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SYNTHESIS OF DERIVATIVES OF PYRAZOLO[3,4-*d*]PYRIMIDINES BY REACTION OF 3,5-BIS(DIMETHYLAMINOMETHYLENE)AMINO-4-METHOXYCARBONYLPYRAZOLE AND 4-CYANOPYRAZOLE WITH AMINES

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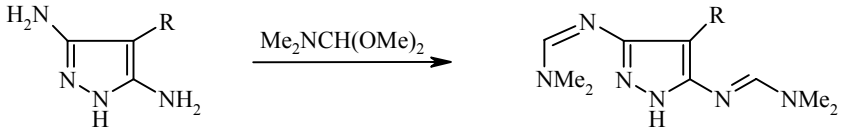
The reaction of 3,5-di-(N,N-dimethylaminomethylene)amino-4-methoxycarbonylpyrazole and 3,5-di-(N,N-dimethylaminomethylene)amino-4-cyanopyrazole with different amines occurs with formation of pyrazolo[3,4-d]pyrimidines. In some reactions, an excess of amines leads to their conversion to N,N-dimethylformamidine derivatives. The structure of the compounds obtained has been confirmed by ^{1}H NMR and ^{13}C spectroscopy.

Keywords: allopurinol, DMF acetal, 4-methoxycarbonylpyrazole, pyrazolo[3,4-*d*]pyrimidine, 4-cyanopyrazole.

Recently we studied the reaction of 1-methyl-3,5-bis(dimethylaminomethylene)amino-4-nitropyrazole with different amines, and we showed that this process occurs regioselectively with cleavage of the amidine moiety at the position 3 [1]. It seemed of interest to study analogous reactions with participation of 3,5-bisformamidinopyrazole derivatives that had in the position 4, instead of a nitro group, such functional groups as methoxycarbonyl or cyano group. In this case, we considered that the presence of these may ensure the possibility of closure of the pyrimidine ring, resulting in novel derivatives of pyrazolo[3,4-*d*]pyrimidine of significant interest for biological study, since such compounds are substituted analogs of the well-known drug allopurinol [2]. We described the synthesis of one of the starting materials, 3,5-diamino-4-methoxycarbonylpyrazole (**1a**) earlier in [3], in connection with study of its reaction with acetoacetic ester [2], and the other starting material 3,5-diamino-4-cyanopyrazole (**1b**) was obtained using the familiar scheme involving reaction of 1,1-dicyano-2,2-dimethylthioethylene with an alcoholic solution of ammonia [4] and then with hydrazine hydrate [5].



1 **2**

1, 2 a R = COOMe, **b** R = CN

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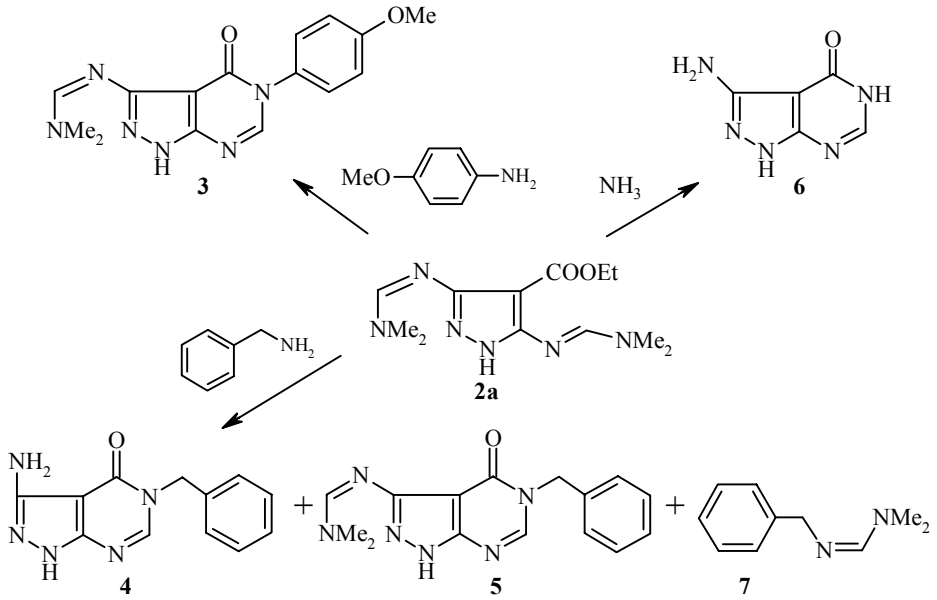
Condensation of pyrazoles **1a,b** with DMF dimethyl acetal occurs smoothly and leads to 3,5-bis(dimethylaminomethylene)amino-4-methoxycarbonyl- and 4-cyanopyrazoles (**2a** and **2b**). We should note that methylation at the position 1, as in the case of 4-nitro derivative [1], does not occur. This is probably explained by the fact that the presence of a stronger electron-acceptor nitro group leads to formation of an appreciably higher concentration of the anion, with localization of the negative charge on the position 1 of the pyrazole ring and substantial facilitation of alkylation at this position with participation of DMF acetal, the alkylating ability of which is well-known [6].

As the amines for studying their reactions with the amidine **2a**, we selected the relatively low-basicity *p*-anisidine (pK_a 5.29) and the more basic benzylamine (pK_a 9.37) and ammonia (pK_a 9.25). In this case, we considered that from the standpoint of possible steric hindrances in the transition state, ammonia is substantially more favorable for nucleophilic attack than benzylamine.

Heating diamidino-4-methoxycarbonylpyrazole **2a** with each of the studied amines led to closure of the pyrimidine ring and accordingly formation of a bicyclic pyrazolo[-3,4-*d*]pyrimidine. In this case, the reaction rates differ quite significantly: for the process to go to completion (TLC), 3 h of boiling in methanol were required for ammonia (bomb, 80°C); for benzylamine, 12 h were required; and for the least basic *p*-anisidine, 24 h were required. We must note that upon reaction with the least basic *p*-anisidine, we observed the 3-amidine derivative **3** exclusively as the reaction product, while with the more basic benzylamine we observed a mixture of 3-amino and 3-amidine derivatives **4** and **5**, each of which was isolated and identified. The reaction of pyrazole **2a** with ammonia (the most basic of the studied amines) led exclusively to the 3-amino derivative **6.**



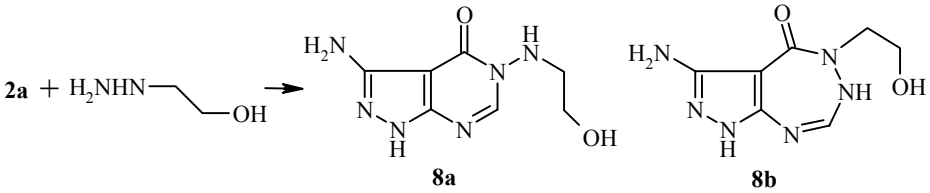
In the case of the reaction with benzylamine, as we had expected, we were able to isolate N-dimethylaminomethylenebenzylformamidine **7** as hydrochloride, along with pyrazole derivatives **4** and **5**. The scheme for the formation of such amidines has been discussed in detail in [1]. We must note that formation of 3-aminopyrazolopyrimidine in the reaction with *p*-anisidine, like the presence of N-dimethylaminomethylene-*p*-anisidine in the reaction mixture, also could be detected by mass spectrometry (we did not isolate these products).

We again emphasize that in the reaction with the basic and sterically small molecule of ammonia, along with pyrimidine cyclization, degradation of the second amidine moiety goes to completion. The basic but bulkier benzylamine reacts more slowly at the second amidine group, and as a result of the reaction a mixture is

formed of 3-amino-5-benzyl- and 5-benzyl-3-dimethylaminomethyleneamino-4-oxopyrazolo[3,4-*d*]pyrimidines (**4** and **5**). In the reaction of the larger and low-basicity molecule of *p*-anisidine, cyclization occurs after the first transamination of the amidine moiety; and attack on the second amidine group in the already formed bicycle of the *p*-anisidine molecule does not occur, and as a result, derivative **3** is isolated as the sole product.

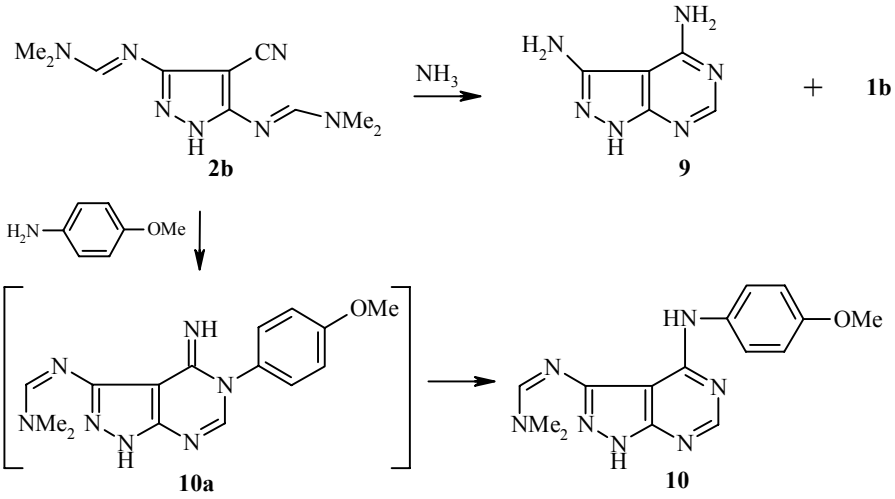
The structure of the pyrazolopyrimidines obtained was confirmed by elemental analysis, mass spectrometry, and NMR spectroscopy.

The successful synthesis of pyrazolopyrimidines allowed us to hope that it would also be possible to carry out the reaction with hydrazines. Usually reaction of amidines of the studied type with hydrazines leads only to formation of an amino group. To study this process, we chose hydroxyethylhydrazine, which reacts smoothly and in high yield (80%) with pyrazole **2a** to form pyrazolopyrimidine **8a**. As we also see in this case, the amidine group in the position 3 is transformed to an amino group.



The structure of the compound **8a** obtained (rather than the possible alternative triazepine derivative **8b**) unambiguously follows from the ^{1}H NMR spectroscopy data.

To study the reaction of diamidine **2b**, we chose ammonia and *p*-anisidine as the nucleophilic partners. By heating pyrazole **2b** with methanolic ammonia in a bomb at 110°C, we obtained a mixture of 3,4-diaminopyrazolo[3,4-*d*]pyrimidine **9** and the diamino derivative **1b**, i.e., along with the pyrimidine cyclization, transformation of both amidine moieties of compound **2b** to amino groups occurs at a comparable rate. Possibly the greater accessibility of the *meso*-amidine positions in nitrile **2b** compared with ester **2a** is connected with the considerably smaller volume of the substituent at the position 4 (the "rod-shaped" cyano group creates considerably less steric hindrance than the methoxycarbonyl group). When the compound **2b** reacts with *p*-anisidine, as in the case of the carbomethoxy derivative, the second amidine group of the molecule is not involved; and not only does pyrimidine cyclization occur, but also Dimroth rearrangement. As a result, 3-dimethylaminomethyleneamino-4-*p*-anisidinopyrazolo[3,4-*d*]pyrimidine is formed (**10**).



The alternative structure **10a** was excluded based on NMR spectroscopy data. The one-dimensional ^{1}H NMR spectrum, δ, ppm: 3.11 (6H, s, $N(CH_3)_2$); 3.76 (3H, s, OCH_3); 6.95 and 7.70 (4H, AA'XX'); 8.28 (1H, s, 6-H); 8.41 (1H, s, H-amidine); 8.68 (1H, s, 4-NH); 12.40 (1H, br. s, 1-NH), is not informative from the standpoint of choosing between structures **10** and **10a**. For this purpose, we took the ROESY, HSQC, HMBC NMR spectra and made an unambiguous assignment in the ^{1}H NMR spectrum (see Table 1) and the ^{13}C NMR spectrum, δ, ppm: 33.8 and 39.5 ($N(CH_3)_2$), 55.1 (OCH_3); 94.1 ($C_{(3a)}$); 114.2 ($C_{(3')}$; $C_{(5')}$); 121.1 ($C_{(6')}$; $C_{(2')}$); 132.1 ($C_{(1')}$); 151.1 ($C_{(3)}$); 154.4 (CH amidine); 154.5 ($C_{(7a)}$); 155.2 ($C_{(4')}$); 155.3 ($C_{(4)}$); 156.1 ($C_{(6)}$). In the ROESY spectrum, we see an intense correlation peak at 8.68/7.70 ppm (4-NH/H-2',6'), which is characteristic of both structures, but the H-6/H-2',6' peak which is expected for structure **10a** does not appear. In the HMQC spectrum, we observe an intense correlation peak at 8.68/121.1 ppm (NH/C-2',6') which is characteristic only of structure **10** but not for **10**a, where the indicated proton and carbon atoms are separated by five bonds. We also took the ^{13}C NMR spectrum (conditions with complete spin–spin decoupling) in DMSO-d_6 with addition of 1:1 H_2O–D_2O mixture. Under these conditions, in the spectrum close to some of the carbon atoms we saw additional signals due to the presence in solution, along with the starting compound **10**, of its deutero analog containing the NDC_6H_4–OCH_3(*p*) group (isotopic shifts). The isotopic shifts reached appreciable values for the following atoms: $C_{(1')}$, Δδ = -0.077 ppm; $C_{(2')}$, $C_{(6')}$, Δδ = -0.118 ppm; $C_{(4)}$, Δδ = -0.245; $C_{(3a)}$, Δδ = -0.029 ppm. We should note that in this case, we do not observe correlations between the absolute value of the isotopic shift and the distance from the deuteration site: $\Delta\delta C_{(1')} < \Delta\delta C_{(2')}$, $C_{(6')}$, $\Delta\delta C_{(1')} < \Delta\delta C_{(4)}$, $\Delta\delta C_{(3a)} < \Delta\delta C_{(1')}$, while a decrease in absolute value of the isotopic shift with distance (two or three bonds) from the deuterated atom is typical. However, the presence of an isotopic shift for the atoms $C_{(1')}$ and $C_{(2')}$, $C_{(6')}$ is also evidence in favor of structure **10**.

Reactions of 4-carbomethoxy- and 4-cyanodiamidinopyrazoles considered in this paper are not only of theoretical interest for organic chemistry, but also from a practical standpoint – they provide an approach to synthesis of novel analogs of allopurinol and xanthine oxidase inhibitors, which is extremely important in searching for new compounds regulating nitrogen oxide exchange in the body.

TABLE 1. Experimental Conditions and Spectral Data for Synthesized Compounds

Com-pound	Reagent	Reaction conditions*	^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz)
2a	AcDMF*[2]	100°C, 4 h	
2b	AcDMF*[2]	100°C, 4 h	
3	*p*-Anisidine	Boiling, 24 h	2.97, 3.03 (6H, s, $N(CH_3)_2$); 3.81 (3H, s, OMe); 8.00 (1H, s, 6-H); 9.12 (1H, br. s, H-amidine); 7.02, 7.35 (AA'XX'); 12.9 (1H, br. s, 1-NH)
4	Benzylamine	Boiling, 12 h	5.09 (2H, s, CH_2); 5.54 (2H, br. s, NH_2); 7.31 (5H, m, Ph); 8.31 (1H, s, 6-H); 12.39 (1H, br. s, 1-NH)
5			2.96, 3.05 (6H, s, $N(CH_3)_2$); 5.07 (2H, s, CH_2); 7.30 (5H, s, Ph); 8.27 (1H, s, 6-H); 9.03 (1H, br. s, H-amidine); 12.8 (1H, br. s, 1-NH)
6	NH_3	Bomb, 80°C, 3 h	
8a	Hydroxyethyl-hydrazine	Boiling, 5 h	3.01 (2H, q, *J* = 5.5, α-CH_2); 3.49 (2H, q, *J* = 5.5, β-CH_2); 4.59 (1H, t, OH); 5.35 (2H, s, 3-NH_2); 6.33 (1H, t, 5-NH); 8.10 (1H, s, 6-H); 12.23 (1H, s, 1-NH)
9	NH_3	Bomb, 110°C, 24 h	
10	*p*-Anisidine	Boiling, 5 days	

* Solvent: MeOH.

*[2] AcDMF: DMF dimethyl acetal.

TABLE 2. Physicochemical Characteristics of Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp*, °C	*m/z* [$M^{+\cdot}$]	Yield, %
		C	H	N			
2a	$C_{12}H_{19}N_5O_2$	54.42 / 54.32	7.20 / 7.22	26.53 / 26.40	139-141	265	91
2b	$C_{11}H_{16}N_6$	56.12 / 56.88	7.02 / 6.94	36.24 / 36.18	186-187	232	89
3	$C_{15}H_{16}N_6O_2$	57.34 / 57.68	5.01 / 5.16	27.12 / 26.91	>270	312	64
4	$C_{12}H_{11}N_5O$	60.08 / 59.74	4.60 / 4.60	29.31 / 29.03	>270	241	43
5	$C_{15}H_{16}N_6O$	61.13 / 60.80	5.35 / 5.44	28.32 / 28.36	>270	296	38
6	$C_5H_5N_5O$	39.71 / 39.74	3.21 / 3.33	46.74 / 46.34	>270	151	87
8a	$C_7H_{10}N_6O_2$	40.02 / 40.00	4.58 / 4.80	39.91 / 39.98	110-112	210	73
9	$C_5H_6N_6$	39.86 / 40.00	4.11 / 4.03	55.82 / 55.97	>400	150	56
10	$C_{15}H_{17}N_7O$	58.04 / 57.87	5.53 / 5.50	31.62 / 31.49	230-232	311	36

* Compounds **2a,b,3,5,10** were crystallized from EtOH, **4,6** were crystallized from H_2O, **8a** was crystallized from MeOH.

EXPERIMENTAL

The NMR spectra were recorded on Bruker AC-200 (200 MHz) and AC-500 (500 MHz) spectrometers. The mass spectra were obtained on a Finnigan SSQ-700 spectrometer with sample injection directly into the ion source. The purity of the products and the course of the reactions were monitored using TLC on Fluka TLC Cards Silica Gel 60778.

The physicochemical and spectral data for the synthesized compounds are given in Tables 1 and 2.

4-Methoxycarbonyl-3,5-bis(dimethylaminomethylene)aminopyrazole (2a) and 4-Cyano-3,5-bis(dimethylaminomethylene)aminopyrazole (2b). Solution of 3,5-diaminopyrazole **1a** or **1b** (6.4 mmol) and DMF dimethyl acetal (3.0 ml) was held for 4 h at 100°C and distilled under vacuum. The remaining oil was triturated with hexane and crystallized from ethanol.

Reaction of Pyrazoles 2a and 2b with Amines. Solution of pyrazole **2a** or **2b** (2.3 mmol) and the corresponding amine (5.75 mmol) was boiled in methanol, cooled, and diluted with a three-fold amount of water and the precipitate was filtered off. **3-Dimethylaminomethyleneamino-5-(4-methoxyphenyl)-4-oxo-pyrazolo[3,4-*d*]pyrimidine (3), 3-Amino-5-benzyl-4-oxopyrazolo[3,4-*d*]pyrimidine (4), 5-Benzyl-3-dimethylaminomethyleneamino-4-oxopyrazolo[3,4-*d*]pyrimidine (5), 3-Amino-4-oxopyrazolo[3,4-*d*]-pyrimidine (6), 3-Amino-5-(β-hydroxyethyl)amino-4-oxopyrazolo[3,4-*d*]pyrimidine (8a), 3,4-Diaminopyrazolo[3,4-*d*]pyrimidine (9), 3-Dimethylaminomethyleneamino-4-(*p*-anisidino)pyrazolo-[3,4-*d*]pyrimidine (10)** were obtained and crystallized from an appropriate solvent.

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