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Alternative I-D exchange reaction on pyrimidine and purine nuclei mediated by tributyltin hydride using THF-d_8 as a deuterium source

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ABSTRACT

A novel method for the regioselective deuteration of pyrimidine and purine rings mediated by Bu_3SnH using THF-d_8 as a deuterium source on the basis of a radical reaction was developed.

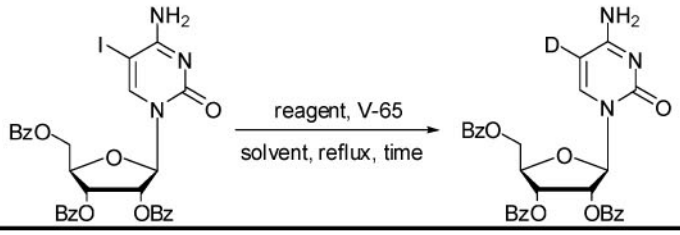
INTRODUCTION

Many organic compounds containing a pyrimidine or purine ring, especially nucleic acid derivatives, have been recognized as biologically important compounds on the basis of their antitumor or virus activities. The development of deuterium-labeling methods of such compounds has been demanded for a wide range of studies involving the metabolism and structural analysis.[1] One of the useful labeling methods so far reported is the radical-mediated iodine–deuterium (I–D) exchange using Bu_3SnD as the D source.[2] During our research related to nucleic acid chemistry, the I–D exchange reaction at the 5-position of 2',3',5'-tri-*O*-benzoyl-5-iodocytidine using Bu_3SnD (98 atm % D) and 2,2'-azobis(2,4-dimethylvaleronitrile) (V-65) was found to proceed with low D incorporation in THF (4% D efficiency, Table 1, entry 1), EtOAc (13% D efficiency), acetone (6% D efficiency), MeOH (22% D efficiency) as a solvent, EtOH (11% D efficiency), or MeCN (19% D efficiency). However, nearly quantitative incorporation (99% D efficiency) was achieved when using THF-d_8 as the solvent (entry 2). It is noteworthy that the efficient D incorporation was also achieved by the use of Bu_3SnH instead of Bu_3SnD (96% D efficiency, entry 3). These results indicate that THF-d_8 plays a crucial role in the present deuteration.[3]

RESULTS AND DISCUSSION

A variety of deuterated solvents were examined as the D source for the D incorporation into the cytidine derivative. As shown in Table 2, the most preferable solvent to achieve a high D content was THF-d_8.[4] Deuterated methanol (CD_3OD) and ethanol (CH_3CD_2OH) gave higher D contents of 92% and 79%, respectively (entries 3 and 6), compared to the deuterated methanol and ethanols possessing different labeling patterns such as CH_3OD, CD_3CH_2OH and CH_3CH_2OD (entries 4, 5 and 7). It appears that the deuteriums on the carbons adjacent to the oxygen of solvents are quite important for the efficient deuteration. When the reaction was carried out in $CD_3CO_2C_2D_5$, a

Table 1 Reaction Using Bu_3SnD or Bu_3SnH in THF or THF-d_8

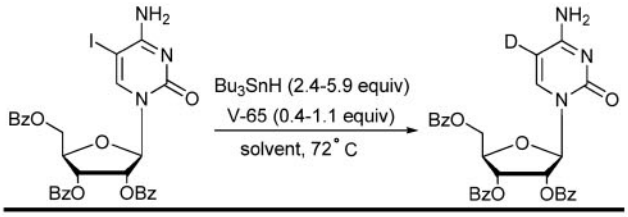


Entry	Substrate (mg)	Reagent (equiv)	V-65 (equiv)	Solvent (mL)	Time (h)	D content[a] (%)	Yield[b] (%)
1	100	Bu_3SnD (1.7)	0.3	THF (2)	4	4	68
2	20	Bu_3SnD (1.2)	0.2	THF-d_8 (2)	1	99	64
3	20	Bu_3SnH (2.4)	0.4	THF-d_8 (2)	2.5	96	42

[a] Determined by ^1H NMR spectroscopy in DMSO-d_6

[b] Isolated yield

Table 2 D Content on Using Various Solvents



Entry	Solvent (100 v/w)[a]	D content (%)[b]
1	THF-d_8	97
2	acetone-d_6	59
3	CD_3OD	92
4	CH_3OD	33
5	CD_3CH_2OH	7
6	CH_3CD_2OH	79
7	EtOD	32
8	CD_3CN	22
9	EtOAc-d_8	59
10	THF-THF-d_8, 1:1[c]	9

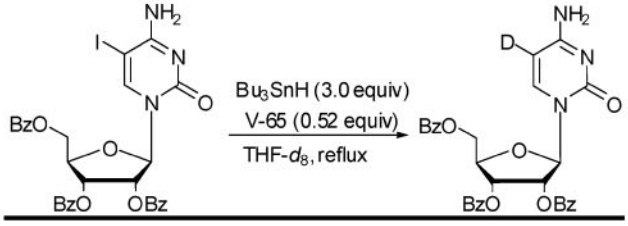
[a] The solvent (mL) use is expressed as the ratio based on the weight (g) of 2', 3', 5'-tri-*O*-benzoyl-5-iodocytidine

[b] Determined by ^{1}H NMR spectroscopy in DMSO-d_6 and D_2O

[c] The ratio of volume to volume

moderate D incorporation was achieved (Table 2, entry 9), while a low D efficiency was obtained in CD_3CN (entry 8). The mixed solvent of THF-d_8 and THF gave a negligible result (only 9% efficiency, entry 10), indicating that a hydrogen transfer from THF more smoothly took place than a deuterium transfer from THF-d_8 on the basis of the deuterium isotope effect. We also found that decreasing the use of THF-d_8 led to lower D contents (Table 3).

Table 3 Effect of Solvent Volume on the D Content



Entry	Use of THF-d_8 (v/w)[a]	D content (%)[b]
1	100	97
2	40	80
3	20	78

[a] The use of THF-d_8 (mL) is expressed as the ratio based on the weight (g) of 2',3',5'-tri-*O*-benzoyl-5-iodocytidine

[b] Determined by ^{1}H NMR spectroscopy in DMSO-d_6 and D_2O

The deuteration of 2',3',5'-tri-*O*-benzoyl-5-iodouridine, 3',5'-di-*O*-*tert*-butyldimethylsilyl-2'-deoxy-5-iodouridine, and 2',3',5'-tri-*O*-*tert*-butyldimethylsilyl-8-iodoadenosine also provided regioselectively deuterated products in high D efficiencies (90–92%). The present I–D exchange method is applicable to the deuteration of both the pyrimidine and purine nucleosides (Figure 1).

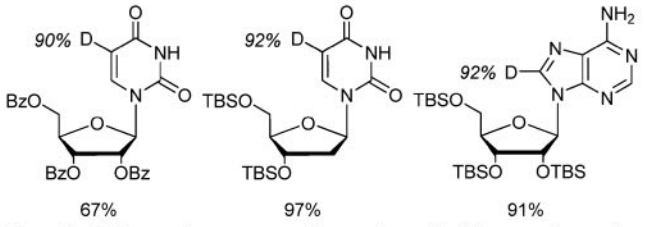


Fig. 1 I–D exchange reaction of pyrimidine and purine nucleosides. The italic numbers indicate the deuterium efficiency.

CONCLUSION

We have developed a new regioselective introduction method of a deuterium atom into pyrimidine and purine nuclei using THF-d_8 as the D source and Bu_3SnH (not necessary to use Bu_3SnD) as a radical mediator.

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