RECENT ADVANCES IN SELECTIVE SYNTHESES OF 6- AND 7-SUBSTITUTED PTERIDINES

Shizuaki Murata,[a)*] Kenji Kiguchi,[a)] and Takashi Sugimoto[b)]

[a)]Graduate School of Human Informatics, Nagoya University,
Chikusa, Nagoya 464-8601, Japan
E-mail: murata@info.human.nagoya-u.ac.jp
[b)]School of Informatics and Sciences, Nagoya University,
Chikusa, Nagoya 464-8601, Japan

Abstract–Novel regioselective methods for construction of biologically important pteridines which contain carbon substituents on the 6- or 7-position using pteridine ring-forming cyclocondensations, nucleophilic substitution reactions, and radical reactions are reviewed.

CONTENTS

(1) INTRODUCTION

Pteridine is one of the most important naturally occurring nitrogen heterocycles in biochemistry and clinical chemistry.[1–3] Some pteridines, such as biopterin cofactor (**1**), tetrahydrofolic acid (**2**), riboflavin, and molibdopterin (**3**),[4] are known to function as cofactors in key steps of enzymatic redox and C_1 transfer processes in all kinds of living organisms. For example, **1** is the real cofactor for phenylalanine hydroxylase and tyrosine hydroxylase of the catecholamine biosynthesis and is used as a potent chemotherapeutic agent for neuropathies such as Parkinsonism etc.[5–9] Various pteridine based compounds which have antifolate activities and disturb thymidine biosynthesis are considered to be powerful antitumor agents.[10,11] In addition, concentrations of neopterin (**4**) and oncopterin (**5**) in serum and urine well reflect activities of the immune system and activities of macrophages, and those samples obtained from patients show much higher concentrations than the healthy controls. Thus, such pteridines are employable as facile indicators for diagnosis of cancer and HIV (human immunodeficiency virus) infection.[12–19] Since these biologically important pteridines usually have substituents on the C(6) position (Figure 1), and in some cases on the C(7) position, regioselective introduction of substituents on those positions of pteridines has long been investigated.[20]

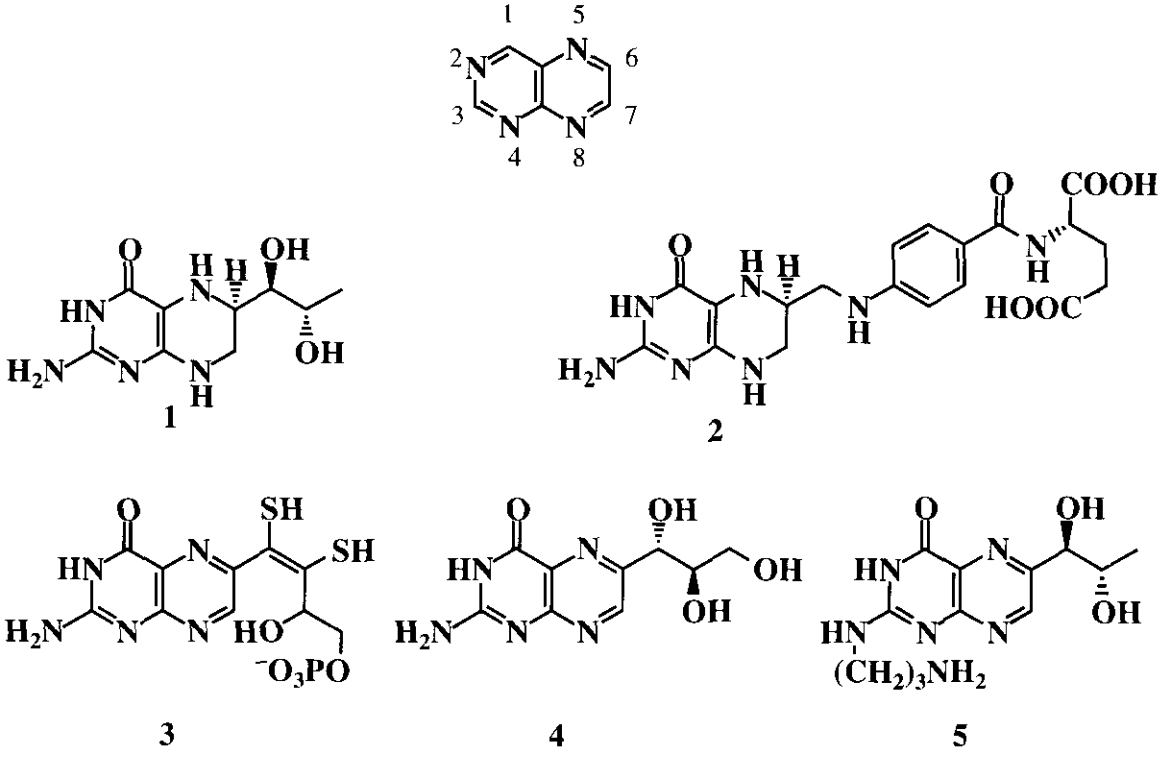
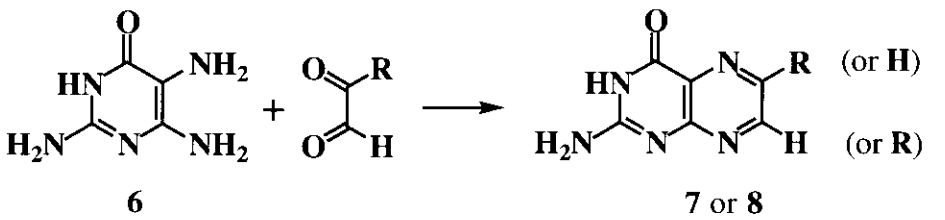


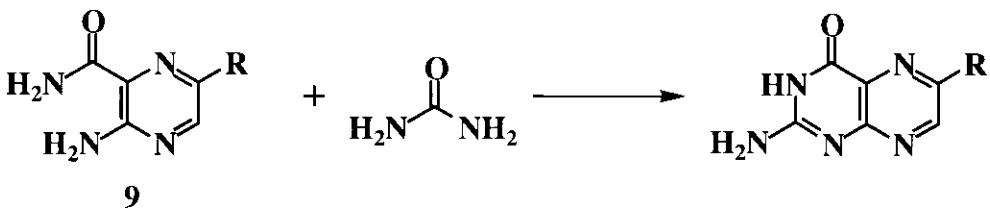
Figure 1. Numbering of the Pteridine Ring and Some Biologically Important Pteridines.

Previously, 6- and 7-substituted pteridines were prepared by the following pteridine ring-forming reactions, from substrates which contain the side chain components:[21] (i) pyrazine ring construction (for example, the Gabriel and Colman synthesis) and (ii) pyrimidine ring construction. The Gabriel and Colman synthesis has been used as a major method of production for the biologically active pteridines described above. The transformations were carried out by the cyclocondensation of the 4,5-diaminopyrimidine derivative (**6**) with an α-dicarbonyl compound. When asymmetric α-dicarbonyl compound (RCOCOH) is employed, however, the reaction usually proceeds in a non-regioselective manner yielding a mixture of 6- and 7-substituted pteridines (**7** and **8**). This result is due to the fact that two directions are possible in the cyclization (eq. 1).

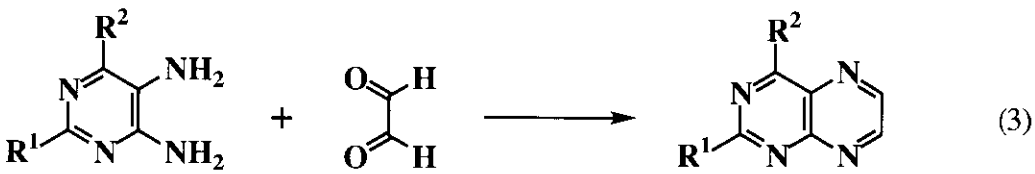
Pyrimidine ring-constructing methods have been employed as an alternative to the pyrazine ring-formation. The total synthesis of **3** and practical syntheses of antifolate agents were performed by using these methods.[22,23] However, the similar problem concerning to the selective preparation of the asymmetrically substituted pyrazine precursor **9** remained in the pyrimidine ring formation illustrated in eq. 2.



6 **7** or **8** (1)



9 (2)



10 (3)

Although 6,7-unsubstituted pteridines (**10**) can be prepared without problems of regioselectivity (eq. 3), these compounds have not been considered as important starting materials for biologically active pteridines for a long time. This is due to the fact that there have been few effective reactions introducing carbon side chains into the C(6) or C(7)

position. Generally, these 6,7-unsubstituted pteridines are hardly soluble not only in most organic solvents but also neutral water. In addition, these compounds contain acidic hydrogen (N–H and O–H) and strongly coordinating nitrogen atoms. Therefore, applications of modern C–C bond formations based on organometallic compounds have been difficult. In this review, we describe recent progress in selective synthesis of 6- or 7- substituted pteridines based on our works in the last decade.

(2) ADVANCES IN THE PYRAZINE RING CONSTRUCTING METHODS

Molecular Orbital Calculation on the Pyrazine Ring-Formation

In the pyrazine ring formation (eq. 1), the regioselectivity would be controlled by reactivities of two amino groups on **6**. Electron densities of these amino groups are affected by the resonance with pyrimidine and electron donating and withdrawing effects of substituents on C(2) and C(6) positions. In order to clarify electronic properties of those amino groups on C(4) and C(5) positions which are numbered respectively as N(7) and N(8), MO calculations were carried out on 4,5-diaminopyrimidine (**11**) and related pyrimidines (**6**, **12** – **15**). These compounds (**6**, **12** – **15**) were often used as key starting materials in the Gabriel and Colman synthesis. Among several semiempirical MO calculation methods to calculate electron densities of N(7) and N(8) of **13**, extended Hueckel and MINDO/3 methods produced results consistent with those obtained by *ab initio* calculation.[24] Other methods (AM1 and PM3) afforded different and inconsistent results. Thus, calculations were performed on **6** and **11** – **15** by using extended Hueckel and MINDO/3 methods, and electron densities are shown in Table 1. The three-dimensional isosurface maps of HOMOs and optimized structures of are illustrated in Figure 2 where all hydrogen atoms, multiple bonds, and atom labels are omitted.[25]

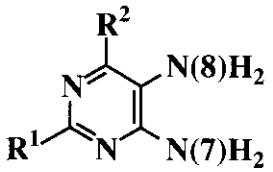


Table 1. Electron Densities[a] of Pyrimidines (6 and 11 – 15).

pyrimidine			ex. Hueckel[b]		MINDO/3		*ab initio*[c]	
R^1	R^2	no.	N(7)	N(8)	N(7)	N(8)	N(7)	N(8)
H	H	**11**	-0.570	-0.634	-0.162	-0.159		
NH_2	NH_2	**12**	-0.318	-0.365	-0.175	-0.108		
NH_2	OH	**6**	-0.301	-0.361	-0.188	-0.161		
NH_2	CH_3O	**13**	-0.313	-0.360	-0.186	-0.171	-0.424	-0.419
OH	OH	**14**	-0.533	-0.692	-0.170	-0.105		
OH	OH	**15**[d]	-0.539	-0.693	-0.163	-0.103		

[a]Mulliken Atomic Charge. [b]Extended Hueckel Method. [c]Obtained from ref. 22. [d]1,3-Dimethyl-2,4-dihydroxypteridine.

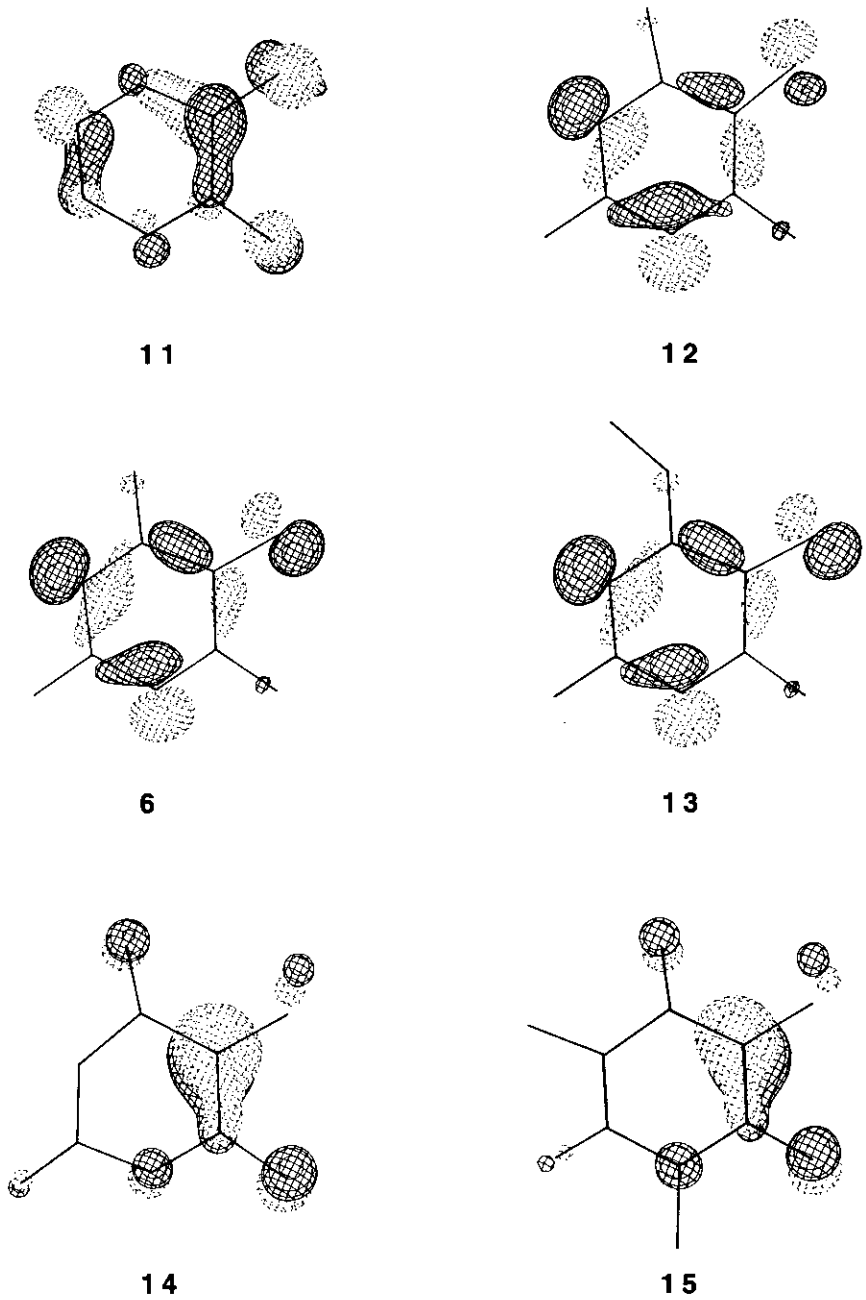
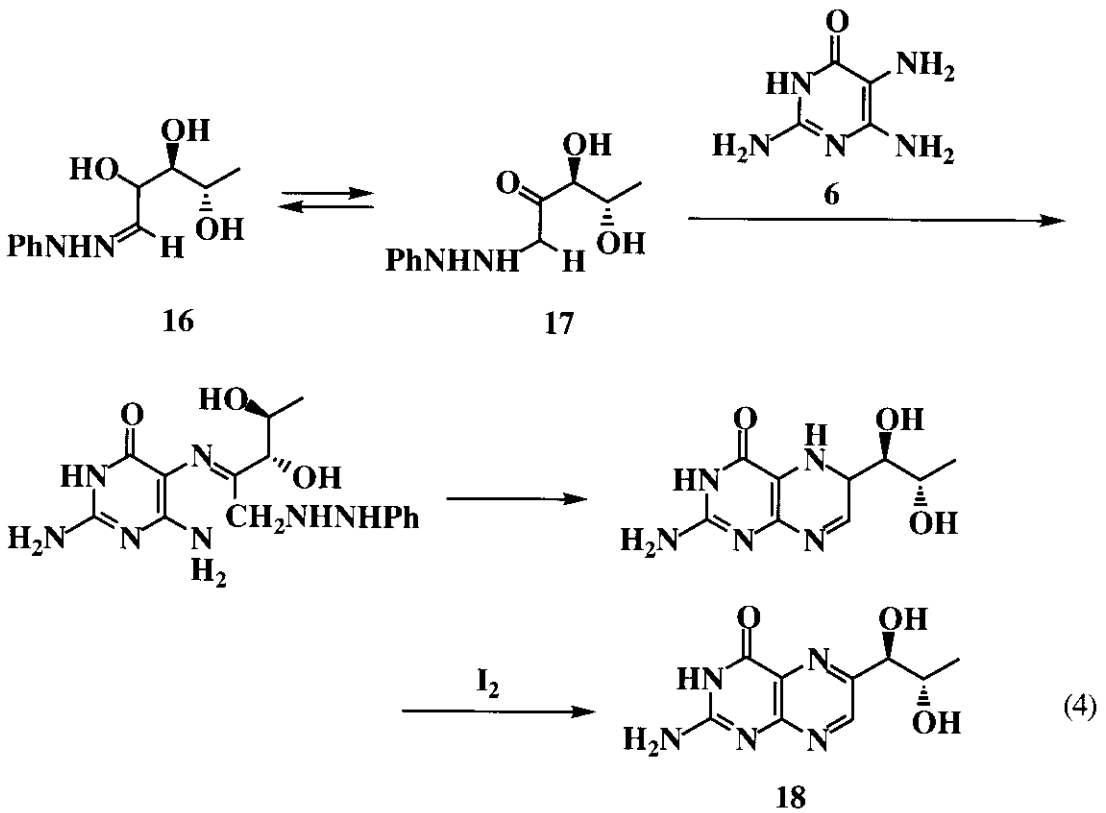


Figure 2. Molecular Orbitals (HOMO) of Pyrimidines Obtained by MINDO/3.

Significant differences of electron densities between N(7) and N(8) of **6** and **11** – **15** were not detected. Though, larger lobes existed on N(8) rather than N(7) in HOMOs of **6**, **12**, and **13** which are precursors of pterin.[26] Lobes on N(7) positions in HOMOs of **14** and **15** used

in the synthesis of lumazine[26] are larger than those on N(8). Therefore, nucleophilic reactivities of N(8) amino groups may be greater than those of N(7) in **6**, **12**, and **13**.

The regioselective pyrazine ring-formation yielded naturally occurring biopterin (**18**) by the reaction of **6** with 5-deoxyarbinose phenylhydrazone (**16**). This reaction is illustrated in eq. 4. It proceeded by means of isomerization of **16** to the keto hydrazine (**17**) (*via* Amadori rearrangement[27]) and Schiff base-forming condensation on N(8).[28,29] The reaction has been used in syntheses of practical amounts (a hundred gram scale) of **1**, **4**, **5**, **18**, and related pterins.

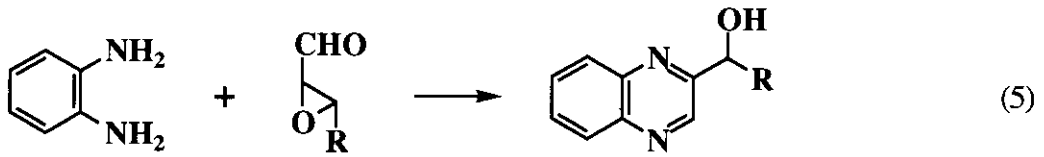


(4)

The Condensation with an Epoxy Aldehyde

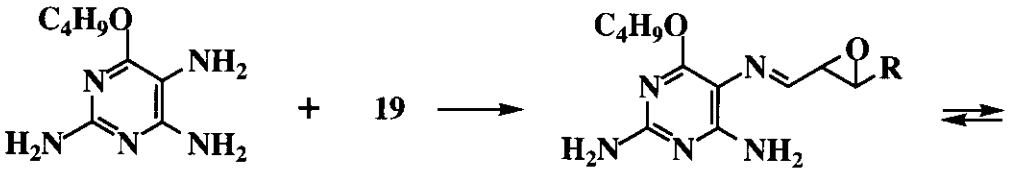
Reactions of formyloxiranes (**19**) with *o*-phenylenediamine in methanol followed by iodine oxidation gave hydroxyalkylquinoxalines (**20**) in good yields (eq. 5).[30] Since many biologically important pteridines contain hydroxyalkyl side chains, the reaction is a good model for the application to pteridine syntheses. Indeed, the reaction of 4-butoxyprimidine (**21**), which is well soluble in organic solvents, with **19** regioselectively afforded the corresponding 6-substituted pteridines (**22**) in moderate yields under the similar conditions.[24] Based on the MO study, the mechanism of the regioselectivity can be explained as follows: the more nucleophilic N(8) of **21** reacted with the formyl group to produce Schiff base (**23**). In turn, it is isomerized to **24** *via* tetrahydropurine and the Schiff

base isomer, as illustrated in eq. 6. In the following sequence of reactions, the 6 π-electrons mode ring closure in **24** occurred to give **22**. Asymmetric synthesis of natural L-*erythro*-biopterin (**18**) was also accomplished by using the optically active formyloxirane ((*S*)-**25**) prepared from the chiral 1,4-pentyndiol derivative (eq. 7).

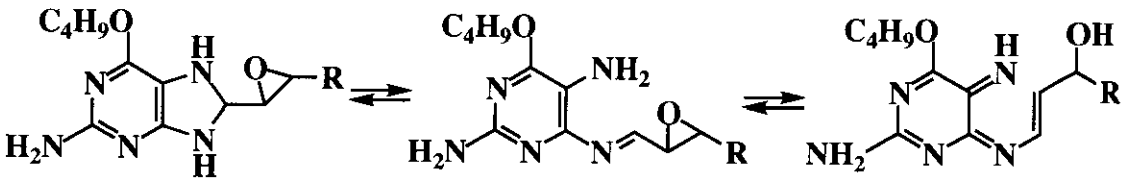


(5)

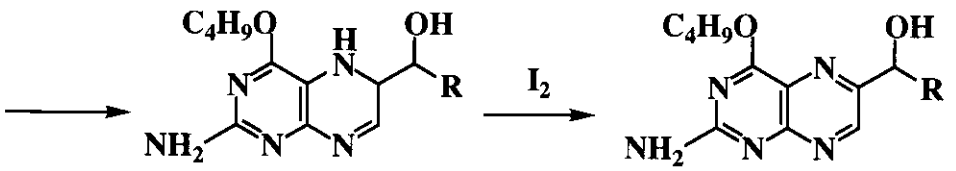
19 **20: R = CH_3** (69%); **C_6H_5** (78%)



21 **23**



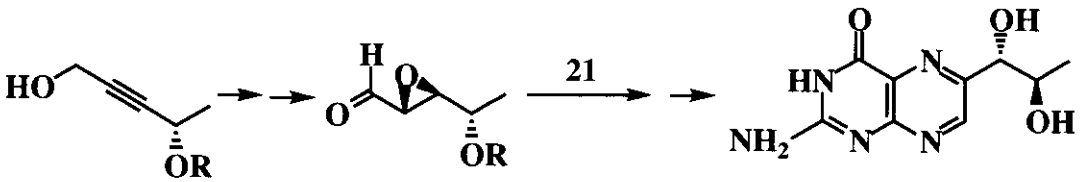
24



(6)

22

R = CH_3; $CH_3CH_2CH_2$; C_6H_5: 20–33% yield



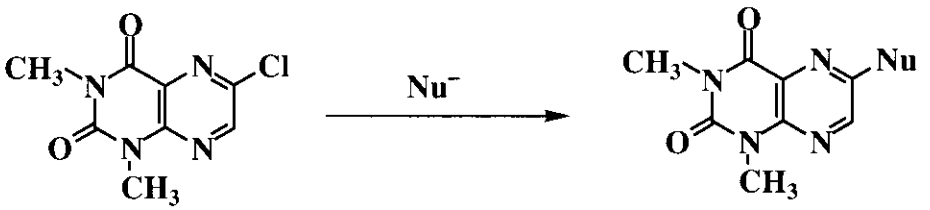
(7)

(*S*)-**25** **18**

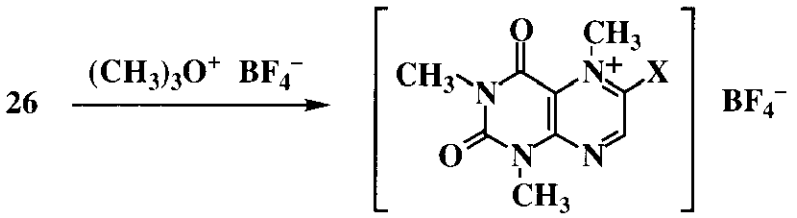
(3) SUBSTITUTION REACTIONS ON PTERIDINE

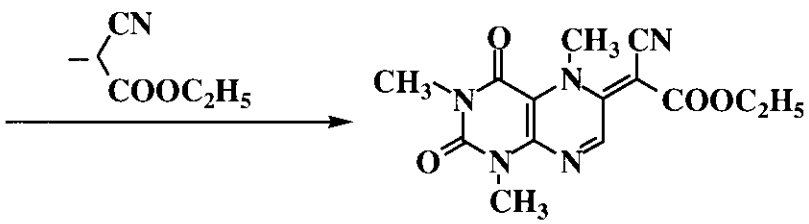
Substitutions of Halogenopteridines

6-Chloropteridine (**26**) and 7-chloropteridine are somewhat reactive toward nucleophilic attack by a heteroatom nucleophile, such as alkoxide, amine, and thiol. The procedure has been employed for the preparation of pteridines (**27**) with a heteroatom substituent on C(6) and C(7) (eq. 8).[31–33] However, substitution of **26** by a usual carbon nucleophile like enolate ion scarcely occurred. For example, the reaction of **26** with an anion of ethyl cyanoacetate proceeded only under the presence of a cationic activator (a Meerwein salt) to give *N*-methylated pteridine (**28**) (eq. 9).[34]



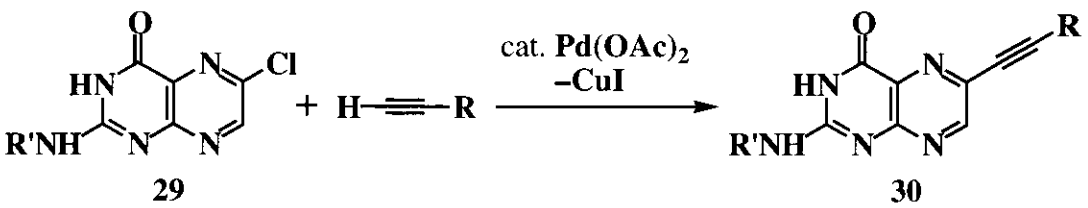
26 **27: Nu = RO, NR_2, RS** (8)



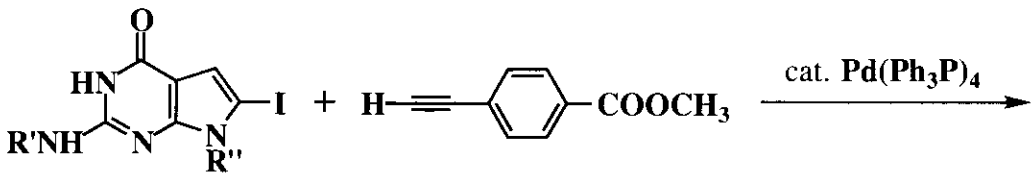


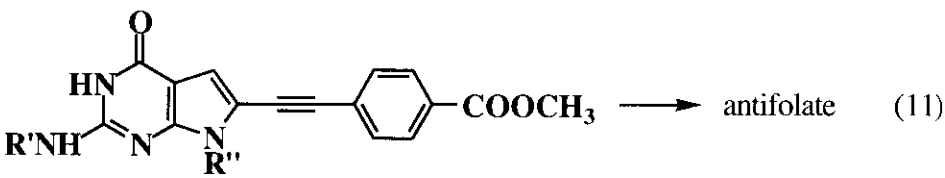
28 (9)

On the other hand, palladium catalyzed coupling reactions (the Taylor coupling: eq. 10) of the 6-chloropteridines (**29**) and 6-bromo- and 6-iodopteridines with acetylene derivatives proceeded effectively to give various 6-alkynylpteridines (**30**) in good yields.[35,36] The reaction has been employed as a very powerful tool for the synthesis of molibdopterin (**3**) and the analogous compound (**31**), which were used as precursors for the synthesis (eq. 11) of new antifolate drugs (LY231154 and so on).[37]



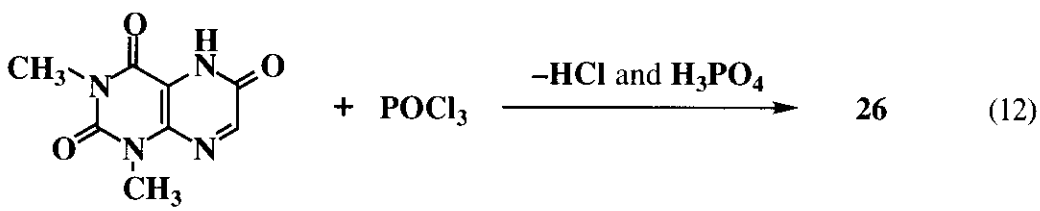
→ **3** and so on (10)





31 → antifolate (11)

Thus, chloropteridines (**26**) are unsatisfactorily reactive toward general nucleophilic substitutions. In addition, the following is the most serious problem in practical scale reactions of chloropteridines. Preparation of **26** is usually carried out using a large excess of phosphoryl chloride as the reactant and solvent, and the reaction formed a large amounts of acidic wastes, such as phosphoric acid and hydrogen chloride (eq. 12).[31] Therefore, developments of new procedures of **26** with less wastes and more reactive alternative substrates of **26** are required.

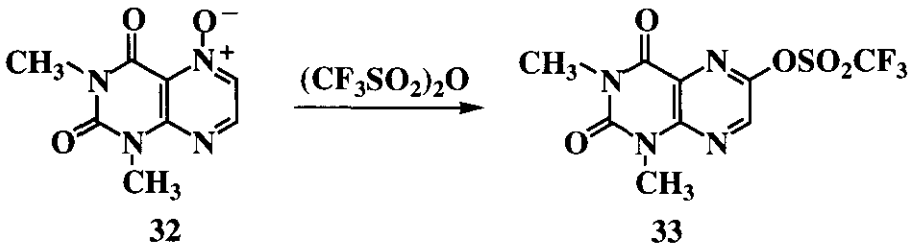


(12)

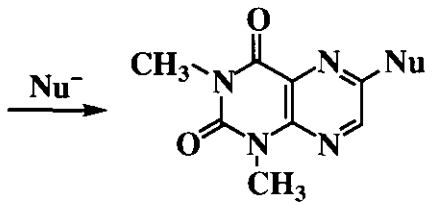
Substitutions of Pteridine Triflates

Generally, organic triflates (trifluoromethanesulfonate) have been considered as one of the most reactive substrates in nucleophilic substitution reaction and employed as an alternate to organic halides, whose electrophilic reactivities toward nucleophiles were insufficient. Triflate

derivative (**33**) of pteridine was prepared regioselectively by the reaction of the *N*-oxide (**32**) with trifluoromethanesulfonic anhydride in 86% yield.[38] The triflate (**33**) is highly soluble in common organic solvents and can be handled even under weakly basic conditions, such as aq. $NaHCO_3$. As expected, **33** is more reactive than **26** and the 6-bromo analog and reacts not only with a wide variety of heteroatom nucleophiles, such as RO^-, R_2NH, RSH, I^-, and SCN^-, but also with carbon nucleophiles, such as enolate ions. The reactions take place without help from cationic accelerator in mild conditions to give corresponding substituted pteridines (**27** and **34**) in high to moderate yields (eq. 13 and 14).[38–40]



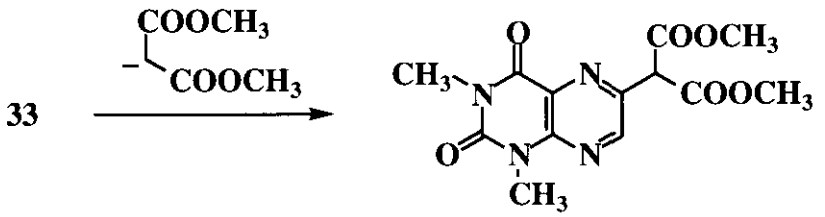
32 **33**



27

Nu: **Br** (66%)
I (58%)
NH_2 (69%)
$N(C_2H_5)_2$ (83%)
SPh (49%)
SePh (95%)

(13)



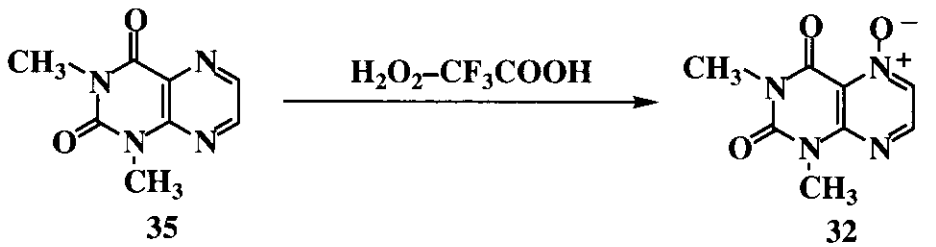
34 (55%)

(14)

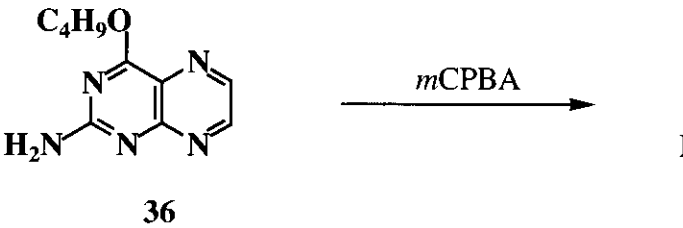
Substitution Reactions Using Pteridine N-*Oxide*

Pteridine *N*-oxides, such as 5-oxide (**32**) and 8-oxide (**37**), were prepared regioselectively from the corresponding pteridines (**35** and **36**) through chemical oxidation (eq. 15 and 16). It is predicted by MO studies on *N*-oxides in the next section that the N–O group increases both nucleophilic and electrophilic reactivities of carbon atoms nearby. Indeed, as illustrated in eq. 17, pteridine *N*-oxide (**32**) reacted with acyl halides and anhydrides to give halogenopteridine (**27**; Nu = Cl or Br) and pteridine acetate(**27**; Nu = CH_3COO), in high yields respectively.[38–42] The reaction of **32** with Z–Nu initially formed the ion pairing

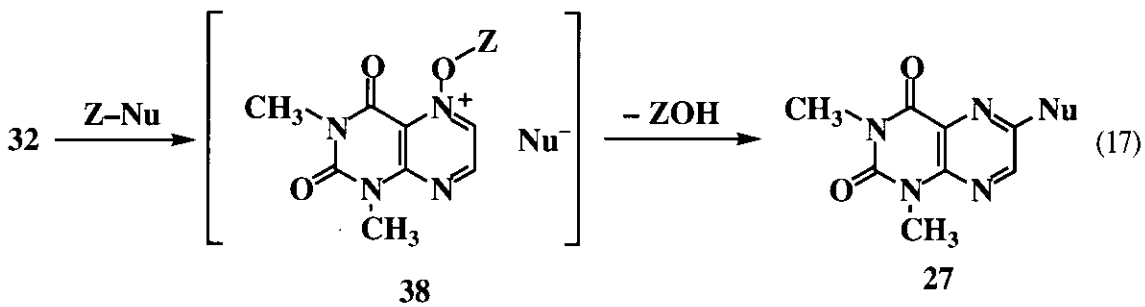
intermediate (**38**). Here, the nucleophilic attack of the internal counter anion (Nu^-: Cl^-, Br^-, and CH_3COO^-) on the iminium carbocation center, followed by the elimination of acetic acid, yielded the 6-substituted pteridines **27**.



35 **32** (15)



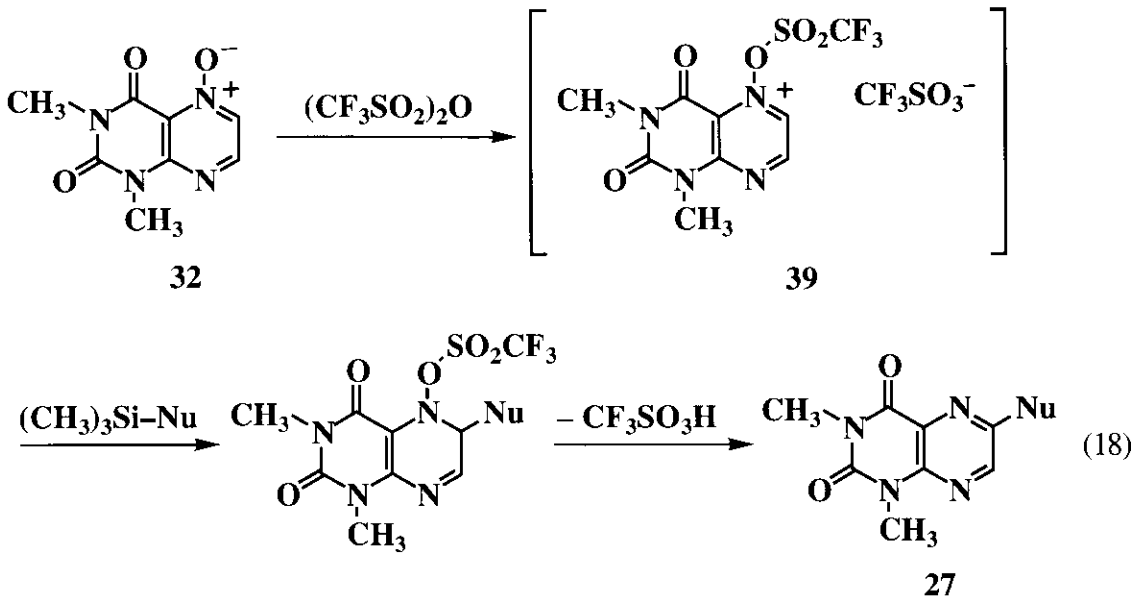
36 **37** (16)



38 **27** (17)

Z = RCO, RSO_2; Nu = Cl, Br, CH_3COO

Since anions like Cl^- and CH_3COO^- have strong nucleophilic properties and are bound tightly with the cationic center in the ion pair (**38**), introduction of the out coming nucleophile instead of the internal anion (Nu^-) into the ion pair is generally difficult. When triflate is employed in the reaction as the counter anion, however, the nucleophilic attack of the external anion on cationic C(6) of the resulting ion pair (**38**) might predominate over the attack of the internal weak nucleophile ($CF_3SO_3^-$). The reaction of **32** with trimethylsilyl isothiocyanate ($(CH_3)_3Si$–NCS) in the presence of trifluoromethanesulfonic anhydride yielded **27** (Nu = SCN) as the major product in 47% yield together with the by-product (**33**) (eq. 18).[38] Unfortunately, these results are only possible when highly nucleophilic silane derivatives are employed. Otherwise, for example, in the reaction with trimethylsilyl iodide, the intramolecular attack of $CF_3SO_3^-$ occurred as the major process to give a mixture of **33** and **27** (Nu = I) in 28 and 14% yields, respectively.

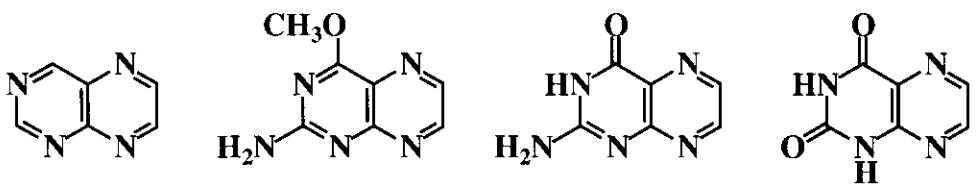


32 39 27 (18)

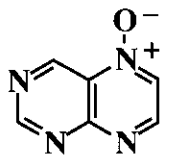
(4) DIRECT INTRODUCTION OF THE SUBSTITUENTS

MO Study on Pteridines

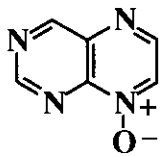
By using semi empirical MO methods (PM3 and MINDO/3), HOMOs and LUMOs of some 6,7-substituted pteridines (**35**, **40** – **43**) and their 5- or 8-oxides (**32**, **44** – **46**) were calculated.[25] In comparison to the C(6) and C(7) positions of the pteridines (**35**, **40** – **43**), their atomic charges are not significantly different.[43,44] However it is obvious that orbital coefficients of HOMOs are larger on C(6) positions than on C(7) positions, and the tendency concerning to LUMOs is opposite (see Table 2). On the other hand, in *N*-oxides (**32**, **44** – **46**), the N–O group increases orbital coefficients of HOMOs on C(6) or C(7) atoms which bound to the N–O group. Orbital coefficients of LUMOs are always larger on C(7) positions. Thus, electrophilic and nucleophilic attacks toward pteridines (**35**, **40** – **43**) seem to occur predominantly on C(6) and C(7) positions, respectively. On the contrary, the nucleophilic attack toward the C(7) position of *N*-oxides (**32**, **44** – **46**) easily occurs.



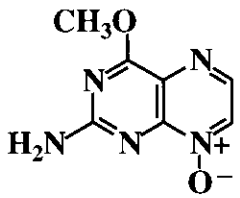
40 41 42 43



44



45



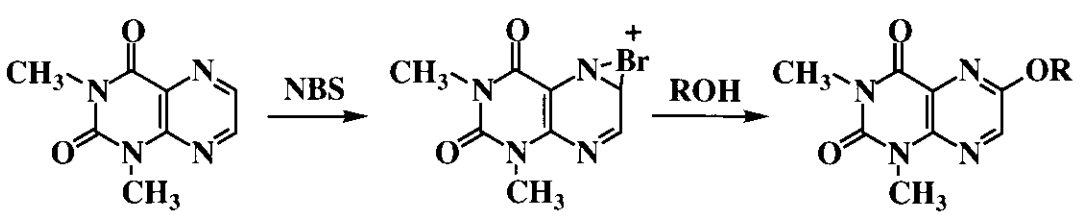
46

Table 2. Orbital Coefficients of HOMOs and LUMOs of Pteridines and the *N*-Oxides.

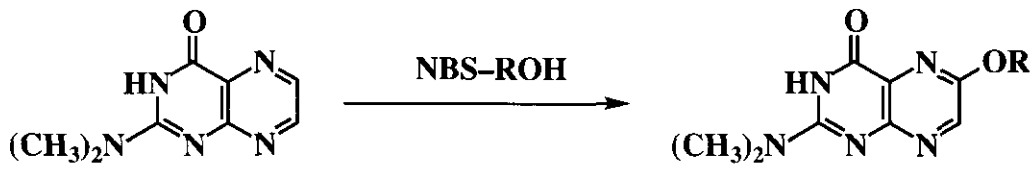
	PM3 method				MINDO/3 method			
	HOMO		LUMO		HOMO		LUMO	
compound	C(6)	C(7)	C(6)	C(7)	C(6)	C(7)	C(6)	C(7)
40	0.0000	0.0000	0.2704	0.3404	0.0000	0.0000	0.2706	0.3506
41	0.3201	0.0380	0.1708	0.4081	0.0012	0.0008	0.1656	0.4411
35	0.3822	0.1509	0.2091	0.5417	0.0004	0.0002	0.0011	0.0018
42	0.3465	0.0929	0.3435	0.3851	0.0001	0.0001	0.0000	0.0001
43	0.4112	0.1746	0.2054	0.5430	0.0000	0.0000	0.0588	0.5371
44	0.5084	0.1440	0.3675	0.1373	0.0007	0.0004	0.2334	0.3004
45	0.1644	0.4639	0.1150	0.3585	0.0005	0.0006	0.1974	0.3116
46	0.2342	0.2697	0.1764	0.3671	0.2988	0.1746	0.0603	0.4216
32	0.5057	0.0392	0.3143	0.5345	0.5173	0.1029	0.0197	0.1149

Electrophilic Substitution

It is known that electrophilic substitution of pteridine is an unfavorable process because of highly electron deficient nature of the pteridine ring system. However, relatively large lobes of HOMOs might direct the attack of an electrophile to the N(5)–C(6) double bond. Indeed, regioselective alkoxylation of the pteridine (**35** and **48**) in an alcohol solution proceeded on C(6) in the presence of NBS (*N*-bromosuccinimide) resulting in good yields of **47** and **49**, respectively. The electrophilic attack of Br^+ made possible the bromonium intermediate. The nucleophilic ring-opening by the alcohol yielded the final product (eq. 19 and 20).[44]



35 47 (19)



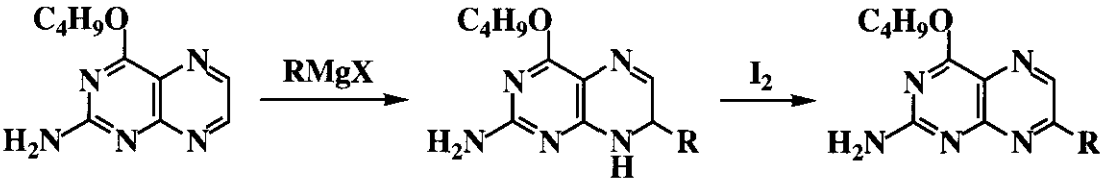
(20)

48 **49**

R = CH_3, CH_2CH_3, $CH_2CH_2CH_3$: 50–77% yields

Reactions with Organometallic Reagents

The nucleophilic addition of a Grignard reagent to the pteridine (**36**) occurred regioselectively on C(7), where the large lobe of LUMO existed, resulting in 7,8-dihydropteridine (**50**). It was in turn oxidized *in situ* to the corresponding 7-substituted pteridine (**51**) by treatment with iodine (eq. 21).[45]

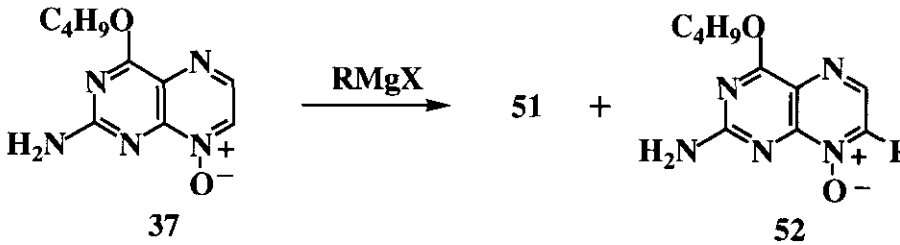


(21)

36 **50** **51**

R = CH_3, n-C_4H_9, i-C_3H_7, t-C_4H_9, C_6H_5: 8–20% yields

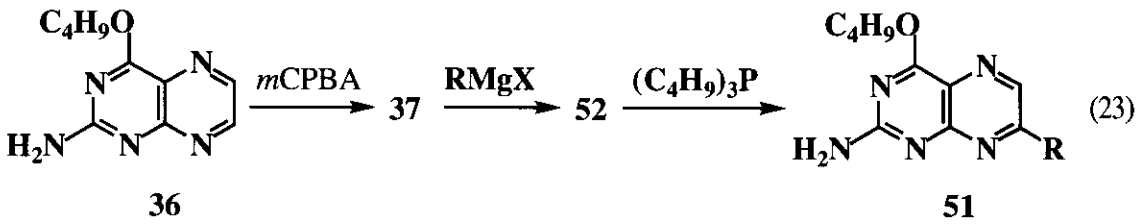
Reaction of the pteridine 8-oxide (**37**) with a Grignard reagent gave a mixture of **51** and its *N*-oxide **52** (eq. 22). Total yields were better than those from **36**.[43,45] Oxidation of **36** to **37** and the reduction of **52** to **51** could be easily performed by the action of *m*CPBA (eq. 16) and tributylphosphine, respectively. Alkylation of **36** by a Grignard reagent was improved *via* the *N*-oxide route (eq. 23). Even in the case using bulky Grignard reagent *t*-C4H9MgBr, which is usually employed as a base or reductant rather than a nucleophile, the substitution of **36** and **37** proceeded as the major pathway to give the 7-*t*-butylated pteridine (**51**: R = *t*-C4H9) and its *N*-oxide (**52**: R = *t*-C4H9) in satisfactory yields. Reactions of **36** and **37** with organolithium reagents, such as methyllithium and phenyllithium, afforded complex mixtures of products. Yields of **51** and **52** were very poor (< 8%).



(22)

37 **52**

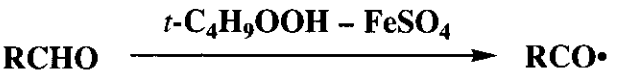
R = CH_3, n-C_4H_9, i-C_3H_7, t-C_4H_9, C_6H_5: 16–48% yields



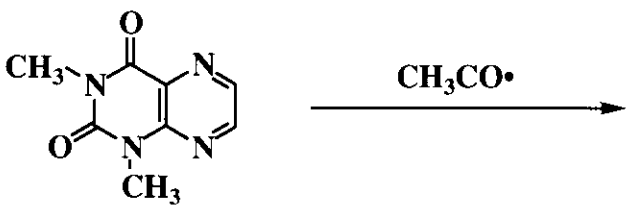
36 51 (23)

Substitution by Radical Intermediates

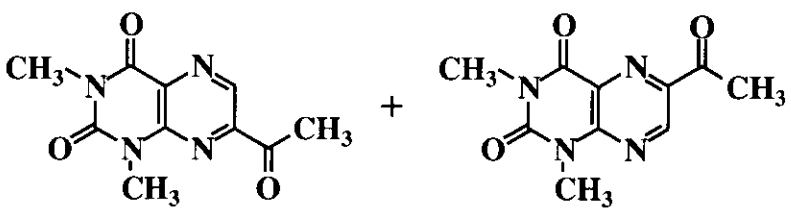
Those procedures using nucleophilic reactions described above always require suitably protected pteridines as soluble substrates in organic solvents. Since radical intermediates can be generated and react without difficulty in an aqueous solvent, homolytic reactions are employed in the reaction of unprotected pteridine.[46,47] An acyl radical prepared from an alkanal by the action of Fe^{2+} and *t*-C_4H_9OOH (Fenton condition, eq. 24) reacted with the pteridine (**35**) in an aqueous solution, resulting in high yields of 7-acylpteridine (**53**) and 6-acylpteridine (**54**) as the major and minor products, respectively. Success was achieved using this method for the selective synthesis of 6-acylpteridine (**56**) by using the starting pteridine (**55**) with its 7-position blocked by the methylthio group.[48,49] The protecting group (SCH_3) could be removed by the treatment with Cu-Al alloy after acid hydrolysis to **57**. Partial reduction of the resulting **58** by means of aluminum amalgam gave deoxysepiapterin (**59**).



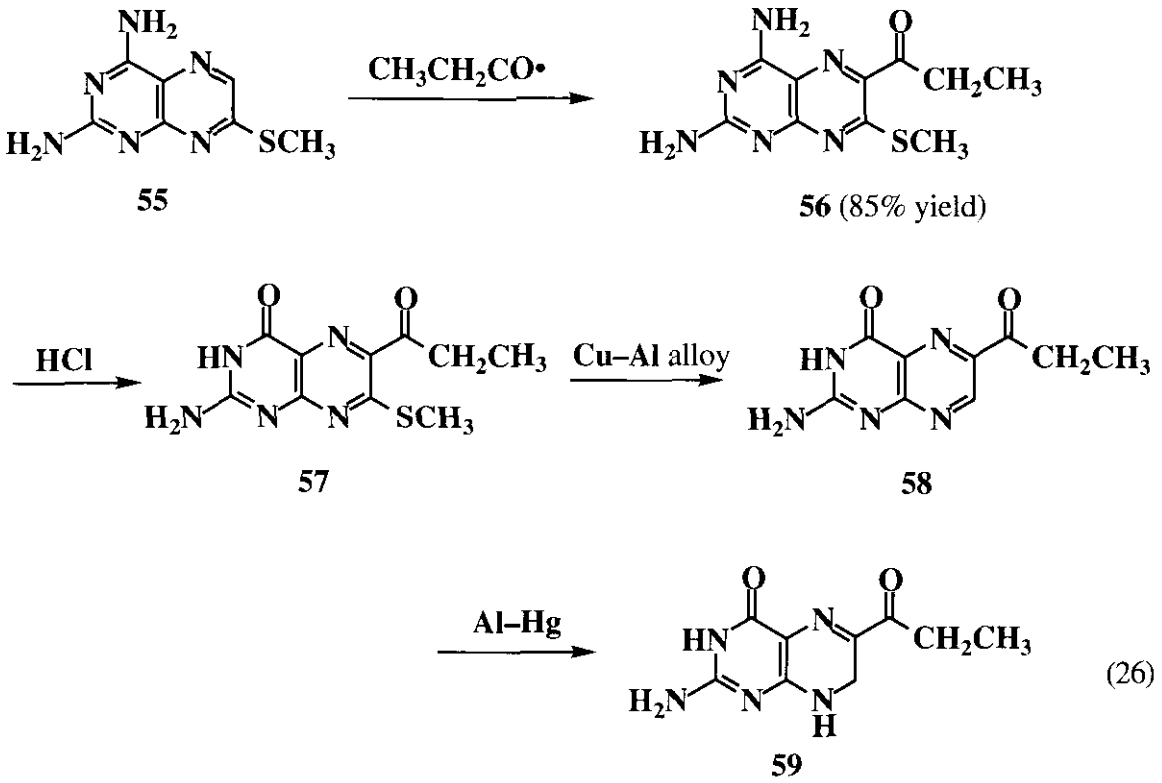
(24)



35

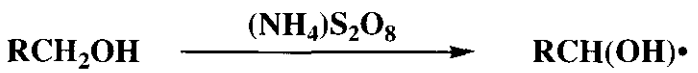


53 (32% yield) + **54** (1.5% yield) (25)

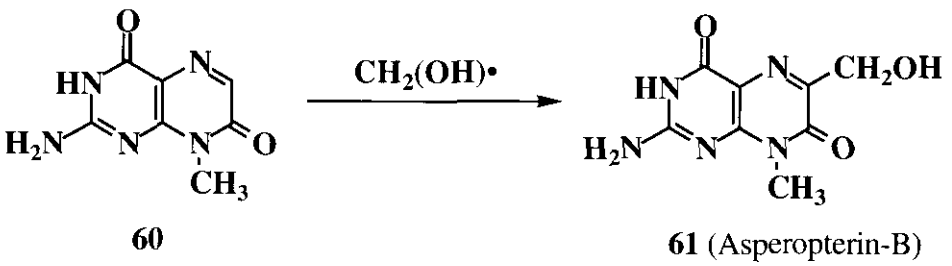


(26)

Hydroxyalkyl radicals, generated from alcohols by the action of ammonium persulfate (eq. 27), reacted with the pteridine (**60**) with a blocking group on the 7-position to give Asperopterin-B (**61**) which is a naturally occurring pteridine.[50]



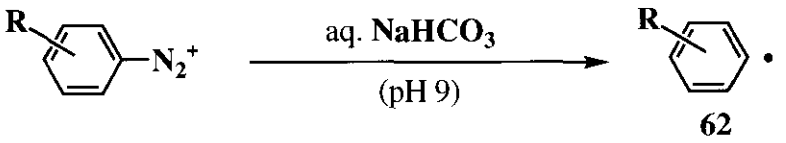
(27)



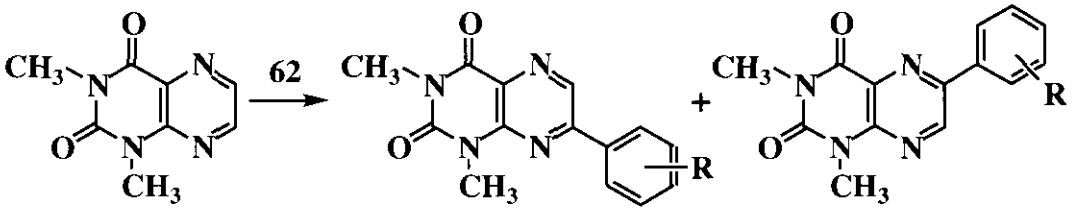
(28)

Arenediazonium salts decompose in aqueous alkaline conditions (in the presence of $NaHCO_3$; pH 9) to generate corresponding aryl radicals (**62**) (R = H, CH_3, Cl, NO_2; ortho, meta, and para) as illustrated in eq. 29. The radical (**62**) reacted with **35** regiospecifically at the original position where N_2^+ was bound, to afford the 7-arylated pteridine (**63**) and 6-

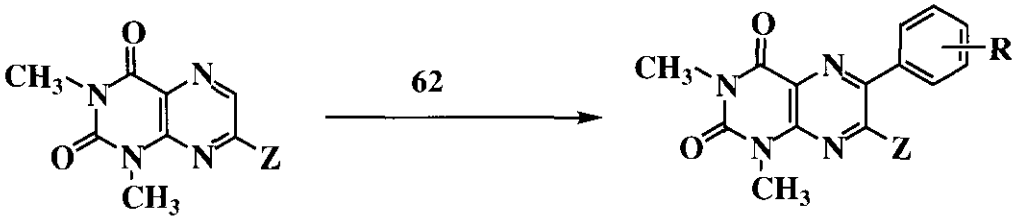
arylpteridine (**64**), as major and minor products. The arylation proceeded on C(6) when the C(7)-blocked substrate (**65**) was employed in the reaction with **62**, resulting in the 6-arylpteridine (**66**) in good yield, along with several by-products.[51–53]



62 (29)



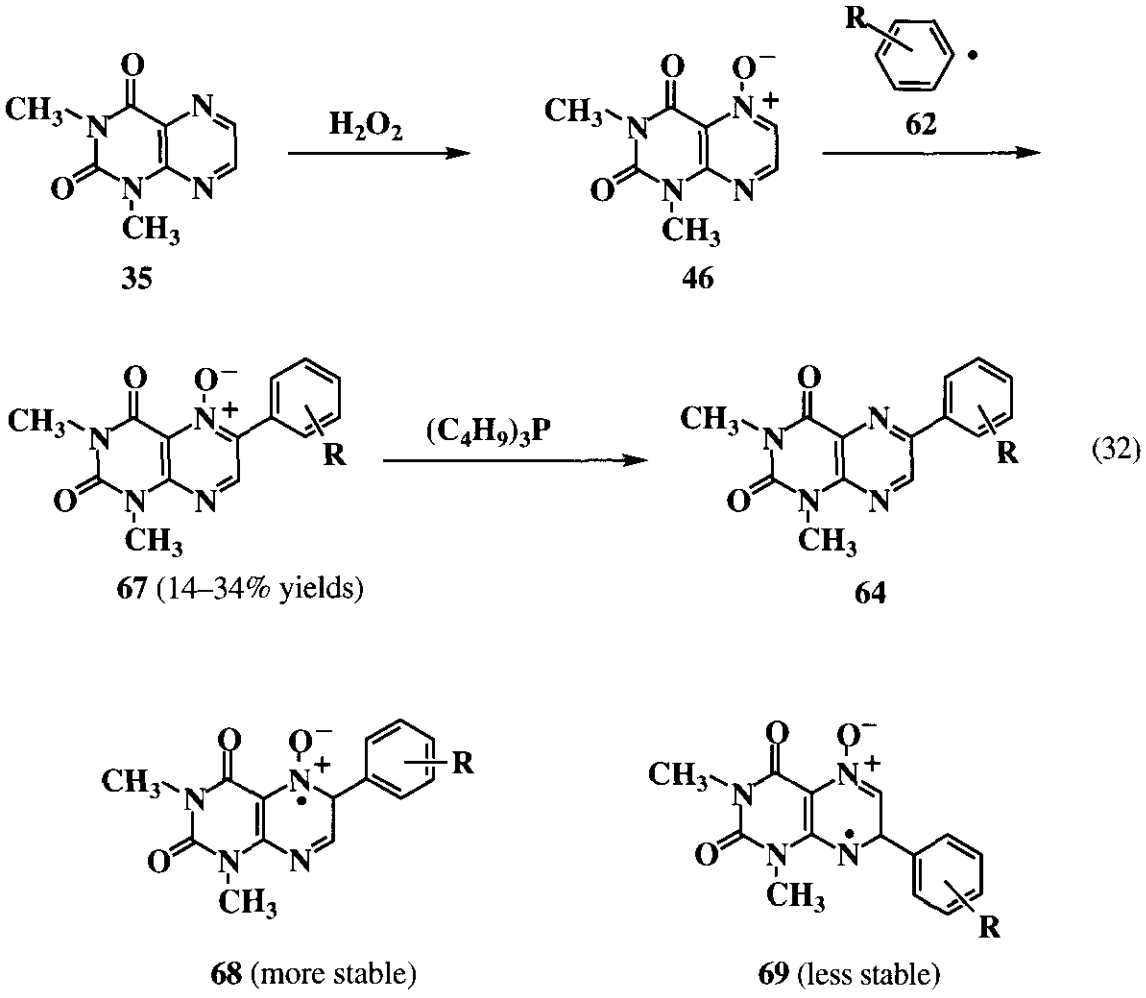
35 **63** (major: 14–37%) **67** (minor: 1–8%) (30)



65 **Z = OH, OCH_3, $N(CH_3)_2$** **66** (39–59% yields) (31)

The C(7) predominant regioselectivities in these homolytic substitutions of pteridines might be elucidated by frontier orbitals (SOMO: singly occupied MO) of pteridines. SOMOs of these pteridines are considered to be the same as LUMOs. Therefore, the C(7) position of **35** (and so on, with the greater lobe of LUMO) is more reactive toward radical species.

Although LUMO of the pteridine 5-oxide (**46**) was expected to introduce the radical (**62**) on the C(7) position, the reaction of **46** with **62** exclusively afforded the opposite product (**67**). Based on MO studies of radical intermediates (**68** and **69**), produced by the initial addition of **62** onto C(6) and C(7), respectively, the mechanism was rationalized as follows. The reaction proceeded predominantly *via* the significantly stable intermediate (**68**: 8.38 kcal/mol lower potential) rather than **69**. Since **67** could be reduced back to the 6-arylpteridine (**64**) by the treatment with tributylphosphine,[52] 7- and 6-arylpteridines (**63** and **64**, respectively) could be regioselectively synthesized either from **35** by using the direct reaction with **62** (eq. 30) or from subsequent reactions with H_2O_2 in CF_3COOH followed by **62** (eq. 32).



(32)

ACKNOWLEDGMENTS

We thank Mr. T. Andoh in School of Informatics and Sciences, Nagoya University for technical supports to MO calculations.

REFERENCES

1. D. J. Brown, "The Chemistry of Heterocyclic Compounds", Vol. 24, Part 3, eds by E. C. Taylor and A. Weissberger, Wiley, New York, 1988.
2. W. Pfleiderer, *J.* Heterocycl. *Chem.*, **1992**, *42*, 583.
3. M. Akino and K. Iwai, *Pteridine*, Kodansha: Tokyo, 1981.
4. S. N. J. Brugmayer and E. I. Stiefel, *J. Chem. Educ.*, **1985**, *62*, 943.
5. W. Lovenberg, R. A. Levine, D. S. Robinson, M. Ebert, A. C. Williams, and D. B. Calne, *Science*, **1979**, *204*, 624.
6. H. Narabayashi, T. Kondo, T. Nagatsu, T. Sugimoto, and S. Matsuura, *Proc. Japan Acad.*, **1982**, *52B*, 283.

7. T. Yamaguchi, T. Nagatsu, T. Sugimoto, S. Matsuura, T. Kondo, R. Iizuka, and H. Narabayashi, *Science*, **1983**, *219*, 75.
8. W. Enders, H. Ibel, L. Kierat, N. Blau, and H.-Ch. Curtius, *Lancet*, **1987**, *2* 223.
9. T. Nagatsu, S. Matsuura, and T. Sugimoto, "Medical Research Reviews", Vol. 9, ed. by G. De Stevens, John Wiley, New York, 1989, p. 25.
10. E. A. Rayl and G. Pizzorno, *Cancer Treat. Res., (Drug Resistance)*, **1996**, *87*, 197.
11. M. C. Hum and B. A. Kamen, *Investigational New Drugs*, **1996**, *14*, 101.
12. C. Huber, D. Fuchs, A. Hausen, A. Margreiter, G. Reibnegger, G. Spielberger, and H. Wachter, *J. Immunol.*, **1983**, *130*, 1047.
13. C. Huber, J. R.; Batchelor, D. Fuchs, A. Hausen, A. Lang, D. Niederwieser, G. Reibnegger, P. Swetly, J. Tropmair, and H. Wachter, *J. Exp. Med.*, **1984**, *160*, 310.
14. W. Woloszcsuk, M. Schwartz, M. Havel, A. Laczkowics, and M. M. Muller, *J. Clin. Chem. Clin. Biochem.*, **1986**, *24*, 729.
15. A. Hausen, D. Fuchs, G. Reibnegger, E. R. Werner, and H. Wachter, *Pteridines*, **1989**, *1*, 3.
16. T. Sugimoto, S. Ogiwara, R. Teradaira, K. Fujita, and T. Nagatsu, *Biogenic Amines*, **1992**, *9*, 77.
17. S. Ogiwara, K. Kiuchi, T. Nagatsu, R. Teradaira, I. Nagatsu, K. Fujita, and T. Sugimoto, *Clin. Chem.*, **1992**, *38*, 1954.
18. S. Ogiwara, T. Nagatsu, R. Teradaira, K. Fujita, and T. Sugimoto, *Biol. Chem. Hoppe-seyler*, **1992**, *373*, 1061.
19. S. Ogiwara, H. Hidaka, T. Sugimoto, R. Teradaira, K. Fujita, and T. Nagatsu, *J. Biochem. (Tokyo)*, **1993**, *113*, 1.
20. Based on the IUPAC nomenclature, atom numberings and naming of pteridine and pyrimidine derivatives are abbreviated as follows. Nitrogen atoms at 5 and 8 positions and carbons at 6 and 7 positions of pteridine are shown as N(5), N(8), C(6), and C(7), respectively. Carbon at 4 and 5 positions of pyrimidine is indicated as C(4) and C(5), respectively.
21. Chap. 3 and 4 of ref. 1.
22. E. C. Taylor and L. A. Leiter, *J. Am. Chem. Soc.*, **1989**, *111*, 285.
23. E. C. Taylor, P. S. Ray, I. S. Darwish, J. L. Johnson, and K. V. Rajagopalan, *J. Am. Chem. Soc.*, **1989**, *111*, 7664.
24. S. Murata, T. Sugimoto, S. Ogiwara, K. Mogi, and H. Wasada, *Synthesis*, **1992**, 303.
25. Semiempirical MO calculations described herein are performed using HyperChem® running on Windows 95®.
26. 2-Amino-4-hydroxypteridine and 2,4-dihydroxypteridine are abbreviated as pterin and lumazine, respectively.
27. E. F. L. Anet, *Adv. Carbohydr. Chem.*, **1964**, *19*, 181.
28. T. Sugimoto and S. Matsuura, *Bull. Chem. Soc. Jpn.*, **1975**, *48*, 3767.
29. T. Sugimoto and S. Matsuura, *Bull. Chem. Soc. Jpn.*, **1979**, *52*, 181.

30. S. Murata, T. Sugimoto, and S. Matsuura, *Heterocycles*, **1987**, *26*, 883.
31. Page 188 – 191 of ref. 1.
32. E. C. Taylor and R. Kobylecki, *J. Org. Chem.*, **1978**, *43*, 680.
33. H. Steppan, J. Hammer, R. Baur, R. Gottlieb, and W. Pfleiderer, *Liebigs Ann. Chem.*, **1982**, 2135.
34. A. Heckel and W. Pfleiderer, *Helv. Chim. Acta*, **1986**, *69*, 704.
35. E. C. Taylor and P. S. Ray, *J. Org. Chem.*, **1987**, *52*, 3997.
36. E. C. Taylor and P. S. Ray, *J. Org. Chem.*, **1988**, *53*, 35.
37. E. C. Taylor, W. B. Young, and C. Spanka, *J. Org. Chem.*, **1996**, *61*, 1261.
38. S. Murata, T. Sugimoto, and K. Murakami, *Pteridines*, **1997**, *8*, 1.
39. S. Murata, T. Sugimoto, M. Kujime, and K. Murakami, unpublished results. See the abstract: S. Murata, T. Sugimoto, and K. Murakami, *Pteridines*, **1997**, *8*, 65.
40. S. Murata, K. Murakami, C. Seo, T. Sugimoto, and M. Kujime, "Chemistry and Biology of Pteridine and Folates 1997", eds by W. Pfleiderer and H. Rokos, Blackwell Science, Berlin, 1997, p. 17.
41. Page 191–192 of ref. 1.
42. W. Pfleiderer, and W. Hutzenlaub, *Chem. Ber.*, **1973**, *106*, 3149 .
43. K. Kiguchi, S. Murata, and T. Sugimoto, *Pteridines*, **1995**, *6*, 160.
44. T. Sugimoto and W. Pfleiderer, *Heterocycles*, **1995**, *41*, 781.
45. S. Murata, K. Kiguchi, and T. Sugimoto, *Heterocycles*, **1993**, *35*, 639.
46. W. Pfleiderer, *Tetrahedron Lett.*, **1984**, *25*, 1031.
47. R. Baur, E. Kleiner, and W. Pfleiderer, *Liebigs Ann. Chem.*, **1984**, 1798.
48. R. Baur, T. Sugimoto, and W. Pfleiderer, *Chem. Lett.*, **1984**, 1025.
49. R. Baur, T. Sugimoto, and W. Pfleiderer, *Helv. Chim. Acta*, **1988**, *71*, 531.
50. T. Sugimoto, S. Murata, S. Mastuura, and W. Pfleiderer, *Tetrahedron Lett.*, **1986**, *27*, 4179.
51. T. Sugimoto and W. Pfleiderer, *Heterocycles*, **1997**, *45*, 765.
52. T. Sugimoto, C. Seo, S. Murata, and W. Pfleiderer, *Pteridines*, **1997**, *8*, 188.
53. T. Sugimoto, C. Seo, and W. Pfleiderer, "Chemistry and Biology of Pteridine and Folates 1997", eds by W. Pfleiderer and H. Rokos, Blackwell Science, Berlin, 1997, p. 69.

Received, 17th February, 1998