Journal of Organometallic Chemistry, 342 (1988) 1–7
Elsevier Sequoia S.A., Lausanne – Printed in The Netherlands

Synthesis of silyl and stannyl pyrimidines *

Cyril Párkányi,

Department of Chemistry, The University of Texas at El Paso, El Paso, TX 79968-0513 (U.S.A.)

Nam Sook Cho and Geon Seek Yoo

Department of Chemistry, Chungnam National University, Dae Jeon 300-31 (Korea)

(Received July 29th, 1987)

Abstract

2,4-Dimethoxy- and 2,4-dibenzyloxy-5-lithiopyrimidines, obtained from the corresponding substituted 5-bromopyrimidines, react with trimethylsilyl chloride or trimethylstannyl chloride to give the appropriate 5-trimethylsilyl or 5-trimethylstannyl derivatives. The following compounds were synthesized by this reaction sequence: 2,4-dimethoxy-5-trimethylsilylpyrimidine (**2**), 2,4-dibenzyloxy-5-trimethylsilylpyrimidine (**3**), 2,4-dimethoxy-5-trimethylstannylpyrimidine (**4**), and 2,4-dibenzyloxy-5-trimethylstannylpyrimidine (**5**). Similarly, 6-chloro-2,4-dimethoxypyrimidine was converted into the 5-lithio derivative which subsequently gave 6-chloro-2,4-dimethoxy-5-trimethylsilylpyrimidine (**6**) and 6-chloro-2,4-dimethoxy-5-trimethylstannylpyrimidine (**7**). In a new modified synthesis of 5-trimethylsilyluracil (**1**), 2,4-dibenzyloxy-5-trimethylsilylpyrimidine (**3**) was smoothly converted into **1** by reaction with trimethylsilyl iodide.

Introduction

As a continuation of our studies of biologically active pyrimidines and purines and their analogs [1–8], we have turned our attention to organometallic pyrimidine derivatives. We now wish to report the synthesis of several silicon- and tin-containing pyrimidines with potential biological activity.

The use of the trimethylsilyl and trimethylstannyl moieties in the synthesis of organosilicon and organotin derivatives is favored by the easy availability of

* Presented, in part, at the 42nd Southwest Regional Meeting of the American Chemical Society, Houston, TX, November 19–21, 1986; and at the 193rd National Meeting of the American Chemical Society, Denver, CO, April 5–10, 1987.

0022-328X/88/$03.50

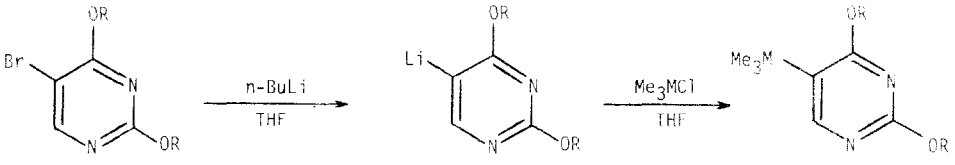
trimethylsilyl chloride and trimethylstannyl chloride, respectively, and by the relative compactness of the trimethylsilyl group [9–11]. A number of syntheses of silyl and stannyl derivatives of various heterocycles have been described in the literature in the last twenty years, in connection with the synthetic potential of these two types of compounds (trimethylsilyl and trimethylstannyl as the leaving groups) [11–13] and their potential biological activity.

Among the systems with one heteroatom, trimethylsilyl and/or trimethylstannyl derivatives of furan, thiophene, and pyridine are known, with the above groups bonded to the ring atoms [12–27]. Several silylated and stannylated five-membered ring heterocycles with two or more heteroatoms, such as the isoxazoles, pyrazoles, and 1,2,3-triazoles, and the derivatives of benzothiazole have been prepared as well [21,28–31]. Although a number of silyl and stannyl pyrimidines have been described [21,32–44], most of these compounds contain silicon bonded to an oxygen atom or a nitrogen atom in the side chain (e.g., the trimethylsilyloxy substituent). Several of the above papers are devoted to the synthesis of nucleoside analogs and to the potential biological activity of the synthesized derivatives [33,37,44]. Among the known compounds with a carbon–silicon or a carbon–tin bond, 5-trimethylsilyluracil (**1**) [39,41], 2,4-dimethoxy-5-trimethylsilylpyrimidine (**2**) [39], 2,4-dibenzyloxy-5-trimethylsilylpyrimidine (**3**) [39], and 5-trimethylstannylpyrimidine [21] can be mentioned as examples.

In the present contribution, we wish to report a modified synthesis of 5-trimethylsilyluracil (**1**) as well as the synthesis of six other silyl- and stannyl-pyrimidines, viz., 2,4-dimethoxy-5-trimethylsilylpyrimidine (**2**), 2,4-dibenzyloxy-5-trimethylsilylpyrimidine (**3**), 2,4-dimethoxy-5-trimethylstannyl pyrimidine (**4**), 2,4-dibenzyloxy-5-trimethylstannylpyrimidine (**5**), 6-chloro-2,4-dimethoxy-5-trimethylsilylpyrimidine (**6**), and 6-chloro-2,4-dimethoxy-5-trimethylstannylpyrimidine (**7**).

Results and discussion

The formation of the carbon–silicon and carbon–tin bonds can be accomplished by a reaction of a trialkylsilicon or trialkyltin chloride with the appropriate organolithium derivatives of the substrates generated by hydrogen–lithium or halogen–lithium exchange [16,43,45–49]. We have used this procedure to prepare the above-mentioned pyrimidines **2**–**7**, according to the equations presented in Schemes 1 and 2.



8, R = Me
9, R = CH_2Ph

10, R = Me
11, R = CH_2Ph

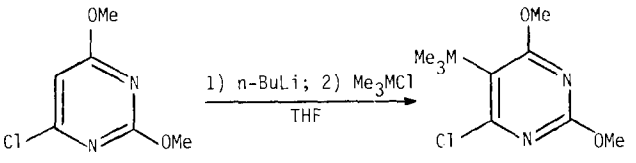
2, R = Me, M = Si
3, R = CH_2Ph, M = Si
4, R = Me, M = Sn
5, R = CH_2Ph, M = Sn

Scheme 1

In the synthesis of the compounds **2**–**5**, 5-bromo-2,4-dimethoxypyrimidine (**8**) [39,50] and 5-bromo-2,4-dibenzyloxypyrimidine (**9**) [39] were converted into the corresponding 5-lithio derivatives **10** and **11** by reaction with n-butyllithium in tetrahydrofuran at −70 °C [39]. This step was successful only when the n-butyllithium solution was precooled to −70 °C before its addition to the reaction mixture. Under these conditions, the color of the solution was pale pink [51], whereas an orange color was observed when n-butyllithium was not precooled [52]. Finally, interaction of **10** and **11** with trimethylsilyl chloride or trimethylstannyl chloride yielded the desired organosilyl and organostannyl derivatives **2**–**5**.

The obtained organosilyl and organostannyl derivatives were purified by chromatography on silica gel, identified on the basis of their elemental analysis and/or ^{1}H NMR spectra, and characterized by their R_F values (thin-layer chromatography). The data (e.g., the melting points) for the two known compounds, **2** and **3**, indicate that we have prepared them in a purer form than previously described [39]. The experimental information available for these compounds is summarized in Table 1.

In a similar fashion, 6-chloro-2,4-dimethoxypyrimidine (**12**) [53,54] was used to obtain 6-chloro-2,4-dimethoxy-5-trimethylsilylpyrimidine (**6**) and 6-chloro-2,4-dimethoxy-5-trimethylstannylpyrimidine (**7**) (Scheme 2 and Table 1).



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6, M = Si

7, M = Sn

Scheme 2

Finally, we wish to report a modified synthesis of 5-trimethylsilyluracil (**1**). Arai and Daves described the synthesis of **1** by a rearrangement of 5-bromo-2,4-bis(trimethylsilyloxy)pyrimidine with n-butyllithium in tetrahydrofuran to the 5-lithium salt of 5-hydroxy-2,4-bis(trimethylsilyloxy)pyrimidine which upon mild hydrolysis with diluted hydrochloric acid at room temperature gave 5-trimethylsilyluracil (**1**) [40]. Zagulyaeva and co-workers [39] obtained 5-trimethylsilyluracil (**1**) in two different ways. In the first case, catalytic hydrogenation of 2,4-dibenzyloxy-5-trimethylsilylpyrimidine (**3**) in ethanol (palladium catalyst, 20 atm) resulted in a removal of the protective benzyloxy groups yielding **1**. Their second approach was analogous to the one used by Arai and Daves.

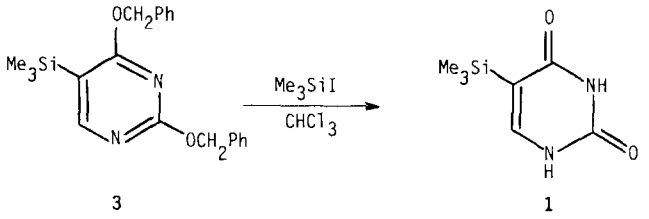
On the one hand, it is known that the removal of the protective alkoxy or aralkoxy substituents in compounds of this type is delicate because the Si–C(sp^2) and Sn–C(sp^2) bonds on heterocyclic rings are very reactive [13,14,28,55]. Thus, e.g., acid hydrolysis and/or catalytic hydrogenation have proven to be difficult in many cases. On the other hand, it has been shown in the literature that trimethylsilyl iodide can be successfully used for the dealkylation of esters, ethers, and phosphate esters [56,59] and that it dealkylates 6-substituted 2,4-dialkoxypyrimidines to uracils in a high yield [60]. We have used trimethylsilyl iodide, with chloroform as the solvent, to convert 2,4-dibenzyloxy-5-trimethylsilylpyrimidine (**3**) into 5-trimethylsilyluracil (**1**) in a 78% yield (Scheme 3). The product obtained by this method was identical in all respects with an authentic sample of 5-trimethylsilyluracil synthesized by using the procedure of Arai and Daves [40].

Table 1

Synthesized 2,4-dialkoxy/diaralkoxy-5-trimethylsilyl/trimethylstannylpyrimidines

Compound	Yield (%)	M.p. (°C)	Mol. formula (mol. wt.)	Analysis (Found (Calcd.) (%))			^{1}H NMR spectrum (60 MHz) δ (ppm) (in $CDCl_3$)
				C	H	N	
1	78	305 (305)[39]	$C_7H_{12}N_2O_2Si$ (184.3)	–	–	–	0.21(9H,s,Me_3Si), 7.19(1H,s,ring), 11.08(2H,broad,2NH) [a,b]
2	40	32–34 (–) [c]	$C_9H_{16}N_2O_2Si$ (212.3)	–	–	–	0.25(9H,s,Me_3Si), 3.96(3H,s,OMe), 3.98(3H,s,OMe), 8.10(1H,s,ring) [b]
3	46	64–65 (48–50)[39]	$C_{21}H_{24}N_2O_2Si$ (364.5)	69.63 (69.20)	6.54 (6.64)	7.66 (7.69)	0.20(9H,s,Me_3Si), 5.39(2H,s,CH_2), 5.41(2H,s,CH_2), 7.36(10H,s,2Ph) 8.25(1H,s,ring)
4	23	28–29	$C_9H_{16}N_2O_2Sn$ (302.9)	–	–	–	0.35(9H,s,Me_3Sn), 3.99(3H,s,OMe), 4.01(3H,s,OMe), 8.25(1H,s,ring)
5	29	59–61	$C_{21}H_{24}N_2O_2Sn$ (455.1)	–	–	–	0.20(9H,s,Me_3Sn), 5.40(4H,s + s,CH_2), [d] 7.35(10H,broad, 2Ph), 8.25(1H,s,ring)
6	56	30–31	$C_9H_{15}ClN_2O_2Si$ (246.7) [e]	43.77 (43.82)	6.40 (6.09)	11.29 (11.36)	0.36(9H,s,Me_3Si), 3.95(3H,s,OMe), 3.99(3H,s,OMe)
7	42	55–57	$C_9H_{15}ClN_2O_2Sn$ (337.3)	32.99 (32.05)	4.84 (4.45)	8.61 (8.31)	0.35(9H,s,Me_3Sn), 3.94(3H,s,OMe), 3.98(3H,s,OMe)

[a] Spectrum measured in $(CD_3)_2SO$. [b] Cf. also ref. [39]. [c] Oil, b.p. 120°C/4 mm Hg [39]. [d] Two overlapping singlets. [e] Molecular weight was determined mass-spectrometrically: molecular ion M^+, at m/e 246. Other important ions: m/e 231 $(M-Me)^+$, 201 $(M-3Me)^+$, 174 $(M-3Me-Si)^+$.



3 1

Scheme 3

The ^{1}H NMR spectra for the compounds under study are presented in Table 1 and were used for their positive identification. It can be seen that the spectra are in an excellent agreement with the proposed structures.

Experimental

Melting points were determined by the capillary method on an electrically heated Thomas–Hoover apparatus and are uncorrected. Elemental analyses were carried out on a Perkin–Elmer apparatus, model 240, at the Korea Research Institute of Chemical Technology, Dae Jeon, Korea. The ^{1}H NMR spectra were measured on a 60 MHz Varian EM-360 spectrometer, with tetramethylsilane as the internal reference.

Commercially available starting materials and solvents (purchased mostly from Aldrich Chemical Company, Milwaukee, WI) were used to synthesize the known 5-bromo-2,4-dimethoxypyrimidine (**8**) and 5-bromo-2,4-dibenzyloxypyrimidine (**9**) whose properties agree with those described in the literature [39,50]. 6-Chloro-2,4-dimethoxypyrimidine (**12**) is also available from Aldrich Chemical Co.

General procedure; trimethylsilylation

5-Bromo-2,4-dibenzyloxypyrimidine (**9**, 2.9 g, 7.8 mmol) and dry tetrahydrofuran (50 ml) were placed in a 250 ml three-necked flask equipped with a dropping funnel, a nitrogen inlet, and a low-temperature thermometer and the mixture was cooled to $-70\,^\circ$C (dry ice/acetone). n-Butyllithium in hexane (5.6 ml of 1.55 *M* solution, 8.7 mmol), precooled to $-70\,^\circ$C, was added under nitrogen at a rate at which the temperature did not rise above $-70\,^\circ$C. The reaction mixture was stirred for 10 min and anhydrous trimethylsilyl chloride (1.5 ml, 1.28 g, 11.8 mmol) was added in a single portion. The dry ice/acetone bath was removed after 10 min and the mixture was stirred for more than 2 h until the temperature reached $0\,^\circ$C. Then the reaction mixture was concentrated under reduced pressure at room temperature, the concentrate was dissolved in methylene chloride (50 ml) and washed with brine. The methylene chloride solution was dried over anhydrous magnesium sulfate, filtered, and concentrated on a rotary evaporator. The crude product was crystallized from hot heptane to give 1.31 g of 2,4-dibenzyloxy-5-trimethylsilylpyrimidine (**3**, 46% yield) (cf. Table 1). The experiment was repeated several times. Analytical sample was obtained by thin-layer chromatography on silica gel with chloroform/heptane as the eluent (10 : 3, vol.)

Using the above general procedure with trimethylsilyl chloride or trimethylstannyl chloride, respectively, the following products were obtained from the appropriate starting materials: 2,4-dimethoxy-5-trimethylsilylpyrimidine (**2**), 2,4-dimethoxy-5-trimethylstannylpyrimidine (**4**), 2,4-dimethoxy-5-trimethylstannylpyrimi-

dine (**5**), 6-chloro-2,4-dimethoxy-5-trimethylsilylpyrimidine (**6**), and 6-chloro-2,4-dimethoxy-5-trimethylstannylpyrimidine (**7**). Experimental data on these compounds are summarized in Table 1.

*5-Trimethylsilyluracil (**1**)*

Using a syringe, trimethylsilyl iodide (2.5 ml, 3.52 g, 17.6 mmol) was added under nitrogen to a solution of 2,4-dibenzyloxy-5-trimethylsilylpyrimidine (**3**, 1.8 g, 4.9 mmol) in dry chloroform. The solution was refluxed for 2 h and concentrated under reduced pressure. The residue was dissolved in ethanol (50 ml), and water (50 ml) was added to the solution to precipitate the desired 5-trimethylsilyluracil (**1**) which was then crystallized from ethanol to give 0.7 g of the pure product (78% yield).

Its melting point and other physical constants agreed with those of an authentic sample of 5-trimethylsilyluracil prepared by the method of Arai and Daves [40] from 5-bromo-2,4-bis(trimethylsilyloxy)pyrimidine and a mixed melting point showed no depression (305 °C, dec.); for ^{1}H NMR spectrum, see Table 1.

Acknowledgements

The authors are grateful to the Welch Foundation, Houston, TX (Grant AH-461, C.P.) and to the Korea Science and Engineering Foundation, Seoul, Korea (N.S.C.) for financial support of this work.

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