Chemistry of Heterocyclic Compounds, Vol. 38, No. 11, 2002

2-QUINAZOLYLGUANIDINES IN HETEROCYCLIZATION REACTIONS. 3.* SYNTHESIS OF 2-[(6-R-4-METHYL-2-QUINAZOLYL)AMINO]PYRIMIDINE-(1H)-ONES

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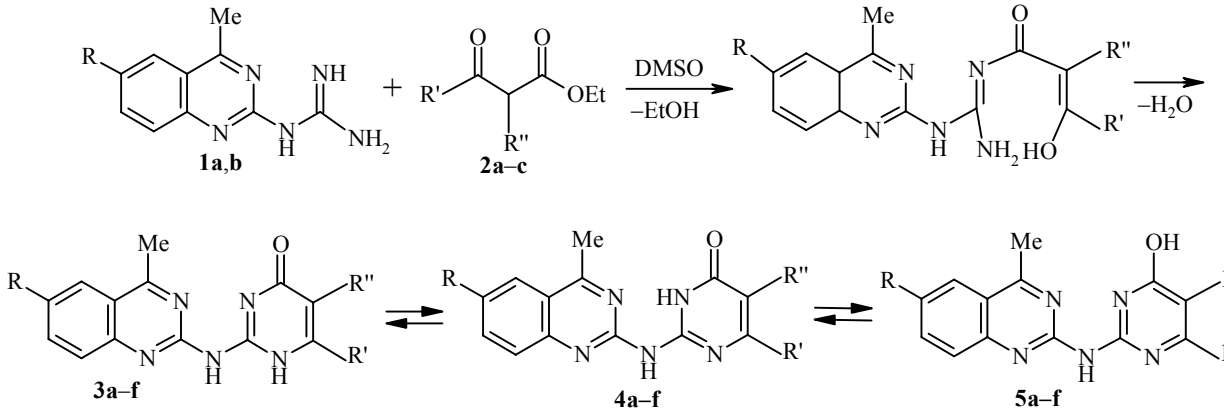
We synthesized 2-(6-R-4-methyl-2-quinazolyl)amino-1,4-dihydropyrimid-4-ones by reaction of 6-R-4-methyl-2-quinazolylguanidines with acylacetic esters.

Keywords: 2-(6-R-methyl-2-quinazolyl)amino-1,4-dihydropyrimid-4-ones, 2-quinazolylguanidines, heterocyclization.

In developing our research on the chemistry of 2-quinazolylguanidines [1], in this work we have studied the reaction of 6-R-4-methyl-2-quinazolylguanidines **1a,b** with acetoacetic (**2a**), benzoylacetic (**2b**), and methylacetoacetic (**2c**) esters. We have established that the indicated compounds easily react in the absence of catalysts when heated up to 100°C in DMSO, and in this case the corresponding 2-[(6-R-4-methyl-2-quinazolyl)amino]-1,4-dihydropyrimidin-4(1H)-ones **3a-f** are formed as the sole product. A probable mechanism for the reaction includes several steps. In the first step, ordinary acylation of the guanidine moiety occurs at the imino group, followed by enolization of the intermediate amino ketone and cyclization with loss of water.



1 a R = H, **b** R = Me; **2 a-c** R' = Me, **a**, **b** R" = H, **c** R" = Me;
3-5 a, **c**, **e** R = H, **b**, **d**, **f** R = Me; **a-d** R' = Me, **e**, **f** R' = Ph; **a**, **b**, **e**, **f** R" = H, **c**, **d** R" = Me

* For Communication 2, see [1].

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 0009-3122/02/3811-1368$27.00

TABLE 1. ^{1}H NMR Spectra of Compounds **3a-f**

Compound	Chemical shifts, δ, ppm
3a	2.20 (3H, s, 6-CH_3); 2.90 (3H, s, 4'-CH_3); 5.70 (1H, s, 5-H); 7.50-8.20 (4H, m, H arom.); 11.00 and 13.55 (2H, br. s, NH)
3b	2.19 (3H, s, 6-CH_3); 2.55 (3H, s, 6'-CH_3); 2.89 (3H, s, 4'-CH_3); 5.73 (1H, s, 5-H); 7.60-8.00 (3H, m, H arom.); 10.90 and 13.20 (2H, two br. s, NH)
3c	1.90 (3H, s, 5-CH_3); 2.19 (3H, s, 6-CH_3); 2.85 (3H, s, 4'-CH_3); 7.30-8.10 (4H, m, H arom.); 11.00 and 13.20 (2H, two br. s, NH)
3d	1.91 (3H, s, 5-CH_3); 2.20 (3H, s, 6-CH_3); 2.50 (3H, s, 6'-CH_3); 2.85 (3H, s, 4'-CH_3); 7.30-8.10 (3H, m, H arom.); 11.00 and 13.25 (2H, two br. s, NH)
3e	2.92 (3H, s, 4'-CH_3); 6.37 (1H, s, 5-H); 7.35-8.10 (9H, m, H arom.); 10.80 and 13.37 (2H, two br. s, NH)
3f	2.45 (3H, s, 6'-CH_3); 2.90 (3H, s, 4'-CH_3); 6.38 (1H, s, 5-H); 7.40-8.10 (8H, m, H arom.); 10.55 and 13.40 (2H, two br. s, NH)

TABLE 2. Characteristics of Compounds **3a-f**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %
		M*	C, %	H, %	N, %		
3a	$C_{14}H_{13}N_5O$	267 / 267.29	62.83 / 62.91	4.97 / 4.90	26.11 / 26.20	260-261	64
3b	$C_{15}H_{15}N_5O$	281 / 281.32	64.13 / 64.04	5.28 / 5.37	24.76 / 24.89	235-236	58
3c	$C_{15}H_{15}N_5O$	281 / 281.32	64.15 / 64.04	5.26 / 5.37	24.74 / 24.89	269-270	54
3d	$C_{16}H_{17}N_5O$	295 / 295.35	65.19 / 65.07	5.93 / 5.80	23.60 / 23.71	258-260	42
3e	$C_{19}H_{15}N_5O$	329 / 329.36	69.21 / 69.29	4.41 / 4.59	21.38 / 21.26	238-240	58
3f	$C_{20}H_{17}N_5O$	343 / 343.40	69.83 / 69.95	4.90 / 4.99	20.42 / 20.39	248-250	60

* According to mass spectral data.

The existence of compounds **3a-f** in the 1,4-dihydropyrimidone form rather than in tautomeric 4(3H)-pyrimidine (**4a-f**) or 4-hydroxypyrimidine (**5a-f**) forms follows from analysis of their ^{1}H NMR spectra (Table 1). Thus the spectra of compounds **3a,b,e,f** show a singlet signal from the olefin 5-H proton at 5.7 ppm or 6.3 ppm, and also two broadened signals at 10.9 ppm and 13.2 ppm from protons of the two NH groups. In the spectra of compounds **3c,d**, which have a substituent in the 5 position, the signals in the 5-7 ppm region are missing.

The 1,4-dihydropyrimidone form of compounds **3** is also consistent with the data in [2, 3]. The characteristics of quinazolylaminopyrimidin-4(1H)-ones **3a-f** are presented in Table 2.

EXPERIMENTAL

The course of the reaction and purity of the compounds obtained were monitored by TLC on Silufol UV-254 plates, eluent methanol, ethylacetate. The ^{1}H NMR spectra were taken on a Bruker AC-300 (300 MHz) in DMSO-d_6, internal standard TMS; the mass spectra were taken on an LKB-9000, ionizing electron energy 70 eV.

The starting 6-R-4-methyl-2-quinazolylguanidines **1a-c** were synthesized by the procedure in [4].

2-[(6-R-4-Methyl-2-quinazolyl)amino]pyrimidin-4(1H)-ones] (3a-f) (General Procedure). Ester **2** (0.012 mol) was added to guanidine **1** (0.01 mol) dissolved in a minimal amount of hot DMSO. The reaction mixture was held at 100°C for 10-12 h; the precipitate that fell out on cooling was filtered out, washed with a minimal amount of dioxane, dried, and recrystallized from dioxane.

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