Regioselective synthesis of 4'-amino-1'H-spiro[cyclohexane-1,2'-(pyrimido[1,2-*a*]benzimidazole)]-3'-carbonitrile in aqueous medium

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A simple, mild and environment-friendly procedure for synthesis of 4'-amino-1'*H*-spiro[cyclohexane-1,2'-(pyrimido[1,2-*a*]benzimidazole)]-3'-carbonitrile is developed using microwave irradiation in water. The product is obtained in short time, in excellent yield, and in a good state of purity. The reaction pathway and the influence of reaction conditions on regiochemistry are also investigated. The regioselectivity in this process is confirmed chemically and by single-crystal X-ray molecular structure determination.

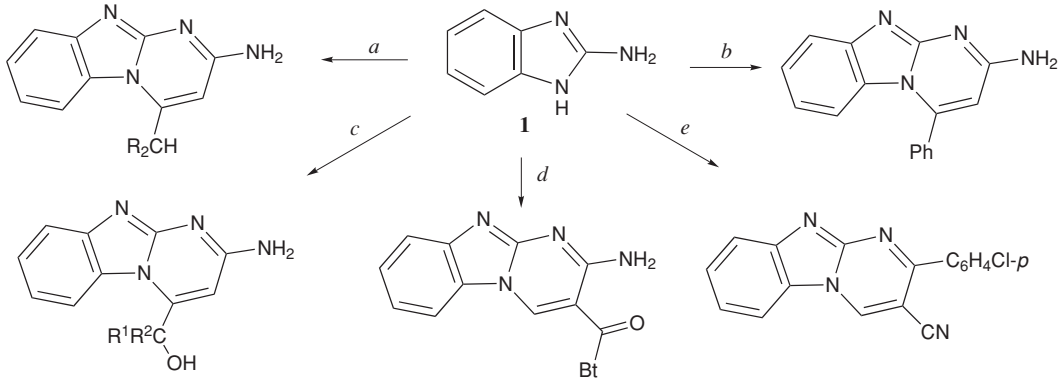
Keywords: fused pyrimidines, benzimidazoles; microwave irradiation, aqueous media

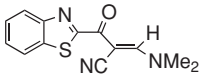
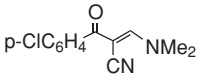
Benzimidazole (1,3-dideazapurine) is an important nucleus, extensively used in medicinal chemistry, notable clinical examples being the antihistaminic Astemizole, the antiulcerative Omeprazole and the fungicide Rabenzazole.[1]

Pyrimido[1,2-*a*]benzimidazoles represent core structures that are useful templates for the design of a variety of compounds. From high throughput screening, a number of analogues have been found to be of pharmacological interest.[2-9]

These biological activities have prompted the development of new general procedures for the synthesis of pyrimido[1,2-*a*] benzimidazoles. Conventionally, these compounds have been synthesised by reaction of 2-aminobenzimidazole with substituted cinnamic acids,[10] with sulfones in acetonitrile,[11] with suitable halogeno-β-diketones,[12] with αβ-unsaturated ketones and hydrochlorides of Mannich base,[13] with ethyl α-arylazo-β-oxobutyrates,[14] with allenic nitriles,[15] with 3-phenylpropyne nitriles,[16] with hydroxyacetylenic nitriles,[17] and with enaminonitriles.[18] Pyrimido[1,2-*a*]benzimidazoles are also synthesised by reaction of 1-ethyl-2-amino-benzimidazoles with 1-bromo-3-chloropropane in toluene,[19] and by the reaction of 1,2-diaminobenzimidazoles with β-dielectrophiles.[20] Cyclocondensation of substituted 3-oxo-propenenitrile with 2-aminobenzimidazole is also reported to give pyrimido[1,2-*a*]benzimidazoles[21] (Scheme 1).

Traditional methods involving the use of volatile organic solvents under reflux and strong acids/bases as catalyst give low yields due to extended reaction times. Further, the products are generally purified by crystallisation or column chromatography with additional use of solvent. Consequently there is need for milder conditions, increased variety of the substituents in the component, and improvement in yields. There is also controversy regarding the structure of the products obtained by the reaction of 2-aminobenzimidazole, including those with allyl,[15] alkyne[16,17] or enaminonitriles.[18,21] An extensive literature survey of reactions of 2-amino-benzimidazole leading to the formation of pyrimido[1,2-*a*]-benzimidazoles indicated that there is a definite need to study the detailed mechanistic pathway and regiochemistry of the



	Reagents / conditions	Reference
a	$R_2C{=}C{=}CH{-}CN$ / Δ, DMF	15
b	$Ph{-}C{\equiv}C{-}CN$ / Δ, DMF	16
c	R^1, $R^2{-}C(HO){-}C{\equiv}C{-}CN$	17
d	 / Δ, Dry xylene	18
e	 / Δ, C_2H_5OH	21

Scheme 1 Literature synthesis of pyrimido[1,2-*a*]benzimidazoles.

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synthetic processes and the development of new methods for the regioselective synthesis of these compounds. The use of water as a reaction medium has attracted attention in recent years,[22] which prompted us to perform these reactions in water.

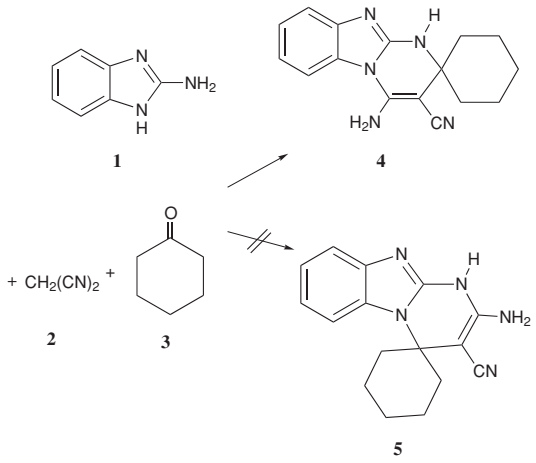
Interest in 'green chemistry' leads to carrying out organic reactions under solvent-free, dry media conditions[23] aimed at reducing the use of toxic solvents and thus preventing pollution in organic synthesis at the source. Reactions under microwave irradiation[24] are clean, fast and economical and provide a non-conventional energy source that has the advantage of short reaction times with high yields and regioselectivity. A further aspect of the present work, multi-component reactions (MCRs), is of increasing importance in organic and medicinal chemistry,[25] particularly where there is a premium on speed, diversity, and efficiency in drug discovery,[26] offering significant advantages over conventional linear-type syntheses.[27,28]

On account of the various biological activities associated with pyrimido[1,2-*a*]benzimidazoles, our ongoing programme to develop benign and expeditious methods for organic transformation under solvent-free conditions using MW irradiation,[29] and our interest in green chemistry using water as energy transfer medium,[30] we planned to synthesise a compound structurally related to the biologically important pyrimido[1,2-*a*]benzimidazoles by reacting 2-amino-benzimidazole with malononitrile and cyclohexanone.

Results and discussion

The synthesis of the target pyrimido[1,2-*a*]benzimidazole (**4**, Scheme 2) by multicomponent condensation was studied under different reaction conditions to find out the best method, giving the product in higher yield with operational simplicity. In the present work we studied the synthesis of 4'-amino-1'*H*-spiro[cyclohexane-1,2'-(pyrimido[1,2-*a*]benzimidazole)]-3'-carbonitrile as shown in Table 1.

A ready reaction took place under neat conditions, without solvent or catalyst, using microwaves, but the product required further purification and recrystallisation was required, giving a somewhat lowered yield. Further, although reaction in ethanol also occurs smoothly, it requires due precautions and modifications in the microwave oven for operational safety. However, a very facile reaction occurred in aqueous medium



Scheme 2 Synthesis of compound **4**.

both on microwave and ultrasonic irradiation. The crystalline product separated after cooling in case of microwaves in high yields with no need for further purification and crystallisation.

To improve the procedure further, the reaction was also studied using cetyl trimethyl ammonium bromide as phase transfer catalyst (Table 1, entries ix and x) but the yield was unaffected, although the reaction time was reduced slightly. Hence it may be concluded that reaction in aqueous medium is the perfect method for this synthesis.

The reaction was also studied under conventional conditions. In the absence of catalyst, no reaction occurred in ethanol, while in aqueous medium a long reaction time was required and a lower yield obtained.

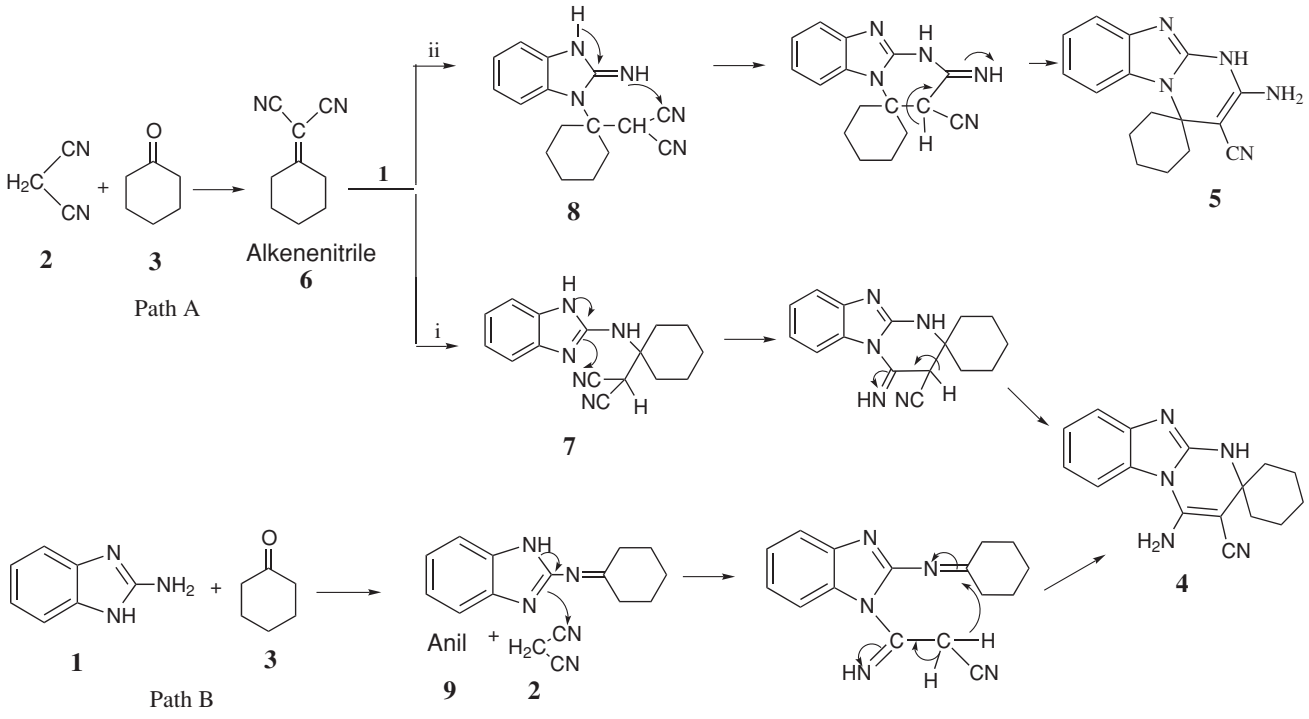
The multi-component condensation reaction of **1**, **2a** and **3** gives a product of molecular formula $C_{16}H_{17}N_5$. Based on literature survey, two possible isomeric structures **4** and **5** may be proposed, as both the amino function and ring nitrogen in 2-aminobenzimidazole are active sites for nucleophilic attack on αβ-unsaturated nitriles[15-18,21] (Scheme 3).

Two routes for the formation of **4** may be postulated. The first route (path A) involves the condensation of carbonyl compound with active methylene reagent to afford the corresponding β–arylacrylonitrile derivative (**6**) followed by

Table 1 Comparative study for synthesis of 4'-amino-1'*H*-spiro[cyclohexane-1,2'-(pyrimido[1,2-*a*]benzimidazole)]-3'-carbonitrile

Entry	Reaction conditions	Method	Time/Yield/%
i	Ethanol (MCR)[a]	Δ	No reaction
ii	Ethanol/Et_3N (MCR)	Δ	7 h/52
iii	Ethanol (MCR)	MW[c]	5 min/82
iv	Ethanol (MCR)	Ultrasound	4 h/86
v	Water (MCR)	Δ	8 h/70
vi	Water (MCR)	MW[c]	10 min/82
vii	Water (MCR)	Ultrasound	6 h/78
viii	Neat (MCR)	MW	3 min/81
ix	Water/PTC[b] (MCR)	MW	8 min/80
x	Water/PTC[b] (MCR)	Ultrasound	3.5 h/80
xi	Alkene nitrile[d] (**2 + 3**) + **1** (ethanol)	MW	8 + 4[f] min/82
xii	Alkene nitrile (**2 + 3**) + **1** (water)	MW	5 + 4[f] min/80
xiii	Anil[e] (**1 + 3**) + **2** (ethanol)	MW	4 + 5[g] min/83
xiv	Anil (**1 + 3**) + **2** (water)	MW	4 + 4[g] min/82

[a]Multi-component reaction carried out in one pot.
[b]Cetyl trimethyl ammonium bromide is used as phase transfer catalyst for entries (ix) and (x).
[c]Power: 600 watt for water and 360 watt for alcohol.
[d]Alkene-nitrile synthesised *in situ* from malononitrile (**2**) + cyclohexanone (**3**).
[e]Anil synthesised *in situ* from 2-aminobenzimidazole (**1**) + cyclohexanone (**3**).
[f]8/5 + 4 indicates, first irradiated for 8 or 5 min gives intermediate, alkene-nitrile (detected by TLC) which was synthesised *in situ* and then further irradiated for 4 min after adding 2-aminobenzimidazole.
[g]4 + 5/4 indicates, first irradiated for 4 min gives intermediate, anil (detected by TLC) which was synthesised *in situ* and then further irradiated for 5 or 4 min after adding malononitrile.



Scheme 3 Pathways to **4**.

addition of exocyclic amino function of 2-aminobenzimidazole (**1**) to the activated double bond system in **6** to form the Michael adduct **7.** This would then undergo intramolecular cyclisation to give **4.** Alternatively, the addition of the ring nitrogen may occur to **6** to form the Michael adduct **8**; this would lead to the formation of regioisomer **5**, which is not observed. The second route (path B) is the condensation of the ketone **3** with 2-aminobenzimidazole to afford the corresponding Schiff base (**9**) in the first step followed by the addition of the active methylene moiety to form **4.**

X-ray crystallographic analysis of the product of the multi-component reaction of **1**, **2** and **3** confirms the structure **4**, indicating the apparently complete regioselectivity of the reaction.

To confirm the pathway we carried out the reaction of the pre-synthesised alkene-nitrile **6** with 2-aminobenzimidazole (path A) and the reaction of anil **9** with malononitrile (path B), where in all cases the identical product (**4**) was obtained. Thus, even in the case of the alkene nitrile the product results from the attack of the amino group (path Ai) and not by the ring nitrogen. This is in contrast to earlier reports in which the reaction of 2-aminobenzimidazole with allyl,[15] alkyne[16,17] or enaminonitriles[18,21] apparently proceeds by initial attack of the ring nitrogen of the benzimidazole, followed by cyclisation to give isomeric pyrimido[1,2-*a*]benzimidazoles.

Molecular structure of $C_{16}H_{17}N_5$ (**4**)

$C_{16}H_{17}N_5$, which crystallises in the space group C2/c, is displayed as an ORTEP diagram in Fig. 1. The structure supports the regioselective formation of the tautomer **4**. The pyrimidobenzimidazole moiety is planar, in agreement with other benzimidazole compounds,[31-34] where the presence of formalized imidazole double bonds can be seen with bond lengths of 1.321(2) for C(7)–N(1) in the imidazole moiety and 1.369(2) Å for C(8)–C(9) in the pyrimido ring suggests the formation of the regioisomer **4**. A similar localised double bond is seen in 2-methyl-3*H*-1,2,4-triazepino[2,3-*a*] benzimidazol-4(5*H*)-one where the C–N bond length is 1.364(6) Å. [31] The bond lengths of 1.401(2) for C(8)–N(2),

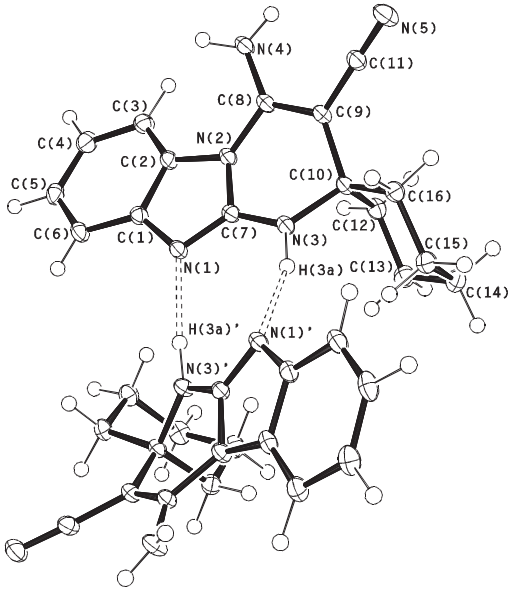
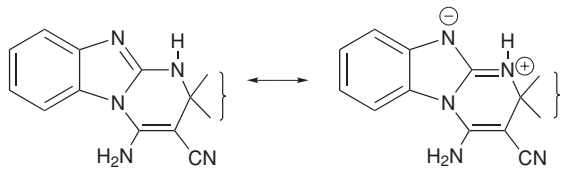


Fig. 1 Crystal structure of **4**.

1.404(2) for C(7)–N(2), 1.479(2) for C(10)–N(3) and 1.528(2) Å for C(9)–C(10) suggest the presence of single bonds between the pairs of atoms. The bond length of 1.333(2) Å for C(7)–N(3), at first appearance, is somewhat shorter than expected. However, partial double-bond character in the C(7)–N(3) bond is consistent with the presence of the hydrogen bond N(3)–H(3a)----N(1)' (Fig. 1) and is also supported by the resonance form depicted in the diagram (Fig. 2). The bond lengths ranging from 1.390(3) to 1.403(3) Å are as expected for the benzene ring, as is that of 1.158(3) Å for the triple bond C(11)–N(5).

The bond angles in the five-membered imidazole ring are in the same range (104.5(2) to 113.4(2)°) as was found for 2-methyl-3*H*-1,2,4-triazepino[2,3-*a*]benzimidazol-4(5*H*)-one (104.1(3) to 113.3(3)°).[31] Similarly, the bond lengths and



4

Fig. 2

angles of the cyclohexane ring are as expected, and Fig. 1 clearly shows that it is in the chair form.

Experimental

Melting points were determined on a Toshniwal apparatus. The compound purity was checked on thin layers of silica gel in various non-aqueous solvent systems, *e.g.* benzene:ethyl acetate (9:1), benzene:dichloromethane (8:2). IR spectra (KBr) were recorded on a Magna FT IR–550 spectrophotometer and ^{1}H and ^{13}C NMR spectra was recorded on Bruker DRX-300 using $CDCl_3$ at 300.15 and 75.47 MHz respectively. TMS was used as internal reference. Mass spectrum was recorded on Kratos 50 mass spectrometer at 70 eV. The microwave-assisted reactions were carried out in a multimode MW oven (Panasonic-NN-781JF) equipped with inverter technology (generating fixed frequency throughout the required time) for realistic control of the microwave operating at 1000 W generating 2450 MHz frequency and ultrasonic bath (Bandelin Sonorex) operating at 230 V generating 33 KHz output frequency.

Synthesis of 4'-amino-1'H-spiro[cyclohexane-1,2'-(pyrimido[1,2-a] benzimidazole)]-3'-carbonitrile (**4**)

This was carried out following the procedures below.

(a) Conventional method: 2-Aminobenzimidazole (**1**) (0.01 mol), malononitrile (**2**) (0.01 mol) and cyclohexanone (**3**) (0.01 mol) were heated to refluxed in ethanol (50 ml) for 3 days. However, no reaction occurred. Triethylamine (4–5 drops) was added to the reaction mixture, when there was an immediate colour change from light yellow to reddish yellow. The reaction was continued for 5 h (TLC control). The reaction mixture was kept overnight at room temperature and the resulting precipitate of **4** was filtered off, washed with ethanol, dried and recrystallised from ethanol.

(b) Neat/microwave heating: An equimolar (0.01 mol) neat mixture of **1**, **2** and **3** in an open vessel was mixed thoroughly with a rod. Heat was evolved and the colour changed from white to pale yellow. The mixture was then irradiated in a MW oven at a power output of 600 W for an appropriate time (monitored by TLC). The mixture took on a dark yellow to reddish colour. After completion of the reaction, ethanol (10 ml, sufficient to dissolve melted solid was added) before filtration. The filtrate was kept overnight in the refrigerator and white shiny crystals formed, which were filtered off and recrystallised from ethanol.

(c) In ethanol/microwave heating: Equimolar (0.01 mol) quantities of **1**, **2** and **3** were placed in a beaker and the minimum quantity of ethanol sufficient to make a slurry was added. The mixture was placed in the MW oven and irradiated at 360 W for 4–5 min (TLC). The product started to separate out immediately after cooling the reaction mixture to room temperature (or in some cases during the course of reaction). The crystalline solid that separated was filtered off and found to be pure on TLC with no need of further recrystallisation.

(d) In ultrasonic bath: equimolar (0.01 mol) quantities of **1**, **2** and **3** were placed in a beaker and dissolved in ethanol containing triethylamine (3–4 drops). The mixture was placed in an ultrasonic bath generating 33 KHz output frequency for 30–40 min (TLC) at room temperature. The product that separated out during the course of the irradiation was filtered off and found to be pure **4** by TLC.

(e) In water/microwave heating: equimolar (0.01 mol) quantities of **1**, **2** and **3** were placed in a beaker and water (10 ml) was added. The mixture was placed in the microwave oven and irradiated at power output 600 watts for 7–8 min (TLC). The product started to separate out immediately after cooling the reaction mixture to room temperature. The crystalline solid that separated out was filtered and found to be pure by TLC.

The yields and reaction times are shown in Table 1; it is evident that synthesis in aqueous medium is the best method. The product formed white shiny crystals (2.28 g, 82%); m.p. 240–241°C.

Table 2: Crystal data and structure refinement for compound **4**

Empirical formula	$C_{16}H_{17}N_5$
Formula weight	279.35
Temperature, K	120(2)
Wavelength , Å	0.71073
Crystal system	Monoclinic
Space group	*P*2/c
a, Å	14.400(1)
b, Å	10.1342(9)
c, Å	11.2659(5)
β, °	103.043(7)
Volume, Å^3	1601.6(2)
Z	4
Density (calculated), g/cm^3	1.159
Absorption coefficient, mm^{-1}	0.073
F(000)	592
Crystal dimensions, mm	0.18 × 0.18 × 0.16
θ range for data collection, °	3.29 to 27.43
Index ranges	$-18 \le h \le 18$, $-13 \le k \le 12$, $-14 \le l \le 12$
Reflections collected	20917
Independent reflections	3625 [R_{int} = 0.0289]
Max. and min. transmission	0.9884 and 0.9870
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3625 / 0 / 259
Goodness-of-fit on F^2	1.075
Final *R* indices [$F^2>4\sigma$ (F^2)]	R_1 = 0.0663, wR_2 = 0.1977
R indices (all data)	R_1 = 0.0737, wR_2 = 0.2069
Extinction coefficient	0.05(1)
Largest diff. peak and hole, e Å^{-3}	1.154 and –0.456

IR (KBr): ν_{max} 3475–3240 (br, NH, NH_2, D-exchangeable), 2925–2875 (br, ali. CH), 2185 (CN), 1610 cm^{-1} (C=N). ^{1}H NMR (DMSO): δ 1.27–1.32 (m, 4H,CH_2), 1.65–1.91 (m, 6H, CH_2), 5.85 (s, 2H, NH_2), 7.05 (t, 1H, H-7), 7.16 (t, 1H, H-8), 7.33 (d, 1H, H-9), 7.61 ppm (d, 1H, H-6). ^{13}C NMR (DMSO): δ 20.4 (CH_2, C_3'), 24.57 (CH_2, C_4'), 36.7 (CH_2, C_6'), 36.9 (CH_2, C_2'), 52.76 (C_2, spiro carbon), 68.36 (C_3, C–CN), 112.06 (C_6), 115 (C_9), 118.5 (C_7), 119.4 (CN), 122.9 (C_8), 129.7 (C_{5a}), 143.63 (C_9, CH– C–N), 148.9 (C_{10}, C=N), 151.58 ppm (C_4, C–NH_2). MS (EI, 70ev): *m/z* 279 (M^+) (41), 236 (100), 223 (24), 198 (1.1), 170 (2.4), 159 (2.0), 144 (2.8), 133 (17), 118 (5.4) Anal. Calc for $C_{16}H_{17}N_5$ (279.34): C, 68.79; H, 6.13; N, 25.07. Found C, 68.99; H, 6.11; N, 25.15%.

X-ray diffraction analysis: A colourless block crystal of compound **4**, $C_{16}H_{17}N_5$, was mounted on a glass fibre. Data were collected on a Bruker-Nonius Kappa CCD area detector diffractometer, with ϕ and ω scans chosen to give a complete asymmetric unit. Cell refinement[35] gave cell constants corresponding to a monoclinic cell whose dimensions are given in Table 2 along with other experimental parameters. An absorption correction was applied.[36]

The structure was solved by direct methods[37] and was refined using the WinGX version[38] of SHELX-97.[39] All of the non-hydrogen atoms were treated anisotropically. Hydrogen atoms were located in the difference map and fully refined. The final cycle of full-matrix least-squares refinement was based on 3625 observed reflections (3157 for $F^2 > 4\sigma(F^2)$) and 259 variable parameters and converged (largest parameter shift was 0.001 times its esd).

Additional material, available from the Cambridge Crystallographic Data Centre (CCDC no. 298206), comprises the final atomic coordinates for all atoms, thermal parameters, and a complete listing of bond distances and angles. Copies of this information may be obtained free of charge on application to The Director, 12 Union Road, Cambridge CB2 2EZ, UK (fax: + 44 1223 336 033; email: deposit@ccdc.cam.ac.uk or www: http: //www.ccdc.cam.ac.uk).

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