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4-OXO-3,4-DIHYDROQUINAZOLINYL- AND BENZIMIDAZOLYL-ACETONITRILES IN ANNELATION REACTIONS OF A HALOQUINOLINE RING

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The interaction of 4-oxo-3,4-dihydroquinazolinyl- and benzimidazolyl-acetonitriles with 2,6-dihalobenzaldehydes leads to 3-(2,6-dihalophenyl)-2-(4-oxo-3,4-dihydro-2-quinazolinyl)acrylonitriles and 2-(1H-benzo[d]imidazol-2-yl)-3-(2,6-dihalophenyl)acrylonitriles respectively. As a result of intramolecular cyclization of these nitriles 4-halo-12-oxo-12H-quino[2,1-b]quinazoline-6-carbonitriles and 4-halobenzo[4,5]-imidazo[1,2-a]quinoline-6-carbonitriles respectively are formed.

Keywords: benzimidazolylacetonitrile, 2-(1H-benzo[*d*]imidazol-2-yl)-3-(2,6-dihalophenyl)acrylonitriles, 4-halobenzo[4,5]imidazo[1,2-*a*]quinoline-6-carbonitriles, 4-halo-12-oxo-12H-quino[2,1-*b*]-quinazoline-6-carbonitriles, 3-(2,6-dihalophenyl)-2-(4-oxo-3,4-dihydro-2-quinazolinyl)acrylonitriles, 4-oxo-3,4-dihydroquinazolinylacetonitrile.

The constant attention to derivatives of 3H-quinazolin-4-one is caused both by the broad spectrum of their biological action [1-5], and by the possibility of structural modification [6,7], particularly the synthesis of new heterocyclic systems based on them.

Among the styrylquinazolones, the condensation products of 3H-quinazolin-4-one with aromatic aldehydes, preparations are known possessing anticancer properties [8].

Previously we synthesized a series of 3-aryl- and 3-pyridyl-2-(4-oxo-3,4-dihydro-2-quinazolinyl)acrylonitriles [7], among which compounds displaying hemostatic activity appeared [9].

In a continuation of our investigations the condensation has been studied in the present work of 2-(4-oxo-3,4-dihydro-2-quinazolinyl)acetonitriles **1a-e** with aromatic 2,6-dihalobenzaldehydes **2a,b** and the perfluoroaldehyde **2c**.

On boiling a mixture of the indicated reactants in dioxane for 2-3 h 3-(2,6-dihalophenyl or pentafluorophenyl)-2-(4-oxo-3,4-dihydro-2-quinazolinyl)acrylonitriles **3a-j** are formed. Crystallization of the product began even after 20-30 min.

On heating compounds **3a-h** in DMF for several hours cyclization products were detected by TLC. These were 4-halo-12-oxo-12H-quino[2,1-*b*]quinazoline-6-carbonitriles **4a-h**, which are formed by intramolecular arylation at a nitrogen atom of the quinazolinone system. Cyclization may be accelerated by the addition of an equimolar quantity of base (triethylamine, pyridine). However its use is undesirable in the condensation of nitriles **1** with aldehydes **2** since the desired products **3** contain contamination by the corresponding cyclization product **4**.

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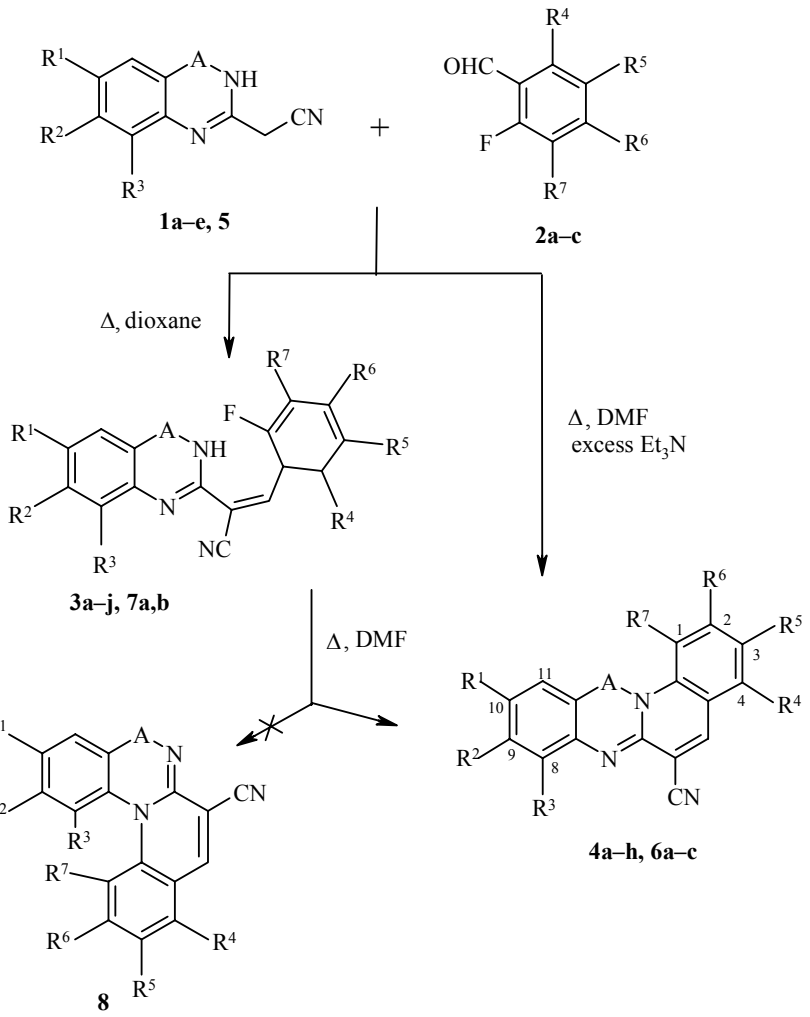

1-4 A = C=O; **5-7** A = bond; **1 a** $R^1 = R^2 = R^3 = H$, **b** R^1 = Me, $R^2 = R^3 = H$, **c** R^1 = Br, $R^2 = R^3 = H$, **d** R^2 = Cl, $R^1 = R^3$= H, **e** $R^1 = R^3$ = Me, R^2 = H; **2 a** R^4 = F, $R^5 = R^6 = R^7$= H, **b** R^4 = Cl, $R^5 = R^6 = R^7$= H, **c** $R^4 = R^5 = R^6 = R^7$ = F; **3**, **4 a-h** $R^5 = R^6 = R^7$= H; **a-e** R^4 = F; **a** $R^1 = R^2 = R^3$ = H, **b** R^1 = Me, $R^2 = R^3$ = H, **c** R^1 = Br, $R^2 = R^3$ = H, **d** R^2 = Cl, $R^1 = R^3$ = H, **e** $R^1 = R^3$ = Me, R^2 = H; **f-h** R^4 = Cl, **f** $R^1 = R^2 = R^3$ = H, **g** R^1 = Br, $R^2 = R^3$ = H, **h** $R^1 = R^3$ = Me, R^2 = H; **3i,j** $R^4 = R^5 = R^6 = R^7$ = F; **i** $R^1 = R^2 = R^3$ = H, **j** R^1 = Me, $R^2 = R^3$ = H; **5, 6a,b, 7a,b** $R^1 = R^2 = R^3$ = H; **a** R^4 = F, $R^5 = R^6 = R^7$ = H, **b** R^4 = Cl, $R^5 = R^6 = R^7$ = H; **6c** $R^1 = R^2 = R^3$ = H, $R^4 = R^5 = R^6 = R^7$ = F

The synthesis of model compounds from benzimidazolylacetonitrile **5** was carried out with the aim of clarifying the direction of arylation (at $N_{(1)}$ or $N_{(3)}$ of the quinazolinone ring). These were 4-halobenzo[4,5]imidazo[1,2-*a*]quinoline-6-carbonitriles **6a-c** through the corresponding 2-(1H-benzo[*d*]imidazol-2-yl)-3-(2,6-dihalophenyl)acrylonitriles **7a,b**.

It should be noted that stopping the reaction of nitrile **5** with aldehydes **2** at the stage of forming substituted acrylonitrile **7** is not always successful. Frequently a significant amount of the cyclization product **6** is formed, which dominates when using perfluorobenzaldehyde **2c**.

The derivatives of both the quinazolinone and of the benzimidazole series **4** and **6** respectively may also be obtained in one step (without isolating condensation products **3** and **7**) in DMF in the presence of an excess of triethylamine.

All the compounds synthesized **3**, **4**, **6**, and **7** are high-melting crystalline substances suitable for further conversions without previous purification.

TABLE 1. Characteristics of 3-(2,6-Dihalophenyl)-2-(4-oxo-3,4-dihydro-2-quinazolinyl)acrylonitriles **3** and 2-(1H-Benzo[*d*]imidazol-2-yl)-3-(2,6-dihalophenyl)acrylonitriles **7**

Compound	Empirical formula	Found, % / Calculated, %		mp, °C*	Yield, %
		N	Cl (Br)		
3a	$C_{17}H_9F_2N_3O$	13.72 / 13.59	—	198-200	81
3b	$C_{18}H_{11}F_2N_3O$	13.21 / 13.00	—	252-253	82
3c	$C_{17}H_8BrF_2N_3O$	10.97 / 10.83	(20.74) / (20.57)	269-270	84
3d	$C_{17}H_8ClF_2N_3O$	12.39 / 12.23	10.43 / 10.31	241-242	87
3e	$C_{19}H_{13}F_2N_3O$	12.60 / 12.46	—	261-262	86
3f	$C_{17}H_9ClFN_3O$	13.07 / 12.90	10.95 / 10.88	244-245	85
3g	$C_{17}H_8BrClFN_3O$	10.49 / 10.38	8.85 / 8.76 (19.90) / (19.75)	258	80
3h	$C_{19}H_{13}ClFN_3O$	11.97 / 11.88	10.18 / 10.02	256-257	84
3i	$C_{17}H_6F_5N_3O$	11.70 / 11.57	—	253-254	82
3j	$C_{18}H_8F_5N_3O$	11.27 / 11.14	—	261-262	80
7a	$C_{16}H_9F_2N_3$	15.07 / 14.94	—	171-172	65
7b	$C_{16}H_9ClFN_3$	14.27 / 14.11	12.11 / 11.91	216-217	53

* After recrystallization from dioxane (**3**, **7b**) or *n*-butanol (**7a**).

The composition and structure of products **3**, **4**, **6**, and **7** were confirmed (Tables 1-4) by the results of elemental analysis and data of IR and NMR spectra.

In the ^{1}H NMR spectra of acrylonitriles **3** and **7** there were signals for the aromatic protons at 7.5-8.2 ppm, a signal for the proton of the CH=CCN fragment at 8.2-8.6, and for the NH group at 12.7-13.4 ppm. Absorption bands were present in the IR spectra of these compounds for the C≡N group at 2230-2250 and for the C=O group at 1660-1670 cm^{-1}, but in the spectra of compounds **7** there were also bands for the NH group at 3330 cm^{-1}.

In the spectra of tetracyclic derivatives **4** and **6** the signals for the aromatic protons were found at 7.5-8.8 ppm. The signal for the NH group was absent, but the signal for the proton of the CH=CCN fragment (in the pyridine ring of these compounds) is displaced by 0.1-0.6 ppm towards low field compared with the signal for the analogous fragment in acrylonitriles **3** and **7**. In the IR spectra of compounds **4** and **6** the absorption band for the C=O group is found at 1685-1700 cm^{-1}, and for the C≡N group at 2240-2250 cm^{-1}.

The interaction between the spatially adjacent H-1 and H-11 protons was recorded with the aid of the NOE for compound **6b**, and its absence was also shown for the quinazolinone derivatives **4**. In the spectra of the latter the signal for the H-1 proton is found at lower field (9.2-9.3 ppm) due to the deshielding influence of the carbonyl group spatially adjacent to it. In the case of compounds **6a,b**, in which such a group is absent, the signal of the H-1 proton is found at 8.6-8.9 ppm.

The facts presented indicate that the intramolecular arylation of compounds **3** occurs at the $N_{(3)}$ atom. The alternative direction of arylation at the $N_{(1)}$ atom, leading to product **8,** does not occur.

TABLE 2. Spectral Characteristics of Compounds **3a-j** and **7a,b**

Compound	IR spectrum, ν, cm^{-1}		^{1}H NMR spectrum (DMSO-d_6), δ, ppm (coupling constants, *J*, Hz)			
	C–O	C≡N	H_{Het}	H_{Ar}	–CH–CCN (1H, s)	NH (1H, br. s)
3a	1670	2240	8.18 (1H, br. d, ^3J = 8.4, H-5); 7.90 (1H, br. t, ^3J = 8.4, H-7); 7.78 (1H, br. d, ^3J = 8.4, H-8); 7.62 (1H, br. t, ^3J = 8.4, H-6)	7.71 (1H, m, H-4); 7.37 (2H, br. t, ^3J = 8.4, H-3, H-5)	8.48	12.89
3b	1665	2230	7.96 (1H, br. s, H-5); 7.67 (2H, m, H-7, H-8); 2.50 (3H, s, $C_{(6)}H_3$)	7.64 (1H, m, H-4); 7.24 (2H, br. t, ^3J = 8.4, H-3, H-5)	8.41	12.76
3c	1670	2240	8.24 (1H, d, ^4J = 2.6, H-5); 7.95 (1H, dd, ^3J = 8.4, ^4J = 2.6, H-7); 7.72 (1H, d, ^3J = 8.4, H-8)	7.65 (1H, m, H-4); 7.24 (2H, br. t, ^3J = 8.4, H-3, H-5)	8.44	13.03
3d	1670	2240	8.15 (1H, d, ^3J = 8.4, H-5); 7.79 (1H, d, ^4J = 2.0, H-8); 7.55 (1H, dd, ^3J = 8.4, *J* = 2.0, H-6)	7.66 (1H, m, H-4); 7.25 (2H, br. t, ^3J = 8.4, H-3, H-5)	8.46	13.00
3e	1665	2230	7.78 (1H, s, H-5); 7.50 (1H, s, H-7); 2.60 (3H, s, $C_{(8)}H_3$); 2.47 (3H, s, $C_{(6)}H_3$)	7.64 (1H, m, H-4); 7.24 (2H, br. t, ^3J = 8.4, H-3, H-5)	8.40	12.73
3f	1660	2230	8.17 (1H, br. d, ^3J = 7.5, H-5); 7.89 (1H, br. t, ^3J = 7.5, H-7); 7.77 (1H, br. d, ^3J = 7.5, H-8); 7.66 (1H, br. t, ^3J = 7.5, H-6)	7.63 (1H, m, H-5); 7.56 (1H, br. d, ^3J = 8.5, H-3); 7.50 (1H, br. t, ^3J = 8.5, H-4)	8.52	12.94
3g	1670	2240	8.25 (1H, br. s, H-5); 8.03 (1H, br. d, ^3J = 8.4, H-7); 7.72 (1H, d, ^3J = 8.4, H-8)	7.66 (1H, m, H-5); 7.57 (1H, br. d, ^3J = 8.4, H-3); 7.51 (1H, br. t, ^3J = 8.4, H-4)	8.53	13.12
3h	1650	2230	7.81 (1H, s, H-5); 7.59 (1H, s, H-7); 2.56 (3H, s, $C_{(8)}H_3$); 2.44 (3H, s, $C_{(6)}H_3$)	7.64 (1H, m, H-5); 7.56 (1H, br. d, ^3J = 8.5, H-3); 7.51 (1H, br. t, ^3J = 8.5, H-4)	8.49	12.85
3i	1680	2240	8.17 (1H, br. d, ^3J = 8.0, H-5); 7.90 (1H, br. t, ^3J = 8.0, H-7); 7.80 (1H, br. d, ^3J = 8.0, H-8); 7.63 (1H, br. t, ^3J = 8.0, H-6)	—	8.44	12.90
3j	1670	2240	7.97 (1H, br. s, H-5); 7.70 (2H, m, H-7, H-8); 2.50 (3H, s, $C_{(6)}H_3$)	—	8.40	12.81
7a	3360*	2250	7.25 (4H, m, H-4, H-7)	7.64 (3H, m, H-3, H-5)	8.20	13.15
7b	3330*	2250	7.64 (2H, m, H-4, H-7); 7.31 (2H, m, H-5, H-6)	7.64 (1H, m, H-5); 7.56 (1H, br. d, ^3J = 8.5, H-3); 7.51 (1H, br. t, ^3J = 8.5, H-4)	8.26	13.36

*Absorption band of NH group.

TABLE 3. Characteristics of Compounds **4a-h** and **6a-c**

Compound	Empirical formula	Found, % / Calculated, %		mp, °C (from DMF)	Yield, %
		N	Cl (Br)		
4a	$C_{17}H_8FN_3O$	14.71 / 14.53	—	205-206	82
4b	$C_{18}H_{10}FN_3O$	13.98 / 13.86	—	208-210	91
4c	$C_{17}H_7BrFN_3O$	11.63 / 11.41	(21.87) / (21.70)	288-289	87
4d	$C_{17}H_7ClFN_3O$	13.23 / 12.98	11.16 / 10.95	220-222	90
4e	$C_{19}H_{12}FN_3O$	13.38 / 13.24	—	264-265	92
4f	$C_{17}H_8ClN_3O$	13.90 / 13.74	11.64 / 11.59	229-230	90
4g	$C_{17}H_7BrClN_3O$	11.20 / 10.92	9.33 / 9.22 (20.81) / (20.78)	308-309	82
4h	$C_{19}H_{12}ClN_3O$	12.75 / 12.59	10.70 / 10.62	269-270	85
6a	$C_{16}H_8FN_3$	16.29 / 16.08	—	299-300	83
6b	$C_{16}H_8ClN_3$	15.28 / 15.13	12.93 / 12.77	312-313	78
6c	$C_{16}H_5F_4N_3$	13.41 / 13.33	—	308-309	75

In the case of compounds **3f-h** and **7b** interaction at position 2 or 6 of the arylating fragment with a Cl or F leaving group respectively is possible. The ^{19}F NMR spectra of compounds **4f-h** and **6b** indicate the absence of fluorine. Consequently reaction occurs at position 6.

The presence of fluorine was confirmed for difluoro and polyfluoro derivatives by ^{19}F NMR spectra. Signals for fluorine atoms were observed at -42.29 (**3a**), -32.86 (**3b**), -33.20 (**3g**), -32.12 (**3h**), 16.23 (2F), 2.50 (1F), and -9.20 (2F) (**3i**), 16.14 (2F), 2.39 (1F), and -9.23 (2F), (**3j**), -42.86 (**4e**), -40.07 (**6a**), -65.06, -66.43, -73.65, and -85.78 ppm (**6c**).

EXPERIMENTAL

A check on the progress of reactions and the purity of the compounds synthesized was carried out by TLC on Silufol UV 254 plates in chloroform–methanol, 9:1. The NMR spectra were measured on a Varian Mercury 400 spectrometer (400 MHz for ^1H nuclei and 376 MHz for ^{19}F) in DMSO-d_6. Internal standard was TMS (^1H NMR) or $CFCl_3$ (^{19}F NMR). The IR spectra were recorded on a Pye-Unicam SP 3-300 instrument. Melting points were measured on a miniature heating stage of the Boetius type with a PHMK 05 observing device (VEB Analytik). The initial compounds **1** were synthesized by the known procedure of [7].

3-(2,6-Dihalophenyl)-2-(4-oxo-3,4-dihydro-2-quinazolinyl)acrylonitriles (3a-j), 2-(1H-Benzo[*d*]-imidazol-2-yl)-3-(2,6-dihalophenyl)acrylonitriles (7a,b) (General Procedure). A mixture of nitrile **1a-e**, **5** (5 mmol) and aldehyde **2a-c** (5 mmol) in dioxane (40 ml) was boiled for 2-3 h, checking the progress of the reaction by TLC. The reaction mixture was cooled, the solid products **3a-j, 7a,b** filtered off, and washed with alcohol. The filtrate was evaporated, and a further quantity of product obtained.

TABLE 4. Spectral Characteristics of Compounds **4a-h** and **6a-c**

Compound	IR spectrum, ν, cm^{-1}		^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz)
	C=O	C≡N	
4a	1700	2250	9.21 (1H, br. d, ^3J = 8.4, H-1); 8.66 (1H, s, H-5); 8.29 (1H, br. d, ^3J = 8.0, H-11); 7.92 (1H, br. t, ^3J = 8.0, H-9); 7.80 (1H, m, H-3); 7.78 (1H, br. d, ^3J = 8.0, H-8); 7.60 (1H, br. t, ^3J = 8.0, H-10); 7.42 (1H, ^3J = 8.4, H-2)
4b	1700	2250	9.21 (1H, br. d, ^3J = 9.0, H-1); 8.62 (1H, s, H-5); 8.08 (1H, br. s, H-11); 7.79 (1H, m, H-3); 7.74 (1H, br. d, ^3J = 8.4, H-9); 7.69 (1H, d, ^3J = 8.4, H-8); 7.41 (1H, br. t, ^3J = 9.0, H-2)
4c	1700	2250	9.19 (1H, br. d, ^3J = 8.6, H-1); 8.88 (1H, s, H-5); 8.38 (1H, br. s, H-11); 8.08 (1H, br. d, ^3J = 8.4, H-9); 7.78 (1H, m, H-3); 7.75 (1H, d, ^3J = 8.4, H-8); 7.56 (1H, br. t, ^3J = 8.6, H-2)
4d	1705	2250	9.20 (1H, br. d, ^3J = 8.8, H-1); 8.88 (1H, s, H-5); 8.28 (1H, d, ^3J = 8.4, H-11); 7.87 (1H, m, H-3); 7.84 (1H, br. s, H-8); 7.66 (1H, br. d, ^3J = 8.4, H-10); 7.55 (1H, br. t, ^3J = 8.8, H-2)
4e	1700	2250	9.27 (1H, br. d, ^3J = 8.8, H-1); 8.59 (1H, s, H-5); 7.89 (1H, s, H-11); 7.80 (1H, m, H-3); 7.57 (1H, s, H-9) 7.41 (1H, br. t, ^3J = 8.8, H-2); 2.62 (3H, s, 8-CH_3); 2.48 (3H, s, $C_{(10)}H_3$)
4f	1690	2240	9.28 (1H, br. d, ^3J = 7.6, H-1); 8.84 (1H, s, H-5); 8.33 (1H, br. d, ^3J = 7.6, H-11); 7.98 (1H, br. t, ^3J = 7.6, H-9); 7.82 (3H, m, H-2, H-3, H-8); 7.66 (1H, br. t, ^3J = 7.6, H-10)
4g*	1685	2240	9.34 (1H, br. d, ^3J = 7.6, H-1); 9.66 (1H, s, H-5); 8.75 (1H, br. s, H-11); 8.08-8.28 (4H, m, H-2, H-3, H-8, H-9)
4h	1700	2250	9.25 (1H, br. d, ^3J = 7.6, H-1); 8.61 (1H, s, H-5); 7.74 (1H, s, H-11); 7.74 (2H, m, H-3, H-2); 7.55 (1H, s, H-9); 2.53 (3H, s, $C_{(8)}H_3$); 2.39 (3H, s, $C_{(10)}H_3$)
6a	—	2240	8.72 (1H, s, H-5); 8.61 (1H, m, H-1); 8.57 (1H, m, H-11); 7.98 (1H, m, H-8); 7.98 (1H, m, H-3); 7.58 (2H, m, H-9, H-10); 7.47 (1H, br. t, ^3J = 7.6, H-2)
6b	—	2240	8.91 (1H, s, H-5); 8.90 (1H, br. d, ^3J = 8.0, H-1); 8.80 (1H, br. d, ^3J = 8.0, H-11); 8.07 (1H, br. d, ^3J =8.0, H-3); 8.00 (1H, br. t, ^3J = 8.0, H-2); 7.85 (1H, br. d, ^3J = 8.0, H-8); 7.65 (2H, m, H-9, H-10)
6b*	—	2240	9.62 (1H, s, H-5); 9.10 (1H, br. d, ^3J = 8.0, H-1); 8.87 (1H, br. d, ^3J = 8.0, H-11); 8.37 (1H, br. t, ^3J = 8.0, H-2); 8.20 (1H, br. d, ^3J = 8.0, H-3); 8.16 (1H, br. d, ^3J = 8.0, H-8); 8.08 (2H, m, H-9, H-10)
6c	—	2240	8.96 (1H, s, H-5); 8.34 (1H, m, H-11); 8.04 (1H, br. d, ^3J = 8.0, H-8); 7.61 (2H, m, H-9, H-10)

* The ^{1}H NMR spectrum was recorded in CF_3CO_2D.

4-Halo-12-oxo-12H-quino[2,1-*b*]quinazolinecarbonitriles (4a-h), 4-Halobenzo[4,5]imidazo[1,2-*a*]-quinoline-6-carbonitriles (6a,b) (General Procedure). A solution of compound **3a-h** or **7a,b** (5 mmol) in DMF (30 ml) was boiled for 5-8 h or for 2-4 h with the addition of triethylamine (5 mmol). After cooling, the solid products **4a-h** or **6a,b** were filtered off, washed with alcohol, and with water. A small amount of product may be isolated after evaporating the filtrate.

1,2,3,4-Tetrafluorobenzo[4,5]imidazo[1,2-*a*]quinoline-6-carbonitrile (6c). Triethylamine (10 mmol) was added to a suspension of nitrile **5** (5 mmol) and compound **2c** (5 mmol) in DMF (20 ml), and the mixture obtained was boiled for 2-3 h. After cooling, the solid was filtered off, washed with alcohol, with water, and product **6c** was obtained. After evaporating the filtrate an additional small quantity of product **6c** was obtained and was crystallized from DMF.

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