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A FACILE METHOD FOR REGIOSELECTIVE 6,7-DISUBSTITUTION OF PTERIDINE

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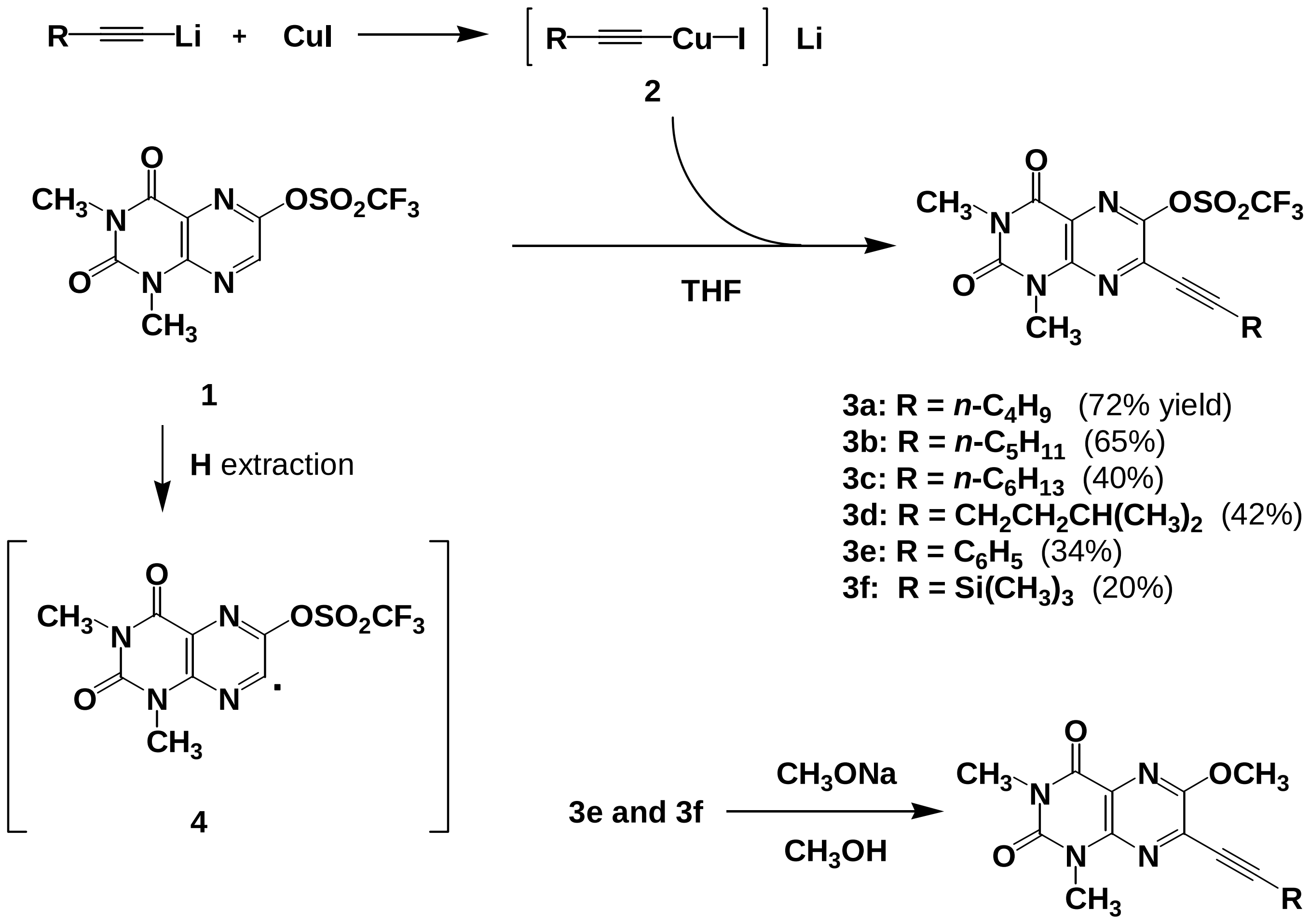
Abstract—Substitution of 1,3-dimethyl-2,4(1*H*,3*H*)-pteridinedione 6-triflate by copper acetylide proceeds regioselectively on the 7-position to give corresponding 7-alkynylpteridine 6-triflate whose triflate group can be subsequently replaced by various nucleophiles.

There are many biologically important pteridines which operate as cofactors of enzymatic redox and C_1 transfer process in almost living organisms.[1] These compounds such as biopterin and folic acid have side chains on the 6-position, and 6,7-disubstituted pteridines like methanopterin are sometimes found in naturally occurring pteridines.[2,3] Therefore, regioselective methodologies introducing substituents onto the 6- and 7-positions have been investigated as one of major targets in chemistry of pteridine.[4] Among many known procedures for 6-substituted pteridine, alkynylation of 6-bromopteridine with acetylene derivatives using palladium catalyzed coupling reaction has been recommended, because acetylenic substituents can be flexibly converted into side chains with various functional groups.[5—9] Recently, we have reported that pteridine 6-triflate was more reactive toward nucleophilic attack than 6-chloro- and 6-bromopteridines,[10,11] and, therefore, substitution by metal acetylides might be valuable as the complemental method. In this communication we would like to describe the reaction of the pteridine 6-triflate with organocopper compounds which yielded unexpected 7-substituted pteridines.



3a: $R = n\text{-}C_4H_9$ (72% yield)
3b: $R = n\text{-}C_5H_{11}$ (65%)
3c: $R = n\text{-}C_6H_{13}$ (40%)
3d: $R = CH_2CH_2CH(CH_3)_2$ (42%)
3e: $R = C_6H_5$ (34%)
3f: $R = Si(CH_3)_3$ (20%)

5: $R = C_6H_5$ **and H**

1,3-Dimethyl-2,4(1*H*,3*H*)-pteridinedione 6-triflate (**1**)[10] reacted with copper acetylide (**2**) prepared by an equimolar reaction of 1-hexynyllithium with copper(I) iodide in THF at –70 °C to give 7-hexynylpteridine (**3a**) in 72% yield as an exclusive product. In the same conditions, reactions of **1** with **2** derived from other 1-alkynes (1-heptyne, 1-octyne, 5-methyl-1-hexyne, phenylacetylene, and trimethylsilylacetylene) gave regioselectively **3b** — **3f** in 20 – 65% yields. Formation of 6-alkynyl- and 6,7-dialkynylpteridines was not detected in the crude reaction mixtures. The reaction did not proceed, when **2** derived from protected acetylenic alcohols (THP and trimethylsilyl ethers of 1-propyne-3-ol and 1-butyn-4-ol) was employed. The structure of the organocopper reagent is important, and among several well known organocopper reagents only **2** which is copper acetylide coordinated by lithium iodide[12] can react with **1** to afford **3**. Indeed, reactions of **1** with strongly nucleophilic organocopper reagents, such as mixed cuprate and so on,[13] and lithium and magnesium acetylides did not afford either 7-substituted nor 6-substituted pteridines, and **1** reacts with Grignard reagent in the presence of Ni(II) catalyst to give 6-substituted pteridine.[14]

It is known that reaction of unsubstituted pteridine with radical intermediates, such as RCO· , RCH(OH)· , and Ph· , occurs in mild conditions to give 6- and 7-monosubstituted pteridines.[4,14] Since the substitution proceeds through pteridine radical like **4** caused by hydrogen extraction from the 6- and 7-position, triflate of **1** is considered to be a protective group which obstructs radical formation rather than a leaving group in the reaction. Triflate of **3**, however, is similarly reactive as **1** in nucleophilic substitution. For example, reaction of **3e** (R = C_6H_5) and **3f** (R = $Si(CH_3)_3$) with sodium methoxide was carried out in methanol at 20 °C to afford 7-alkynyl-6-methoxypteridines (**5**) (R = C_6H_5 and H) in quantitative yields, respectively. Here, trimethylsilyl group which is a protective group of acetylenic hydrogen was cleaved during the reaction.

Thus, conceptually new utility of triflate, although it is the most powerful leaving group in pteridine chemistry, is found, and **1** is confirmed to be a versatile starting material for not only 6- and 7-substituted pteridines but also 6,7-disubstituted pteridines.

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EXPERIMENTAL

Preparation of 3a, a Typical Example: To a solution of 1-hexyne (0.32 g, 4.0 mmol) in THF (15 mL) was added a 1.6 M solution of *n*-butyllithium in hexane (1.5 mL, 2.4 mmol) at –70 °C. After 0.5 h, dry copper(I) iodide (0.40 g, 2.0 mmol) was added, and the mixture was stirred for additional 1 h. To the resulting yellowish brown suspension was added **1** (0.34 g, 1.0 mmol), and allowed to react for 3 h. The mixture was powered into a saturated solution of NH_4Cl, and organic components were extracted with CH_2Cl_2 (30 mL x 3). Solvents were removed *in vacuo*, and the residue was subjected to column chromatography on silica gel eluting with 5:1 (*v*/*v*) mixture of toluene and ethyl acetate. Recrystallization of the crude product from hexane gave pure **3a** (0.3 g, 72%) as colorless needles which satisfied spectroscopic analyses and elemental analysis. Characteristic physical and analytical properties of **3a** – **3f** are shown in Table 1.

Table 1. Physical and Analytical Properties of 3.

product No.	mp/°C	TLC a) R_f	UV b) λ_{max}/nm (log ε)			^{13}C NMR (δ/ppm) c) sp carbons	
3a	93	0.53	361 (4.27)	260 (4.45)		74.6	107.7
3b	50—51	0.56	360 (4.25)	258 (4.44)		74.6	107.8
3c	45—46	0.53	361 (4.25)	261 (4.45)		74.6	107.8
3d	92—93	0.56	362 (4.26)	260 (4.43)		74.5	107.8
3e	191	0.50	376 (3.99)	322 (3.63)	245 (4.05)	82.5	103.8
3f	144—145	0.58	363 (4.27)	61 (4.47)		96.8	113.6

a) Plate: SiO_2; Eluant: 5:1 toluene/ethyl acetate (*v*/*v*). b) In methanol. c) In $CDCl_3$.

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