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The synthesis of hydroxy-pyrrolizidines and indolizidines from cyclopropenones: towards hyacinthacines, australines and jenamidines

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The reaction of cyclic imines (1-pyrrolines and piperidines) with a cyclopropenone leads to pyrrolizidines and indolizidines, respectively, each with a hydroxy group on the carbon atom of the bridgehead. The cyclopropenone functions as an all-carbon 1,3-dipole equivalent towards the cyclic imine in this reaction, and the cyclic imines used include polyhydroxylated systems, thus allowing access to australine, alexine and hyacinthacine type compounds. The pyrrolizidine products contain the core of the jenamidine and bohemamine natural products which are of interest as cell-proliferation inhibitors and cell-cell adhesion inhibitors.

Keywords:
hyacinthacine;
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jenamidine;
pyrrolizidine and indolizidine;
cyclopropenone

In this paper, we describe a new synthesis of bridgehead (7a- and 8a-) hydroxy-substituted pyrrolizidines and indolizidines (14) (see Scheme 1) from the reaction of cyclic imines (11, n = 1 or 2) with cyclopropenones (12), a process that we believe proceeds through the rapid aerial oxidation of a transient intermediate (13).

Scheme 1: Synthesis of hydroxy-pyrrolizidines and indolizidines

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The reaction of cyclic imines with cyclopropenones is a process that we have studied previously using cyclic imines (15) that are 2-substituted (X = O, S; R = Me, Et), and we have shown that a range of alkoxy- and alkylthio-substituted cyclic imines react to give bicyclic systems (16) in the azetidinopyrrole (n = 0), pyrrolizidine (n = 1), indolizidine (n = 2) and pyrroloazepine (n = 3) classes, as summarized in Scheme 2.

Scheme 2: The use of 2-substituted cyclic imines

In order to produce compounds with a bridgehead hydrogen, a feature common to natural products (1)-(5), (7) and (9a), we sought to explore the reactions of 2-unsubstituted cyclic imines with cyclopropenones, and report the results of this study herein. We began our study with the synthesis of the imines (17)-(21) shown in Figure 2, with the ultimate goal of natural product syntheses.

Figure 2: Cyclic imines selected for study

Imine (17) was selected to allow, after reaction with an appropriate cyclopropenone, direct access to analogues (13) (see Scheme 1) of the jenamidines (9a) and, after manipulation of the enone functionality and/or side-chains, access to jenamidines A2/A3 themselves. Imine (18) was accessed by cyclisation of 4-aminobutylaldehyde diethyl acetal which was stabilised as its zinc iodide complex. Imine (18) was chosen ultimately to explore access to hyacinthacines B1/B2 (2), but also to a range of potentially interesting hydroxymethyl pyrrolizidines, and we synthesised it as a single enantiomer using anaza-Wittig based route starting from L-glutamic acid exactly as described by Banfi et al. Imines (19) and (20) were chosen as they offer a potential route into indolizidines such as (5) and analogues, and these imines were made by an adaptation of reported N-chlorination-dehydrochlorination sequences. Imine (21) was chosen due to its ready availability and its potential to allow access to polyhydroxylated pyrrolizidines, including hyacinthacine A2 (1) and australine (3) and/or their epimers, after pyrrolidine reduction and benzyl deprotection.

With imines (17)-(21) synthesised as described,17-21 we started to explore their reactivity towards diphenylcyclopropenone (12a; R = R' = Ph), phenylcyclopropenone (12b; R = H, R' = Ph) and cyclopropenone (12c; R = R' = H). Diphenylcyclopropenone is commercially available, whilst phenylcyclopropenone and cyclopropenone were synthesised as described in the literature. Cyclopropenones have attracted recent interest as all-carbon 1,3-dipole equivalents,16,22 as alkyne precursors in click processes,23 and as novel catalytic platforms. The first cyclopropenone reactions performed in our current study, as shown in Scheme 3, were those of imines (17) and (20) (the most readily available) with commercially available diphenylcyclopropenone (12a). These two reactions occurred extremely smoothly, but we were surprised to discover an extra 16 mass units in the mass spectra of the products. This, together with the absence of a C-H signal (the expected bridgehead C-H) in each of the 1H and 13C-NMR spectra, the presence of an additional quaternary carbon (13C) and a clear OH in the infra-red and 1H-NMR spectra, led us to believe that the products that had formed were the alcohols (14a) and (14b), rather than the expected compounds (13a) and (13b). Alcohols (14a) and (14b) were isolated in 61% and 84% yields, respectively. Compound (14a) was crystalline and found to be suitable for study by X-ray crystallography (Figure 3),24 which confirmed that the structure was that predicted. We assume that the expected adducts (13a), via their enol tautomers (22), are unusually susceptible to aerial oxidation, and that the initial product of oxidation, the hydroperoxide (23) (Scheme 3), undergoes O-O cleavage to form the isolated alcohols (14). It is known that enols and their derivatives can undergo easy oxidation to α-hydroxy ketones,25 even in the absence of catalyst, photosensitisors or photoinducers.26 Similarly, 3-hydroxypyroles have been shown to undergo photooxidation to give highly reactive hydroperoxides which are easily intercepted in synthetically useful processes,27 lending further credence to the involvement of species (22) / (23). We cannot rule out the possibility that cyclopropenones, cyclic enaminones or their hydroxypyrrole tautomers, behave as photosensitisors or photoinducers. In other catalyst-free aerobic oxidation systems involving enols, it has been noted that free-radical traps fail to halt the reaction or give ESR signals, and that intermediate peroxides can be detected.28 It is also possible that intermediate (23) acts as an oxidising agent towards compound (22) in order to produce the final product (14). Further mechanistic studies are underway in our laboratory.
Other imines and cyclopropenones behaved in the same manner and the results are summarised in Table 1. Imines (17), (18) and (19) reacted with phenylcyclopropenone to give compounds (14c), (14d) and (14e) as single regioisomers (R = H, R = Ph; easily identified by HMBC), presumably due to the attack of the cyclopropenone (12) by the imine at the least hindered carbon, as we observed when working with this and other mono-substituted cyclopropenones before. With imines (18), (20) and (21), the products (14e-i) were isolated as single diastereoisomers. Each of the pyrrolizidines (14e-g) showed the CH3OTBDMS and OH groups to be cis to each other (nOesy).

We were unable to determine the relative stereochemistry in indolizidine (14h), but by analogy to that observed in compounds (14e-g), we have tentatively assigned the OH and Me groups as cis to each other. Pyrrolizidine (14i) was formed from the chiral pool derived enantiomer25 imine (21). The stereochemistry of the new stereocentre – the bridgehead OH – was established by nOesy which showed the OH to be cis to the adjacent OBn and cis to the CH3OBn group, and also confirmed the relative stereochemistry of the other chiral centres. In the case of compound (14i), the enol (22) was the initial isolated product but underwent quantitative conversion (CDCl3, NMR tube) into the 7α-hydroxypyrrolizidine (14i) over 24 hours. Whilst this is significant in terms of the proposed mechanism in Scheme 3, this was the only system where we were able to observe enol formation. The use of imine (21) has allowed us to produce systems that are closely related to the hyacinthacine, australine and alexine natural products (1)-(3). The 7α-hydroxy-pyrrolizidines (14, n = 1) produced from the pyrrolines (17), (18) and (21) have a core structure that is closely related to the 7α-hydroxy-pyrrolizidine natural products (8), (9b) and (10). It is of note that natural product (9a) has a hydrogen at the bridgehead position and this presents the intriguing possibility that the jenamidine B/β (9b) may arise from jenamidine A/α (9a) through the type of mechanism presented in Scheme 3. Natural products (8) and (10) may have similar origins, and we are actively pursuing this possibility.

Current studies in our laboratory are focusing upon the synthesis of hyacinthacine, australine, alexine and castanospermine (and their epimers), and their 7α-/8α-hydroxy analogues. A programme of study focused on the synthesis of 8α-hydroxy analogues of the alkylated indolizidines (such as compound 5) is also underway alongside our continuing studies on the jenamidines.

Table 1: 7α-/8α-Hydroxy-indolizidines and pyrrolizidines from cyclopropenones (12) and imines (17)-(21)

<table>
<thead>
<tr>
<th>Product</th>
<th>n</th>
<th>Imine</th>
<th>12, R' and R&quot;</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14a</td>
<td>1</td>
<td>17</td>
<td>R' = R&quot; = Ph</td>
<td>61</td>
</tr>
<tr>
<td>14b</td>
<td>2</td>
<td>19</td>
<td>R' = R&quot; = Ph</td>
<td>84</td>
</tr>
<tr>
<td>14c</td>
<td>1</td>
<td>17</td>
<td>R' = H, R&quot; = Ph</td>
<td>26</td>
</tr>
<tr>
<td>14d</td>
<td>2</td>
<td>19</td>
<td>R' = H, R&quot; = Ph</td>
<td>57</td>
</tr>
<tr>
<td>14e</td>
<td>1</td>
<td>18</td>
<td>R' = H, R&quot; = Ph</td>
<td>36</td>
</tr>
<tr>
<td>14f</td>
<td>1</td>
<td>18</td>
<td>R' = R&quot; = H</td>
<td>30</td>
</tr>
<tr>
<td>14g</td>
<td>1</td>
<td>18</td>
<td>R' = R&quot; = Ph</td>
<td>37</td>
</tr>
<tr>
<td>14h</td>
<td>2</td>
<td>20</td>
<td>R' = R&quot; = H</td>
<td>33</td>
</tr>
<tr>
<td>14i</td>
<td>1</td>
<td>21</td>
<td>R' = R&quot; = H</td>
<td>34</td>
</tr>
</tbody>
</table>

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References and notes
