Chemistry of Heterocyclic Compounds, Vol. 46, No. 11, February, 2011 (Russian Original Vol. 46, No. 11, November, 2010)

QUINAZOLINES. 4*. ACYLATION OF QUINAZOLINE-2,4-DIONES WITH AROMATIC ACIDS CHLORIDES IN THE PRESENCE OF FERRIC CHLORIDE HEXAHYDRATE

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The interaction of quinazoline-2,4-diones with aromatic acids chlorides in nitrobenzene has been investigated in the presence of $FeCl_3 \cdot 6H_2O$. Optimum conditions for the acylation reaction have been developed, the used 4-substituted benzoyl chlorides have been put in order of relative activity, depending on the degree of their electrophilicity.

Keywords: 6-aroylquinazoline-2,4-diones, quinazoline-2,4-diones, aromatic acid chlorides, acylation, X-ray structural analysis.

Quinazoline derivatives have a broad spectrum of biological activity. Among them are found fungicides, insecticides, bactericides, plant growth regulators [2], and also substances have been discovered possessing anticholine esterase, anticonvulsive, sedative, tranquilizing, bronchodilating, and other activities [3-8].

Previously we have studied the acylation of benzoxazolin-2-ones [9, 10], benzothiazolin-2-ones [11, 12], and benzimidazolin-2-ones [13,14] with aromatic acid chlorides using small quantities of catalysts. In a continuation of our investigations on electrophilic substitution in a series of quinazoline derivatives [1] and with the aim to broaden the boundaries of the rules previously developed [9-14], the acylation of quinazoline-2,4-diones **1a-c** with aromatic acid chlorides **2a-e** in the presence of small quantities of ferric chloride hexahydrate has been studied in the present work. The physicochemical characteristics of the 6-aroyl-quinazoline-2,4-diones **3a-o** synthesized in good yield are given in Table 1.

We determined the optimum conditions for acylation. The highest yields for compounds **3** were achieved at molar reactant ratios of **1**:**2**:$FeCl_3 \cdot 6H_2O$ = 1:1.5:0.01.

It was shown that the reaction rate depended on the character of the substituent in reactants **1** and **2**. The yields of products **3** were greater in the case of 1,3-dimethylquinazoline-2,4-dione **1c**, than in the case of quinazoline-2,4-dione **1a**.

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* Communication 3, see [1].

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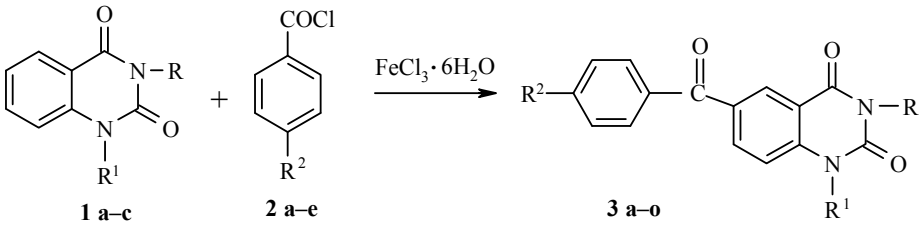
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1702-1708, November, 2010. Original article submitted May 5, 2010.



1 a–c **2 a–e** **3 a–o**

1 a R = R^1 = H, **b** R = H, R^1 = Me, **c** R = R^1 = Me; **2 a** R^2 = H, **b** R^2 = Me, **c** R^2 = OMe, **d** R^2 = Br, **e** R^2 = NO_2; **3a–e** R = R^1 = H, **f–j** R = H, R^1 = Me, **k–o** R = R^1 = Me, **a,f,k** R^2 = H, **b,g,l** R^2 = Me, **c,h,m** R^2 = OMe, **d,i,n** R^2 = Br, **e,j,o** R^2 = NO_2

This may probably be explained by the positive inductive (+I) and mesomeric (+M) effects of the methyl groups, increasing the nucleophilicity of the dione molecule and facilitating electrophilic attack from the side of the acylating agent **2**.

The results of experiments carried out under identical conditions with acylating agents **2a-e** indicate the varied activity of the latter decreasing in the series:

4-$O_2NC_6H_4COCl$ > 4-BrC_6H_4COCl > $PhCOCl$ > 4-MeC_6H_4COCl > 4-$MeOC_6H_4COCl$

TABLE 1. Physicochemical Characteristics of Compounds **3a-o**

Com-pound	Empirical formula	Found, % / Calculated, % N	mp, °C*	Yield, %
3a	$C_{15}H_{10}N_2O_3$	11.26 / 10.52	325-326	54
3b	$C_{16}H_{12}N_2O_3$	9.81 / 10.00	338-339	45
3c	$C_{16}H_{12}N_2O_4$	9.76 / 9.45	331-333	41
3d	$C_{15}H_9BrN_2O_3$	7.93 / 8.11	380-382	70
3e	$C_{15}H_9N_3O_5$	13.26 / 13.50	298-300	76
3f	$C_{16}H_{12}N_2O_3$	9.81 / 10.00	302-304	62
3g	$C_{17}H_{14}N_2O_3$	9.35 / 9.52	307-308	51
3h	$C_{17}H_{14}N_2O_4$	8.69 / 9.03	300-301	45
3i	$C_{16}H_{11}BrN_2O_3$	8.14 / 7.79	296-298	74
3j	$C_{16}H_{11}N_3O_5$	13.29 / 12.92	310-311	82
3k	$C_{17}H_{14}N_2O_3$	9.83 / 9.52	191-192	68
3l	$C_{18}H_{16}N_2O_3$	9.33 / 9.09	140-141	55
3m	$C_{18}H_{16}N_2O_4$	8.86 / 8.64	133-135	49
3n	$C_{17}H_{13}BrN_2O_3$	7.81 / 7.50	218-220	77
3o	$C_{17}H_{13}N_3O_5$	12.17 / 12.38	240-241	86

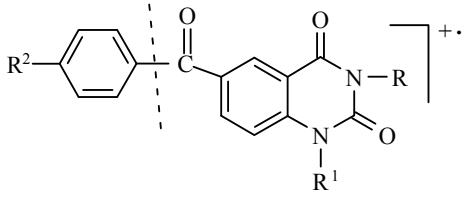
*Solvents for recrystallization: ethanol (compounds **3a-j**,**n**,**o**) and benzene (compounds **3k-m**).

The introduction of electrophilic substituents (NO_2, Br) into the benzoyl chloride molecule leads to the increase of acylation products **3** yields but the introduction of an electron-withdrawing group (Me, MeO) to the reduction in them.

The composition and structure of the synthesized compounds **3a-o** were confirmed by the results of elemental analysis and data of IR spectra and mass spectrometry (Table 2), ^{1}H NMR spectra (Table 3), and in the case of compound **3k** by the data of X-ray analysis also.

Absorption bands for the stretching vibrations of the 6-C=O group (1670-1685 cm^{-1}) and for the CH out-of-plane deformation vibrations of the 1,2,4-trisubstituted benzene ring (805-825 and 870-885 cm^{-1}) were characteristic of the IR spectra of compounds **3a-o** (Table 2).

In the mass spectra of compounds **3a-o** peaks were detected for molecular and fragment ions confirming completely the proposed structures (Table 2). The mass spectra of compounds **3a-o**, independent of the substituents R, R^1, and R^2 nature, showed similar fragmentation with cleavage of the Ar–CO bond.



There were characteristic signals in the ^{1}H NMR spectra of compounds **3a-o** (Table 3) for protons of the quinazolinedione fragment, a doublet for H-5 at 8.18-8.21 (^mJ = 1.7-1.9), a doublet of doublets for H-7 at 8.03-8.07 (^mJ = 1.7-1.9 and ^oJ = 8.5-8.6), and also a doublet for H-8 at 7.59-7.66 ppm (^oJ = 8.5-8.6 Hz). Multiplets for the aromatic protons of the acyl residue were found at 7.45-7.55 ppm, signals of the protons of the alkyl substituents R, R^1, and R^2 were at fairly high field (2.30-3.81), and the protons of the NH group were at low field (9.51-11.87 ppm).

We have carried out an X-ray structural investigation of compound **3k** to represent the spatial structure of acylation products **3**. The general form of the **3k** molecule is shown in Fig. 1. Bond lengths and valence angles are close to the usual values [15].

TABLE 2. IR and Mass Spectra of Compounds **3a-o**

Compound	IR spectrum, ν, cm^{-1}		Mass-spectrum, $[M]^+$ *m/z* (I_{rel}, %)
	2-C=O, 4-C=O, 6-C=O	1-NH, 3-NH	
3a	1715, 1700, 1670	3200, 3090	266 (27)
3b	1710, 1695, 1675	3210, 3100	280 (37)
3c	1710, 1695, 1675	3220, 3110	296 (41)
3d	1715, 1700, 1680	3230, 3120	344 (52) (for ^{79}Br)
3e	1715, 1700, 1685	3240, 3130	311 (36)
3f	1715, 1700, 1670	3070	280 (41)
3g	1710, 1695, 1675	3080	294 (61)
3h	1710, 1700, 1675	3090	310 (43)
3i	1715, 1700, 1680	3100	358 (48) (for ^{79}Br)
3j	1715, 1700, 1685	3110	325 (54)
3k	1710, 1700, 1670	—	294 (100)
3l	1710, 1695, 1675	—	308 (86)
3m	1710, 1695, 1675	—	324 (81)
3n	1710, 1700, 1680	—	372 (83) (for ^{79}Br)
3o	1710, 1700, 1685	—	339 (77)

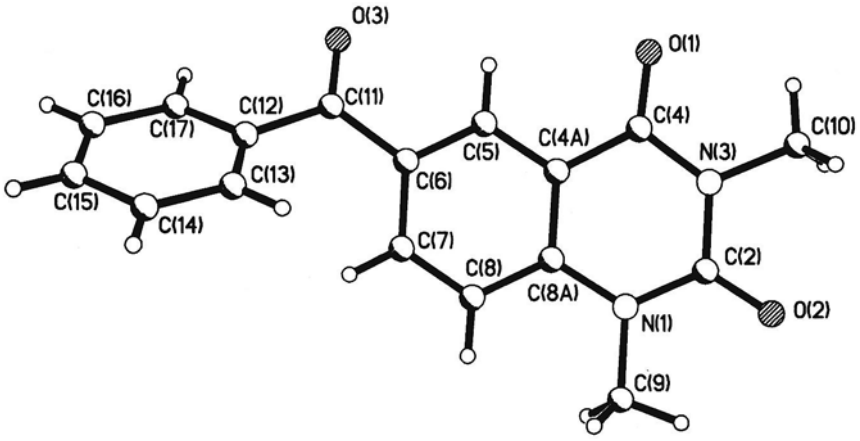


Fig. 1. Spatial structure of the compound **3k** molecule.

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

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)
3a	11.87 (1H, s, H-3); 9.51 (1H, s, H-1); 8.18 (1H, d, $J_{5,7}$ = 1.7, H-5); 8.05 (1H, dd, $J_{7,5}$ = 1.7, $J_{7,8}$ = 8.5, H-7); 7.62 (1H, d, $J_{8,7}$ = 8.5, H-8); 7.45 (5H, m, C_6H_5)
3b	11.86 (1H, s, H-3); 9.53 (1H, s, H-1); 8.19 (1H, d, $J_{5,7}$ = 1.7, H-5); 8.03 (1H, dd, $J_{7,5}$ = 1.7, $J_{7,8}$ = 8.6, H-7); 7.63 (1H, d, $J_{8,7}$ = 8.6, H-8); 7.48 (4H, m, C_6H_4); 2.30 (3H, s, C_6H_4–C$\underline{H}_3$)
3c	11.84 (1H, s, H-3); 9.53 (1H, s, H-1); 8.19 (1H, d, $J_{5,7}$ = 2.2, H-5); 8.01 (1H, dd, $J_{7,5}$ = 2.2, $J_{7,8}$ = 8.6, H-7); 7.59 (1H, d, $J_{8,7}$ = 8.6, H-8); 7.48 (4H, m, C_6H_4); 3.81 (3H, s, C_6H_4–OC$\underline{H}_3$)
3d	11.81 (1H, s, H-3); 9.55 (1H, s, H-1); 8.21 (1H, d, $J_{5,7}$ = 1.8, H-5); 8.03 (1H, dd, $J_{7,5}$ = 1.8, $J_{7,8}$ = 8.6, H-7); 7.64 (1H, d, $J_{8,7}$ = 8.6, H-8); 7.50 (4H, m, C_6H_4)
3e	11.85 (1H, s, H-3); 9.60 (1H, s, H-1); 8.24 (1H, d, $J_{5,7}$ = 1.7, H-5); 8.05 (1H, dd, $J_{7,5}$ = 1.7, $J_{7,8}$ = 8.5, H-7); 7.65 (1H, d, $J_{8,7}$ = 8.5, H-8); 7.51 (4H, m, C_6H_4)
3f	11.72 (1H, s, H-3); 8.21 (1H, d, $J_{5,7}$ = 1.7, H-5); 8.08 (1H, dd, $J_{7,5}$ = 1.7, $J_{7,8}$ = 8.5, H-7); 7.62 (1H, d, $J_{8,7}$ = 8.5, H-8); 7.53 (5H, m, C_6H_5); 3.45 (3H, s, 1-CH_3)
3g	11.71 (1H, s, H-3); 8.20 (1H, d, $J_{5,7}$ = 1.8, H-5); 8.07 (1H, dd, $J_{7,5}$ = 1.8, $J_{7,8}$ = 8.6, H-7); 7.65 (1H, d, $J_{8,7}$ = 8.6, H-8); 7.50 (4H, m, C_6H_4); 3.44 (3H, s, 1-CH_3); 2.31 (3H, s, C_6H_4–C$\underline{H}_3$)
3h	11.69 (1H, s, H-3); 8.19 (1H, d, $J_{5,7}$ = 1.8, H-5); 8.06 (1H, dd, $J_{7,5}$ = 1.8, $J_{7,8}$ = 8.6, H-7); 7.64 (1H, d, $J_{8,7}$ = 8.6, H-8); 7.55 (4H, m, C_6H_4); 3.82 (3H, s, C_6H_4–OC$\underline{H}_3$); 3.44 (3H, s, 1-CH_3)
3i	11.70 (1H, s, H-3); 8.20 (1H, d, $J_{5,7}$ = 1.7, H-5); 8.05 (1H, dd, $J_{7,5}$ = 1.7, $J_{7,8}$ = 8.6, H-7); 7.66 (1H, d, $J_{8,7}$ = 8.6, H-8); 7.52 (4H, m, C_6H_4); 3.44 (3H, s, 1-CH_3)
3j	11.71 (1H, s, H-3); 8.20 (1H, d, $J_{5,7}$ = 1.8, H-5); 8.04 (1H, dd, $J_{7,5}$ = 1.8, $J_{7,8}$ = 8.5, H-7); 7.63 (1H, d, $J_{8,7}$ = 8.5, H-8); 7.49 (4H, m, C_6H_4); 3.44 (3H, s, 1-CH_3)
3k	8.21 (1H, d, $J_{5,7}$ = 1.9, H-5); 8.03 (1H, dd, $J_{7,5}$ = 1.9, $J_{7,8}$ = 8.6, H-7); 7.64 (1H, d, $J_{8,7}$ = 8.6, H-8); 7.47 (5H, m, C_6H_5); 3.38 (3H, s, 1-CH_3); 3.22 (3H, s, 3-CH_3)
3l	8.19 (1H, d, $J_{5,7}$ = 1.8, H-5); 8.04 (1H, dd, $J_{7,5}$ = 1.8, $J_{7,8}$ = 8.5, H-7); 7.67 (1H, d, $J_{8,7}$ = 8.5, H-8); 7.45 (4H, m, C_6H_4); 3.37 (3H, s, 1-CH_3); 3.21 (3H, s, 3-CH_3); 2.31 (3H, s, C_6H_4–C$\underline{H}_3$)
3m	8.20 (1H, d, $J_{5,7}$ = 1.8, H-5); 8.05 (1H, dd, $J_{7,5}$ = 1.8, $J_{7,8}$ = 8.6, H-7); 7.66 (1H, d, $J_{8,7}$ = 8.6, H-8); 7.46 (4H, m, C_6H_4); 3.80 (3H, s, C_6H_4–OC$\underline{H}_3$); 3.36 (3H, s, 1-CH_3); 3.21 (3H, s, 3-CH_3)
3n	8.21 (1H, d, $J_{5,7}$ = 1.7, H-5); 8.05 (1H, dd, $J_{7,5}$ = 1.7, $J_{7,8}$ = 8.5, H-7); 7.63 (1H, d, $J_{8,7}$ = 8.5, H-8); 7.46 (4H, m, C_6H_4); 3.37 (3H, s, 1-CH_3); 3.20 (3H, s, 3-CH_3)
3o	8.19 (1H, d, $J_{5,7}$ = 1.8, H-5); 8.03 (1H, dd, $J_{7,5}$ = 1.8, $J_{7,8}$ = 8.6, H-7); 7.62 (1H, d, $J_{8,7}$ = 8.6, H-8); 7.45 (4H, m, C_6H_4); 3.36 (3H, s, 1-CH_3); 3.20 (3H, s, 3-CH_3)

The quinazolinedione nucleus and benzene ring are planar with the precision of ±0.035 and ±0.005 Å respectively. The 6-C=O group is turned relative to the plane of the benzene ring and the quinazolinedione nucleus by 31.3(1) and 28.0(1)° respectively, which is characteristic for carbonyl groups linked with aromatic systems [16]. No anomalously short intermolecular contacts were detected in the crystal.

EXPERIMENTAL

The IR spectra were recorded on a Perkin-Elmer Spectrum GX Fourier spectrometer in KBr disks. The ^{1}H NMR spectra were taken on a UNITY 400$^+$ (400 MHz) spectrometer in DMSO-d_6, internal standard was TMS. Mass spectra were recorded on a Kratos MS-30 instrument with direct insertion of sample into the ion source (ionization energy 70 eV). A check on the progress of reactions and the homogeneity of the synthesized compounds was effected by TLC on Sorbfil (Russia) and Whatman® UV-254 (Germany) plates in the solvent system benzene–ethanol, 5:1, developing with $KMnO_4$ (1 g) in H_2SO_4 (4 ml) and H_2O (96 ml).

6-Benzoylquinazoline-2,4-dione (3a). A mixture of quinazoline-2,4-dione **1a (**1.62 g, 10 mmol), benzoyl chloride **2a** (2.1 g, 15 mmol), and $FeCl_3 \cdot 6H_2O$ (0.027 g, 0.1 mmol) in nitrobenzene (15 ml) was maintained at 200-210°C for 4 h. The solvent was steam distilled, the solid filtered off, washed with water, dried, and recrystallized. Compound **3a** (1.43 g, 54%) was obtained.

6-Aroylquinazoline-2,4-diones 3b-o were synthesized analogously.

X-ray Structural Investigation. The crystals of 6-benzoyl-1,3-dimethylquinazoline-2,4-dione (**3k**) were obtained from a solution in acetone by slow evaporation of the solvent. The X-ray structural investigation was carried out on a Stoe Stadi-4 diffractometer (MoKα-radiation, graphite monochromator, ω/2θ scanning) at room temperature. No absorption corrections were introduced. Crystallographic data were: monoclinic, space group $P2_1/n$, a = 7.665(4), b = 14.388(6), c = 13.032(9) Å, β = 105.73(5)°, V = 1383.4(13) Å^3, M_r = 294.30, Z = 4, d_{calc} = 1.413 g/cm^3, μ =0,099, scanning region $2\theta \leq 50°$, crystal size 0.50 x 0.25 x 0.25 mm.

The structure was solved by the direct method with the SHELXS-97 program and refined by the least squares method in an isotropic–anisotropic approximation with the SHELXL-97 program. The coordinates of the methyl group hydrogen atoms were found from an electron density difference synthesis. The positions of the remaining hydrogen atoms were established geometrically and were refined with fixed isotropic displacement parameters $U_{iso} = nU_{eq}$, where n = 1.2 for methylene groups and the aromatic ring, and U_{eq} is the equivalent isotropic displacement parameter of the corresponding carbon atoms. Refinement parameters were wR_2 = 0.143, S = 1.19 (for all 2436 reflections), R_1 = 0.065 (1145 $I \geq 2\sigma(I)$).

Details of the X-ray analysis in the form of a CIF file have been deposited in the Cambridge structural data Base (deposit CCDC 765943).

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