Diastereoselective ritter reactions of chiral cyclic N-acyliminium ions: synthesis of pyrido- and pyrrolo [2,3-d] oxazoles and 4-hydroxy-5-N-acylaninopyrrolidines and 5-hydroxy-6-N-acylaninopiperidines

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Abstract
Pyrido- and pyrrolo[2,3-d]oxazoles can be conveniently prepared in high yield from the Ritter reaction of nitriles and in situ generated chiral cyclic N-acyliminium ions. cis-4-Hydroxy-5-acylamino pyrrolidines and cis-5-hydroxy-6-acylamino piperidines can be readily obtained by acid hydrolysis of these bicyclic heterocyclic compounds, respectively.

Keywords
Diastereoselective, ritter, reactions, chiral, cyclic, Acyliminium, ions, synthesis, pyrido, pyrrolo, oxazoles, Hydroxy, acylaminopyrrolidines, Hydroxy, acylaminopiperidines, CMMB

Disciplines
Life Sciences | Physical Sciences and Mathematics | Social and Behavioral Sciences

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Pyrido- and pyrrolo[2,3-d]oxazoles can be conveniently prepared in high yield from the Ritter reaction of nitriles and in situ generated chiral cyclic N-acyliminium ions. Cis-4-hydroxy-5-acylamino-pyrrolidines and cis-5-hydroxy-6-acylamino-piperidines can be readily obtained by acid hydrolysis of these bicyclic heterocyclic compounds, respectively.

The 2-acylamino-pyrrolidine and piperidine structural motif is found in several biologically active natural and synthetic products. For example, odorine 1, (+)-odorinol 2 and its enantiomer, (-)-odorinol and the aglains are 2-acylamino-pyrrolidine alkaloids isolated from Aglaia odorata Lour. (+)-Odorinol 2 showed significant inhibitory activity on P-388 lymphocytic leukemia cell growth. The naturally occurring N-aminosugar, siastatin B 3 has neuraminidase and B-glucuronidase inhibition activities. While related 2-acetamido-piperidine derivatives show antimetastatic activity on tumor cells and inhibition of tumor cell heparanase, heperan sulfate 2-O-sulfotransferase, N-acetylhexosaminidases, influenza virus neuraminidase and glucosidases.

The incorporation of the 2-acylamino group in these molecules often requires a multi-step sequence and thus a more direct route would be desirable. We report here that these types of substituted heterocycles can be conveniently prepared in a highly diastereoselective manner from the Ritter reaction of nitriles and cyclic N-acyliminium ions generated in situ from the (5S)-hydroxy-2-pyrrolidinone and (6S)-hydroxy-2-piperidinone derivatives 4 and 6, respectively.

Treatment of (4S)-42 in a solution of the nitriles 7a-c at rt with BF3.Et2O (5 equiv) for 16 h followed by a mild basic work up (saturated aqueous NaHCO3 solution) and purification by column chromatography resulted in formation of the pyrrolo[2,3-d]oxazoles 8a-c in excellent yields (86-93%, Scheme 1, Table 1, entries 1-3). Treatment of (4S)-4 with the nitrile 7d (3 equiv) at rt in nitromethane solution with BF3.Et2O (5 equiv) for 16 h resulted in formation of the pyrrolo[2,3-d]oxazole 8d in 91% yield (Scheme 1, Table 1, entry 4). Interestingly, treatment of the O-benzyl ether analogue of 4, (4S)-5, with the nitriles 7b-c also resulted in formation of the pyrrolo[2,3-d]oxazoles 8b-c in high yields (87% and 80%, respectively, Table 1, entries 5-6). The corresponding N-benzylamides 10b-c were also isolated in yields of 77% and 63%, respectively (Scheme 1).

The 6-membered ring hemi-aminal (5S)-6 (dr = 3 : 1) was prepared from the known N-PMB-(3S)-hydroxyglutarimide by NaBH4 reduction. The major trans-isomer of (5S)-6 could be selectively crystallized from the mixture and its structure was established by X-ray crystallographic analysis (Supporting Information). Treatment of the diol (5S)-6 (dr = 3 : 1) with the nitriles 7a-d, under similar conditions to that of (4S)-4 (BF3.Et2O (5 equiv), rt for 16 h and finally at reflux for 30 min to 3 h), resulted in formation of the corresponding pyrido[2,3-d]oxazoles 9a-d in good to excellent yields (Table 1, entries 7-10). The use of the less nucleophilic 4-nitrobenzonitrile (7e) resulted in only recovered starting hemiaminal 6 (Table 1, entry 11).

Acid hydrolysis of 8a-b with 6N HCl/MeOH (1 : 1) at rt for 25 min provided the corresponding cis-hydroxy-amides 11a-b, respectively, in respective yields of 42% and 70%, Scheme 1. This method was less efficient (35-30% yields) for the synthesis of corresponding 6-membered ring analogues 12a-b from the acid hydrolysis of 9a-b (Scheme 1). This hydrolysis method also gave several other minor uncharacterizable products by TLC analysis. A much improved yield of 67% for 12b was achieved by hydrolysis using silica gel and CHCl3/H2O (100 : 1) at rt for 16 h and then at reflux for 2 h. An analogous acid hydrolysis (6N HCl/MeOH (1 : 1) at rt) of the aromatic derivatives 8c-d or 9c-d gave only recovered starting material, whereas more forcing conditions (50 °C)
resulted in a complex mixture of products. The stereochemistry of the products 11a and 11b was determined to be cis based on the coupling constants J₄,₅, which were 5.0 and 5.6 Hz, respectively. On related systems, J₄,₅ is typically 0-2.5 Hz for the trans isomers and 6.0-7.5 Hz for the corresponding cis-isomers.16,17 The highly crystalline hydroxyamides 12a-b were shown to have also have the cis-stereochemistry from their single-crystal X-ray structural analysis (Supporting Information).

**Scheme 1**

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Product</th>
<th>(yield, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>8a (93)</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>8b (90)</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>8c (86)</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>8d (91)a</td>
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<td>5</td>
<td>5</td>
<td>8b (87)</td>
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<tr>
<td>6</td>
<td>5</td>
<td>8c (80)</td>
</tr>
<tr>
<td>7</td>
<td>6</td>
<td>9a (99)</td>
</tr>
<tr>
<td>8</td>
<td>6</td>
<td>9b (91)</td>
</tr>
<tr>
<td>9</td>
<td>6</td>
<td>9c (58)a</td>
</tr>
<tr>
<td>10</td>
<td>6</td>
<td>9d (79)a</td>
</tr>
<tr>
<td>11</td>
<td>6</td>
<td>9e (0)</td>
</tr>
</tbody>
</table>

* MeNO₂ as solvent, 3 equiv of 7d. **Starting 6 was also isolated in 21% recovered yield.

These reactions are notable for providing products with high cis-diastereoselectivities. Typically the addition of nucleophiles to the iminium ions generated in situ from 4, 5 and 6 show modest diastereoselectivities.13,17 To rationalize the high diastereoselectivities and the stereochemical outcomes of these reactions we suggest that attack of the nitriles 7a-d on the intermediate N-acyliminium ion A (Ritter reaction) is reversible and gives a mixture of the Ritter intermediates B and C (Scheme 2). Because of its cis-stereochemistry intermediate B more readily cyclizes to the oxazolidine cationic intermediate D. Deprotonation or O-debenzylation of D gives the oxazolidine E. When R⁰ in D is Bn, the benzyl cation that is formed undergoes a Ritter reaction with the nitriles 7b-c to give the N-benzyl amides 10b-c, respectively (Scheme 2). The optical rotations of compounds 9a-d and 12a-b, were notably small or essentially zero, suggesting that 6 may have undergone racemization under the reaction conditions. This was confirmed by converting 12b to its (S)- or (R)-Mosher’s esters by treating samples of 12b with (R)- or (S)-Mosher’s acid chloride, respectively. ¹H NMR analysis of these derivatives indicated essentially a 1 : 1 mixture of diastereomers were produced.¹⁹ In contrast the optical rotations of compounds 8a-d and 11a-b, were relatively large in magnitude. ¹H NMR analysis of the analogous Mosher’s esters of 11b indicated high enantiomeric purity (95% ee). It seems likely therefore that hemi-aminal 6 underwent ring-opening to the corresponding α-hydroxy aldehyde-secondary amide (PMBN(H)COCH₂CH₂CH(OH)CHO) which undergoes racemization, through a Lewisacid catalysed enolization process of the α-hydroxy aldehyde moiety, prior to re-cyclization back to 6 and then the subsequent Ritter reaction. This does not seem to be a problem in the 5-membered ring series.

**Scheme 2**

Under oxidative reaction conditions (MnO₂, toluene at reflux) the pyrido[2,3-d]oxazole 9c was converted to the oxazol[4,5-b]pyridin-5(4H)-one 13 in 62% yield (Scheme 3). The analogous pyrrolo[2,3-d]oxazole 8c however, failed to provide the corresponding oxidized product when exposed to the same reaction conditions.

**Table 1**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material</th>
<th>Product (yield, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>8a (93)</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>8b (90)</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>8c (86)</td>
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<td>6</td>
<td>9e (0)</td>
</tr>
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* MeNO₂ as solvent, 3 equiv of 7d. **Starting 6 was also isolated in 21% recovered yield.
In conclusion, pyrido- and pyrrolo[2,3-]oxazolines can be conveniently prepared in high yield from the Ritter reaction of nitriles and chiral cyclic N-acyliminium ions. Cis-4-hydroxy-5-acylamino-pyrroolidines and cis-5-hydroxy-6-acylamino-piperidines can be readily obtained by acid hydrolysis of these bicyclic heterocyclic compounds, respectively. The compounds derived from the 6-membered hemiaminal 6 are obtained in racemic form.

**Experimental**

**General** Unless stated, CDCl₃ was used as a solvent for all ¹H NMR (500 MHz) and ¹³C NMR (125 MHz) measurements. All IR spectra were determined as neat samples. All solutions were dried over anhydrous MgSO₄. Petrol refers to the hydrocarbon fraction of boiling point 40-60 °C.

(3aR,6aS)-4-Benzyl-2-methyl-6,6a-dihydro-3H-pyrrolo[2,3-d]oxazol-5(4H)-one (8a). To a solution of diol 4 (0.10 g, 0.483 mmol) in acetonitrile (3 mL) at 0 °C was added dropwise BF₃·Et₂O (0.192 g, 1.35 mmol). The reaction mixture was warmed to rt and stirred for 16 h. Saturated NaHCO₃ was added to the reaction solution so the reaction was heated at reflux for 30 min. The reaction was cooled and the volatiles were removed in vacuo. The crude product was purified by column chromatography [EtOAc (3 x 10 mL), dried (Na₂SO₄) filtered and concentrated in vacuo] to give the title compound (0.103 g, 93%) as a colorless oil.

To a solution of the oxazoline 9b (92 mg, 0.304 mmol) in MeOH/H₂O (10 mL of a 9 : 1 v/v mixture) was added drops of concentrated hydrochloric acid and the solution was stirred at rt for 6 h. The volatiles were removed in vacuo and the residue was purified by column chromatography [EtOAc to 4% MeOH / EtOAc (99 : 1)] to yield 12b (35 mg, 0.090 mmol, 30%) as a colorless solid.

To a solution of the oxazoline 9b (75 mg, 0.248 mmol) in chloroform (20 mL) was added silica gel (2 g) and the resulting homogeneous solution was stirred at rt for 16 h upon which the TLC analysis indicated an incomplete reaction so the solution was heated at reflux for 30 min. The reaction was quenched at 0 °C with saturated NaHCO₃ (10 mL) and brine (50 mL) and then allowed to stir for 10 min. The resulting mixture was extracted with EtOAc (3 x 70 mL), dried and concentrated in vacuo to yield the crude product. Flash chromatography (EtOAc, Rₜ = 0.31) of the crude product yielded 9b (164 mg, 0.543 mmol, 91%) as a colorless oil.

**Scheme 3**

In conclusion, pyrido- and pyrrolo[2,3-d]oxazolines can be conveniently prepared in high yield from the Ritter reaction of nitriles and chiral cyclic N-acyliminium ions. Cis-4-hydroxy-5-acylamino-pyrroolidines and cis-5-hydroxy-6-acylamino-piperidines can be readily obtained by acid hydrolysis of these bicyclic heterocyclic compounds, respectively. The compounds derived from the 6-membered hemiaminal 6 are obtained in racemic form.
mmol) in anhydrous toluene (10 mL) was added activated manganese(IV) dioxide (146 mg of 85% activity, 1.43 mmol, 10 eq) and the suspension was heated at 100 °C for 16 h. TLC analysis indicated an incomplete reaction so a further portion of manganese(IV) dioxide (146 mg, 10 eq) was added at then heated at reflux for 4 h whereupon, TLC analysis showed complete consumption of the oxazoline (the product is fluorescent and the oxazoline is not). The reaction was filtered through a short plug of silica (5 cm), eluted with EtOAc and the volatiles removed in vacuo. The crude product was purified by column chromatography [10% EtOAc/Petrol (Rf = 0.29)] yielding 13 (28.5 mg, 0.086 mmol, 62%) as a pale yellow solid. Mp 120-122 °C.

Acknowledgment. We thank the Australian Research Council and the University of Wollongong for financial support.

Supporting Information Available. Full experimental procedures and characterisation data as well as copies of the 1H NMR and 13C NMR spectra of all new compounds. Crystal-refinement data and ORTEP plots of compounds 6, 12a and 12b (CCDC #668234, 668235, 668236). This material is available free of charge via the Internet as http://pubs.acs.org.

References
(6) Kawase Y; Takahashi M; Takatsuki T; Arai M; Nakajima M; Tansawa K. J. Antibiot. 1996, 49, 61-64.
(13) Prepared according to Huang, P.-Q. Synlett 2006, 1133-1149.


(20) The 1H NMR spectra of the (S)- or (R)-Mosher’s ester derivatives of 12b both showed two sets of doublet peaks (1:1 ratio) for the benzylic methylene signals CH₂CH₂PMP (see Supporting Information).