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Tris(trimethylsilyl)[^{2}H]silane-Triethylborane System Producing The Highly Diastereoselective Deuteration (> 99:1) of 2'-Bromo-2'-Deoxy- and 2'-*O*-Phenoxythiocarbonylribonucleosides at 0°C

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Abstract: Reductive protylation and deuteration reactions using $(Me_3Si)_3SiH$- and $(Me_3Si)_3Si^2H$-Et_3B systems were investigated in view of the differences in bond energy and bond length between the Si-H of $(Me_3Si)_3SiH$ and the Sn-H of Bu_3SnH. Higher diastereoselectivity was obtained in comparison with the reactions using the Bu_3SnH - and Bu_3Sn^2H-Et_3B systems; the $(Me_3Si)_3SiH$ system gave remarkable diastereoselectivity of 98.7% at 0°C, whereas the other system required temperatures below -70°C. © 1997 Elsevier Science Ltd.

The reductive deuteration reaction of 2'-bromo-2'-deoxy-3',5'-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl) (TIPDS) ribonucleosides with a tributyltin deuteride (Bu_3Sn^2H)-triethylborane (Et_3B) system in THF below -70°C has recently been shown to proceed efficiently to give (2'*R*)-2'-deoxy[2'-^{2}H]ribonucleosides with high diastereoselectivity (2'*R*:2'*S* = > 99:1).[1] Similarly, the reductive protylation reaction of 2'-bromo-2'-deoxy-3',5'-*O*-TIPDS-[2'-^{2}H]ribonucleosides with Bu_3SnH-Et_3B below -70°C was found to give the corresponding (2'*S*)-isomers efficiently.[2]

Our research interest has focused on the reaction using tris(trimethylsilyl)[^{2}H]silane [$(Me_3Si)_3Si^2H$] in place of Bu_3Sn^2H, in view of the differences in bond energy[3] and bond length[4] between the Si-H of $(Me_3Si)_3SiH$ and the Sn-H of Bu_3SnH, i.e., 79 kcal/mol and 74 ± 2 kcal/mol, and 1.489 Å and 1.696 Å, respectively. It has been demonstrated that the donating hydrogen atom attached to the silicon atom of $(Me_3Si)_3SiH$ is rather sterically hindered by the three trimethylsilyl groups, as compared to that attached to the tin atom of Bu_3SnH. Alternatively, the releasing point upon donating the hydrogen atom from tris(trimethylsilyl)silane to the 2'-yl radical, resulting from the reaction of the 2'-bromonucleoside derivative with a tris(trimethylsilyl)silyl radical, in the transition state of the former case is likely to be in somewhat closer proximity to the radical than that of the latter case. Therefore, it might be expected that reductive protylation and deuteration reactions, using $(Me_3Si)_3SiH$ and $(Me_3Si)_3Si^2H$, would reflect the steric effect, and yield higher diastereoselectivity in comparison with those using Bu_3SnH and Bu_3Sn^2H.

Based on this expectation, reductive protylation reactions of a 2'-bromodeoxynucleoside derivative using the $(Me_3Si)_3SiH$-Et_3B system and the Bu_3SnH-Et_3B system were performed, by the use of 2'-bromo-2'-deoxy-3',5'-*O*-TIPDS-[2'-^{2}H]uridine[2] (**1**-^{2}H) as a model compound, at a temperature range from -78°C to room temperature (Scheme 1). The results are summarized in Table 1, and show that the $(Me_3Si)_3SiH$-Et_3B system gave significantly higher diastereoselectivity than the Bu_3SnH-Et_3B system, and yielded a 98.7:1.3 mixture of (2'*S*)- (**2**) and (2'*R*)-2'-deoxy-3',5'-*O*-TIPDS-[2'-^{2}H]uridine (**3**), even at 0°C. The excellence of

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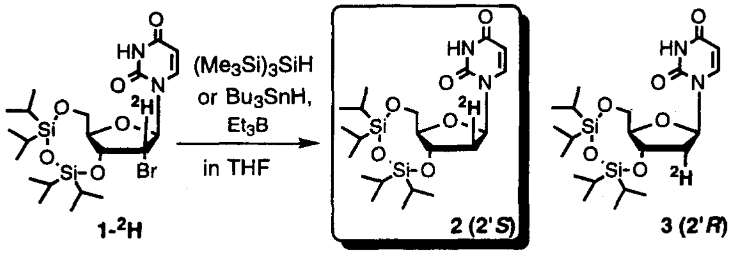
This communication is dedicated to the late Professor Tsujiaki Hata, Chiba Institute of Technology.

the $(Me_3Si)_3SiH$-Et_3B system over the Bu_3SnH-Et_3B system is highlighted in Fig. 1, which is a plot of the d.e. (%) of **2** against the reaction temperature. The high diastereoselectivity of the former reaction is exemplified by that performed at 0°C in Fig. 2. The feasibility of this highly diastereoselective protylation reaction at 0°C will promote its acceptance as a practical procedure for the synthesis of **2** and related compounds.



Scheme 1

Table 1. Effect of Reagents and Temperature on Diastereoselectivity[a]

Entry	Reagent	Temp.(°C)	d.e. (%) of **2**	Yield (%)
1	$(TMS)_3SiH$	-78.5	99.8	88
2		-51.8	98.6	71
3		-24.9	97.4	99
4		0.1	97.4	90
5		10.6	97.0	quant.
6		22.1	94.0	93
7	Bu_3SnH	-78.0	94.0	97
8		-52.7	90.6	78
9		-26.6	87.2	72
10		0.1	83.6	87
11		25.0	81.4	94

[a] The reactions were all performed on a 0.1 mmolar scale. Yields are of the isolated products. The d.e. (%) of **2** are based on the ratios of the (2'*R*)- and (2'*S*)-isomers determined by ^{1}H-NMR at 400 MHz. The temperatures for all entries were the highest observed during the dropwise addition of Et_3B.

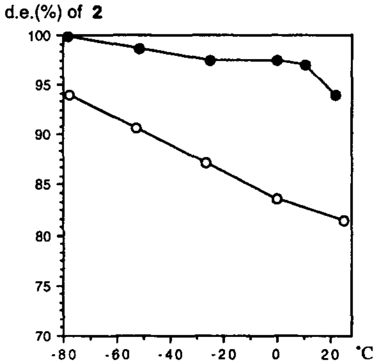


Figure 1. Cross-correlation of entries in Table 1 between the d.e. (%) of **2** and the reaction temperature in reactions conducted with $(Me_3Si)_3SiH$ (●) and Bu_3SnH (○).

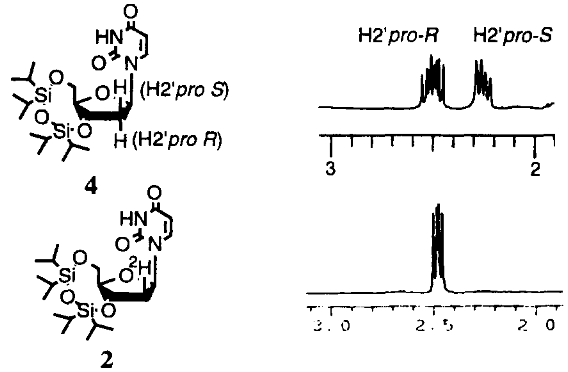
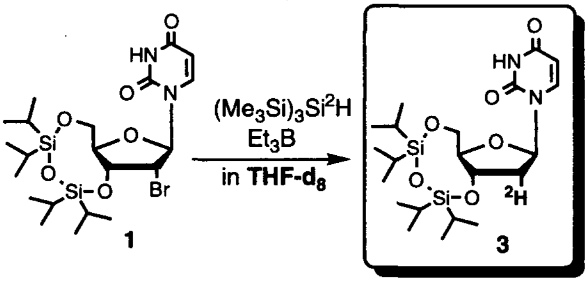


Figure 2. The ^{1}H-NMR spectrum (400 MHz) of **2**, obtained by the reaction conducted with $(Me_3Si)_3SiH$-Et_3B at 0°C, clearly shows the absence of the H-2'pro-*S* proton signal in comparison with that of **4**.

The reductive deuteration reaction of 2'-bromo-2'-deoxy-3',5'-*O*-TIPDS-uridine (**1**) with $(Me_3Si)_3Si^2H$-Et_3B in THF was performed, but it unexpectedly gave 2'-deoxy-3',5'-*O*-TIPDS-uridine (**4**) in addition to **3** (main product) even at -78°C. The hydrogen atom introduced at the 2' position of **4** is easily assumed to originate from the hydrogens at the 2 and 5 positions of THF, on the basis of their susceptibility toward hydrogen abstraction under radical reaction conditions. Based on the aforementioned assumption regarding the differences in bond energy[3] and bond length,[4] alternatively, the deuterio group of the tris(trimethylsilyl)[^{2}H]silane is less susceptible toward deuteron abstraction by the 2'-yl radical arising from **1** than that of the tributyltin deuteride, and thus the hydrogens attached to the 2 and 5 positions of the solvent THF might participate in the reaction as hydrogen atom donors to the extent of the 10% yield of **4**. Therefore, the reaction was performed in THF-d_8 in place of THF under the same conditions, and remarkably gave **3** at reaction temperatures of -78°C, 0°C, and room temperature, which was pure by NMR spectroscopy. The spectra in Fig. 3 clearly show the absence of both the H2' *pro-R* proton signal and the *J* network through the H-1' proton and the H2' *pro-R* proton and the H3' proton and the H2' *pro-R* proton in the ribose ring.



Scheme 2

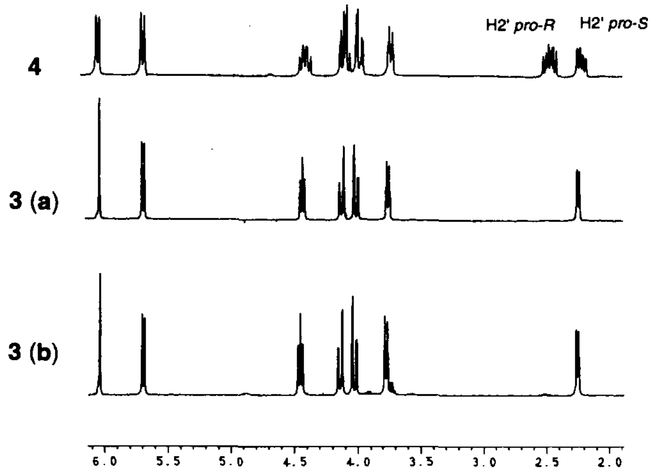


Figure 3. ^{1}H-NMR spectra (400 MHz) of nondeuterated compound **4** (top), and **3**, obtained by the reaction conducted with $(Me_3Si)_3Si^2H$-Et_3B in THF-d_8 at 0°C (**a**) and at room temperature (**b**).

Moreover, the reaction was performed in 2,2,5,5-tetramethyltetrahydrofuran (TMTHF), hexane, benzene, or toluene. TMTHF was found to be a possible substitute of THF-d_8 (89% yield, 2'*R*:2'*S* = > 99:1 at 0°C and 87% yield, 2'*R*:2'*S* = > 99:1 at room temperature). However, the reaction in hexane gave **3** in poor yields, from 21% to 39%, and those in benzene and toluene gave **3** and **4** (2% in benzene, 10% in toluene) concomitantly, although the total yield of each reaction was 95%.

Lastly, the reaction of 2'-*O*-phenoxythiocarbonyl(PTC)-3',5'-*O*-TIPDS-uridine[5] was performed at 0°C in the same way as above, using the $(Me_3Si)_3Si^2H$-Et_3B system in TMTHF, and also gave **3** (89% yield) as the sole product; the lack of formation of **2** was confirmed by ^{1}H-NMR spectroscopy. Given the feasibility of *O*-PTC protection, the reaction of 2'-*O*-PTC-3',5'-*O*-TIPDS-β-D-ribofuranosylthymine was also performed under the same conditions, and yielded the corresponding mixture of (2'*R*)- and (2'*S*)-isomers[1] (81% yield, 2'*R* : 2'*S* = > 99: 1).

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