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# Synthesis of novel 5-amino-6-ethoxy-2-alkylpyrimidine-4-carbonitriles

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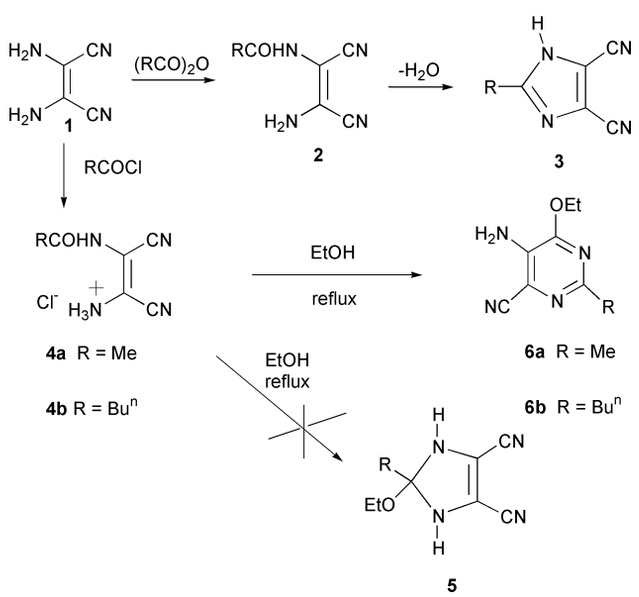
**Formation of highly functionalised 5-amino-6-ethoxy-2-alkylpyrimidine-4-carbonitriles has been shown to occur by simply refluxing in ethanol the *N*-(2-ammonio-1,2-dicyanovinyl)alkylamide chloride or, under acid catalysis conditions, *N*-(2-amino-1,2-dicyanovinyl)acetamide derivatives, which are readily prepared from diaminomaleodinitrile.**

From previous work carried out by our group,[1–8] and by others,[9] diaminomaleodinitrile (DAMN) has become established as a versatile intermediate for the synthesis of imidazoles and purine derivatives. As part of an ongoing investigation into the synthesis of some potential angiotensin (II) receptor antagonists we were interested in the preparation of 2-substituted-4,5-dicyanoimidazoles. Begland[10] has shown previously that such compounds may be obtained from DAMN either by oxidation of its Schiff base derivatives using DDQ or DISN, or by dehydration of monoamide derivatives of DAMN.[10,11] It was decided to follow the latter route and the monoamide, as its hydrochloride salt, was obtained as a yellow powder in almost quantitative yield by reaction between DAMN and an equimolar quantity of acetyl chloride in ethyl acetate at room temperature (Scheme 1). However, when this salt was heated under




**Scheme 1**

reflux in ethanol for 1–2 h in the expectation that it might cyclise to the 4,5-dicyanoimidazole, TLC analysis indicated conversion to a new product, isolated after chromatography as pale yellow needles in 44% yield. Microanalysis data were consistent with a molecular formula $C_8H_{10}N_4O$ and the $^1H/^{13}C$ NMR and mass spectra indicated that an ethoxy group from the ethanol had been incorporated into the product, and the IR spectrum showed a single, sharp $\nu$(CN) absorption at 2215 $cm^{-1}$.† Our initial thought was that the compound might be the imidazole **5** (R = Me) as a similar compound (**5**, R = H) has been claimed as a by-product (5–7% yield) from the reaction between DAMN and triethyl orthoformate under reflux.[12] However, although such a structure fitted the microanalytical spectroscopic data, it would not account for the 100% molecular ion observed in the mass spectrum, nor its apparent stability towards elimination of ethanol. A single crystal X-ray determination (Fig. 1) established the structure as 5-amino-6-ethoxy-2-methylpyrimidine-4-carbonitrile **6a**.‡ A similar reaction of the hydrochloride salt of amide **4** (R = $Bu^n$) with ethanol gave a 53% yield of pyrimidine **6b**, indicating that this is a general reaction (see Scheme 1). The reaction is clearly acid catalysed for when amide **2** (R = Me) (prepared in quantitative yield from DAMN and acetic anhydride[13]) was heated in ethanol for 48 h only unchanged starting material was recovered. Whereas, a repeat of the reaction after addition of 1 equivalent of an ethanol solution of hydrogen chloride gave pyrimidine **6a** in 65% yield.

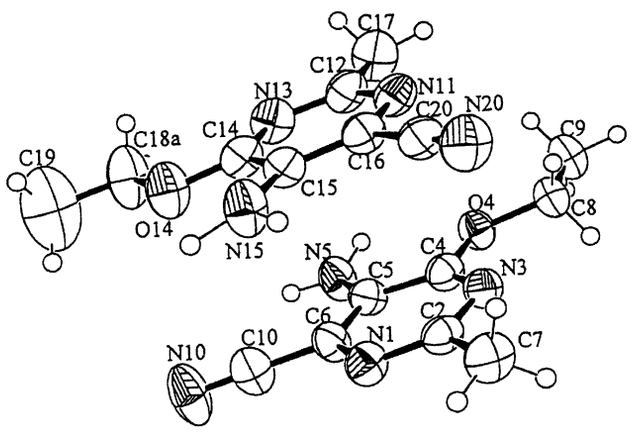



**Fig. 1** X-Ray structure of 5-amino-6-ethoxy-2-methylpyrimidine-4-carbonitrile.

Pyrimidine formation is interesting as it implies rotation around the $C_1$–$C_2$ double bond of the salt at some stage of the reaction. The most rational explanation being the formation of the imidoyl chloride, *via* a nitrilium salt, and reaction with ethanol to give an imidate, which then cyclises (see Scheme 2). Whether bond rotation occurs at the nitrilium salt, imidoyl chloride or the imidate stage is unclear, but it may well be linked to weakening of the double bond due to the push–pull system involved. We believe the imidoyl chloride to be a critical intermediate in this reaction, as the use of other acid catalysts, such as sulfuric and acetic acids under similar conditions gives only traces of **6**. Rotation of the $C_1$–$C_2$ double bond

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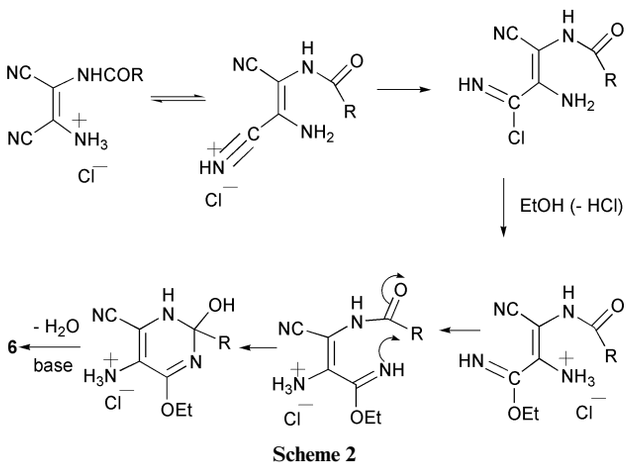


**Scheme 2**

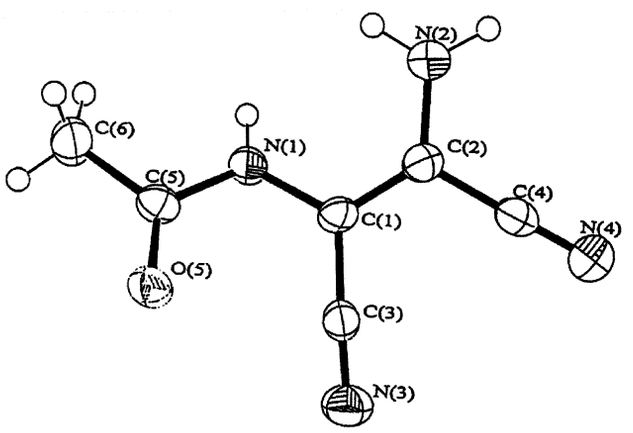


**Fig. 2** X-Ray crystal structure of *N*-(2-amino-1,2-dicyanovinyl)-acetamide.

is reported to occur in the conversion of DAMN to diiminosuccinonitrile, DISN under the influence of oxidising agents such as $MnO_2$, $PdO_2$ or $Fe^{3+}$ salts,[14,15] and conversion of DAMN to diaminofumaronitrile, DAFN,[16] and to 4-amino-5-cyanoimidazole, AIC,[17,18] but these last two reactions only occur under the influence of UV light. An X-ray structure determination on the amide **2** (R = Me, Fig. 2)§ shows a normal $C_1$–$C_2$ double bond distance of 1.341 Å and, not surprisingly, there is no hydrogen bonding between the O atom of the amide carbonyl group and the amino group attached to $C_2$. There is nothing from the X-ray structure to account for any weakening of the C=C bond in the starting amide, and this would support the argument that rotation only occurs after protonation of the nitrile group.

There are, of course, many methods available for the synthesis of pyrimidines, but on a practical level this reaction represents a simple, one step synthesis of highly functionalised pyrimidines from cheap, and readily available starting materials.

## Notes and references

† *N*-(2-Ammonio-1,2-dicyanovinyl)acetamide chloride (1.0 g, 5.0 mmol) was refluxed in ethanol (20 $cm^3$) for 1.5 h, before cooling the mixture to room temperature and neutralising to pH 7. Removal of the solvent gave a dark brown solid which was chromatographed (silica, EtOAc–DCM 1:1) to give **6a** (0.4 g, 44%). Mp 67–69 °C [Found: C, 53.8; H, 5.6; N, 31.5; *m/z* (FAB) $(M + 1)^+$ 179, 100%; $C_8H_{10}N_4O$ requires C, 53.9; H, 5.6; N, 31.5%; *M* 178]; $\delta_H$ 400 MHz ($CDCl_3$) 1.43 (t, 3H, $^3J_{8,7}$ 7.14 Hz, $H_8$), 2.50 (s, 3H, $H_9$), 4.49 (br s, 2H, $NH_2$), 4.51 (q, 2H, $^3J_{7,8}$ 7.14 Hz, $H_7$) ppm; $\delta_C$ 100 MHz ($CDCl_3$) 158.4 (C2), 156.8 (C6), 132.4 (C4), 118.0 (C5), 115.4 (CN), 63.9 (C7), 25.2 (C9), 14.6 (C8) ppm; $\nu_{max}$ (KBr disc) 3480m, 3350m sh, 2980w, 2950w, 2215m, 1650m, 1560m, 1490m sh, 1470m sh, 1390m, 1270m, 1240w, 1150m, 1040w $cm^{-1}$.

‡ *Crystal data*: $C_8H_{10}N_4O$, $M = 179.2$, triclinic, $a = 8.9484(10)$, $b = 10.087(2)$, $c = 11.163(2)$ Å, $\alpha = 78.86(2)$, $\beta = 89.33(2)$, $\gamma = 69.04(2)°$, $V$ 921.4(3) $Å^3$, space group $P\bar{1}$, $Z = 2$, $D_x = 1.285$ mg $m^{-3}$, yellow needles. Crystal dimensions 0.35 × 0.35 × 0.25 mm. $\mu$(Mo-Kα) = 0.091 $mm^{-1}$, 3461 reflections measured, 3232 unique ($R_{int} = 0.0342$) which were used in all calculations. The final $wR(F^2)$ was 0.2497 (all data). At C18 the structure is disordered over two sites C18a and C18b. CCDC reference number 207/508. See http://www.rsc.org/suppdata/p1/b0/b009804n/ for crystallographic files in .cif format.

§ *Crystal data*: $C_6H_6N_4O$, $M = 150.15$, monoclinic, $a = 4.6631(10)$, $b = 17.102(2)$, $c = 9.1625(10)$ Å, $\alpha = 90.00(2)$, $\beta = 93.764(10)$, $\gamma = 90.00(2)°$, $V$ 729.1(2) $Å^3$, space group $P2_1/c$, $Z = 4$, $\mu$(Mo-Kα) = 0.101 $mm^{-1}$, 1438 reflections measured, 1277 unique ($R_{int} = 0.0238$), $D_x$ 1.368 mg $m^{-3}$, colourless needles. Crystal dimensions: 0.35 × 0.35 × 0.15 mm. The final $wR(F^2)$ was 0.1215 (all data).


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