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Nucleophilic Substitution in Some 5-Chloropyrimidines. Synthesis and Properties of Condensed Pyridopyrimidines

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Abstract—Reaction of hetarylacetonitriles **1** with 5-chloro-2-(methylsulfonyl)-4-pyrimidinecarbonyl chloride affords a series of new ketonitriles **3e**–**h**. The reactions of compounds **3** with aliphatic amines were studied. In the reaction of **3c**, **d**, **g** with aliphatic amines the replacement of methylsulfonyl group took place to give products **4**. In the reaction of **3a** with aliphatic amines 3-NR^1R^2-5-oxo-5*H*-pyrimido-[4,5-c]quinolizin-6-yl cyanides **5a**–**d** were formed. Compounds **3** cyclized into fused pyridopyrimidines **6**–**10** in the presence of Et_3N and the displacement of methylsulfonyl group in **6**, **7**, **9** by amines was investigated. © 2000 Elsevier Science Ltd. All rights reserved.

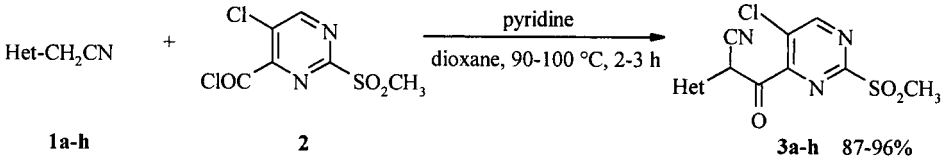
In our previous paper,[1] we reported a preparation of 2-[5-chloro-2-(methylsulfonyl)-4-pyrimidinyl]-2-oxo-1-(2-hetaryl)-ethyl cyanides **3a**–**d**. As an extension of our studies we synthesized some other ketonitriles **3e**–**h**. The interaction between 4-*R*-2-thiazolyl- (**1e**, **f**) or 5-*R*-2-benzimidazolyl-acetonitrile (**1g**, **h**) with 5-chloro-2-(methylsulfonyl)-4-pyrimidinecarbonyl chloride leads to new ketonitriles **3e**–**h**.

There are two leaving groups in the pyrimidine ring of compounds **3**: the chlorine atom in the 5-position and the methylsulfonyl group in the 2-position. It is known that structural analogues of ketonitriles of type **3** such as 2-chlorobenzoylderivatives react by intramolecular nucleophilic substitution with formation of condensed heterocycles (Scheme 1).[2–4]

However, it is well known that 5-chloropyrimidines are not very susceptible to nucleophilic substitution, the methylsulfonyl group in the 2-position being more active. In this paper we investigate properties of 2-[5-chloro-2-(methylsulfonyl)-4-pyrimidinyl]-2-oxo-1-(2-hetaryl)ethyl cyanides and their derivatives in reactions of nucleophilic substitution.

As we have previously reported,[1] the reaction of benzimidazolyl derivatives **3c** with aliphatic amines has shown that methylsulfonyl group was substituted regioselectively. It appears that the benzothiazolyl **3d** and benzoxazolyl derivatives **3g** react in the same way. The structure of compounds **4a**–**c** was supported by analytical and spectral evidence. The ^{1}H NMR spectra of these compounds exhibit the exchangeable signal of a chelate proton (13.2–13.5 ppm), the presence of an amine moiety, along with aromatic protons signals, while the C-6 pyrimidine proton is observed at 8.44–8.57 ppm (Scheme 2).

In contrast,[5] when the starting material was the 2-[5-chloro-2-(methylsulfonyl)-4-pyrimidinyl]-2-oxo-1-(2-pyridyl)ethyl



Het = 1a, 3a 2-pyridyl, 1b, 3b 2-quinolyl,
1c, 3c 1-R-2-benzimidazolyl, 1d, 3d 2-benzothiazolyl,
1e, 3e 4-methyl-2-thiazolyl, 1f, 3f 4-phenyl-2-thiazolyl,
1g, 3g 2-benzoxazolyl, 1h, 3h 6-nitro-2-benzoxazolyl.

Scheme 1.

Keywords: nucleophilic substitution; 5-chloropyrimidines; pyridopyrimidines; cyclization.
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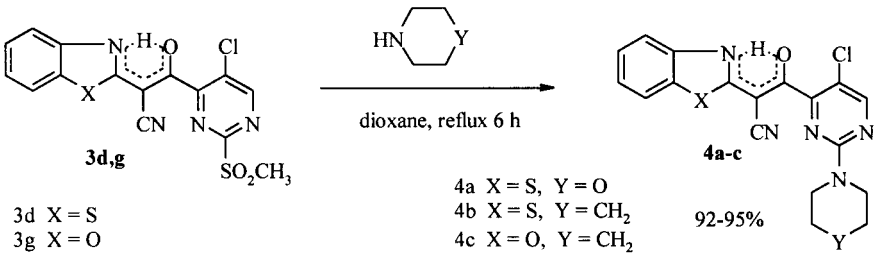
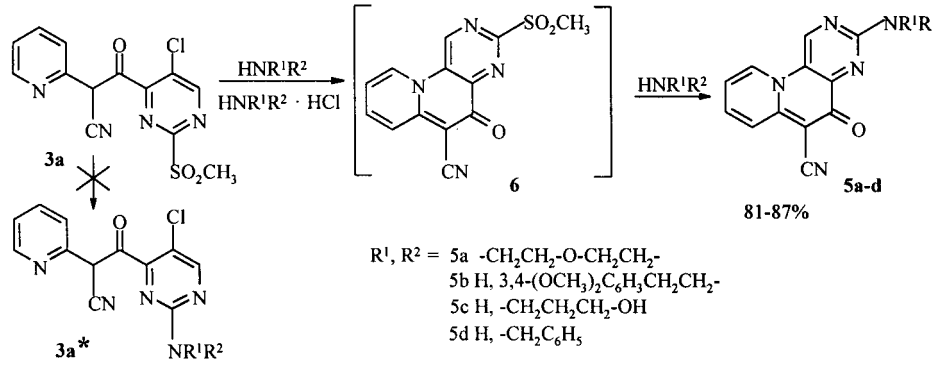
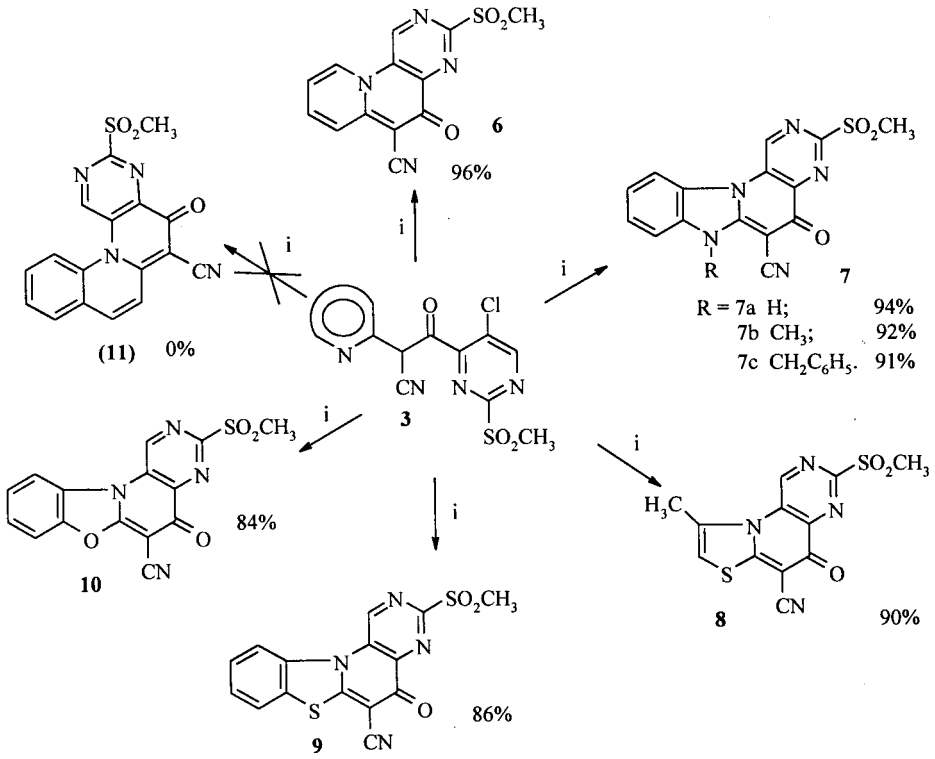


Scheme 2.

cyanide **3a** all our efforts at recovering **3a*** failed. In all cases the only isolated products were the hitherto unknown 3-NR^{1}R^2-5-oxo-5*H*-pyrimido-[4,5-*c*]quinolizin-6-yl cyanides **5a**–**d**. There are no absorption bands corresponding to methylsulfonyl group in the IR spectra of these compounds. The ^{1}H NMR spectra show the presence of an amine moiety, along with aromatic proton signals. Elemental analysis of each compound indicates no trace of Cl or S and we assume that the reaction of **3a** with amines proceeds through the formation of cyclic intermediate **6** which cannot be isolated under the reaction conditions. Formation of **3a*** and further transformation into **5** seems improbable since the chlorine atom in the 5-C position of the pyrimidine ring is insensitive to the nucleophilic attack.



Scheme 3.



Scheme 4. [i]: Et_3N, dioxane, reflux.

Table 1. Physical and analytical data for compounds **6–10**

Compd[a]	Molecular formula	Yield (%)	Analysis (%), Calcd./Found			IR (KBr) cm^{-1}	^1H NMR δ (ppm) recorded in DMSO-d_6/CF_3COOD		
			C	H	N		H-1 (s)	SO_2CH_3 (s)	Other H
6	$C_{13}H_8N_4O_3S$	96	52.00	2.69	18.66	(CN) 2200	10.49	3.55	9.58 (1H, d, *J*=7.2 Hz, H-10), 8.05 (1H, dd, *J*=8.8, 6.5 Hz, H-8), 7.8 (1H, dd, *J*=8.8, 1.1 Hz, H-7), 7.38 (1H, ddd, *J*=7.2, 6.5, 1.1 Hz, H-9)
			51.86	2.90	18.74	(SO_2) 1310 1130			
							10.72	3.75	9.99 (1H, H-10), 8.64 (2H, H-8 and H-7), 8.07 (1H, H-9)
7a	$C_{15}H_9N_5O_3S$	94	53.09	2.67	20.64	(CN) 2225	10.40	3.53	8.64 (1H, dd, *J*=7.4 2.0 Hz, H-11), 7.7–7.35 (3H, m, H-10+H-9+H-8)
			53.18	2.68	20.60	(SO_2) 1330 1125			
							10.73	3.70	8.60 (1H, m, H-11), 7.98 (3H, m, H-10+H-9+H-8)
7b	$C_{16}H_{11}N_5O_3S$	92	54.39	3.14	19.82	(CN) 2205	10.44	3.51	8.68 (1H, dd, *J*=7.4, 2.0 Hz, H-11), 7.9 (1H, m, H-8), 7.7–7.5 (2H, m, H-10+H-9), 4.16 (3H, s, N-CH_3)
			54.50	2.99	19.74	(SO_2) 1305 1125			
							10.75	3.67	8.65 (1H, H-11), 8.0 (3H, H-10+H-9 and H-8), 4.56 (3H, s, N-CH_3)
7c	$C_{22}H_{15}N_5O_3S$	91	61.53	3.52	16.31	(CN) 2210	10.48	3.51	8.73 (1H, m, H-11), 7.85–7.4 (3H, m, H-10+H-9 and H-8), 7.34 (5H, m, Ph), 6.02 (2H, s, CH_2-Ph)
			61.39	3.67	16.34	(SO_2) 1305 1130			
							10.79	3.70	8.68 (1H, m, H-11), 8.0–7.91 (3H, m, H-10+H-9, H-8), 7.5–7.25 (5H, m, Ph), 6.25 (2H, s, CH_2-Ph)
8	$C_{12}H_8N_4O_3S_2$	90	44.99	2.52	17.49	(CN) 2205	10.19	3.52	7.47 (1H, s, H-8), 3.00 (3H, s, CH_3)
			45.19	2.30	17.45	(SO_2) 1130 1130	10.67	3.70	7.63 (1H, s, H-8), 3.28 (3H, s, CH_3)
9	$C_{15}H_8N_4O_3S_2$	86	50.56	2.26	15.72	(CN) 2210	10.49	3.53	8.70 (1H, m, H-11), 8.27 (1H, m, H-8), 7.7 (2H, m, H-10 and H-9)
			50.41	2.32	15.70	(SO_2) 1300 1140			
							10.80	3.71	8.70 (1H, m, H-11), 8.28–7.88 (3H, m, H-8+H-9 and H-10)
10	$C_{15}H_8N_4O_4S$	84	52.94	2.37	16.46	(CN) 2210	10.48	3.54	8.75 (1H, m, H-11), 8.09 (1H, m, H-8), 7.7 (2H, m, H-10 and H-9)
			53.09	2.47	16.40	(SO_2) 1315 1135			
							10.61	3.70	8.50 (1H, m, H-11), 7.85–8.09 (2H, m, H-8+H-9 and H-10)

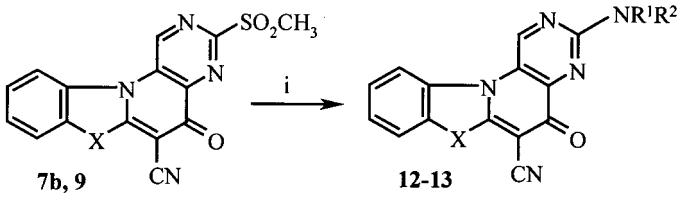
[a] All compounds **6–10** have mp >330°C.

In addition, substitution of the strong σ-electron-withdrawing group $-SO_2CH_3$ with a π-donating group $-NAlk_2$ deactivates the 5-C position (Scheme 3).

While defining the melting points of ketonitriles **3**, after reaching the melting point all substances decomposed with release of a gas and formation of crystals, which did not melt even at 330°C. Because, these compounds contain no Cl, we assume intramolecular cyclization. Furthermore the potential of conducting the above-mentioned reaction under reflux of compounds **3** in dioxane with Et_3N was established. The reaction cannot proceed to completion without base.

Novel compounds **6–10** were fully identified by the IR analytical and spectroscopic properties. The IR spectra of these substances exhibit two strong absorption peaks at 1300–1315 and 1125–1140 cm^{-1} ascribed to the sulfonyl stretching modes and absorption band at 2200–2225 cm^{-1} corresponding to a conjugated nitrile group. The ^1H NMR spectra recorded in DMSO-d_6 show, in addition to the aromatic proton's signals, a low field singlet (1H) assigned to the proton at C-1, and a singlet at 3.51–3.54 ppm integrating for three protons corresponding to methylsulfonyl group, but lack the signal of the exchangeable chelate proton. The low field shift of the signal of the proton of pyrimidine ring (1.2 ppm) in comparison to the starting ketonitrile can be explained in terms of influence of ring current and neighboring bridgehead nitrogen atom. Alteration of chemical shifts of protons in CF_3COOD suggests the protonation of the molecule on the oxygen atom with positive charge transfer into the bridgehead nitrogen atom. The absence of IR carbonyl absorption at 1750–1640 cm^{-1}, for **6–10**, allowed us to suggest with some confidence that there is a significant contribution of a bipolar structure to these cyclic molecules (Scheme 4, Table 1).

According to the ease of cyclization the starting compounds



7b, 12 X = N-CH_3
9, 13 X = S

Scheme 5. [i]: HNR^1R^2, dimethylformamide, 90–100°C.

Table 2. Physical and analytical data for compounds **12** and **13**

Compd	X	R^1, R^2	IR (KBr) cm^{-1}	^{1}H NMR δ (ppm) recorded in DMSO-d_6	
				H-1 (s)	Other H
12a	N–CH_3	–$(CH_2)_2$–O–$(CH_2)_2$–	(CN) 2200	9.77	3.79 (8H, m, morpholine-H), 4.07 (3H, s, N-CH_3), 7.48 (2H, m, H-9 + H-10), 7.75 (1H, dd, *J*=7.0, 2.1 Hz, H-8), 8.43 (1H, dd, *J*=7.4, 2.0 Hz, H-11)
12b	N–CH_3	–$(CH_2)_2$–N(CH_3)–$(CH_2)_2$–	(CN) 2200	9.81	2.25 (3H, s, N-CH_3 piperazine), 2.58, 3.87 (8H, 2m, piperazine-H), 4.07 (3H, s, N-CH_3), 7.25–7.55 (2H, m, H-9 + H-10), 7.82 (1H, dd, *J*=7.0, 2.1 Hz, H-8), 8.48 (1H, dd, *J*=7.4, 2.0 Hz, H-11)
12c	N–CH_3	–$(CH_2)_5$–	(CN) 2200	9.73	1.64, 3.88 (10H, 2m, piperidine-H), 4.07 (3H, s, N-CH_3), 7.30–7.61 (2H, m, H-9 + H-10), 7.79 (1H, dd, *J*=7.0, 2.1 Hz, H-8), 8.42 (1H, dd, *J*=7.4, 2.0 Hz, H-11)
12d	N–CH_3	H, –$CH_2C_6H_5$	(CN) 2200 (NH) 3320	9.74	4.06 (3H, s, N-CH_3), 4.63 (2H, d, NHC*H*$_2$) 7.2–7.5 (7H, m, H-9 + H-10 and Ar*H*), 7.78 (1H, dd, *J*=7.0, 2.1 Hz, H-8), 8.35 (1H, broad s, NH), 8.44 (1H, dd, *J*=7.4, 2.0 Hz, H-11)
12e	N–CH_3	H, 3,4-$(OCH_3)_2C_6H_3CH_2CH_2$–	(CN) 2200 (NH) 3375	9.71	2.90 (2H, t, C*H*$_2$Ar), 3.62 (2H, m, NHC*H*$_2$), 3.72, 3.76 (6H, 2s, 2 OCH_3), 4.08 (3H, s, N-CH_3), 6.86 (3H, m, Ar*H*), 7.35–7.53 (2H, m, H-9 + H-10), 7.78 (1H, dd, *J*=7.0, 2.1 Hz, H-8), 7.86 (1H, broad s, NH), 8.44 (1H, dd, *J*=7.4, 2.0 Hz, H-11)
12f	N–CH_3	H, –$CH_2CH_2OCH_3$	(CN) 2195 (NH) 3260	9.73	3.31 (3H, s, OCH_3), 3.56 (4H, m, NHC*H*$_2$C*H*$_2$), 4.08 (3H, s, N-CH_3), 7.31–7.7 (3H, m, H-9 + H-10 and NH), 7.78 (1H, dd, *J*=7.0, 2.1 Hz, H-8), 8.44 (1H, dd, *J*=7.4, 2.0 Hz, H-11)
12g	N–CH_3	H, cyclohexyl–	(CN) 2200 (NH) 3400	9.72	1.35, 1.84 (10H, 2m, cyclohexyl-H), 3.86 (1H, m, NHC*H*), 4.08 (3H, s, N-CH_3), 7.35–7.65 (3H, m, H-9 + H-10 and NH), 7.78 (1H, dd, *J*=7.0, 2.1 Hz, H-8), 8.44 (1H, dd, *J*=7.4, 2.0 Hz, H-11)
13a	S	–$(CH_2)_2$–O–$(CH_2)_2$–	(CN) 2205	9.84	3.8 (8H, m, morpholine-H), 7.47–7.67 (2H, m, H-9 + H-10), 8.19 (1H, dd, *J*=7.0, 2.2 Hz, H-8), 8.48 (1H, dd, *J*=7.6, 1.7 Hz, H-11)
13b	S	H, 3,4-$(OCH_3)_2C_6H_3CH_2CH_2$–	(CN) 2195 (NH) 3250	9.75	2.85 (2H, t, C*H*$_2$Ar), 3.62 (2H, m, NHC*H*$_2$), 3.70, 3.76 (6H, 2s, 2 OCH_3), 6.85 (3H, m, Ar*H*), 7.46–7.67 (2H, m, H-9 + H-10), 8.02 (1H, broad s, NH), 8.18 (1H, dd, *J*=7.0, 2.2 Hz, H-8), 8.47 (1H, dd, *J*=7.6, 1.7 Hz, H-11)

3 can be arranged in the following order: 2-pyridyl->1-Alk-2-benzimidazolyl->1*H*-2-benzimidazolyl->4-methyl-2-thiazolyl->2-benzothiazolyl->2-benzoxazolyl->2-quinolyl-derivatives. Hence it appears clear that this intramolecular nucleophilic cyclization does not only depend on basicity of heterocyclic but also on steric hindrance arising at the reaction center during the cyclization stage. It can be explicitly shown in the comparison of the ease of cyclization of pyridyl-**3a** and quinolyl-**3b** derivatives. In the last case steric hindrance caused by hydrogen atom at C-8 position of quinolyl ring makes the cyclization impossible. At the same time pyrimidine derivatives **3a** of similar basicity cyclize especially easily and can be explained in terms of lesser steric hindrance at the reaction center.

Like starting ketonitriles, pyridopyrimidines **6**–**10** contain a mobile methylsulfonyl group. Substances **7b**, **9** react with aliphatic amines in DMF at 90–100°C (Scheme 5, Table 2). Treatment of **6** with aliphatic amines under conditions identical to that described for ketonitrile **3a** (Scheme 2) gave the corresponding pyrimido[4,5-*c*]quinolizines **5a**–**d**.

Earlier the cyclization of 2-[5-chloro-2-(methylmercapto)-4-pyrimidinyl]-2-oxo-1-(2-hetaryl)ethyl cyanides was described.[2] The reaction is conducted with prolonged reflux of these substances in DMF with high boiling tertiary amines, and it has been shown that 1*H*-2-benzimidazolyl- and 2-benzothiazolyl- derivatives of above-mentioned compounds did not react. We succeeded in obtaining the

cyclic derivatives of 1*H*-2-benzimidazolyl-, 2-benzothiazolyl, and even 2-benzoxazolyl. The products **8**–**10** are the first examples of the ring systems pyrimido[4′,5′:5,6]pyrido[2,1-*b*]-[1,3]thiazole, benzo[*d*]pyrimido[4′,5′:5,6]pyrido[2,1-*b*]-[1,3]thiazole, benzo[*d*]pyrimido[4′,5′:5,6]pyrido[2,1-*b*][1,3]-oxazole, respectively.

In summary, extension of the limit of application of cyclization of such 5-chloropyrimidines is possible provided the pyrimidine ring contains a strong σ-electron-withdrawing group ($-SO_2CH_3$), that activates the 5-site of the ring towards intramolecular nucleophilic attack.

Experimental

Melting points were determined using an Electrothermal melting point apparatus and are uncorrected. The IR spectra were recorded on a Pye Unicam SP 3-300 spectrometer as potassium bromide pellets and frequencies are expressed in cm^{-1}. NMR spectra were obtained on a Bruker WP-100 SY spectrometer in the solvent indicated with tetramethylsilane as an internal standard and chemical shifts reported in ppm (δ) and J=values in Hz. The synthesis of **2**, **3a**–**d** has been reported elsewhere.[1,6]

General procedure for the preparation of 2-[5-chloro-2-(methylsulfonyl)-4-pyrimidinyl]-2-oxo-1-(2-hetaryl)-ethyl cyanides 3

To a solution of the corresponding 2-hetarylacetonitriles 1 (10 mmol) in 20 ml of dry dioxane, pyridine (10 mmol) and 5-chloro-2-(methylsulfonyl)-4-pyrimidinecarbonyl chloride 2 (2.55 g, 10 mmol) were added. The reaction mixture was heated to 90–100°C for 2–3 h. The solvent was evaporated in vacuo. The resulting residue was suspended in cold water, the precipitate was isolated by filtration, dried and recrystallized from dimethylformamide.

2-[5-Chloro-2-(methylsulfonyl)-4-pyrimidinyl]-1-(4-methyl-1,3-thiazol-2-yl)-2-oxoethyl cyanide (3e). This compound was prepared from 4-methyl-2-thiazolylacetonitrile **1e** in 96% yield as a yellow solid, mp 246–246.5°C (dec.); [Found: C, 40.5; H, 2.5 N, 15.8. $C_{12}H_9ClN_4O_3S_2$ requires C, 40.40; H, 2.54; N, 15.70%]; δ_H (100 MHz, DMSO-d_6) 2.35 (3H, s, ArCH_3), 3.45 (3H, s, SO_2Me), 7.07 (1H, s, thiazole-H), 9.38 (1H, s, pyrimidine-H), 13.1–13.3 (1H, br s); ν_{max}(potassium bromide) 2190 (CN), 1300, 1128 (SO_2Me) cm^{-1}.

2-[5-Chloro-2-(methylsulfonyl)-4-pyrimidinyl]-1-(4-phenyl-1,3-thiazol-2-yl)-2-oxoethyl cyanide (3f). This compound was prepared from 4-phenyl-2-thiazolylacetonitrile **1f** in 94% yield as a yellow solid, mp 225.5–226.5°C (dec.); [Found: C, 48.9; H, 2.4; N, 13.4. $C_{17}H_{11}ClN_4O_3S_2$ requires C, 48.75; H, 2.65; N, 13.38%]; δ_H (100 MHz, DMSO-d_6) 3.45 (3H, s, SO_2Me), 7.42–7.89 (6H, m, thiazole-H and Ph-H), 9.37 (1H, s, pyrimidine-H), 13.25–13.4 (1H, br s); ν_{max} (potassium bromide) 2195 (CN), 1312, 1135 (SO_2Me) cm^{-1}.

1-(1,3-Benzoxazol-2-yl)-2-[5-chloro-2-(methylsulfonyl)-4-pyrimidinyl]-2-oxoethyl cyanide (3 g). This compound was prepared from 2-benzoxazolylacetonitrile 1 g in 87% yield as a straw solid, mp 244–245°C (dec.); [Found: C, 48.0; H, 2.2; N, 14.9. $C_{15}H_9ClN_4O_4S$ requires C, 47.82; H, 2.41; N, 14.87%]; δ_H (100 MHz, DMSO-d_6) 3.47 (3H, s, SO_2Me), 7.35–8.0 (4H, m, benzoxazole-H), 9.43 (1H, s, pyrimidine-H), 13.4–13.5 (1H, broad s); ν_{max}(potassium bromide) 2200 (CN), 1320, 1132 (SO_2Me) cm^{-1}.

2-[5-Chloro-2-(methylsulfonyl)-4-pyrimidinyl]-1-(5-nitro-1,3-benzoxazol-2-yl)-2-oxoethyl cyanide (3h). This compound was prepared from 5-nitro-2-benzoxazolylacetonitrile **1h** in 90% yield as a straw solid, mp 279.5–280.5°C (dec.); [Found: C, 47.9; H, 2.1; N, 16.6. $C_{15}H_8ClN_5O_6S$ requires C 42.72; H, 1.91; N, 16.60%]; δ_H (100 MHz, DMSO-d_6) 3.47 (3H, s, SO_2Me), 7.35–8.0 (4H, m, benzoxazole-H), 9.43 (1H, s, pyrimidine-H), 13.4–13.5 (1H, br s); ν_{max}(potassium bromide) 2200 (CN), 1320, 1132 (SO_2Me) cm^{-1}.

1-(1,3-Benzothiazol-2-yl)-2-(5-chloro-2-morpholino-4-pyrimidinyl)-2-oxoethyl cyanide (4a). 1-(1,3-Benzothiazol-2-yl)-2-[5-chloro-2-(methylsulfonyl)-4-pyrimidinyl]-2-oxoethyl cyanide **3d** (3.93 g, 10 mmol) in dioxane (12 ml) and morpholine (20 mmol) was heated at reflux for 6 h. The reaction mixture was evaporated under reduced pressure and the residue washed with water. The solid was collected by filtration, dried and recrystallized from dioxane gave (3.75 g, 94%) as a straw solid, mp 221–221.5°C; [Found: C, 54.3; H, 3.7; N, 17.4. $C_{18}H_{14}ClN_5O_2S$ requires C, 54.07; H, 3.53; N, 17.51%]; δ_H (100 MHz, DMSO-d_6) 3.69 (8H, m, morpholine-H), 7.3–7.81 (4H, m, benzothiazole-H), 8.56 (1H, s, pyrimidine-H), 13.2–13.4 (1H, br s); ν_{max}(potassium bromide) 2190 (CN) cm^{-1}.

1-(1,3-Benzothiazol-2-yl)-2-(5-chloro-2-piperidino-4-pyrimidinyl)-2-oxoethyl cyanide (4b). Prepared as above, from 1-(1,3-benzothiazol-2-yl)-2-[5-chloro-2-(methylsulfonyl)-4-pyrimidinyl]-2-oxoethyl cyanide **3d** (3.93 g, 10 mmol) in dioxane (12 ml) and piperidine (20 mmol) in 3.78 g, 95% yield, as a straw solid, mp 213–213.5°C (dioxane); [Found: C, 57.5; H, 3.8; N, 17.6. $C_{18}H_{14}ClN_5O_2S$ requires C, 57.36; H, 4.05; N, 17.60%]; δ_H (100 MHz, DMSO-d_6) 1.58, 3.75 (10H, 2m, piperidine-H), 7.3–8.1 (4H, m, benzothiazole-H), 8.52 (1H, s, pyrimidine-H), 13.2–13.4 (1H, br s); ν_{max}(potassium bromide) 2198 (CN) cm^{-1}.

1-(1,3-Benzoxazol-2-yl)-2-(5-chloro-2-piperidino-4-pyrimidinyl)-2-oxoethyl cyanide (4c). Prepared as above, from **3g** (1.88 g, 5 mmol) in dioxane (10 ml) and piperidine (10 mmol) in 1.75 g, 92% yield, as a straw solid, mp 227.5–228°C (dioxane); [Found: C, 59.6; H, 4.0; N, 18.4. $C_{19}H_{16}ClN_5O_2$ requires C, 59.77; H, 4.22; N, 18.34%]; δ_H (100 MHz, DMSO-d_6) 1.59, 3.75 (10H, 2m, piperidine-H), 7.3–8.5 (4H, m, benzoxazole-H), 8.52 (1H, s, pyrimidine-H), 13.4–13.5 (1H, br s); ν_{max}(potassium bromide) 2200 (CN) cm^{-1}.

Method A for preparing compound 5 from 3a (see Ref. 5)

Method B for preparing compound 5 from 6. A mixture of 0.6 g (2 mmol) of 3-methylsulfonyl-5-oxo-5*H*-pyrimido-[4,5-*c*]quinolizin-6-yl cyanide **6** and (4 mmol) of the corresponding amine in 30 ml of dioxan was heated at reflux for 3–3.5 h. After cooling, the precipitate was collected by

filtration and washed with water, dried and recrystallized from dimethylformamide to give target compounds **5**.

3-Morpholino-5-oxo-5*H*-pyrimido[4,5-*c*]quinolizin-6-yl cyanide (5a). This yellow solid compound had mp >300°C (dec.) yield 88% (Method B), [Found: C, 62.6; H, 4.2; N, 22.8. $C_{16}H_{13}N_5O_2$ requires C, 62.53; H, 4.26; N, 22.79%]; δ_H (100 MHz, DMSO-d_6) 9.80 (1H, s, H-1), 9.33 (1H, d, *J*=7.2, H-10), 7.87 (1H, dd, *J*=8.8, 6.5, H-8), 7.54 (1H, dd, *J*=8.8, 1.1, H-7), 7.23 (1H, ddd, *J*=7.2, 6.5, 1.1, H-9), 3.8 (8H, m, morpholine); ν_{max}(potassium bromide) 2200 (CN) cm^{-1}.

3-[(3,4-Dimethoxyphenethyl)amino]-5-oxo-5*H*-pyrimido-[4,5-*c*]quinolizin-6-yl cyanide (5b). This yellow solid compound had mp >300°C, yield 87% (Method A), 90% (Method B); [Found: C, 65.9; H, 4.8; N, 17.4. $C_{22}H_{19}N_5O_3$ requires C, 65.83; H, 4.77; N, 17.45%]; δ_H (100 MHz, DMSO-d_6) 9.71 (1H, s, H-1), 9.28 (1H, d, *J*=7.2 Hz, H-10), 8.06 (1H, br s, NH), 7.85 (1H, dd, *J*=8.8, 6.5 Hz, H-8), 7,62 (1H, dd, *J*=8.8, 1.1 Hz, H-7), 7.19 (1H, ddd *J*=7.2, 6.5, 1.1 Hz, H-9), 6.85 (3H, m, aromatic-H), 3.72, 3.76 (6H, 2s, 2 OCH_3), 3.64 (2H, m, NH-CH_2), 2.85 (2H, t, CH_2-Ar); ν_{max}(potassium bromide) 2195 (CN) cm^{-1}.

3-[(3-Hydroxypropyl)amino]-5-oxo-5*H*-pyrimido[4,5-*c*]-quinolizin-6-yl cyanide (5c). This yellow solid compound had mp 287–288°C, yield 91% (Method B); [Found: C, 61.0; H, 4.5; N, 23.7. $C_{15}H_{13}N_5O_2$ requires C, 61.01; H, 4.44; N, 23.72%]; δ_H (100 MHz, DMSO-d_6) 9.70 (1H, s, H-1), 9.30 (1H, d, *J*=7.2 Hz, H-10), 8.07 (1H, br s, NH), 7.85 (1H, dd, *J*=8.8, 6.5 Hz, H-8), 7.62 (1H, dd, *J*=8.8, 1.1 Hz, H-7), 7.21 (1H, ddd, *J*=7.2, 6.5, 1.1 Hz, H-9), 4.5 (1H, br s, OH), 3.48 (4H, m, NHCH_2CH_2CH_2OH), 1.74 (2H, q, NH–CH_2CH_2CH_2OH); ν_{max}(potassium bromide) (NH) 3400, 2195 (CN) cm^{-1}.

3-(Benzylamino)-5-oxo-5*H*-pyrimido[4,5-*c*]quinolizin-6-yl cyanide (5d). This yellow solid compound had mp 317–318°C, yield 90% (Method B); [Found: C, 69.8; H, 3.9; N, 21.4. $C_{19}H_{13}N_5O$ requires C, 69.72; H, 4.00; N, 21.39%]; δ_H (100 MHz, DMSO-d_6) 9.70 (1H, s, H-1), 9.30 (1H, d *J*=7.2 Hz, H-10), 8.62 (1H, br s, NH), 7.85 (1H, dd, *J*=8.8, 6.5 Hz, H-8), 7.62 (1H, dd, *J*=8.8, 1.1 Hz, H-7), 7.4–7.1 (6H, m, H-9+Ph), 4.66 (2H, d, *J*=6.8 Hz, NHCH_2Ph); ν_{max}(potassium bromide) (NH) 3300, (CN) 2195 cm^{-1}.

General procedure for the preparation of compounds 6–10

A mixture of the corresponding 2-[5-chloro-2-(methylsulfonyl)-4-pyrimidinyl]-2-oxo-1-(2-hetaryl)ethyl cyanide **3** (10 mmol) and triethylamine (10 mmol) in 20 ml of dioxan was refluxed for several hours. After the reaction, the precipitate was collected by filtration, washed with water, dried and recrystallized from dimethylformamide.

3-Methylsulfonyl-5-oxo-5*H*-pyrimido[4,5-*c*]quinolizin-6-yl cyanide (6). This product was prepared according to the general procedure, as a yellow solid, reaction time 30 min, mp >330°C.

3-(Methylsulfonyl)-5-oxo-5,7-dihydrobenzo[4′,5′]imidazo-[2′,1′:6,1]pyrido[3,2-*d*]pyrimidine-6-carbonitrile (7a). This product was prepared according to the general procedure, as a yellow solid, reaction time 3 h, mp >330°C.

7-Methyl-3-(methylsulfonyl)-5-oxo-5,7-dihydrobenzo-[4′,5′]imidazo[2′,1′:6,1]pyrido[3,2-*d*]pyrimidine-6-carbonitrile (7b). This product was prepared according to the general procedure, as a yellow solid, reaction time 1.5 h, mp >330°C.

7-Benzyl-3-(methylsulfonyl)-5-oxo-5,7-dihydrobenzo[4′,5′]-imidazo[2′,1′:6,1]pyrido[3,2-*d*]pyrimidine-6-carbonitrile (7c). This product was prepared according to the general procedure, as a yellow solid, reaction time 2 h, mp >330°C.

9-Methyl-3-(methylsulfonyl)-5-oxo-5*H*-pyrimido[4′,5′:5,6]-pyrido[2,1-*b*][1,3]thiazole-6-carbonitrile (8). This product was prepared according to the general procedure, as a yellow solid, reaction time 3 h, mp >330°C.

3-(Methylsulfonyl)-5-oxo-5*H*-benzo[*d*]pyrimido[4′,5′:5,6]-pyrido[2,1-*b*][1,3]thiazole-6-carbonitrile (9) This product was prepared according to the general procedure, as a yellow solid, reaction time 4.5 h, mp >330°C.

3-(Methylsulfonyl)-5-oxo-5*H*-benzo[*d*]pyrimido[4′,5′:5,6]-pyrido[2,1-*b*][1,3]oxazole-6-carbonitrile (10). This product was prepared according to the general procedure, as a yellow solid, reaction time 6 h, mp >330°C.

General procedure for the preparation of compounds 12 and 13

To a suspension of 7-methyl-3-(methylsulfonyl)-5-oxo-5,7-dihydrobenzo[4′,5′]imidazo[2′,1′:6,1]pyrido [3,2-*d*]pyrimidine-6-carbonitrile **7b** (10 mmol) in 10 ml of dry dimethylformamide the corresponding amine (20 mmol) was added. The reaction mixture heated to 90–100°C for 2–3 h. After cooling, the precipitate was collected by filtration washed with water, dried and recrystallized from dimethylformamide.

7-Methyl-3-morpholino-5-oxo-5,7-dihydrobenzo[4′,5′]-imidazo[2′,1′:6,1]pyrido[3,2-*d*]pyrimidine-6-carbonitrile (12a). This product was prepared according to the general procedure in 96% yield as a yellow solid, mp >300°C; [Found: C, 63.4; H, 4.5; N, 23.4. $C_{19}H_{16}N_6O_2$ requires C, 63.33; H, 4.47; N, 23.32%].

7-Methyl-3-(4-methylpiperazino)-5-oxo-5,7-dihydrobenzo-[4′,5′]imidazo[2′,1′:6,1]pyrido[3,2-*d*]pyrimidine-6-carbonitrile (12b). Prepared as above in 90% yield as a yellow solid, mp >300°C; [Found: C, 64.2; H, 5.1; N, 26.2. $C_{20}H_{19}N_7O$ requires C, 64.33; H, 5.13; N, 26.26%].

7-Methyl-3-piperidino-5-oxo-5,7-dihydrobenzo[4′,5′]-imidazo[2′,1′:6,1]pyrido[3,2-*d*]pyrimidine-6-carbonitrile (12c). Prepared as above in 96% yield as a yellow solid, mp >300°C; [Found: 66.9; H, 5.2; N, 23.3. $C_{20}H_{18}N_6O$ requires C, 67.03; H, 5.06; N, 23.45%].

7-Methyl-3-benzylamino-5-oxo-5,7-dihydrobenzo[4′,5′]-

imidazo[2′,1′:6,1]pyrido[3,2-*d*]pyrimidine-6-carbonitrile (12d). Prepared as above in 95% yield as a yellow solid, mp >300°C; [Found: 69.4; H, 4.3; N, 22.1. $C_{22}H_{16}N_6O$ requires C, 69.46; H, 4.24; N, 22.09%].

7-Methyl-3-(3,4-dimethoxyphenethylamino)-5-oxo-5,7-dihydrobenzo[4′,5′]imidazo[2′,1′:6,1]pyrido[3,2-*d*]pyrimidine-6-carbonitrile (12e). Prepared as above in 94% yield as a yellow solid, mp >300°C; [Found: C, 65.9; H, 4.9; N, 18.5. $C_{25}H_{22}N_6O_3$ requires C, 66.07; H, 4.88; N, 18.49%].

7-Methyl-3-(2-methoxyethylamino)-5-oxo-5,7-dihydrobenzo[4′,5′]imidazo[2′,1′:6,1]pyrido[3,2-*d*]pyrimidine-6-carbonitrile (12f). Prepared as above in 93% yield as a yellow solid, mp >300°C; [Found: C, 62.1; H, 4.5; N, 24.0. $C_{18}H_{16}N_6O_2$ requires C, 62.06; H, 4.63; N, 24.12%].

7-Methyl-3-cyclohexylamino-5-oxo-5,7-dihydrobenzo-[4′,5′]imidazo[2′,1′:6,1]pyrido[3,2-*d*]pyrimidine-6-carbonitrile (12 g). Prepared as above in 93% yield as a yellow solid, mp >300°C; [Found: C, 67.7; H, 5.4; N, 22.5. $C_{21}H_{20}N_6O$ requires C, 67.73; H, 5.41; N, 22.57%].

3-Morpholino-5-oxo-5*H*-benzo[*d*]pyrimido[4′,5′:5,6]-pyrido[2,1-*b*][1,3]thiazole-6-carbonitrile (13a). This product was prepared according to the general procedure for the compounds **12** and **13** in 93% yield as a yellow solid, mp >300°C; [Found: C, 59.4; H, 3.5; N, 19.2. $C_{18}H_{13}N_5O_2S$ requires C, 59.49; H, 3.61; N, 19.27%].

3-(3,4-Dimethoxyphenethylamino)-5-oxo-5*H*-benzo[*d*]-pyrimido[4′,5′:5,6]pyrido[2,1-*b*][1,3]thiazole-6-carbonitrile (13b). This product was prepared according to the general procedure for the compounds **12** and **13** in 93% yield. as a yellow solid, mp >300°C; [Found: C, 63.1; H, 4.0; N, 15.4. $C_{24}H_{19}N_5O_3S$ requires C, 63.01; H, 4.19; N, 15.31%].

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