Solvent-free synthesis and structural characterization of azolyl-substituted pyrimidines

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Base-catalyzed trimerization of *N*-cyanomethylazoles under pressure and in solvent-free conditions afforded 4-amino-2,6-bis(azol-1-ylmethyl)-5-(azol-1-yl)pyrimidines (**1**–**3**) in 33–67% yields. The structures of these compounds was determined by a combination of NMR techniques and X-ray crystallography. The 4-amino groups show a restricted rotation around the C–N bond; the free energy of activation for this process was determined by variable temperature experiments. In the crystal structure of the pyrazol-1-yl derivative, the amino group shows a distorted planar geometry in both independent molecules and acts as a double hydrogen bond donor towards two of the three pyrazole rings, forming ribbons of $R_2^2(10)$ rings.

The importance of 4-aminopyrimidine derivatives is due to the presence of this structural motif in many naturally occurring compounds, for instance cytosine in the structure of nucleic acids. Within this context, numerous 4-aminopyrimidines have been described and some of these compounds are antibiotics, for instance bacimethrin, while others are active against yeast and bacteria or, like phleomycin and bleomycin, show antineoplastic activity.[1] Moreover, the structure of the 4-aminopyrimidine unit allows the formation of bimolecular cyclic hydrogen-bonded motifs in organic crystal structures. A recent publication[2] describes the high occurrence of this motif in the Cambridge Structural Database.[3]

Crystal engineering is recognised today as an important field of supramolecular chemistry having a similar rigor and strategy as that of synthetic methodologies.[4–6] An efficient supramolecular synthetic methodology requires a good knowledge of the strength and directional characteristics of intermolecular interactions, which can be hydrogen bonds, π-interactions, complexation of metals and combinations of these interactions.[7] As far as aminopyrimidines are concerned, hydrogen bonds have been used in intermolecular self-assemblies with cyanuric and barbituric acid derivatives,[8,9] as well as in the design of receptors for oligonucleotides and carbohydrates.[10,11]

In this paper, we describe the preparation and structural characterisation of azolyl 4-aminopyrimidines. These compounds show interesting structures for inter- and intramolecular hydrogen-bonding motifs and also for metal complexation, which may lead to new structures with potential applications in crystal engineering and molecular recognition.

Results and discussion

Cyclotrimerization of aliphatic nitriles to 4-aminopyrimidines has been performed by basic catalysis with an alkoxide in the corresponding alcohol under pressure in a sealed tube.[12–14] We envisaged the synthesis of azolylpyrimidines **1**–**3** by cyclotrimerization of azolylacetonitriles **4**–**6** in solvent-free conditions (Scheme 1).

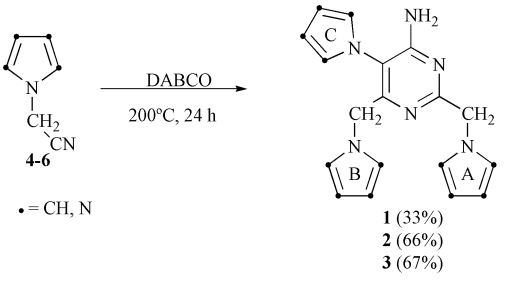
The starting azolylacetonitriles were synthesised by alkylation of the corresponding azole (**7**–**9**) with bromoacetonitrile using sodium hydride as the base in THF or, alternatively, employing solid-liquid phase-transfer catalysis in the absence of solvent. The choice of one or other methodology depended on the azole (Scheme 2).

Although the cyclotrimerisations were performed in a closed vessel, the absence of solvent permitted the use of a milder base, such as an amine (DABCO) instead of an alkoxide, and markedly reduced the risk of overpressure and explosion.

The structures of these pyrimidine derivatives were established by ^{1}H and ^{13}C NMR spectroscopies as well as X-ray crystallography. This latter technique was used in the case of **1**, because suitable crystals were obtained for the X-ray analysis only for this compound.

X-Ray crystallographic study

Selected intra- and intermolecular parameters of **1** are given in Table 1 according to the numbering scheme depicted in Fig. 1.



1: Pyrazole, 2: Imidazole, 3: 1,2,4-Triazole.

Scheme 1

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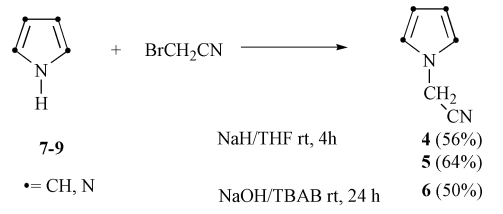


Scheme 2

Inspection of the torsion angles shows a change in the disposition of the pyrazole A with respect to the pyrimidine ring, that is the conformation around the C2–C12A bond, in both independent molecules. In addition, the greatest differences in the external angles at C2 are a consequence of the lower N1–C2–C12A–N7A torsion angle in molecule 1 and also of the weak interactions in which this pyrazole is involved (Table 1).

Some degree of delocalisation has been observed within the pyrimidine ring although it presents the same pattern of bond distances and angles as the 23 6-aminopyrimidine structures (criteria: $R < 0.10$, neither disorder nor metals and no diamino and triamino derivatives) retrieved from the Cambridge Structural Database.[3] Discrepancies in the *ipso* C atoms of the pyrimidine, mainly at C4 and C5, could be due to the electronic properties of the substituents.

The pyrazole substituents, lying on both sides of the central ring (A on one side *vs.* B, C on the other), prevent $NH_2\cdots N$ hydrogen-bonding interactions with the N atoms of the pyrimidine ring in contrast to what happens in almost all of the retrieved compounds. Both amino groups adopt a distorted planar hybridisation (Table 1).

The two independent molecules are hydrogen-bonded in a similar way as far as the $NH_2\cdots N$ contacts are concerned. The interactions of the amino groups with two pyrazole N8 atoms, labelled as B and C, result in the formation of ribbons built from $R_2^2(10)$ rings[15] whose propagation occurs by unit cell translations along the *c* axis (labels a–d in Table 1 and dotted lines inFig. 2). Ribbons, related by a twofold-screw axis, are held together into corrugated sheets by weak C–$H\cdots N/\pi$ interactions[16] where pyrazole A in molecule 1 is involved in three donor-acceptor interactions while pyrazole A in molecule 2 only accepts an interaction (labels e–g in Table 1 and dashed lines in Fig. 2). Centrosymmetrical sheets are further connected by C–$H\cdots\pi$ contacts, involving both pyrimidines and the pyrazole A of molecule 2, producing a three-dimensional network (labels h, i and j, respectively, in Table 1). All weak C–$H\cdots N/\pi$ interactions (labels e–j, Table 1) display distances in the expected range[16] and the donors are pointed towards the N lone pair of pyrazoles A and to the midpoint of the pyrimidines and pyrazoles A. The $R_2^2(10)$ ring is analogous to one of the most frequent 24 cyclic hydrogen-

Table 1 Selected geometrical parameters (Å, °). CP and CA represent the centroids of the pyrimidine and pyrazole ring A while Σα corresponds to the sum of the angles around the N13 amino group. Data retrieved from the CSD are followed by the standard deviation of the sample

	1	**2**	CSD
N1–C2	1.326(4)	1.336(4)	1.331(9)
N3–C4	1.348(4)	1.350(4)	1.343(9)
C5–C6	1.415(4)	1.409(4)	1.415(16)
C2–N3	1.338(4)	1.323(4)	1.335(13)
C4–C5	1.370(4)	1.371(4)	1.368(16)
C6–N1	1.343(4)	1.344(4)	1.348(13)
N13–C6	1.339(4)	1.341(4)	1.335(11)
Σα	357(5)	355(5)	359(1)
C6–N1–C2	117.0(3)	116.6(3)	117.3(13)
C2–N3–C4	115.5(3)	115.6(3)	115.2(14)
C4–C5–C6	117.7(3)	118.6(3)	116.2(12)
N1–C6–N13	117.8(3)	118.4(3)	
N1–C2–C12A	118.6(3)	115.7(3)	
N1–C2–N3	127.3(3)	127.8(3)	126.6(16)
N3–C4–C5	122.3(3)	121.6(3)	124.1(18)
C5–C6–N1	120.2(3)	119.7(3)	120.5(9)
N3–C4–C12B	114.0(3)	116.5(3)	
C4–C5–N7C	122.4(3)	121.2(3)	
N1–C2–C12A–N7A	26.4(4)	−81.6(4)	
N3–C4–C12B–N7B	57.0(4)	55.4(4)	
C4–C5–N7C–N8C	77.1(4)	78.4(4)	
C2–C12A–N7A–N8A	−94.6(4)	−103.1(3)	
C4–C12B–N7B–N8B	80.6(4)	92.8(4)	

Hydrogen interactions: D–H···A[a]	D–H	D···A	H···A	D–H···A
a: N13–H131(Mol.1)···N8B(Mol.2)	0.83(4)	3.189(5)	2.69(4)	120(3)
b: N13–H132(Mol.1)···N8C(Mol.2)	0.84(4)	3.000(2)	2.17(4)	169(4)
c: N13–H131(Mol.2)···N8B(Mol.1) [i]	0.88(4)	3.112(5)	2.53(5)	125(3)
d: N13–H132(Mol.2)···N8C(Mol.1) [i]	0.92(4)	3.020(4)	2.10(4)	178(4)
e: C10B–H10B(Mol.1)···N8A(Mol.1) [ii]	0.99(5)	3.380(5)	2.67(5)	129(4)
f: C11A–H11A(Mol.1)···N8A(Mol.2) [iii]	0.99(5)	3.472(5)	2.65(5)	140(4)
g: C11B–H11B(Mol.2)···CA(Mol.1) [iv]	1.01(6)	3.527(4)	2.75(7)	134(5)
h: C10C–H10C(Mol.1)···CP(Mol.1) [v]	0.97(6)	3.498(5)	2.70(5)	139(4)
i: C10C–H10C(Mol.2)···CP(Mol.2) [vi]	0.91(5)	3.491(4)	2.75(7)	134(5)
j: C11B–H11B(Mol.1)···CA(Mol.2) [vii]	0.90(5)	3.552(4)	2.72(5)	154(5)

[a] Symmetry operations are: (*i*) $x, y, 1+z$; (*ii*) $x, y, -1+z$; (*iii*) $1/2-x, -1/2+y, 1-z$; (*iv*) $1/2-x, 1/2+y, 1-z$; (*v*) $1/2+x, 1/2-y, z$; (*vi*) $-1/2+x, 1/2-y, z$; (*vii*) $1/2+x, 1/2-y, -1+z$.

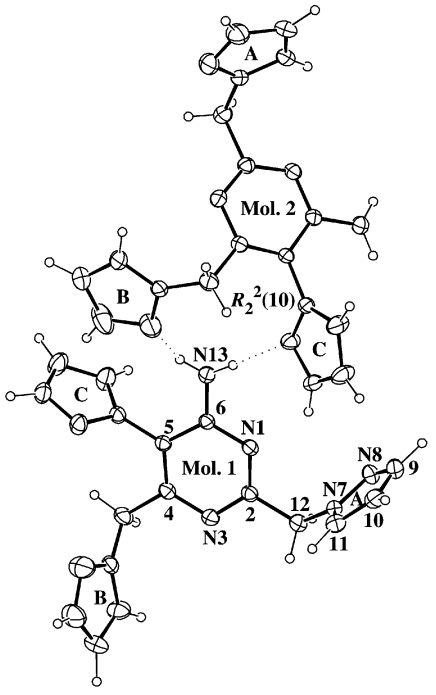


Fig. 1 Asymmetric unit of **1** showing the numbering scheme. Displacement parameters are drawn at the 30% level. Dotted lines indicate hydrogen bonds

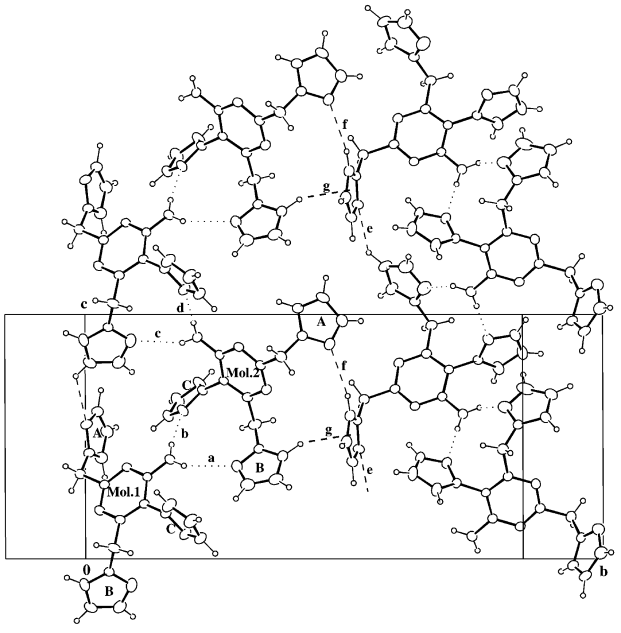


Fig. 2 A partial packing diagram of **1** showing one sheet formed by twofold-screw-related hydrogen-bonded ribbons. N–H···N hydrogen bonds, within the ribbons, are indicated by dotted lines (labelled a–d in Table 1) whereas C–H···N/π contacts connecting ribbons are indicated by dashed lines (labelled e–g in Table 1).

bonded motifs in organic structures[2] (D–H···A; D, A = O or N) for which the acceptor atoms are two alternating oxygen atoms of the 18-crown-6 molecule in its complexes with RNH_2.

NMR spectroscopy

The NMR data (chemical shifts and coupling constants) of **1**–**3** are collected in Table 2. These compounds are characterised by the presence of three similar but not identical azole units. The ^{1}H NMR spectra were assigned by a combination of NOE difference spectroscopy and homonuclear proton-proton and heteronuclear carbon-proton correlation experiments.

Assignment of azoles in the 2 position was performed by NOE difference spectroscopy. Saturation of the CH_2-2 group led to NOE effects with protons of ring A: 5-H in the pyrazole and the 1,2,4-triazole (compounds **1** and **3**, respectively) and 2-H and 5-H in the imidazole of compound **2** (Fig. 3).

Saturation of the CH_2-6 group gave rise to a similar NOE effect but in this case, with the protons of pyrazoles B and C, in positions 6 and 5 of the pyrimidine. The assignment of the azoles in positions 5 (ring C) and 6 (ring B) was performed by considering the response to the saturation of CH_2-6, with the effect being more marked in the 6-azole unit (Fig. 3), and taking into account that the proton in azole-5, which is directly attached to the pyrimidine ring, should be deshielded by the anisotropy of the aromatic ring.

Once the nature of the 5-H protons had been ascertained, the remaining protons were assigned through H,H correlation experiments. In compound **3**, where correlations were not observed, the 3-H protons were assigned by comparison with compounds **1** and **2**. Subsequently, the ^{13}C NMR signals of the azole substituents were assigned by C,H correlation experiments. The ^{13}C NMR signals of the pyrimidine ring were assigned by considering the effect of the substituents and the multiplicities in the coupled spectra. In this respect, C-2 and C-6 appear as triplets by virtue of two-bond coupling with the CH_2 groups, while C-4 and C-5 appear as singlets.

The NH_2 groups in each case exhibit a very broad signal at $\delta \sim 7$ at 293 K in DMSO-d_6. Increasing the temperature produces a sharpening of the signal up to 373 K and a high-field shift due to the increased mobility and exchange rate at high temperature (Table 3). A plot of the chemical shift against temperature gives a very good linear correlation (Fig. 4).

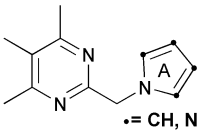
The NMR spectra of **1** and **3** were recorded in $CDCl_3$ in order to show the variation of the chemical shift of the NH_2 signal at low temperature. Unfortunately, the low solubility of **2** in apolar solvents prevented the acquisition of spectra for this compound. The NMR spectra of **1** and **3** at 293 K both show a broad singlet at $\delta = 5.63$. When the NMR spectra were recorded at 213 K, two broad singlets were observed at $\delta = 6.32$ and 5.47 for **1** and $\delta = 5.79$ and 5.38 for **3**. Variable temperature experiments allowed the determination of the coalescence temperatures as well as the corresponding free energies of activation (Table 4).

It is interesting to note that, as a consequence of the variation of the NH chemical shift with temperature, the coalescence is not produced at the mid-point between the two signals. Indeed, the signal at higher chemical shift shows a high-field shift upon increasing the temperature, while no significant changes with temperature are observed for the signal with the lower chemical shift until coalescence is reached (Table 5 and Fig. 5).

Restricted rotation in aminotriazines and -pyrimidines occurs by delocalisation of the nitrogen lone pair in the azine ring and this phenomenon has been studied by lineshape analysis,[18] ^{15}N[19] and ^{17}F NMR spectroscopy.[20] However, to the best of our knowledge, this is the first time that the coalescence of the signals for the NH_2 group in 4-aminopyrimidines has been detected. In cytosine, the free energy of activation has been determined by lineshape analysis and Hoffman–Forsen analysis, in the cytosine-guanine base pair, showing that hydrogen bonding impedes the rotation of one amino group in cytosine but not in guanine.[21] In compound **1**, and probably in compound **3**, rotation of the NH_2 group should be impeded by the intramolecular hydrogen bond with the nitrogen lone pair of N-2 in ring C.

In conclusion, solvent-free conditions provide an efficient route to 4-amino-2,6-bis(azol-1-ylmethyl)-5-(azol-1-yl)pyrimidines. The structures have been elucidated and the free energies of activation for the rotation of the 4-amino group have been

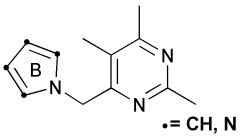
Table 2 NMR spectra of azolylpyrimidines **1**–**3** in DMSO solvent (δ, J in Hz)



1: Pyrazole, 2: Imidazole, 3: 1,2,4-Triazole.

		H-2	H-3	H-4	H-5	CH_2-2
1	δ	—	7.40 (d)	6.25 (dd)	7.71 (d)	5.21 (s)
	J		1.81	2.27	2.27	
				1.81		
2	δ	7.63 (br s)	—	6.88 (t)	7.10 (t)	5.08 (s)
	J			0.98	1.22	
3	δ		7.93 (s)	—	8.29 (s)	5.33 (s)

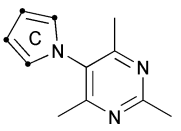
		C-2	C-3	C-4	C-5	CH_2-2
1	δ	—	138.79 (ddd)	105.19 (dt)	131.04 (dm)	57.00 (t)
	^1J		184.32	175.76	187.88	140.76
	^nJ		8.39	9.06		
	^nJ		6.15			
2	δ	137.85 (dm)	—	128.16 (dt)	120.21 (ddd)	51.73 (t)
	^1J	206.48		187.12	193.39	140.76
	^nJ			11.20	16.60	
	^nJ				3.64	
3	δ	—	151.33 (dd)	—	153.33 (dd)	54.04 (t)
	^1J		206.23		208.49	142.02
	^nJ		11.84		12.09	



		H-2	H-3	H-4	H-5	CH_2-6
1	δ	—	7.35 (d)	6.17 (dd)	7.51 (d)	4.80 (s)
	J		1.81	2.27	2.27	
				1.81		
2	δ	7.36 (br s)	—	6.83 (t)	6.89 (t)	4.59 (s)
	J			0.98	1.00	
3	δ		7.87 (s)	—	8.26 (s)	4.91 (s)

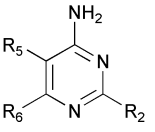
		C-2	C-3	C-4	C-5	CH_2-6
1	δ	—	138.68 (ddd)	105.19 (dt)	130.98 (ddd)	51.22 (t)
	^1J		183.82	175.76	191.07	141.01
	^nJ		7.75	9.06	9.21	
	^nJ		5.75		4.60	
2	δ	137.63 (dm)	—	128.00 (dt)	119.84 (ddd)	45.93 (t)
	^1J	204.43		186.78	189.86	141.51
	^nJ			11.04	16.62	
	^nJ				3.13	
3	δ	—	144.96 (dd)	—	151.33 (dd)	48.88 (t)
	^1J		213.32		206.23	143.02
	^nJ		7.47		11.84	

Table 2 (continued)



		H-2	H-3	H-4	H-5	NH
1	δ	—	7.81 (d)	6.55 (dd)	7.96 (d)	7.3 (brs)
	J		1.82	2.49	2.49	
				1.82		
2	δ	7.25 (t)	—	7.18 (t)	7.26 (t)	7.2 (brs)
	J	1.00		0.98	1.22	
3	δ		8.49 (s)	—	8.75 (s)	7.3 (brs)

		C-2	C-3	C-4	C-5
1	δ	—	141.74 (ddd)	107.32 (dt)	132.97 (dd)
	^1J		174.30	172.74	181.93
	^nJ		8.09	8.90	9.42
	^nJ		6.74		4.59
2	δ	138.12 (ddd)	—	130.01 (dt)	120.68 (ddd)
	^1J	211.52		188.98	192.88
	^nJ	10.55		11.08	16.87
	^nJ	6.59			3.30
3	δ	—	145.16 (dd)	—	146.58 (dd)
	^1J		212.63		215.80
	^nJ		7.58		7.3



		C-2	C-4	C-5	C-6
1	δ	164.11 (t)	160.32 (s)	116.15 (s)	157.92 (t)
	^2J	6.08			5.23
2	δ	164.34 (t)	160.67 (s)	112.54 (s)	158.61 (t)
	^2J	7.54			4.51
3	δ	164.22 (t)	160.24 (s)	112.68 (s)	157.98 (t)
	^2J	6.12			4.38

determined. These compounds show interesting structures with possible application in crystal engineering. In compound **1**, the presence of the pyrazole groups prevents the formation of the classical hydrogen-bond interactions in 4-aminopyrimidines. On the contrary, intermolecular hydrogen bonds with two pyrazole units form ribbons connected by C–H···N/π contacts to produce a three-dimensional network. Moreover, the nitrogen lone pairs of pyrazoles A and B and that of pyrimidine N-1 can adopt a conformation so as to produce a tripod ligand with possible applications in coordination chemistry. Work in this area is currently in progress in our group.

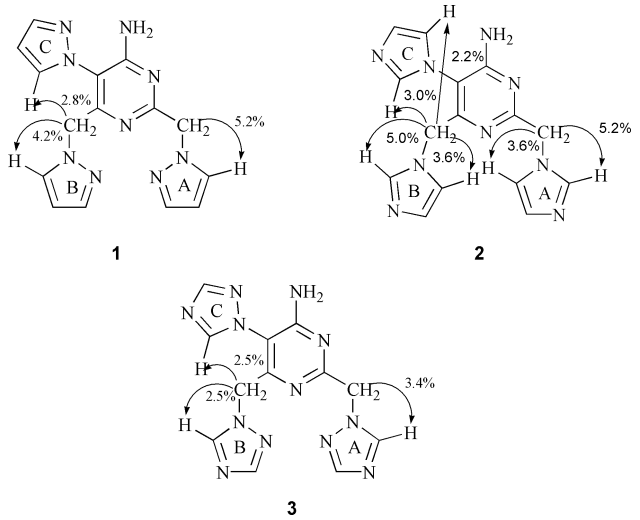


Fig. 3 Selected NOE for compounds **1**–**3**.

Table 3 NH_2 chemical shift variation at high temperature (solvent DMSO-d_6)

T/K	1	2	3
313	6.808	7.068	7.181
333	6.724	6.875	7.109
353	6.63	6.792	7.018
373	6.536	6.681	6.934
393	6.446	6.58	6.826
413	6.355	6.486	6.734
433	6.267	6.369	6.637
453	6.2	6.287	6.548

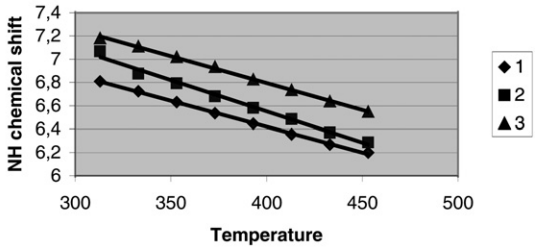


Fig. 4 NH_2 chemical shift variation at high temperature (solvent DMSO-d_6).The fits to the lines are: $y = -0.0044x + 8.20$, $R^2 = 0.999$ for **1**; $y = -0.0054x + 8.70$, $R^2 = 0.991$ for **2**; $y = -0.0046x + 8.64$, $R^2 = 0.999$ for **3**.

Table 4 Coalescence temperatures and calculated $\Delta G^{\ddagger}$ for compounds **1** and **3**.[17]

	1	**3**
T_c/K	250	245
ν_A	1896.094	1735.81
ν_B	1639.73	1699.675
$\Delta\nu$	256.364	36.135
$\Delta G^{\ddagger}$/kJ mol^{-1}	48 ± 1	51 ± 1

Experimental

Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 299.94 and 75.429 MHz, respectively, on a Varian Unity 300 spectrometer. Chemical shifts are reported in ppm (δ) using Me_4Si as the reference, and coupling constants J are given in Hz. The IR spectra were obtained with a Nicolet-550 FTIR spectrophotometer. Flash column chromatography was performed on silica gel 60 (Merck, 230–400 mesh). The cyanomethylazoles were distilled using a Kugelrohr apparatus.

Syntheses

Synthesis of 1-cyanomethylazoles. To a solution of the appropriate azole (50 mmol) in dry THF (35 mL) was added sodium hydride (60% suspension in mineral oil, 2 g, 50 mmol) under an argon atmosphere. The mixture was stirred until the evolution of hydrogen had finished. A solution of bromoacetonitrile (3.5 mL, 50 mmol) in dry THF (10 mL) was added dropwise. The reaction mixture was stirred at room temperature for 4 h. The solvent was evaporated *in vacuo* and the residue was extracted with dichloromethane (3×15 mL), filtered and concentrated. The crude product was washed with hexane (2×5 mL) and distilled under reduced pressure.

Table 5 NH_2 chemical shift variation at low temperature for compound **1** (solvent $CDCl_3$)

T/K	NH-1	NH-2
213	6.323	5.468
223	6.095	5.518
233	5.939	5.547
243	5.767	5.556
248	5.700	5.579
253	5.632	5.632

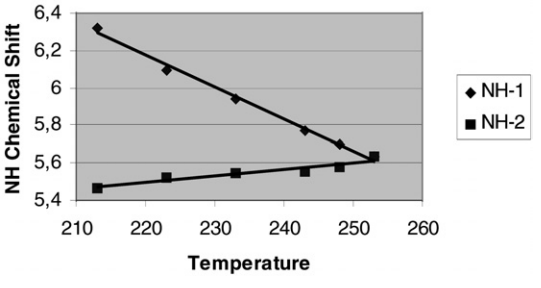


Fig. 5 NH_2 chemical shift variation at low temperature for compound **1**, solvent $CDCl_3$. The fits to the lines are: $y = -0.017x + 9.92$, $R^2 = 0.993$ for **NH-1**; $y = 0.0034x + 4.74$, $R^2 = 0.920$ for **NH-2**.

*1-Cyanomethylpyrazole (**4**).* Yield (3 g, 56%), b.p. 75 °C (oven temperature)/0.1 mmHg. IR (neat): 2258, 1518, 1394, 1289 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.09 (s, 2H, CH_2), 6.35 (dd, $J = 2.44$, 1.95 Hzm 1H, 4-H), 7.53 (d, $J = 2.44$ Hz, 1H, 5-H), 7.58 (d, $J = 1.95$ Hz, 1H, 3-H). ^{13}C NMR ($CDCl_3$): δ 39.36 (CH_2), 107.48 (4-C), 114.02 (CN), 129.81 (5-C), 141.14 (3-C).

*1-Cyanomethylimidazole (**5**).* Yield (3.4 g, 64%), b.p. 112 °C (oven temperature)/0.5 mmHg. IR (neat): 2260, 1504, 1422, 1286 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 4.97 (s, 2H, CH_2), 7.06 (d, $J = 1.22$ Hz, 1H, 5-H), 7.13 (d, $J = 1.46$ Hz, 1H, 4-H), 7.58 (br s, 1H, 2-H). ^{13}C NMR ($CDCl_3$): δ 34.23 (CH_2), 113.70 (CN), 118.85 (4-C), 130.61 (5-C), 136.89 (2-C).

*1-Cyanomethyltriazole (**6**).* 1,2,4-Triazole (3.45 g, 50 mmol), finely ground potassium hydroxide (3.1 g, 55 mmol) and tetrabutylammonium bromide (TBAB; 0.81 g, 2.5 mmol) were mixed and the reaction vessel submerged in an ultrasonic cleaning bath (50 W, 200 MHz) for 15 min. Bromoacetonitrile (3.48 mL, 50 mmol) was added at 0 °C and the reaction was stirred at room temperature for 24 h. The product was extracted with dichloromethane (3×25 mL) and filtered through Florisil. The solvent was evaporated and the mixture was distilled under reduce pressure using a Kugelrohr apparatus to give the desired product. Yield (2.7 g, 50%), b.p. 100 °C (oven temperature)/0.5 mmHg. IR (neat): 2258, 1506, 1450, 1418, 1276 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.17 (s, 2H, CH_2), 8.05 (s, 1H, 5-H), 8.28 (s, 1H, 3-H). ^{13}C NMR ($CDCl_3$): δ 37.12 (CH_2), 112.48 (CN), 143.50 (5-C), 153.10 (3-C).

General procedure for the synthesis of 4-amino-1,3-diazines. A mixture of the appropriate nitrile (1 g, 9.3 mmol) and 1,4-diazabicyclo[2.2.2]octane (DABCO; 0.350 g, 3.1 mmol) under an argon atmosphere was placed into a sealed screw-cap reaction vessel[22] and introduced into a stainless steel block. The mixture was stirred for 24 h at 200 °C. Reaction mixture was allowed to cool to room temperature and the products were purified by extraction with the appropriate solvent.

*4-Amino-2,6-bis(pyrazol-1-ylmethyl)-5-(pyrazol-1-yl)pyrimidine (**1**).* The crude was extracted with ethyl acetate (3×15 mL) filtered and purified by column chromatography on silica gel using ethyl acetate–methanol (7:3) as the eluent. Then dichloromethane (15 mL) was added to the mixture and this was washed with 3 mL of HCl (10%). The aqueous phase was neutralised and extracted with dichloromethane (3×5 mL). Yield 0.330 g, 33% of diazine, m.p. 117–119 °C. MS (EI): m/z 322.2003 (M + 1). IR (KBr): 3457, 3287, 1635, 1588, 1394 cm^{-1}.

*4-Amino-2,6-bis(imidazol-1-ylmethyl)-5-(imidazol-1-yl)pyrimidine (**2**).* **2** was synthesised from 1-cyanomethylimidazole (0.083 g, 0.77 mmol) and DABCO (0.029 g, 0.25 mmol). The crude material was extracted with dichloromethane (3×15 mL) and was purified by column chromatography on silica gel using ethyl acetate–methanol (7:3) as the eluent. Yield 0.055 g, 66% of diazine, m.p. 234–235 °C. MS (EI): m/z

322.2259 (M + 1). IR (KBr): 3308, 3140, 1653, 1584, 1495 cm^{-1}.

*4-Amino-2,6-bis(triazol-1-ylmethyl)-5-(triazol-1-yl)pyrimidine (**3**)*. The crude material was extracted with ethanol (3 × 15 mL) and purified by column chromatography on silica gel using ethanol with 1% of diethylamine as the eluent. Yield 0.670 g, 67% of diazine, m.p. 220–221 °C. MS (EI): *m*/*z* 324.1815 (M). IR (KBr): 3316, 3194, 1652, 1595, 1507 cm^{-1}.

X-Ray analysis

Crystals of **1** were grown from a solution in ethyl acetate immersed in an atmosphere of hexane. Data were collected using a Seifert XRD3000-S four-circle diffractometer and graphite-monochromated CuKα radiation. The structure was solved by direct methods[23] and refined on F_{obs} by least-squares procedures. All hydrogens were obtained from difference Fourier synthesis and included and refined isotropically in the last cycles. Most of the calculations were carried out with the XTAL[24] set of programs running on a DEC3000-300X workstation. Crystal data for **1**: $C_{15}H_{15}N_9$, $M = 321.35$, monoclinic, $a = 10.861(1)$, $b = 25.535(4)$, $c = 11.340(1)$ Å, $\beta = 89.301(11)°$, $U = 3144.6(7)$ $Å^3$, $T = 293$ K, space group $P2_1/a$, $Z = 8$, $\mu = 0.742$ mm^{-1}, 5762 reflections measured, 3391 unique [$I > \sigma(I)$] ($R_{int} = 0.010$), which were used in the refinements. The final R and wR were 0.047 and 0.058 (observed reflections).

CCDC reference number 171217. See http://www.rsc.org/suppdata/nj/b2/b200169c/ for crystallographic data in CIF or other electronic format.

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