Abstract: A one-pot, Ugi-type three-component coupling process between an aldehyde, an isocyanide and proline tetrazole is reported, leading to new heterocyclic structures in good to excellent yields.

Key words: multicomponent reactions, heterocycles, tetrazole, Ugi reaction, proline derivatives

A multicomponent reaction (MCR) is one in which three or more starting materials react together in a single vessel to form a product which incorporates portions of all the components. MCRs are highly efficient, not only due to their convergent nature, but also because of superior atom economy, and straightforward experimental procedures.

MCRs involving isocyanides are among the most versatile, in terms of the number and variety of compounds which can be generated, and the Ugi reaction is one of the most extensively utilised of these processes. In addition to the diversity which can be generated in the Ugi reaction alone, a range of alternative scaffolds have been created, either by using secondary post-condensation reactions or bifunctional components. For example, several groups have reported the use of α- and β-amino acids in such couplings to generate unique acyclic or heterocyclic structures. However, whilst a survey of the literature reveals that (L)-proline has been used in an Ugi-type four-centre/three-component coupling, tetrazoles such as proline tetrazole and homotetrazole derivative, have not been investigated in this context. It was thus thought that new heterocyclic structures could potentially be generated by simply replacing the traditional α-amino acid component with an α-amino tetrazole.

In our initial study, isovaleraldehyde and p-methoxyphenyl isocyanide were reacted together with either proline, tetrazole or homotetrazole as the bifunctional components (Table 1).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Bifunctional component</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)a</th>
<th>drb</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>48</td>
<td>6,7</td>
<td>39c</td>
<td>1:1.6</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>48</td>
<td>8</td>
<td>60</td>
<td>2.5:1</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>24</td>
<td>9,10</td>
<td>67d</td>
<td>1.2:1</td>
</tr>
</tbody>
</table>

a Overall isolated yield of both isomers.
b Determined by 1H NMR spectroscopy of the crude product mixture.
c Isomers separated by column chromatography (26% major, 13% minor).
d Isomers separated by preparative HPLC (33% major, 29% minor).

Although diastereomeric ratios were moderate to low, it was pleasing to find that, in each reaction, just two isomers of product were formed (Table 1), where there are potentially four. However, although the relationship of the chiral centres could be ascertained, it was not possible to assign the double-bond geometry of the products at this point: a later study was to reveal this information.

In this initial screen, in the case of proline (Table 1, entry 1), a moderate 39% overall yield of bicycles 6 and 7 was found. More encouraging though was that homotetrazole derivative 3 was also a successful substrate, providing the...
desired product 8 in a good 60% yield (Table 1, entry 2),
despite the fact that formation of seven- rather than six-
membered ring was required. Finally, it was pleasing to
discover that the proline tetrazole itself gave the best yield
of products 9 and 10 (Table 1, entry 3), and therefore the
remainder of our investigations centred on the formation
of this unit.

This new heterocyclic framework comprises a rigid 5–6–5-
fused core structure and two points of substitution (alde-
hyde and isocyanide), with potential application in medic-
inal chemistry and compound library synthesis. As
alluded to previously, it is important to note that there are
four possible products which may be formed in this reac-
tion (Figure 2): epimers of the chiral centre containing the
aldehyde substituent, and two double bond isomers, fur-
ther discussion of which follows later.

Figure 2 Possible isomers in the Ugi coupling with tetrazole 2

The reaction is an Ugi-type four-centre/three-component
coupling where the pyrrolidine and the tetrazole act as the
tethered bifunctional amine/acid component, together
with the aldehyde and isocyanide as the remaining two.
With respect to the reaction mechanism, it is plausible that
the iminium ion 15 is attacked by the isocyanide to give
intermediate 16 (Scheme 1), and ring closure would then
result in formation of product 17.

Following this promising initial result, we turned our at-
tention to the optimisation of reaction conditions. Firstly,
a solvent screen was carried out, with proline tetrazole 18,
benzyl isocyanide 19 and isovaleraldehyde 4 (Table 2).
It was found that diastereoselectivity and yield were
strongly affected by solvent. While methanol gave the
lowest yield (Table 2, entry 1), diethyl ether, acetonitrile
and tetrahydrofuran all provided moderate to good yields
and diastereoselectivities (Table 2, entries 2–4). Howev-
er, in terms of diastereoselectivity, the best results were
found in both toluene and dichloromethane (Table 2, en-
tries 5 and 6), although dichloromethane was considered
optimal, as the yield was excellent (92%) and the diaste-
reoselection good (6.5:1).

Having chosen dichloromethane as solvent, reaction
scope was next explored. Firstly, a range of isocyanides
were investigated (Table 3), and it was found that all reac-
tions were complete within 24 hours. Thus, all further re-
actions were also given this standard reaction time for
operational convenience.

The desired products were generally obtained in excellent
yields with moderate to good diastereoselectivity. The
exceptions were the PMP example (Table 3, entry 1), which
gave a slightly lower yield (67%) and the tert-butyl exam-
ple (Table 3, entry 6), which cleanly provided a single iso-
mer in high yield (91%), directly from the reaction
mixture. p-Substituted phenyl isocyanides as well as ben-
zyl isocyanide provided the desired products as a mixture
of only two isomers (Table 3, entries 1–4), whilst interest-
ingly, cyclohexyl isocyanide afforded the desired product
as a mixture of three isomers (Table 3, entry 5), which
could potentially be epimers of the chiral centre contain-
ing the iso-butyl group, as well as double bond isomers.
Having screened a range of isocyanides, the scope of aldehydes in the reaction was next investigated. It was found that unsaturated aldehydes did not react under these reaction conditions, a finding consistent with their reduced electrophilicity. Therefore, linear, branched and more functionalised aldehydes were used in the same reaction process and, pleasingly, most examples afforded the desired products in good to excellent yield and moderate to good selectivity (Table 4).

The best result was obtained with isovaleraldehyde (4), which afforded the desired product in an excellent 93% yield, with moderate selectivity, as a mixture of two isomers (Table 4, entry 1). Each of the remaining aldehydes led to the desired heterocyclic product as a mixture of three isomers in good yields and moderate to good selectivity (Table 4, entries 2–5), with cyclohexanecarboxaldehyde being the best yielding of these examples (Table 4, entry 3), and with hexanal showing the greatest selectivity (Table 4, entry 2).

In order to determine the stereochemical outcome of these reactions, NMR studies were conducted on 20 (major isomer) and 25 (Figure 3), and it was interesting to observe that the NOE data suggested contrasting results in each case. For the benzyl substituted compound 20, a strong NOE enhancement was found between the Ha and Hb protons (Figure 3), suggesting that they are syn to one another. No such enhancement was found in the tert-butyl case (25), suggesting that the protons are anti. In addition, an NOE enhancement was seen between Ha and the tert-butyl protons in 25, suggesting that the tert-butyl group is trans to the tetrazole. In contrast, no NOE enhancement between Hc and the benzyl protons in 20 was observed, implying that the benzyl substituent is cis to the tetrazole moiety.

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Table 3 Isocyanide Scope

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Ratio of products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9</td>
<td>10</td>
<td>67</td>
<td>1.2:1:0</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td></td>
<td>90</td>
<td>2.1:1:0</td>
</tr>
<tr>
<td>3</td>
<td>22</td>
<td></td>
<td>93</td>
<td>1.7:1:0</td>
</tr>
<tr>
<td>4</td>
<td>23</td>
<td></td>
<td>93</td>
<td>6.8:1:0</td>
</tr>
<tr>
<td>5</td>
<td>24</td>
<td></td>
<td>90</td>
<td>7.3:2.3:1</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
<td></td>
<td>91f</td>
<td>single isomer</td>
</tr>
</tbody>
</table>

Table 4 Aldehyde Scope

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Ratio of products</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>23</td>
<td></td>
<td>93</td>
<td>6.8:1:0</td>
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<td>2</td>
<td>26</td>
<td></td>
<td>71</td>
<td>9.4:1.9:1</td>
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<td>3</td>
<td>27</td>
<td></td>
<td>83</td>
<td>6.7:1.5:1</td>
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<td>4</td>
<td>28</td>
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<td>67</td>
<td>2.8:1.2:1</td>
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<td>5</td>
<td>29</td>
<td></td>
<td>74</td>
<td>4.3:1.4:1</td>
</tr>
</tbody>
</table>

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* Isolated yield of all isomers.
* Determined by 1H NMR spectroscopy of the crude product mixture.
* Major isomer (syn).
* Minor isomer (anti).
* Mixture of isomers.
* Crude yield.
Due to their crystalline nature, it was possible to obtain X-ray crystal structures of both compounds and thus, unambiguously confirm the original stereochemical assignment (Figure 4).\textsuperscript{11} For the benzyl case 20, this places the iso-butyl group in the pseudo-equatorial position and the benzyl group 	extit{cis} to the tetrazole. In the tert-butyl case 25 it appears that the extra steric bulk of this group forces it to be placed 	extit{trans} to the tetrazole. This in turn causes such a large steric clash with the iso-butyl group that it is forced to occupy the pseudo-axial position on the ring, placing protons H\textsubscript{a} and H\textsubscript{b} anti to one another.

In summary, a facile method for the synthesis of a new heterocycle class has been developed. All three components were used in equimolar amounts and reactions proceeded at room temperature. The scope of the reaction has been successfully demonstrated by examining a range of isocyanide and aldehyde components, and structures of two examples have been determined by NMR and X-ray analysis. In addition to applications in library synthesis, these new heterocycles broaden the scaffolds that are accessible through Ugi reactions and have potential in medicinal chemistry.

All reactions were carried out under an atmosphere of argon in oven-dried glassware. Petroleum ether (PE) used refers to the 40–60 °C boiling point fraction of petroleum. Diethyl ether and tetrahydrofuran were distilled over calcium hydride and lithium aluminium hydride; dichloromethane, methanol, acetonitrile and toluene were distilled over calcium hydride. Proline tetrazole 2 was prepared by a literature procedure.\textsuperscript{12} All other reagents and solvents were used as supplied. Flash column chromatography was carried out using Merck Kieselgel (230–400 mesh).\textsuperscript{13} NMR spectra were recorded on a Bruker DRX-600 spectrometer. Where coincident coupling constants were observed in the NMR spectrum, the apparent (app) multiplicity of the proton concerned is reported. For spectra recorded in CDCl\textsubscript{3}, residual protic solvent CHCl\textsubscript{3} ([δ\textsubscript{H} = 7.26 ppm]) was used as an internal standard.\textsuperscript{14} C NMR spectra were recorded on the same spectrometer at 150 MHz, using central resonance of CDCl\textsubscript{3} ([δ\textsubscript{C} = 77.0 ppm]) as the internal reference. Accurate mass data were obtained on Micromass Q-TOF by electrospray ionisation (ESI). Optical rotations were measured on a Perkin Elmer 343 polarimeter ([α]\textsubscript{D}\textsuperscript{25} +2.2 (c 0.45, CHCl\textsubscript{3}).

IR (film): 2957, 1775 (C=O), 1690 (C=N), 1606, 1505 cm\textsuperscript{-1}. 1H NMR (600 MHz, CDCl\textsubscript{3}): δ = 7.11 (2 H, d, J = 8.8 Hz, 2 × H-14), 6.85 (2 H, d, J = 8.8 Hz, 2 × H-13), 4.07 (1 H, dd, J = 9.2, 5.0 Hz, H-5), 3.79 (3 H, s, H\textsubscript{a}-16), 3.76 (1 H, app t, J = 8.1 Hz, H-9), 3.17–3.13 (1 H, m, H\textsubscript{b}-6), 2.75 (1 H, app q, J = 8.6 Hz, H\textsubscript{a}-4), 2.48–2.40 (1 H, m, H\textsubscript{a}-4), 2.12–2.03 (1 H, m, H\textsubscript{b}-4), 1.92–1.83 (3 H, m, H-3 and H\textsubscript{b}-7), 1.68–1.60 (2 H, m, H\textsubscript{b}-8), 1.01 (3 H, d, J = 6.7 Hz, H\textsubscript{b}-1), 0.97 (3 H, d, J = 6.6 Hz, H\textsubscript{a}-2).

13C NMR ([150 MHz, CDCl\textsubscript{3}]): δ = 169.7 (C-11), 157.1 (C-15), 149.5 (C-10), 136.5 (C-12), 124.7 (C-14), 113.9 (C-13), 57.4 (C-9), 55.4 (C-3), 55.4 (C-16), 52.5 (C-6), 40.4 (C-8), 31.8 (C-10), 23.5 (C-7), 22.6 (C-1 or C-2), 22.2 (C-1 or C-2).

No NOE enhancement observed between H-5 and H-9.

HRMS (ESI): [m/z] + [M + H]\textsuperscript{+} calcd for C\textsubscript{18}H\textsubscript{24}N\textsubscript{2}O\textsubscript{3}: 317.1865; found: 317.1856.

IR (film): 2955, 1775 (C=O), 1693 (C=N), 1505 cm\textsuperscript{-1}. 1H NMR (500 MHz, CDCl\textsubscript{3}): δ = 7.07 (2 H, d, J = 8.8 Hz, 2 × H-14), 6.84 (2 H, d, J = 8.8 Hz, 2 × H-13), 4.00 (1 H, dd, J = 9.1, 4.5 Hz, H-5), 3.80–3.74 (4 H, m, H-9 and H\textsubscript{a}-16), 2.94–2.88 (1 H, m, H\textsubscript{b}-6), 2.57 (1 H, app q, J = 8.4 Hz, H\textsubscript{a}-4), 2.41–2.33 (1 H, m, H\textsubscript{b}-4), 2.15–2.09 (1 H, m, H\textsubscript{b}-4), 1.96–1.84 (4 H, m, H-3, H\textsubscript{b}-7 and H\textsubscript{a}-8), 1.74–1.68 (1 H, m, H\textsubscript{a}-8), 1.00 (3 H, d, J = 6.4 Hz, H\textsubscript{b}-1), 0.97 (3 H, d, J = 6.2 Hz, H\textsubscript{a}-2).

13C NMR ([150 MHz, CDCl\textsubscript{3}]): δ = 169.6 (C-11), 157.0 (C-15), 149.1 (C-10), 136.7 (C-12), 124.4 (C-14), 113.9 (C-13), 63.4 (C-9), 55.4 (C-3), 55.4 (C-16), 52.5 (C-6), 40.4 (C-8), 31.8 (C-10), 23.6 (C-7), 22.6 (C-1 or C-2), 22.2 (C-1 or C-2).

NOE enhancement observed between H-5 and H-9.

HRMS (ESI): [m/z] + [M + H]\textsuperscript{+} calcd for C\textsubscript{18}H\textsubscript{24}N\textsubscript{2}O\textsubscript{3}: 317.1865; found: 317.1860.

IR (film): 2958, 1657 (C=O), 1579, 1501 cm\textsuperscript{-1}. 1H NMR (500 MHz, CDCl\textsubscript{3}): (insoluble mixture of isomers, minor isomer starred) δ = 6.97 (2 H, d, J = 9.0 Hz, 2 × H-14), 6.95 (2 H, d, J = 9.0 Hz, 2 × H-15), 6.73 (2 H, d, J = 8.8 Hz, 2 × H\textsuperscript{+}-14), 6.62 (2 H, d, J = 8.9 Hz, 2 × H\textsuperscript{+}-15), 4.26 (1 H, dd, J = 9.1, 5.5 Hz, 1H NMR (500 MHz, CDCl\textsubscript{3}): (insoluble mixture of isomers, minor isomer starred) δ = 6.97 (2 H, d, J = 9.0 Hz, 2 × H-14), 6.95 (2 H, d, J = 9.0 Hz, 2 × H-15), 6.73 (2 H, d, J = 8.8 Hz, 2 × H\textsuperscript{+}-14), 6.62 (2 H, d, J = 8.9 Hz, 2 × H\textsuperscript{+}-15), 4.26 (1 H, dd, J = 9.1, 5.5 Hz, 1H NMR (500 MHz, CDCl\textsubscript{3}): (insoluble mixture of isomers, minor isomer starred) δ = 6.97 (2 H, d, J = 9.0 Hz, 2 × H-14), 6.95 (2 H, d, J = 9.0 Hz, 2 × H-15), 6.73 (2 H, d, J = 8.8 Hz, 2 × H\textsuperscript{+}-14), 6.62 (2 H, d, J = 8.9 Hz, 2 × H\textsuperscript{+}-15), 4.26 (1 H, dd, J = 9.1, 5.5 Hz,
Figure 5

H-5, 4.11 (1 H*, dd, J = 10.0, 5.3 Hz, H*-5), 3.83 (3 H, s, H17-),
3.73 (3 H*, s, H*-17), 3.64 (1 H*, app t, J = 6.5 Hz, H*-6), 3.48
(1 H, dd, J = 15.5, 2.0 Hz, H-10), 3.40–3.29 (1 H and 1 H*, m, H-9
and H*-10), 3.25 (1 H*, app dt, J = 5.4, 8.9 Hz, H*-6), 3.08 (1 H,
app dt, J = 4.8, 8.6 Hz, H-6), 3.05–2.97 (2 H*, m, H*-9 and H*-10),
2.95 (1 H, dd, J = 15.5, 11.0 Hz, H10-), 2.73 (1 H, dd, J = 15.3,
8.6 Hz, H-6), 2.22–2.06 (1 H and 1 H*, m, H1-8 and H*-8), 1.96–
1.85 (1 H, m, H3-7), 1.83–1.75 (1 H, m, H4-7), 1.72–1.60 (1 H and
2 H*, m, H1-8, H3-3 and H*-3), 1.55 (1 H*, app dt, J = 7.0, 14.9
Hz, H*-7), 1.48–1.35 (1 H and 1 H*, m, H-3 and H*-7), 1.33–1.22
(1 H and 1 H*, m, H4-4 and H*-4), 1.15–1.08 (1 H*, m, H3-4),
1.07–1.00 (1 H, m, H4-4), 0.98 (3 H*, d, J = 6.6 Hz, H*-1), 0.86
(3 H*, d, J = 6.6 Hz, H*-2), 0.71 (3 H, d, J = 6.6 Hz, H1-1), 0.58
(3 H, d, J = 6.6 Hz, H2-2).

1H NMR (150 MHz, CDCl3): δ = 157.6 (C*-16), 157.6 (C-16),
153.4 (C-12), 153.2 (C*-11), 152.7 (C-11), 145.3 (C*-12), 139.0
(C-13), 138.3 (C*-13), 121.9 (C*-15), 121.4 (C-15), 114.5 (C-14),
114.3 (C*-14), 62.3 (C*-5), 55.5 (C-17), 55.3 (C*-17), 54.7 (C-5),
51.5 (C-9), 51.4 (C*-9), 51.2 (C-6), 50.8 (C*-6), 34.4 (C*-4), 34.2
(C-4), 32.1 (C-8), 32.0 (C*-8), 29.8 (C-10), 28.7 (C*-10), 25.0 (C*-3),
24.7 (C-3), 23.1 (C*-1), 22.9 (C-1), 21.9 (C-2), 21.8 (C*-2), 21.2
(C-7), 20.9 (C*-7).

HRMS (ESI): mlz [M + H]+ calcd for C19H26N6O: 355.2246; found:
355.2255.
(6R,10aS)-5-(4-Methoxyphenylimino)-6-iso-butyl-8,9,10,10a-tetrahydro-6H-tetrazolo[1,5-a]pyrrolo[2,1-c]pyrazine (9); Major Isomer

White crystalline solid; mp 122–124 °C; Rf 0.44 (PE–EtOAc, 1:1); [α]D25 = −202.8 (c 0.33, CHCl3).

IR (film): 3436, 3280, 2960, 1711 (C=N), 1607 cm−1.

1H NMR (600 MHz, CDCl3): δ = 6.86 (2 H, d, J = 7.8 Hz, 2 × H-13), 6.73 (2 H, d, J = 8.4 Hz, 2 × H-14), 4.77 (1 H, br s, H-9), 3.95 (1 H, br s, H-5), 3.81 (3 H, s, H-16), 3.11 (1 H, br s, H-6), 2.60–2.47 (2 H, m, H-6 and H-8), 2.40–2.32 (1 H, m, H-8), 2.11–1.88 (3 H, m, H-3, H-4 and H-7), 1.87–1.70 (2 H, m, H-3 and H-4), 1.02 (3 H, app s, H-9), 0.98 (3 H, app s, H-2).

13C NMR (150 MHz, CDCl3): δ = 156.9 (C-15), 156.1 (C-10), 140.3 (C-11), 139.7 (C-12), 120.4 (C-10), 114.3 (C-13), 58.6 (C-5), 57.0 (C-9), 55.4 (C-16), 44.6 (C-6), 37.5 (C-4), 29.9 (C-8), 24.5 (C-3), 23.4 (C-2), 23.0 (C-7), 21.8 (C-1).

NOE enhancement observed between H-5 and H-9 (3.7%).


(6S,10aS)-5-(4-Methoxyphenylimino)-6-iso-butyl-8,9,10,10a-tetrahydro-6H-tetrazolo[1,5-a]pyrrolo[2,1-c]pyrazine (10); Minor Isomer

White crystalline solid; mp 139–141 °C; Rf 0.32 (PE–EtOAc, 1:1); [α]D25 = +162 (c 0.15, CHCl3).

IR (film): 3436, 3280, CDCl3, 2960, 1711 (C=N), 1607 cm−1.

1H NMR (600 MHz, CDCl3): δ = 7.86 (2 H, d, J = 8.7 Hz, 2 × H-13), 6.88 (2 H, d, J = 8.3 Hz, 2 × H-14), 4.71 (1 H, dd, J = 8.3, 1.7 Hz, H-9), 4.18 (1 H, dd, J = 10.7, 4.6 Hz, H-16), 3.83 (3 H, s, H-16), 3.08 (1 H, dt, J = 2.5, 8.2 Hz, H-6), 2.57–2.49 (2 H, m, H-6 and H-8), 2.45–2.39 (1 H, m, H-8), 2.01–1.91 (1 H, m, H-7), 1.82–1.73 (2 H, m, H-3 and H-7), 1.54 (1 H, ddd, J = 14.6, 10.8, 7.5 Hz, H-4), 1.32–1.25 (1 H, m, H-4), 0.77 (3 H, d, J = 6.7 Hz, H-1), 0.68 (3 H, d, J = 6.5 Hz, H-2).

13C NMR (150 MHz, CDCl3): δ = 157.3 (C-15), 154.8 (C-10), 151.0 (C-11), 138.5 (C-12), 120.3 (C-10), 114.6 (C-13), 55.5 (C-16), 54.1 (C-5), 51.2 (C-6), 51.0 (C-9), 40.1 (C-4), 29.8 (C-8), 24.5 (C-3), 23.0 (C-2), 22.6 (C-1).

No NOE enhancement observed between H-5 and H-9.


(6,8S,10aR)-5-Benzylimino-6-iso-butyl-8,9,10,10a-tetrahydro-6H-tetrazolo[1,5-a]pyrrolo[2,1-c]pyrazine (20); Major Isomer

White crystalline solid; mp 82–84 °C; Rf 0.55 (PE–EtOAc, 1:1); [α]D25 = -163 (c 0.135, CHCl3).

IR (film): 2960, 1711 (C=O), 1607 cm−1.

1H NMR (600 MHz, CDCl3): δ = 7.47 (2 H, d, J = 7.5 Hz, 2 × H-14), 7.38 (2 H, app t, J = 7.5 Hz, 2 × H-15), 7.27 (1 H, t, J = 7.5 Hz, H-16), 5.35 (1 H, d, J = 18.0 Hz, H-12), 5.26 (1 H, d, J = 18.0 Hz, H*-12), 4.78 (1 H, dd, J = 8.3, 2.1 Hz, H-9), 3.93–3.88 (1 H, m, H-5), 3.02 (1 H, app dt, J = 3.5, 8.5 Hz, H-6), 2.57–2.50 (1 H, m, H-8), 2.39–2.33 (1 H, m, H-8), 2.29 (1 H, app q, J = 8.7 Hz, H-6), 2.05–1.99 (1 H, m, H-4), 1.98–1.89 (2 H, m, H-3 and H-7), 1.75–1.68 (2 H, m, H-3 and H-7), 1.01 (3 H, d, J = 6.7 Hz, H3-1), 0.97 (3 H, d, J = 6.5 Hz, H2-2).

13C NMR (150 MHz, CDCl3): δ = 156.1 (C-10), 140.0 (C-11), 139.6 (C-13), 128.4 (C-15), 127.3 (C-14), 126.9 (C-16), 58.9 (C-5), 57.1 (C-9), 54.5 (C-12), 44.5 (C-6), 37.8 (C-4), 29.8 (C-8), 24.5 (C-3), 23.3 (C-1), 22.8 (C-7), 22.0 (C-2).

NOE enhancement observed between H-5 and H-9 (4.2%).
(6,8,10aS)-5-Cyclohexylimino-6-iso-buty1-8,9,10,10a-tetrahydro-6H-tetrazol-1,5a-ypyrollo[2,1-c]pyrazine (24); Major Isomer

White crystalline solid; mp 115–118 °C; NOE enhancement observed between H-5 and H-9 (4.1%).


(Z,6R,10aS)-5-Benzylimino-6-cyclohexyl-8,9,10,10a-tetrahydro-6H-tetrazol-1,5a-ypyrollo[2,1-c]pyrazine (27); Major Isomer

White crystalline solid; mp 131–133 °C; NOE enhancement observed between H-5 and H-9 (4.7%).


(2,6R,10aS)-5-Butyl-6-cyclopropyl-8,9,10,10a-tetrahydro-6H-tetrazol-1,5a-ypyrollo[2,1-c]pyrazine (28); Major Isomer

Sticky dark-yellow oil; Rf = 0.25 (PE–EtOAc, 1:1); [α]D25 +77.8 (c 0.93, CHCl3).

IR (film): 2972, 1670 (C=H), 1606 cm⁻¹.

1H NMR (600 MHz, CDCl₃): δ = 7.48 (2 H, d, J = 7.6 Hz, 2 × H-16), 7.36 (2 H, app t, J = 7.6 Hz, 2 × H-17), 7.27 (1 H, t, J = 7.4 Hz), 5.39 (1 H, d, J = 17.8 Hz, H-12), 5.15 (1 H, d, J = 17.8 Hz, H-14), 4.77 (1 H, dd, J = 8.8, 2.4 Hz, H-11), 3.42 (1 H, d, J = 9.4 Hz, H-7), 2.93 (1 H, app dt, J = 4.8, 8.7 Hz, H-8), 2.54–2.46 (1 H, m, H-10), 2.38 (1 H, d, J = 11.5 Hz, H-4), 2.31 (1 H, app q, J = 8.6 Hz, H-6), 2.25–2.18 (1 H, m, H-10), 2.09–2.02 (1 H, m, H-9), 1.96 (1 H, d, J = 13.1 Hz, H-5), 1.93–1.86 (1 H, m, H-9), 1.83–1.76 (1 H, m, H-1), 1.76–1.59 (3 H, m, H-1-2 and H-9), 1.42–1.28 (2 H, m, H-2 and H-3), 1.27–1.11 (2 H, m, H-1 and H-2), 1.03–0.94 (1 H, m, H-4).

13C NMR (150 MHz, CDCl₃): δ = 156.3 (C-10), 136.5 (C-11), 58.7 (C-5), 58.0 (C-12), 57.0 (C-9), 44.3 (C-6), 37.8 (C-4), 34.3 (C-14), 33.1 (C-18), 29.9 (C-8), 25.6 (C-17), 24.7 (C-3), 24.1 (C-15), 24.0 (C-16), 23.2 (C-1), 22.9 (C-7), 22.0 (C-2).

NOE enhancement observed between H-5 and H-9 (4.6%).


(2,6,10aS)-5-Benzylidinomino-6-benzoxymethyl-8,9,10a-tetrahydro-6H-tetrazolo[1,5-a]pyrrolo[2,1-c]pyrazine (29);

Major Isomer

Brown oil; Rf 0.31 (PE–EtOAc, 1:1); [α]D25 +72.8 (c 1.53, CHCl3).

IR (film): 2956, 2179 (C=O) cm–1.

1H NMR (600 MHz, CDCl3): δ = 7.34–7.25 (10 H, m, H-1, 2 × H-2, 2 × H-3, 3 × H-16, 2 × H-17 and H-18), 5.31 (1 H, d, J = 18 Hz, H2-14), 5.26 (1 H, d, J = 19.7 Hz, H-14), 4.67 (1 H, d, J = 12.3 Hz, H-5), 4.65 (1 H, d, J = 12.3 Hz, H-5), 4.58 (1 H, dd, J = 7.9, 3.7 Hz, H-11), 4.21 (1 H, dd, J = 10.4, 4.1 Hz, H-6), 4.11–4.06 (1 H, m, H-7), 3.93 (1 H, dd, J = 10.4, 7.4 Hz, H b-5), 2.98 (1 H, app dt, J = 4.6, 8.7 Hz, H-8), 2.62–2.50 (2 H, m, H-8 and H-10), 2.39–2.31 (1 H, m, H-9), 2.05–1.96 (1 H, m, H-9), 1.84–1.76 (1 H, m, H-9).

13C NMR (150 MHz, CDCl3): δ = 155.5 (C-12), 139.3 (C-15), 137.7 (C-4), 137.3 (C-13), 128.4, 127.9, 127.8, 127.3, 126.9 (C-1, C-2, C-3, C-16, C-17 and C-18), 73.6 (C-5), 67.6 (C-6), 61.3 (C-7), 57.3 (C-11), 54.6 (C-14), 45.9 (C-8), 28.9 (C-10), 22.5 (C-9).

NOE enhancement observed between H-7 and H-11 (5.1%).


(E,3SR,7aRS)-(1-Benzyl-tetrahydro-3-iso-butyl-1H-pyrrolo[1,2-a]imidazol-2(3H)-yldeneaminomormonitrile (30)j

White crystalline solid; mp 77–79 °C; Rf 0.28 (PE–EtOAc, 1:1).

IR (film): 2956, 2179 (C≡N) cm–1.

1H NMR (600 MHz, CDCl3): δ = 7.36–7.28 (3 H, m, 2 × H-15 and H-16), 7.22 (2 H, d, J = 7.0 Hz, 2 × H-14), 4.88 (1 H, d, J = 14.8 Hz, H2-12), 4.76–4.72 (1 H, m, H-9), 4.14 (1 H, dd, J = 14.8 Hz, H2-12), 3.97 (1 H, app d, J = 10.1 Hz, H-5), 3.19–3.13 (1 H, m, H-6), 2.57 (1 H, dd, J = 15.7, 10.0 Hz, H-6), 2.03–1.95 (1 H, m, H-8), 1.93–1.87 (1 H, m, H-3), 1.86–1.72 (4 H, m, H-4, H-7 and H-8), 1.37–1.29 (1 H, m, H-4), 1.01 (3 H, d, J = 6.6 Hz, H2-1), 0.95 (3 H, d, J = 6.7 Hz, H2-2).

13C NMR (150 MHz, CDCl3): δ = 176.0 (C-11), 134.5 (C-13), 129.0 (C-15), 128.2 (C-16), 128.0 (C-14), 117.5 (C-10), 82.1 (C-9), 68.0 (C-5), 55.4 (C-6), 45.9 (C-12), 39.8 (C-4), 28.7 (C-8), 25.3 (C-3), 23.8 (C-7), 23.4 (C-1), 20.8 (C-2).

No NOE enhancement observed between H-5 and H-9.


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(10) In addition to the two usual isomers, reaction in methanol confirmed by full characterisation, including an X-ray crystal structure (see reference 11).

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Crystallographic data (excluding structure factors) for the structures 20, 25 and 30 have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-612544, CCDC-612545 and CCDC-612546, respectively. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. [Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk].


**Figure 6** Decomposition product 30