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Synthesis of 1- and 4-substituted piperazin-2-ones via Jocic-type reactions with N-substituted diamines

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Enantiomerically-enriched trichloromethyl-containing alcohols, obtained by asymmetric reduction, can be transformed regioselectively into 1-substituted piperazinones by modified Jocic reactions with little or no loss of stereochemical integrity. This methodology can be easily used to synthesise important pharmaceutical compounds such as the fluorobenzyl intermediate of a known PGGTase-I inhibitor.

Introduction

Substituted piperazin-2-ones, and related piperazines, are important pharmacophores which can be found in several medicinally relevant compounds, such as nonsteroidal androgen receptor antagonists, hepatitis C virus replication inhibitors, DPP-4 inhibitors, elastase inhibitors, PGGTase-I inhibitors, antidepressants, HDAC inhibitors, neurokinin receptor antagonist GW597599, melanocortin receptors, CCR5 receptor antagonists, anti-bacterials, bradykinin receptor antagonists, serotonin receptor antagonists, GPIIIb/IIIa antagonists, PET probes for Rho-kinases, and conformationally constrained peptides. Whilst the synthesis of enantiomerically enriched 1- and 4-substituted piperazin-2-ones have been reported in the literature it still remains a great challenge. To date enantiomerically-pure substituted piperazin-2-ones can be made by the dynamic resolution of α-halo chiral esters and manipulation of ‘chiral pool’ compounds such as naturally-occurring amino acids. α-Trichloromethylalcohols are important intermediates in synthesis. Previously, we reported the enantioselective reduction of trichloromethyl ketones using ruthenium transfer hydrogenation catalysts and the subsequent Jocic-type reactions of the products to give enantiomerically enriched amino-amides.

Scheme 1 Previously reported work.

Results

Due to the medicinal relevance of 1-substituted piperazin-2-ones we attempted to develop a generic method for the synthesis of this class of compounds. Boc-protection of (S)-1 lead to (S)-2 in excellent yield and without significant loss of stereochemical integrity (Scheme 2). However, deprotonation of the amide NH with sodium hydride and subsequent alkylation with benzyl bromide lead to the formation of the product (S)-3 with 45 % e.e. (a loss of 40 % e.e.).

Scheme 2 Reagents and conditions: (i) Boc₂O, NaOH, H₂O, rt, 17 h; (ii) NaH, THF, 0 ºC, 90 mins, then BnBr, 0 ºC to rt, 18 h.

We therefore investigated the regioselectivity and enantiospecificity of Jocic-type reactions of enantiomerically enriched trichloromethyl-substituted alcohol (R)-4 (95 % e.e.) with unsymmetrical mixed-primary-secondary 1,2- and 1,3-diamines (Table 1). Generally, as the size of the nitrogen substituent R² of the secondary amine increases the formation of 1-substituted piperazin-2-ones is favoured. With R² = methyl (entry 2) there is no preference for either the 1- or 4-substituted piperazin-2-one, giving an equal mixture of 7 and 8 in high enantiomeric excess. However, increasing the size of the amine substituent gives a much improved ratio (R² = Et, 75 : 25, entry 3), which increases further with R² = isopropyl to 95 : 5 (entry 4).

We also showed that this reaction worked well with N-phenylethylendiamine, which gives the 1-substituted product (S)-12 in 52 % yield and 98 % e.e. (entry 5). It is possible to synthesise substituted diazapen-2-ones 13 and 14 with N-benzyl-1,3-propanediamine (entry 6). The formation of the 1-substituted piperazin-2-one may be favoured by the preferential attack of the less sterically encumbered primary amine opening the 2,2-dichloroepoxide. The regioselectivity of related reactions of achiral trichloro-tertiary-alcohols also favours 1-substituted products, but with lower regioselectivity. Crystal structures of racemic samples 5, 6 and 12 confirmed the regiochemistry of
these products (Figure 1). Some 4-substituted isomers (S)-6, (S)-8 or 14 were independently synthesised by alkylation of the related N-unsaturated piperazinones 1 and 12 or diazepane 15 in the presence of mild base without deterioration of enantioselectivity (Table 2).

Table 1 Jocic-type reactions with unsymmetrical diamines

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Ratio&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt;</th>
<th>e.e.&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>a : b</td>
<td>a : b</td>
<td>a : b</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>CH₂Ph</td>
<td>93 : 7</td>
<td>76</td>
<td>94&lt;sup&gt;d&lt;/sup&gt;</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>CH₃</td>
<td>50 : 50</td>
<td>46</td>
<td>94&lt;sup&gt;d&lt;/sup&gt;</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>CH₃CH₂</td>
<td>75 : 25</td>
<td>72</td>
<td>96&lt;sup&gt;d&lt;/sup&gt;</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>CH₂(CH₂)₂</td>
<td>95 : 5</td>
<td>72</td>
<td>99</td>
<td>11</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>1 : 1</td>
<td>52</td>
<td>98</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>CH₂Ph</td>
<td>73 : 27</td>
<td>53</td>
<td>99</td>
<td>97</td>
</tr>
</tbody>
</table>

<sup>a</sup> by ¹H NMR of crude product of racemic reaction; <sup>b</sup> isolated yield; <sup>c</sup> by chiral HPLC analysis; <sup>d</sup> by chiral HPLC analysis on N-Boc derivative.

Figure 1 Crystal structures of racemic 5, 6 and 12 establishing Jocic reaction regiospecificity.

Table 2 Aminoaalkylations with mild base.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>n</th>
<th>S.M.&lt;sup&gt;a&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt;</th>
<th>e.e.&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>1</td>
<td>(S)-CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>37</td>
<td>95</td>
<td>(S)-8</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>2</td>
<td>(S)-CH₃Ph</td>
<td>58</td>
<td>95</td>
<td>(S)-6</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>2</td>
<td>15&lt;sup&gt;e&lt;/sup&gt;CH₃Ph</td>
<td>&gt;95&lt;sup&gt;d&lt;/sup&gt;</td>
<td>n/a</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>1</td>
<td>(S)-CH&lt;sub&gt;2&lt;/sub&gt;CH₃</td>
<td>50</td>
<td>98</td>
<td>(S)-20</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> starting material, see table 1 for e.e.; <sup>b</sup> racemic starting material; <sup>c</sup> isolated yield; <sup>d</sup> conversion by ¹H NMR; <sup>e</sup> by chiral HPLC analysis.

Despite the synthesis of analogous seven-membered lactams often occurring with lower rates of ring closure than six-membered rings, the synthesis of N-unsaturated<sup>24</sup> and 4-benzyl diazepanones (Table 1, entry 6) is possible. N-Arylation does however significantly impede ring closure in favour of intermolecular amide formation, with no 1-phenyl diazepane being formed. A trace amount of the 4-phenyl regioisomer was however produced showing that the ring closure of the primary amine is again relatively fast. The unexpected diamine product was independently synthesised using a N<sup>1</sup>-protected arylated diamine (Scheme 4).

Scheme 4 Reagents and conditions: (i) H₂N(CH₂)₃NHPPh, NaOH, BnNEt₃Cl, CH₂Cl₂, H₂O, 17 h, rt; (ii) H₂N(CH₂)₃NPhCH₂Ph, NaOH, BnNEt₃Cl, CH₂Cl₂, H₂O, 17 h, rt, 18%; (iii) 10% Pd/C, HCO₂NH₄, MeOH, reflux, 3 h, 60%.

A single methyl group provides a small degree of selectivity in the reaction of a phenylenediamine (18 and 19), and the relative reactivity of N-phenyl and N-benzyl ends of an unsymmetrical ethylene diamine is also less selective (20 and 21) (Scheme 5).
We found that \( \delta \) (400 MHz; CDCl\(_3\)) on Bruker (1 mL) on ice.

It is known that Jocic / Bargellini reactions that proceed via dichloroepoxide intermediates\(^{21k}\) can also be performed in alcohols instead of chlorinated solvents.\(^{21g,h,21m,30}\) We found that with amine nucleophiles a high, but not perfect, level of stereochemical integrity could be obtained in the amino amide products, however yields are lower in the biphasic reaction system (Scheme 8).

**Scheme 7 Reagents and conditions:** (a) (R,R)-TsDPENRu(p-cymene)Cl (5 mol %), formic acid/triethylamine (5:2), N\(_2\), 28 °C, 17 h; (d) N-4-fluorobenzylethane-1,2-diamine, BrNEt\(_3\)Cl, NaOH, H\(_2\)O, CH\(_2\)Cl\(_2\) 5 °C to rt, 17 h.

**Scheme 8 Reagents and conditions:** \(^{a}\) NaOH (5 equiv.), MeOH, 55 °C. \(^{b}\) NaOMe (5 equiv.), MeOH, rt.

**Conclusions**

The stereospecific and regioselective synthesis of 1-substituted piperazin-2-ones, where the order of addition of the diamine to the notionally 1,2-bis-electrophilic trichloromethyl-alcohol, is controlled by the size of the amine substituent. The good levels of regiocontrol for N-benzyl piperazinones is particularly useful as many there are many examples of this substructure are found in compounds with potentially medicinal activity. The reactions in methanol show that this process has some potentially useful possibilities for a simpler mono-phasic system.

**Acknowledgements**

We wish to thank University of Warwick (studentship for MSP, URSS funding for MWME) for funding, Johnson Matthey Plc for the kind donation of catalyst 3, and Prof. Martin Wills for use of, and help with, chiral GC analysis. The Oxford Diffraction Gemini XRD system was obtained with support from Advantage West Midlands and part funded by the European Regional Development Fund.

**Experimental**

**General Information:**

\(^{1}\)H and \(^{13}\)C NMR spectra were recorded in CDCl\(_3\) on Bruker Advance DRX 250, 300, 400 and 600 MHz spectrometers at room temperature. Chemical shifts are reported in parts per million (ppm) and referenced from CDCl\(_3\) (\( \delta \)\(_\text{H} = 7.26\) ppm and \( \delta \)\(_\text{C} = 77.0\) ppm). Coupling constants (\( J \)) are rounded to the nearest 0.5 Hz. \(^{1}\)H and \(^{13}\)C assignments were established on the basis of \(^{1}\)H-\(^{1}\)H COSY, DEPT, HMQC and HMBD correlations. All commercially available solvents and chemicals were used without further purification.

**Representative Procedure for Jocic-type Reactions with Amines: Synthesis of 1-benzyl-3-phenethylpiperazin-2-one 5 and 4-benzyl-3-phenethylpiperazin-2-one 6:**

\( (R)-1,1,1\)-Trichloro-4-phenylbutan-2-ol (R)-4 (254 mg, 1 mmol, 1 equiv., 95 % e.e.) and benzyltriethylammonium chloride (4.6 mg, 0.02 mmol, 0.02 equiv.) were stirred in CH\(_2\)Cl\(_2\) (1 mL) on ice. \( \text{N-Benzyl-1,2-ethylenediamine (0.75 mL}, 5 \text{ mmol, 5 equiv.) was added, and the mixture was stirred at 10 minutes before the dropwise addition of NaOH (10 M aq.) (0.5 mL, 5 mmol, 5 equiv.). The reaction mixture was stirred for a further 15 minutes on ice before being allowed to warm to room temperature where it was stirred for 17 hours. Distilled water (15 mL) was added and the mixture was extracted with CH\(_2\)Cl\(_2\) (3 x 15 mL). The organic extracts were combined, dried (MgSO\(_4\)) and concentrated to vacuo. The residue was purified by silica column chromatography (50 % ethyl acetate in 40-60 petroleum ether to 10 % MeOH in ethyl acetate) to give (S)-1-benzyl-3-phenethylpiperazin-2-one 5 as a yellow solid (224 mg, 76 %, 94 % e.e.) and benzyltriethylammonium chloride (4.6 mg, 0.02 mmol, 0.02 equiv.) were stirred in CH\(_2\)Cl\(_2\) (1 mL) on ice. \( \text{N-Benzyl-1,2-ethylenediamine (0.75 mL}, 5 \text{ mmol, 5 equiv.) was added, and the mixture was stirred at 10 minutes before the dropwise addition of NaOH (10 M aq.) (0.5 mL, 5 mmol, 5 equiv.). The reaction mixture was stirred for a further 15 minutes on ice before being allowed to warm to room temperature where it was stirred for 17 hours. Distilled water (15 mL) was added and the mixture was extracted with CH\(_2\)Cl\(_2\) (3 x 15 mL). The organic extracts were combined, dried (MgSO\(_4\)) and concentrated to vacuo. The residue was purified by silica column chromatography (50 % ethyl acetate in 40-60 petroleum ether to 10 % MeOH in ethyl acetate) to give (S)-1-benzyl-3-phenethylpiperazin-2-one 5 as a yellow solid (224 mg, 76 %, 94 % e.e.) and benzyltriethylammonium chloride (4.6 mg, 0.02 mmol, 0.02 equiv.) were stirred in CH\(_2\)Cl\(_2\) (1 mL) on ice.
Notes and references

† Electronic Supplementary Information (ESI) available: synthesis details, NMR spectra, chiral HPLC chromatograms and crystallographic details. Crystal structures have been deposited at the Cambridge Crystallographic Data Centre and assigned the deposition numbers CCDC 1022612-1022614. See DOI: 10.1039/b000000x/.


