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THE REACTION OF 2-HETARYLACETONITRILES WITH HETEROCYCLIC HALOALDEHYDES

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The reaction of 4-oxo-3,4-dihydroquinazolyl- and benzimidazolylacetonitriles with 2-chloro-2-quinolinecarbaldehydes and 1-aryl-5-chloro-3-methyl-1H-pyrazole-4-carbaldehydes gave the corresponding 3-(2-chloro-3-quinolyl)-2-(4-oxo-3,4-dihydro-2-quinazolyl)-2-propenenitriles and 3-(1-aryl-5-chloro-3-methyl-1H-4-pyrazolyl)-2-hetaryl-2-propenenitriles. Intramolecular cyclization of these compounds gives 15-oxo-15H-benzo[6,7][1,8]naphthyridino[2,1-b]quinazoline-6-carbonitriles, 1-aryl-3-methyl-11-oxo-1,11-dihydropyrazolo[4',3':5,6]pyrido[2,1-b]quinazoline-5-carbonitriles, and 1-aryl-3-methyl-1H-benzo[4,5]imidazo[1,2-a]pyrazolo[4,3-e]pyridine-5-carbonitriles.

Keywords: 1-aryl-3-methyl-1H-benzo[4,5]imidazo[1,2-*a*]pyrazolo[4,3-*e*]pyridine-5-carbonitrile, 1-aryl-3-methyl-11-oxo-1,11-dihydropyrazolo[4',3':5,6]pyrido[2,1-*b*]quinazoline-5-carbonitrile, 1-aryl-5-chloro-3-methyl-1H-pyrazole-4-carbaldehyde, 3-(1-aryl-5-chloro-3-methyl-1H-4-pyrazolyl)-2-benzimidazolyl-2-propenenitrile, benzimidazolylacetonitrile, 15-oxo-15H-benzo[6,7][1,8]naphthyridino[2,1-*b*]-quinazoline-6-carbonitrile, 4-oxo-3,4-dihydroquinazolylacetonitrile, 3-(1-aryl-5-chloro-3-methyl-1H-4-pyrazolyl)-2-quinazolyl-2-propenenitrile, 3-(2-chloro-3-quinolyl)-2-(4-oxo-3,4-dihydro-2-quinazolyl)-2-propenenitrile, 2-chloro-3-quinolinecarbaldehyde.

We have previously studied the regioselectivity of the intramolecular hetarylation reactions of 3-(haloaryl)-2-(4-oxo-3,4-dihydro-2-quinazolyl)acrylonitriles [1, 2] which had been prepared by condensation of quinazolylacetonitriles with the corresponding *o*-halobenzaldehydes. It was of interest to study this reaction for 3-(halohetaryl)-2-(4-oxo-3,4-dihydro-2-quinazolyl)acrylonitriles. The latter were prepared by the reaction of quinazolylacetonitriles **1** with azine and azole series haloaldehydes.

Reaction of 2-chloro-7-methyl-3-quinolinecarbaldehyde with 2-(1H-benzo[*d*]imidazol-2-yl)acetonitrile was studied in [3] and gave 7-methylbenzo[*g*]benzo[4,5]imidazo[1,2-*a*][1,8]naphthyridine-2-carbonitrile in 85% yield.

The reaction of 2-(4-oxo-3,4-dihydroquinazolin-2-yl)acetonitriles **1** with 2-chloro-3-quinoline-carbaldehydes **2** has not been studied before. It was found that heating the reaction mixture for 1.5-2 h resulted in the formation of 3-(2-chloroquinol-3-yl)-2-(4-oxo-3,4-dihydroquinazolin-2-yl)-2-propenenitriles **3** (Scheme 1).

The ^{1}H NMR spectra of compounds **3** showed signals for the quinazoline aromatic protons at 7.2-8.0 ppm and the NH group protons at 12.8-12.9 ppm. The methine proton was characterized by the presence of a one proton singlet to low field at 8.9-9.1 ppm. The quinoline fragment protons in the molecule appear in the range 7.5-8.8 ppm, the lowest field of which is the singlet for the H-4 proton. In the IR spectra the C=O and C≡N absorption bands were seen at 1680-1665 and 2240-2220 cm^{-1} respectively.

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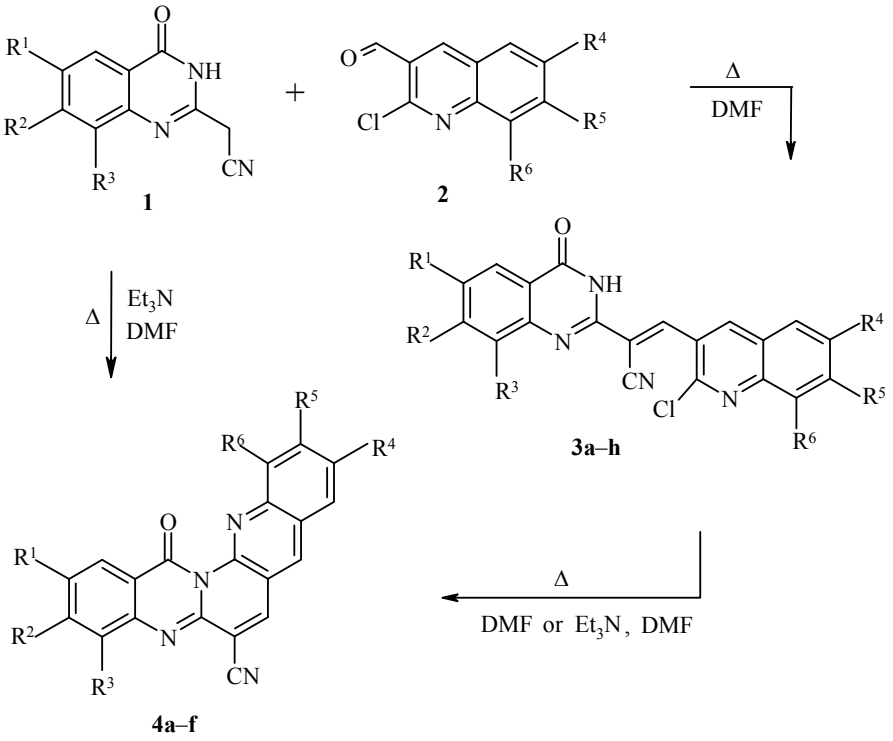
The composition and structure of the products **3** were confirmed by their ^{1}H NMR spectra (Table 1) and by elemental analytical results.

Heating compounds **3** for 5-6 h in DMF or for 1-2 h in the presence of an equivalent amount of triethylamine gave the intramolecular cyclization products 15-oxo-15H-benzo[6,7][1,8]naphthyridino[2,1-*a*]-quinazoline-6-carbonitriles **4** (method A).

Scheme 1



3 a $R^1 = R^5 = R^6 = Me$, $R^2 = R^3 = R^4 = H$; **b** $R^1 = R^2 = OMe$, $R^3 = R^4 = H$, $R^5 = R^6 = Me$;
c $R^1 = I$, $R^2 = R^3 = R^4 = R^5 = R^6 = H$; **d** $R^1 = R^2 = OMe$, $R^3 = R^4 = R^5 = H$, $R^6 = Me$;
e $R^1 = R^3 = R^6 = Me$, $R^2 = R^4 = R^5 = H$; **f** $R^1 = Br$, $R^2 = R^3 = R^5 = R^6 = H$, $R^4 = OMe$;
g $R^1 = R^3 = Me$, $R^2 = R^4 = R^5 = H$, $R^6 = OMe$; **h** $R^1 = R^2 = R^3 = R^4 = R^5 = H$, $R^6 = OMe$;
4 a $R^1 = R^3 = R^6 = Me$, $R^2 = R^4 = R^5 = H$; **b** $R^1 = Me$, $R^2 = R^3 = R^5 = R^6 = H$, $R^4 = OMe$;
c $R^1 = R^3 = R^4 = R^6 = Me$, $R^2 = R^5 = H$; **d** $R^1 = Br$, $R^2 = R^3 = R^4 = R^5 = R^6 = H$; **e** $R^1 = R^2 = OMe$, $R^3 = R^5 = H$, $R^4 = R^6 = Me$;
f $R^1 = R^2 = OMe$, $R^3 = R^4 = R^5 = R^6 = H$

As in the case of the condensation of quinazolylacetonitriles **1** with aromatic *o*-haloaldehydes [1, 2] the cyclization occurs at the $N_{(3)}$ atom of the quinazolone ring (Scheme 2, structure **A**) as indicated by the ^{1}H NMR spectroscopic data. The quinazoline ring aromatic protons in compound **4** are observed at 7.5-8.4 ppm. If attack at the $N_{(1)}$ atom occurred the H-4 proton (Scheme 2, structure **B**) would undergo a marked paramagnetic shift relative to the remaining quinazoline protons as a result of the steric proximity to the quinoline ring nitrogen atom (Scheme 2). Evidently structure **B** is not realized, specifically as a result of the steric hindrance arising during its formation.

The signal for the H-8 proton occurs to lowest field (8.7-9.4 ppm) and this can fall together with the H-7 proton signal (8.6-8.8 ppm). The remaining quinoline fragment proton signals occur at 7.5-8.2 ppm. The quinazoline proton signals undergo a 0.5-07 ppm paramagnetic shift when compared with those in the starting propenenitriles **3**. The IR spectra of compound **4** show absorption bands for the C=O group at 1680-1670 and C≡N group at 2220 cm^{-1}.

TABLE 1. Characteristics of the Synthesized Compounds **3a-h**

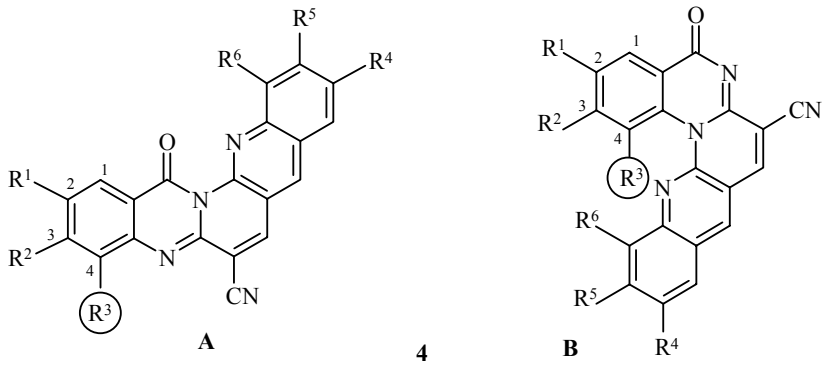
Compound	Empirical formula	Found, % / Calculated, %		mp, °C*	Yield, %	^{1}H NMR spectrum (DMSO-d_6), δ, ppm, SSCC (*J*, Hz)			
		N	Cl (Br)			$H_{quinazolone}$	$H_{quinoline}$	–CH=CCN (1H, s)	NH (1H, br. s)
1	2	3	4	5	6	7	8	9	10
3a	$C_{23}H_{17}ClN_4O$	14.05 / 13.98	8.96 / 8.84	284-285	67	7.97 (1H, s, H-5); 7.66 (2H, m, H-7,8); 2.56 (3H, s, 6-CH_3)	8.73 (1H, s, H-4); 7.85 (1H, d, ^3J= 8.3, H-5,); 7.53 (1H, d, ^3J= 8.3, H-6); 68 (3H, s, 8-CH_3); 2.53 (3H, s, 7-CH_3)	8.91	12.85
3b	$C_{24}H_{19}ClN_4O_3$	12.73 / 12.54	8.12 / 7.93	>360	59	7.49 (1H, s, H-5); 7.20 (1H, s, H-8); 3.95 (3H, s, 7-OCH_3); 3.92 (3H, s, 6-OCH_3)	8.74 (1H, s, H-4); 7.89 (1H, d, ^3J= 8.4, H-5); 7.60 (1H, d, ^3J= 8.4, H-6,); 2.62 (3H, s, 8-CH_3); 2.55 (3H, s, 7-CH_3)	8.97	12.86
3c	$C_{20}H_{10}ClIN_4O$	11.75 / 11.56	7.40 / 7.31	329-331	61	8.54 (1H, d, ^4J= 2.0, H-5); 8.19 (1H, dd, ^3J= 8.4, ^4J= 2.0, H-7); 7.56 (1H, d, H-8)	8.89 (1H, s, H-4), 8.19 (1H, d, ^3J= 8.2, H-8), 8.02 (1H, d, ^3J= 8.2, H-5), 7.97 (1H, t, ^3J= 8.2, H-6), 7.74 (1H, t, ^3J= 8.2, H-7)	8.83	12.85
3d	$C_{23}H_{17}ClN_4O_3$	13.08 / 12.94	8.26 / 8.19	285-286	60	7.50 (1H, s, H-5); 7.22 (1H, s, H-8); 3.96 (3H, s, 7-OCH_3); 3.92 (3H, s, 6-OCH_3)	8.77 (1H, s, H-4); 7.99 (1H, d, ^3J= 8.0, H-5), 7.80 (1H, d, ^3J= 8.0, H-7), 7.65 (1H, t, ^3J= 8.0, H-6); 2.69 (3H, s, 8-CH_3)	9.02	12.88

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9	10
3e	$C_{23}H_{17}ClN_4O$	14.05 / 13.98	8.97 / 8.84	304-305	67	7.80 (1H, s, H-5); 7.58 (1H, s, H-7); 2.57 (3H, s, 8-CH_3); 2.44 (3H, s, 6-CH_3)	8.80 (1H, s, H-4); 8.00 (1H, d, ^3J= 8.0, H-5); 7.81 (1H, d, ^3J= 8.0, H-7); 7.66 (1H, t, ^3J= 8.0, H-6); 2.70 (3H, s, 8-CH_3)	9.06	12.94
3f	$C_{21}H_{12}BrClN_4O_2$	12.11 / 11.98	7.72 / 7.58 (17.21) / (17.08)	314-315	63	8.32 (1H, d, ^4J= 2.0, H-5); 8.02 (1H, dd, ^3J= 8.0, ^4J= 2.0, H-7); 7.70 (1H, d, ^3J= 8.0, H-8)	8.67 (1H, s, H-4); 7.89 (1H, d, ^3J= 8.5, H-8); 7.55 (1H, dd, ^3J= 8.5, ^4J= 2.4, H-7); 7.51 (1H, d, ^4J= 2.4, H-5); 3.93 (3H, s, 6-OCH_3)	8.80	12.90
3g*[2]	$C_{23}H_{17}ClN_4O_2$	13.69 / 13.44	8.61 / 8.50	272-273	66	8.42 (1H, s, H-5); 7.98 (1H, s, H-7); 2.87 (3H, s, 8-CH_3); 2.69 (3H, s, 6-CH_3)	9.45 (1H, s, H-4); 8.11 (1H, t, ^3J= 8.3, H-6); 8.02 (1H, d, ^3J= 8.3, H-7); 7.85 (1H, d, ^3J= 8.3, H-5); 4.45 (3H, s, 8-OCH_3)	8.66	Exchange with D_2O
3h*[2]	$C_{21}H_{13}ClN_4O_2$	14.57 / 14.41	9.29 / 9.12	284-285	63	8.76 (1H, d, ^3J= 8.3, H-8); 8.26 (1H, t, ^3J= 8.3, H-6); 8.20 (1H, d, ^3J= 8.3, H-5); 7.98 (1H, t, ^3J= 8.3, H-7)	9.50 (1H, s, H-4); 8.14 (1H, t, ^3J= 8.3, H-6); 8.06 (1H, d, ^3J= 8.3, H-7); 7.88 (1H, d, ^3J= 8.3, H-5); 4.45 (3H, s, 8-OCH_3)	8.76	Exchange with D_2O

* After recrystallization from DMF.
*[2] ^{1}H NMR spectra measured in CF_3CO_2D.

Scheme 2



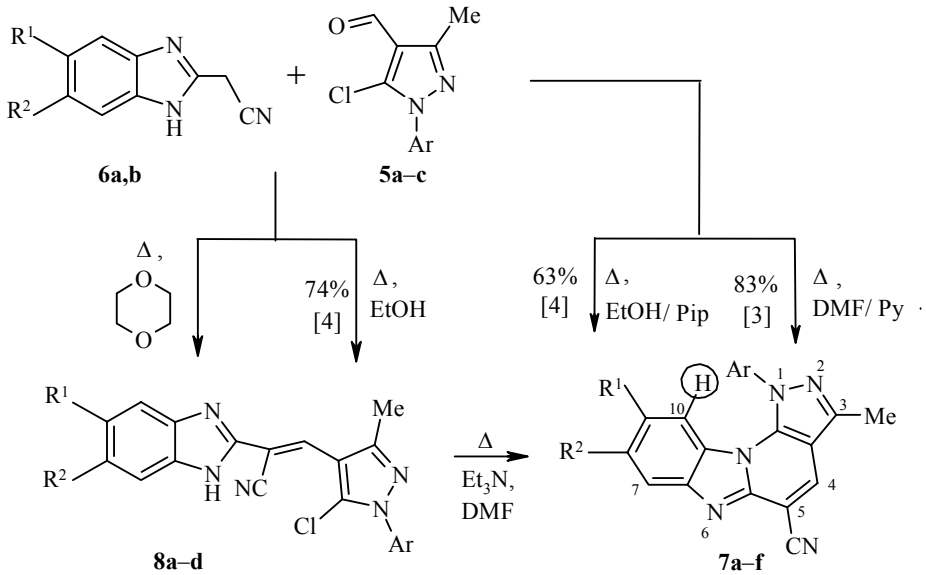
The pentacyclic compound **4** (Table 2) can by synthesized in a single stage, one pot reaction without isolating the product **3** by heating a mixture of the nitrile **1** with aldehyde **2** in the presence of one equivalent of triethylamine for 4-5 h (method B).

Hence 15-oxo-15H-benzo[6,7][1,8]naphthyridino[2,1-*b*]quinazoline-6-carbonitrile **4** can be prepared by the regioselective intramolecular hetarylation of compounds **3** formed from nitriles **1** and aldehydes **2** or directly from the latter reagents in the presence of base.

The next step in the study of the reaction of the 2-hetarylacetonitriles with chloro(het)arylcarbaldehydes was investigation of the behaviour of azole series chlorocarbaldehydes in this reaction, in fact of 1-aryl-5-chloro-3-methyl-1H-pyrazole-4-carbaldehydes **5**. The reaction of 2-(1H-benzo[*d*]imidazol-2-yl)acetonitrile **6a** with 3-R-5-chloro-1-phenyl-1H-pyrazole-4-carbaldehyde had been previously investigated [3, 4].

The authors of [3] reported that heating the starting materials in DMF in the presence of a 10% excess of pyridine gave the intramolecular cyclization product 3-methyl-1-phenyl-1H-benzo[4,5]imidazo[1,2-*a*]-pyrazolo[4,3-*e*]pyridine-5-carbonitrile **7a** in 83% yield (Scheme 3). Later in [4] there was reported the synthesis

Scheme 3



6a, **7a-c**, **8a,b** $R^1 = R^2 = H$; **6b**, **7d**,**e**,**f**, **8c**,**d** $R^1 = R^2 = Me$, **5a**, **7a**,**d**, **8a**,**c** Ar = Ph,
5b, **7b**,**e**, **8b**,**d** Ar = 4-MeC_6H_4, **5c**, **7c**,**f** Ar = 4-FC_6H_4

TABLE 2. Characteristics of the Synthesized Compounds **4a-f**

Compoun	Empirical formula	Found, % / Calculated, %		mp, °C*	Yield, %	^{1}H NMR spectrum, δ, ppm, SSCC (*J*, Hz)*^{2}		
		N	Br			H-1–H-4	H-7 (1H, s)	H-8–H-12
4a	$C_{23}H_{16}N_4O$	15.50 / 15.37	—	328-329	77	7.92 (1H, s, H-1); 7.49 (1H, s, H-3); 2.63 (3H, s, 4-CH_3); 2.53 (3H, s, 2-CH_3)	8.62	8.73 (1H, s, H-8); 7.86 (1H, d, ^3J= 8.0, H-9); 7.70 (1H, d, ^3J= 8.0, H-11); 7.52 (1H, t, ^3J= 8.0, H-10); 2.78 (3H, s, 12-CH_3)
4b	$C_{22}H_{14}N_4O_2$	15.41 / 15.29	—	299-301	75	8.09 (1H, s, H-1); 7.70 (2H, m, H-3,4); 2.45 (3H, s, 2-CH_3)	8.69	8.71 (1H, s, H-8); 7.95 (1H, d, ^3J= 8.5, H-12); 7.51 (1H, dd, ^3J= 8.5, ^4J= 2.8, H-11); 7.45 (1H, d, ^4J= 2.8, H-9); 3.96 (3H, s, 10-OCH_3)
4c	$C_{24}H_{18}N_4O$	14.96 / 14.80	—	343-344	74	7.92 (1H, s, H-1); 7.49 (1H, s, H-3); 2.63 (3H, s, 4-CH_3); 2.50 (3H, s, 2-CH_3)	8.55	8.55 (1H, s, H-8); 7.56 (1H, s, H-9); 7.51 (1H, s, H-11); 2.72 (3H, s, 12-CH_3); 2.50 (3H, s, 10-CH_3)
4d	$C_{20}H_9BrN_4O$	14.14 / 13.96	20.19 / 19.92	362-363	71	8.40 (1H, d, ^4J= 2.4, H-1); 8.00 (1H, dd, ^3J= 8.4, ^4J= 2.4, H-3); 7.77 (1H, d, ^3J= 8.4, H-4)	8.81	8.91 (1H, s, H-8); 8.15 (1H, d, ^3J= 8.4, H-12); 8.06 (1H, d, ^3J= 8.4, H-9); 7.94 (1H, t, ^3J= 8.4, H-10); 7.71 (1H, t, ^3J= 8.4, H-11)
4e	$C_{24}H_{18}N_4O_3$	13.78 / 13.65	—	237-239	75	8.14 (1H, s, H-1); 7.67 (1H, s, H-4); 4.27 (6H, s, 2-OCH_3, 3-OCH_3)	8.73	9.41 (1H, s, H-8); 8.19 (1H, s, H-9); 8.12 (1H, s, H-11); 3.06 (3H, s, 12-CH_3); 2.78 (3H, s, 10-CH_3)
4f	$C_{22}H_{14}N_4O_3$	14.74 / 14.65	—	346-348	73	8.15 (1H, s, H-1); 7.66 (1H, s, H-4); 4.00 (6H, s, 2-OCH_3, 3-OCH_3)	8.70	8.86 (1H, s, H-8); 8.13 (1H, d, ^3J= 8.0, H-12); 8.05 (1H, d, ^3J= 8.0, H-9); 7.92 (1H, t, ^3J= 8.0, H-10); 7.69 (1H, t, ^3J= 8.0, H-11)

* Compound **4** was crystallized from DMF.

*^{2} The ^{1}H NMR spectra were measured in DMSO-d_6 (compounds **4a-d,f**) or CF_3CO_2D (compound **4a**).

of the condensation product 2-(1H-benzo[*d*]imidazol-2-yl)-3-(5-chloro-1,3-diphenyl-1H-4-pyrazolyl)-2-propenenitrile of type **8** formed in 74% yield by heating a mixture of 2-(1H-benzo[*d*]imidazol-2-yl)acetonitrile **6a** in ethanol with the aldehyde mentioned above.

By carrying out the reaction in the presence of piperidine it did not stop at the stage of formation of product **8** but the authors separated the type **7a** cyclic product 1,3-diphenyl-1H-benzo[4,5]imidazo[1,2-*a*]-pyrazolo[4,3-*e*]pyridine-5-carbonitrile (Scheme 3) in 63% yield from the reaction mixture. However, the characteristics and spectroscopic data for compounds **7,8** were not presented in [4].

As already noted in our previous work on alternative routes for intramolecular (het)arylation [1, 2], derivatives based on 2-(1H-benzo[*d*]imidazol-2-yl)acetonitrile are convenient models for establishing the direction of cyclization. In this connection we repeated the work of the authors in [4], broadening the range of investigated compounds and strictly determining the structure of the condensation products obtained **7a-f** and **8a-d** (Scheme 3). It should be noted that the reaction of nitrile **6** with aldehyde **5** when heated in dioxane over 1-1.5 h gave the first stage reaction products **8a-d** which were separated and characterized for the first time.

The ^{1}H NMR spectra of compounds **8a-d** (Table 3) showed the aromatic protons signals in the range 7.2-7.6 ppm and the signals of the vinyl proton appeared as a singlet at 8.09-8.19 ppm. The NH stretching vibrations were seen in the IR spectra at 3350-3300 cm^{-1} and CN at 2240-2230 cm^{-1}.

The occurrence of the intramolecular hetarylation in compounds **8** is shown particularly by the absence in the ^{1}H NMR and IR spectra of the products **7** of the NH group proton. The signals for the aromatic ring protons in the cyclic compounds **7a-f** (Table 4) were seen at 5.5-7.9 ppm. It was also noted that the H-10 signal undergoes a strong 1.2-1.9 ppm diamagnetic shift when compared with its value in the starting compounds **8** as a result of the phenyl ring current.

Continuing our study of the intramolecular hetarylation of model compounds based on hetarylacetonitriles we have worked on the reaction of quinazolinylacetonitriles **1** with the aldehydes **5**. Refluxing a mixture of these substances in dioxane over 7-10 h gave 3-(1-aryl-5-chloro-3-methyl-1H-4-pyrazolyl)-2-(4-oxo-3,4-dihydro-2-quinazolinyl)-2-propenenitriles **9a-k**.

In the ^{1}H NMR spectra of compounds **9a-k** (Table 3) the aromatic protons signals were observed in the range 7.2-8.4 ppm. The methine proton appeared to low field (8.3-8.4 ppm) as singlet and the quinazoline ring NH group protons were seen at 12.7-12.9 ppm.

Heating the propenenitriles **9** in DMF in the presence of triethylamine over 2-3 h gave the intramolecular cyclization product 1-aryl-3-methyl-11-oxo-1,11-dihydropyrazolo[4',3':5,6]pyrido[2,1-*b*]-quinazoline-5-carbonitriles **10a-f** (Scheme 4, Table 4).

The spectroscopic data we obtained for the model cyclic compounds **7** permitted an unambiguous determination of the direction of the intramolecular hetarylation, in fact based on the presence of a diamagnetic shift of the signal of one of the protons (H-10 in structure **A** or H-11 in structure **B**).

In the ^{1}H NMR spectra of compounds **10a-f** the H-10 proton undergoes a 0.3-0.4 ppm diamagnetic shift when compared with starting compounds **9**, moreover found at higher field than the H-8 signal which is not typical for the order of quinazolinone fragment proton signals. The signals for the remaining aromatic protons are seen at 7.2-8.0 ppm. The signal for the H-4 proton is shifted by 0.4-0.5 ppm to low field relative to its value in the noncyclic compounds **9**.

Hence the products **10** are assigned the structure **A** and the sterically strained structure **B** is not realized.

It should be noted that all of the propenenitrile derivatives **3, 8** and **9** are converted to the corresponding intramolecular cyclization structures **4, 7** and **10** at their melting points.

Hence the tetracyclic products (compound **10** and 1-aryl-3-methyl-1H-benzo[4,5]imidazo[1,2-*a*]-pyrazolo[4,3-*e*]pyridine-5-carbonitriles **7**) are readily formed as a result of the regioselective intramolecular annelation of the heterocyclic fragment in the 3-(1-aryl-5-chloro-3-methyl-1H-4-pyrazolyl)-2-hetaryl-2-propenenitriles **9** and **8** respectively (prepared by condensation of 2-hetarylacetonitriles with 1-aryl-5-chloro-3-methyl-1H-4-pyrazolylcarbaldehydes).

TABLE 3. Characteristics of the Synthesized Compounds **8** and **9**

Compound	Empirical formula	Found, % / Calculated, %		mp, °C*	Yield, %	^{1}H NMR spectrum (DMSO-d_6), δ, ppm, SSCC (*J*, Hz)			
		N	Cl (Br)			$H_{quinazolone/benzimidazole}$	$H_{pyrazole}$	–CH=CCN (1H, s)	NH (1H, br. s)
1	2	3	4	5	6	7	8	9	10
8a	$C_{20}H_{14}ClN_5$	19.57 / 19.46	9.98 / 9.85	103-104	65	7.61 (2H, d, ^3J= 7.6, H-4,7); 7.22 (2H, m, H-5,6)	7.50-7.60 (5H, m, C_6H_5); 2.44 (3H, s, 3-CH_3)	8.14	12.96
8b	$C_{21}H_{16}ClN_5$	18.86 / 18.73	9.70 / 9.48	214-215	80	7.65 (2H, d, ^3J= 7.6, H-4,7); 7.22 (2H, m, H-5,6)	7.47 (2H, d, ^3J= 8.0, H-2,6); 7.35 (2H, d, ^3J= 8.0, H-3,5); 2.43 (3H, s, 4-$\underline{CH_3}$Ar); 2.45 (3H, s, 3-CH_3)	8.13	12.98
8c	$C_{22}H_{18}ClN_5$	18.21 / 18.06	9.29 / 9.14	143-145	67	7.60 (1H, s, H-4); 7.34 (1H, s, H-7); 2.36 (6H, s, 5-CH_3, 6-CH_3)	7.50–7.62 (5H, m, C_6H_5); 2.47 (3H, s, 3-CH_3)	8.19	Exchange with D_2O
8d	$C_{23}H_{20}ClN_5$	17.66 / 17.43	8.97 / 8.82	210-212	64	7.47 (1H, s, H-4); 7.32 (1H, s, H-7); 2.35 (6H, s, 5-CH_3, 6-CH_3)	7.48 (2H, d, ^3J= 8.0, H-2,6); 7.34 (2H, d, ^3J= 8.0, H-3,5); 2.43 (3H, s, 4-$\underline{CH_3}$Ar); 2.49 (3H, s, 3-CH_3)	8.09	Exchange with D_2O
9a	$C_{22}H_{16}ClN_5O$	17.58 / 17.43	8.91 / 8.82	250-251	75	7.97 (1H, s, H-5); 7.62 (2H, m, H-7,8); 2.48 (3H, s, 6-CH_3)	7.62 (5H, m, C_6H_5); 2.44 (3H, s, 3-CH_3)	8.38	12.73
9b	$C_{21}H_{13}BrClN_5O$	15.23 / 15.01	7.74 / 7.60; (17.24) / (17.12)	280-281	69	8.23 (1H, s, H-5); 8.00 (1H, d, ^3J= 8.0, H-7); 7.69 (1H, d, ^3J= 8.0, H-8)	7.60 (5H, m, C_6H_5); 2.42 (3H, s, 3-CH_3)	8.40	12.96

TABLE 3 (continued)

1	2	3	4	5	6	7	8	9	10
9c	$C_{21}H_{13}ClIN_5O$	13.75 13.63	7.05 6.90	285-286	72	8.41 (1H, d, ^4J= 2.0, H-5); 8.14 (1H, dd, ^3J= 8.4, ^4J= 2.0, H-7); 7.52 (1H, d, ^3J= 8.4, H-8)	7.60 (5H, m, C_6H_5); 2.42 (3H, s, 3-CH_3)	8.39	12.92
9d	$C_{21}H_{13}Cl_2N_5O$	16.74 16.59	16.92 16.79	253-254	74	8.15 (1H, d, ^3J= 8.3, H-5); 7.81 (1H, s, H-7); 7.61 (1H, m, H-6)	7.61 (5H, m, C_6H_5); 2.44 (3H, s, 3-CH_3)	8.42	12.92
9e	$C_{23}H_{18}ClN_5O$	16.97 16.84	8.71 8.52	265-266	76	7.80 (1H, s, H-5); 7.62 (1H, s, H-7); 2.57 (3H, s, 8-CH_3); 2.43 (3H, s, 6-CH_3)	7.62 (5H, m, C_6H_5); 2.43 (3H, s, 3-CH_3)	8.38	12.70
9f	$C_{22}H_{16}ClN_5O$	17.62 17.43	8.98 8.82	241-242	78	8.14 (1H, d, ^3J= 8.0, H-5); 7.82 (1H, t, ^3J= 8.0, H-7); 7.74 (1H, d, ^3J= 8.0, H-8); 7.53 (1H, t, ^3J= 8.0, H-6)	7.47 (2H, d, ^3J= 8.0, H-2,6); 7.35 (2H, d, ^3J= 8.0, H-3,5); 2.42 (3H, s, 4-CH_3Ar); 2.44 (3H, s, 3-CH_3)	8.36	12.72
9g	$C_{22}H_{15}BrClN_5O$	14.78 14.57	7.55 7.37; (16.85) (16.62);	300-301	74	8.23 (1H, d, ^4J= 2.0, H-5); 8.00 (1H, dd, ^3J= 8.4, ^4J= 2.0, H-7); 7.69 (1H, d, ^3J= 8.4, H-8)	7.49 (2H, d, ^3J= 8.0, H-2,6); 7.40 (2H, d, ^3J= 8.0, H-3,5); 2.40 (3H, s, 4-CH_3Ar); 2.41 (3H, s, 3-CH_3)	8.39	12.95
9h	$C_{22}H_{15}ClIN_5O$	13.44 13.27	6.90 6.72	293-294	71	8.41 (1H, d, ^4J= 2.0, H-5); 8.13 (1H, dd, ^3J= 8.4, ^4J= 2.0, H-7); 7.52 (1H, d, ^3J= 8.4, H-8)	7.49 (2H, d, ^3J= 8.4, H-2,6); 7.39 (2H, d, ^3J= 8.4, H-3,5); 2.40 (3H, s, 4-CH_3Ar); 2.41 (3H, s, 3-CH_3)	8.38	12.91
9i	$C_{22}H_{15}Cl_2N_5O$	16.29 16.05	16.49 16.25	253-254	73	8.15 (1H, d, ^3J= 8.0, H-5); 7.81 (1H, s, H-8); 7.61 (1H, d, ^3J= 8.0, H-6)	7.51 (2H, d, ^3J= 8.0, H-2,6); 7.41 (2H, d, ^3J= 8.0, H-3,5); 2.42 (3H, s, 4-CH_3Ar); 2.43 (3H, s, 3-CH_3)	8.41	12.92
9j	$C_{24}H_{20}ClN_5O_3$	15.30 15.16	7.84 7.68	288-289	75	7.47 (1H, s, H-5); 7.17 (1H, s, H-8); 3.97 (3H, s, 7-OCH_3); 3.93 (3H, s, 6-OCH_3)	7.47 (2H, d, ^3J= 8.0, H-2,6); 7.35 (2H, d, ^3J= 8.0, H-3,5); 2.43 (3H, s, 4-CH_3Ar); 2.44 (3H, s, 3-CH_3)	8.30	12.58
9k	$C_{24}H_{20}ClN_5O$	16.51 16.29	8.44 8.25	269-270	77	7.80 (1H, s, H-5); 7.59 (1H, s, H-7); 2.56 (3H, s, 8-CH_3); 2.42 (3H, s, 6-CH_3)	7.50 (2H, d, ^3J= 8.0, H-2,6); 7.41 (2H, d, ^3J= 8.0, H-3,5); 2.41 (3H, s, 4-CH_3Ar); 2.43 (3H, s, 3-CH_3)	8.37	12.69

* Compounds **8a-d, 9a-k** were crystallized from ethanol.

TABLE 4. Characteristics of the Synthesized Compounds **7a-f** and **10a-f**

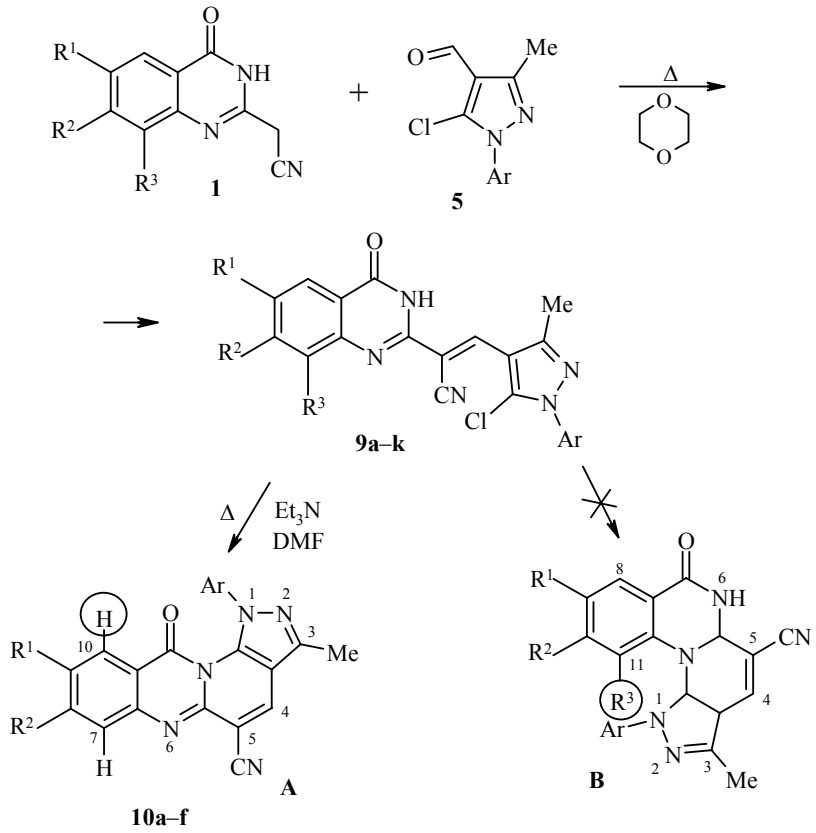
Compound	Empirical formula	Found, % / Calculated, %		mp, °C*	Yield, %	^{1}H NMR spectrum (DMSO-d_6), δ, ppm, SSCC (*J*, Hz)		
		N	Cl (Br)			H-7–H-10	H-4 (1H, s)	1-Ar, 3-CH_3
1	2	3	4	5	6	7	8	9
7a	$C_{20}H_{13}N_5$	21.89 / 21.66	—	294-295, (300 [3])	85 (83 [3])	7.81 (1H, d, ^3J = 7.6, H-7); 7.36 (1H, t, ^3J = 7.6, H-8); 6.83 (1H, t, ^3J = 7.6, H-9); 5.93 (1H, d, ^3J = 7.6, H-10)	8.69	7.59 (5H, m, C_6H_5); 2.58 (3H, s, 3-CH_3)
7b	$C_{21}H_{15}N_5$	20.85 / 20.76	—	293-294	87	7.85 (1H, d, ^3J = 7.6, H-7); 7.40 (1H, t, ^3J = 7.6, H-8); 6.89 (1H, t, ^3J = 7.6, H-9); 6.03 (1H, d, ^3J = 7.6, H-10)	8.72	7.47 (2H, d, ^3J = 8.0, H-2,6); 7.39 (2H, d, ^3J = 8.0, H-3,5); 2.54 (3H, s, 4-$\underline{CH_3}$Ar); 2.59 (3H, s, 3-CH_3)
7c	$C_{20}H_{12}FN_5$	20.77 / 20.52	—	259-260	79	7.88 (1H, d, ^3J = 7.6, H-7); 7.42 (1H, t, ^3J = 7.6, H-8); 6.98 (1H, t, ^3J = 7.6, H-9); 5.98 (1H, d, ^3J = 7.6, H-10)	8.82	7.73 (2H, m, H-2,6); 7.48 (2H, m, H-3,5); 2.57 (3H, s, 3-CH_3)
7d	$C_{22}H_{17}N_5$	20.08 / 19.93	—	335-336	84	7.59 (1H, s, H-7); 5.49 (1H, s, H-10); 2.28 (3H, s, 8-CH_3); 1.88 (3H, s, 9-CH_3)	8.75	7.66 (5H, m, C_6H_5); 2.57 (3H, s, 3-CH_3)
7e	$C_{23}H_{19}N_5$	19.35 / 19.16	—	361-362	82	7.59 (1H, s, H-7); 5.53 (1H, s, H-10); 2.31 (3H, s, 8-CH_3); 1.93 (3H, s, 9-CH_3)	8.80	7.60 (2H, d, ^3J = 8.0, H-2,6); 7.49 (2H, d, ^3J = 8.0, H-3,5); 2.53 (3H, s, 4-$\underline{CH_3}$Ar); 2.57 (3H, s, 3-CH_3)

TABLE 4 (continued)

1	2	3	4	5	6	7	8	9
7f	$C_{22}H_{16}FN_5$	19.26 / 18.96	—	>300	80	7.67 (1H, s, H-7); 5.67 (1H, s, H-10); 2.32 (3H, s, 8-CH_3); 1.99 (3H, s, 9-CH_3)	8.80	7.80 (2H, m, H-2,6); 7.54 (2H, m, H-3,5); 2.57 (3H, s, 3-CH_3)
10a	$C_{22}H_{15}N_5O$	19.31 / 19.17	—	207-208	94	7.65 (1H, s, H-10); 7.74 (1H, d, ^3J = 8.2, H-8); 7.68 (1H, d, ^3J = 8.2, H-7); 2.49 (3H, s, 9-CH_3)	8.81	7.41 (5H, m, C_6H_5); 2.50 (3H, s, 3-CH_3)
10b	$C_{21}H_{12}ClN_5O$	18.32 / 18.15	9.35 / 9.19	310-311	94	7.82 (1H, d, ^3J = 8.2, H-10); 7.75 (1H, s, H-7); 7.41 (1H, d, ^3J = 8.2, H-9)	8.77	7.36 (5H, m, C_6H_5); 2.53 (3H, s, 3-CH_3)
10c	$C_{22}H_{15}N_5O$	19.29 / 19.17	—	214-215	97	8.22 (1H, d, ^3J = 8.0, H-10); 7.53 (1H, t, ^3J = 8.0, H-8); 7.45 (1H, d, ^3J = 8.0, H-7); 7.25 (1H, t, ^3J = 8.0, H-9)	8.75	7.93 (2H, br. d, H-2,6); 7.24 (2H, br. d, H-3,5), ^3J = 8.0; 2.32 (3H, s, 4-CH_3Ar); 2.50 (3H, s, 3-CH_3)
10d	$C_{22}H_{14}BrN_5O$	15.91 / 15.76	(18.19) / (17.98)	>360	93	8.03 (1H, dd, ^3J = 8.5, ^4J = 2.5, H-8); 7.93 (1H, d, ^4J = 2.5, H-10); 7.72 (1H, d, ^3J = 8.5, H-7)	8.87	7.31 (2H, d, ^3J = 8.2, H-2,6); 7.21 (2H, d, ^3J = 8.2, H-3,5); 2.35 (3H, s, 4-CH_3Ar); 2.50 (3H, s, 3-CH_3)
10e	$C_{22}H_{14}ClN_5O$	17.77 / 17.52	8.96 / 8.87	301-303	97	7.83 (1H, d, ^3J = 8.2, H-10); 7.71 (1H, s, H-7); 7.39 (1H, d, ^3J = 8.2, H-9)	8.74	7.22 (2H, d, ^3J = 8.2, H-2,6); 7.15 (2H, d, ^3J = 8.2, H-3,5); 2.39 (3H, s, 4-CH_3Ar); 2.52 (3H, s, 3-CH_3)
10f	$C_{24}H_{19}N_5O_3$	16.63 / 16.46	—	296-297	86	7.20 (1H, s, H-10); 7.13 (1H, s, H-7); 3.97 (3H, s, 8-OCH_3); 3.80 (3H, s, 9-OCH_3)	8.77	7.27 (2H, d, ^3J = 8.0, H-2,6); 7.18 (2H, d, H-3,5); 2.34 (3H, s, 4-CH_3Ar); 2.49 (3H, s, 3-CH_3)

* Compounds **7, 10** were crystallized from DMF.

Scheme 4



9a-e, **10a**,**b** Ar = Ph; **9f-k**, **10c-f** Ar = 4-C_6H_4Me; **9 a** R^1 = Me, R^2 = R^3 = H, **b**,**g** R^1 = Br, R^2 = R^3 = H, **c**,**h** R^1 = I, R^2 = R^3 = H, **d**,**i** R^1 = R^3 = H, R^2 = Cl, **e**,**k** R^1 = R^3 = Me, R^2 = H, **f** R^1 = R^2 = R^3 = H, **j** R^1 = R^2 = OMe, R^3 = H; **10 a** R^1 = Me, R^2 = H, **b**,**e** R^1 = H, R^2 = Cl, **c** R^1 = R^2 = H, **d** R^1 = Br, R^2 = H, **f** R^1 = R^2 = OMe

The results obtained by studying the intramolecular (het)arylation of derivatives based on 2-(4-oxo-3,4-dihydro-2-quinazolinyl)acetonitriles allow us to deduce that the main factor influencing the direction of attack in these reactions is the steric environment of the nitrogen atom to which this attack is directed.

EXPERIMENTAL

Monitoring of the course of the reaction and the purity of the compounds synthesized was carried out by TLC on Silufol UV-254 plates in the system chloroform–methanol (9:1). ^{1}H NMR spectra were measured on a Varian Mercury 400 (400 MHz) spectrometer with TMS as internal standard. IR spectra were recorded on a Pye-Unicam SP 3-300 instrument for KBr tablets. Melting points were measured on a Boetius type microheating table with a VEB Analytik PHMK 05 observing attachment. Starting materials were synthesized by a known method: nitriles **1** [5], nitriles **6** [6], 2-chloro-3-quinolinecarbaldehydes **2** [7, 8], and 1-aryl-5-chloro-3-methyl-1H-4-pyrazolecarbaldehydes **5** [9].

3-(2-Chloroquinolin-3-yl)-2-(4-oxo-3,4-dihydroquinazolin-2-yl)-2-propenenitriles 3a-h (General Method). A mixture of the acetonitrile **1** (5 mmol) and 2-chloro-3-quinolinecarbaldehyde **2** (5 mmol) in DMF (25 ml) was heated on a water bath for 1.5-2 h until the starting nitrile **1** had disappeared (TLC). The precipitate was filtered off, washed with alcohol, and dried.

15-Oxo-15H-benzo[6,7][1,8]naphthyridino[2,1-*b*]quinazoline-6-carbonitrile (4a). A. A solution of the propenenitrile **3e** (5 mmol) in DMF (30 ml) was refluxed for 5-6 h or for 1-2 h in the presence of triethylamine (5 mmol). The precipitate was filtered off, washed with water, alcohol (water in the case of the use of triethylamine), and dried. A small amount of the product **4a** can be separated from the mother liquor by the addition of water (15 ml).

15-Oxo-15H-benzo[6,7][1,8]naphthyridino[2,1-*b*]quinazoline-6-carbonitriles (4b-f) (General Method). B. A mixture of the acetonitrile **1** (5 mmol), aldehyde **2** (5 mmol) and triethylamine (5 mmol) in DMF (30 ml) was refluxed for 4-5 h monitoring the completion of the reaction chromatographically. The precipitate was filtered off, washed with water and then alcohol, and dried. A small amount of product **4** was separated by the addition of water (15 ml) to the mother liquor.

3-(1-Aryl-5-chloro-3-methyl-1H-4-pyrazolyl)-2-(1H-benzo[*d*]imidazol-2-yl)-2-propenenitriles (8a-d) (General Method). The corresponding 1-aryl-5-chloro-1H-4-pyrazolecarbaldehyde **5** (6 mmol) was added to a solution of the acetonitrile **6** (6 mmol) in dioxane (15 ml) and refluxed for 1.5-2 h until the starting acetonitrile had disappeared (TLC). The reaction mixture was cooled and the precipitate was filtered off, washed with alcohol, and dried. A small amount of additional product can be separated after evaporation of the filtrate.

The compounds obtained are suitable for further reaction without initial purification.

1-Aryl-3-methyl-H-benzo[4,5]imidazo[1,2-*a*]pyrazolo[4,3-*e*]pyridine-5-carbonitriles (7a,b,d,e) (General Method). A. Triethylamine (0.7 ml, 5 mmol) was added to a solution of the propenenitrile **8** (5 mmol) in DMF (20 ml) and refluxed for 2 h until the starting compound had disappeared (TLC). Water (10-15 ml) was added to the reaction mixture and the precipitate formed was filtered off, washed with alcohol, and dried.

1-Aryl-3-methyl-1H-benzo[4,5]imidazo[1,2-*a*]pyrazolo[4,3-*e*]pyridine-5-carbonitriles (7c,f) (General Method). B. The corresponding aldehyde **5** (5 mmol) and triethylamine (0.7 ml, 5 mmol) were added to a solution of the acetonitrile **6** (5 mmol) in DMF (15 ml). The mixture was refluxed for 4 h until the starting acetonitrile had disappeared (TLC). The reaction mixture was cooled, the precipitate was filtered off (if no precipitate, water (10 ml) was added for its formation), washed with alcohol, and dried. In the first case an additional amount of product can be separated by the addition of water (10 ml) to the filtrate of the reaction mixture.

3-(1-Aryl-5-chloro-3-methyl-1H-4-pyrazolyl)-2-(4-oxo-3,4-dihydro-2-quinazolinyl)-2-propenenitriles (9a-k) (General Method). A mixture of the acetonitrile **1** (10 mmol) and the aldehyde **5** (10 mmol) in dioxane (30 ml) was refluxed for 7-10 h, monitoring the completion of the reaction chromatographically. The reaction mixture was cooled and the precipitate was filtered off, washed with water, and dried.

1-Aryl-3-methyl-11-oxo-1,11-dihydropyrazolo[4',3':5,6]pyrido[2,1-*b*]quinazoline-5-carbonitriles (10a-f) (General Method). A solution of 2-propenenitrile **9** (3 mmol) in DMF (30 ml) was treated with triethylamine (3 mmol) and refluxed for 2-3 h, monitoring the completion of the reaction chromatographically. The precipitated product **10** was filtered from the cooled reaction mixture, washed with alcohol and water, and dried. Part of the product was obtained from the mother liquor by the addition of water (15 ml).

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