Three-component synthesis of 4-aryl-5-cyano-2-hetarylaminopyrimidines

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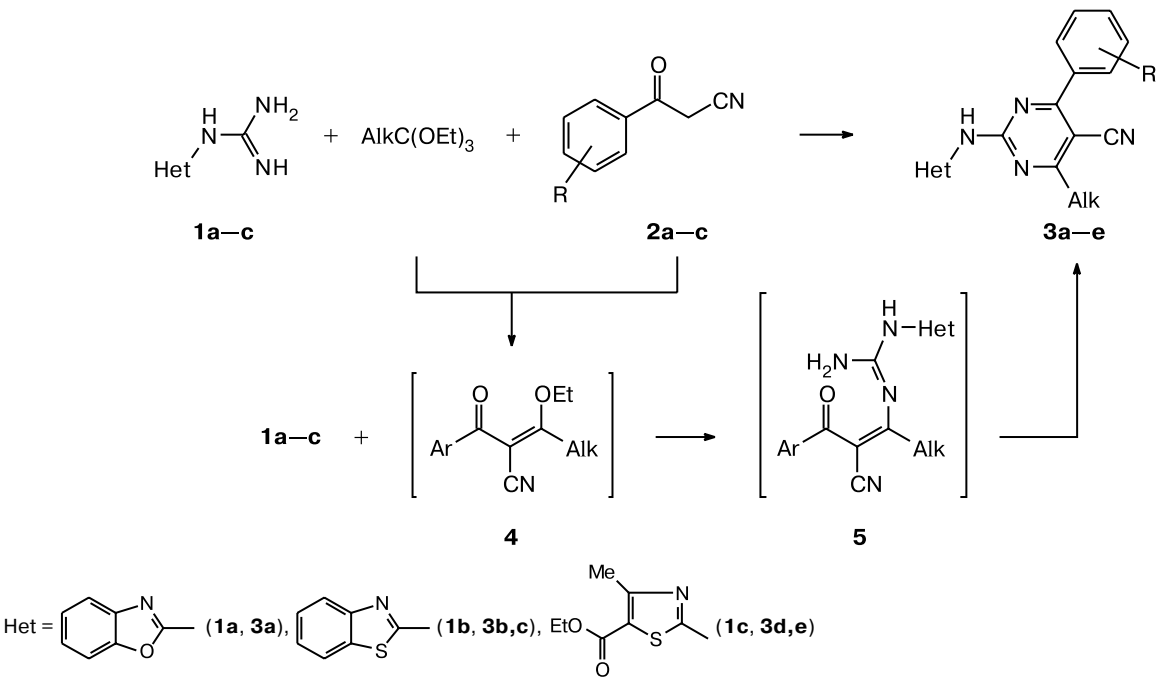
Three-component condensation of benzooxazol-2-yl-, benzothiazol-2-yl-, and 5-ethoxycarbonyl-4-methyl-1,3-thiazol-2-ylguanidines with orthoesters and aroylacetonitriles afforded 4-aryl-5-cyano-2-hetarylaminopyrimidines.

Key words: benzooxazol-2-ylguanidine, benzothiazol-2-ylguanidine, 5-ethoxycarbonyl-4-methyl-1,3-thiazol-2-ylguanidine, orthoesters, aroylacetonitriles, 4-aryl-5-cyano-2-hetarylaminopyrimidines, three-component condensation.

Earlier,[1] we have found that hetarylguanidines **1a—c** (Het — benzooxazol-2-yl (**1a**), benzothiazol-2-yl (**1b**), and 5-ethoxycarbonyl-4-methyl-1,3-thiazol-2-yl (**1c**)) enter into a three-component condensation with triethyl orthoformate and dimedone to give the corresponding *N*-hetaryl-*N*-(oxotetrahydroquinazolyl)amines. Later,[2] we have employed linear β-dicarbonyl compounds (ethyl acetoacetate derivatives and acetoacetamides) in this reaction and obtained pyrimidine derivatives.

Here, we extended this reaction to aroylacetonitriles **2a—c** (Scheme 1). Heating of an equimolar mixture of compounds **2** with guanidines **1a—c** in an excess of boil-

Scheme 1



2	R	3	Alk	R	Yield (%)	3	Alk	R	Yield (%)
a	4-Cl	**a**	H	4-Cl	66	**d**	H	4-MeO	60
b	H	**b**	H	H	57	**e**	Me	H	51
c	4-MeO	**c**	H	4-MeO	54				

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ing orthoester for 15—20 min gave the corresponding 4-aryl-5-cyano-2-hetarylaminopyrimidines **3a—e**. The most probable reaction pathway involves the formation of ylidene derivative **4**, which reacts with hetarylguanidines **1a—c** through replacement of the ethoxy group. Subsequent intramolecular cyclization of intermediate **5** closes a pyrimidine ring.

The IR spectra of compounds **3a—e** show a characteristic absorption band of the cyano group (2200 cm^{-1}) and bands due to the vibrations of aromatic rings (1600, 1570, and 1530 cm^{-1}).

Experimental

The course of the reactions was monitored and the purity of the compounds obtained was checked by TLC on Silufol UV-254 plates with $CHCl_3$—AcOEt (1 : 2) as an eluent. ^{1}H NMR spectra were recorded on a Bruker AC-300 instrument (300 MHz) in DMSO-d_6 with Me_4Si as the internal standard. IR spectra were recorded on a Specord IR-75 spectrometer (KBr pellets).

Benzooxazolyl- and benzothiazolylguanidines **1a,b** were prepared as described earlier[3] for benzooxazolylguanidine by a reaction of 2-aminophenol or 2-aminobenzenethiol with dicyandiamide in a hydrochloric acid solution.

5-Ethoxycarbonyl-4-methyl-1,3-thiazol-2-ylguanidine (1c). Ethyl 2-chloroacetoacetate (0.01 mol) was added to a mixture of amidinothiourea (0.01 mol) and anhydrous sodium acetate (0.012 mol) in anhydrous ethanol (10 mL). The reaction mixture was refluxed for 0.5 h. The precipitate that formed was filtered off, washed with water and propan-2-ol, and recrystallized from DMF. The yield was 75—80%, m.p. >300 °C.

Aroylacetonitriles 2a—c were prepared according to a known procedure.[4]

4-Aryl-5-cyano-2-hetarylaminopyrimidines 3a—e (general procedure). Orthoester (5 mL) was added to a pulverized mixture of hetarylguanidine (0.01 mol) and aroylacetonitrile (0.01 mol). After refluxing for 15—20 min, the crystallized reaction mixture was diluted with propan-2-ol and the precipitate was filtered off and recrystallized from DMF.

2-(1,3-Benzooxazol-2-ylamino)-4-(4-chlorophenyl)-5-cyanopyrimidine (3a), m.p. 285—287 °C. Found (%): C, 62.28; H, 2.97; N, 20.34. $C_{18}H_{10}ClN_5O$. Calculated (%): C, 62.17; H, 2.90; N, 20.14. ^{1}H NMR, δ: 7.19—7.53 (m, 8 H, H arom.); 8.56 (s, 1 H, H pyrimidine); 11.94 (s, 1 H, NH). IR, ν/cm^{-1}: 2200 (C≡N); 1600, 1570 (Ar).

2-(1,3-Benzothiazol-2-ylamino)-5-cyano-4-phenylpyrimidine (3b), m.p. 282—284 °C. Found (%): C, 65.46; H, 3.23; N, 21.35. $C_{18}H_{11}N_5S$. Calculated (%): C, 65.64; H, 3.37; N, 21.26. ^{1}H NMR, δ: 7.12—7.55 (m, 9 H, H arom.); 8.44 (s, 1 H, H pyrimidine); 12.04 (s, 1 H, NH). IR, ν/cm^{-1}: 2200 (C≡N); 1600, 1570, 1530 (Ar).

2-(1,3-Benzothiazol-2-ylamino)-5-cyano-4-(4-methoxyphenyl)pyrimidine (3c), m.p. >300 °C. Found (%): C, 63.73; H, 3.61; N, 19.32. $C_{19}H_{13}N_5OS$. Calculated (%): C, 63.50; H, 3.65; N, 19.49. ^{1}H NMR, δ: 4.32 (s, 3 H, OMe); 7.25—7.58 (m, 8 H, H arom.); 8.55 (s, 1 H, H pyrimidine); 12.14 (s, 1 H, NH). IR, ν/cm^{-1}: 2850 (Me); 2200 (C≡N); 1600, 1570 (Ar).

Ethyl 2-{[5-cyano-4-(4-methoxyphenyl)pyrimidin-2-yl]amino}-4-methyl-1,3-thiazole-5-carboxylate (3d), m.p. 255—257 °C. Found (%): C, 57.78; H, 4.41; N, 17.55. $C_{19}H_{17}N_5O_3S$. Calculated (%): C, 57.71; H, 4.33; N, 17.71. ^{1}H NMR, δ: 1.34 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.0 Hz); 2.12 (s, 3 H, Me); 4.30 (q, 2 H, $OC\underline{H}_2CH_3$, J = 7.0 Hz); 4.36 (s, 3 H, OMe); 7.21, 7.65 (both d, 2 H each, H arom., J = 7.6 Hz); 9.10 (s, 1 H, H pyrimidine); 12.11 (br.s, 1 H, NH). IR, ν/cm^{-1}: 2950, 2820 (Me); 2200 (C≡N); 1620, 1570 (Ar).

Ethyl 2-[(5-cyano-6-methyl-4-phenylpyrimidin-2-yl)amino]-4-methyl-1,3-thiazole-5-carboxylate (3e), m.p. 261—263 °C. Found (%): C, 60.15; H, 4.40; N, 18.32. $C_{19}H_{17}N_5O_2S$. Calculated (%): C, 60.14; H, 4.52; N, 18.46. ^{1}H NMR, δ: 1.34 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.0 Hz); 2.12, 2.71 (both s, 3 H each, Me); 4.30 (q, 2 H, $OC\underline{H}_2CH_3$, J = 7.0 Hz); 7.20—7.52 (m, 5 H, H arom.); 12.11 (br.s, 1 H, NH). IR, ν/cm^{-1}: 2940, 2840 (Me); 2220 (C≡N); 1610, 1570 (Ar).

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