, δ, ppm: 1.12 t (major), 1.15 t (minor) (3H, $CH_2C\mathbf{H}_3$, J = 7.5 Hz); 2.28–2.37 m (2H, $C\mathbf{H}_2CH_3$); 3.79 s (minor), 3.84 s (major) (3H, MeO); 6.95 t (major), 7.15 t (minor) (1H, $MeOC_6\mathbf{H}_4$, J = 7.5 Hz); 7.10 d (major), 7.31 d (minor) (1H, H_{arom}, J = 7.3 Hz); 7.21 t (major), 7.25 m (minor) (1H, $MeOC_6\mathbf{H}_4$, J = 7.6 Hz); 7.28 d (major), 7.32–7.33 m (minor) (1H, $MeOC_6\mathbf{H}_4$, J = 7.7 Hz); 7.43–7.47 m (2H, H_{arom}); 7.51–7.58 m (2H, H_{arom}); 8.68 s (minor), 8.74 s (major) (1H, 4-H); 9.46 br.s (major), 9.68 br.s (minor) (1H, NH).

2-Amino-5-cyano-*N*-(2-ethylphenyl)-1-(2-methoxyphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (IIIc). Yield 71%, white powder, mp 256–258°C (from acetone–EtOH, 4:1). ^{1}H NMR spectrum, δ, ppm: 1.12 t (3H, $CH_2C\mathbf{H}_3$, J = 7.5 Hz), 2.33 q (2H, $C\mathbf{H}_2CH_3$, J = 7.5 Hz), 3.84 s (3H, MeO), 6.95 t (1H, $MeOC_6\mathbf{H}_4$, J = 7.5 Hz), 7.10 d (1H, H_{arom}, J = 7.3 Hz), 7.21 t (1H, $MeOC_6\mathbf{H}_4$, J = 7.6 Hz), 7.28 d (1H, $MeOC_6\mathbf{H}_4$, J = 7.7 Hz), 7.44 m (2H, H_{arom}), 7.54 d (2H, H_{arom}, J = 6.5 Hz), 8.74 s (1H, 4-H), 9.46 br.s (1H, NH); signals from the NH_2 group were not observed, presumably because of fast exchange. ^{13}C NMR spectrum, δ_C, ppm: 13.63, 23.06, 55.60, 84.98, 93.16, 111.62, 117.68, 120.03, 125.95, 126.41, 127.98, 128.02, 128.72, 129.88, 130.23, 132.18, 140.93, 146.38, 152.80, 156.89, 159.29, 164.85. Found, %: C 67.92; H 5.01; N 14.33. $C_{22}H_{20}N_4O_3$. Calculated, %: C 68.03; H 5.19; N 14.42.

(*E*)-2,4-Dicyano-N^1-(2-ethylphenyl)-N^5-(2-methoxyphenyl)pent-2-enediamide (V). Yield 60%, yellow powder, mp 237–238°C (first from acetone and then from acetone–EtOH, 4:1). IR spectrum, ν, cm^{-1}: 3470, 3420 (NH); 2210, 2190 (C≡N); 1635 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.16 t (3H, $CH_2C\mathbf{H}_3$, J = 7.3 Hz), 2.57 q (2H, $C\mathbf{H}_2CH_3$, J = 7.3 Hz), 3.86 s (3H, MeO), 6.89 t (1H, H_{arom}, J = 7.6 Hz), 7.96 t (1H, H_{arom}, J = 6.9 Hz), 7.04 d (2H, H_{arom}, J = 7.8 Hz), 7.15 t (1H, H_{arom}, J = 7.3 Hz), 7.19 d (1H, H_{arom}, J = 7.4 Hz), 7.71 d (1H, H_{arom}, J = 9.3 Hz), 8.06 s (1H, 4-H), 8.22 br.s and 8.24 br.s (1H each, NH), 8.27 d (1H, H_{arom}, J = 7.9 Hz). ^{13}C NMR spectrum, δ_C, ppm: 14.31, 24.37, 56.51, 73.84, 75.45, 111.07, 118.88, 120.46, 121.07, 122.81, 124.07, 124.63, 126.48, 128.80, 129.03, 135.96, 137.28, 148.00, 164.03, 164.67. Mass spectrum: m/z 388.4 (I_{rel} 100%) $[M]^+$. Found, %: C 67.92; H 5.01; N 14.33. $C_{22}H_{20}N_4O_3$. Calculated, %: C 68.03; H 5.19; N 14.42. M 388.424.

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