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

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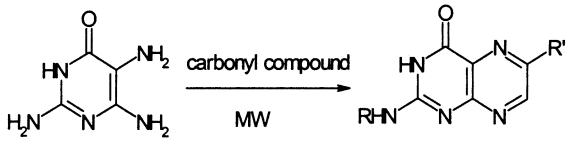
Abstract—The pyrazine ring was developed in a pyrimidine and in a benzene by Isay type condensations under microwave irradiation to afford pterin and quinoxaline systems. Interestingly, the desired isomerically free 6-substituted pterins including pterin sugar derivatives were synthesised in moderate 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 C_4-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 studies[2] on moco[3] 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.

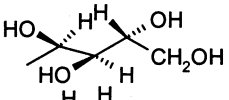
The condensation of 5,6-diaminopyrimidine with an unsymmetrical α,β-dicarbonyl compound leads to the preferential formation of the unwanted 7- rather than the 6-isomer. A one-pot synthesis of 6-methylpterin, **1a** (9:1 molar ratio)[4a] involved the condensation of triamine **3** with methylglyoxal with a controlled (0–5°C) temperature and using sodium bisulphite to mask the more reactive aldehyde function. Such regiospecificity was solved by Taylor's[4b] 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)-3*H*-pteridin-4-one **1c** has been clearly reviewed by Joule et al.[4c]

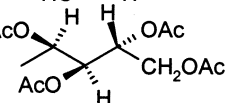
We took the advantage of microwave-assistance (MW) in reactions[5] to study the fusion of a pyrazine ring onto a pyrimidine for the synthesis of pterins to check the

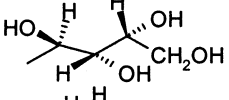


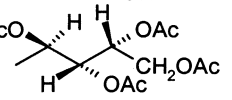
3 **1**

1a: R = H, R' = CH_3, **1b:** R = Piv, R' = CH_3,









Scheme 1.

Keywords: molybdenum cofactor; 6-substituted pterins; microwave; quinoxalines; Isay condensation.

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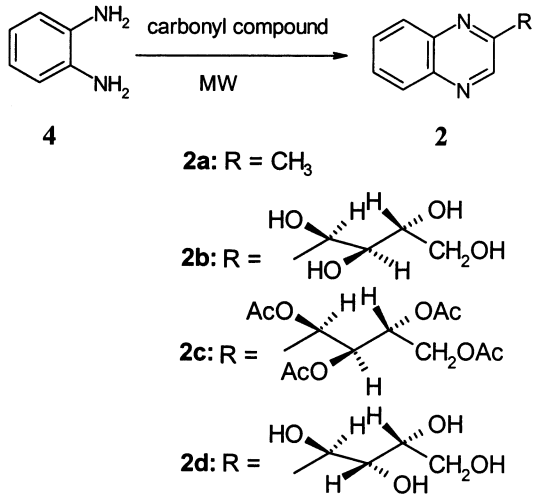

Scheme 2.

regiospecificity, if there is any, and also onto a benzene for the synthesis of quinoxalines. We describe here our success in achieving a facile, regiospecific, synthesis of **1a** and the pterin sugars **1c** and **1e** (Scheme 1) by a simple direct condensation without addition of sodium bisulphite or hydrazine hydrate as well as the synthesis of quinoxalines **2a**, **2b** and **2d** (Scheme 2) under microwave irradiation. The reaction conditions and yields are summarised in Table 1. A mixture of triamine **3** and methylglyoxal (entry 1) was irradiated in an open flask using a household[6] microwave oven to afford **1a** in 70% yield. Condensation with 1,3-dihydroxyacetone (DHA) (entry 2) and 1,1-dichloroacetone (entry 3) also led to the formation of **1a** only, but in a poor yield. However, this condensation reaction further prompted us to irradiate the triamine **3** and aldohexoses (entries 4 and 5), which gave the pterin sugar derivatives **1c** and **1e** with the expected side-chain length and functionality at each of the four carbon atoms. The regiospecificity was confirmed by ^{1}H NMR. Further, *o*-phenylenediamine **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[8] in both organic and aqueous media being the characteristic of pterins, the ^{1}H NMR spectroscopic studies[9] 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 δ 8.72 for **1b** and at δ 8.94 for **1f** accounting for the C_7-H proton in their ^{1}H NMR spectra is in agreement[10] with the assigned structures. The formation of 7-methylpterin was not observed as evidenced by the ^{1}H NMR spectrum. Recently we have reported[11] 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

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

[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 **1c** (entries 1–4) give mixtures of both 6- and 7-isomers.

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6. *Typical experimental procedure:* A mixture of 2,5,6-triaminopyrimidin-4(3*H*)-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 **1c**, **1e** and **2b**, respectively.
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9. The ^{1}H NMR spectra were found to be identical to those reported earlier. Compound **1b** (78%). Mp 320–322°C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 12.33 (br s, 1H, N*H*), 8.72 (s, 1H, C_7-*H*), 8.35 (br s, 1H, N*H*), 2.75 (s, 3H, C_6-CH_3), 1.36 (s, 9H). Compound **1f** (40%). Mp 108–110°C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 12.60 (br s, 1H, N*H* amide), 10.23 (br s, 1H, lactam N*H*), 8.94 (s, 1H, C_7-*H*), 6.05 (d, 1H, C_1'-*H*, J=8.9 Hz), 5.72 (dd, 1H, C_2'-*H*, J=2.6, 2.6 Hz), 5.59–5.56 (m, 1H, C_3'-*H*), 4.24 (qd, 2H, C_4'-H_2, J=5.5, 5.5, 6.9 Hz, 6.9), 2.45 (s, 3H, -NHCOCH_3), 2.15, 2.13, 2.05, 1.96 (4×s, 12H, -OCOCH_3×4). $[\alpha]_D^{25}$ −17.31 (*c* 1, chloroform). Mass (FAB, MH$^+$): 494 (100%). Compound **2a** (95%). ^{1}H NMR ($CDCl_3$, 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. ^{1}H NMR ($CDCl_3$, 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, C_2'-*H*, J=3.1, 3.1 Hz), 5.40–5.37 (m, 1H, C_3'-*H*), 4.25 (qd, 2H, C_4'-H_2, J=2.7, 2.7, 5.0, 5.0 Hz), 2.22, 2.09, 2.04, 1.91 (4×s, 12H, 4×OCOCH_3). Mass (FD, M^+): 418 (100%).
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