A Novel Four-Component Reaction for the Diastereoselective Synthesis of Some New Spiro Pyrrolizidines via 1,3-Dipolar Cycloaddition of Azomethine Ylides

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Abstract: With regard to green chemistry, atom-efficient transformations of easily available starting materials into complex organic building blocks become increasingly important. Here, a novel four-component condensation of ninhydrin, 1,2-phenylene diamine, proline and N-aryl maleimides to some new spiro pyrrolizidines via 1,3-dipolar cycloadditions of azomethine ylides, under microwave irradiation or classical conditions, is reported.

Key words: spiro pyrrolizidines, azomethine ylides, 1,3-dipolar cycloadditions

Multicomponent reactions (MCRs) have emerged as a powerful tool for delivering the molecular diversity needed in the combinatorial approaches for the preparation of bioactive compounds. MCRs leading to interesting heterocyclic scaffolds are particularly useful for the creation of diverse chemical libraries of ‘drug-like’ molecules for biological screening. The combination of three or more small molecular weight building blocks in a single operation leads to high combinatorial efficacy. Here we report a novel four-component synthesis of some new spiro pyrrolizidine derivatives employing one-pot condensation of ninhydrin, 1,2-phenylene diamine, proline and N-aryl maleimides as building blocks.

Pyrrolizidine alkaloids have attracted a great deal of interest because of their wide distribution in nature and their variegated biological activities.

The Ugi and the Biginelli reactions are two important classes of multicomponent condensations that have been successfully applied to the synthesis of heterocyclic scaffolds. In the context of our general interest in multiple component reactions and as a part of our ongoing research program in the area of cycloaddition reactions, we herein report the facile and four-component synthesis of some novel spiro pyrrolizidine derivatives through diastereoselective 1,3-dipolar cycloaddition of azomethine ylides with N-aryl maleimides (Scheme 1).

The multi-component diversity elements are introduced by simple addition of one equivalent of 1,2-phenylene diamine to one equivalent of ninhydrin in DMSO (2–3 mL) as a solvent. This is followed by addition of the L-proline and N-aryl maleimides (one equivalent) and the reactants are further exposed to microwave to afford the corresponding spiro pyrrolizidines that were characterized as 5 (Scheme 1).

The compounds were characterized on the basis of their elemental analyses as well as IR, 1H NMR, 13C NMR, and mass spectral data. High diastereomeric excess of reaction was deduced on the basis of 1H NMR spectra through which no or traces of endo-isomer could be detected. It is noteworthy that adducts 5 have four chiral centers, but their synthesis affords only one diastereomer, due to the dipole configuration 8 and exo-transition state structure, that has been mentioned by Grigg and his co-workers later, in their extensive studies. The stereochemistry of the cycloadducts 5a–f was deduced on the basis of the 1H NOESY and coupling constants of 3a, 3b and 8a protons and comparison with related systems. The possibility of the other isomer forming via an endo-transition state was ruled out by 1H NOESY studies. For example in the case of 5a, irradiation of the H 3a at δ = 3.72 (J = 9.8 Hz, J = 6.5 Hz) caused a considerable enhancement of the signal for proton of 8a at δ = 4.36 (J = 9.8 Hz), but a little enhancement of the signal for H 8a at δ = 5.04. The signal in

Scheme 1

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the 13C NMR spectrum at 74.29 ppm corresponds to spiro carbon. The signals in the 13C NMR at 53.96, 54.84 and 67.25 ppm indicate the presence of the pyrrolizidine ring.

On the other hand, heating the same reaction mixture in DMSO under reflux conditions afforded the products in longer reaction times as shown in Table 1. These results showed the utility of the microwave irradiation in organic synthesis and its advantages in comparison with classical heating, especially in processes that need strong heating and/or vigorous reaction conditions.13

Presumably, the reaction proceeds through condensation of ninhydrin and 1,2-phenylene diamine to indenoquinoxaline-11-one 6 followed by formation of azomethine ylide 8 by thermal decarboxylation of mixtures of L-proline and indenoquinoxaline-11-one 6. The formed 1,3-dipole 8 subsequently undergoes cycloaddition reaction with N-aryl maleimide as dipolarophile, to produce, stereoselectively, the new adduct 5 (Scheme 2).

In summary, the multicomponent reaction described herein provides a simple and direct entry into a number of interesting novel spiro pyrrolizidine derivatives that may be of value in medicinal chemistry. We have demonstrated that microwave irradiation can greatly facilitate this condensation reaction.

Table 1  Synthesis of 5a–f under Microwave or Reflux Conditions

<table>
<thead>
<tr>
<th>5</th>
<th>R₁</th>
<th>R₂</th>
<th>Microwave</th>
<th>Yield (%)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>Reflux</th>
<th>Time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>CH₃</td>
<td>Cl</td>
<td>5</td>
<td>89</td>
<td>3.5</td>
<td>79</td>
<td>3</td>
<td>86</td>
</tr>
<tr>
<td>b</td>
<td>CH₃</td>
<td>CH₃</td>
<td>3</td>
<td>95</td>
<td>2</td>
<td>86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c</td>
<td>H</td>
<td>Cl</td>
<td>5</td>
<td>87</td>
<td>3.5</td>
<td>76</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d</td>
<td>H</td>
<td>H</td>
<td>4</td>
<td>90</td>
<td>3</td>
<td>80</td>
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<td></td>
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<tr>
<td>e</td>
<td>CH₃</td>
<td>H</td>
<td>3</td>
<td>93</td>
<td>2.5</td>
<td>82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>f</td>
<td>CH₃</td>
<td>H</td>
<td>3</td>
<td>91</td>
<td>2.5</td>
<td>80</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Scheme 2

Four-Component Diastereoselective Synthesis Spiro Pyrrolizidines; General Procedures

Procedure A: To ninhydrin (0.178 g, 1 mmol) was added 1,2-phenylene diamine (0.108 g, 1 mmol) in DMSO (2–3 mL). The mixture was stirred for 10 min. To this solution was then added L-proline (0.115 g, 1 mmol) and N-phenyl maleimide (0.173 g, 1 mmol). The contents were taken in a pyrex test tube, placed in an alumina bath inside the microwave oven and irradiated for 3–5 min With a power of 600 W. After cooling, water added to the mixture and the separated solid was filtered off and recrystallized in EtOH to give a pure solid (90%).

Procedure B: To ninhydrin (0.178 g, 1 mmol) was added 1,2-phenylene diamine (0.108 g, 1 mmol) in DMSO (10 mL). The mixture was stirred for 10 min. To this solution was then added L-proline (0.115 g, 1 mmol) and N-phenyl maleimide (0.173 g, 1 mmol) and refluxing at 100 ºC was continued for a further 3 h. After cooling, water was added to the mixture and the separated solid was filtered off and recrystallized in EtOH to give a pure solid (80%).

IR (KBr): 1710 (C=O) cm⁻¹.

1H NMR (500 MHz, CDCl₃): δ = 1.88, 2.13, 2.45 (m, 4 H, 2 × CH₂), 2.47 (s, 3 H, CH₃), 2.50 (s, 3 H, CH₃), 2.80, 3.01 (m, 2 H, H₆a,₆b), 3.72 (dd, J = 9.8 Hz, J = 6.5 Hz, 1 H, H₃a), 4.36 (d, J = 9.8 Hz, 1 H, H₈a), 5.04 (m, 1 H, H₃b), 7.02–8.23 (m, 10 H, arom).

13C NMR (125 MHz, CDCl₃): δ = 20.56, 20.73 (2 × CH₃), 25.92, 31.02, 50.24 (3 × CH₂), 53.96, 54.84, 67.25 (3 × CH₃aliphatic), 74.29 (Cspiro, s), 123.02, 126.23, 128.13, 129.00, 129.05, 129.38, 130.72, 130.74, 131.54, 134.43, 139.28, 139.87, 140.09, 140.68, 141.93, 144.71, 152.44, 161.08 (aromatic), 174.32, 177.28 (2 × C=O).

MS: m/z (%) = 520 (60) [M⁺], 366 (100), 285 (60), 246 (75), 170 (15), 110 (60), 77 (20), 41 (35).

1H NOESY (%): irradiation of H₃a caused enhancement of H₈a (9.2), H₃b (1.5) and H₆a (1.8); C₃₁H₂₅N₄O₂Cl.

IR (KBr): 1705 (C=O), 1605 (C=C) cm⁻¹.

1H NMR (500 MHz, CDCl₃): δ = 1.88, 2.14, 2.45 (m, 4 H, 2 × CH₂), 2.47 (s, 3 H, CH₃), 2.50 (s, 3 H, CH₃), 2.57 (s, 3 H, CH₃), 2.80, 3.04 (m, 2 H, H₆a,₆b), 3.73 (dd, J = 9.9 Hz, J = 6.5 Hz, 1 H, H₃a), 4.39 (d, J = 9.9 Hz, 1 H, H₈a), 5.06 (m, 1 H, H₃b), 6.96–8.22 (m, 10 H, arom).

13C NMR (125 MHz, CDCl₃): δ = 20.52, 20.73, 21.56 (3 × CH₃), 25.90, 30.94, 50.18 (3 × CH₂), 54.10, 54.77, 67.25 (3 × CH₃aliphatic), 74.29 (Cspiro, s), 122.98, 126.24, 126.74, 128.94, 129.25, 129.66, 129.86, 130.62, 131.48, 134.38, 138.71, 139.30, 139.88, 140.49, 141.92, 144.92, 152.44, 161.20 (aromatic), 174.64, 177.65 (2 × C=O).

The δ values in bold were observed in the 1H NMR spectrum at 74.29 ppm.
MS: $m/z$ (%) = 500 (35) [M$^+$], 366 (75), 285 (80), 246 (100), 187 (15), 110 (65), 77 (25), 44 (45).

1H NOESY (%): irradiation of H$_3a$ caused enhancement of H$_8a$ (8.5), H$_{1b}$ (1.2) and H$_{1a}$ (2); CH$_2$N$_2$O$_2$.

5c
IR (KBr): 1710 (C=O) cm$^{-1}$.

1H NMR (500 MHz, CDCl$_3$): $\delta = 1.88, 2.12, 2.46$ (m, 4 H, 2 × CH$_2$), 2.79, 3.04 (m, 2 H, H$_{6a,6b}$), 3.75 (dd, $J = 9.9$ Hz, $J = 6.5$ Hz, 1 H, H$_{1a}$), 4.39 (d, $J = 9.9$ Hz, 1 H, H$_{1a}$), 5.03 (m, 1 H, H$_{3b}$), 7.01–8.26 (m, 12 H, arom).

13C NMR (CDCl$_3$, 125 MHz): $\delta = 54.25, 54.71, 67.31$ (3 CH$_{aliphatic}$), 74.18 (s, C$_{spiro}$), 123.36, 126.31, 126.79, 128.73, 129.25, 129.50, 129.68, 129.94, 130.34, 130.78, 130.80, 131.64, 134.53, 139.38, 139.97, 140.20, 140.75, 141.95, 144.81, 152.54, 161.28 (aromatic), 174.56, 177.53 (2 × C=O).

MS: $m/z$ (%) = 486 (75) [M$^+$], 366 (100), 285 (35), 246 (40), 110 (20), 77 (10), 41 (10).

1H NOESY (%): irradiation of H$_3a$ caused enhancement of H$_8a$ (9.4), H$_{1b}$ (1.5) and H$_{1a}$ (2.2); CH$_2$N$_2$O$_2$.

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References:


