Transformations of *ortho*-methoxyaryl(hetaryl)carboxamides into quinazolin-4-one and pyrido[2,3-*d*]pyrimidin-4-one derivatives

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ortho-Chloroaryl(hetaryl)carboxamides containing one or two nitro groups at positions 3 and/or 5 of the ring undergo condensation accompanied by the pyrimidine ring closure on refluxing in an excess of sodium methoxide to form bicyclic products, *viz.*, quinazolin-4-one, pyrido[2,3-*d*]pyrimidin-4-one, and pyrido[4,3-*d*]pyrimidin-4-one derivatives. The scheme of cyclization processes was proposed. The structures of the reaction products were confirmed by a number of physicochemical data, including X-ray diffraction analysis.

Key words: dinitrobenzamide, quinazolin-4-one, pyrido[2,3-*d*]pyrimidin-4-one, 4-chloro-5-nitronicotinamide, pyrido[4,3-*d*]pyrimidin-4-one, 4,6-dichloro-5-pyrimidinocarboxamide, X-ray diffraction analysis.

Earlier,[1,2] we have synthesized a series of 3,5-dinitrobenzenecarboxamide derivatives containing a dialkyldithiocarbamoyl substituent at position 2 and found that these compounds have high antituberculosis activity. As part of our continuing studies, it was of interest to prepare new 3,5-dinitrobenzenecarboxamides containing no dialkyldithiocarbamoyl fragments and investigate their biological activities. It should be noted that the properties of different di- and trinitrobenzenecarboxamides have received considerable study, because some of them are known to be energetic compounds[3] and have found use in industry. Most methods for the synthesis of nitrobenzamides are based on nitration of the corresponding benzoic acids followed by transformations to give acid chloride and amide.[4,5] This approach was used to synthesize 2-chloro-3,5-dinitrobenzenecarboxamide **1** starting from salicylic acid.[6]

We prepared the corresponding 2-methoxy derivative **2** by the reaction of 2-chlorobenzamide **1** with an equimolar amount of sodium methoxide in methanol (Scheme 1). In addition to the target compound **2**, we found an insignificant impurity of another compound with a molecular weight of 432 among the reaction products. Based on the results of different physicochemical methods, we assigned the structure of 2-(2-methoxy-3,5-dinitrophenyl)-6,8-dinitroquinazolin-4-one (**3**) to the latter product.

The ^{1}H NMR spectra of compound **3** show four doublets corresponding to H(5), H(7), H(4′), and H(6′) in the aromatic proton region (see the Experimental section). The ^{13}C NMR spectrum (Table 1) has signals for 15 carbon atoms. Low-field signals were assigned to the C(2), C(4), and C(2′) atoms (see Table 1). A group of signals observed at higher field (at δ 141.5—146.8) corresponds to the carbon atoms bound to the oxygen and nitrogen atoms, *viz.*, C(6), C(8), C(8a), C(3′), and C(5′). The signals for the quaternary C(4a), C(1′), C(5), C(7), C(4′), and C(6′) atoms appear at high field (the assignment of the latter atoms was made based on the HSQC spectrum). The detailed assignment of the ^{13}C signals in the spectrum of compound **3** was made by comparing the chemical shifts in the spectra of **3** and its *N*-methyl-substituted derivative **4**.

The structure of quinazolinone **3** was unambiguously established by X-ray diffraction (Fig. 1). Selected interatomic distances and bond angles in the structure of compound **3** are given in Table 2. Further investigation demonstrated that the reaction of amide **1** with a threefold excess of sodium methoxide afforded exclusively quinazolinone **3**. This compound was prepared in higher yield by refluxing methoxy derivative **2** with one mole of sodium methoxide in methanol. Methylation of quinazolinone **3** with diiodomethane in the presence of potassium car-

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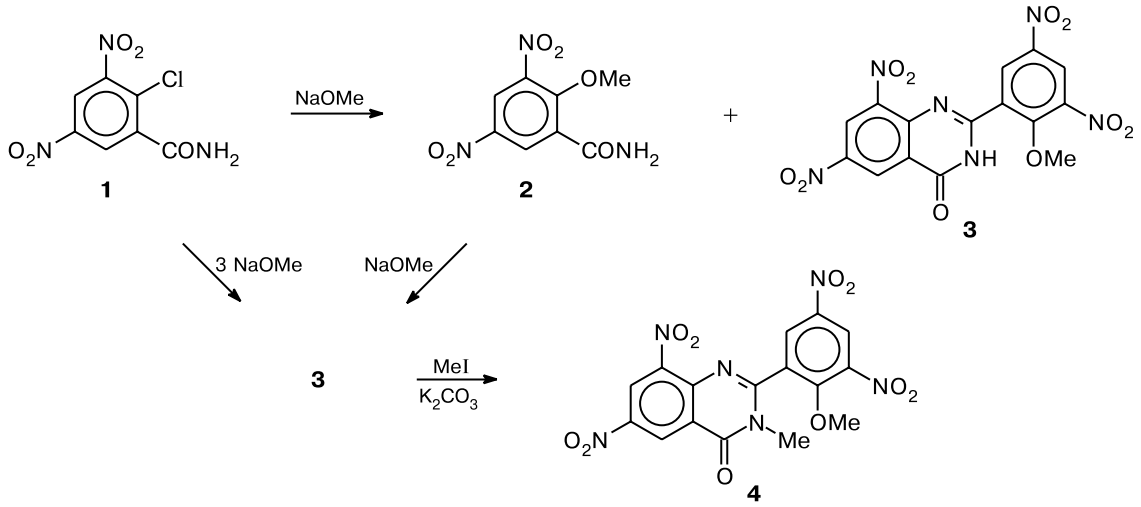
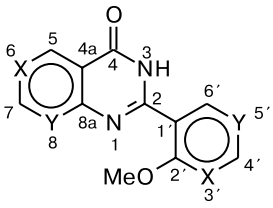
Scheme 1



bonate was demonstrated to occur selectively at NH to give 3-methylquinazolinone **4**. The HMBC spectrum of this compound (see Table 1) shows correlation peaks at δ 3.39/156.1 (N(3)Me/C(2)), 3.39/159.4 (N(3)Me/C(4)), and 9.04/159.4 (H(5)/C(4)). The replacement at the nitrogen atom in position 1 would give rise to a correlation peak of N(1)Me with C(8a), but the spectrum shows correlation peaks only with H(5) and H(7). The use of the HMBC spectrum enabled us to assign all ^{13}C signals in the spectra of compounds **4** and **3** (see Table 1), because it is evident that methylation should not be accompanied by a substantial change in the chemical shifts.



3, 4: X = Y = C—NO_2; **10, 11:** X = C—NO_2, Y = N

To confirm the proposed scheme of condensation, it was necessary to elucidate whether other aromatic compounds containing the methoxy substituent in the *ortho* position with respect to the amide group can un-

Table 1. ^{13}C NMR spectroscopic data for compounds **3**, **4**, **10**, and **11**

Atom	δ[a]			
	3	**4**	**10**	**11**
2	155.4	156.1 (N(3)Me)	155.5 (H(6′))	157.1 (N(3)Me, H(6′))
4	159.5	159.4 (N(3)Me, H(5))	161.2	161.0 (N(3)Me)
4a	123.5	122.4	116.6 (116.0)	117.9
5	124.4	122.8	131.4	132.0
6	146.6	146.2 (H(7))	141.8 (H(5), H(7))	142.1 (H(5), H(7))
7	122.8	122.5	150.6	150.7
8	[b]	142.2 (H(7))	—	—
8a	144.2	144.4 (H(5), H(7))	161.2 (H(5), H(7))	159.4 (H(5), H(7))
1′	128.7	130.7	116.0 (116.6)	114.7
2′	154.7	154.5 (C(2′)OMe, H(6′))	163.6 (C(2′)OMe, H(6′), H(4′))	162.5 (C(2′)OMe, H(6′), H(4′))
3′	[b]	142.0 (142.6)	—	—
4′	123.4	122.6	146.8	146.3
5′	[b]	142.6 (142.0)	139.1 (H(6′))	139.3 (H(4′), H(6′))
6′	130.2	129.4	135.6	135.0
N(3)Me	—	33.6	—	32.7
C(2′)OMe	64.0	63.5	55.6	55.6

[a] The protons, which show correlation peaks with the indicated atoms in the HMBC spectrum, are given in parentheses.
[b] δ 141.4, 143.0, and 144.0.

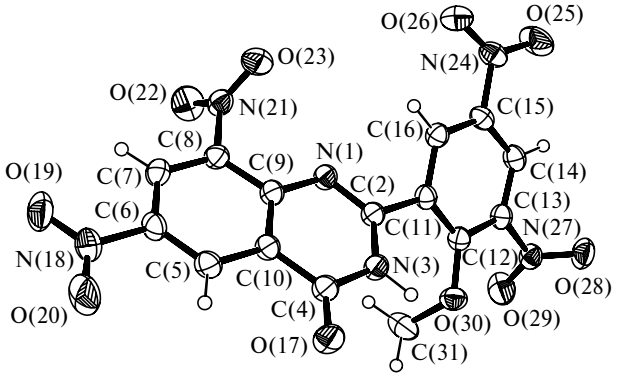


Fig. 1. Molecular structure of compound **3** (X-ray diffraction data) with displacement ellipsoids drawn at the 40% probability level.

Table 2. Selected bond lengths and bond angles in molecule **3**

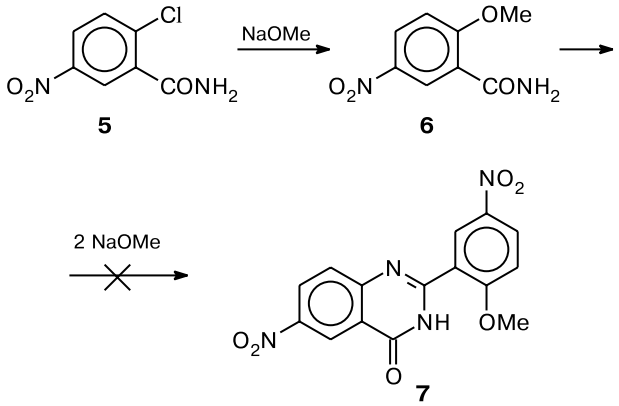
Bond	*d*/Å	Angle	ω/deg
N(1)—C(2)	1.298(2)	C(2)—N(1)—C(9)	116.93(15)
N(1)—C(9)	1.373(2)	N(1)—C(2)—N(3)	124.58(16)
C(2)—N(3)	1.366(2)	C(2)—N(3)—C(4)	122.82(16)
C(2)—C(11)	1.491(2)	N(3)—C(4)—C(10)	114.07(15)
C(4)—O17)	1.218(2)	C(6)—C(5)—C(10)	118.96(17)
C(4)—C(10)	1.464(3)	C(5)—C(6)—C(7)	122.58(17)
C(5)—C(6)	1.369(3)	C(8)—C(7)—C(6)	117.45(17)
C(5)—C(10)	1.389(2)	C(7)—C(8)—C(9)	123.03(17)
C(6)—C(7)	1.390(3)	N(1)—C(9)—C(10)	123.08(17)
C(6)—N(18)	1.469(2)	N(1)—C(9)—C(8)	119.96(16)
C(7)—C(8)	1.365(3)	C(10)—C(9)—C(8)	116.89(16)
C(8)—C(9)	1.409(3)	C(5)—C(10)—C(9)	120.99(17)
C(8)—N(21)	1.468(2)	C(5)—C(10)—C(4)	120.54(16)
C(9)—C(10)	1.405(2)	C(9)—C(10)—C(4)	118.45(16)

dergo analogous cyclization and whether the presence of two nitro groups is a necessary condition.

For this purpose, we synthesized 2-chloro-5-nitrobenzenecarboxamide **5** according to a known procedure[4] and transformed this compound into methoxy derivative **6** (Scheme 2). Refluxing of the latter with different amounts of sodium methoxide in methanol as well as an attempt to perform this process in an autoclave at 150 °C with a twofold excess of sodium methoxide did not lead to the pyrimidine ring closure and the formation of quinazolinone **7**. In all cases, the starting compound **6** was recovered.

This experiment provided evidence that the electron-withdrawing properties of one nitro group are insufficient for the nucleophilic substitution of the methoxy group in compound **6**. This fact has been studied in detail for other compounds.[7] Then we examined the possibility of the pyrimidine ring closure for a compound containing not only the nitro group at position 5 but also an electron-withdrawing group at position 3. For this purpose, we synthesized 2-chloro-5-nitronicotinoyl chloride by nitration of 2-hydroxynicotinic acid with fuming nitric acid

Scheme 2

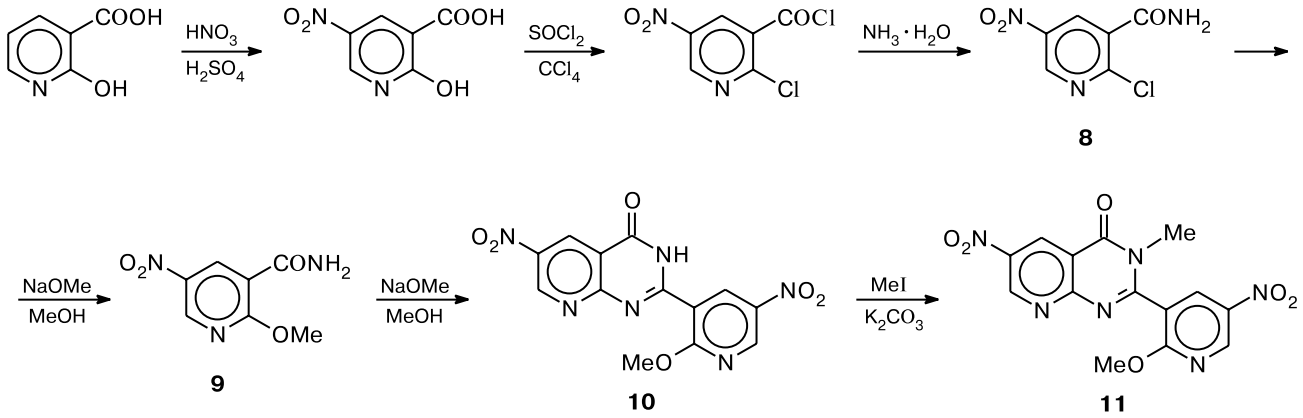


followed by treatment with thionyl chloride. The reaction of this acid chloride with 25% aqueous ammonia at −20 °C produced 2-chloro-5-nitropyridine-3-carboxamide (**8**) in 86% yield. The reaction of the latter with an equimolar amount of sodium methoxide gave the target 2-methoxy-5-nitropyridine-3-carboxamide **9** in high yield[8] (Scheme 3). It was found that refluxing of compound **9** in methanol in the presence of sodium methoxide afforded 2-(2-methoxy-5-nitropyridin-3-yl)-6-nitropyrido[2,3-*d*]pyrimidin-4-one (**10**) in 22% yield.

With the aim of establishing the structure of compound **10**, we methylated the latter with diiodomethane in the presence of potassium carbonate. This reaction was demonstrated to give exclusively methyl derivative **11**. The ^{13}C NMR, HSQC, and HMBC spectra of compounds **10** and **11** were compared with the corresponding spectra of **3** and **4** (see Table 1). The similarity of the chemical shifts of particular signals (for example, for C(2) and C(4)) and the changes in the shifts of other signals (for C(7), C(4′), and C(8a)) upon the replacement of the benzene ring with the pyridine moiety in the series of the above-mentioned four compounds, as well as the presence of identical correlation peaks in the HMBC spectra, confirm the structures of **10** and **11**.

Our experiments showed that the presence of a strong electron-withdrawing substituent at position 3 (which needs not be the second nitro group) is a necessary condition for the cyclization reaction under consideration. To elucidate the role of the nitro group at position 5 of the ring, we examined the possibility of condensation of two 4-methoxy-5-nitronicotinamide molecules (**12**). Compound **12** was synthesized starting from 4-hydroxynicotinic acid **13**.[9] Nitration of acid **13** was carried out with the use of fuming nitric acid and sulfuric acid. However, refluxing for 10 h was required to complete the reaction. It should be noted that nitration of salicylic acid with a nitrating mixture was completed within 30 min, whereas nitration of 2-hydroxynicotinic acid required 1 h for completion (both reactions proceeded at room tem-

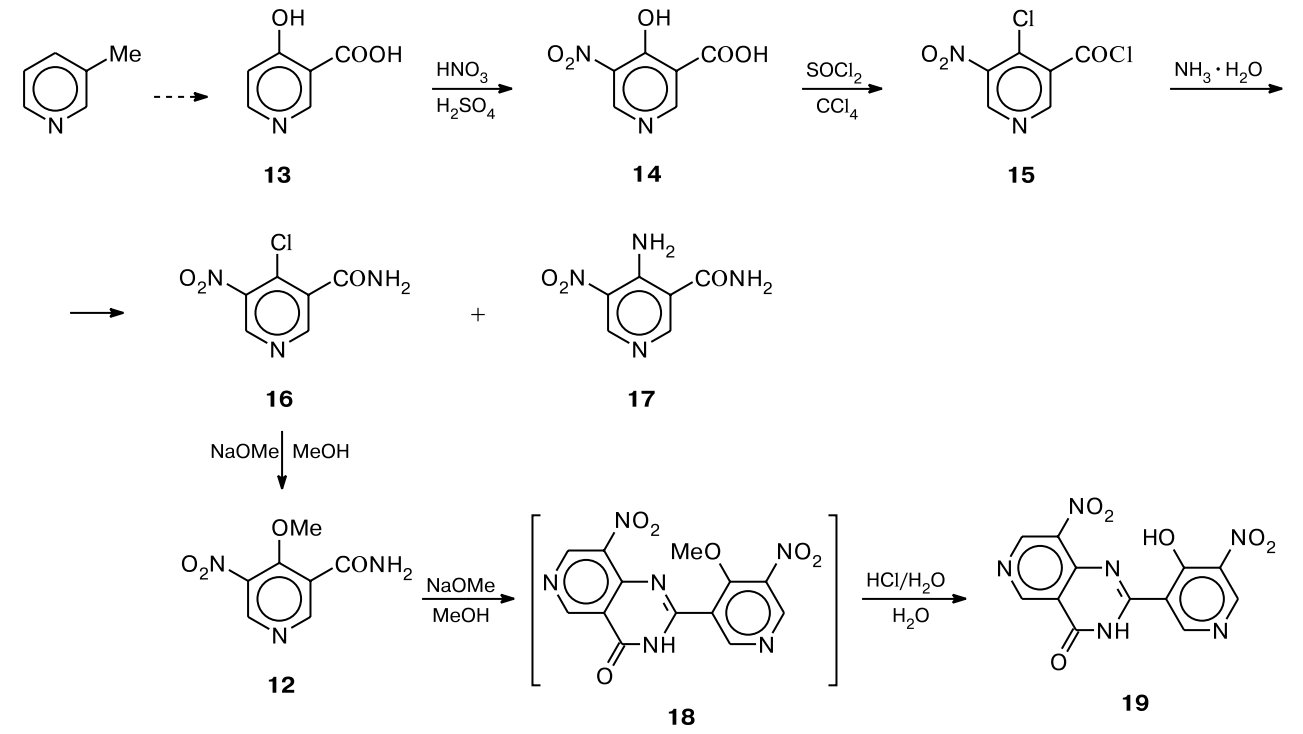
Scheme 3



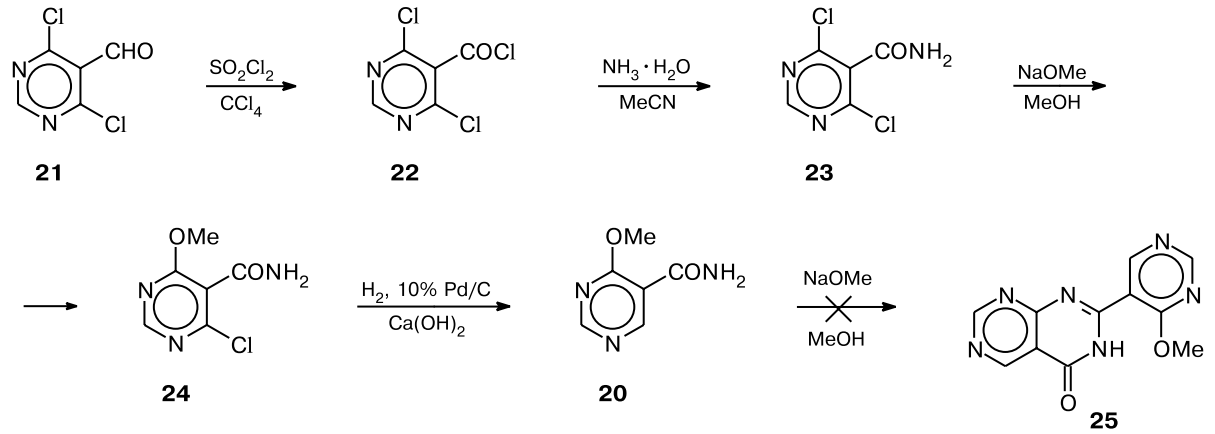
perature). Treatment of the resulting nitro acid **14** with thionyl chloride smoothly afforded the corresponding acid chloride **15**, which was used in the reaction with 12% aqueous ammonia at −20 °C. We isolated a mixture of compounds consisting of the target 4-chloro-5-nitronicotinamide **16** (80%) and the corresponding 4-amino derivative **17** (20%). The reaction of 4-chloropyrimidine **16** with an equimolar amount of sodium methoxide produced methoxy derivative **12** in high yield.

Study of the behavior of the resulting compound **12** in a refluxing methanolic solution of sodium methoxide showed that this reaction also produced 2-(4-methoxy-5-nitropyridin-3-yl)-8-nitropyrido[4,3-*d*]pyrimidin-4-one (**18**). It should be noted that we succeeded in isolating only the hydrolysis product of methoxypyridine **18**, *viz.*, 2-(4-hydroxy-5-nitropyridin-3-yl)-8-nitropyrido[4,3-*d*]pyrimidin-4-one (**19**), in low yield after dilution of the reaction mixture with water and its acidification with aqueous hydrochloric acid. This product was characterized by various physicochemical methods (see the Experimental section). Therefore, the formation of the pyridopyrimidine system cannot be excluded by using mononitro derivatives of pyridine instead of bis-nitro-substituted benzene, although the pyridyl group is known[7] to have a lower electron-withdrawing ability than the nitrophenyl group.

Scheme 4

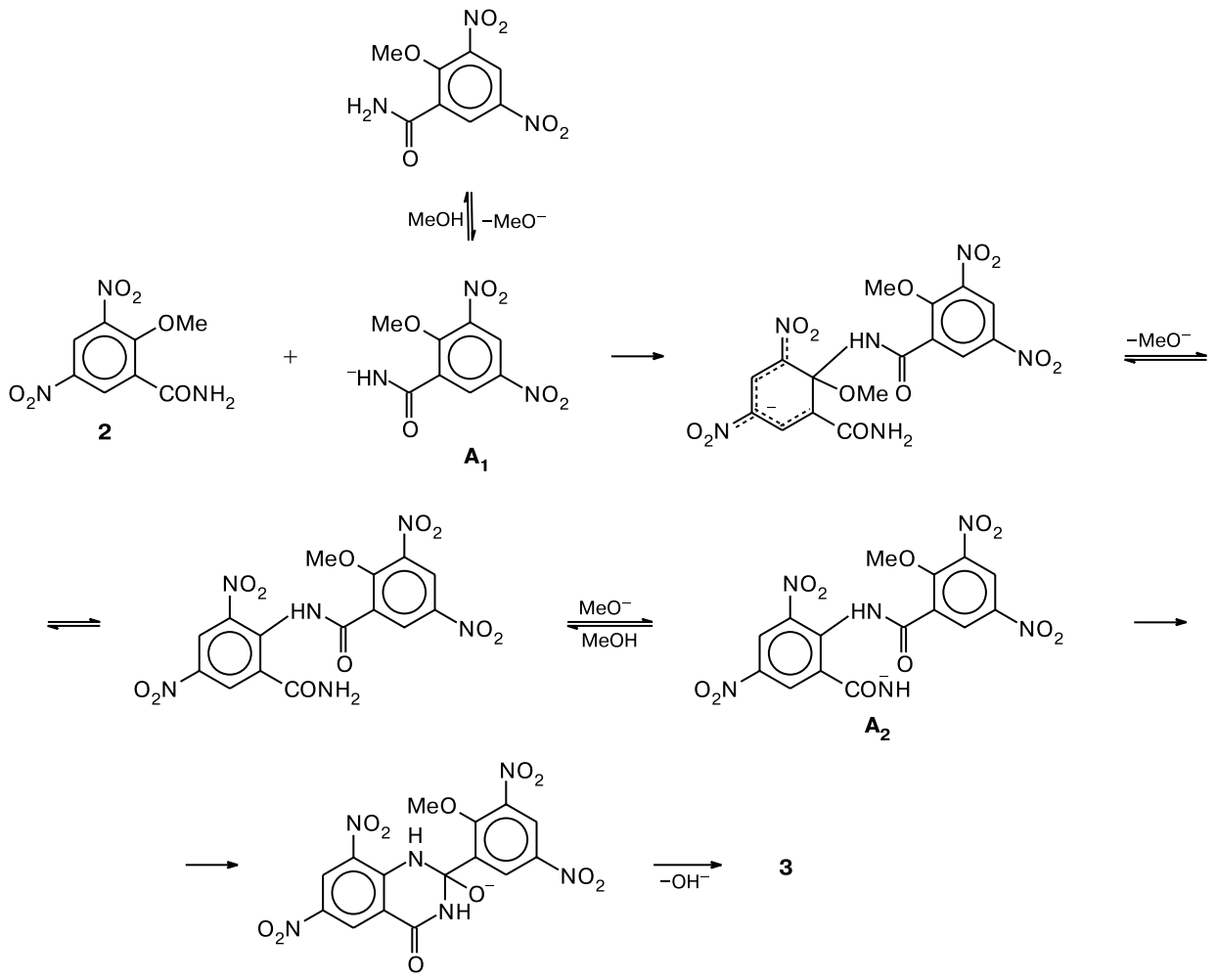


Scheme 5



It is also of interest to find out whether compounds devoid of nitro groups can be involved in the condensation under study. Hence, it was worthwhile to study this reaction with 5-carbamoyl-4-methoxypyrimidine (**20**) containing two "pyridine" nitrogen atoms instead of the nitro groups. This compound was synthesized based on 4,6-dichloro-5-formylpyrimidine (**21**),[10] which was treated with sulfuryl chloride in the presence of AIBN

Scheme 6



(2,2′-azobis(isobutyronitrile)) to prepare acid chloride **22** (Scheme 5) in high yield. Interestingly, the latter is a quite stable compound and can be purified by both recrystallization from petroleum ether and, which is very unusual for acid chlorides, by column chromatography (silica gel, dichloromethane as the eluent). Apparently, this is associated with steric shielding of the acid chloride fragment by two adjacent bulky chlorine atoms. The reaction of acid chloride **22** with aqueous ammonia at 0 °C smoothly afforded the corresponding amide **23**, which, in turn, reacted with an equimolar amount of sodium methoxide in methanol to give 4-methoxy derivative **24**. The chlorine atom was eliminated according to a known procedure[11,12] involving hydrogenation of chlorinated aromatic derivatives with hydrogen in the presence of palladium on carbon and potassium hydroxide (0.5 mol). The yield of pyrimidine **20** was 75%. We also demonstrated that refluxing of this compound with sodium methoxide in a methanolic solution, including refluxing over a long period of time (72 h), did not afford pyrimidopyrimidine **25**, the starting pyrimidine **20** being isolated from the reaction mixture in all cases. Apparently, the above-mentioned weaker electron-withdrawing effect of the "pyridine" nitrogen atoms compared to the nitro groups plays a critical role.

Taking into account all results of our investigation, the most probable pathways of condensation of *ortho*-methoxyaryl(hetaryl)carboxamides in the presence of sodium methoxide are presented in Scheme 6.

The transformation of the starting compound into the N-anion (**A_1**) is the key step of the scheme of the self-condensation under consideration (see Scheme 6). The possibility of the formation of this anion is determined by the presence of powerful electron-withdrawing substituents in the aromatic ring and the presence of an efficient base, such as the methoxide anion, in the system. The addition of this anion to dinitroamide **2** gives rise to a σ complex (which is, apparently, preceded by the formation of a π complex) structurally similar to Meisenheimer salts. Here, the most probable mechanism is analogous to the usual nucleophilic bimolecular aromatic substitution.[13] The subsequent synthesis of quinazoline derivatives or their heteroanalogs also most likely includes the intermediate formation of the N-anion (**A_2**).

Experimental

The IR spectra were recorded on a Perkin—Elmer 457 instrument in Nujol mulls. The mass spectra (EI) were obtained on a Finnigan SSQ-710 mass spectrometer with direct inlet of the sample into the ion source. The NMR spectra were recorded on Bruker AC-200 and Bruker DRX-500 spectrometers in DMSO-d_6. The purity of the products was checked and the course of the reactions was monitored by TLC on Merck TLC-254 Silicagel 60 plates (hexane—acetone, 3 : 1, as the eluent; visualization with UV light). The melting points were determined on an Electrothermal 9100 instrument (UK).

The ^{13}C NMR spectra of compounds **3**, **4**, **10**, and **11** are given in Table 1. The physicochemical characteristics, elemental analysis data, and yields of the reaction products are given in Table 3.

2-Methoxy-3,5-dinitrobenzamide (2), 2-methoxy-5-nitrobenzamide (6), and 5-carbamoyl-6-chloro-4-methoxypyrimidine (24) (general procedure). A freshly prepared solution (10 mL) of sodium methoxide (0.35 g of sodium (15 mmol) in 10 mL of methanol) was added to a solution of chloroamide **1**, **5**, or **23** (15 mmol) in methanol (50 mL) at a temperature lower than <3 °C. The reaction mixture was allowed to stand at room temperature for 3 h and diluted with cold water (100 mL). The white precipitate that formed was filtered off. Methoxy derivatives **2**, **6**, or **24** were recrystallized from methanol, acetic acid, or water, respectively.

2-(2-Methoxy-3,5-dinitrophenyl)-6,8-dinitroquinazolin-4-one (3). A suspension of benzamide **2** (1.0 g, 4 mmol) and sodium methoxide (0.22 g, 4 mmol) in methanol (30 mL) was refluxed for 24 h. Then the reaction mixture was cooled and filtered. The residue was washed with methanol (30 mL). The filtrate was acidified with 35% aqueous HCl to pH ~3. The precipitate of quinazolinone **3** that formed was filtered off and recrystallized from methanol. Single crystals of the solvate **3**·MeOH were obtained. ^{1}H NMR (DMSO-d_6), δ: 3.91 (s, 3 H, C(2′)OMe); 8.80 (d, 1 H, H(6′), J = 2.7 Hz); 8.99 (d, 1 H, H(5), J = 2.3 Hz); 9.00 (d, 1 H, H(4′), J = 2.7 Hz); 9.24 (d, 1 H, H(7), J = 2.3 Hz); 13.70 (br.s, 1 H, N(3)H).

Pale yellow single crystals of the solvate of quinazoline **3** with methanol were prepared by slow evaporation of a methanolic solution of **3**. X-ray diffraction data were collected on an automated four-circle CAD-4 diffractometer (Cu-Kα radiation, graphite monochromator, ω scanning technique). The unit cell parameters were determined using 25 reflections in the θ angle range of 23—32° by autoindexing and refined to a = 8.2558(11) Å, b = 8.4096(11) Å, c = 13.9019(15) Å, α = 99.486(12)°, β = 90.308(15)°, γ = 94.85(2)°, V = 948.4(12) Å^3, space group $P\bar{1}$, Z = 2. A total of 3475 reflections were measured in the θ angle range of 3—70°. The absorption correction was applied based on the ψ scan of six reflections.

The structure was solved by direct methods using the SHELXS-97 program package.[14] The positional and thermal parameters of the nonhydrogen atoms were refined anisotropically by the full-matrix least-squares method using the SHELXL-97 program package.[14] The coordinates of the hydrogen atoms were determined from difference Fourier syntheses or calculated geometrically. The refinement converged to the R factor of 0.042 using 2619 reflections with $I > 2\sigma(I)$.

The detailed characteristics of X-ray diffraction data collection, parameters of the solution and refinement of the molecular and crystal structure of **3**, and the atomic coordinates of **3** were deposited with the Cambridge Structural Database (CCDC 274255).

2-(2-Methoxy-3,5-dinitrophenyl)-3-methyl-6,8-dinitroquinazolin-4-one (4). A suspension of quinazolinone **3** (0.18 g, 0.42 mmol), diiodomethane (1.0 mL, 1.6 mmol), and potassium carbonate (0.086 g, 0.62 mmol) in acetone (15 mL) was kept for 1 h and filtered. The residue was washed with acetone, the filtrate was concentrated, and the oily residue was treated with water. Quinazolinone **4** (a yellow compound) was filtered off

Table 3. Physicochemical characteristics, elemental analysis data, and yields of the reaction products

Compound	Yield (%)	M.p. /°C	Found / Calculated (%)			Molecular formula	MS, m/z (I_{rel} (%))
			C	H	N		
2	74	166—167	39.71 / 39.84	2.87 / 2.93	17.54 / 17.42	$C_8H_7N_3O_6$	241 $[M]^+$ (7)
3	33	203—205	41.38 / 41.68	1.79 / 1.87	19.56 / 19.44	$C_{15}H_8N_6O_{10}$	432 $[M]^+$ (8)
4	19	186—187	42.97 / 43.06	2.02 / 2.26	18.81 / 18.83	$C_{16}H_{10}N_6O_{10}$	446 $[M]^+$ (8)
6	78	212—213	48.93 / 48.98	4.20 / 4.11	14.39 / 14.28	$C_8H_8N_2O_4$	196 $[M]^+$ (6)
8	64	181—183	35.73 / 35.75	2.09 / 2.00	21.01 / 20.85	$C_6H_4ClN_3O_3$	201 $[M]^+$ (29)
9	83	228—230	42.69 / 42.65	3.76 / 3.58	21.28 / 21.31	$C_7H_7N_3O_4$	197 $[M]^+$ (32)
10	22	174—176	45.27 / 45.36	2.52 / 2.34	24.53 / 24.41	$C_{13}H_8N_6O_6$	344 $[M]^+$ (4)
11	18	159—161	46.92 / 46.93	3.89 / 2.81	23.43 / 23.46	$C_{14}H_{10}N_6O_6$	358 $[M]^+$ (25)
12	51	172—174	42.73 / 42.65	3.65 / 3.58	21.34 / 21.31	$C_7H_7N_3O_4$	197 $[M]^+$ (27)
14	62	217—219	39.23 / 39.14	2.14 / 2.19	15.29 / 15.22	$C_6H_4N_2O_5$	184 $[M]^+$ (8)
16	55	189—190	35.81 / 35.75	2.07 / 2.00	20.89 / 20.85	$C_6H_4ClN_3O_3$	201 $[M]^+$ (17)
17	10	179—181	39.76 / 39.57	3.45 / 3.32	30.78 / 30.76	$C_6H_6N_4O_3$	182 $[M]^+$ (12)
19	7	234—236	43.47 / 43.65	2.03 / 1.83	25.58 / 25.45	$C_{12}H_6N_6O_6$	330 $[M]^+$ (36)
20	82	181—182	47.12 / 47.06	4.65 / 4.61	27.42 / 27.44	$C_6H_7N_3O_2$	153 $[M]^+$ (7)
22	76	30—32	28.39 / 28.40	0.47 / 0.48	13.24 / 13.25	$C_5HCl_3N_2O$	211 $[M]^+$ (18)
23	53	202—204	31.21 / 31.28	1.46 / 1.57	22.05 / 21.89	$C_5H_3Cl_2N_3O$	192 $[M]^+$ (2)
24	75	—	38.49 / 38.42	3.30 / 3.22	22.47 / 22.40	$C_6H_6ClN_3O_2$	187 $[M]^+$ (4)

and purified by column chromatography (silica gel 60, chloroform—methanol, 10 : 1, as the eluent).

2-Chloro-5-nitronicotinamide (8). A solution of 2-chloro-5-nitronicotinoyl chloride (5.0 g, 23 mmol) in acetonitrile (20 mL) was slowly added dropwise with vigorous stirring to 25% aqueous ammonia (200 mL) at −20 °C. The reaction mixture was allowed to stand until it warmed up to 0 °C (15 min) and immediately extracted with ethyl acetate (3×50 mL). The ethyl acetate extracts were combined, treated with activated carbon, dried with sodium sulfate, and concentrated *in vacuo*. The resulting pale yellow precipitate as large crystals was recrystallized from ethanol. ^{1}H NMR (DMSO-d_6), δ: 3.39 (s, 3 H, N(3)Me); 3.90 (s, 3 H, C(2′)OMe); 8.82 (d, 1 H, H(6′), J = 2.7 Hz); 8.99 (d, 1 H, H(4′), J = 2.7 Hz); 9.04 (d, 1 H, H(5), J = 2.3 Hz); 9.24 (d, 1 H, H(7), J = 2.3 Hz).

2-Methoxy-5-nitronicotinamide (9). A freshly prepared solution (10 mL) of sodium methoxide (0.12 g of sodium (5 mmol) in 10 mL of methanol) was added to a solution of chloronicotinamide **8** (0.5 g, 2.5 mmol) in methanol (50 mL) at a temperature lower than 3 °C. Then the reaction mixture was allowed to stand at room temperature for 3 h, diluted with cold water (100 mL), and acidified with concentrated HCl to pH ~7. The white precipitate of nicotinamide **9** that formed was filtered off and recrystallized from a methanol—DMF mixture.

2-(2-Methoxy-5-nitropyridin-3-yl)-6-nitropyrido[2,3-*d*]pyrimidin-4-one (10). A solution of nicotinamide **9** (0.8 g, 4.1 mmol) and sodium methoxide (0.22 g, 4.1 mmol) in methanol (15 mL) was heated to 100 °C for 30 min. The reaction mixture was cooled, diluted with water (80 mL), and acidified with 35% HCl to pH ~3. The precipitate of pyridopyrimidinone **10** that formed was filtered off and purified by column chromatography (silica gel 60, chloroform—methanol, 15 : 1, as the eluent). ^{1}H NMR (DMSO-d_6), δ: 4.10 (s, 3 H, C(2′)OMe); 8.87 (d, 1 H, H(6′), J = 2.6 Hz); 9.06 (d, 1 H, H(5), J = 2.7 Hz); 9.29 (d, 1 H, H(4′), J = 2.6 Hz); 9.66 (d, 1 H, H(7), J = 2.7 Hz); 13.65 (br.s, 1 H, N(3)H).

2-(2-Methoxy-5-nitropyridin-3-yl)-3-methyl-6-nitropyrido[2,3-*d*]pyrimidin-4-one (11). A suspension of pyridopyri-

midinone **10** (0.11 g, 0.32 mmol), diiodomethane (0.08 mL, 1.28 mmol), and potassium carbonate (0.066 g, 0.48 mmol) in a mixture of acetone (3 mL) and *N*-methylpyrrolidone (1 mL) was kept for 24 h. Then the reaction mixture was filtered off, concentrated to 2 mL, and diluted with water (15 mL). Pyridopyrimidinone **11** was filtered off and purified by column chromatography (silica gel 60, hexane—acetone, 20 : 1, as the eluent). ^{1}H NMR (DMSO-d_6), δ: 3.38 (s, 3 H, N(3)Me); 4.10 (s, 3 H, C(2′)OMe); 8.83 (d, 1 H, H(6′), J = 2.6 Hz); 9.14 (d, 1 H, H(5), J = 2.7 Hz); 9.33 (d, 1 H, H(4′), J = 2.6 Hz); 9.70 (d, 1 H, H(7), J = 2.7 Hz).

4-Methoxy-5-nitronicotinamide (12). A freshly prepared solution (10 mL) of sodium methoxide (sodium (0.11 g, 5 mmol) in 10 mL of methanol) was added to a solution of nicotinamide **16** (1.0 g, 5 mmol) in methanol (50 mL) at room temperature. The reaction mixture was allowed to stand for 3 h, diluted with cold water (100 mL), and filtered. Methoxy derivative **12** was obtained in a yield of 0.48 g. The filtrate was extracted with ethyl acetate (3×30 mL), and the organic phase was dried with sodium sulfate and concentrated to obtain an additional amount of pyridine **12** (0.28 g). The products were combined and recrystallized from water.

4-Hydroxy-5-nitronicotinic acid (14). A solution of 4-hydroxynicotinic acid (8.0 g, 58 mmol) in a mixture of concentrated sulfuric acid (70 mL) and fuming nitric acid (16 mL) was kept at 100 °C for 10 h. Then the reaction mixture was cooled and poured into crushed ice (400 g). The white precipitate of pyridine **14** that formed was filtered off and recrystallized from ethanol.

4-Chloro-5-nitronicotinoyl chloride (15). A suspension of pyridine **14** (5.7 g, 31 mmol) in a mixture of carbon tetrachloride (70 mL), thionyl chloride (15 mL), and DMF (0.5 mL) was heated to reflux for 9 h. The resulting solution was concentrated and oily acid chloride **15** was used in the further synthesis without additional purification. MS, m/z (I_{rel} (%)): 220 $[M]^+$ (20). $C_6H_2Cl_2N_2O_3$.

4-Chloro-5-nitronicotinamide (16) and 4-amino-5-nitronicotinamide (17). A solution of acid chloride **15** (7.0 g, 32 mmol) in acetonitrile (20 mL) was slowly added dropwise with vigorous stirring to 25% aqueous ammonia (200 mL) at 0 °C. The reaction mixture was allowed to stand for 15 min and extracted with ethyl acetate (5×50 mL). The ethyl acetate fractions were combined, treated with activated carbon, dried with sodium sulfate, and concentrated *in vacuo*. The bright yellow solid residue was crystallized from water, while nicotinamide **16** (3.8 g) was collected on a filter (the latter was then recrystallized from ethanol), and nicotinamide **17** precipitated from the aqueous filtrate (0.9 g) as yellow-green needle-like crystals.

2-(4-Hydroxy-5-nitropyridin-3-yl)-8-nitropyrido[4,3-*d*]pyrimidin-4-one (19) was prepared under conditions analogous to the synthesis of quinazolinone **3**. The product was purified by column chromatography (silica gel 60, chloroform—methanol, 5 : 1, as the eluent). ^{1}H NMR (DMSO-d_6), δ: 15.70 (br.s, 1 H, OH); 8.67, 9.13, 9.23, and 9.34 (all br.s, 1 H each, H(7), H(5), H(6′), H(4′)).

4-Chloropyrimidine-5-carboxamide (20). A solution of 5-carbamoyl-4-chloro-6-methoxypyrimidine (**24**) (0.6 g, 3.2 mmol) in ethanol (25 mL) was reduced with hydrogen in the presence of palladium on carbon (10%, 0.03 g) and potassium hydroxide (0.12 g, 1.6 mmol). After 3 h, the reaction mixture was filtered, the filtrate was concentrated, and the residue was recrystallized from a methanol—DMF mixture.

4,6-Dichloropyrimidine-5-carboxylic acid chloride[15] (22). Sulfuryl chloride (1.5 mL) and 2,2′-azobis(2-methylpropionitrile) (Aldrich, USA) (100 mg) were added to a solution of pyrimidine **21** (2.0 g, 11 mmol) in carbon tetrachloride (20 mL). The reaction mixture was refluxed for 7 h and concentrated. Acid chloride **22** was purified by column chromatography (silica gel 60, dichloromethane as the eluent). After recrystallization from petroleum ether (70/100), a white crystalline product was obtained in a yield of 1.8 g. ^{1}H NMR (DMSO-d_6), δ: 8.92. ^{13}C NMR (DMSO-d_6), δ: 131.5 (C(5)); 156.5 (C(4) and C(6)); 158.7 and 162.6 (C(2) and COCl).

4,6-Dichloropyrimidine-5-carboxamide (23) was prepared analogously to 4-chloro-5-nitronicotinamide (**16**) and recrystallized from Pr^{i}OH.

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