The first microwave-assisted regiospecific synthesis of 6-substituted pterins

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Abstract—The pyrazine ring was developed in a pyrimidine and in a benzene by isay type condensations under microwave irradiation to afford pterin and quinoxaline systems. Interestingly, the desired isomerically free 6-substituted pterins including pterin sugar derivatives were synthesised in moderate to good yields whereas mixtures of both 6- and 7-isomers (major) are generally obtained using conventional Isay type condensations. © 2002 Elsevier Science Ltd. All rights reserved.

Pterins were identified as the fluorescent chromophores isolated from the wing pigments of European butterflies (Lepidoptera) as long ago as the nineteenth century.1

Almost all the pteridine natural products like folic acid, biopterin, neopterin, as well as the synthetic anticancer drug methotrexate possess substitution at C-6 of the pteridine ring. In all the oxomolybdoenzymes of the molybdenum cofactor (moco) and the precursor, compound Z of moco, a C₄-side chain is linked via C-6 to the pterin ring. There has been a remarkable interest in the regiospecific synthesis of pterins in order to develop preparations of these complex molecules. We were interested in developing a new method for the preparation of highly functionalised heterocycles with the desired side chain length and functionality that would be appropriate in our synthetic studies2 on moco3 utilising a readily available starting material and simple experimental procedure with complete regio-control.

This paper describes, for the first time, a convenient regiospecific synthesis of 6-substituted pterins 1a, 1c and 1e as well as quinoxalines 2a, 2b and 2d using a microwave-assisted direct Isay type condensation reaction.

The condensation of 5,6-diaminopyrimidine with an unsymmetrical α,β-dicarbonyl compound leads to the preferential formation of the unwanted 7- rather than the 6-isomer. A one-pot synthesis of 6-methylpterin, 1a (9:1 molar ratio)3a involved the condensation of triamine 3 with methylglyoxal with a controlled (0–5°C) temperature and using sodium bisulphite to mask the more reactive aldehyde function. Such regiospecificity was solved by Taylor’s4b general and unequivocal multistep pteridine synthesis and isomerically free 1a was synthesised in good yield. The synthesis of 2-amino-6-(1,2,3,4-tetrahydroxybutyl)-3H-pteridin-4-one 1c has been clearly reviewed by Joule et al.4c

We took the advantage of microwave-assistance (MW) in reactions5 to study the fusion of a pyrazine ring onto a pyrimidine for the synthesis of pterins to check the

Scheme 1.
amine 4 provides a convenient route to quinoxalines and its condensation with appropriate carbonyl compounds (entries 6–10) results in the formation of 2-substituted quinoxalines 2a, 2b and 2d in good yields. Extremely poor solubility in both organic and aqueous media being the characteristic of pterins, the \(^1\)H NMR spectroscopic studies of the 6-substituted pterins were performed with the 2-pivaloyl amide derivative 1b and the acetamide-tetraacetate derivatives 1d and 1f. The appearance of a sharp singlet at \(\delta 8.72\) for 1b and at \(\delta 8.94\) for 1f accounting for the C-7-H proton in their \(^1\)H NMR spectra is in agreement with the assigned structures. The formation of 7-methylpterin was not observed as evidenced by the \(^1\)H NMR spectrum. Recently we have reported that 6-formylpterin and quinoxalin-2-carboxaldehyde can be obtained from 1b and 2a, respectively, using a microwave assisted selenium dioxide oxidation reaction. Hence the problem of formation of isomeric mixtures of 6- and 7-substituted pterins by the classical Isay type reaction has potentially been overcome by this simple environmentally friendly and economic method.

We have thus developed a new method for the synthesis of 6-substituted pterins and pterin sugar derivatives and 2-substituted quinoxalines under microwave conditions. In addition to its simple reaction conditions, this procedure has the advantages of very short reaction times, simple experimental and work-up procedures and most importantly, its regiospecificity for the C-6 position of the pterin which makes it useful for the synthesis of pterin and also quinoxaline heterocycles.

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**Table 1. The MW assisted Isay condensations between appropriate amines (3 and 4) with various carbonyl compounds**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diamine</th>
<th>Carbonyl compound</th>
<th>Product</th>
<th>MW conditions and time</th>
<th>Yield(^a)</th>
<th>MW (%)</th>
<th>Literature(^b), Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>Methylglyoxal</td>
<td>1a</td>
<td>150 W, 62 s</td>
<td>70</td>
<td>80(^{a})</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>DHA</td>
<td>1a</td>
<td>300 W, 64 s</td>
<td>40</td>
<td>30(^{a})</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>1,1-Dichloroacetone</td>
<td>1a</td>
<td>300 W, 75 s</td>
<td>28</td>
<td>15(^{b})</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>D(+)-Glucose</td>
<td>1c</td>
<td>300 W, 270 s</td>
<td>40</td>
<td>30(^{c})</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>D(+)-Galactose</td>
<td>1e</td>
<td>300 W, 270 s</td>
<td>38</td>
<td>95(^{c})</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>Methylglyoxal</td>
<td>2a</td>
<td>150 W, 120 s</td>
<td>95</td>
<td>90(^{c})</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td>DHA</td>
<td>2a</td>
<td>300 W, 65 s</td>
<td>48</td>
<td>95(^{c})</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>1,1-Dichloroacetone</td>
<td>2a</td>
<td>150 W, 35 s</td>
<td>42</td>
<td>95(^{c})</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>4</td>
<td>D(+)-Glucose</td>
<td>2b</td>
<td>300 W, 270 s</td>
<td>60</td>
<td>20(^{d})</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>4</td>
<td>D(+)-Galactose</td>
<td>2d</td>
<td>300 W, 270 s</td>
<td>60</td>
<td>20(^{d})</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Isolated yields. All new compounds (1e, 2d) were characterised by \(^1\)H NMR as their tetraacetate (e.g. 1f, 2c) derivatives. The spectroscopic data of the compounds 1b, 1f, 2a and 2c are given in Ref. 9.

\(^b\) The literature methods for the synthesis of 1a and 1e (entries 1–4) give mixtures of both 6- and 7-isomers.
References

1. (a) Hopkins, F. G. Nature 1889, 40, 335; (b) Hopkins, F. G. Nature 1891, 45, 197; (c) Hopkins, F. G. Nature 1892, 45, 581.


6. Typical experimental procedure: A mixture of 2,5,6-triaminopyrimidin-4(3H)-one hydrochloride 3 (2.0 g) and methylglyoxal (1.5 g, 40% in water) was placed in a microwave oven (BPL 800G, indicates the commercial name of the microwave oven) and subjected to irradiation at 150 W for an optimised time (62 s). Water was then added and the resulting slurry was centrifuged. The solid separated was filtered through a sintered funnel, washed well with water and then with ethanol, and dried in vacuum. The bright yellow solid (1.2 g, 70%, mp>350°C) after pivaloylation with pivalic anhydride followed by purification gave a cream coloured solid 1b (1.4 g, 78%, mp 230–232°C). Compounds 1d, 1f and 2c were obtained by condensation followed by direct acetylation of 1e, 1f and 2b, respectively.


9. The 1H NMR spectra were found to be identical to those reported earlier. Compound 1b (78%). Mp 320–322°C. 1H NMR (CDCl3, 500 MHz): δ 12.33 (br s, 1H, NH), 8.72 (s, 1H, C2-H), 8.35 (br s, 1H, NH), 2.75 (s, 3H, C6-CH3), 1.36 (s, 9H). Compound 1f (40%). Mp 108–110°C. 1H NMR (CDCl3, 500 MHz): δ 12.60 (br s, 1H, NH amide), 10.23 (br s, 1H, lactam NH), 8.94 (s, 1H, C2-H), 6.05 (d, 1H, C2-H, J = 8.9 Hz), 5.72 (dd, 1H, C2-H, J = 2.6, 2.6 Hz), 5.59–5.56 (m, 1H, C2-H), 4.24 (qd, 2H, C2-H2, J = 5.5, 5.5, 6.9 Hz, 6.9), 2.45 (s, 3H, -NCOCH3), 2.15, 2.05, 1.96 (4×s, 12H, -OCOCH3×4), [x]25D −17.31 (c 1, chloroform). Mass (FAB, MH +): 494 (100%). Compound 2a (95%). 1H NMR (CDCl3, 500 MHz): δ 8.58 (s, 1H, quinoxalin-2-yl), 7.92 (d, 1H, J = 8.0 Hz), 7.87 (d, 1H, J = 8.0 Hz), 7.60–7.54 (m, 2H), 2.66 (s, 3H). Compound 2c (65%). Mp 110–112°C. 1H NMR (CDCl3, 500 MHz): δ 8.84 (s, 1H, quinoxalin-2-yl), 8.10–8.08 (m, 2H), 7.79–7.77 (m, 2H), 6.33 (d, 1H, J = 3.1 Hz), 5.79 (dd, 1H, C2-H, J = 3.1, 3.1 Hz), 5.40–5.37 (m, 1H, C4-H), 4.25 (qd, 2H, C4-H2, J = 2.7, 2.7, 5.0, 5.0 Hz), 2.22, 2.09, 2.04, 1.91 (4×s, 12H, 4×OCOCH3). Mass (FD, M+): 418 (100%).
