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# Solvent-Free Regioselective Synthesis of 6- and 7-Substituted Pteridines under Microwave Irradiation*

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**Abstract**—Reactions of 5,6-diaminouracils with α-keto aldehydes over acidic and neutral aluminum oxide under microwave irradiation gave the corresponding 6- and 7-substituted 1,2,3,4-tetrahydropteridine-2,4-diones in 63–79% yield with high regioselectivity.

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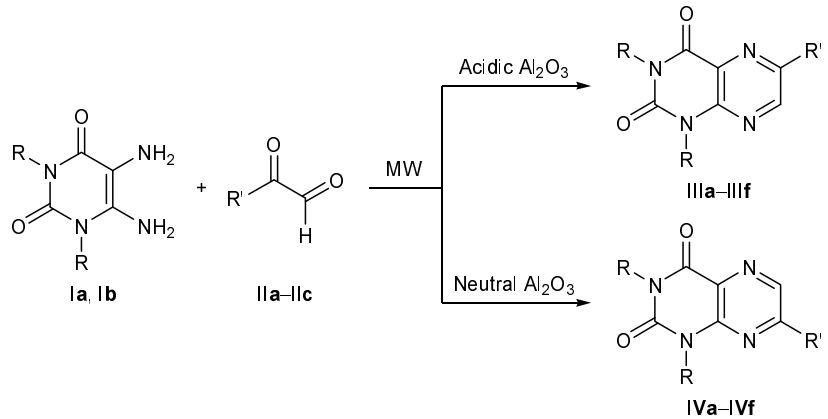
In the recent years, reagents supported on inorganic oxides, such as aluminum oxide, clays, silicas, and zeolites, in combination with microwave irradiation attract increased attention [1, 2]. An interesting aspect is also performing reactions under solvent-free conditions, which makes it possible to work in open vessels thus avoiding the risk of high pressure [3].

Substituted pteridines are widely distributed in plant and animal kingdoms [4]. Many naturally occurring pteridine compounds possess a carbofunctional group in the pyrazine fragment [4, 5]. Pteridine derivatives are usually synthesized by condensation of 5,6-diaminopyrimidines with 1,2-dicarbonyl compounds [4]. However, reactions with unsymmetrical 1,2-dicarbonyl compounds are characterized by low regioselectivity, and the products are mixtures of the corresponding 6- and 7-substituted pteridine derivatives. Even the use of aldehyde protecting reagents failed to improve the regioselectivity [6–8]. Several alternative methods have also been developed to overcome poor regioselectivity, but they are not free from some limitations [9–11].

In the present communication we describe a simple highly regioselective synthesis of 6- and 7-substituted pteridines without a solvent under microwave irradiation [12, 13] in the presence of acidic and neutral aluminum oxide [14] (Scheme 1, see table). Initial 5,6-diaminouracils **I** were synthesized by the procedure described in [4]. Different α-keto aldehydes were prepared by oxidation of the corresponding aceto-

**Scheme 1.**




**I**, R = H (**a**), Me (**b**); **II**, R' = Me (**a**), Ph (**b**), *p*-$ClC_6H_4$ (**c**); **III**, **IV**, R = H, R' = Me (**a**), Ph (**b**), *p*-$ClC_6H_4$ (**c**); R = Me, R' = Me (**d**), Ph (**e**), *p*-$ClC_6H_4$ (**f**).

* The text was submitted by the authors in English.

Yields, melting points, and UV spectra of 6- and 7-substituted 1,2,3,4-tetrahydropteridine-2,4-diones **IIIa**–**IIIf** and **IVa**–**IVf**

| Compound no. | Yield, % | mp, °C (published data) | UV spectrum (MeOH), $\lambda_{max}$, nm (log$\varepsilon$) |
|---|---|---|---|
| **IIIa** | 71 | 304 (305) [15] | 279 (4.51), 366 (3.91) |
| **IIIb** | 63 | >300 (380–382) [10] | 28 1 (5.35), 376 (3.96) |
| **IIIc** | 68 | >300 (>300) [16] | 285 (4.49), 366 (4.33) |
| **IIId** | 65 | 200 (201–203) [17] | 288 (4.21), 336 (3.86) |
| **IIIe** | 79 | 260 (258–259) [18] | 280 (4.33), 359 (3.95) |
| **IIIf** | 70 | 251 (250) [18] | 284 (4.17), 360 (4.82) |
| **IVa** | 75 | >300 (>300) [15] | 234 (4.11), 288 (2.1), 331 (3.88) |
| **IVb** | 71 | >300 (374–378) [15] | 234 (4.25), 268 (4.26), 371 (4.03) |
| **IVc** | 75 | >300 (>300) [16] | 231 (4.41). 278 (4. 1), 363 (4.21) |
| **IVd** | 69 | 163–164 (163) [19] | 235 (4.09), 286 (2.1), 329 (3.89) |
| **IVe** | 72 | >300 (308–309) [18] | 231 (3.89), 283 (3.5), 354 (3.84) |
| **IVf** | 73 | >300 (317–318) [18] | 233 (4.45), 287 (4.7), 357 (4.39) |

phenones with selenium dioxide [20]. The condensation of 5,6-diaminouracil (**Ia**) with 2-oxoproanal in the presence of acidic aluminum oxide under microwave irradiation afforded 71% of 6-methyl-1,2,3,4-tetrahydropteridine-2,4-dione (**IIIa**) in 4 min. An analogous reaction carried out over neutral aluminum oxide gave 7-methyl-substituted isomer **IVa** in 75% yield.

The structure of compounds **IIIa** and **IVa** was confirmed by spectral methods and by comparison with published data. Likewise, the condensations of 5,6-diaminouracil and 5,6-diamino-1,3-dimethyluracil with 2-oxopropanal, 2-oxo-2-phenylethanal, and 2-*p*-chlorophenyl-2-oxoethanal over acidic and neutral aluminum oxide afforded the corresponding 6- and 7-substituted pteridines **IIIb**–**IIIf** and **IVb**–**IVf**, respectively (see table; Scheme 1).

## EXPERIMENTAL

The melting points were determined on a Thomas Hoover Capillary melting point apparatus and are uncorrected. The purity of the products was checked by thin-layer chromatography on silica gel plates (Merck). All microwave-assisted reactions were carried out in a Padmini Essentia Model Brownie domestic microwave oven. The UV spectra were measured on a Shimadzu UV-260 spectrophotometer. Acidic and neutral aluminum oxides were purchased from Fine Chemicals and were used without additional treatment.

**6-Substituted 1,2,3,4-tetrahydropteridine-2,4-diones IIIa–IIIf (***general procedure***).** A mixture of 0.5 mmol of 5,6-diaminouracil or 5,6-diamino-1,3-dimethyluracil, 0.5 mmol of the corresponding α-keto aldehyde, and 1.5 g of acidic aluminum oxide was thoroughly ground, placed in a 25-ml borosil beaker, and irradiated in a microwave oven over a period of 4 min (with an interval after every 1 min). After withdrawal from the oven, the temperature inside the beaker was 110–120°C. The mixture was allowed to cool down to room temperature, treated with 50 ml of methanol, and filtered through celite 545, the filtrate was evaporated under reduced pressure, and the crude product was recrystallized from aqueous ethanol.

**7-Substituted 1,2,3,4-tetrahydropteridine-2,4-diones IVa–IVf** were synthesized in a similar way using neutral aluminum oxide.

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