HIGHLY REGIOSELECTIVE ALKYLATION OF PTERIDINE

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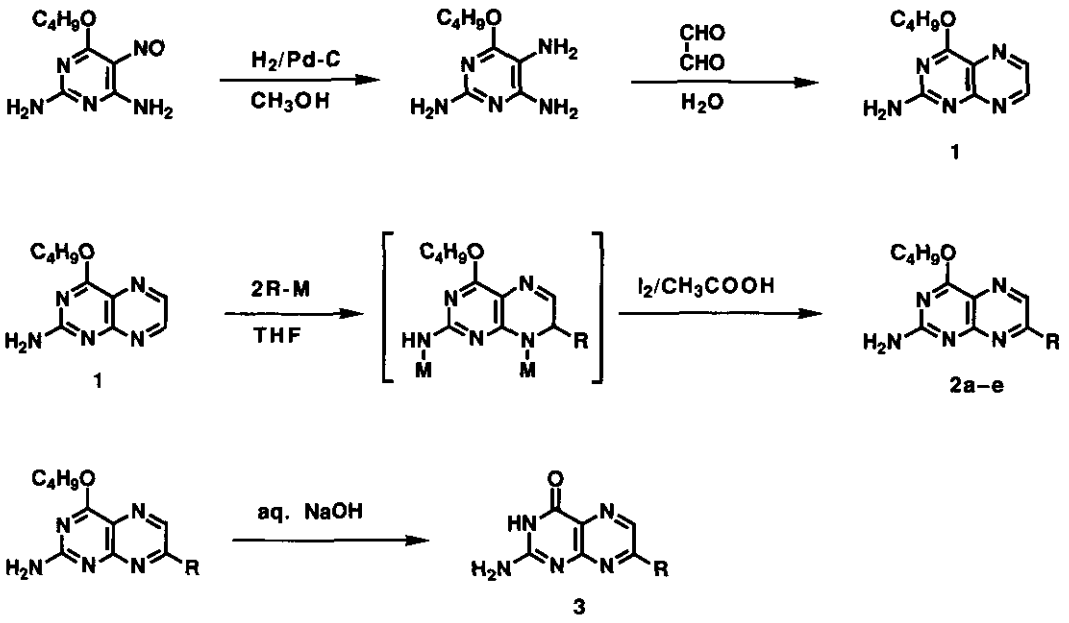
Abstract—Reaction of 2-amino-4-butoxypteridine with a Grignard reagent or an alkyllithium followed by iodine oxidation gives the 7-substituted pteridine, regioselectively.

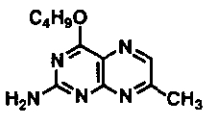
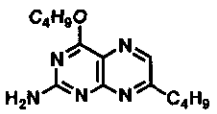
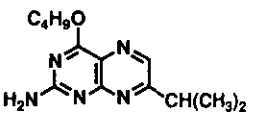
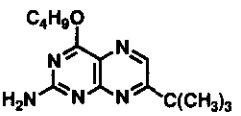
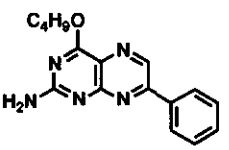
2-Amino-4-hydroxypteridines are one of the most important nitrogen heterocycles, since the tetrahydro derivatives are coenzymes in the metabolic systems for neurotransmitters (catecholamines and indoleamine),[1] pyrimidinenucleotides,[2] and methionine.[3] Chemical synthesis of these pteridines has been carried out mainly by using the pyrazine ring-forming condensation of 6-hydroxy-2,4,5-triaminopyrimidine with 2-oxoaldehydes. However, there are several limitations in the condensation. For example, the condensation of 6-hydroxy-2,4,5-triaminopyrimidine with 2-oxopropanal proceeded non regioselectively to give a mixture of 6- and 7-methylpteridines.[4] Addition of a nucleophile toward 2-amino-4-hydroxypteridine seems to be the most straightforward process to synthesize various substituted pteridines. Since 2-amino-4-hydroxypteridine is very insoluble not only in organic solvents but in water (pH 7) and the pteridine contains 2 acidic hydrogens, it has been difficult to apply the organometallic reagents for C-alkylation of the pteridine. We have recently reported that 2-amino-4-butoxypteridines are soluble in common organic solvents and these are employable for usual treatments in organic synthesis like silica gel column chromatography.[5] Described herein are preliminary results of the reaction of 2-amino-4-butoxypteridine (1) with organometallic reagents.



2-Amino-4-butoxypteridine (**1**) was synthesized by condensation of 6-butoxy-2,4,5-triaminopyrimidine, which was prepared in situ by catalytic (5% Pd-C) hydrogenation of 6-butoxy-2,4-diamino-5-nitroso-pyrimidine in methanol, with glyoxal in 50% yield. Reaction of **1** with 3 equivalents of a Grignard reagent or an organolithium reagent proceeded in THF at 20 °C. After protonation and oxidative work up by addition of a solution of 2 equiv. of iodine in acetic acid, the 7-substituted pteridine (**2a–e**) was obtained. The regioselectivity was very high, and formation of 6-substituted isomers has not be recognized by ^{1}H nmr and hplc analyses.[6] Dialkyl- and polyalkylpteridines have not formed during the reaction. All results are summarized in Table I. Cleavage of the butoxy group in **2** was performed by alkaline hydrolysis (1M KOH, 20 °C, 16 h) to give the 2-amino-4-hydroxypteridine derivative (**3**).[5]

Because electron density of the C^7 position seemeds to be decreased more than the C^6 position by the resonance structure of 2-amino-4-alkoxypteridine, the nucleophile predominantly attacked on the carbon. Although yields are relatively low, this reaction is a general and easy procedure for regioisomerically pure 7-alkyl-2-amino-4-hydroxypteridines and is the reading investigation for application of organometallic reagent in the chemistry of pteridine.

Table I. Reaction of 1 with an Organometallic Reagent.

Entry	R–M	Product No.	Structure	yield/%[a]	^{1}H nmr (δ/ppm of C^{6}H)[b]
1	CH_3MgBr	2a		16	8.41
2	C_4H_9MgBr	2b		6	8.40
3	C_4H_9Li	2b	—	7	—
4	$(CH_3)_2CHMgBr$	2c		16	8.44
5	$(CH_3)_3CMgCl$	2d		8	8.66
6	C_6H_5MgBr	2e		21	9.04

[a]Isolated yield after silica-gel column chromatography. [b]Observed in $CDCl_3$.

The following is a typical example of the reaction: to a solution of 1 (401 mg, 1.8 mmol) in THF (10 ml) was added slowly at 0 °C a solution of phenylmagnesium bromide, which was prepared from bromobenzene (1.04 g, 6.6 mmol) and magnesium (187 mg, 7.7 mmol) in THF (10 ml). After 2 h stirring at 20 °C, to this was added a solution of I_2 (931 mg, 3.7 mmol) in acetic acid (10 ml). The mixture was diluted by chloroform (50 ml) and washed by saturated aqueous $Na_2S_2O_3$ solution (50 ml, 5 times), saturated $NaHCO_3$ (3 x 30 ml),

and water (2 x 30 ml). The organic solution was dried over $MgSO_4$ and solvent was removed in vacuo. The residue was subjected to a column of silica gel eluting with 60% ethyl acetate in toluene. Pure **2e** (108 mg, 20% yield) was obtained as yellow powder.

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6 ^1H nmr chemical shifts of hydrogen on the C^6 position ($C^6\underline{H}$) are generally higher than $C^7\underline{H}$. For example, **1** exhibited 2 doublets on δ 8.72 ($C^7\underline{H}$) and 8.43 ppm ($C^6\underline{H}$). The chemical shift of 2-amino-4-butoxy-6-methylpteridine, the regioisomer of **2a**, was δ 8.71 ppm. See ref. 5.

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