One-pot synthesis of enantiopure pyrrolopyrrolizines

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<td>Manuscript ID:</td>
<td>jo-2020-02103v.R1</td>
</tr>
<tr>
<td>Manuscript Type:</td>
<td>Note</td>
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<tr>
<td>Date Submitted by the Author:</td>
<td>n/a</td>
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<td>Complete List of Authors:</td>
<td>Pertejo, Pablo; Universidad de Burgos Facultad de Ciencias González-Saiz, Beatriz; Universidad de Burgos Facultad de Ciencias Quesada, Roberto; Universidad de Burgos, Química García-Valverde, Maria; Universidad de Burgos, Department of Chemistry</td>
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One-pot synthesis of enantiopure pyrrolopiperazines

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Supporting Information Placeholder

ABSTRACT: A simple one-pot protocol for the synthesis of fused pyrrolopiperazines with a complete diastereoselectivity has been developed. This novel methodology combined the Ugi reaction with a spontaneous enamine alkylation on a multicomponent domino reaction, starting from non-protected diamines and arylglyoxals.

Introduction

Piperazines and pyrrolopiperazines represent privileged scaffolds in medicinal chemistry. Their drug-like properties and synthetic versatility make them excellent candidates to develop ligands for diverse protein receptors in drug discovery programs. Thus, these heterocyclic structures are found in many drugs and drug candidates with different pharmacological activity (Figure 1). A large number of methodologies have been described for the synthesis of these heterocycles, many of them starting from non-protected 1,2-diamines, such as the reductive amination of dicarbonyl compounds, the cyclocondensation with diols via borrowing hydrogen, the reductive coupling of diimines, the dination of allenes or the Michael addition-based multicomponent domino reaction involving 1,3-dicarbonyl compounds.

Figure 1. Drugs containing piperazine scaffold

Within the realm of multicomponent reactions (MCR), those based on the isocyanide chemistry (IMCR) have demonstrated the greatest versatility in the synthesis of piperazines, although the use of non-protected diamines in IMCR is rather limited. In fact, the use of non-protected primary diamines in the classical Ugi four component reaction (U-4CR) has been mainly focused in the construction of polymers and macrocycles. Actually, the synthesis of small molecules using diamines in the Ugi-4CR usually requires protecting groups in order to avoid competitive reactions. Thus, the use of primary non-protected 1,2-diamines usually affords 2-aminopyrazines as a result of an interrupted Ugi reaction, where the nitrilium ion, intermediate in the Ugi reaction, reacts intramolecularly with the second amine group of the diamine avoiding the incorporation of the carboxylic component. Furthermore, when secondary non-protected diamines are employed in the Ugi reaction, the four components are integrated in the final product with a different connectivity to the classical Ugi 4-CR adduct, the split-Ugi adduct. In this case, although the carboxylic component is incorporated and the imino anhydride intermediate is generated, the expected Mumm rearrangement does not take place since the nitrogen atom involved in the Ugi reaction becomes a tertiary amine. In this situation the second secondary amine provokes the rearrangement leading to the migration of the acyl moiety to this position. For all these reasons, there are only a handful of examples of classical Ugi reaction with non-protected diamines, all of them sharing a common feature, the use of functionalized aldehydes in order to block the second amine group in the first stage of the reaction. In an effort to increase the applicability of non-protected diamines in the synthesis of piperazines through the Ugi-4CR, we envisaged the combination of non-protected 1,2-diamines with arylglyoxals (Scheme 1).

Scheme 1. Primary non-protected diamines in the Ugi reaction
1. Interrupted Ugi reaction

\[
\text{Ar-NH}_2 + \text{R}^1 \text{CHO} \rightarrow \text{ArCONH}-\text{R}^1 + \text{H}_2\text{O}
\]

2. Functionalized aldehydes and diamines in the Ugi reaction

\[
\text{Ar-NH}_2 + \text{R}^1 \text{CHO} \rightarrow \text{ArCONH}-\text{R}^1 + \text{H}_2\text{O}
\]

3. This work: One step synthesis of pyrrolopiperazines

\[
\text{Ar-NH}_2 + \text{R}^1 \text{CHO} \rightarrow \text{ArCONH}-\text{R}^1 + \text{H}_2\text{O}
\]

**Results and discussion**

Initially, we decided to use ethylenediamine 1a, phenylglyoxal 2a, acetic acid 3a and cyclohexyl isocyanide 4a as starting reactants. The Ugi reaction was carried out under standard conditions,13 therefore the diamine 1a (1 equiv) was mixed with a solution of phenylglyoxal 2a (1 equiv) in methanol. The cyclohexyl isocyanide 4a (1 equiv) and the acetic acid 3a (1 equiv) were then added and the mixture was stirred at room temperature for one day. After work up, the reaction mixture was analyzed by NMR techniques, being the piperazine 5 the only product observed, as a mixture of imine/enamine tautomers (Scheme 2, see Supporting Information).

Furthermore, the result was identical to the one obtained when we synthesized and isolated the diimine (A) in scheme 3 from the ethylenediamine 1a and the phenylglyoxal 2a,18 and then it was treated with the isocyanide 4a and the carboxylic acid 3a, showing that this diimine A was an intermediate in this synthesis.

**Scheme 2. One-pot synthesis of piperazines from non-protected ethylenediamine**

\[
\text{Ar-NH}_2 + \text{R}^1 \text{CHO} \rightarrow \text{ArCONH}-\text{R}^1 + \text{H}_2\text{O}
\]

This result prompted us to explore the characteristic reactivity of enamines as nucleophiles,19 introducing an electrophilic position on the carboxylic acid component in order to furnish a fused lactam with the piperazine system. We chose 3-bromopropionic acid 3b and the reaction was carried out in the conditions described above. Gratefully, the cyclization to γ-lactam took place spontaneously,20 yielding the corresponding pyrrolopiperazine 6a (Table 1, Entry 1) through a multicomponent-domino reaction. In order to determine the scope of this reaction, we also used the 2,3-dimethyl-2,3-butanediamine 1b, along with different aryglyoxals 2a-b and isocyanides 4a-c affording different pyrrolopiperazines 6a-f. We observed lower yields when the hindered diamine 1b was used (Entries 4-6 vs 1-3, Table 1).

**Table 1. One-pot synthesis of pyrrolopiperazines 6 from non-protected 1,2-diamines**

<table>
<thead>
<tr>
<th>Entry</th>
<th>1 (R¹)</th>
<th>2 (Ar)</th>
<th>4 (R²)</th>
<th>6 (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>1a (H)</td>
<td>2a (C₆H₅)</td>
<td>4a (C₆H₁₁)</td>
<td>6a (92)</td>
</tr>
<tr>
<td>2</td>
<td>1a (H)</td>
<td>2a (C₆H₅)</td>
<td>4b (bBu)</td>
<td>6b (88)</td>
</tr>
<tr>
<td>3</td>
<td>1a (H)</td>
<td>2b (4-CIC₆H₄)</td>
<td>4a (C₆H₁₁)</td>
<td>6c (89)</td>
</tr>
<tr>
<td>4</td>
<td>1b (CH₃)</td>
<td>2a (C₆H₅)</td>
<td>4a (C₆H₁₁)</td>
<td>6d (72)</td>
</tr>
<tr>
<td>5</td>
<td>1b (CH₃)</td>
<td>2a (C₆H₅)</td>
<td>4b (bBu)</td>
<td>6e (58)</td>
</tr>
<tr>
<td>6</td>
<td>1b (CH₃)</td>
<td>2a (C₆H₅)</td>
<td>4c (nBu)</td>
<td>6f (68)</td>
</tr>
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</table>

a. Isolated products yields

To account for this result, we proposed a mechanistic pathway starting from the cyclic diimine A. The complete chemoselectivity observed in the following step can be explained by the different reactivity of these imines. Thus, the Ugi reaction would take place exclusively on the aldimine, while the aromatic ketimine would remain unchanged, affording selectively the imino anhydride intermediate B. The Mumm rearrangement would yield the corresponding Ugi adduct, a cyclic imine C_{imine} in equilibrium with its tautomer, the cyclic enamine C_{enamine}. In the last step the enamine would react spontaneously with formal HBr elimination yielding the corresponding pyrrolopiperazine 6 (Scheme 3).

**Scheme 3. Proposed mechanistic pathway**

Interestingly, the new stereogenic center is created in the last cyclization step and not during the Ugi reaction.21 This is remarkable, since the stereoselectivity achieved in the Ugi reaction is usually poor.22 Thus, we attempted the
stereochemical control in the generation of the new stereogenic center by using symmetric diamine derivatives bearing chiral centres. Enantiopure diamines, (1S,2S)-1,2-cyclohexanediamine 1c and (1S,2S)-1,2-diphenylethlenediamine 1d, and meso-diamines, cis-diaminocyclohexane 1e and meso-1,2-diphenylethlenediamine 1f were assayed employing the same protocol described above, and the corresponding pyrrolopiperazines 7a-j were obtained with total diastereoselectivity in excellent yields, regardless of the nature of the diamine employed (Scheme 4). The configuration of the new stereogenic centers was determined by NOESY experiments. Moreover, structural analyses by X-ray diffraction confirmed the determined stereochemistry (see Supporting Information).

Scheme 4. One-pot diastereoselective synthesis of pyrrolopyrazines 7

The complete diastereoselectivity observed in the last cyclization step was also studied computationally. This result can be explained by the reaction through the preferred conformations in the cyclic enamine intermediate, determined by DFT calculations using Gaussian 09.24 Thus, in the synthesis of 7a, the most stable conformation of the enamine intermediate favors the Si face attack of the enamine, while for the synthesis of 7d, 7g and 7i the preferred conformation favors the Re face attack (Figure 2, see Supporting Information).

Figure 2. Energies calculated (in gas phase) for the most stable conformations of the enamine intermediate in the synthesis of 7a and 7g

Conclusion

In this work we have developed an efficient and simple methodology for the synthesis of enantiopure pyrrolopiperazines through a multicomponent domino reaction, Ugi/enamine alkylation, using non-protected diamines in a one-pot sequence with high yield, and total diastereoselectivity when diamines bearing stereogenic centers are used.

Experimental section

General methods. Melting points are not corrected. Optical rotations were measured on a Zeiss D-7082 Polarimeter in a 1 dm cell and concentrations are given in g/100 ml. 1H and 13C NMR spectra were recorded in CDCl3 at 300 and 75 MHz, respectively, on a Varian Mercury 300 system, DEPT-135 experiments were conducted to assign carbon-13 signals. Chemical shifts are reported in parts per million with respect to residual solvent protons, and coupling constants are reported in hertz. High resolution mass spectra were recorded in on a 6545 Q-TOF Agilent LC-MS mass spectrometer (positive electrospray ionization mode, ESI (+)).

General procedure for the synthesis of pyrrolopyrazines 6 and 7. The corresponding diamine 1a-d (1 mmol) was added to a solution of arylglyoxal 2a-c (1 mmol) in methanol (10 ml). The solution was stirred for 10 min at room temperature. Then the 3-bromopropionic acid 3b (1 mmol) and the isocyanide 2a-b (1 mmol) were added to the solution and the mixture was stirred for 24 h. Then the solvent was removed and the residue was dissolved in dichloromethane and washed first with 10%
aqueous HCl solution, and then with saturated aqueous Na2CO3 solution. The organic phase was dried over anhydrous Na2SO4, filtered and concentrated to dryness. The residue was purified by column chromatography.

**N-Cyclohexyl-6-oxo-1-phenyl-3,4,6,7,8a-hexahydropyrrolo[1,2-b]pyrazine-8a-carboxamide (6a).** White solid (Hexane/AcOEt, 2:1). Yield: 312 mg, 92 %. M. p. 158-160 °C. 1H NMR (300 MHz, CDCl3) δ: 7.70-7.66 (m, 2H), 7.37-7.30 (m, 3H), 6.00 (d, J = 8.3 Hz, 2H), 3.99-3.72 (m, 4H), 3.23-3.13 (m, 1H), 2.86-2.67 (m, 2H), 2.27-2.19 (m, 1H), 1.94-0.93 (m, 11H). 13C{1H} NMR (75MHz, CDCl3) δ: 173.3 (Cq), 168.1 (Cq), 166.5 (Cq), 135.8 (Cq), 130.4 (CH2a), 128.4 (CH2a), 127.6 (CH2a), 66.6 (Cq), 49.4 (CH), 47.5 (Cq), 34.4 (CH2), 32.8 (CH2), 32.4 (CH2), 30.7 (CH2), 29.9 (CH2), 25.2 (CH2), 24.9 (CH2), 24.7 (CH). HRMS (ESI) m/z: [M + H]+ Calcd for C38H37N5O2 340.2020; Found 340.2222.

**N-(Tert-Butyl)-6-oxo-1-phenyl-3,4,6,7,8a-hexahydropyrrolo[1,2-b]pyrazine-8a-carboxamide.**

Brown solid (Hexane/AcOEt, 2:1). Yield: 275 mg, 88 %. M. p. 106-108 °C. 1H NMR (300 MHz, CDCl3) δ: 7.75-7.63 (m, 2H), 7.43-7.31 (m, 3H), 5.52 (s, 1H), 4.10-3.94 (m, 2H), 3.91-3.80 (m, 1H), 3.26-3.12 (m, 1H), 2.91-2.70 (m, 2H), 2.35-2.11 (m, 1H), 1.94-1.82 (m, 1H), 1.28 (s, 9H). 13C{1H} NMR (75MHz, CDCl3) δ: 173.3 (Cq), 168.1 (Cq), 166.1 (Cq), 135.6 (Cq), 130.5 (CH2a), 128.5 (CH2a), 127.5 (CH2a), 67.2 (Cq), 52.5 (Cq), 47.7 (CH2), 34.3 (CH2), 30.8 (CH2), 29.6 (CH2), 28.4 (CH). HRMS (ESI) m/z: [M + H]+ Calcd for C38H44N5O2 314.1863; Found 314.1866.

**1-(4-Chlorophenyl)-N-cyclohexyl-6-oxo-3,4,6,7,8a-hexahydropyrrolo[1,2-b]pyrazine-8a-carboxamide (6b).** White solid (Hexane/AcOEt, 2:1). Yield: 332 mg, 89 %. M. p. 188-190 °C. 1H NMR (300 MHz, CDCl3) δ: 7.68 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 8.7 Hz, 2H), 5.84 (d, J = 8.2 Hz, 1H), 4.06-3.67 (m, 4H), 3.33-3.11 (m, 1H), 2.95-2.65 (m, 2H), 2.42-2.18 (m, 1H), 2.10-0.81 (m, 11H). 13C{1H} NMR (75MHz, CDCl3) δ: 173.3 (Cq), 167.9 (Cq), 165.8 (Cq), 136.7 (Cq), 134.2 (Cq), 129.1 (CH2a), 128.6 (CH2a), 66.6 (Cq), 49.4 (CH), 47.5 (Cq), 34.6 (CH2), 32.9 (CH2), 32.5 (CH2), 30.6 (CH2), 29.9 (CH2), 25.2 (CH2), 24.8 (CH2), 24.7 (CH). HRMS (ESI) m/z: [M + H]+ Calcd for C38H37ClN5O2 374.2160; Found 374.1630; Found 374.1632.
(34,5a,8aS)-N-Cyclohexyl-6-oxo-1,3,4-triphenyl-3,4,6,7,8,8a-hexahydropyrrolo[1,2-a]pyrazine-8a-carboxamide (7d). Yellow solid. (Hexane/AcOEt, 3:1). Yield 452 mg, 92 %. M. p. 60-62 °C. [α]D = -105.4° (c = 0.48, CH3OH). 1H NMR (300 MHz, CDCl3) δ: 7.87-7.83 (m, 2H), 7.48-7.45 (m, 3H), 7.33-7.23 (m, 8H), 7.14-7.10 (m, 2H), 5.60 (s, 1H), 5.02 (d, J = 8.3 Hz, 1H), 4.88 (d, J = 8.3 Hz, 1H), 2.92-2.64 (m, 2H), 2.40-2.18 (m, 2H), 1.23 (s, 9H). 13C[1H] NMR (75 MHz, CDCl3) δ: 175.5 (Cq), 171.4 (Cq), 169.4 (Cq), 140.0 (Cq), 138.5 (Cq), 136.6 (Cq), 136.6 (Cq), 130.5 (Cq), 128.3 (Cq), 128.8 (Cq), 128.0 (Cq), 127.9 (Cq), 127.7 (Cq), 127.6 (Cq), 127.6 (Cq), 67.3 (Cq), 65.7 (Cq), 59.7 (Cq), 49.2 (Cq), 32.5 (Cq), 32.4 (Cq), 32.3 (Cq), 30.2 (Cq), 29.7 (Cq), 25.2 (Cq), 24.7 (Cq), 24.6 (Cq). HRMS (ESI) m/z: [M + H]+ Caled for C44H32N4O2 692.2466; Found 692.2665.

(34,5a,8aS)-N-(tert-Butyl)-6-oxo-1,3,4-triphenyl-3,4,6,7,8,8a-hexahydropyrrolo[1,2-a]pyrazine-8a-carboxamide (7e). Yellow solid. (Hexane/AcOEt, 4:1). Yield 404 mg, 87 %. M. p. 56-58 °C. [α]D = -105.4° (c = 0.57, CH3OH). 1H NMR (300 MHz, CDCl3) δ: 7.87-7.83 (m, 2H), 7.48-7.45 (m, 3H), 7.33-7.23 (m, 8H), 7.14-7.10 (m, 2H), 5.60 (s, 1H), 5.02 (d, J = 8.3 Hz, 1H), 4.88 (d, J = 8.3 Hz, 1H), 2.92-2.64 (m, 2H), 2.40-2.18 (m, 2H), 1.23 (s, 9H). 13C[1H] NMR (75 MHz, CDCl3) δ: 175.5 (Cq), 171.4 (Cq), 169.4 (Cq), 140.0 (Cq), 138.5 (Cq), 136.6 (Cq), 136.6 (Cq), 130.5 (Cq), 128.3 (Cq), 128.8 (Cq), 128.0 (Cq), 127.9 (Cq), 127.7 (Cq), 127.6 (Cq), 127.6 (Cq), 67.3 (Cq), 65.7 (Cq), 59.7 (Cq), 49.2 (Cq), 32.5 (Cq), 32.4 (Cq), 32.3 (Cq), 30.2 (Cq), 29.7 (Cq), 25.2 (Cq), 24.7 (Cq), 24.6 (Cq). HRMS (ESI) m/z: [M + H]+ Caled for C44H32N4O2 692.2466; Found 692.2665.

(34,5a,8aS)-N-Butyl-6-oxo-1,3,4-triphenyl-3,4,6,7,8,8a-hexahydropyrrolo[1,2-a]pyrazine-8a-carboxamide (7f). Pale yellow solid. (Hexane/AcOEt, 5:1). Yield 274 mg, 59 %. M. p. 141-143 °C. [α]D = -51.1° (c = 0.44, CH3OH). 1H NMR (300 MHz, CDCl3) δ: 7.90-7.78 (m, 2H), 7.50-7.38 (m, 3H), 7.36-7.22 (m, 8H), 7.18-7.05 (m, 2H), 5.62 (t, J = 5.7 Hz, 5.21 (d, J = 7.1 Hz, 1H), 4.98 (d, J = 7.1 Hz, 1H), 3.14 (td, J = 13.2, 7.1 Hz, 1H), 2.98-2.78 (m, 3H), 2.30-2.20 (m, 2H), 1.36-1.04 (m, 4H), 0.83 (t, J = 7.2 Hz, 3H). 13C[1H] NMR (75 MHz, CDCl3) δ: 175.1 (Cq), 170.1 (Cq), 140.0 (Cq), 138.3 (Cq), 136.1 (Cq), 130.7 (Cq), 128.6 (Cq), 128.5 (Cq), 128.4 (Cq), 128.0 (Cq), 127.9 (Cq), 127.8 (Cq), 127.7 (Cq), 127.6 (Cq), 66.7 (Cq), 64.5 (Cq), 58.5 (Cq), 39.9 (Cq), 32.1 (Cq), 30.9 (Cq), 30.3 (Cq), 20.0 (Cq), 13.6 (Cq). HRMS (ESI) m/z: [M + H]+ Caled for C42H30N4O2 663.2489; Found 663.2504.

(34R,5aS,9aR)-N-Cyclohexyl-1-oxo-4-phenyl-1,2,3,5a,5a,6,7,8,9,9a-decahydroxypropyrolo[1,2-a]quinazoline-3a-carboxamide (7g). Pale yellow solid. (Hexane/AcOEt, 3:1). Yield 365 mg, 93 %. M. p. 156-158 °C. 1H NMR (300 MHz, CDCl3) δ: 7.75 (dd, J = 7.6, 2.0 Hz, 2H), 7.47-7.38 (m, 3H), 5.61 (d, J = 8.2 Hz, 1H), 4.43-4.25 (m, 1H), 1.32-2.39 (m, 2H), 3.00-2.77 (m, 2H), 2.48-2.31 (m, 3H), 1.88-0.81 (m, 17H). 13C[1H] NMR (75 MHz, CDCl3) δ: 174.8 (Cq), 169.2 (Cq), 163.9 (Cq), 138.3 (Cq), 130.1 (Cq), 128.4 (Cq), 128.0 (Cq), 66.3 (Cq), 56.6 (Cq), 48.6 (Cq), 46.7 (Cq), 33.8 (Cq), 32.4 (Cq), 32.3 (Cq), 32.2 (Cq), 31.2 (Cq), 25.8 (Cq), 25.3 (Cq), 24.6 (Cq), 24.4 (Cq), 20.7 (Cq). HRMS (ESI) m/z: [M + Na]+ Caled for C63H43Na3N9O12 1155.3208; Found 1155.3212.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Copies of 1H NMR, 13C NMR and high-resolution mass spectra, and computational data (PDF).

X-ray crystallographic data for compounds 7a and 7g (CIF).

CCDC 1982178-1982179

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Author Contributions
The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes
The authors declare no competing financial interest.

ACKNOWLEDGMENT
Funding from Consejería de Educación de la Junta de Castilla y León (project BU075G19) is gratefully acknowledged.

REFERENCES


23. X-Ray analysis for 7a was carried out on the racemic form of 7a synthesized from (+)-1,2-cyclohexyldiamine.