The Reaction of Enaminones with Carboxamidines: A Convenient Route for the Synthesis of Polyaza Heterocycles

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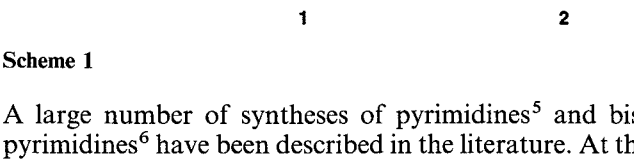
A simple and efficient synthetic method to polyaza heterocyclic structures containing 1,3-pyrimidine units has been developed. It is based on the reaction of the enaminones such as **5**, **7** and **9** with the appropriate carboxamidines under basic conditions. By this procedure several new polyaza heterocycles have been prepared in good yields.

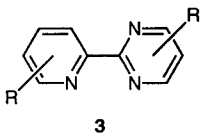
Enaminones **1** are of considerable interest due to their valuable use as synthetic intermediates[1,3] to prepare more complex and difficult to obtain compounds. The reaction of formamide acetals[2] and their derivatives with ketones under mild conditions gives good to excellent yields of enaminones.[3] Bredereck et al.[4] have found that the enaminone formed from the acetophenone (R = Ph) gave, after treatment with guanidine carbonate in the presence of sodium ethoxide and ethanol, 2-amino-4-phenylpyrimidine (**2**) in 84% yield (Scheme 1). However, the enaminones derived from cyclohexanone, acetone and ethyl methyl ketone were converted to the corresponding pyrimidines in low yields.



Scheme 1

A large number of syntheses of pyrimidines[5] and bispyrimidines[6] have been described in the literature. At the same time, few pyridylpyrimidines and polypyridylpyrimidines such as **3** and **4** have been reported.[7] The preparation of 2,4-disubstituted pyrimidines and related derivatives by reaction of the α-oxoketene dithioacetals with different carboxamidines in benzene or benzene – DMF solution in the presence of sodium hydride, has been reported by Potts et al.[8] By this procedure, some 2,4-disubstituted-6-(methylthio)pyrimidine and polypyrimidinediyls were obtained in moderate yields. Very recently, Lehn et al.[9] have described the synthesis of new aza heterocyclic structures containing 1,3-pyrimidine units using a procedure which involved a Pd(II)-catalyzed cross-coupling reaction.[10] The properties of the corresponding chelating ruthenium(II) complexes were also studied.[11] This elegant work highlighted the potential for the design of new and attractive macroheterocycles containing the pyrimidine unit.

In keeping with our studies concerning the synthesis of new types of polypyridine[12] as potential chelating agents, we sought mild and efficient conditions to prepare a polyaza structure containing 1,3-pyrimidine units. In this study we describe the first application of enaminones for the synthesis of a variety of 4-(2-pyridyl)pyrimidines and



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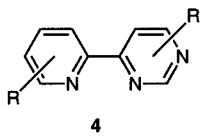

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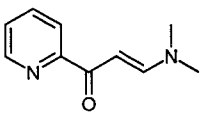

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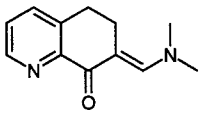

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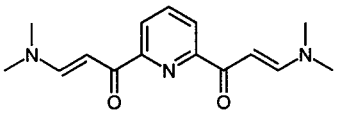

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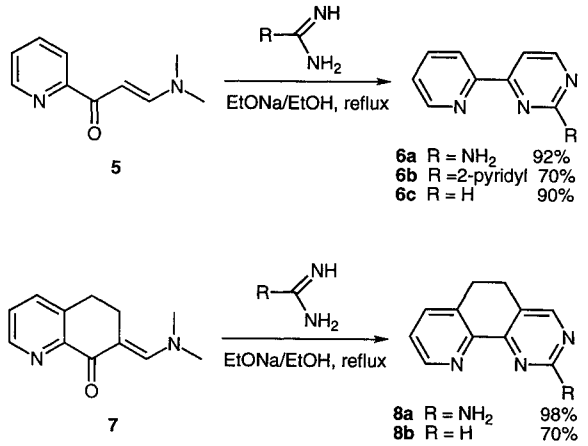
methylene bridged pyridylpyrimidines. The present procedure is based on the condensation of the enaminones **5**, **7** and **9**, easily obtained from their corresponding ketones in excellent yield, with carboxamidines under basic conditions.

Several new bidentate polyaza heterocycles have been synthesized in high yield according to Scheme 2. 2-[3-(*N*,*N*-Dimethylamino)-1-oxoprop-2-en-1-yl]pyridine (**5**) was obtained quantitatively from the 2-acetylpyridine and *N*,*N*-dimethylformamidine dimethylacetal, using modified conditions previously described by Jameson et al.[13] The condensation of **5** with 1.25 equivalents of guanidine nitrate in the presence of 2 equivalents of sodium ethoxide resulted, after 16 hours, in the formation of the 2-amino-4-(2-pyridyl)pyrimidine (**6a**) in 92% overall yield. This compound was purified by crystallization from dichloromethane/diethyl ether and its structure was solved by X-ray analysis.[14] Bis-2,4-(2-pyridyl)pyrimidine (**6b**) was obtained in 70% yield upon treatment of **5** with the 2-pyridinecarboxamidine, prepared conveniently from its nitrile, sodium methoxide and ammonium chloride,[18] in the same fashion as for **6a**. In contrast, the reaction with the pyridinecarboxamidine was rapid and the enaminone was completely consumed after 5 hours. It is noteworthy that in the procedure described by Potts et al.[8] which used the α-oxoketene dithioacetals, the 2-pyridinecarboxamidine led to the desired pyrimidine, but with a lower yield (10%). Compound **6b** can act as a bi- or tridentate ligand, due to the rotation of the 2-pyridyl moiety about the carbon–carbon bond. The transformation of **5** to **6c** carried out under the conditions used for **6a** gives the desired product in only 30% yield. However, **6c** could be obtained in 90% yield by condensation using 3 equivalents of formamidine acetate and 3 equivalents of sodium ethoxide.

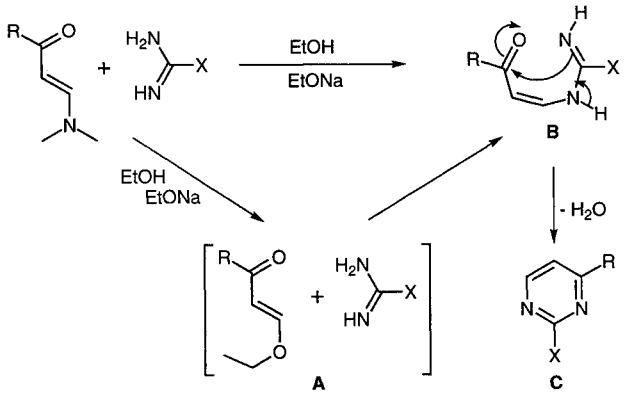


Scheme 2

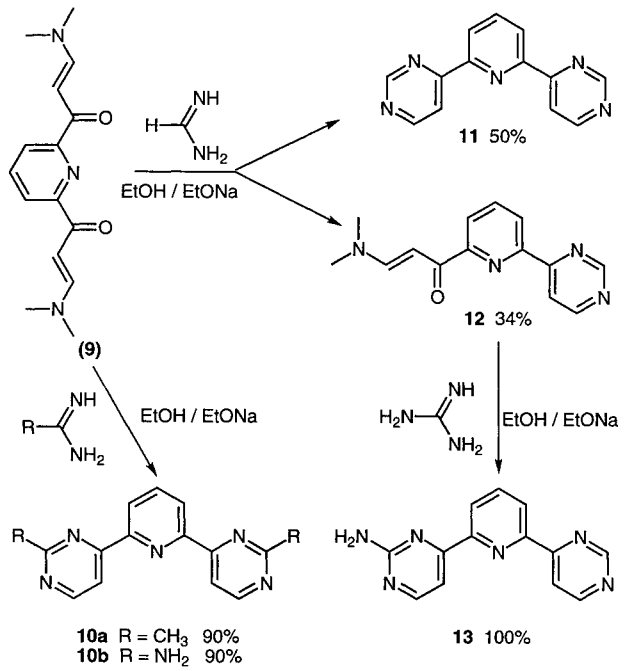
Ring-annulated pyridylpyrimidines may also be obtained by this simple and efficient procedure. The reaction of 5,6,7,8-tetrahydro-7-[(dimethylamino)methylidene]-8-oxoquinoline (**7**)[19] with amidines such as guanidine and formamidine occurs readily under basic conditions leading to the methylene bridged pyridylpyrimidines **8a** and **8b** in high yields (Scheme 2). The amino compound **8a** was synthesized with an excellent yield (98%) by condensation of **7** with guanidine nitrate under the same conditions as for **6a**. A 70% isolated yield was obtained for the derivative **8b** by reaction of the enaminone **7** with formamidine acetate in the same fashion as described for **6c**.

The general mechanistic pathways for the formation of the pyrimidine from the corresponding enaminone with amidines can be rationalized as shown[20] (Scheme 3). One of the most important characteristics in the reactivities of the enaminones is the displacement of the *N,N*-dimethylamino groups by different nucleophiles.[3] One probable way might be the attack of the amidine on the enaminone to give **A** which on subsequent intramolecular cyclisation followed by elimination of water yields pyrimidine **B**. The *N,N*-dimethylamino groups could also undergo nucleophilic displacement by ethoxide and then the acryloyl derivatives **C** would be formed prior to the attack of the amidine on the enaminone and formation of pyrimidine. However, **C** could not be isolated at any stage of the reaction and its structure was not confirmed. But it is known that the condensation of acryloyl derivatives, such as **C**, with amidine leads to the corresponding pyrimidines in good yields.[21]

The use of heterocyclic bis(*N,N'*-dimethylenaminone) provides an opportunity to extend the number of heterocyclic units in this system. For example, the reaction of 2,6-bis[(*N,N'*-dimethylamino)-1-oxoprop-2-en-1-yl]pyridine (**9**) with 5 equivalents of acetamidine chloride and 5 equivalents of sodium ethoxide in hot ethanol (16 hours) resulted in the formation of **10a** in 90% yield (Scheme 4). In this case, the reaction was very clean and the desired product was purified by precipitation from cooled ethanol as a pale yellow powder which could be recrystallized from dichloromethane/diethyl ether. The condensation of **9** with 2.5 equivalents of guanidine nitrate and 3 equivalents of sodium ethoxide in boiling ethanol gives the diamino derivative **10b** with 90% yield. This material was purified by precipitation from hot ethanol as a white powder.



Scheme 3



Scheme 4

In contrast, the reaction of **9** with 5 equivalents of formamidine acetate and 5 equivalents of sodium ethoxide in refluxing ethanol (16 hours) resulted in the formation of a mixture of **11** and **12**. The purification of this mixture by silica gel column chromatography (ethyl acetate/pentane; 8 : 2) gave, after the usual workup, crystallized **11** and **12**, in 50% and 34% yield, respectively. These two products were recrystallized and their structures were solved by X-ray diffraction.[14] It is important to point out that variation of the quantities of formamidine and sodium ethoxide, the time of the reaction and the concentration of mixture did not influence the yield of **11**. The enaminone **12** was used to prepare quantitatively the monoaminopolyaza heterocycle **13** as a white powder in the same fashion as described for **6a**.

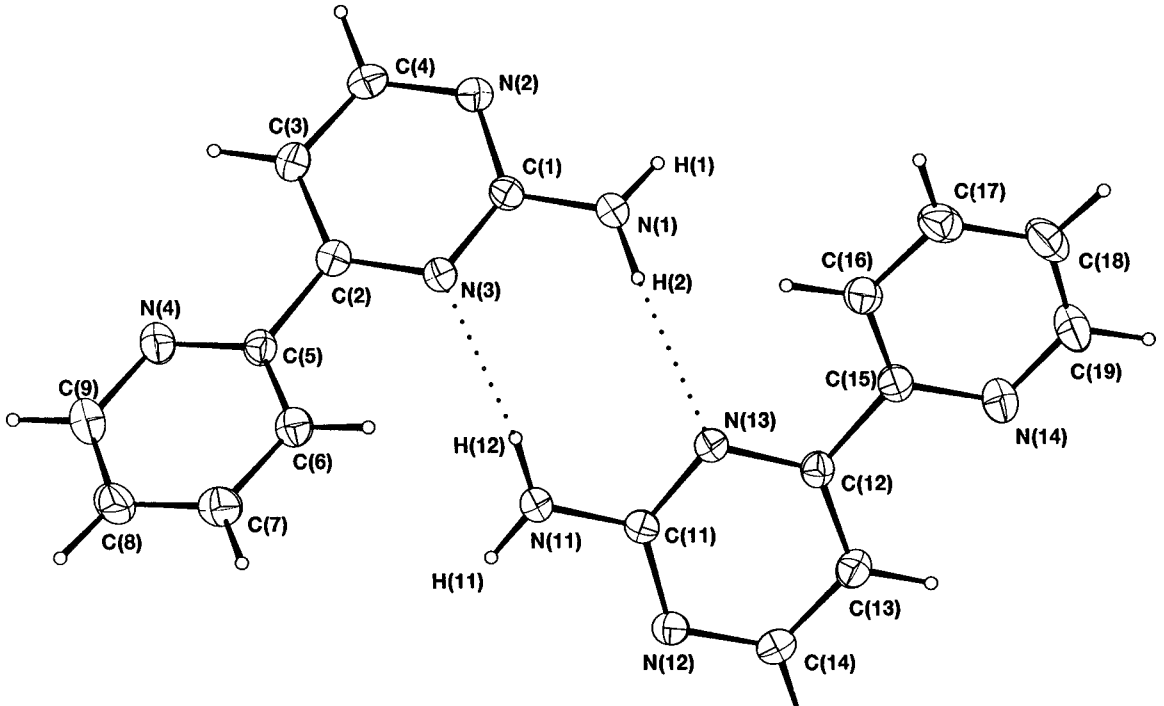


Figure 1: Molecular structure of **6a** with atoms labelling scheme, illustrating the hydrogen bond between the two independent molecules within the asymmetric unit. Ellipsoids represent 30% probability.
N(1)-C(1) = 1.338(2), N(11)-C(11) = 1.338(2), N(2)-C(1) = 1.347(2), N(12)-C(11) = 1.351 (2), N(2)-C(4) = 1.326 (3), N(12)-C(14) = 1.325 (3), N(3)-C(1) = 1.350 (2), N(13)-C(11) = 1.353 (2), N(3)-C(2) = 1.336 (2), N(13)-C(12) = 1.341 (2), N(4)-C(5) = 1.337 (3), N(14)-C(15) = 1.342 (3), N(4)-C(9) = 1.338 (3), N(14)-C(19) = 1.340 (3), C(2)-C(3) = 1.386 (3), C(12)-C(13) = 1.374 (3), C(2)-C(5) = 1.491 (3), C(12)-C(15) = 1.493 (3), C(3)-C(4) = 1.379 (3), C(13)-C(14) = 1.374 (3), C(5)-C(6) = 1.384 (3), C(15)-C(16) = 1.381 (3), C(6)-C(7) = 1.382 (3), C(16)-C(17) = 1.382 (3), C(7)-C(8) = 1.374 (3), C(17)-C(18) = 1.366 (4), C(8)-C(9) = 1.373 (4), C(18)-C(19) = 1.366 (4) Å.

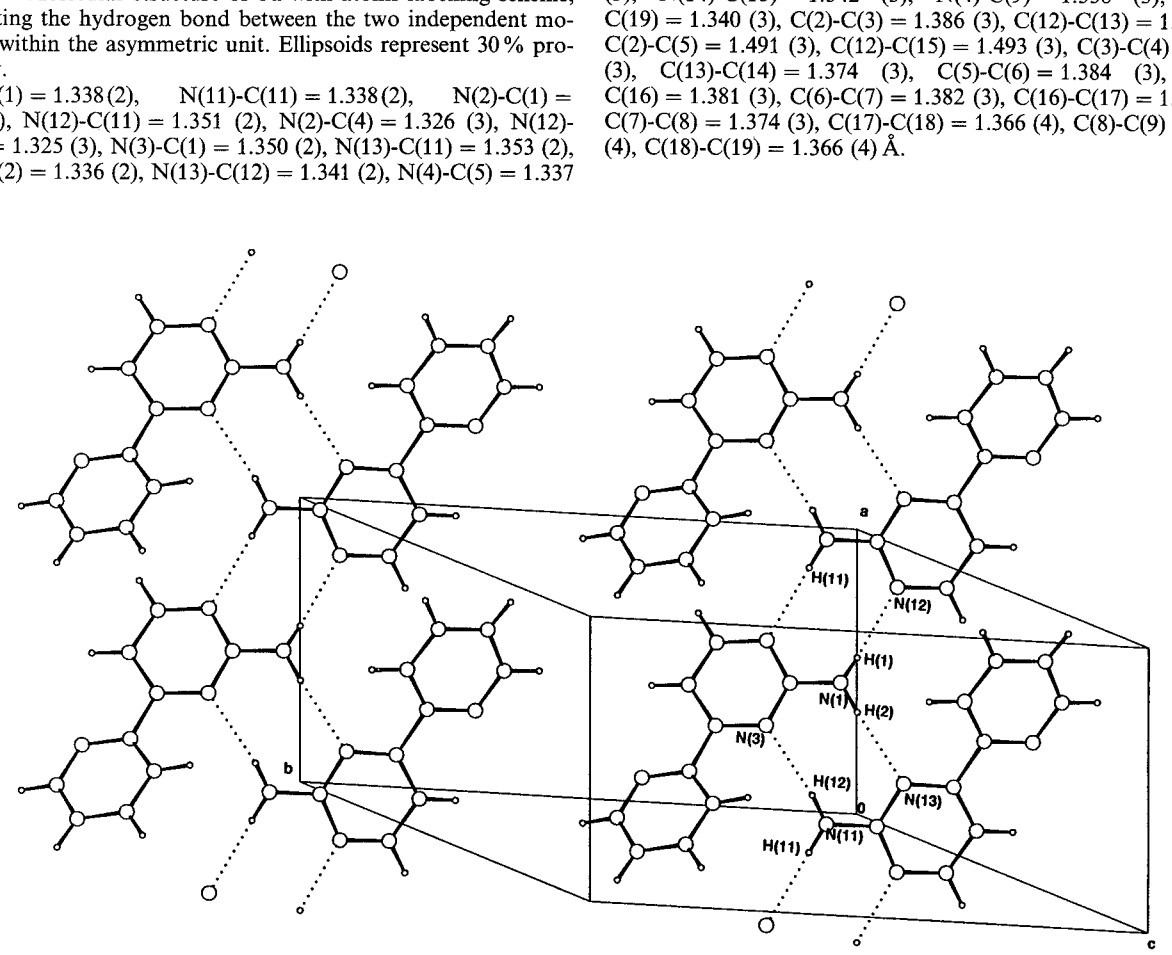


Figure 2: Packing diagram showing the hydrogen bond chains developing along the a axis. For **6a.** N(1)-H(2)---N(13): 0.89 (2), 3.138 (2), 2.25 (2), 176 (2); N(11)-H(12)---N(3): 0.87 (2), 3.088 (2), 170.2; N(1)-H(1)---$N(12)_{(1+x,y,z)}$: 0.88 (2), 3.038 (2), 2.19 (2), 163 (2); $N(11)_{(1+x,y,z)}$-$H(11)_{(1+x,y,z)}$---N(2): 0.89 (2), 3.114 (2), 2.23 (2), 169 (2) for X-H, X---Y, H---Y bonds and X-H---Y angles respectively, (Å, °).

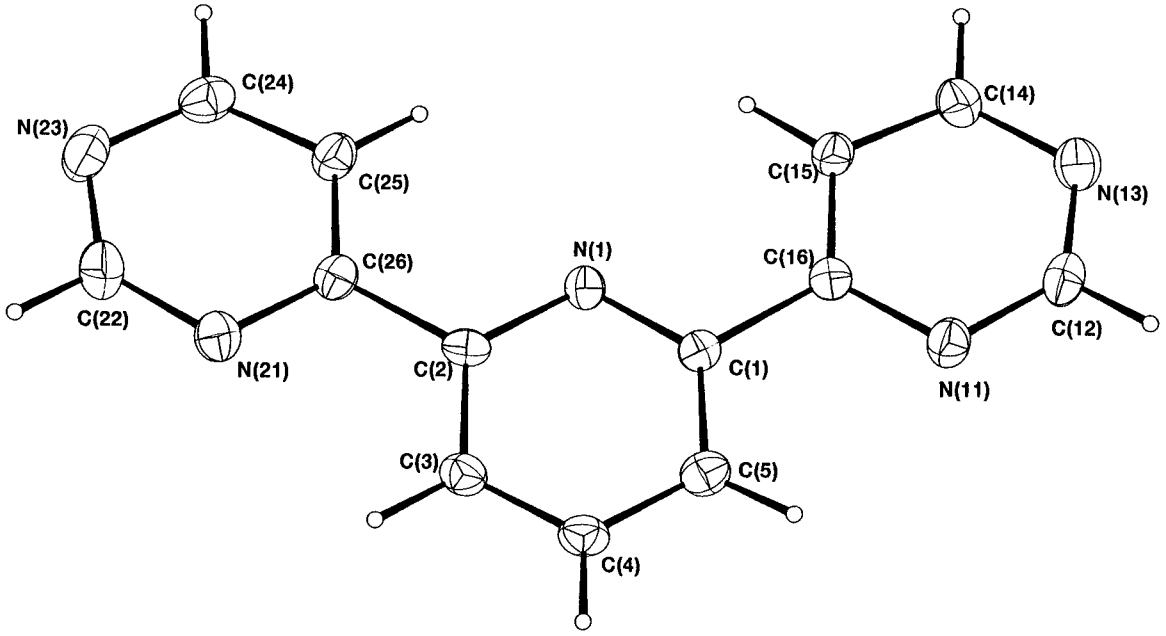


Figure 3: Molecular structure illustrating the planar conformation of **11**. Ellipsoids represent 30% probability. N(1)-C(1) = 1.332 (5), C(1)-C(5) = 1.380 (6), N(1)-C(2) = 1.341 (5), C(1)-C(16) = 1.493 (5), N(11)-C(12) = 1.323 (6), C(2)-C(3) = 1.397(6), N(11)-C(16) = 1.335 (5), C(2)-C(26) = 1.485(5), N(13)-C(12) = 1.321 (6), C(3)-C(4) = 1.370 (6), N(13)-C(14) = 1.334 (5), C(4)-C(5) = 1.374 (6), N(21)-C(22) = 1.323 (6), C(14)-C(15) = 1.372 (6), N(21)-C(26) = 1.341 (5), C(15)-C(16) = 1.385 (6), N(23)-C(22) = 1.325 (7), C(24)-C(25) = 1.361 (6), N(23)-C(24) = 1.329 (6), C(25)-C(26) = 1.378 (6) Å.

The molecular structure of **6a** as determined by X-ray analysis is shown wih its atoms labelling scheme in Figure 1. The asymmetric unit is built up from two independent molecules. Each NH_2 group of any independent molecule is engaged through NH---N hydrogen interactions with the pyrimidine nitrogen atoms of two molecules related to each other by unit translation along the **a** axis, making an infinite chain parallel to this axis as shown in Figure 2. The crystal is built up of symmetrically related chains that do not have any interactions between them. A similarly hydrogen-bonded system was already observed in the structure of 2-aminopyrimidine.[22]

In both molecules, nitrogen atoms of the pyridine ring are *trans* with respect to nitrogen atoms N(3) and N(13) of the pyrimidine rings in order to minimise electronic repulsion between lone pairs of N atoms. The pyridine and pyrimidine rings are twisted to each other along the C(2)-C(5) and C(12)-C(15) bonds resulting in dihedral angles between the rings of 21.2° and 16.6°, respectively. The nitrogen atoms of the amino groups are planar, and the short C—N distances (1.338(2) Å) are within the range observed for a carbon-nitrogen double bond. These are indicative of C=N *p*-bonding with electron delocalisation of the nitrogen lone pair towards the pyrimidine ring.

The molecular structure of **11** with its atoms labelling scheme is shown in Figure 3. The molecule has an essentially planar conformation with the largest deviation from the plane being −0.078 Å at C(25). The nitrogen N(1) of the pyridine ring is *trans* with respect to nitrogen atoms N(11) and N(21) of the pyrimidine rings. Such conformation minimizes electronic repulsions between lone pairs of nitrogen atoms.

The molecular structure of **12** with its atoms labelling scheme is shown in Figure 4. There is a C-H---O hydrogen interaction between two molecules related by an inversion center as described in Figure 4, but hydrogen bonding does not develop all along the cell, it is limited to these two molecules. The pyridine and pyrimidine rings are twisted with respect to each other making a dihedral angle of 10.9°. As observed in compounds **6a** and **11**, nitrogen atoms of the pyridine and pyrimidine rings are in the *trans* position with respect to each other. The nitrogen of the dimethylamino group is perfectly planar with the sum of the angles around it equal to 360°. The C(3)-N(1) distance, 1.324(4) Å, is within the range for a carbon-nitrogen double bond. As in **6a** there is a C=N *p*-bonding with delocalisation of the nitrogen lone pairs towards the C(3), C(2) and C(1) chain. This chain and the oxygen of the ketone make a perfect plane which is slightly twisted with respect to the pyridine ring with a dihedral angle of 14.5°. The N(1), C(3) and C(2) fragment might be regarded as an azaallyl group.

In conclusion, we have found a new, convenient and efficient way to synthesize polyaza structures containing 1,3-pyrimidine units. The examples described in this preliminary study show the potential of this synthetic method and demonstrate that the pyrimidine moiety can be successfully introduced into organised assemblies via condensation of an enaminone with the appropriate amidine. This use of enaminones in the preparation affords excellent yields of polyaza structures and this can be applied to the design and synthesis of higher polyaza heterocyclic homologous such as pentacyclic 2,6-bis[2-(2-pyridyl)-4-pyrimidyl]pyridine and heptacyclic 2,6-bis[2-(6-bipyridyl)-4-pyrimidyl]pyridine.[23] In a preliminary study, we

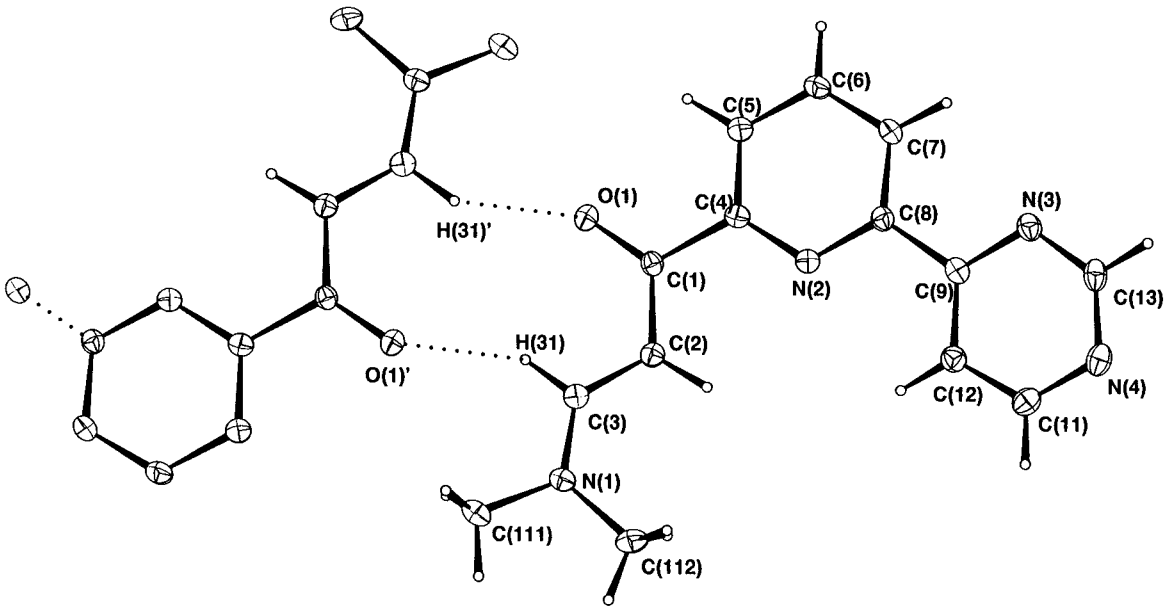


Figure 4: Molecular structure illustrating H bonds between centrosymmetrically related molecules of **12**. Ellipsoids represent 30% probability. C(3)-H(31)---O(1)$_{(-x,-y,-z)}$: 0.98, 3.341 (3), 2.58, 135 (2), for C-H, C---O, H---O bonds and C-H---O angle respectively, (Å, °).
N(1)-C(3) = 1.324 (4), C(1)-C(2) = 1.419 (4), N(1)-C(111) = 1.452 (4), C(1)-C(4) = 1.517 (4), N(1)-C(112) = 1.446 (4), C(2)-C(3) = 1.365 (4), N(2)-C(4) = 1.341 (4), C(4)-C(5) = 1.379 (4), N(2)-C(8) = 1.342 (4), C(5)-C(6) = 1.379 (4), N(3)-C(9) = 1.344 (4), C(6)-C(7) = 1.384 (4), N(3)-C(13) = 1.331 (4), C(7)-C(8) = 1.395 (4), N(4)-C(11) = 1.345 (4), C(8)-C(9) = 1.482 (4), C(4)-C(13) = 1.322 (5), C(9)-C(12) = 1.380(4), O(1)-C(1) = 1.246(3), C(11)-C(12) = 1.376 (4) Å.

treated **6b** with *cis*-Ru-(bpy)$_2$Cl$_2$·2H$_2$O, where bpy = 2,2′-bipyridine, followed by ammonium hexafluorophosphate. A complex was obtained in 80% yield, which ^{1}H NMR and FAB mass spectral analysis indicated to be [Ru(bpy)$_2$(**6b**)] 2PF$_6$. Further studies will explore the coordination chemistry of these polyaza heterocyclic compounds.

All reactions were carried out under an inert Ar atmosphere. H^1 NMR spectra were recorded with a Brucker AM-250 (250 MHz) and AC-200 (200 MHz) spectrometer, and chemical shifts are reported in ppm downfield from Me$_4$Si in CDCl$_3$ or HMDS in DMSO-d_6. These instruments were also used for ^{13}C spectra. All melting points are uncorrected. IR spectra were obtained from a Perkin-Elmer 883 or FT-1725X spectrometers. CI Mass spectra and FAB mass spectra (*m*-nitrobenzyl alcohol matrix) were recorded with a quadripolar Nermag R10-10H instrument. Elemental analysis were performed by LCC (Laboratoire de Chimie de Coordination) Microanalytical Service. Column chromatography purifications were performed with Merck alumina (70–230 mesh ASTM), deactivated with 8% H$_2$O.

2-Amino-4-(2-pyridyl)pyrimidine (6a):
A solution of guanidine nitrate (1.73 g, 14.2 mmol) in abs. EtOH (15 mL) was added to a stirred solution of **5** (2 g, 11.3 mmol) in boiling abs. EtOH (10 mL) and stirring was continued for 20 min. To this mixture was then added Na (0.52 g, 22.6 mmol) in abs. EtOH (10 mL) and the reaction mixture was refluxed for 16 h. The solution was allowed to cool to r.t. and the precipitate was removed by filtration followed by concentration of the filtrate under reduced pressure. The desired compound was purified by crystallization from CH$_2$Cl$_2$/Et$_2$O; yield: 1.8 g (92%); mp 132–137°C

^{1}H NMR (CDCl$_3$): δ = 8.7 (d, 1H, J = 4.4 Hz), 8.45 (d, 1H, J = 5.1 Hz), 8.33 (d, 1H, J = 7.9 Hz), 7.8 (dd, 1H, J = 7.7 Hz), 7.63 (d, 1H, J = 5.1 Hz), 7.35 (dd, 1H, J = 7.0, 4.7 Hz), 6.45 (s, NH$_2$).
^{13}C NMR (CDCl$_3$): δ = 163.9, 163.2, 159.1, 154.2, 149.3, 136.8, 124.9, 121.3, 107.8.
MS: m/z = 173 (MH$^+$, 100%).
Anal. (C$_9$H$_8$N$_4$) (172.19): C: 62.94 (calc. 62.78), H: 4.52 (calc. 4.68), N: 32.54 (calc. 32.54).

2,4-Bis(2-pyridyl)pyrimidine (6b):
According to the preparation of **6a**, to **5** (1 g, 5.68 mmol) in hot abs. EtOH (15 mL) was added 1.25 equiv. of 2-pyridinecarboxamidine in abs. EtOH (10 mL) followed by the addition of 2 equiv. of Na in abs. EtOH (15 mL). The mixture was refluxed for 5 h. Then the solution was concentrated under reduced pressure and the residue dissolved in CH$_2$Cl$_2$ (50 mL) followed by removal of the precipitate by filtration. The filtrate was concentrated and the residue was purified by column chromatography on alumina (EtOAc) to give **6b**; yield: 0.9 g (70%) as a white crystalline powder; mp 105–110°C.

^{1}H NMR (CDCl$_3$): δ = 9.0 (d, 1H), 8.8 (d, 1H, J = 5.1 Hz), 8.81 (ddd, 1H, J = 4.7, 1.8, 0.9 Hz), 8.68 (ddd, 1H, J = 4.7, 1.8, 0.9 Hz), 8.66–8.57 (m, 2H), 8.31 (d, 1H, J = 5.1 Hz), 7.83 (ddd, 2H, J = 7.7, 7.7, 1.8 Hz), 7.35 (m, 2H).
^{13}C NMR (CDCl$_3$): δ = 163.0, 158.8, 154.7, 153.6, 149.9, 149.3, 136.9, 136.7, 125.3, 124.7, 123.4, 122.2, 121.7, 116.9
MS: m/z = 235 (MH$^+$, 100%).
Anal. (C$_{14}$H$_{10}$N$_4$) (234.26): C: 72.03 (calc. 71.78), H: 4.26 (calc. 4.30), N: 23.71 (calc. 23.92).

4-(2-Pyridyl)pyrimidine (6c):
To a stirred solution of **5** (3 g, 17 mmol) in abs. EtOH (10 mL) at reflux was added a solution of formamidine acetate (5.32 g, 51.1 mmol) in abs. EtOH (15 mL) and stirring was continued for 10 min. After this, a solution of Na (1.17 g, 51.1 mmol) in abs. EtOH (10 mL) was added to the reaction mixture and the reflux maintained for 16 h, after which time it was allowed to cool to r.t. The solution was concentrated under vacuum and the solid residue dissolved in CH$_2$Cl$_2$ (100 mL). The precipitate was filtered and the filtrate concentrated. The desired compound was purified by column chromatography on alumina (EtOAc) to give **6c**; yield: 2.4 g (90%) as a pale yellow crystalline powder which was recrystallized from CH$_2$Cl$_2$/Et$_2$O; mp 77–80°C.

^{1}H NMR ($CDCl_3$): δ = 9.28 (s, 1 H), 8.86 (d, 1 H, J = 5.2 Hz), 8.71 (d, 1 H, J = 4.5 Hz), 8.5 (d, 1 H, J = 7.9 Hz), 8.38 (dd, 1 H, J = 5.2, 1.3 Hz), 7.85 (dd, 1 H, 7.7, 7.7 Hz), 7.4 (ddd, 1 H, J = 7.5, 4.7, 1.1 Hz).

^{13}C NMR ($CDCl_3$): δ = 162.5, 158.6, 157.9, 153.6, 149.5, 137.0, 125.3, 121.5, 117.3.

MS: m/z = 158 (MH^+, 100 %).

Anal. ($C_9H_7N_3$) (157,17): C: 68.81 (calc. 68.77), H: 4.43 (calc. 4.48), N: 26.45 (calc. 26.73).

2-Amino-5,6,7,8-tetrahydropyrido[3,2-*h*]quinazoline (8a):
This compound was prepared in 100 % isolated yield according to the procedure described for **6a**. After the workup the residue was purified by chromatography on alumina deactivated with 8 % H_2O, (EtOAc/MeOH, 1:1). The desired product crystallized in cold MeOH; mp 259–267 °C.

^{1}H NMR ($CDCl_3$): δ = 8.7 (dd, 1 H, J = 4.6, 1.6 Hz), 8.2 (s, 1 H), 7.6 (dd, 1 H, J = 7.7, 1.6 Hz), 7.3 (dd, 1 H, J = 7.7, 4.6 Hz), 4.2 (s, NH_2), 2.97 (m, 2 H), 2.8 (dd, 2 H).

^{13}C NMR ($CDCl_3$): δ = 159.9, 159.0, 150.6, 149.4, 138.3, 137.9, 126.8, 120.7, 63.9, 28.2, 23.7.

MS: m/z = 199 (MH^+, 100 %).

Anal. ($C_{11}H_{10}N_4$) (198.22): C: 66.69 (calc. 66.66), H: 4.99 (calc. 5.08), N: 28.32 (calc. 28.26).

5,6,7,8-Tetrahydropyrido[3,2-*h*]quinazoline (8b):
This compound was prepared according to the procedure described for **6c**. The reaction of **7** (4 g, 19.8 mmol) with 3 equiv. of formamidine acetate and 3 equiv. of NaOEt in boiling abs. EtOH gave, after workup and purification by column chromatography on alumina (EtOAc), **8b**; yield: 2.5 g (70 %) which crystallized from CH_2Cl_2/Et_2O; mp 169–174 °C.

^{1}H NMR ($CDCl_3$): δ = 9.2 (s, 1 H), 8.74 (d, 1 H, J = 4.6 Hz), 8.66 (s, 1 H), 7.62 (d, 1 H, J = 7.3 Hz), 7.33 (dd, 1 H, J = 7.6, 4.6 Hz), 3.03 (m, 4 H).

^{13}C NMR ($CDCl_3$): δ = 158.0, 156.1, 149.3, 149.0, 136.1, 135.0, 129.8, 125.1, 26.4, 23.5.

MS: m/z = 183 (M^+, 100 %).

Anal. ($C_{11}H_9N_3$) (183.21): C: 72.16 (calc. 72.12), H: 5.03 (calc. 4.95), N: 22.81 (calc. 22.93).

2,6-Bis[(*N*,*N*'-dimethylamino)-1-oxoprop-2-en-1-yl]pyridine (9):
To 2,6-diacetylpyridine (3 g, 18.8 mmol) was added *N*,*N*-dimethylformamide dimethylacetal (10 mL, 75.2 mmol, 4 equiv.). The reaction mixture was then heated at 120 °C for 16 h. After concentration of the solution under reduced pressure, **9** was obtained; yield: 5 g (100 %) after crystallization from THF/Et_2O; mp 222–230 °C.

^{1}H NMR ($CDCl_3$): δ = 8.22 (dd, 2 H, J = 7.6, 7.6 Hz), 7.93 (d, 2 H, J = 12.7 Hz), 7.9 (dd, 1 H, J = 7.4, 7.4 Hz), 6.62 (d, 2 H, J = 12.7 Hz), 3.2 (s, 6 H), 3.00 (s, 6 H).

^{13}C NMR ($CDCl_3$): δ = 186.5, 154.4, 154.3, 137.2, 123.4, 91.2, 44.9, 36.9.

IR (KBr): ν = 1646 cm^{-1} (CO).

MS: m/z = 274 (MH^+, 100 %).

Anal. ($C_{15}H_{19}N_3O_2$) (273.33): C: 65.80 (calc. 65.91), H: 7.17 (calc. 7.00), N: 15.32 (calc. 15.38).

2,6-Bis(2-methyl-4-pyrimidyl)pyridine (10a):
This compound was prepared in 90 % isolated yield by condensation of **9** with the acetamidine chloride using the procedure described for the synthesis of **12**; mp 197–200 °C.

^{1}H NMR ($CDCl_3$): δ = 8.82 (d, 2 H, J = 5.2 Hz), 8.62 (d, 2 H, J = 7.8 Hz), 8.31 (d, 2 H, J = 5.2 Hz), 8.03 (dd, 1 H, J = 7.8, 7.8 Hz), 2.84 (s, 6 H).

^{13}C NMR ($CDCl_3$): δ = 168.0, 162.3, 157.9, 153.7, 138.1, 123.0, 114.1, 26.1

Anal. ($C_{15}H_{13}N_5$) (263.30): C: 68.7 (calc. 68.42), H: 4.97 (calc. 4.98), N: 26.33 (calc. 26.6).

2,6-Bis(2-amino-4-pyrimidyl)pyridine (10b):
This product was obtained in 90 % yield according to the procedure used for the preparation of **6a** by using 2.5 equiv. of guanidine nitrate and 3 equiv. of EtONa. The desired product precipitated from EtOH; mp > 350 °C.

^{1}H NMR (DMSO-d_6): δ = 8.57 (d, 2 H, J = 4.9 Hz), 8.52 (d, 2 H, J = 7.4 Hz), 8.27 (dd, 1 H, J = 7.3, 7.3 Hz), 7.77 (d, 2 H, J = 4.9 Hz), 6.95 (s, 2 NH_2).

^{13}C NMR (DMSO-d_6): δ = 169.6, 155.9, 150.5, 148.4, 140.4, 127.6.

Anal. ($C_{13}H_{11}N_7$) (265.28): C: 59.11 (calc. 58.86), H: 4.22 (calc. 4.18), N: 36.67 (calc. 36.96).

2-Bis(4-pyrimidyl)pyridine (11) and 2-[(*N*,*N*-Dimethylamino)-1-oxoprop-2-en-1-yl]-6-(4-pyrimidyl)pyridine (12):
To a stirred solution of **9** (1.2 g, 4.39 mmol) in boiling abs. EtOH (20 mL) was added a solution of formamidine acetate (2.28 g, 21.95 mmol, 5 equiv.) in abs. EtOH (15 mL). After this, a solution of Na (0.5 g, 21.95 mmol, 5 equiv.) in abs. EtOH (15 mL) was slowly added with a cannula to the mixture (30 min) and reflux maintained for 16 h. The solution was allowed to cool to r.t. the EtOH was removed under reduced pressure; the residue was then dissolved in CH_2Cl_2 and the precipitate removed by filtration. The filtrate was concentrated and the mixture was purified by column chromatography on alumina (EtOAc/pentane, 8 : 2) to give **11**; yield: 0.5 g (50 %) as a white powder and **12**; yield: 0.4 g (34 %).

11; mp 190–193 °C.

^{1}H NMR ($CDCl_3$): δ = 9.34 (d, 2 H, J = 1.4 Hz), 8.93 (d, 2 H, J = 5.2 Hz), 8.65 (d, 2 H, J = 7.8 Hz), 8.52 (dd, 2 H, J = 5.2, 1.4 Hz), 8.1 (dd, 1 H, J = 7.8, 7.8 Hz).

^{13}C NMR ($CDCl_3$): δ = 162.0, 158.7, 157.9, 153.4, 138.4, 123.2, 117.3.

MS: m/z = 236 (MH^+, 100 %).

Anal. ($C_{13}H_9N_5$) (235.54): C: 66.42 (calc. 66.38), H: 3.85 (calc. 3.85), N: 29.73 (calc. 29.77).

12; mp 168–170 °C.

^{1}H NMR ($CDCl_3$): δ = 9.3 (d, 1 H, J = 1.4 Hz), 8.9 (d, 1 H, J = 5.2 Hz), 8.58 (dd, 1 H, J = 8.9, 1.1 Hz), 8.46 (dd, 1 H, J = 5.2, 1.4 Hz), 8.28 (dd, 1 H, J = 8.8, 1.1 Hz), 7.98 (dd, 1 H, J = 7.8, 7.8 Hz), 7.97 (d, 1 H, J = 12.6 Hz), 6.61 (d, 1 H, J = 12.6 Hz), 3.2 (s, 3 H), 3.00 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 185.9, 162.4, 158.5, 157.7, 155.7, 154.6, 152.0, 137.8, 123.6, 123.1, 117.3, 90.74, 45.05, 37.3.

IR (KBr): ν = 1644 cm^{-1} (CO).

MS: m/z = 255 (MH^+, 100 %).

Anal. ($C_{14}H_{14}N_4O$) (254.29): C: 66.13 (calc. 66.13), H: 5.67 (calc. 5.55), N: 21.90 (calc. 22.03).

6-(2-Amino-4-pyrimidyl)-2-(4-pyrimidyl)pyridine (13):
This material was obtained in 100 % isolated yield according to the procedure described for the synthesis of **6a** as a white powder; mp 310 °C (dec).

^{1}H NMR (DMSO-d_6): δ = 9.32 (d, 1 H, J = 1.3 Hz), 8.92 (d, 1 H, J = 5.2 Hz), 8.6 (dd, 2 H, J = 7.8, 1.0 Hz), 8.55–8.48 (m, 4 H), 8.02 (dd, 1 H, J = 7.8, 7.8 Hz), 7.84 (d, 1 H, J = 5.0 Hz), 6.6 (s, NH_2).

^{13}C NMR (DMSO-d_6): δ = 162.1, 161.8, 159.5, 158.8, 155.1, 152.5, 138.8, 122.7, 122.2, 117.4, 102.5

MS: m/z = 251 (MH^+, 100 %).

HRMS: m/z = 250.09 (MH^+), m/z (calc.) = 250.26 (MH^+).

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(14) Crystal Data: $(C_9H_8N_4)_2$ **(6a)**, M = 344.38, Monoclinic, space group $P2_1/c$, a = 7.524(9), b = 20.419(7), c = 11.690(4) Å, β = 107.76(8), V = 1710(2) Å^3, Z = 4, Dc(gr/cm^3) = 1.34, MoKα radiation, λ = 0.71073 Å, μ(cm^{-1}) = 0.816, F(000) = 720. Colorless prismatic crystals (0.45 × 0.22 × 0.80 mm). 3228 reflexions collected ($2\theta < 50°$, 295 K), 1841 used [$I > 3\sigma(I)$], R = 0.035, R_w = 0.044, A_r coefficients: 4.33, 0.684 and 2.98.
$C_{11}H_9N_5$ **(11)**, M = 235.25, Monoclinic, space group $P2_1$, a = 9.782(2), b = 3.850(1), c = 14.601(6) Å, β = 93.67(2)°, V = 549(3) Å^3, Z = 2, DC(gr/cm^3) = 1.42, Mokα radiation, λ = 0.71073 Å, μ(cm^{-1}) = 0.860, F(000) = 244. Colorless parallelepiped crystal (0.40 × 0.35 × 0.30 mm), 1177 reflexions collected ($2\theta < 50°$, 295 K), 827 used [$I > 1\sigma(I)$], R = 0.055, R_w = 0.049, A_r coefficients: 5.78, − 2.91 and 4.02.
$C_{14}H_{14}N_4O$ **(12)**, M = 254.29, Monoclinic, space group $P2_1/a$, a = 14.135(3), b = 5.224(5), c = 17.432(5) Å, β = 103.20(2)°, V = 1251(2) Å^3, Z = 4, Dc(gr/cm^3) = 1.34, MoKα radiation, λ = 0.71073 Å, μ(cm^{-1}) = 0.836, F(000) = 536. Colorless parallelepiped (0.50 × 0.44 × 0.35 mm), 2568 reflexions collected ($2\theta < 50°$, 295 K), 1365 used for refinement [$I > 3\sigma(I)$], R = 0.058, R = 0.061, A_r coefficients: 17.2, − 21.3, 14.4 and − 6.91.
For the three compounds, data were collected on a Nonius CAD4 four circle diffractometer using Mo radiation and graphite oriented monochromator. Cell parameters were obtained from the setting angles of well centered 25 reflexions in the range $11 < \theta < 13°$. The structure was solved by direct methods (SIR92)[15] and refined by least-squares procedures on Fobs. All hydrogens were obtained from difference Fourier synthesis but only H attached to the amino groups in compound **6a** were defined. All other hydrogens attached to C atoms were introduced in idealized positions. Their atomic coordinates were recalculated after each cycle. They were given isotropic thermal parameters 20% higher than those of the carbon to which they were attached. The weighting scheme used in the last refinement cycles was $w = w'[1-(\Delta F/6\sigma(F_o)^2]^2$[16] where $w' = 1/\Sigma_1^n A_r T_r(x)$ with n coefficients A_r for the Chebyshev polynomial $A_r T_r(x)$ where x was $F_c/F_c(max)^2$. Criteria for a satisfactory complete analysis were the ratios of rms shift to standard deviation less than 0.1 and no significant features in final difference maps. The calculations were carried out with the CRYSTALS package programs[17] running on a PC486 DX266. Atomic coordinates, anisotropic thermal parameters for non hydrogen atoms and atomic coordinates for H atoms have been deposited at the Cambridge Crystallographic Data Center. Copies of the data can be obtained free of charge, on application to the Director, CDCC, 12 Union Road Cambridge CB2 IE2, UK.
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