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THREE-COMPONENT CONDENSATION OF HETARYLGUANIDINES WITH ALDEHYDES (KETONES) AND DICARBONYL COMPOUNDS

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The three-component condensation of benzoxa(thia)zolylguanidines, aldehydes (ketones), and β-dicarbonyl compounds (acetyl- and benzoylacetone, ethyl acetoacetate, acetoacetanilides, cyclohexanedione-1,3 and its derivatives) has been studied.

Keywords: acetoacetanilides, acetylacetone, aldehydes, benzoxazolylguanidine, benzoylacetone, benzthiazolylguanidine, cyclohexanedione-1,3, β-dicarbonyl compounds, ethyl acetoacetate, ketones, three-component condensation.

Reactions involving nitrogen-containing binucleophiles opens the way to the design of various linear and condensed heterocyclic systems possessing a wide range of biological activity. In consequence these reactions have been studied intensively [1-10]. (Thio)ureas and their alkyl derivatives [1-3], 3-amino-1,2,4-triazole [4,5], aminopyrazol and aminotetrazole [6], and 2-aminobenzimidazole [7,8] have been used in three-component condensations with aldehydes and β-dicarbonyl compounds (ethyl acetoacetate, dimedone). In contrast, guanidine and its derivatives, which have considerable synthetic potential [9], have been studied comparatively little in such reactions. We have previously studied three-component condensations of benzoxa(thia)zolylguanidines (**1a,b**), triethyl orthoformate, and β-dicarbonyl compounds [10]. The objective of the present work was to study the reactivity of the guanidines **1a,b** in three-component condensation reactions with aldehydes (ketones) and β-dicarbonyl compounds: acetyl- and benzoylacetone, ethyl acetoacetate, acetoacetanilides, cyclohexanedione-1,3 and it derivatives.

It was found that boiling equimolar mixtures of a guanidine **1a,b,** cyclohexanedione (dimedone) **2**, and aromatic aldehydes **3** gave the 4-aryl-2-[1,3-benzoxa(thia)zol-2-ylamino]-1,4,5,6,7,8-hexahydro-5-quinazolinones **6a-c** in 40-70% yields. Use of cyclopenta(hexa)nones **4a,b** or isatin **5** in place of the aldehyde gave the corresponding spirocondensed systems **7** and **8** on boiling in 2-propanol. In the latter likely the more reactive β-carbonyl group of isatin took part in the condensation (Scheme 1).

Reaction of the guanidine **1** – aldehyde **3** – acetylacetone system did not give the expected acetyldihydropyrimidine **9**. The reaction products in this case were the 4,6-dimethyl-2-benzoxa(thia)zolylaminopyrimidines **10**, the synthesis of which from **1** and acetylacetone we have described previously [11]. However in the case of benzoylacetone, which reacted with great difficulty in a two-component

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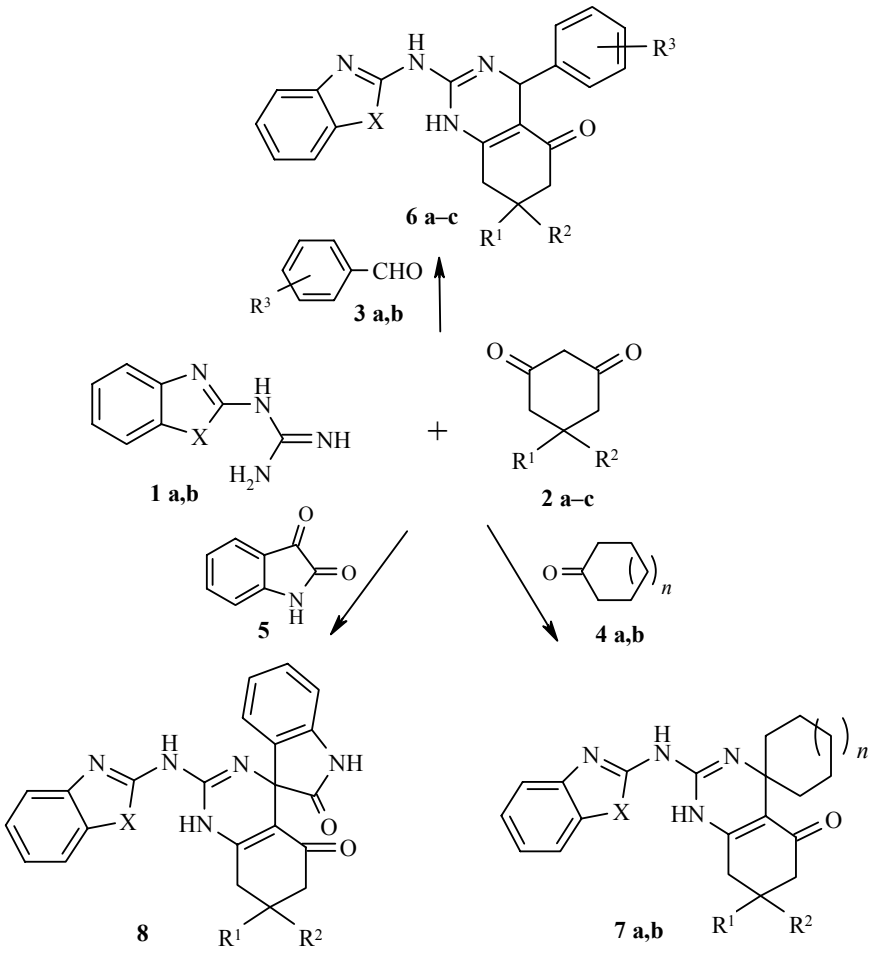
Scheme 1



1 a X = O, **b** X = S; **2 a** $R^1 = R^2$ = H, **b** $R^1 = R^2$ = Me, **c** R^1 = H, R^2 = 4-FC_6H_4;
3 a R^3 = H, **b** R^3 = 2-Cl; **4 a** *n* = 0, **b** *n* = 1; **6 a** X = O, $R^1 = R^2 = R^3$ = H; **b** X = O,
$R^1 = R^2$ = Me, R^3 = 2-Cl; **c** X = S, $R^1 = R^3$ = H, R^2 = 4-FC_6H_4; **7 a** X = O, $R^1 = R^2$ = Me, *n* = 0,
b X = S, $R^1 = R^2$ = H, *n* = 1; **8** X = S, $R^1 = R^2$ = Me

condensation with the guanidines **1**, product was isolated in high yield from the three-component condensation. Since the acetyl group in this case is considerably more reactive than the benzoyl group, the product was assigned structure **12** (Scheme 2).

Boiling an equimolar mixture of the guanidines **1a,b**, ethyl acetoacetate, and benzaldehyde again did not give the product of the component condensation **15**, but the product of the cyclization of guanidine with ethyl acetoacetate **14**, which had been described previously [11], was isolated. However, when acetoacetanilides **16** were used the reaction gave the expected products, dihydropyrimidinedicarboxamides **17**.

Signals of the aromatic protons were observed in the 7.0-7.9 ppm range and the two NH protons in the ranges 9.9-10.3 and 10.0-11.3 ppm respectively were observed in the ^{1}H NMR spectra of the synthesized compounds **6-8**, **12**, and **17**. Beside that, in compound **8** the singlet of NH proton of the isatin fragment was observed at 9.52 ppm, and compounds **17a,b** gave carboxamide NH proton singlets at 9.64 and 9.57 ppm respectively. The protons on $C_{(4)}$ of the dihydropyrimidine unit in compounds **6**, **12**, and **17** gave characteristic signals in the 5.7-5.9 ppm region. In compounds **6b** and **8** the two CH_2 groups of the hexahydroquinazoline unit

Scheme 2

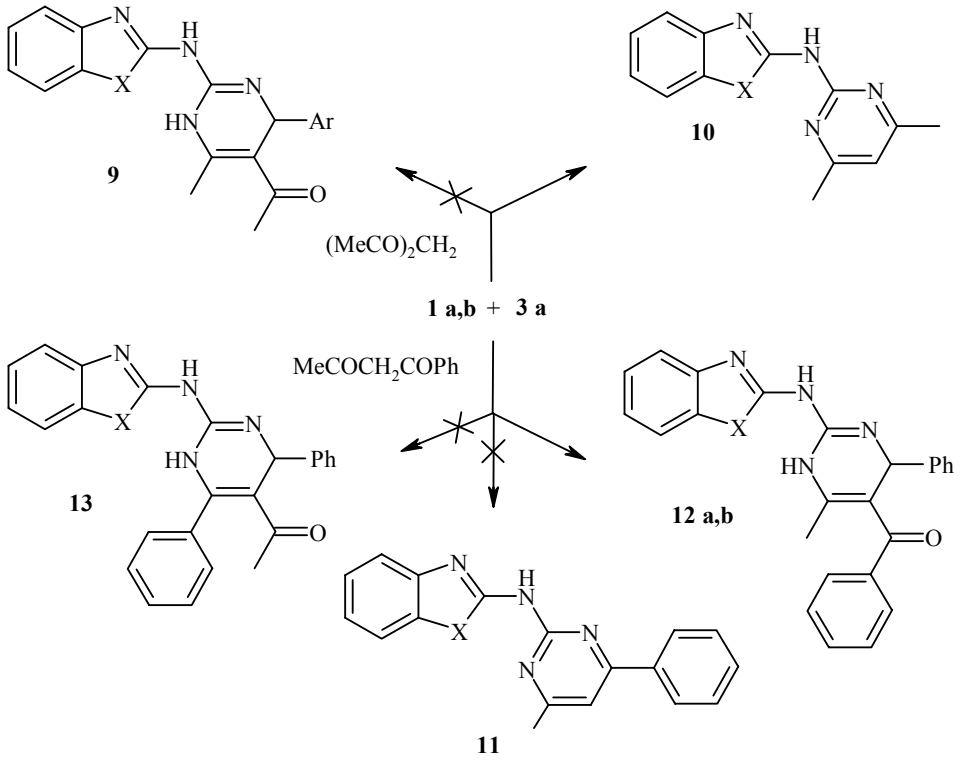
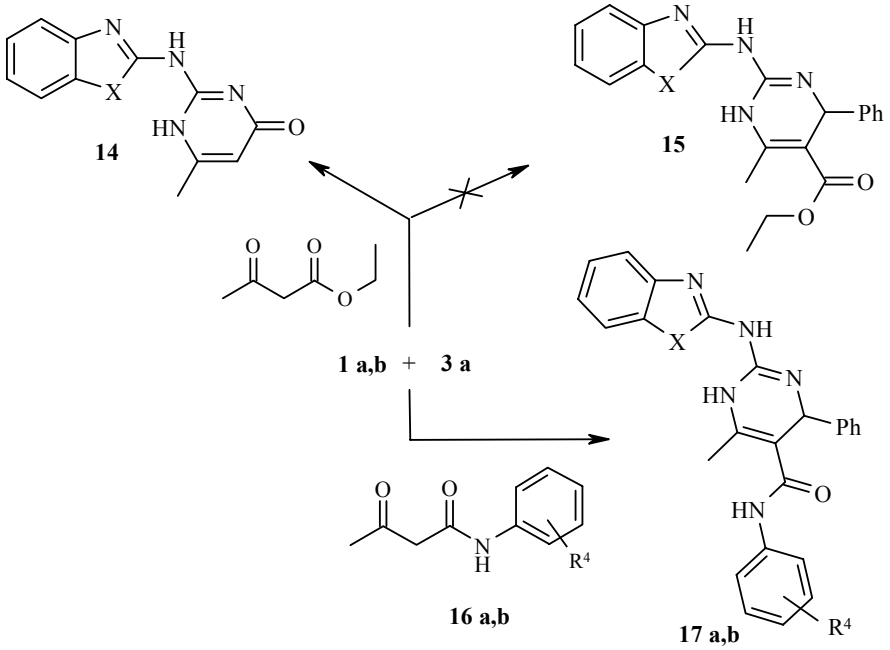


TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			M*/M[1]	mp, °C	Yield, %
		C	H	N			
6a	$C_{21}H_{18}N_4O_2$	70.53 / 70.38	5.01 / 5.06	15.35 / 15.63	358 / 358.41	287-289	68
6b	$C_{23}H_{21}ClN_4O_2$	65.41 / 65.63	5.03 / 5.11	13.32 / 13.31	420 / 420.96	>300	65
6c	$C_{27}H_{21}FN_4OS$	69.54 / 69.21	4.52 / 4.45	12.01 / 11.96	468 / 468.56	274-276	59
7a	$C_{21}H_{24}N_4O_2$	69.41 / 69.21	6.64 / 6.56	15.65 / 15.37	364 / 364.47	265-267	61
7b	$C_{20}H_{22}N_4OS$	65.14 / 65.55	6.05 / 6.11	15.23 / 15.29	366 / 366.50	>300	32
8	$C_{24}H_{21}N_5O_2S$	65.12 / 64.99	4.77 / 4.88	15.85 / 15.79	443 / 443.53	240-242	30
12a	$C_{25}H_{20}N_4OS$	70.47 / 70.73	4.75 / 4.58	13.25 / 13.20	424 / 424.48	270-272	67
12b	$C_{25}H_{20}N_4O_2$	73.56 / 73.51	4.94 / 4.95	13.65 / 13.72	408 / 408.46	264-266	64
17a	$C_{25}H_{21}N_5OS$	68.42 / 68.32	4.82 / 4.58	15.78 / 15.93	439 / 439.54	262-263	39
17b	$C_{31}H_{25}N_5O_3$	72.44 / 72.22	4. 89 / 4.78	13.56 / 13.58	515 / 515.58	259-261	34

* M – found, M^1 – calculated.

form two separate AB systems, the signals of which have the characteristic form of a double of doublets in the 2.1-2.3 and 2.4-2.6 ppm regions. In compound **7a** the signals of the protons of the cyclopentane unit overlap this region.



16 a R^4 = H, **b** R^4 = 4-PhO; **17 a** X = S, R^4 = H, **b** X = O, R^4 = 4-PhO

TABLE 2. ^{1}H NMR Spectra of the Compounds Synthesized

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)
6a	2.02-2.35 (6H, m, aliph.); 5.69 (1H, s, $C_{(4)}$-pyrimidine); 7.10-7.45 (9H, m, arom.); 9.92 (1H, s, NH); 10.56 (1H, s, NH)
6b	1.10 (6H, s, 2 CH_3); 2.19 (1H, d, *J* = 18.0, CH_2); 2.26 (1H, d, *J* = 18.0, CH_2); 2.52 (1H, d, *J* = 14.0, CH_2); 2.60 (1H, d, *J* = 14.0, CH_2); 5.92 (1H, s, $C_{(4)}$-pyrimidine); 7.09-7.51 (8H, m, arom.); 10.22 (1H, s, NH); 10.63 (1H, s, NH)
6c	2.60-2.95 (5H, m, aliph.); 5.72 (1H, s, $C_{(4)}$-pyrimidine); 7.08-7.55 (13H, m, arom.); 9.98 (1H, s, NH); 10.65 (1H, s, NH)
7a	1.03 (6H, s, 2CH_3); 1.60-1.95 (6H, m, aliph.); 2.20-2.55 (6H, m, aliph.); 7.10-7.22 (2H, m, arom.); 7.42 (2H, t, *J* = 7.2, arom.); 10.01 (1H, s, NH); 10.35 (1H, s, NH)
7b	1.26-2.44 (16H, m, aliph.); 7.24 (1H, t, *J* = 7.2, arom.); 7.41 (1H, t, *J* = 7.2, arom.); 7.64 (1H, d, *J* = 7.2, arom.); 7.86 (1H, d, *J* = 7.2, arom.); 10.11 (1H, s, NH); 10.39 (1H, s, NH)
8	1.06 (3H, s, CH_3); 1.12 (3H, s, CH_3); 2.15 (1H, d, *J* = 18.0, CH_2); 2.22 (1H, d, *J* = 18.0, CH_2); 2.50 (1H, d, *J* = 14.0, CH_2); 2.63 (1H, d, *J* = 14.0, CH_2); 7.06-7.39 (6H, m, arom.); 7.61 (1H, d, *J* = 7.2, arom.); 7.81 (1H, d, *J* = 7.2, arom.); 9.52 (1H, s, NH); 10.21 (1H, s, NH); 11.35 (1H, s, NH)
12a	1.86 (3H, s, CH_3); 5.79 (1H, s, $C_{(4)}$-pyrimidine); 7.05-7.70 (14H, m, arom.); 10.20 (1H, s, NH); 10.32 (1H, s, NH)
12b	1.80 (3H, s, CH_3); 5.74 (1H, s, $C_{(4)}$-pyrimidine); 7.10-7.75 (14H, m, arom.); 9.98 (1H, s, NH); 10.13 (1H, s, NH)
17a	2.16 (3H, s, CH_3); 5.78 (1H, s, $C_{(4)}$-pyrimidine); 6.98-7.15 (5H, m, arom.); 7.32-7.47 (9H, m, arom.); 9.64 (1H, s, NH); 10.02 (1H, s, NH); 10.18 (1H, s, NH)
17b	2.21 (3H, s, CH_3); 5.83 (1H, s, $C_{(4)}$-pyrimidine); 6.86-7.17 (7H, m, arom.); 7.27-7.44 (9H, m, arom.); 7.62 (2H, d, *J* = 7.2, arom.); 9.57 (1H, s, NH); 9.92 (1H, s, NH); 10.03 (1H, s, NH)

EXPERIMENTAL

The course of the reactions and the purity of the products were monitored by TLC on Merck UV-254 plates. ^{1}H NMR spectra were recorded on a Bruker AC-300 (300 MHz) (IOKh, Moscow) in DMSO-d_6 with TMS as internal standard, and mass spectra were recorded with an LKB 9000 machine with 70 eV energy of the ionizing electrons.

4-Aryl-2-(1,3-benzoxa(thia)zol-2-ylamino)- 1,4,5,6,7,8-hexahydro-5-quinaxolinones 6a-c. A mixture of guanidine **1** (5 mmol), cyclohexanedione **2** (5 mmol), and arylaldehyde **3** (5.5 mmol) in dioxane (15 ml) was boiled for 3 h, the precipitate was filtered off, washed with dioxane, and crystallized from DMF.

2-(1,3-Benzoxazol-2-ylamino)-4,4'-spirocyclopentano-7,7-dimethyl-1,4,5,6,7,8-hexahydro-5-quinazolinone (7a), 2-(1,3-Benzthiazol-2-ylamino)-4,4'-spirocyclohexano-7,7-dimethyl-1,4,5,6,7,8-hexahydro-5-quinazolinone (7b), and 2-(1,3-Benzthiazol-2-ylamino)-4,4'-spiro[3-(2-indolinone)]-7,7-dimethyl-1,4,5,6,7,8-hexahydro-5-quinazolinone (8) were synthesized by the preceding method using the corresponding ketone, 2-propanol as solvent, and were crystallized from dioxane.

2-(1,3-Benzoxa(thia)zol-2-ylamino)-5-benzoyl 6-methyl-4-phenyl-1,4-dihydro-pyrimidine 12a,b. A mixture of guanidine **1** (5 mmol), benzoylacetone (5 mmol), and arylaldehyde **3** (5.5 mmol) in dioxane (5 ml) was boiled for 5 h, precipitate was filtered off, and crystallized from a dioxane–DMF mixture.

N-5-Aryl-2-(1,3-benzoxa(thia)zol-2-ylamino)-4-aryl-6-methyl-1,4-dihydro-5-pyrimidinedicarboxamides 17a,b were obtained analogously to compounds **7, 8**.

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