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# The $PdCl_2/R_3SiH$ System for the Silylation of Nucleosides

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**Abstract:** Convenient syntheses of TIPDS-$Cl_2$ and TBDMS-Br from the corresponding hydrides were obtained by using catalytic $PdCl_2$ and $CCl_4$ or $CH_2Br_2$, respectively. These systems can be successfully applied in tandem procedures for improved silylation of nucleosides. 

*Keywords:* Nucleosides, Silicon halides, Protecting groups, Palladium and compounds

The protection/deprotection of hydroxyl moieties is essential for those who manipulate organic molecules. Since the introduction of silyl ethers as protecting groups in organic synthesis [1,2], a number of methodologies have been developed to accomplish these transformations. In nucleoside chemistry, trisubstituted silicon halides are largely used for synthetic and analytical purposes [3,4]. However, they are not always stable, commercially available, and/or economically accessible. Therefore, there is a constant demand for new approaches in this field.

Siloxane **2** (TIPDS-$Cl_2$) was introduced as a silylating agent for the simultaneous protection of the 3' and 5' hydroxyl groups in nucleosides [5,6] and this step was conveniently included in the strategy for the conversion of ribo- to 2'-deoxyribo-nucleosides [7,8]. However, this reagent is quite expensive. In connection with our findings on the $PdCl_2$-catalyzed reduction of halides [9] and alcohols [10] by $Et_3SiH$, we now report a new synthesis of **2**.[3] The reaction of the corresponding hydride **1** with $CCl_4$ (equimolar amounts) in the presence of catalytic $PdCl_2$ (2 mol%) at 60°C for 2h affords the dichloride in an 85% yield after distillation (eq. 1). The main advantages of this procedure are: (i) the absence of solvent, which is significant from an environmental point of view [11], (ii) the use of $CCl_4$ as an inexpensive halogen source, (iii) the mild reaction conditions.

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[2] Visiting Scientist. Permanent address: Dipartimento Farmaco-Chimico, Università di Messina, Villaggio SS. Annunziata, 98168 Messina, Italy
[3] Siloxane **1** (TIPDS-$H_2$) is approximately three times less expensive than siloxane **2** (TIPDS-$Cl_2$).

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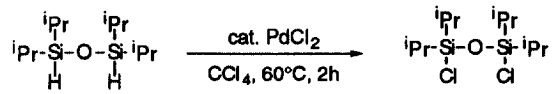
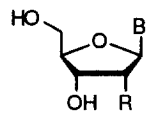


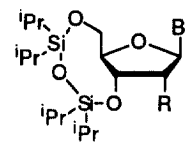

1 2, 85% (1)

Next we investigated the one-pot silylation of nucleosides starting from the silane **1**. The silylations were accomplished by adding a pyridine solution of the substrates to the reaction medium where the compound **2** was formed in the absence of a solvent. The reaction temperatures and times did not differ substantially from the literature, i.e. -35°C to r.t., overnight. The results for the 2'-deoxyribo derivatives **3** and **4** and the corresponding ribo compounds **5** and **6** are reported in Table 1 and are comparable with those reported by using the commercially available TIPDS-$Cl_2$ [7,8].

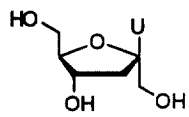
**Chart 1**



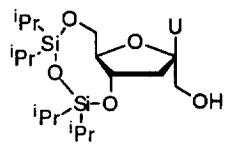
**3**: R = H, B = Uracil
**4**: R = H, B = Adenine
**5**: R = OH, B = Uracil
**6**: R = OH, B = *N*-Bz-Adenine



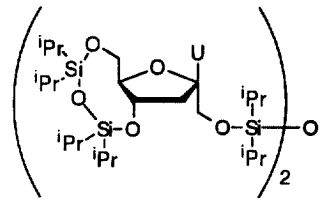
**7**: R = H, B = Uracil
**8**: R = H, B = Adenine
**9**: R = OH, B = Uracil
**10**: R = OH, B = *N*-Bz-Adenine



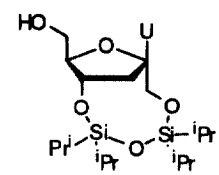
**11**



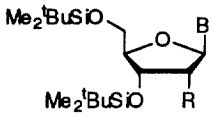
**12**



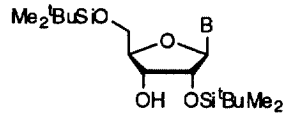
**13**



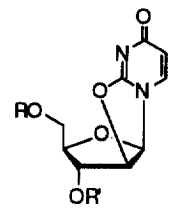
**14**



**15**: R = H, B = Uracil
**16**: R = OH, B = Uracil
**17**: R = OH, B = *N*-Bz-Adenine



**18**: B = Uracil
**19**: B = *N*-Bz-Adenine



**20**: R = R' = H
**21**: R' = H, R = OSi$^t$BuMe$_2$
**22**: R' = R = OSi$^t$BuMe$_2$

Table 1
Silylation of Some nucleosides (cf. Chart 1)

| Substrate[a] | Product | Yield, % | Substrate | Temp./time | Product | Yield,% |
|---|---|---|---|---|---|---|
| **3** | **7** | 80 | **3**[c] | 0°C/2h | **15** | 85 |
| **4** | **8** | 80 | **5**[d] | 0°C/4h | **16+18**[f] | 73 |
| **5** | **9** | 87 | **6**[d] | 25°C/2h | **17+19**[g] | 68 |
| **6** | **10** | 80 | **20**[e] | 25°C/4h | **21** | 80 |
| **11** | **12+13+14**[b] | 85 | **20**[e] | 25°C/4h | **22** | 85 |

[a] TIPDS-$H_2$:$CCl_4$:Nucleoside = 1.2:1.2:1; Conditions: -35°C to r.t./overnight.
[b] **12:13:14** = 38:38:24.
[c] $Me_2{}^tBuSiH$:$CH_2Br_2$:Nucleoside = 1.2:1.2:1.
[d] $Me_2{}^tBuSiH$:$CH_2Br_2$:Nucleoside = 5..2:5.2:1.
[e] $Me_2{}^tBuSiH$:$CH_2Br_2$:Nucleoside = 2.4:2.4:1.
[f] **16:18** = 25:75.
[g] **17:19** = 19:81.

Regarding the case of the psicofuranosyluracil **11**, it was previously reported [12] that its silylation was difficult due to the presence of the two primary hydroxyl groups, and the published procedure resulted in a very low yield of **12**. In our hands, by using both our procedure and that reported, the conversion of nucleoside **11** was almost complete and three silylated products were formed with an 85% overall yield. After work-up, the compounds **12**, **13** and **14** were isolated in the ratio of 38:38:24 and characterized.[4]

The preparation of a variety of silyl halides by using $PdCl_2/R_3SiH$ in the presence of different halogen sources is straightforward and one can access commercially unavailable silicon halides.[5] This was the case of $Me_2{}^tBuSiBr$ (TBDMS-Br) and its application to a tandem procedure without isolation for the silylation of nucleosides. By heating $Me_2{}^tBuSiH$ for 1h at 60°C in the presence of an equimolar amount of $CH_2Br_2$ and catalytic $PdCl_2$ (2 mol%), the silyl bromide was indeed obtained in a 90% yield. The silylations were then accomplished by adding a pyridine solution of the substrates to the reaction mixture. The results are also shown in Table 1. The silylation was generally accomplished in a good to high yield after purification [14] thus showing that the silylation occured with little decomposition by this tandem procedure.

It is worth pointing out that the use of TBDMS-Br led to the improvement of the silylation procedure in terms of reactivity and selectivity. The reaction time was shortened

[4] Flash-chromatography by using n-hexane containing increasing amounts of ethyl acetate as eluent afforded the three compounds which have the following characteristics (TLC in ethyl acetate: n-hexane 2:1).
Compound **12** (white foam, $R_f$ = 0.60, 30% yield) with the same spectral characteristic described in literature [12].
Compound **13**, (oil, $R_f$ = 0.90, 30% yield). $^1$HNMR ($CDCl_3$) δ, 0.88 (m, 42H), 2.3 (dd, 1H, J = 10.7, 13.0 Hz), 2.9 (dd, 1H, J = 6.8, 13.0 Hz), 4.0 (m, 6H), 5.7 (d, 1H, J = 8.5 Hz), 7.9 (d, 1H, J=8.5 Hz), 8.9 (broad s, 1H). $^{13}$CNMR ($CDCl_3$) δ, 163.7, 150.4, 141.6, 100.8, 97.0, 85.3, 67.8, 64.9, 60.1, 39.1, 17.5, 17.3, 17.1, 17.0, 16.9, 13.5, 13.3, 13.1, 12.9, 12.8. The presence of a dimer in the TIPDS-$Cl_2$ protection step was first reported in the case of a purine derivative [13].
Compound **14** (oil, $R_f$ = 0.81, 20% yield). $^1$HNMR ($CD_3OD$) δ, 1.03 (m, 28H), 2.4 (dd, 1H, J = 3.2, 14.7 Hz), 2.8 (dd, 1H, J = 6.1, 14.7 Hz), 3.8 (m, 2H), 4.2 (m, 5H), 5.5 (d, 1H, J = 8.3 Hz), 8.1 (d, 1H, J=8.3 Hz). $^{13}$CNMR ($CDCl_3$) δ, 164.0, 150.4, 141.5, 102.6, 99.6, 89.9, 71.2, 65.5, 61.9, 43.1, 17.2, 17.1, 16.9, 13.3, 13.2, 12.9, 12.7. Attempts to influence the composition of the silylated mixture were unsuccessful.
[5] For best results, $CCl_4$ or hexachloroethane, $CH_2Br_2$ and $CH_3I$ were used for chlorides, bromides and iodides respectively [10].

in many cases, thus avoiding overnight treatments which were previously required to improve the yields. Table 1 shows that the reaction of nucleoside **20** with $Me_2{}^tBuSiBr$ can be driven either to the 5' monoprotected (**21**) or to the 3',5' doubly protected derivative (**22**), by varying the amount of silylating agent used. It is also worth mentioning that the silyl bromide does not affect the oxazolidine ring under these circumstances or even upon prolonged heating. Another interesting case is the reaction of nucleoside **5** with TBDMS-Br. Table 1 shows that in the presence of an excess of the silylating agent, the 2',5'-diprotected derivatives of the ribonucleosides **5** and **6** were the major products. There was no trace of the triprotected derivative and there were minor quantities of the separable 3',5'-diprotected product. Analogous results were previously reported by using $Me_2{}^tBuSiCl$ in the presence of nitrate and DABCO/ silver salts [15]. Since the 2',5'-diprotected compound is directly used in nucleotide synthesis, our procedure represents an improvement which can be easily extended to other silicon protecting groups, even for commercially unavailable silyl derivatives.

**General procedure for silylation:** A Wheaton reactor equipped with a Mininert valve was charged with $PdCl_2$ (2 mol%) and the desired silicon hydride. To this stirred suspension an equimolar amount of halogenating agent was added in one portion and the reaction mixture was kept at 60°C. GC analysis of the reaction mixture showed the formation of the silyl halide which was complete within 1-2 h. The reactor was then cooled to the desired temperature and a 0.15M pyridine solution of the nucleoside was added. TLC monitoring showed the progress of the reaction and the work-up followed standard procedures.

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