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Formation of Pyrimidin-2-ylcyanamide and 2-Aminopyrimidine in the Reaction of Aniline Derivatives with Cyanamide and Dimethylamino-1-pyridyl-2-propenone

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Abstract—Substituted *o*- and *p*-nitroanilines and *m*-benzylaminoanilines in the reaction with cyanamide failed to yield the corresponding arylguanidines, and in the presence of 3-dimethylamino-1-(3-pyridyl)-2-propen-1-one formed 4-pyridyl-substituted pyrimidin-2-ylcyanamides and 2-amino-pyrimidines.

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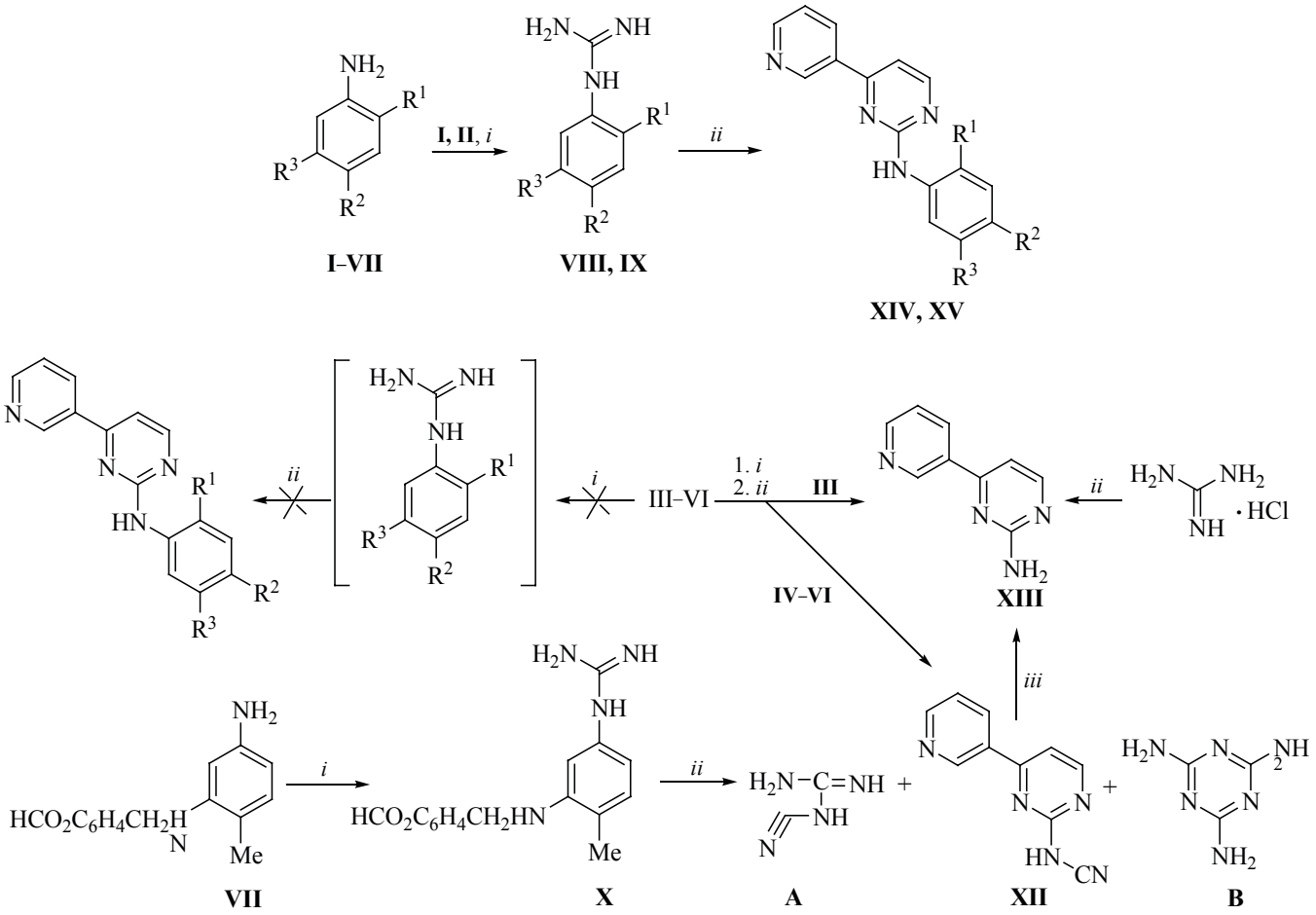
Guanidine condensation with β-dicarbonyl compounds or with their latent forms, e.g., aminovinyl ketones is a general procedure for the synthesis of 2-aminopyrimidines [1]. A general method of synthesis was developed underlain by the reaction of arylguanidines with dimethylaminopropenones providing a wide range of 2-arylaminopyrimidines [2–5]. Arylguanidine that as a binucleophile formed the N^1–C^2–N^3 fragment of the pyrimidine ring was commonly obtained by the reaction of aniline derivative with cyanamide.

Aiming at the synthesis of a series of 2-arylaminopyrimidines we investigated in this transformations sequence substituted anilines **I–VII**. For instance, 2-methyl-5-nitro-aniline (**I**) and 4-methyl-3-nitroaniline (**II**) added the cyanamide in the presence of 65% nitric acid to give in 90–93% yield arylguanidines **VIII** and **IX** respectively. However we failed to obtain guanidines in analogous conditions from substituted nitroanilines **III–V**. The crystalline substances isolated in these reactions proved to be the nitrates of the initial anilines. The same result was obtained in the reaction of cyanamide with benzylaminoaniline (**VI**), although its isomer aniline **VII** afforded guanidine **X** in 75% yield. Cyanamide under the reaction conditions formed a dimer, cyanoguanidine **A,** and trimer, 2,4,6-triamino-1,3,5-triazine **B,** which were detected by GC-MS analysis of the reaction mixture (Scheme 1).

Obviously, anilines **III–VI** do not react with cyanamide due to the weak nucleophilicity of amines and/or their salts. This result with derivatives **III–VI** having in contrast to anilines **I, II** an electron-acceptor nitro group in the *ortho*- or *para*-position with respect to the reaction site is quite understandable in the case of the electronic contral of this reaction. The reaction with cyanamide of derivative **VI** unlike compound **VII** is probably impeded by the *ortho*-methyl groups close to the reaction site. However interestingly the steric factor of the methyl substituent in 2-methyl-5-nitroaniline (**I**) does not hamper the formation of guanidine **VIII**.

We attempted to synthesize pyrimidines from anilines **III–VI**, cyanamide, and 3-dimethylamino-1-(3-pyridyl)-2-propen-1-one (**XI**) without isolation and purification of intermediate reaction products. The filtered and washed precipitate formed at heating the aniline derivative with cyanamide was treated with dimethylaminopropenone **XI** in 2-propanol in the presence of sodium hydroxide. Thus

Scheme 1.



R^1 = Me, R^2 = H, R^3 = NO_2 (**I, VIII, XIV**); R^1 = H, R^2 = Me, R^3 = NO_2 (**II, IX, XV**); R^1 = NO_2, R^2 = R^3 = H (**III**); R^1 = CH_3, R^2 = NO_2, R^3 = H (**IV**); R^1 = CF_3, R^2 = NO_2, R^3 = H (**V**); R^1 = Me, R^2 = H, R^3 = $NHCH_2C_6H_4CO_2Me$ (**VI**). *i* = NH_2CN, HNO_3, Δ; *ii* = 3-$C_5H_4NC(O)HC{=}CHNMe_2$ (**XI**), *i*-PrOH, NaOH, Δ; *iii* = H_2NNH_2, Ni-Ra, MeOH, Δ.

we obtained *N*-[4-(3-pyridinyl)-pyrimidin-2-yl]cyanamide (**XII)** from compounds **IV–VI** and 4-(3-pyridyl)-2-aminopyrimidine (**XIII**) from compound **III**. Pyrimidine **XII** reduced with hydrazine hydrate was converted into pyrimidine **XIII**,which by the TLC data and all physicochemical parameters (IR, NMR, and mass spectra) was identical to a sample of pyrimidine independently synthesized from 3-dimethylamino-1-pyridyl-2-propen-1-one and guanidine carbonate.

Pyrimidine **XII** was also isolated in the reaction of guanidine **X** with 3-dimethylamino-1-(3-pyridyl)-2-propen-1-one (**XI**). This fact may be due to the low activity of arylguanidine **X** in the condensation reaction because of the poor solubility. The low stability of proper guanidine **X** is hardly probable since under the used conditions of the condensation *m*-nitroarylguanidines **VIII, IX** are quite stable and are converted into the corresponding nitroarylpyrimidines **XIV, XV** in preparative yields [6, 7].

Inasmuch as the nitrile moiety of the cyanamide may be regarded as an equivalent of a carbonyl group the inactivity of the primarily arising nitrates of nitroanilines **III–V** and benzylaminoaniline **VII** in the reaction of the nucleophilic addition in question is due to the low nucleophilicity of these substrates. Using hydrochloric instead of nitric acid we succeeded to obtain in the reaction of *p*-nitroaniline with cyanamide 4-nitrophenylguanidine hydrochlorid in 25% yield. The ability of aniline derivatives **I–VII** to add cyanamide is well consistent with the data of the simplest calculations of the partial charges on the nitrogen atom of the amino group (see the table).

Partial charge on nitrogen atom in aniline derivatives and arylguanidine yields

Initial compound	Partial charge on nitrogen atom[a]	Guanidine yield, %
Cyanamide	–0.115 (NH_2) –0.561 (CN)	
Aniline	0.108	–
2-Methylaniline	0.092	–
2-Methyl-5-nitroaniline (**I**)	0.100 (NH_2) 1.231 (NO_2)	92
4-Methyl-3-nitroaniline (**II**)	0.090 (NH_2) 1.234 (NO_2)	93
2-Nitroaniline (**III**)	0.117 (NH_2) 1.211 (NO_2)	Does not form
2-Methyl-4-nitroaniline (**IV**)	0.155 (NH_2) 1.213 (NO_2)	Does not form
3-Nitroaniline	0.108 (NH_2) 1.240 (NO_2)	90
4-Nitroaniline	0.166 (NH_2) 1.215 (NO_2)	25
2-Trifluoromethyl-4-nitroaniline (**V**)	0.050 (NH_2) 1.214 (NO_2)	Does not form
2-Methyl-5-(4-carboxybenzyl-amino)aniline (**VI**)	0.084 (NH_2) 0.151 (NH)	Does not form
4-Methyl-3-(4-carboxybenzyl-amino)aniline (**VII**)	0.088 (NH_2) 0.153 (NH)	67
2-Methyl-4-(4-carboxybenzylamino)-aniline	0.020 (NH_2) 0.091 (NH)	–

[a] The data were obtained by the extended semiempirical Hueckel method by the calculation program ChemOffice (Chem.3D.Ultra 9.0) using the standard set of initial parameters.

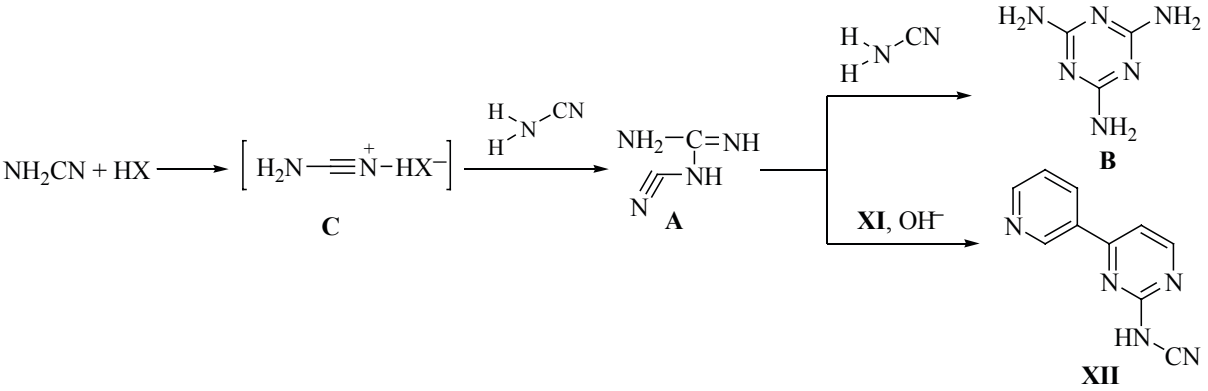
Cyanamide under the reaction conditions reacts with acid to give the intermediate salt form **C** that as a nucleophile adds the second (and further the third) cyanamide molecule giving cyanoguanidine **A** and triaminotriazine **B** (Scheme 2).

Cyanoguanidine **A** and triaminotriazine **B** generated from cyanamide apparently precipitated with the nitrtes of the derivatives and were present in the precipitate brought further into the condensation with compound **XI**. In the second stage of the transformations cyanamide dimer **A** was involved as a competeing binucleophile into the cyclocondensation with 3-dimethylamino-1-pyridyl-2-propen-1-one (**XI**) instead of derivatives **III–VII** affording pyrimidine **XII**. As the source of pyrimidine **XIII** served likely the guanidine in situ generated by triaminotriazine **B** labile under the reaction conditions since the labile behavior under these conditions both of pyrimidine **XII** and cyanoguanidine **A** was hardly probable.

EXPERIMENTAL

IR spectra were recorded on a Fourier spectrophotometers Nicolet Protege-460 and Specord 75IR from pellets with KBr in the range 400–4000 cm^{-1}. ^1H and ^{13}C NMR spectra were registered on a spectrometer Bruker Avance-500 at operating frequencies 500 (^1H) and 125 MHz (^{13}C), internal reference TMS. Chromatographic analysis and recording of mass spectra were performed on instruments Hewlett Packard 6850/5973 and Thermo Scientific Trace GC Ultra/DSQ II in the electron impact mode at the energy 70 eV. The reaction progress was monitored by TLC on Merk DC-Plasticfolien Kieselgel 60 F_{254} plates, eluent chloroform– methanol, 95 : 5.

Scheme 2.



HX = HNO_3, HCl.

Arylguanidines VIII–X. General procedure [4, 5, 7]. To a solution of 0.01 mol of nitroaniline **I, II, VII** in 15 ml of anhydrous ethanol at cooling to 0°C was added dropwise 0.45 ml (0.01 mol) of 65% nitric acid; yellow dispersion formed. At the end of self-heating 1 ml (0.012 mol) of 50% water solution of cyanamide was added, and the reaction mixture was boiled for 12 h. Then again 1 ml (0.012 mol) of 50% water solution of cyanamide and 0.45 ml (0.01 mol) of 65% nitric acid were added (pH of the reaction mixture ~3), and the heating was continued for 6–18 h. The separated precipitate of the guanidine nitrate was filtered off, washed with the mixture ethanol–ethyl ether, 1 : 1, and recrystallized from ethanol.

***N*¹-Amino(imino)methyl-2-methyl-5-nitroaniline nitrate (VIII).** Yield 92%, slightly colored crystals, mp 220–224°C (mp 219–226°C from 2-propanol [6]). IR spectrum, ν, cm^{-1}: 3490, 3360, 3150, 1680, 1580, 1515, 1475, 1310. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.30 s (3H, CH_3), 3.34 s (1H, NH), 6.57 br.s (3H, NH_2, NH), 6.78 d (1H, H_{arom}, ^3J 8.5 Hz), 7.24 d (1H, H_{arom}, ^4J 2.5 Hz), 7.30 d.d (1H, H_{arom}, ^3J 8.5, ^4J 2.5 Hz). ^{13}C NMR spectrum, δ, ppm: 17.40, 122.30, 122.57, 132.00, 134.30, 143.50, 146.16, 155.87. Mass spectrum, *m/z* (I_{rel}, %): $[M]^+$ 194 (100), $[M - Me]^+$ 179 (78), $[M - NO_2]^+$ 147 (43), $[M + 1]^+$ 195 (10), 106, 94, 77. Found, %: N 27.54. $C_8H_{11}N_5O_5$. Calculated, %: N 27.24.

***N*¹-Amino(imino)methyl-4-methyl-3-nitroaniline nitrate (IX).** Yield 91%, slightly colored crystals, mp 218°C. IR spectrum, ν, cm^{-1}: 3380, 1690–1580, 1550, 1345. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.50 s (3H, Me), 5.07 br.s (4H, NH, NH_2), 7.03 d.d (1H, H_{arom}, ^3J 8.2, ^4J 2.2 Hz), 7.19 d (1H, H_{arom}, ^3J 8.2 Hz), 7.39 d (1H, H_{arom}, ^4J 2.2 Hz). ^{13}C NMR spectrum, δ, ppm: 19.09, 117.95, 123.03, 128.07, 132.25, 149.07, 149.83, 153.15. Mass spectrum, *m/z* (I_{rel}, %): $[M]^+$ 194 (100), $[M - Me]^+$ 179 (67), $[M - NO_2]^+$ 147 (33). Found, %: N 27.64. $C_8H_{11}N_5O_5$. Calculated, %: N 27.24.

***N*¹-Amino(imino)methyl-4-methyl-3-(4-carboxybenzylamino)aniline nitrate (X).** Yield 67%, red-violet light crystals, mp 136–138°C. IR spectrum, ν, cm^{-1}: 3480, 3360, 3150, 1680, 1580, 1475, 1310. Mass spectrum, *m/z* (I_{rel}, %): $[C_6H_5CO_2]^+$ 121 (100), $[M]^+$ 298 (90), 135 (60), 107 (25), 89 (25), 77. Found, %: N 18.90. $C_{16}H_{19}N_5O_5$. Calculated, %: N 19.38.

***N*¹-Amino(imino)methyl-4-nitroaniline hydrochloride** was similarly prepared from 4-nitroaniline using hydrochloric acid instead of nitric acid. Yield 25%, slightly colored crystals, mp 280–282°C. IR spectrum, ν, cm^{-1}: 3400, 3160, 2950, 1680, 1630, 1580, 1520, 1350. Mass spectrum, *m/z* (I_{rel}, %): $[M]^+$ 179.98 (100), $[M - NH_2CNH]^+$ 137.97, 107.96 (34), 91.96 (21), $[NH_2CNH]^+$ 42.95 (39). Found, %: N 25.44. $C_7H_9ClN_4O_2$. Calculated, %: N 25.87.

Reaction of derivatives III–VII with cyanamide and 3-dimethylamino-1-(pyridin-3-yl)-2-propenone (XI). From the reaction mixture obtained by the above procedure from anilines **III–VII** with cyanamide in the presence of nitric acid the precipitate was filtered off and added to the solution of 1 equiv of 3-dimethylamino-1-(3-pyridyl)-2-propen-1-one (**XI**) in 2-propanol. Into the mixture a hot solution of 1.2 equiv of NaOH in 2-propanol was added, and the mixture was boiled for 18–24 h. The precipitate was filtered off, washed with 2-propanol and ethyl ether (3 × 50 ml).

From compounds **IV–VI** ***N*-[4-(pyridin-3-yl)pyrimidin-2-yl]cyanamide (XII)** was obtained. Yield 75%, slightly colored crystals, mp 232–234°C. IR spectrum, ν, cm^{-1}: 3380 (NH), 2160 (C≡N), 1445, 1567. ^{1}H NMR spectrum (D_2O), δ, ppm: 7.09 d (1H, H_{arom}, ^4J 5.3 Hz), 7.47 d.d (1H, H_{arom}, ^3J 7.9, ^4J 5.0 Hz), 8.25 t (1H, H_{arom}, ^4J 1.8 Hz), 8.26 d (1H, H_{arom}, ^3J 5.3 Hz), 8.53 d.d (1H, H_{arom}, ^3J 4.9, ^4J 1.5 Hz), 8.93 d (1H, H_{arom}, ^4J 1.7 Hz). ^{13}C NMR spectrum (D_2O), δ, ppm: 108.30, 124.35, 125.68, 132.64, 135.96, 147.32, 150.37, 159.32, 163.39, 167.52. Mass spectrum: $[M]^+$ 197. Found, %: N 36.01. $C_{10}H_7N_5$. Calculated, %: N 35.51. *M* 197.20.

From compound **III 4-(pyridin-3-yl)-pyrimidin-2-ylamine (XIII)** was obtained. Yield 70%, slightly colored crystals, mp 180–182°C. IR spectrum, ν, cm^{-1}: 3540, 3380 (NH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 5.22 br.s (2H, NH_2), 7.07 d (1H, H_{arom}, ^3J 5.4 Hz), 7.41 d.d (1H, H_{arom}, ^3J 7.8, ^4J 4.8 Hz), 8.31 d (1H, H_{arom}, ^3J 7.8 Hz), 8.40 d (1H, H_{arom}, ^3J 5.4 Hz), 8.71 d (1H, H_{arom}, ^4J 4.7 Hz), 9.20 s (1H, H_{arom}). ^{13}C NMR spectrum, δ, ppm: 107.61, 123.56, 132.76, 134.41, 148.49, 151.38, 159.20, 162.94, 163.31. Mass spectrum: $[M]^+$ 173.

By GC-MS analysis of the reaction mixture cyanoguanidine **A** [mass spectrum, *m/z* (I_{rel}, %): $[M]^+$ 84 (100), 68 (54), 43 (100), $C_2H_4N_4$] and 2,4,6-triamino-1,3,5-triazine **B** [mass spectrum, *m/z* (I_{rel}, %): $[M]^+$ 126, 85 (20), 68 (12), 43 (50), $C_3H_6N_6$] were detected.

Comound **XIII** was also obtained by reduction of compound **XII** with hydrazine hydrate in the presence

of Raney nickel by procedure [6]. Into a solution of 0.01 mol of pyrimidine **XII** in 30 ml of methanol containing 0.006 mol of Raney nickel was added dropwise at stirring 0.04 mol of 80% solution of hydrazine hydrate in 1 ml of methanol. The reaction mixture was stirred for 15 min at 50–60°C and 1 h at room temperature, filtered through a celite bed, the filtrate was evaporated, the reaction product was recrystallized. Yield 68%, physicochemical characteristics were identical to the properties of above described compound **XIII**, and of that obtained by the condensation of propenone **XI** with guanidine hydrochloride.

To a solution of 5.3 g (0.03 mol) of compound **XI** in 2-propanol was added 2.8 g (0.03 mol) of guanidine hydrochloride, then a hot solution of 1.4 g (0.035 mol) of NaOH in 2-propanol. The reaction mixture was boiled for 12 h, the precipitate was filtered off, washed with 2-propanol (3 × 50) ml, and purified by precipitation with hexane from the solution in dichloromethane. Yield 3.8 g (75%), slightly colored crystals, mp 180–182°C.

Physicochemical parameters of compound **XIV** were published in [7].

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