One-Pot Annulation of Pyrimidine Ring on Azoles Under Microwave Irradiation and Solvent-Free Conditions

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Abstract: Azole Schiff bases 2a–f are annulated diastereoselectively with glycine and acetic anhydride, under microwave irradiation and solvent-free conditions, to yield 6,7-dihydro-5H-1,3,4-oxa(thia)diazolo[3,2-a]pyrimidin-5-ones 4a–f in a one-pot procedure.

Keywords: Schiff bases, 1,3,4-oxa(thia)diazolopyrimidines, solvent free, microwave, stereoselective synthesis

Pyrimidines have a long history of applications in pharmaceutical and agrochemical industries. Various pyrimidine derivatives in which this ring system is annulated on biologically versatile heterocycles are active in a wide spectrum of biological and therapeutic areas.1–6

In recent years increased interest has arisen in organic synthesis using microwave (MW) methodology owing to several advantages, such as enhanced reaction rates and higher yields of pure products under milder conditions,7,8 a consequence of the selective absorption of microwave energy by polar molecules or polar transition state intermediates formed during the course of the reaction.9 Furthermore, with increasing environmental consciousness the development of eco-friendly synthetic methods would be welcome. In this respect organic synthesis under solvent-free conditions is a basic protocol because solvents are often environmentally unfavourable.

Prompted by the above reports and in pursuing our work on new cyclization methods,9–11 we have devised an expeditious and highly diastereoselective one-pot annulation of pyrimidine ring on azoles to give 4 using microwaves in catalyst- and solvent-free conditions (Scheme 1).

In the envisaged annulation, an intimate mixture of glycine, a Schiff base 2, and acetic anhydride was intermittently irradiated for 0.5 min in an unmodified domestic microwave oven, followed by thorough mixing for 2 minutes outside the oven to ensure minimum loss of acetic anhydride by evaporation. This intermittent irradiation-mixing cycle was repeated for the total irradiation time (Table 1). For comparison purposes, the temperature of the bulk reaction mixture was also measured immediately after MW irradiations and was found to be <75 °C. That the effect of microwaves may not be purely thermal9,12 is supported by the fact that the reaction could not be com-
then thoroughly mixed outside the MW oven for 2 min and again irradiated for another 0.5 min. This intermittent irradiation-mixing cycle was repeated for the total irradiation time (Table 1). Then, H₂O (30 mL) was added to the mixture and stirred well. The yellowish precipitate thus obtained was washed with H₂O to give the crude product which was recrystallized from EtOH to afford a diastereomeric mixture (>97:<3; in the crude products the ratio was >95:<5 as determined by ¹H NMR spectroscopy). The products on second recrystallization from EtOH furnished an analytical sample of a single diastereomer ⁴ (Table 1). On the basis of ¹H NMR spectra and literature precedent,¹⁰¹³,¹⁴ cis stereochemistry was assigned to ⁴, as the coupling constant (J₆,₇ = 4 Hz) for ⁴ was lower than that of the minor (<3%) diastereomer (trans), J₆,₇ = 9 Hz.

Isolation of ³a and ³d and Their Conversion into the Corresponding Annulated Products ⁴a and ⁴d

The procedure followed was the same as described above for the synthesis of ⁴ except that the time of MW irradiation in this case was 3 min instead of 5–7 min as above. The adducts ³ were recrystallized from EtOH to give a diastereomeric mixture (>96:<4; in the crude isolates, the ratio was >93:<7 as determined by ¹H NMR spectroscopy) which was again recrystallized from EtOH to obtain analytical samples of ³a and ³d. The adducts ³a and ³d were assigned the erythro (syn) stereochemistry, as their ¹H NMR spectra exhibited a lower value of coupling constant, J cyclic NCH, acyclic NCH = 4 Hz, than that of the minor (<4%) diastereomer (threo or anti), J cyclic NCH, acyclic NCH = 9 Hz.¹⁰,¹⁵,¹⁶ Finely powdered intermediate compounds ³a and ³d were intermittently MW irradiated for 4 min in the same way as described for the synthesis of ⁴ to give the corresponding annulated products ⁴a and ⁴d quantitatively.

³a Yield: 48%; mp 249–252 °C.
IR (KBr): 1800 (C=O) cm⁻¹.
¹H NMR (DMSO-d₆/TMS): /c₁₀₀ = 2.12 (s, 3 H, CH₃), 6.69 (d, 1 H, J = 4 Hz, acyclic NCH), 6.80 (d, 1 H, J = 4 Hz, cyclic NCH), 7.11–8.02 (m, 10 H arom), 9.88 (br s, 1 H, NH).
MS: m/z = 348.

³d Yield: 45%; mp 280–283 °C.
IR (KBr): 1795 (C=O) cm⁻¹.
¹H NMR (DMSO-d₆/TMS): /c₁₀₀ = 2.11 (d, 1 H, J = 4 Hz, acyclic NCH), 6.78 (d, 1 H, J = 4 Hz, cyclic NCH), 7.10–8.00 (m, 10 H arom), 9.86 (br s, 1 H, NH).
Table 1  Compounds 4 and 5 Prepared under Solvent-Free Conditions

<table>
<thead>
<tr>
<th>Product</th>
<th>Time, MW in Min (Oil Bath in h)</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt; MW (Oil Bath)</th>
<th>Mp (°C)</th>
<th>&lt;sup&gt;1&lt;/sup&gt;H NMR (DMSO-d&lt;sub&gt;6&lt;/sub&gt;/TMS) δ, J (Hz)</th>
<th>MS m/z (M&lt;sup&gt;+&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>5 (12)</td>
<td>85 (43)</td>
<td>231–233</td>
<td>2.10 (s, 3 H, CH&lt;sub&gt;3&lt;/sub&gt;), 6.63 (d, 1 H, J = 4, 7-H), 6.76 (dd, 1 H, J = 4, 8, 6-H), 7.10–8.00 (m, 10 H&lt;sub&gt;arom&lt;/sub&gt;), 8.63 (br s, 1 H, NH)</td>
<td>348</td>
</tr>
<tr>
<td>4b</td>
<td>5 (12)</td>
<td>86 (40)</td>
<td>237–239</td>
<td>2.11 (s, 3 H, CH&lt;sub&gt;3&lt;/sub&gt;), 3.76 (s, 3 H, OCH&lt;sub&gt;3&lt;/sub&gt;), 6.64 (d, 1 H, J = 4, 7-H), 6.78 (dd, 1 H, J = 4, 8, 6-H), 7.13–7.98 (m, 9 H&lt;sub&gt;arom&lt;/sub&gt;), 8.61 (br s, 1 H, NH)</td>
<td>378</td>
</tr>
<tr>
<td>4c</td>
<td>5 (12)</td>
<td>88 (45)</td>
<td>216–218</td>
<td>2.13 (s, 3 H, CH&lt;sub&gt;3&lt;/sub&gt;), 6.66 (d, 1 H, J = 4, 7-H), 6.80 (dd, 1 H, J = 4, 8, 6-H), 7.15–8.02 (m, 9 H&lt;sub&gt;arom&lt;/sub&gt;), 8.63 (br s, 1 H, NH)</td>
<td>382</td>
</tr>
<tr>
<td>4d</td>
<td>7 (14)</td>
<td>79 (42)</td>
<td>273–275</td>
<td>2.09 (s, 3 H, CH&lt;sub&gt;3&lt;/sub&gt;), 6.61 (d, 1 H, J = 4, 7-H), 6.75 (dd, 1 H, J = 4, 8, 6-H), 6.86–7.79 (m, 10 H&lt;sub&gt;arom&lt;/sub&gt;), 8.59 (br s, 1 H, NH)</td>
<td>364</td>
</tr>
<tr>
<td>4e</td>
<td>6 (13)</td>
<td>81 (41)</td>
<td>281–283</td>
<td>2.10 (s, 3 H, CH&lt;sub&gt;3&lt;/sub&gt;), 3.74 (s, 3 H, OCH&lt;sub&gt;3&lt;/sub&gt;), 6.63 (d, 1 H, J = 4, 7-H), 6.77 (dd, 1 H, J = 4, 8, 6-H), 7.11–7.80 (m, 9 H&lt;sub&gt;arom&lt;/sub&gt;), 8.60 (br s, 1 H, NH)</td>
<td>394</td>
</tr>
<tr>
<td>4f</td>
<td>6 (13)</td>
<td>84 (44)</td>
<td>277–278</td>
<td>2.12 (s, 3 H, CH&lt;sub&gt;3&lt;/sub&gt;), 6.64 (d, 1 H, J = 4, 7-H), 6.78 (dd, 1 H, J = 4, 8, 6-H), 7.13–7.79 (m, 9 H&lt;sub&gt;arom&lt;/sub&gt;), 8.62 (br s, 1 H, NH)</td>
<td>398</td>
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<tr>
<td>5a</td>
<td>0.5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>92</td>
<td>238–241</td>
<td>2.92 (s, 2 H, NH&lt;sub&gt;2&lt;/sub&gt;), 6.61 (d, 1 H, J = 4, 7-H), 6.74 (dd, 1 H, J = 4, 8, 6-H), 7.06–7.99 (m, 10 H&lt;sub&gt;arom&lt;/sub&gt;)</td>
<td>306</td>
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<tr>
<td>5b</td>
<td>0.5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>89</td>
<td>232–233</td>
<td>2.94 (s, 2 H, NH&lt;sub&gt;2&lt;/sub&gt;), 3.75 (s, 3 H, OCH&lt;sub&gt;3&lt;/sub&gt;), 6.62 (d, 1 H, J = 4, 7-H), 6.73 (dd, 1 H, J = 4, 8, 6-H), 7.11–7.96 (m, 9 H&lt;sub&gt;arom&lt;/sub&gt;)</td>
<td>336</td>
</tr>
<tr>
<td>5c</td>
<td>0.5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>94</td>
<td>190–191</td>
<td>2.97 (s, 2 H, NH&lt;sub&gt;2&lt;/sub&gt;), 6.64 (d, 1 H, J = 4, 7-H), 6.77 (dd, 1 H, J = 4, 8, 6-H), 7.13–7.80 (m, 9 H&lt;sub&gt;arom&lt;/sub&gt;)</td>
<td>340</td>
</tr>
<tr>
<td>5d</td>
<td>0.5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>90</td>
<td>217–218</td>
<td>2.89 (s, 2 H, NH&lt;sub&gt;2&lt;/sub&gt;), 6.60 (d, 1 H, J = 4, 7-H), 6.72 (dd, 1 H, J = 4, 8, 6-H), 6.87–7.79 (m, 10 H&lt;sub&gt;arom&lt;/sub&gt;)</td>
<td>322</td>
</tr>
<tr>
<td>5e</td>
<td>0.5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>93</td>
<td>233–235</td>
<td>2.87 (s, 2 H, NH&lt;sub&gt;2&lt;/sub&gt;), 3.77 (s, 3 H, OCH&lt;sub&gt;3&lt;/sub&gt;), 6.61 (d, 1 H, J = 4, 7-H), 6.73 (dd, 1 H, J = 4, 8, 6-H), 6.98–7.78 (m, 9 H&lt;sub&gt;arom&lt;/sub&gt;)</td>
<td>352</td>
</tr>
<tr>
<td>5f</td>
<td>0.5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>95</td>
<td>225–228</td>
<td>2.91 (s, 2 H, NH&lt;sub&gt;2&lt;/sub&gt;), 6.63 (1 H, J = 4, 7-H), 6.75 (dd, 1 H, J = 4, 8, 6-H), 7.00–7.80 (m, 9 H&lt;sub&gt;arom&lt;/sub&gt;)</td>
<td>356</td>
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</table>

<sup>a</sup> All compounds gave satisfactory microanalyses: C ± 0.32, H ± 0.19, N ± 0.23, and compared favorably with samples obtained by an alternative method. 4a–f: IR (KBr): 1635–1640, 1680–1690 cm<sup>–1</sup> (C=O); 5a–f: IR (KBr): 1680–1695 cm<sup>–1</sup> (C=O).

<sup>b</sup> Yields of isolated and purified products. The yields of 5 represent the deacetylated products.

<sup>c</sup> The time in h used for deacetylation with H<sub>2</sub>SO<sub>4</sub>.


MS: m/z = 364.

6-Amino-6,7-dihydro-5H-1,3,4-oxa(thia)diazolo[3,2-α]pyrimidin-5-ones 5; General Procedure

Compound 4 (5 mmol) was refluxed in a mixture of H<sub>2</sub>SO<sub>4</sub>–H<sub>2</sub>O (15 mL, 4:3, v/v) for 30 min. The reaction mixture was cooled, the desired product 5 was precipitated by adding concd NH<sub>4</sub>OH (d = 0.88) under ice-cooling and recrystallized from EtOH (Table 1).

Acknowledgment

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References

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