Pergamon

Tetrahedron Letters, Vol. 38, No. 39, pp. 6835-6836, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01619-5

A New, General and Regioselective Method for the Synthesis of 2,6-Disubstituted 4-Aminopteridines

Shahriyar Taghavi-Moghadam and Wolfgang Pfleiderer*

Fakultät für Chemie, Universität Konstanz, Postfach 5560, D-78434 Konstanz, Germany

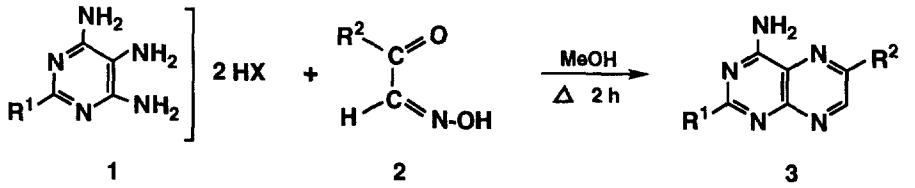
Abstract: A new synthetic method for the preparation of 2,6-disubstituted 4-aminopteridines is described. Treatment of 2-substituted 4,5,6-triaminopyrimidines with α-ketoaldoximes in MeOH affords in a regioselective one-step reaction 2,6-disubstituted 4-aminopteridines in high yield.
© 1997 Elsevier Science Ltd.

The classical synthetic route to pteridines was developed by Isay and Gabriel[1] and involves condensations of 5,6-diaminopyrimidines with 1,2-dicarbonyl compounds. Syntheses using symmetrical 1,2-dicarbonyl derivatives present no regioselectivity problems, but unsymmetrical dicarbonyl components give 6- and 7-substituted product mixtures of ambiguous structures. In special cases, pH-variations effect the orientation[1] but a defined regioselective synthesis affords usually an unambiguous approach as demonstrated by the Timmis[1], the Polonovski-Boon[1] and the Taylor[1] reaction, respectively. Since the majority of naturally occurring pteridines possess a side-chain in 6-position special interest in the development of a simple synthetic approach leading to 6-substituted pteridines even in technical scale is obvious.

Our new method works especially well for the regioselective synthesis of 2,6-disubstituted 4-aminopteridines and is derived from an observation by Kang, Soyka and Pfleiderer[2] using oximinoacetone for the preparation of 1,3,6-trimethyllumazine in a two-step condensation reaction starting from 5,6-diamino-1,3-dimethyluracil.

The general application of the regioselective synthesis could be demonstrated by the condensation of 2-substituted 4,5,6-triaminopyrimidine dihydrohalides (**1**; X=Br, Cl) with α-ketoaldoximes **2** to form 2,6-disubstitued 4-aminopteridines (**3**) in good to excellent yields (scheme 1). We are able to prepare the 6-substituted pteridines derivatives **3a-t** in a facile one-step reaction with high purity[6]. The 6-halomethyl-pteridines **3b, c, h, l, m, q, r** are especially valuable intermediates from a synthetic point of view due to easy nucleophilic substitution reactions in the side-chain leading to folic acid analogues such as the important anti-cancer agents aminopterin and methotrexate, respectively[3].

Additionally a great synthetic potential can be attributed to the 6-substituted 2,4-diaminopteridines which are easily converted into the corresponding pterins by either alkaline or acid hydrolysis of the 4-amino-group offering even more flexibility of the new approach[5].



1 2 3

3	X	R^1	R^2	Yield [%]
a	Cl	NH_2	CH_3	81
b	Br	NH_2	CH_2Br	88
c	Cl	NH_2	CH_2Cl	79
d	Cl	NH_2	CH_2CH_3	76
e	Cl	NH_2	C_6H_5	93
f	Cl	NH_2	p-CH_3-C_6H_4	88
g	Cl	H	CH_3	31
h	Cl	H	CH_2Cl	66
i	Cl	H	C_6H_5	88
j	Cl	H	p-CH_3-C_6H_4	90

3	X	R^1	R^2	Yield [%]
k	Cl	SCH_3	CH_3	47
l	Br	SCH_3	CH_2Br	61
m	Cl	SCH_3	CH_2Cl	74
n	Cl	SCH_3	C_6H_5	97
o	Cl	SCH_3	p-CH_3-C_6H_4	97
p	Cl	C_6H_5	CH_3	61
q	Br	C_6H_5	CH_2Br	73
r	Cl	C_6H_5	CH_2Cl	87
s	Cl	C_6H_5	C_6H_5	88
t	Cl	C_6H_5	p-CH_3-C_6H_4	89

Acknowledgement: We are grateful to the LONZA AG, Visp/ Switzerland for the financial support of this project.

REFERENCES AND NOTES

1. For general references on pteridine chemistry: Pfleiderer, W. in "Comprehensive Heterocyclic Chemistry", Katritzky A.R ; Rees C. W., eds, Vol 3, Part 2B, Pergamon Press, Oxford, 1984, p 263-327.
2. Kang, Y.; Soyka, R.; Pfleiderer,W. *J.Heterocyclic Chem.* **1987**, *24*, 597-601.
3. Montgomery, J.A.; Piper, J.R.; Elliott, R.D.; Roberts, E.C.; Temple, C.; Shealy, Y.F. *J. Heterocyclic Chem.* **1987**, *24*, 279-282.
4. ^{1}H NMR (250 MHz, ppm, DMSO-d_6), δ (s, 1H, C(7)-H,): **3a:** 8.60, **3b:** 8.84, **3c:** 8.84, **3d:** 8.63, **3e:** 9.33, **3f:** 9.31, **3g:** 8.97, **3h:** 9.21, **3i:** 9.69, **3j:** 9.68, **3k:** 8.85, **3l:** 9.09, **3m:** 9.09, **3n:** 9.61, **3o:** 9.57, **3p:** 8.97, **3q:** 9.21, **3r:** 9.21, **3s:** 9.74, **3t:** 9.70.
5. The results of these studies have been applied for a patent by LONZA AG, Visp-Basel / Switzerland Pfleiderer, W.; Taghavi-Moghadam, Schweiz. Patentgesuch-No. 03503/95.
6. **Typical procedure :** A suspension of 5 mmol 2-substituted 4,5,6-triaminopyrimidine dihydrohalide (**1**; X=Br, Cl) in 50 ml methanol was treated with a solution of 7.5 mmol of an α-ketoaldoxime (**2**) in 10 ml of MeOH at reflux temperature for 2h. The corresponding reaction products (**3**) were collected after neutralisation with conc. NH_3 at room temperature, washed with methanol , ether and dried at 100 °C in an oven. The isomer purity of the isolated products was proven by ^{1}H NMR spectroscopy since the chemical shift of the H-C(7) in the pteridine system is decisive for the structural assignments of the isomers[4].

(*Received in Germany* 15 *July* 1997; *accepted* 4 *August* 1997)