6,8-Dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione: a novel approach to imidazoline (imidazole) ring annulation based on the S_N^H methodology

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The $N_{(2)}$-oxide and 3-amino derivatives of the title compound react with alkylamines in the presence of an oxidant to produce condensed imidazolines or their imidazole analogues.

Condensed imidazoles, particularly purines and benzimidazoles, are very important heterocyclic compounds.[1–3] They are widely used in organic synthesis to prepare pharmaceuticals, pesticides and thermally stable polymers. They are also constituents of natural compounds such as nucleic acids and vitamin B_{12}. Consequently, the synthesis of imidazole systems is of considerable interest. The traditional synthetic methods involve the annulation of an imidazole ring to another aromatic system as summarised in Scheme 1 (**A**–**D**). Here, we report a novel approach to the construction of condensed imidazole and imidazoline rings (Scheme 1, **E**–**G**).

We found earlier[4] that 6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione $N_{(2)}$-oxide **1** reacts with ammonia, primary or secondary amines in the presence of $KMnO_4$ or $AgPy_2MnO_4$ to give a mixture of 3-amino derivatives **2** and **3** in overall yields of 50–68% (Scheme 2). A similar reaction with cyclohexylamine or isopropylamine unexpectedly affords imidazolines **4a**,**b** in 4.5 and 10% yields, respectively, along with amines **3a**,**b**. The molecular structure of 3-cyclohexyl-6,8-dimethyl-7,9-dioxo-2,3,6,7,8,9-hexahydroimidazo[4′,5′:3,4]pyridazino[6,5-*d*]pyrimidine-2-spirocyclohexane **4a** was confirmed by the X-ray diffraction analysis of its perchlorate (Figure 1).†

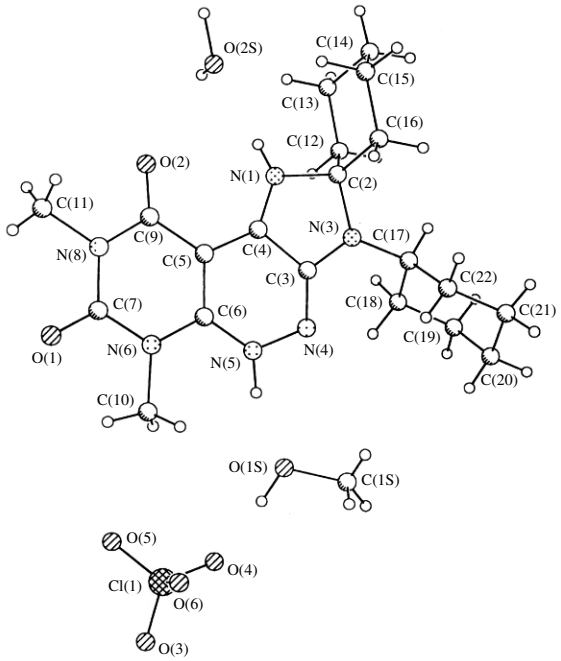
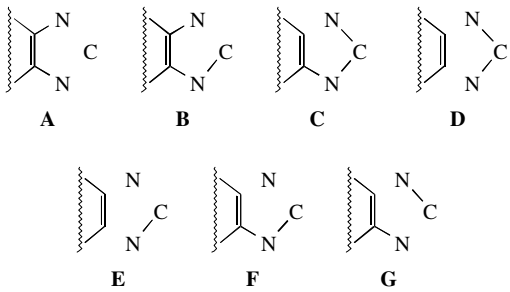
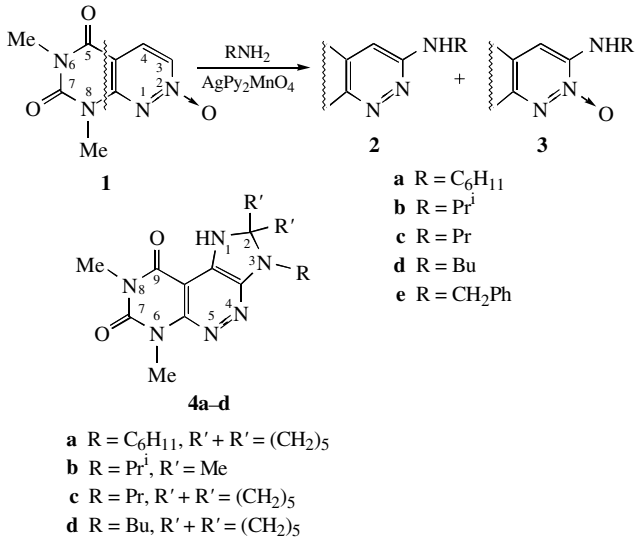


Figure 1 General view of **4a** perchlorate. Selected bond lengths (Å): N(1)–C(4) 1.310(2), N(1)–C(2) 1.482(2), N(3)–C(3) 1.351(2), N(3)–C(2) 1.4790(19), N(4)–C(3) 1.304(2), N(4)–N(5) 1.3891(19), N(5)–C(6) 1.325(2), C(5)–C(9) 1.443(2), N(6)–C(6) 1.367(2), N(6)–C(7) 1.396(2), N(8)–C(9) 1.381(2), N(8)–C(7) 1.395(2), C(3)–C(4) 1.449(2), C(4)–C(5) 1.387(2), C(5)–C(6) 1.408(2); selected bond angles (°): C(4)–N(1)–C(2) 112.48(13), C(3)–N(3)–C(2) 111.28(13), C(3)–N(4)–N(5) 114.52(13), C(6)–N(5)–N(4) 125.07(13), C(6)–N(6)–C(7) 122.04(14), C(9)–N(8)–C(7) 124.28(14), N(3)–C(2)–N(1) 100.04(13), N(4)–C(3)–C(4) 124.93(15), N(3)–C(3)–C(4) 107.38(13), N(1)–C(4)–C(3) 108.50(14), C(5)–C(4)–C(3) 118.01(14), C(4)–C(5)–C(6) 116.37(14), C(6)–C(5)–C(9) 120.62(14), N(5)–C(6)–C(5) 121.05(14), N(6)–C(6)–C(5) 119.30(14), N(8)–C(7)–N(6) 117.19(14), N(8)–C(9)–C(5) 115.81(14).



Scheme 1

The transformation of **1** into **4a** is likely to occur *via* 3-cyclohexylamino derivative **2a**, as shown in Scheme 3. Compound **2a** undergoes a second addition across the C=N bond of



Scheme 2

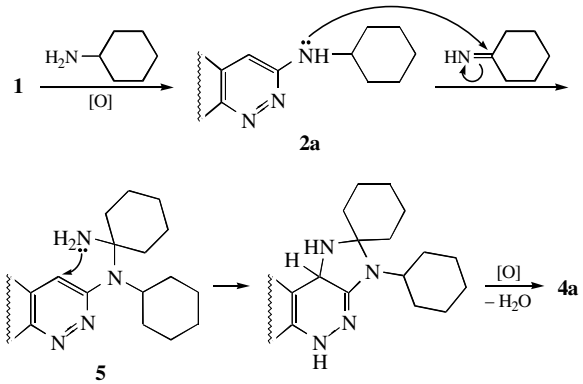
† *Crystallographic data for* **4a**: at 110 K crystals of $C_{20}H_{29}N_6O_2 \cdot H_2O \cdot MeOH$ are monoclinic, space group $P2_1/c$, $a = 8.9740(19)$ Å, $b = 10.055(2)$ Å, $c = 27.162(6)$ Å, $\alpha = 90°$, $\beta = 90.744(4)°$, $\gamma = 90°$, $V = 2450.7(9)$ Å^3, $Z = 4$, $M = 525.99$, $d_{calc} = 1.426$ g cm^{-3}, μ(MoKα) = 0.213 mm^{-1}, $F(000) = 1116$. Intensities of 15260 reflections were measured with a Smart diffractometer at 110 K and 5997 independent reflections ($R_{int} = 0.0266$) were used in further refinement. The structures were solved by direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic-isotropic approximation. Hydrogen atoms were located from the Fourier synthesis and refined in the isotropic approximation. The refinement converged to $wR_2 = 0.1386$ and GOF = 1.041 for all independent reflections [$R_1 = 0.0495$ was calculated against F for 4460 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXL-97 on an IBM PC AT. Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2002. Any request to the CCDC for data should quote the full literature citation and the reference number 1135/114.

cyclohexanone imine (generated *in situ* from cyclohexylamine) to give *gem*-diamine **5**. Subsequent intramolecular amination and oxidation steps furnish spirocyclic product **4a**. Imidazoline **4b** is evidently formed in the same manner. This mechanism is supported by the observation that specially prepared 3-amino derivatives **2a** and **2b**, upon treatment with cyclohexylamine or isopropylamine in the presence of $AgPy_2MnO_4$, form compounds **4a** and **4b**, respectively, in 60–65% yields.‡

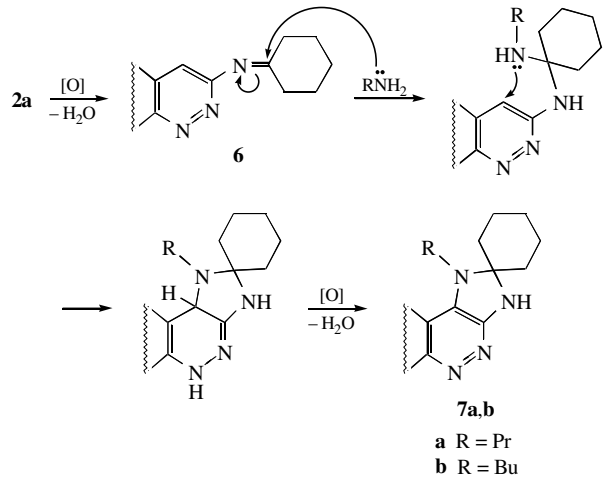
The use of various combinations of 3-aminopyridazines **2** and alkylamines results in the synthesis of other fused imidazolines and even imidazoles. Thus, the reaction of **2c** and **2d** with cyclohexylamine gives spiroimidazolines **4c** and **4d**, respectively.§ At the same time, the interaction of **2a** with propylamine or butylamine produces isomeric imidazoline **7a** or **7b**¶ and possibly proceeds *via* imine **6** (Scheme 4).

3-Benzylamino derivative **2e** reacts with alkylamines such as **2a**. However, in these cases, adducts **8** are oxidized to imidazoles **9a**–**d** (Scheme 5).†† When compounds **2a** and **2c** were treated with benzylamine in the presence of an oxidant, isomeric imidazoles **10a** and **10b** were obtained (Scheme 6).‡‡

One more significant finding concerns the nature of hydrogen atom substitution accompanying imidazole-ring closure. Previously, three different mechanisms have been reported for such cyclizations: nitrene (radical) insertion into a C–H bond,[5] electrophilic cyclization[6] and vicarious nucleophilic substitution.[7] As



Scheme 3



a R = Pr
b R = Bu

Scheme 4

‡ *Typical procedure for the synthesis of* **4**: To a stirred solution of **2a** (0.43 g, 1.5 mmol) in cyclohexylamine (30 ml), $AgPy_2MnO_4$ (0.9 g, 2.3 mmol) was added in portions at 15–20 °C. After stirring for a week at 20 °C, the liquid phase was concentrated to dryness. The residue was extracted with boiling $CHCl_3$ (50 ml). TLC on Al_2O_3 ($CHCl_3$) followed by recrystallization from EtOH gave **4a** (0.37 g, 65%) as yellow crystals.

All compounds **4** gave analytical and spectral data consistent with their structures.

For *3-cyclohexyl-6,8-dimethyl-7,9-dioxo-2,3,6,7,8,9-hexahydroimidazo[4',5':3,4]pyridazino[6,5*-d*]pyrimidine-2-spirocyclohexane* **4a**: mp > 320 °C (decomp.). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.20–1.90 (m, 18H, cyclohexyl), 2.66 (m, 2H, cyclohexyl), 3.06 (m, 1H, cyclohexyl), 3.34 [s, 3H, Me–N(6)], 3.59 [s, 3H, Me–N(8)], 7.59 [s, 1H, NH]. IR (Nujol, ν/cm^{-1}): 1677, 1698 (C=O), 3445 (N–H). MS, *m/z*: 384 (M^+).

For *3-isopropyl-2,2,6,8-tetramethyl-7,9-dioxo-2,3,6,7,8,9-hexahydroimidazo[4',5':3,4]pyridazino[6,5*-d*]pyrimidine* **4b**: yield 60%, mp > 300 °C (decomp.). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.55 (d, 6H, CHMe_2, *J* 6.8 Hz), 1.60 (s, 6H, CMe_2), 3.35 [s, 3H, Me–N(6)], 3.60 [s, 3H, Me–N(8)], 3.62 [m, 1H, C*H*Me_2], 7.17 [s, 1H, NH]. IR (Nujol, ν/cm^{-1}): 1671, 1699 (C=O), 3434 (N–H). MS, *m/z*: 304 (M^+).

§ For *3-propyl-6,8-dimethyl-7,9-dioxo-2,3,6,7,8,9-hexahydroimidazo[4',5':3,4]pyridazino[6,5*-d*]pyrimidine-2-spirocyclohexane* **4c**: yield 19%, mp 242–244 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 0.94 [t, 3H, CH_2CH_2Me, *J* 7.4 Hz], 1.05–1.80 (m, 10H, cyclohexyl), 1.84 (m, 2H, CH_2CH_2Me), 3.32 (t, 2H, CH_2CH_2Me, *J* 7.3 Hz), 3.35 [s, 3H, Me–N(6)], 3.58 [s, 3H, Me–N(8)], 7.57 (s, 1H, NH). IR (Nujol, ν/cm^{-1}): 1670, 1700 (C=O), 3430 (N–H).

For *3-butyl-6,8-dimethyl-7,9-dioxo-2,3,6,7,8,9-hexahydroimidazo[4',5':3,4]pyridazino[6,5*-d*]pyrimidine-2-spirocyclohexane* **4d**: yield 4%, mp 183–185 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 0.93 (t, 3H, $CH_2CH_2CH_2Me$, *J* 7.4 Hz), 1.10–1.93 (m, 14H, cyclohexyl, $CH_2CH_2CH_2Me$), 3.37–3.48 (m, 2H, $CH_2CH_2CH_2Me$), 3.35 [s, 3H, Me–N(6)], 3.59 [s, 3H, Me–N(8)], 7.53 (s, 1H, NH). IR (Nujol, ν/cm^{-1}): 1633, 1700 (C=O), 3327 (N–H).

¶ All compounds **7** gave analytical and spectral data consistent with their structure.

For *1-propyl-6,8-dimethyl-7,9-dioxo-2,3,6,7,8,9-hexahydroimidazo[4',5':3,4]pyridazino[6,5*-d*]pyrimidine-2-spirocyclohexane* **7a**: yield 26%, mp 135–137 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.00 (t, 3H, CH_2CH_2Me, *J* 7.4 Hz), 1.17–2.14 (m, 10H, cyclohexyl and CH_2CH_2Me), 3.37 [s, 3H, Me–N(6)], 3.59 (m, 2H, cyclohexyl), 3.65 [s, 3H, Me–N(8)], 4.00 (m, 2H, CH_2CH_2Me), 9.26 (s, 1H, NH). IR (Nujol, ν/cm^{-1}): 1633, 1700 (C=O), 3420 (N–H).

For *1-butyl-6,8-dimethyl-7,9-dioxo-2,3,6,7,8,9-hexahydroimidazo[4',5':3,4]pyridazino[6,5*-d*]pyrimidine-2-spirocyclohexane* **7b**: yield 8%, mp 120–121 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 0.94 (t, 3H, $CH_2CH_2CH_2Me$, *J* 7.3 Hz), 1.17–1.74 (m, 10H, cyclohexyl and $CH_2CH_2CH_2Me$), 2.10–2.15 (m, 2H, $CH_2CH_2CH_2Me$), 3.37 [s, 3H, Me–N(6)], 3.61–3.67 (m, 2H, cyclohexyl), 3.65 [s, 3H, Me–N(8)], 3.91–4.11 (m, 2H, $CH_2CH_2CH_2Me$), 9.25 [s, 1H, NH]. IR (Nujol, ν/cm^{-1}): 1633, 1687 (C=O), 3353 (N–H). MS, *m/z*: 358 (M^+).

†† All compounds **9** gave analytical and spectral data consistent with their structures.

For *1-propyl-2-phenyl-6,8-dimethylimidazo[4',5':3,4]pyridazino[6,5*-d*]pyrimidine-7,9(6*H*,8*H*)-dione* **9a**: yield 63%, mp 237–239 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 0.64 (t, 3H, CH_2CH_2Me, *J* 7.4 Hz), 1.60 (m, 2H, CH_2CH_2Me), 3.50 [s, 3H, Me–N(6)], 4.00 [s, 3H, Me–N(8)], 4.90 (t, 2H, CH_2CH_2Me, *J* 7.3 Hz], 7.57–7.78 (m, 5H, Ph). IR (Nujol, ν/cm^{-1}): 1675, 1705 (C=O).

For *1-butyl-2-phenyl-6,8-dimethylimidazo[4',5':3,4]pyridazino[6,5*-d*]pyrimidine-7,9(6*H*,8*H*)-dione* **9b**: yield 64%, mp 177–180 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 0.67 (t, 3H, $CH_2CH_2CH_2Me$, *J* 7.3 Hz), 0.95–1.10 (m, 2H, $CH_2CH_2CH_2Me$), 1.40–1.55 (m, 2H, $CH_2CH_2CH_2Me$), 3.53 [s, 3H, Me–N(6)], 3.99 [s, 3H, Me–N(8)], 4.95 (t, 2H, $CH_2CH_2CH_2Me$, *J* 7.4 Hz), 7.53–7.78 (m, 5H, Ph). IR (Nujol, ν/cm^{-1}): 1700, 1713 (C=O).

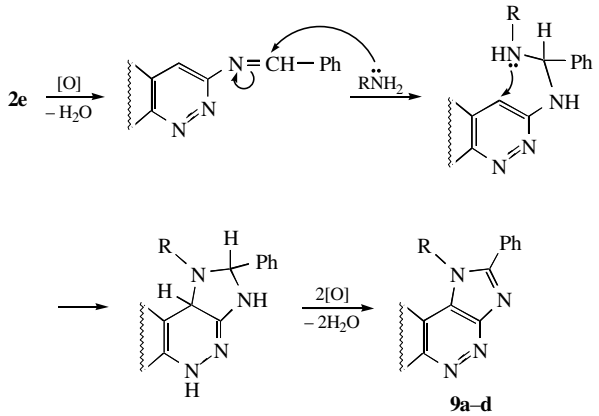
For *1-cyclohexyl-2-phenyl-6,8-dimethylimidazo[4',5':3,4]pyridazino[6,5*-d*]pyrimidine-7,9(6*H*,8*H*)-dione* **9c**: yield 37%, mp 279–281 °C (decomp.). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 0.80–2.00 (m, 10H, cyclohexyl), 3.54 [s, 3H, Me–N(6)], 3.99 [s, 3H, Me–N(8)], 5.45 (m, 1H, cyclohexyl), 7.48–7.68 (m, 5H, Ph). IR (Nujol, ν/cm^{-1}): 1670, 1700 (C=O). MS, *m/z*: 390 (M^+).

For *1-benzyl-2-phenyl-6,8-dimethylimidazo[4',5':3,4]pyridazino[6,5*-d*]pyrimidine-7,9(6*H*,8*H*)-dione* **9d**: yield 18%, mp 198–200 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 3.43 [s, 3H, Me–N(6)], 3.97 [s, 3H, Me–N(8)], 6.23 (s, 2H, CH_2Ph), 6.71–7.20 (m, 5H, CH_2Ph), 7.49–7.75 (m, 5H, Ph). IR (Nujol, ν/cm^{-1}): 1670, 1703 (C=O).

‡‡ All compounds **10** gave analytical and spectral data consistent with their structures.

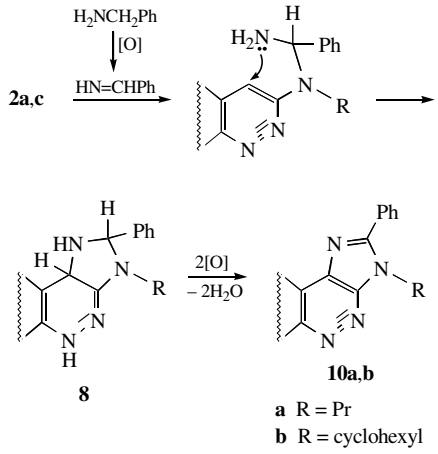
For *2-phenyl-3-propyl-6,8-dimethylimidazo[5',4':3,4]pyridazino[6,5*-d*]pyrimidine-7,9(6*H*,8*H*)-dione* **10a**: yield 6%, mp 221–223 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 0.91 (t, 3H, CH_2CH_2Me, *J* 7.4 Hz), 1.95–2.04 (m, 2H, CH_2CH_2Me), 3.54 [s, 3H, Me–N(6)], 3.96 [s, 3H, Me–N(8)], 4.54 (t, 2H, CH_2CH_2Me, *J* 7.6 Hz), 7.24–7.79 (m, 5H, Ph). IR (Nujol, ν/cm^{-1}): 1653, 1700 (C=O).

For *2-phenyl-3-cyclohexyl-6,8-dimethylimidazo[5',4':3,4]pyridazino[6,5*-d*]pyrimidine-7,9(6*H*,8*H*)-dione* **10b**: yield 14%, mp 275–276 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.29–2.93 (m, 10H, cyclohexyl), 3.52 [s, 3H, Me–N(6)], 3.95 [s, 3H, Me–N(8)], 4.51 (m, 1H, cyclohexyl), 7.24–7.79 (m, 5H, Ph). IR (Nujol, ν/cm^{-1}): 1670, 1700 (C=O). MS, *m/z*: 390 (M^+).



Scheme 5

can be seen, our case is essentially different in this sense and represents an example of classical nucleophilic substitution of a hydrogen during imidazole-ring annulation.



Scheme 6

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