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

Vishnu V. R. Kondakal, M. Ilyas Qamar, Karl Hemming*

Institute for Materials, Medicines and Molecular Sciences, Division of Chemistry, School of Applied Sciences, University of Huddersfield, Queensgate, Huddersfield, West Yorkshire, HD1 3DH, United Kingdom

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*Corresponding author. Tel.: +0-44-1484-472188; fax: +0-44-1484-472182; e-mail: k.hemming@hud.ac.uk

The pyrrolizidine\(^1\) and indolizidine\(^1b,2\) heterocycles attract significant attention due to their biological activity, and synthetic challenges that they present.\(^1,2\) Typical compounds, shown in Figure 1, are natural iminosugars such as hyacinthacines A\(^1\)/A\(^2\) (1),\(^3\) hyacinthacines B\(^1\)/B\(^2\) (2),\(^3\) australine (3) (and its bridgehead epimer alexine),\(^3\) and castanospermine (4),\(^4\) which have attracted interest as glycosidase inhibitors. Glycosidases play important roles in a number of diseases including many cancers, lysosomal storage disorders such as Gaucher’s disease, and type II diabetes.\(^7\) Iminosugars have also gained interest as antiviral compounds and antibiotics.\(^7\) Also of importance are indolizidine alkaloids with alkyl substituents, such as the amphibian derived indolizidine 195B (5),\(^5\) and related systems.\(^1b,9\) These continue to attract interest as, for example, inhibitors of nicotinic receptor-channels and neuromuscular transmission. Of particular interest to our work are pyrrolizidines such as bohemamine (6)\(^10\) and the related de-epoxidised NP25302,\(^11\) a rare pyrrolizidin-1-one sub-class isolated from Actinosporangium sp. and from marine Streptomyces sp., members of which have shown significant cell-cell adhesion inhibitory activity. The structurally related fungal derived pyrrolizin-1-ols, ephelmins A and B (7)\(^12\) are lanosterol synthase inhibitors. Of great relevance to the work reported in this paper are systems that have a hydroxy group on the carbon atom at the bridgehead such as the antitumour, antibiotic, and antiviral clazamycins A and B (8),\(^13\) jenamidines B\(^1\)/B\(^2\) (9b) and C (10),\(^11a,14\) and the synthetic 8a-hydroxy-indolizidines.\(^15\)

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).

**Keywords:** hyacinthacine; alexine; jenamidine; pyrrolizidine and indolizidine; cyclopropenone

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.

**ARTICLE INFO**

**ABSTRACT**

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The pyrrolizidine\(^1\) and indolizidine\(^1b,2\) heterocycles attract significant attention due to their biological activity, and synthetic challenges that they present.\(^1,2\) Typical compounds, shown in Figure 1, are natural iminosugars such as hyacinthacines A\(^1\)/A\(^2\) (1),\(^3\) hyacinthacines B\(^1\)/B\(^2\) (2),\(^3\) australine (3) (and its bridgehead epimer alexine),\(^3\) and castanospermine (4),\(^4\) which have attracted interest as glycosidase inhibitors. Glycosidases play important roles in a number of diseases including many cancers, lysosomal storage disorders such as Gaucher’s disease, and type II diabetes.\(^7\) Iminosugars have also gained interest as antiviral compounds and antibiotics.\(^7\) Also of importance are indolizidine alkaloids with alkyl substituents, such as the amphibian derived indolizidine 195B (5),\(^5\) and related systems.\(^1b,9\) These continue to attract interest as, for example, inhibitors of nicotinic receptor-channels and neuromuscular transmission. Of particular interest to our work are pyrrolizidines such as bohemamine (6)\(^10\) and the related de-epoxidised NP25302,\(^11\) a rare pyrrolizidin-1-one sub-class isolated from Actinosporangium sp. and from marine Streptomyces sp., members of which have shown significant cell-cell adhesion inhibitory activity. The structurally related fungal derived pyrrolizin-1-ols, ephelmins A and B (7)\(^12\) are lanosterol synthase inhibitors. Of great relevance to the work reported in this paper are systems that have a hydroxy group on the carbon atom at the bridgehead such as the antitumour, antibiotic, and antiviral clazamycins A and B (8),\(^13\) jenamidines B\(^1\)/B\(^2\) (9b) and C (10),\(^11a,14\) and the synthetic 8a-hydroxy-indolizidines.\(^15\) Jenamidine A\(^1\)/A\(^2\) (9a) inhibits proliferation of leukemia cell line K-562 with a reported GI\(_{50}\) of 1.9 µg/mL\(^11a,14\).

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

* Corresponding author. Tel.: +0-44-1484-472188; fax: +0-44-1484-472182; e-mail: k.hemming@hud.ac.uk
We began our study with the synthesis of the imines (with cyclopropenones, and report the results of this study herein. We showed that a range of alkoxy- and alkylthio-substituted cyclic imines react to give bicyclic systems (shown in Scheme 2). Alcohols (α-hydroxy ketones) 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), which confirmed that the structure was that predicted. We assume that the expected adducts (13), via their enol tautomers (22), are unusually susceptible to aerobic 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 facile oxidation to α-hydroxy ketones even in the absence of catalyst, photosensitiser or photoinciter. Similarly, 3-hydroxypyrroles have been shown to undergo photooxidation to give highly reactive hydroperoxides which are easily intercepted in synthetically useful processes, 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 photoincitors. 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. 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.

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 A1/A2 themselves. Imine (17) was accessed by cyclisation of 4-aminobutyraldehyde diethyl acetal which was stabilised as its zinc iodide complex. Imine (18) was chosen ultimately to explore access to hyacinthacine (B\(_1\)/B\(_2\), but also to a range of potentially interesting hydroxymethyl pyrrolizidines, and we synthesised it as a single enantomier 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 Nchlorination-dehydrochlorination sequences. Imine (21) was chosen due to its ready availability and its potential to allow access to polyhydroxylated pyrrolizidines, including hyacinthacine A1 (1) and australine (3) and/or their epimers, after pyrrolidinone reduction and benzyl deprotection.

With imines (17)-(21) synthesised as described, we started to explore their reactivity towards diphenylylcyclopropenone (12a; \(R^1 = R^2 = Ph\)), phenylcyclopropenone (12b; \(R^1 = H, R^2 = Ph\)) and cyclopropenone (12c; \(R^1 = R^2 = H\)). Diphenylylcyclopropenone 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, as alkyl precursors in click processes, 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 diphenylylcyclopropenone (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 \(^{13}\)C and \(^{1}\)H-NMR spectra, the presence of an additional quaternary carbon (\(^{13}\)C) and a clear OH in the infra-red and \(^{1}\)H-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), which confirmed that the structure was that predicted. We assume that the expected adducts (13), via their enol tautomers (22), are unusually susceptible to aerobic 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 facile oxidation to α-hydroxy ketones even in the absence of catalyst, photosensitiser or photoinciter. Similarly, 3-hydroxypyrroles have been shown to undergo photooxidation to give highly reactive hydroperoxides which are easily intercepted in synthetically useful processes, 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 photoincitors. 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. 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.

**Figure 1:** Indolizidine and pyrrolizidine natural products

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.

**Figure 2:** Cyclic imines selected for study

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

| Table 1: 7a-/8a-Hydroxy-indolizidines and pyrrolizidines from cyclopropenones (12) and imines (17)-(21) |
|---|---|---|---|---|
| Product | n | Imine | 12, R' and R'' | Yield (%) |
| 14a | 1 | 17 | R' = R'' = Ph | 61 |
| 14b | 2 | 19 | R' = R'' = Ph | 84 |
| 14c | 1 | 17 | R' = H, R'' = Ph | 26 |
| 14d | 2 | 19 | R' = H, R'' = Ph | 57 |
| 14e | 1 | 18 | R' = H, R'' = Ph | 36 |
| 14f | 1 | 18 | R' = R'' = H | 30 |
| 14g | 1 | 18 | R' = R'' = Ph | 37 |
| 14h | 2 | 20 | R' = R'' = H | 33 |
| 14i | 1 | 21 | R' = R'' = H | 34 |

Acknowledgements

This work was supported by University of Huddersfield Studentships (to V. V. R. K. and M. I. Q.). We thank Dr Neil McIay, University of Huddersfield, for NMR and mass spectroscopic support, Dr Craig Rice, University of Huddersfield, for X-ray crystallographic studies, and the EPSRC national mass spectroscopy service, University of Wales, Swansea for HRMS.

References and notes


21. We would like to thank a reviewer for useful comments on these aspects of the manuscript.