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Reaction of 2-hetarylacetonitriles with ethyl 2-alkylsulfanyl-4-chloro-5-pyrimidinecarboxylates. Synthesis of new condensed pyrimidines

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Abstract—Reactions of 2-hetarylacetonitriles **1** with ethyl 2-alkylsulfanyl-4-chloro-5-pyrimidinecarboxylates **4** were studied. The interaction of pyridine, benzimidazole and benzothiazole derivatives **1a**–**d** affords a series of new condensed pyridopyrimidines **5**–**7**. In the case of benzoxazole- and 4-arylthiazole derivatives **1e**–**h** ethyl 4-[(2-hetaryl)-cyano-methyl]-2-alkylsulfanylpyrimidine-5-carboxylates **9a**–**f** were formed. Reactions of quinazoline derivatives **1i**,**k** afford stable intermediates **9h**,**i** which formed the cyclic compound **12** of angular structure in the presence of potash. The influence of the basicity of heterocycles and of steric factors on the intramolecular acylation reaction was studied.

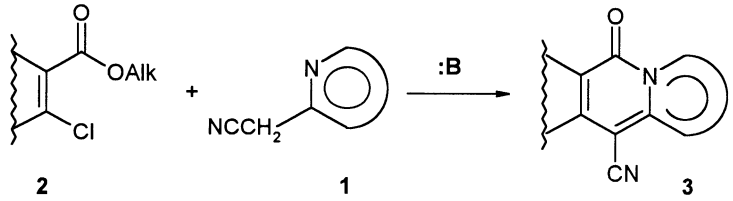
1. Introduction

2-Hetarylacetonitriles **1** are versatile reagents which have been extensively utilized in heterocyclic synthesis. Many reactions were developed in the last few years, for which the synthetic potential of 2-hetarylacetonitriles toward (di)electrophiles was used.[1] As reported recently, reaction of **1** with esters of 2-halogen(hetero)aromatic acids **2** in the presence of a base gives rise to the formation of nitrogen bridgehead heterocycles **3** of linear structure as shown in Scheme 1.[2]

In previous investigations of this reaction type 2-halogenbenzoates and (iso)nicotinates were used. As an extension of our work on the nucleophilic substitution in the pyrimidine ring,[3] we decided to replace benzoic or pyridine acid type building blocks by the more reactive pyrimidine analog. On the other hand by using different hetarylacetonitriles a variety of hitherto unknown condensed pyrimidines should become accessible. In this connection we studied the reaction of **1** with ethyl 2-alkylsulfanyl-4-chloro-5-pyrimidinecarboxylates **4a**,**b**. Compounds **4a**,**b** have been frequently used as starting materials for the synthesis of various condensed pyrimidines and compounds of potential medicinal interest.[4]

2. Results and discussion

In the first series of experiments 2-hetarylacetonitriles **1a**–**d** were treated with **4** in dimethylformamide in the presence of potassium carbonate (method A). After 1.5–2 h of refluxing,



2 **1** **3**

Scheme 1.

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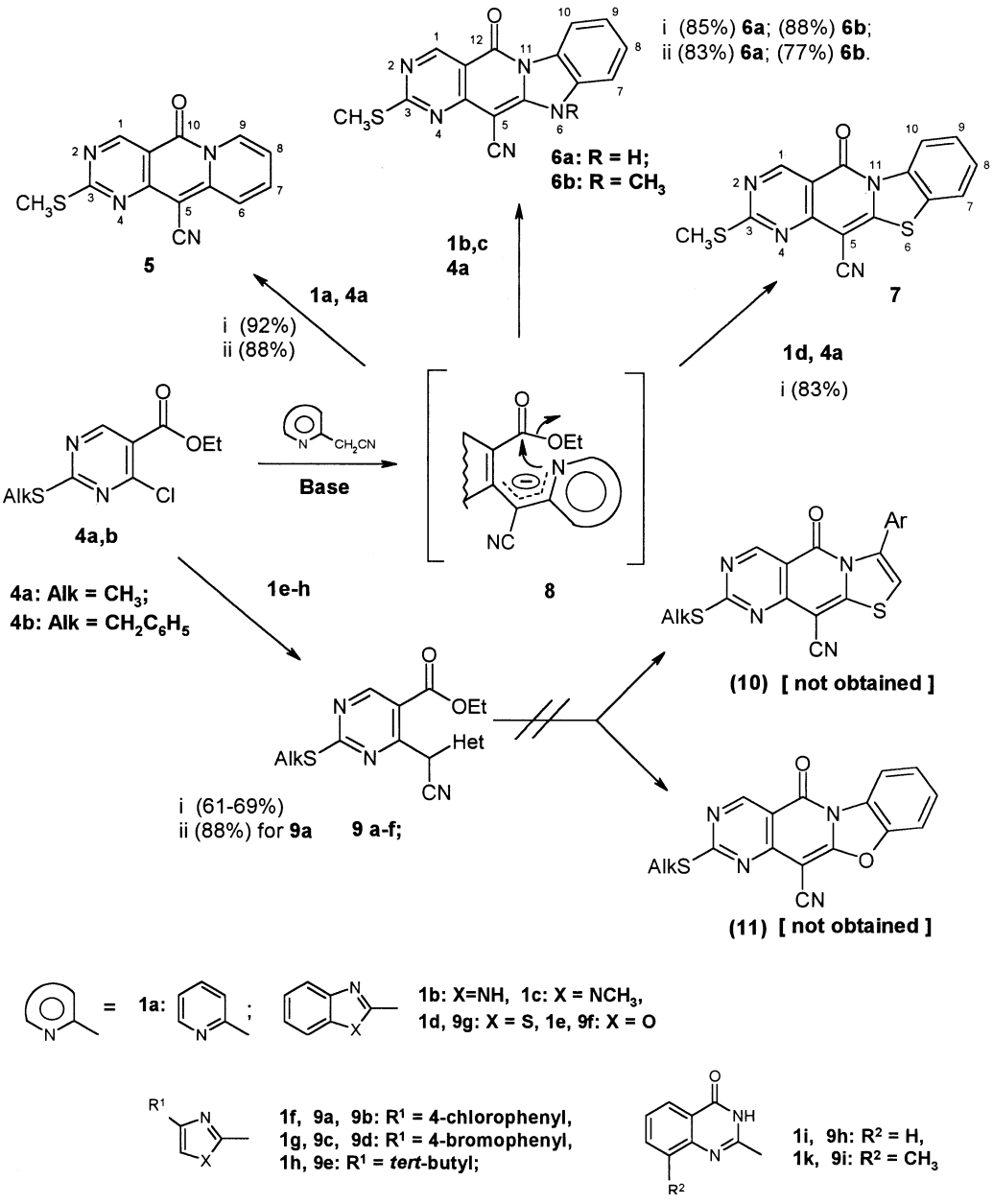


Scheme 2. *Reagent and conditions*: (i) DMF, K_2CO_3, reflux, 1.5–2 h; (ii) DMSO, Et_3N, 25°C, 12 h.

followed by aqueous work-up, the expected condensed pyridopyrimidines **5**–**7** were isolated as solids in good to high yields (83–92%). One can assume that the reaction starts with the formation of the carbanion of the active methylene group in compounds **1a**–**d** followed by nucleophilic attack at the C-4 position of the pyrimidine **4** to give **8** (Scheme 2). This intermediate **8**, which could not be isolated under these reaction conditions underwent intramolecular cyclization through acylation at the nitrogen atom of the heterocyclic moiety leading to **5**–**7**. The results of elemental analysis and the spectroscopic data are in agreement with the structures of the compounds **5**–**7**.

The ^{1}H NMR spectra recorded in CF_3COOD show, in addition to the signals of aromatic protons, a low field singlet (1H) assigned to the proton at C-1, and a 3H-singlet at 2.97–3.00 ppm corresponding to the methylsulfanyl group, but no signal for an ester group. The doublet (1H) at 9.42, 8.70, 8.77 and 9.15 ppm, respectively, can be attributed to the aromatic proton at position 9 for compound **5** and position 10 for compounds **6a**,**b** and **7**; it is significantly low field shifted in comparison to the signals of the other aromatic protons caused by the influence of the neighboring highly anisotropic carbonyl group. The IR spectra of these substances exhibit a strong absorption band at 1697–1710 cm^{-1} ascribed to the carbonyl stretching modes and an absorption band at 2217–2229 cm^{-1} corresponding to a conjugated nitrile group.

Interestingly, when benzoxazol-2-yl-acetonitrile **1e** or 4-Ar- or 4-*tert*-Bu-thiazol-2-ylacetonitriles **1f**–**h** were used as the RCH_2CN building block, the interaction with **4a**,**b** under the same reaction condition did not afford the corresponding pyridopyrimidines **10** or **11**, but compounds containing an

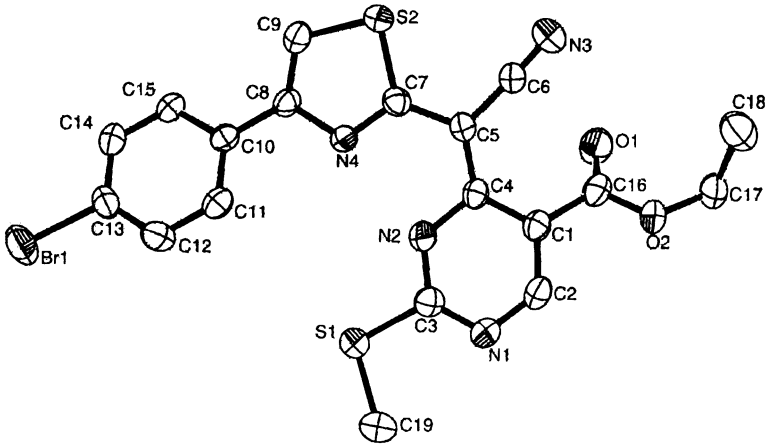


Figure 1. Crystal structure of compound **9c** with the atom numbering used in X-ray study.

ester group, which were identified as ethyl 4-[(2-hetaryl)-cyanomethyl]-2-alkylsulfanylpyrimidine-5-carboxylates **9a–f** (Scheme 2).

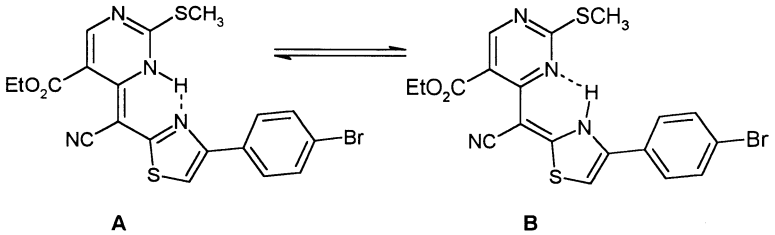
The structure of compound **9c** has been determined by X-ray diffraction method (Fig. 1). The planar configuration of C(5) indicates its sp^2 hybridisation.

Therefore we can assume that the structure of compound **9c** is best described by the tautomeric structures **A–B** (Scheme 3). This assumption is confirmed by the almost planar geometry of the fragments N(2)–C(4)–C(5)–C(7)–N(4). Analysis of bond lengths in the molecule indicates a significant contribution of structure **A**. Analysis of a difference map of electron density demonstrates that the hydrogen atom in this fragment is disordered with equal occupancies over two sites located at the N(2) and N(4) atoms.

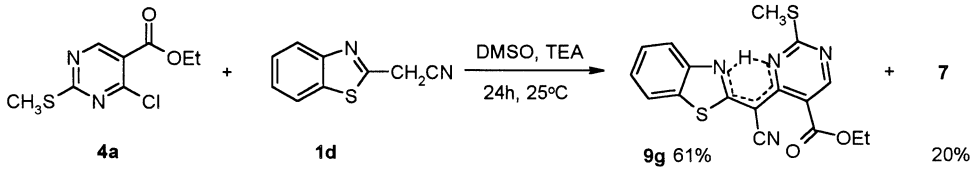
The structure of compounds **9a–f** was also confirmed by analytical and spectral data. The ^{1}H NMR spectra of these compounds, recorded in DMSO-d_6 exhibit the exchangeable signal of a chelate proton (13.2–13.5 ppm), the presence of a benzoxazole for **9f** and a thiazole moiety for **9a–e**, and the signals of an ester group. In the IR spectra, characteristic stretching vibrations for the conjugated nitrile and a carbonyl group were observed as strong bands at 2205–2195 cm^{-1} for the cyano group and 1730–1715 cm^{-1} for the carbonyl group, respectively. Such behaviour of compounds **1e–h** as compared with **1a–d** can be explained in terms of steric hindrance (caused by aryl or *tert*-Bu substituent), arising at the reaction center (heterocyclic nitrogen atom) during the cyclization stage. On the other hand the low basicity of benzoxazol makes the cyclization less likely.

It is noteworthy that, in the reactions of the 2-hetarylacetonitriles with 2-halogen(het)aromatic acid esters compounds of type **9** never have been isolated.[2] In order to obtain the intermediates like **9** for the 2-hetarylacetonitriles **1a–d** we have decided to repeat this reaction under milder conditions.

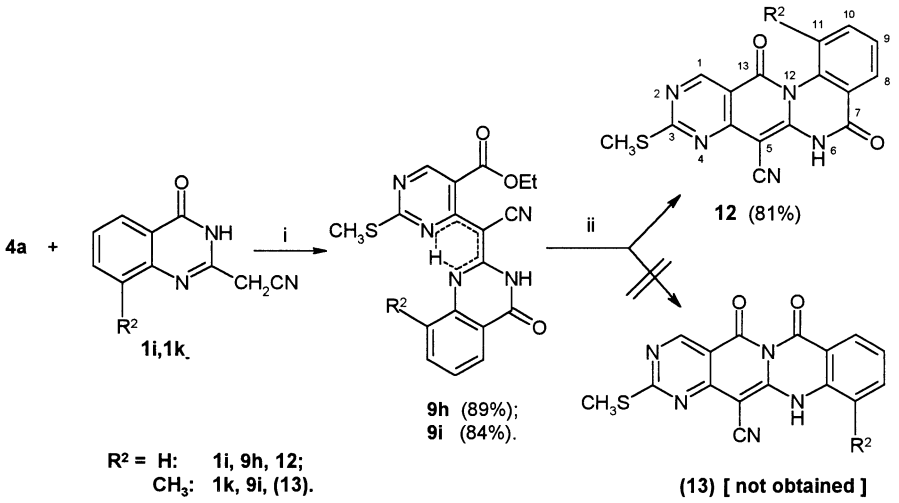
2-Hetarylacetonitriles **1a–d** were allowed to react in the presence of triethylamine, overnight in DMSO (method B) with **4a** at room temperature. The formed condensed pyridopyrimidines **5–7** were isolated by filtration as almost insoluble solids. Only in the case of benzothiazol-2-yl-acetonitrile **1d**, we isolated the intermediate ethyl 4-[benzothiazol-2-yl)-cyano-methyl]-2-alkylsulfanylpyrimidine-5-carboxylate **9g** from the mother liquor in 61% yield (Scheme 4).



Scheme 3.



Scheme 4.



Scheme 5. *Reagent and conditions*: (i) DMSO, Et_3N, 25°C, 24 h; (ii) Dioxane, K_2CO_3, reflux, 2.5–3 h.

The lower reactivity of the benzothiazole in comparison with the pyridyl and benzimidazole derivatives may be due to the lower basicity of benzothiazole. On the other hand, method B appears to be more preferable for the preparation of compounds **9**, due to the more convenient isolation and higher yields.

It became essential to compare the influence of basicity and steric factors on the intramolecular acylation reaction. This goal was reached by using the 2-(4-oxo-3,4-dihydro-2-quinazolinyl)acetonitriles **1i**,**k** as valuable model compounds to study this type of cyclization, because of the presence of two non-equivalent nitrogen atoms in their nucleus. After futile attempts to conduct the reaction of **1i**,**k** with **4a** under method A conditions, we decided to use the step by step methology (method B) (Scheme 5).

When **1i**,**k** were allowed to react in the presence of triethylamine in DMSO with **4a** over night at room temperature the ethyl 4-[(8-R^2-4-oxo-3,4-dihydro-quinazolin-2-yl)-cyano-methyl]-2-methylsulfanylpyrimidine-5-carboxylates **9h**,**i** were formed. The cyclization is now posible at N1 or N3 of the ring, forming either the pyridopyrimidines **12** or **13**. Position N1 is electronically favored, but cyclization to N3 is more preferential due to the steric point of view. We found that the cyclization of **9h** proceeds exclusively at N1 affording product **12**. On the other hand we were not able to cyclize **9i**.

It is beyond doubt, that steric hindrance at N1 is quite considerable if R^2=CH_3. NMR data were used to confirm the angular structure of compound **12**. In the case of linear structure **13** the chemical shifts of the protons in the quinazolin-4(3*H*)-one part of the molecule should not changed significantly in comparison with the starting compounds **9h** or **1i**. In the ^{1}H NMR spectrum of the isolated compound we observed three low field signals: 1H singlet at 9.31 ppm, 1H doublets at 9.12 and 8.54 ppm assigned to the protons at C-1, C-11 and C-8, respectively. Indeed, the signal of H-11 (9.12 ppm) is low field shifted compared with the chemical

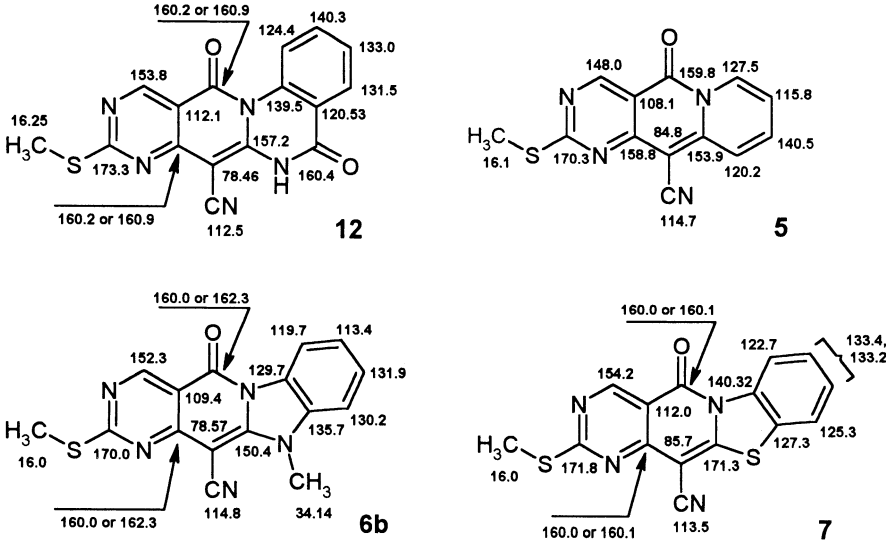


Figure 2. δ Values for ^{13}C NMR signals for compounds **5**, **6b**, **7**, **12**. The signals at 160.2/160.9 for **12**; 160.0/162.3 for **6b**; 160.0/160.1 for **7** could not be unambiguously identified using COSY, NOESY, HSQC and HMBC experiments.

shifts observed for the starting compounds (δ arom-*H* in **1i** and **9h**: 7.7–7.8 ppm). Such a deshielding can be explained by the influence of the carbonyl group if it is closed to the considered proton, and therefore indicating the angular structure **12**.

Hence it appears clear that the cyclization rate of primarily formed products of type **8** depends on both the basicity of heterocyclic fragment and the steric surroundings of the heterocyclic nitrogen atom. However, the way of reaction in the case of compound **9h** (regioselective attack on N1 of the quinazolin-4(3*H*)-one ring) allowed us to suggest that this intramolecular nucleophilic acylation turns out to be more sensitive to the basicity factor.

The total assigments of ^{1}H and ^{13}C NMR spectra of the first representatives of the new heterocyclic systems pyrimido[4′,5′-4,5]pyrido[1,2-*a*]quinazoline **12**, pyrimido-[5,4-*c*]quinolizine **5**, pyrimido[4′,5′-4,5]pyrido[1,2-*a*]-benzimidazole **6b**, pyrimido[4′,5′-4,5]pyrido[2,1-*b*]benzo-thiazole **7** were achieved by the concerted utilization of COSY, NOESY, HSQC and HMBC experiments (Fig. 2).

In conclusion, it is demonstrated that the result of the interaction between 2-hetarylacetonitriles **1** and ethyl 2-alkylsulfanyl-4-chloro-5-pyrimidinecarboxylates **4** depends on both the nature of the heterocycle and the reaction conditions. It has been shown that for some 2-hetarylacetonitriles this reaction offers a simple and convenient method for the synthesis of new condensed pyridopyrimidines. On the other hand we succeeded in isolating for the first time the intermediates **9**, and this confirms the mechanism.

3. Experimental

3.1. General

Melting points were determined using an Electrothermal melting point apparatus and are uncorrected. IR spectra were obtained on a Nicolet impact 400 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-300 or Bruker AVANCE 500 spectrometer. MS were determined on a Varian 212 instrument at 70 eV. Elemental analysis were obtained on a Perkin–Elmer CHN 240 A or 240 B. The following hetarylacetonitriles **1b**,[5] **1c**,[6] **1d**,[7] **1e**,[8] **1f–h**,[9] **1i**[10] and ethyl 2-alkylsulfanyl-4-chloropyrimidine-5-carboxylates[3] were synthesized according to the literature procedures. Other materials were purchased from Aldrich Chemical Company without further purification.

3.2. X-Ray structure determination

$C_{19}H_{15}BrN_4O_2S_2$, FW 272.27, monoclinic space group *P*2(1)/*c*, *Z*=4, *T*=293 K, *a*=7.941 (3), *b*=11.486 (4), *c*=22.315 (9) Å, β=96.79 (3)°, *V*=2021.1 (13) Å^3, D_c=1.562 g/cm^3, *F*(000)=960, graphite monochromated radiation Mo(K_α) with λ=0.71073 Å, μ=2.263 mm^{-1}. The intensities of 3571 reflections (3491 independent, R_{int}=0.036) were measured on a Siemens P3/PC automatic four-cycle diffractometer ($\theta/2\theta$ scan $2<\theta<50°$). Absorption correction was made by semi-empirical method using Ψ-scan (T_{min}=0.2512, T_{max}=0.708). The structure was solved by direct method using SHELX97 program package.[11] Positions of the hydrogen atoms were located from difference maps of electron density and refined using riding model with $U_{iso}=nU_{eq}$ of non-hydrogen atom bonded with hydrogen given (n=1.5 for methyl group and n=1.2 for remaining hydrogen atoms). The structure refined in anisotropic approximation by full-matrix least squares method versus F^2 to wR_2=0.1167 for 3491 reflections (R_1=0.045 for 2306 reflections with $F>4\sigma(F)$, S=1.009). Tables of bond distances and angels, atomic coordinates, and anisotropic thermal parameters for **9c** (CCDC 167934) have been deposited at the Cambrige Crystallographic Data Centre.

3.3. Synthesis

3.3.1. 2-(8-Methyl-4-oxo-3,4-dihydro-2-quinazolyl)acetonitrile 1k. This compound was prepared according to the procedures described in the literature for **1i**, in 73% yield as white solid, mp 227°C; δ_H (300 MHz, DMSO-d_6), 12.45 (1H, broad s, NH), 7.93 (1H, d, *J*=7.91 Hz, 5-H), 7.68 (1H, d, *J*=7.3 Hz, 7-H), 7.39 (1H, dd, *J*=7.91, 7.3 Hz, 6-H), 4.17 (2H, s, CH_2), 2.55 (3H, s, CH_3); δ_C (75.4 MHz, DMSO-d_6) 161.5, 147.2, 146.4, 135.0, 134.9, 126.3, 123.4, 120.9, 115.6, 24.5, 16.8; ν_{max} (potassium bromide) 3190 (NH), 2275 (CN), 1680 (CO) cm^{-1}. (Found: C, 65.97; H, 4.59; N, 21.31. $C_{11}H_9N_3O$ requires C, 66.32; H, 4.55; N, 21.09%).

3.4. Synthesis of compounds 5–7: method A

A mixture of the corresponding 2-hetarylacetonitriles **1** (5 mmol), ethyl 4-chloro-2-methylsulfanyl-5-pyrimidine-carboxylate **4a** (1.16 g, 5 mmol) and K_2CO_3 (0.69 g, 5 mmol) in dry dimethylformamide (20 ml) was refluxed for 1.5–2 h. The reaction mixture was evaporated under reduced pressure, the residue was suspended in water (100 ml) and acidified with acetic acid (2 ml), the residue was collected by filtration, washed with water, dried and recrystallized from dimethylformamide.

3.5. Synthesis of compounds 5, 6: method B

To a solution of the corresponding 2-hetarylacetonitriles **1** (5 mmol), ethyl 4-chloro-2-methylsulfanyl-5-pyrimidine-carboxylate **4a** (1.16 g, 5 mmol) in dry dimethylsulfoxid (10 ml), triethylamine (0.56 g/0.76 ml, 5.5 mmol) was added. After 24 h at room temperature the solid precipitate was isolated by filtration, washed with water, dried and recrystallized from dimethylformamide. Additional crop of **5**, **6** was obtained by adding water (50 ml) to the filtrate. The solid was collected and recrystallized from dimethyl-formamide.

3.5.1. 3-Methylsulfanyl-5-cyano-11-oxo-pyrimido[5,4-*c*]-quinolizine 5. This compound was prepared from pyridin-2-yl-acetonitrile **1a** and **4a** in 92% (method A) and in 88% (method B) as yellow crystals with mp>330°C. δ_H (300 MHz, CF_3COOD) 9.48 (1H, s, H-1), 9.42 (1H, d, *J*=6.89 Hz, H-9), 8.42 (1H, dd, *J*=8.49, 7.55 Hz, H-7), 8.34 (1H, d, *J*=8.49 Hz, H-6), 7.71 (1H, dd, 6.89, 7.55 Hz, H-8), 2.98 (3H, s, SCH_3); ν_{max} (potassium bromide) 2229 (CN), 1710 (CO) cm^{-1}. (Found: C, 58.08;

H, 2.97; N, 20.65. $C_{13}H_8N_4OS$ requires C, 58.20; H, 3.01; N, 20.88%).

3.5.2. 3-Methylsulfanyl-5-cyano-12-oxopyrimido[4′,5′-4,5]pyrido[1,2-*a*]benzimidazole 6a. This compound was prepared from 1*H*-benzimidazol-2-yl-acetonitrile **1b** and **4a** in 85% (method A) and in 83% (method B) as yellow crystals with mp>330°C. δ_H (300 MHz, CF_3COOD) 9.41 (1H, s, H-1), 8.70 (1H, d, *J*=8.2 Hz, H-10), 7.85–7.71 (4H, m, H-8, H-9+H-7), 2.97 (3H, s, SCH_3); ν_{max} (potassium bromide) 2220 (CN), 1699 (CO) cm^{-1}. (Found: C, 58.88; H, 2.97; N, 22.65. $C_{15}H_9N_5OS$ requires C, 58.62; H, 2.95; N, 22.77%).

3.5.3. 3-Methylsulfanyl-6-methyl-5-cyano-12-oxopyrimido[4′,5′-4,5]pyrido[1,2-*a*]benzimidazole 6b. This compound was prepared from 1-methyl-benzimidazol-2-yl-acetonitrile **1c** and **4a** in 88% (method A) and in 77% (method B) as yellow crystals with mp>330°C. δ_H (300 MHz, CF_3COOD) 9.40 (1H, s, H-1), 8.77 (1H, d, *J*=8.2 Hz, H-10), 7.85 (1H, m, H-8), 7.78–7.75 (2H, m, H-9+H-7), 4.46 (3H, s, NCH_3), 2.97 (3H, s, SCH_3); ν_{max} (potassium bromide) 2217 (CN), 1697 (CO) cm^{-1}. (Found: C, 59.64; H, 3.33; N, 21.50. $C_{16}H_{11}N_5OS$ requires C, 59.80; H, 3.45; N, 21.79%).

3.5.4. 3-Methylsulfanyl-5-cyano-12-oxopyrimido[4′,5′-4,5]pyrido[2,1-*b*]benzothiazole 7. This compound was prepared from benzothiazol-2-yl-acetonitrile **1d** and **4a** in 83% (method A) as yellow crystals with mp>330°C. δ_H (300 MHz, CF_3COOD) 9.54 (1H, s, H-1), 9.15 (1H, d, *J*=8.38 Hz, H-10), 8.05 (1H, d, *J*=7.44 Hz, H-7), 7.87 (1H, dd, *J*=8.38, 7.77 Hz, H-9), 7.82 (1H, dd, *J*=7.44, 7.77 Hz, H-8), 3.00 (3H, s, SCH_3); ν_{max} (potassium bromide) 2223 (CN), 1697 (CO) cm^{-1}. (Found: C, 55.29; H, 2.32; N, 16.97. $C_{15}H_8N_4OS_2$ requires C, 55.54; H, 2.49; N, 17.27%).

3.6. Preparation of ethyl 4-[(2-hetaryl)-cyano-methyl]-2-alkylsulfanylpyrimidine-5-carboxylates 9a–d,f: method A

A mixture of the corresponding 2-hetarylacetonitriles **1e–g** (5 mmol), ethyl 4-chloro-2-alkylsulfanyl-5-pyrimidine-carboxylates **4a**,**b** (5 mmol) and K_2CO_3 (0.69 g, 5 mmol) in dry dimethylformamide (20 ml) was refluxed for 1.5–2 h. The reaction mixture was evaporated under reduced pressure, the residue was suspended in water (100 ml) and acidified with acetic acid (2 ml), the residue was collected by filtration, washed with water, dried and recrystallized with charcoal from dioxane.

3.7. Preparation of ethyl 4-[(2-hetaryl)-cyanomethyl]-2-alkylsulfanylpyrimidine-5-carboxylates 9a,h,i: method B

To a solution of the corresponding 2-hetarylacetonitriles **1f**,**i**,**k** (5 mmol) and ethyl 4-chloro-2-alkylsulfanyl-5-pyrimidinecarboxylate **4a** (1.16 g, 5 mmol) in dry dimethylsulfoxid (10 ml) triethylamine (0.56 g/0.76 ml, 5.5 mmol) was added. After 24 h at room temperature, water (100 ml) was added and the mixture acidified with acetic acid (2 ml). The formed residue was collected by filtration, washed with water, dried and recrystallized from dioxane.

3.7.1. Ethyl 4-{[4-(4-chloro-phenyl)-thiazol-2-yl]-cyano-methyl}-2-methylsulfanylpyrimidine-5-carboxylate 9a. This compound was prepared from 4-(4-chloro-phenyl)-thiazol-2-yl-acetonitrile **1f** and **4a** in 69% yield (method A) and 88% (method B) as yellow crystals with mp 199–201°C (dioxane). δ_H (300 MHz, DMSO-d_6) 13.05 (1H, broad s), 7.97–7.89 (4H, m, arom-H), 7.41 (2H, d, *J*=8.53 Hz, arom-H), 4.29 (2H, q, *J*=7.12 Hz, CH_2CH_3), 2.82 (3H, s, SCH_3), 1.31 (3H, t, *J*=7.12 Hz, CH_2CH_3); ν_{max} (potassium bromide) 2203 (CN), 1729 (CO_2Et) cm^{-1}; EIMS: *m*/*z*=430 (M^+). (Found: C, 52.90; H, 3.43; N, 12.94. $C_{19}H_{15}ClN_4O_2S_2$ requires C, 52.96; H, 3.51; N, 13.00%).

3.7.2. Ethyl 2-benzylsulfanyl-4-{[4-(4-chloro-phenyl)-thiazol-2-yl]-cyanomethyl}-pyrimidine-5-carboxylate 9b. This compound was prepared from 4-(4-chloro-phenyl)-thiazol-2-yl-acetonitrile **1f** and **4b** in 64% (method A) yield as yellow crystals with mp 163°C (dioxane). δ_H (300 MHz, DMSO-d_6) 13.05 (1H, broad s), 8.04–7.92 (4H, m, arom-H), 7.52–7.32 (6H, m, arom-H), 4.79 (2H, s, Ph-CH_2), 4.29 (2H, q, *J*=7.12 Hz, CH_2CH_3), 1.31 (3H, t, *J*=7.12 Hz, CH_2CH_3); ν_{max} (potassium bromide) 2203 (CN), 1729 (CO_2Et) cm^{-1}; EIMS: *m*/*z*=506 (M^+). (Found: C, 59.43; H, 3.70; N, 10.90. $C_{25}H_{19}ClN_4O_2S_2$ requires C, 59.22; H, 3.78; N, 11.05%).

3.7.3. Ethyl 4-{[4-(4-bromo-phenyl)-thiazol-2-yl]-cyano-methyl}-2-methylsulfanylpyrimidine-5-carboxylate 9c. This compound was prepared from 4-(4-bromo-phenyl)-thiazol-2-yl-acetonitrile **1g** and **4a** in 66% yield (method A) as yellow crystals with mp 205°C (dioxane). δ_H (300 MHz, DMSO-d_6) 13.05 (1H, broad s), 7.98–7.92 (4H, m, arom-H), 7.60 (2H, d, *J*=8.52 Hz, arom-H), 4.29 (2H, q, 7.12 Hz, CH_2CH_3), 2.80 (3H, s, SCH_3), 1.31 (3H, t, *J*=7.12 Hz, CH_2CH_3); ν_{max} (potassium bromide) 2198 (CN), 1725 (CO_2Et) cm^{-1}; EIMS: *m*/*z*=476 (M^++1). (Found: C, 48.01; H, 3.24; N, 11.44. $C_{19}H_{15}BrN_4O_2S_2$ requires C, 48.01; H, 3.18; N, 11.79%).

3.7.4. Ethyl 2-benzylsulfanyl-4-{[4-(4-bromophenyl)-thiazol-2-yl]-cyanomethyl}-pyrimidine-5-carboxylate 9d. This compound was prepared from 4-(4-bromo-phenyl)-thiazol-2-yl-acetonitrile **1g** and **4b** in 61% yield (method A) as yellow crystals with mp 165°C (dioxane). δ_H (300 MHz, DMSO-d_6) 13.05 (1H, broad s), 8.04–7.92 (4H, m, arom-H), 7.52–7.32 (6H, m, arom-H), 4.74 (2H, s, Ph-CH_2), 4.27 (2H, q, *J*=7.12 Hz, CH_2CH_3), 1.30 (3H, t, *J*=7.12 Hz, CH_2CH_3); ν_{max} (potassium bromide) 2203 (CN), 1723 (CO_2Et) cm^{-1}; EIMS: *m*/*z*=552 (M^++1). (Found: C, 54.28; H, 3.42; N, 10.24. $C_{25}H_{19}BrN_4O_2S_2$ requires C, 54.45; H, 3.47; N, 10.16%).

3.7.5. Ethyl 4-[(benzoxazol-2-yl)-cyanomethyl)]-2-alkyl-sulfanylpyrimidine-5-carboxylate 9f. This compound was prepared from benzoxazol-2-yl-acetonitrile **1e** and **4a** in 57% yield (method A) as yellow crystals with mp 239–241°C (dioxane). δ_H (300 MHz, DMSO-d_6) 8.82 (1H, s, pyrim-H), 7.68 (1H, m, Ar-H), 7.60 (1H, m, arom-H), 7.34 (2H, m, arom-H), 4.31 (2H, q, *J*=7.10 Hz, CH_2CH_3), 2.53 (3H, s, SCH_3), 1.33 (3H, t, *J*=7.10 Hz, CH_2CH_3); ν_{max} (potassium bromide) 2205 (CN), 1715 (CO_2Et) cm^{-1}; EIMS: *m*/*z*=354 (M^+). (Found: C, 57.54; H, 3.96 N, 15.97. $C_{17}H_{14}N_4O_3S$ requires C, 57.62; H, 3.98; N, 15.81%).

3.7.6. Ethyl 4-[(4-oxo-3,4-dihydro-quinazolin-2-yl)-cyanomethyl]-2-methylsulfanyl-pyrimidine-5-carboxylate 9h. This compound was prepared from (4-oxo-3,4-dihydro-quinazolin-2-yl)-acetonitrile **1i** and **4a** in 89% yield (method B) as pale yellow crystals with mp 232°C (dioxane). δ_H (300 MHz, DMSO-d_6) 13.80 (1H, broad s), 12.10 (1H, broad s), 8.50 (1H, s, pyrimid-H), 7.99 (1H, d, J=7.8 Hz, arom-H), 7.79 (2H, m, arom-H), 7.4 (1H, m, arom-H), 4.32 (2H, q, J=7.12 Hz, CH_2CH_3), 2.67 (3H, s, SCH_3), 1.33 (3H, t, J=7.12 Hz, CH_2CH_3); ν_{max} (potassium bromide) 2203 (CN), 1723 (CO_2Et), 1716 (CONH) cm^{-1}; EIMS: m/z=381 (M^+). (Found: C, 56.64; H, 3.98; N, 18.10. $C_{18}H_{15}N_5O_3S$ requires C, 56.68; H, 3.96; N, 18.36%).

3.7.7. Ethyl 4-[(8-methyl-4-oxo-3,4-dihydro-quinazolin-2-yl)-cyanomethyl]-2-methylsulfanyl-5-pyrimidinecarboxylate 9i. This compound was prepared from (8-methyl-4-oxo-3,4-dihydro-quinazolin-2-yl)-acetonitrile **1k** and **4a** in 84% yield (method B) as pale yellow crystals with mp 254°C (dioxane). δ_H (300 MHz, DMSO-d_6) 13.80 (1H, broad s), 12.00 (1H, broad s), 8.59 (1H, s, pyrimid-H), 7.90 (1H, d, J=7.8 Hz, arom-H), 7.72 (1H, m, arom-H), 7.45 (1H, m, arom-H), 4.31 (2H, q, J=7.12 Hz, CH_2CH_3), 2.63 (3H, s, SCH_3), 2.57 (3H, s, Ar-CH_3), 1.33 (3H, t, J=7.12 Hz, CH_2CH_3); ν_{max} (potassium bromide) 2203 (CN), 1729 (CO_2Et), 1710 (CONH) cm^{-1}; EIMS: m/z=395 (M^+). (Found: C, 57.60; H, 4.29; N, 17.77. $C_{19}H_{17}N_5O_3S$ requires C, 57.71; H, 4.33; N, 17.71%).

3.7.8. Ethyl 4-[(4-*tert*-butyl-thiazol-2-yl)-cyanomethyl]-2-methylsulfanylpyrimidine-5-carboxylate 9e. To a solution of 4-*tert*-butyl-thiazol-2-yl-acetonitrile **1h** (0.9 g, 5 mmol) and ethyl 4-chloro-2-methylsulfanyl-5-pyrimidinecarboxylate **4a** (1.16 g, 5 mmol) in dry dimethylsulfoxid (10 ml), triethylamine (0.56 g/0.76 ml, 5.5 mmol) was added. After 24 h at room temperature, water (100 ml) was added and the mixture acidified with acetic acid (2 ml). The mixture was extracted with EtOAc (3×20 ml), the combined organic layers were washed with water (2×50 ml), and dried over magnesium sulfate. After evaporation of the solvent the residue was recrystallized from ethanol yielding 1.41 g (75%) **9e** as yellow crystals with mp 148°C. δ_H (300 MHz, DMSO-d_6) 13.30 (1H, broad s), 8.25 (1H, s, pyrim-H), 6.98 (1H, s, thiazole-H), 4.28 (2H, q, J=7.10 Hz, CH_2CH_3), 2.72 (3H, s, SCH_3), 1.33–1.22 (12H, m, CH_2CH_3 and $3CH_3$); ν_{max} (potassium bromide) 2203 (CN), 1727 (CO_2Et) cm^{-1}. (Found: C, 54.14; H, 5.47; N, 14.89. $C_{17}H_{20}N_4O_2S_2$ requires C, 54.23; H, 5.35; N, 14.88%).

3.7.9. Ethyl 4-[(benzothiazol-2-yl)-cyanomethyl)]-2-methylsulfanylpyrimidine-5-carboxylate 9g. To a solution of benzothiazol-2-yl-acetonitrile **1d** (0.87 g, 5 mmol) and ethyl 4-chloro-2-methylsulfanyl-5-pyrimidinecarboxylate **4a** (1.16 g, 5 mmol) in dry dimethylsulfoxid (10 ml), triethylamine (0.56 g/0.76 ml, 5.5 mmol) was added. After 24 h at room temperature the solid precipitate was isolated by filtration, washed with water and dried, yielding 0.32 g (20%) **7**. To the filtrate water (100 ml) was added and the mixture acidified with acetic acid (2 ml). The formed precipitate was collected by filtration, washed with water, dried and recrystallized from dioxane. 1.13 g (61%) **9g** were obtained as yellow crystals. Mp 197–199°C. δ_H (300 MHz, DMSO-d_6) 13.20 (1H, broad s), 8.51 (1H, s, pyrim-H), 7.99 (1H, d, J=7.8 Hz, arom-H), 7.73 (1H, d, J=8.0 Hz, arom-H), 7.51 (1H, dd, J=8.0, 7.51 Hz, arom-H), 7.35 (1H, dd, J=7.8, 7.51, arom-H), 4.35 (2H, q, J=7.11 Hz, CH_2CH_3), 2.72 (3H, s, SCH_3), 1.37 (3H, t, J=7.11 Hz, CH_2CH_3); ν_{max} (potassium bromide) 2198 (CN), 1723 (CO_2Et) cm^{-1}; EIMS: m/z=370 (M^+). (Found: C, 55.10; H, 3.73; N, 15.34. $C_{17}H_{14}N_4O_2S_2$ requires C, 55.12; H, 3.81; N, 15.12%).

3.7.10. 3-Methylsulfanyl-5-cyano-pyrimido[4′,5′-4,5]-pyrido[1,2-*a*]quinazoline-7,13-dion 12. A mixture of ethyl 4-[(4-oxo-3,4-dihydro-quinazolin-2-yl)-cyano-methyl]-2-methylsulfanylpyrimidine-5-carboxylate **9h** (0.76 g, 2 mmol) and K_2CO_3 (0.55 g, 4 mmol) in dry dioxane (30 ml) was refluxed for 2.5 h. The reaction mixture was evaporated under reduced pressure, the residue was suspended in water (100 ml) and the mixture acidified with conc. HCl (3 ml), the precipitate was collected by filtration, washed with water and acetone yielding 0.54 g (81%) **12** as a white solid with mp>330°C. δ_H (300 MHz, CF_3COOD) 9.31 (1H, s, H-1), 9.12 (1H, d, J=8.87 Hz, H-11), 8.54 (1H, d, J=7.86 Hz, H-8), 8.01 (1H, dd, J=8.87, 7.96 Hz, H-10), 7.85 (1H, dd, 7.86, 7.96 Hz, H-9), 2.99 (3H, s, SCH_3); ν_{max} (potassium bromide) 2223 (CN), 1710 (CO) cm^{-1}. (Found: C, 57.26; H, 2.69; N, 20.66. $C_{16}H_9N_5O_2S$ requires C, 57.31; H, 2.71; N, 20.88%).

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