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Diastereoselective 1,3-dipolar cycloaddition of pyrylium ylides with chiral enamides†

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Chiral enamides 5f–i were found to react with pyrylium ylides to give cycloadducts 6d–i in good yields with an excellent level of stereoselectivity. The chiral auxiliary was successfully removed on hydrogenolysis of compound 6f in continuous flow (H-Cube) resulting in the first asymmetric synthesis of complex amine 8.

Introduction

1,3-Dipolar cycloaddition of pyrylium ylides 1 with activated alkenes is a powerful synthetic tool providing direct access to the 8-oxa-bicyclo[3,2,1]octane motif 2 (Fig. 1). Common in a number of biologically active natural products such as englerin A,3 aspergillin PZ,5 the oxygen bridged bicycle 2 has potential as a scaffold for the development of pharmaceuticals.

Our group became involved in finding new applications for this interesting reaction,7 with particular attention drawn to the discovery of new polarophiles and reaction conditions. Indeed, the use of nitrogen as an alkene activator will allow direct synthesis of the bicyclic amine 2 (X = NH2). Therefore it is proposed that attachment of chiral auxiliaries on the nitrogen will allow a stereoselective 1,3-dipolar cycloaddition. Only one example of a diastereoselective 1,3-dipolar cycloaddition of pyrylium ylides with chiral acrylic esters was reported by Chen and co-workers.8

Results and discussion

All starting materials for this study were prepared according to literature procedures. Acetoxy pyrones 4a–c were prepared from corresponding furyl alcohols or fructose.9 Enamides 5a, 5f and 5g were prepared via palladium catalysed trans-vinyllations,10 ynamide 5e and enamides 5b–d and 5h were prepared by copper catalysed cross-couplings.11

At first we decided to establish the best cycloaddition conditions for reactions with non-chiral enamides (Table 1). Acetoxy pyrone 4a was reacted under triethyl amine promoted conditions (A)2 and thermal conditions (B).1

Under both sets of conditions the reactions with the simplest enamine 5a proceeded smoothly to give the desired product 6a. The yield was marginally better under thermal conditions, although this reaction required a significantly longer time to reach complete conversion of the starting material. The slightly lower yield of the base-promoted reaction was due to formation of the pyrylium ylide dimer 7 as a minor byproduct. Reaction of the trans-ynamide 5b produced the product 6b but in a lower yield, while the cis-ynamide 5c gave no detectable cycloaddition. Cycloaddition of the gem-disubstituted alkene 5d gave a different product, which decomposed upon attempts at purification by column chromatography. Our tentative assignment of the structure 6c was made on the basis of the crude 1H NMR analysis, which showed the absence of the enone double bond, and instead the presence of resonances corresponding to the double bond of the cyclic enol ether. Formation of this regioisomer is unusual and will be further investigated in a separate study. The ynamide 5e gave no cycloaddition products under either thermal or base catalysed conditions.

Having established that the mono-substituted double bond gave the best yields of the cycloadduct, we proceeded to...
investigate the reactions of chiral enamides 5f–h under base promoted milder reaction conditions (Table 2).

Gratifyingly, cycloaddition reactions of terminal enamides 5f–h proceeded in moderate to good yields and the products were formed as single diastereoisomers. Chiral trans-enamide 5i gave cycloadduct 6i in a lower yield as was expected from our initial experiments. The relative stereochemistry of the cycloadducts was established via X-ray analysis of 6d (Fig. 2) and further correlation of the NMR data for the products.

The stereochemical outcome of the reactions can be rationalized by the model presented in Fig. 3. The enamide assumes the preferred conformation and the endo cycloaddition happens on the least hindered face of the alkene giving rise to the observed stereochemistry of the adducts.

To conclude this study we decided to demonstrate possible cleavage of the chiral auxiliary. Cycloadduct 6f was reduced on a continuous flow hydrogenation setup (H-Cube) to give both reduction of the enone double bond and cleavage of the chiral auxiliary. We discovered that direct purification of the primary amine by column chromatography was problematic due to its high polarity and the crude product was converted into an aceta-mide 8, which was isolated in a 50% yield after two steps (Scheme 1).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Cycloadditions with simple enamides 5a–e</th>
</tr>
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<tbody>
<tr>
<td><img src="image" alt="Cycloaddition Reaction" /></td>
<td><img src="image" alt="Cycloaddition Reaction" /></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Enamide</th>
<th>Conditions</th>
<th>Time (d)</th>
<th>Product</th>
<th>Yield</th>
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</thead>
<tbody>
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<td>72%</td>
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<tr>
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<tr>
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<td><img src="image" alt="Cycloaddition Conditions" /></td>
<td>1.5</td>
<td><img src="image" alt="Product" /></td>
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</table>

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Conclusions

In summary, we have demonstrated the first example of the use of amides as alkene activators in the 1,3-dipolar cycloaddition reactions of pyrylium ylides. The use of chiral oxazolidinones as chiral auxiliaries leads to highly stereoselective cycloadditions and the first asymmetric synthesis of the bicyclic amine 8.

Table 2  Cycloadditions with chiral enamides 5f–i

<table>
<thead>
<tr>
<th>Pyrone</th>
<th>Enamide</th>
<th>Temp</th>
<th>Time (h)</th>
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<th>Yield (%)</th>
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<tr>
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<td>rt</td>
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<td><img src="image" alt="Product 6i" /></td>
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</table>
Experimental section

All reactions were carried out under an inert atmosphere (N₂) unless stated otherwise. Reaction solvents (toluene, CH₂Cl₂) were freshly distilled from calcium hydride under a N₂ atmosphere prior to use. All NMR spectral data was collected on Bruker DRX-500 or Bruker A V-400 spectrometers. IR spectra were collected on a Perkin-Elmer Spectrum One FT-IR spectrometer, optical rotations were measured on a Perkin-Elmer 2410 polarimeter and mass-spectra data was collected on a Waters GCT-Premier spectrometer with NanoMate attachment.

Base promoted cycloadditions (method A)

To a stirred solution of acetoxy pyrones 4 (1.28 mmol) and enamides 5 (6.4 mmol) in toluene (7 mL) was added triethylamine (696 µL, 5.12 mmol) in three equal portions over a period of 36 h at room temperature. Stirring was continued for another 12 h when TLC analysis indicated complete consumption of the starting material 4. Solvents and volatiles were removed under reduced pressure and the residue was purified by column chromatography (40–60 petroleum ether–ethyl acetate 3 : 1) to give the cycloadducts 6.

Thermal cycloadditions (method B)

A solution of acetoxy pyrones 4 (1.28 mmol) and enamides 5 (6.4 mmol) in toluene (7 mL) was placed in a sealed tube containing a Teflon stirrer bar. The sealed tube was flushed with N₂, sealed with a Teflon screw-cap and heated in an oil bath (150 °C) under stirring until TLC indicated complete consumption of the starting material 4 (usually after a period of 4 days). The reaction mixture was allowed to cool down, volatiles were removed under reduced pressure and the residue was purified by column chromatography (40–60 petroleum ether–ethyl acetate 3 : 1) to give the cycloadducts 6.

Cycloadduct 6a a white solid: m.p. 76 °C; λmax(KBr) 1740 (m), 1686 (s); m/z (ES⁺) found 208.0974 (MH⁺) C₁₁H₁₂NO₂ requires 208.0974; ¹H (500 MHz, CDCl₃) δ 1.82 (1H, ddd, J 14.0, 6.0, 1.5 Hz), 2.04 (2H, m), 2.40 (2H, t, J 8.5 Hz), 2.67 (1H, ddd, J 14.0, 9.0, 6.0 Hz), 3.28 (2H, m), 4.56 (1H, d, J 9.0 Hz), 4.70 (1H, dt, J 10.0, 6.0 Hz), 5.40 (1H, dd, J 6.0, 4.5 Hz), 6.15 (1H, dd, J 10.0, 1.5 Hz), 7.22 (1H, dd, J 10.0, 4.5 Hz). ¹³C (125 MHz, CDCl₃) 0.0, 0.9, 12.6, 17.5, 28.2, 44.7, 56.3, 69.2, 109.2, 132.5, 157.8, 177.5.

Cycloadduct 6b a white solid: m.p. 90–91 °C; λmax(KBr) 1752 (s), 1697 (m); m/z (ES⁺) found 221.1121 (MH⁺) C₁₀H₁₄NO₃ requires 221.1123; ¹H (500 MHz, CDCl₃) δ 1.38 (3H, d, J 6.0 Hz), 2.01 (2H, m), 2.27 (1H, m), 2.41 (2H, t, J 9.0), 3.29 (2H, m), 4.13 (1H, app t, J 6.0 Hz), 5.13 (1H, dd, J 6.0, 5.0 Hz), 6.11 (1H, dd, J 10.0, 1.5 Hz), 7.21 (1H, dd, J 10.0, 5.0 Hz). ¹³C (125 MHz, CDCl₃) 0.0, 0.9, 12.6, 17.5, 28.2, 44.7, 56.3, 69.2, 109.2, 132.5, 157.8, 177.5.

Cycloadduct 6c a white solid: m.p. 98 °C; λmax(KBr) 1740 (m), 1690 (s); m/z (ES⁺) found 300.1236 (MH⁺) C₁₂H₁₆NO₃ requires 300.1236; ¹H (500 MHz, CDCl₃) δ 1.00 (3H, d, J 6.0 Hz), 2.10 (2H, m), 2.13 (1H, m), 2.33 (1H, m), 2.41 (2H, t, J 9.0), 2.67 (1H, ddd, J 10.0, 4.5, 1.5 Hz), 4.09 (1H, app s), 4.10 (1H, app s), 4.20 (1H, dd, J 10.0, 6.0, 4.5 Hz), 4.50 (1H, dd, J 8.5, 1.5 Hz), 5.00 (1H, dd, J 6.0, 4.5 Hz), 6.10 (1H, dd, J 10.0, 1.5 Hz), 7.00 (1H, dd, J 10.0 Hz), 7.10 (1H, d, J 10.0 Hz), 7.3 (5H, m); ¹³C (125 MHz, CDCl₃) 29.7, 37.9, 55.7, 58.9, 66.6; 74.9, 80.2, 127.5, 127.7, 129.1, 129.2, 135.1, 151.1, 157.7, 196.4.

Cycloadduct 6d a white solid: m.p. 131 °C; [α]D²⁰ = +370.1 (c = 0.95, CHCl₃); λmax(KBr) 1750 (s), 1696 (s); m/z (ES⁺) found 320.1236 (MH⁺) C₁₃H₁₄NO₂ requires 320.1236; ¹H (500 MHz, CDCl₃) δ 1.80 (1H, dd, J 13.5, 1.5 Hz), 2.70 (2H, m), 3.10 (1H, dd, J 13.5, 4.0 Hz), 3.88 (1H, dd, J 14.0, 9.0, 8.5 Hz), 4.09 (1H, app s), 4.10 (1H, app s), 4.20 (1H, dd, J 10.0, 6.0, 4.5 Hz), 4.50 (1H, dd, J 8.5, 1.5 Hz), 5.00 (1H, dd, J 6.0, 4.5 Hz), 6.10 (1H, dd, J 10.0, 1.5 Hz), 7.10 (1H, d, J 10.0 Hz), 7.3 (5H, m); ¹³C (125 MHz, CDCl₃) 29.7, 37.9, 55.7, 58.9, 66.6; 74.9, 79.4, 80.2, 127.5, 127.7, 129.1, 129.2, 135.1, 151.1, 157.7, 196.4.

Cycloadduct 6e a white solid: m.p. 168–170 °C; [α]D²⁰ = +8.8 (c = 1.0, CHCl₃); λmax(KBr) 1755 (s), 1708 (s), 1409 (s); m/z (ES⁺) found 286.1089 (MH⁺) C₁₆H₂₀NO₄ requires 286.1079; ¹H (400 MHz, CDCl₃) δ 1.68 (1H, dd, J 13.5, 1.5 Hz), 2.28 (1H, ddd, J 13.5, 10.0, 8.5 Hz), 4.02 (1H, dd, J 10.0, 8.5, 4.5 Hz), 4.21 (1H, dd, J 8.5, 3.0 Hz), 4.38 (1H, dd, J 8.0, 1.5 Hz), 4.61 (1H, dd, J 8.5, 3.0 Hz), 4.68 (1H, dd, J 8.5, 3.0 Hz), 5.36 (1H, dd, J 6.0, 4.5), 6.17 (1H, dd, J 10.0, 1.5 Hz), 7.20–7.45 (6H, m). ¹³C (125 MHz, CDCl₃) 29.3, 56.0, 61.5, 70.4, 74.5, 80.1, 126.2, 127.9, 129.5, 127.9, 138.3, 150.9, 158.3, 190.4.

Cycloadduct 6f a white solid: m.p. 195–199 °C; [α]D²⁰ = +25.9 (c = 2.8, CHCl₃); λmax(KBr) 1742 (s), 1685 (s), 1400 (s); m/z (ES⁺) found 384.1230 (MNa⁺) C₂₂H₁₉NO₅Na requires
Cartridge at 80 °C on the H-Cube hydrogenation setup working.

A solution of cycloadduct 6f (68 mg, 0.19 mmol) in EtOAc–AcOH (10:1, 5 mL) was continuously passed through a Pd/C cartridge at 80 °C on the H-Cube hydrogenation setup working in full hydrogenation mode until TLC indicated disappearance of compounds running mid-plate in hexane–EtOAc 2:1 mixture. Solvents were removed under vacuum and to the residual ammonium acetate salt was added DCM (10 mL), Et3N (0.5 mL, excess) and acetic anhydride (0.2 mL, excess). The resulting mixture was stirred for 6 h and concentrated. The residue was purified by flash column chromatography (40–60 petrol–EtOAc 3:1) to give the product 8 (17.4 mg, 50% as a colourless oil: [α]D20 = +115.5 (c = 0.10, CHCl3); λmax (thin film) 3490 (br m), 2950 (m), 1720 (s), 1650 (s); m/z (ES+) found 184.0981 (MH+) C30H14NO4 requires 184.0974; 1H (500 MHz, CDCl3) δ 1.68 (1H, dd, J 14.0, 1.5 Hz), 2.09 (3H, s), 2.13 (1H, m), 2.28 (1H, dd, J 13.0, 7.5 Hz), 2.41 (1H, dd, J 17.0, 8.0 Hz), 2.58–2.76 (2H, m), 4.40 (1H, d, J 8.0 Hz), 4.44 (1H, app t, J 6.5 Hz), 4.52 (1H, dd, J 13.0, 10.0, 6.5 Hz). 13C (125 MHz, CDCl3) 3.35, 6.7, 15.1, 20.4, 53.8, 58.8, 63.8, 157.2, 197.9.

Acknowledgements
We would like to thank DEL NI for studentships (CS and PM), Almac for a studentship (YMB), Dr P Nockemann (QUB) for the X-ray analysis and Dr G Trevitt (Almac) for the use of the H-Cube.

Notes and references
3 For a recent review and examples see: V. Singh, U. M. Krishna, V. Vikrant and G. K. Trivedi, Tetrahedron, 2008, 64, 3405.

Acetamide 8
A solution of cycloadduct 6f (68 mg, 0.19 mmol) in EtOAc–AcOH (10:1, 5 mL) was continuously passed through a Pd/C cartridge at 80 °C on the H-Cube hydrogenation setup working in full hydrogenation mode until TLC indicated disappearance of compounds running mid-plate in hexane–EtOAc 2:1 mixture. Solvents were removed under vacuum and to the residual ammonium acetate salt was added DCM (10 mL), Et3N (0.5 mL, excess) and acetic anhydride (0.2 mL, excess). The resulting mixture was stirred for 6 h and concentrated. The residue was purified by flash column chromatography (40–60 petrol–EtOAc 3:1) to give the product 8 (17.4 mg, 50% as a colourless oil: [α]D20 = +115.5 (c = 0.10, CHCl3); λmax (thin film) 3490 (br m), 2950 (m), 1720 (s), 1650 (s); m/z (ES+) found 184.0981 (MH+) C30H14NO4 requires 184.0974; 1H (500 MHz, CDCl3) δ 1.68 (1H, dd, J 14.0, 1.5 Hz), 2.09 (3H, s), 2.13 (1H, m), 2.28 (1H, dd, J 13.0, 7.5 Hz), 2.41 (1H, dd, J 17.0, 8.0 Hz), 2.58–2.76 (2H, m), 4.40 (1H, d, J 8.0 Hz), 4.44 (1H, app t, J 6.5 Hz), 4.52 (1H, dd, J 13.0, 10.0, 6.5 Hz). 13C (125 MHz, CDCl3) 3.35, 6.7, 15.1, 20.4, 53.8, 58.8, 63.8, 157.2, 197.9.

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