SYNTHESIS OF N^6,2',3',5'-TETRABENZOYL-β-D-ADENOSINE CATALYZED BY METAL IODIDES

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Abstract —— *N*-Glycosylation of N^6-benzoyl-N^6,N^9-bis(trimethylsilyl)adenine with methyl 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl carbonate was effectively promoted by several metal iodides and a desired coupling product, N^6, 2', 3', 5'-tetrabenzoyl-β-D-adenosine (**3**), was obtained in high yield when SbI_3 or TeI_4 was used as a catalyst. In the case of using SnI_2 as a catalyst, nearly equal amounts of **3** and 2', 3', 5'-tribenzoyl-β-D-adenosine (**4**), a N^6-debenzoylated product of **3**, were produced in acetonitrile whereas **3** was obtained as a major product in other nitrile solvents.

It is well known that natural and synthetic adenosine derivatives show various biological activities.[1] Syntheses of their analogs have been studied in order to apply these compounds to therapies and the methodologies for their syntheses, at the same time, have been developed for the past thirty years. Among them, coupling reactions between trimethylsilylated adenine derivatives and protected 1-*O*-acetyl sugars using Lewis acids such as TMSOTf and $SnCl_4$ are frequently employed for their syntheses.[2,3] Recently, we have reported that several β-D-ribofuranosides were synthesized in high yields from methyl 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl carbonate (**1**) and trimethylsilylated nucleoside bases by using a catalytic amount of $SnCl_2$, a weak Lewis acid.[4] In the case of the *N*-glycosylation of N^6-

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benzoyl-N^6,N^9-bis(trimethylsilyl)adenine (**2**) with **1**, however, the reaction was carried out under relatively severe conditions (refluxing in propionitrile by using 50 mol% of $SnCl_2$) and two coupling products, N^6, 2', 3', 5'-tetrabenzoyl-β-D-adenosine (**3**) and 2', 3', 5'-tribenzoyl-β-D-adenosine (**4**), a N^6-debenzoylated product of **3**, were produced. It is also known that the coupling reaction between purine moiety and sugar moiety using Lewis acid catalyst often afforded a desired coupling product (9-isomer of purine ring) in low yield due to the formation of by-products, mainly 3- and 7-isomers of purine ring.[5] Thus, to develop an efficient catalyst in the above coupling reaction is still desired for the preparation of purine nucleosides.

In this communication, we would like to describe new and effective catalysts such as SnI_2, SbI_3, and TeI_4 for the synthesis of **3** by the *N*-glycosylation of N^6-benzoyl-N^6,N^9-bis(trimethylsilyl)adenine (**2**) with methyl 2, 3, 5-tri-*O*-benzoyl-β-D-ribofuranosyl carbonate (**1**) under mild conditions.

First, the catalytic effect of four tin(II) halides was examined by taking a *N*-glycosylation of **2** with **1**, which is used as a glycosyl donor for *O*- and *N*-glycosylations,[6] in refluxing acetonitrile as a model reaction (Table 1). The reactivity sequence of tin(II) halides was found to be in the following order, I > Br > Cl >> F, when 20 mol% of the catalysts were used (Entries 1, 2, 4, 6). In the case of using 50 mol% of $SnCl_2$, the coupling products (**3** and **4**) were obtained in moderate yields (Entry 3). In contrast, the above two coupling products were obtained in 87% and 91% yields, respectively, when 50 mol% of $SnBr_2$ or 30 mol% of SnI_2 was used (Entries 5, 7). Also, SnI_4 proved to be more effective catalyst compared with $SnCl_4$ in the above coupling reaction (Entries 8, 9). The results indicate that SnI_2 is the most effective among tin(II) halides examined.

Next, several metal halides were screened in order to find an effective catalyst other than SnI_2 (Table 2); in analogy with $SnCl_2$, the yields of coupling products were very low when 20 mol% of metal chloride such as $SbCl_3$, $TeCl_4$ or $GeCl_4$ was used (Entries 1, 2, 3). On the other hand, the coupling products were obtained in moderate yields in the case of using 20 mol% of BiI_3, which was used as an effective catalyst for aldol and Michael reactions (Entry 4).[7] Moreover, **3** was obtained in 82% yield along with a slight amount of **4** when 20 mol% of SbI_3 was used (Entry 5). It is noteworthy that **3** was obtained in 93% yield without accompanying the formation of **4** when 20 mol% of TeI_4 was used (Entry 6). In the case of using 20 mol% of TMSOTf or TMSI, which was frequently employed in the syntheses of nucleoside analogs,[2,8] **3** was obtained under the same conditions in 82% and

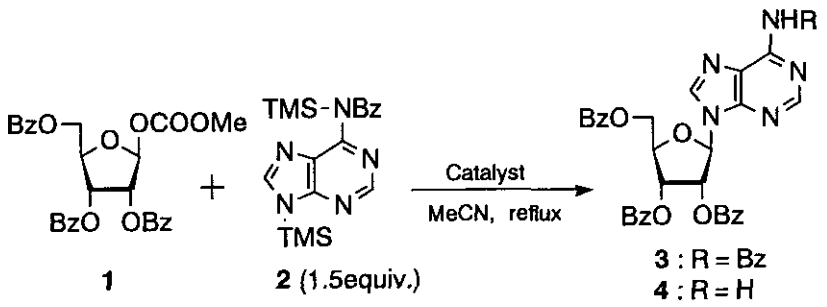


Table 1. *N*-Glycosylation of **2** with **1** Catalyzed by Tin Halides

Entry	Catalyst (mol%)	Time / h	Yield / %		
			3	**4**	Total
1	SnF_2 (20)	16	-	-	NR
2	$SnCl_2$ (20)	10	3	3	6
3	$SnCl_2$ (50)	18	19	39	58
4	$SnBr_2$ (20)	8	39	18	57
5	$SnBr_2$ (50)	8	43	44	87
6	SnI_2 (20)	8	46	28	74
7	SnI_2 (30)	8	49	42	91
8	$SnCl_4$ (20)	10	4	3	7
9	SnI_4 (20)	8	19	52	71

Table 2. *N*-Glycosylation of **2** with **1** Catalyzed by Metal Salts

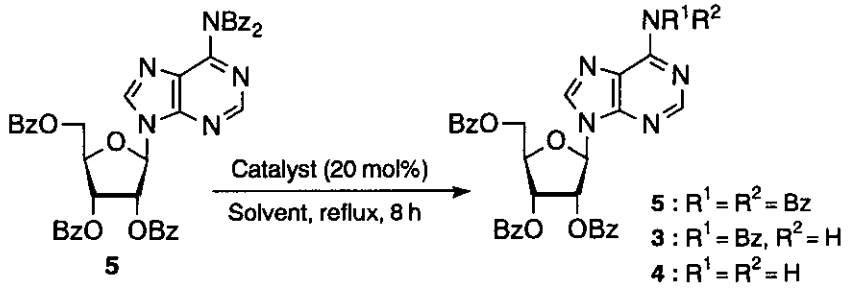
Entry	Catalyst (mol%)	Time / h	Yield / %		
			3	**4**	Total
1	$SbCl_3$ (20)	16	4	3	7
2	$TeCl_4$ (20)	16	12	-	12
3	$GeCl_4$ (20)	10	4	2	6
4	BiI_3 (20)	8	61	2	63
5	SbI_3 (20)	8	82	6	88
6	TeI_4 (20)	8	93	trace	93
7	TMSI (20)	8	44	2	46
8	TMSOTf (20)	8	82	2	84

44% yields along with a slight amount of **4**, respectively (Entries 7, 8). The results indicate that SbI_3 and TeI_4 are also suitable catalysts for the *N*-glycosylation of **2** with **1**. The above metal iodides are easy to handle compared with TMSOTf and TMSI because these metal iodides are relatively moisture-stable and crystalline solids.

Interestingly, the ratio of coupling products (**3** to **4**) in the *N*-glycosylation of **2** with **1** varied according to the catalysts used; that is, when SnI_2 was used, a significant amount of the N^6-debenzoylated product (**4**) was obtained (42% yield) whereas almost no N^6-debenzoylation took place when SbI_3 or TeI_4 was used. Moreover, when a N^6-debenzoylation of N^6, 2', 3', 5'-tetrabenzoyl-β-D-adenosine was tried by using 20 mol% of several metal iodides, complete N^6-debenzoylation took place when SnI_2 was used, in spite of the absence of other nucleophile except the iodide in the reaction system. The N^6-debenzoylation was not observed in the case of using NaI, CuI, TeI_4 or PbI_2, and a small amount of N^6-debenzoylated product was obtained when ZnI_2, BiI_3, SbI_3 or MgI_2 was used. Following experiments were tried in order to study a significant factor of this phenomenon. The N^6-debenzoylation of N^6, N^6, 2', 3', 5'-pentabenzoyl-β-D-adenosine, which had an unstable N^6-benzoyl group,[9] was tried under several conditions (see Table 3). It is clear that SnI_2 possesses high potency toward the N^6-debenzoylation because mono- and di-debenzoylated products were obtained in 31% and 43% yields, respectively (Entry 1). When 1, 2-dichloroethane was used as a solvent, the amount of the N^6-debenzoylated products decreased to a great extent (Entry 2). This suggests that a participation of acetonitrile also plays an important role on the N^6-debenzoylation. The effect of several counter anions of tin(II) is shown in Entries 3-6. The N^6-debenzoylated products were obtained in every case when tin(II) salts were used and the amounts of the N^6-debenzoylated products were influenced by the kind of the counter anions of tin(II) salts.

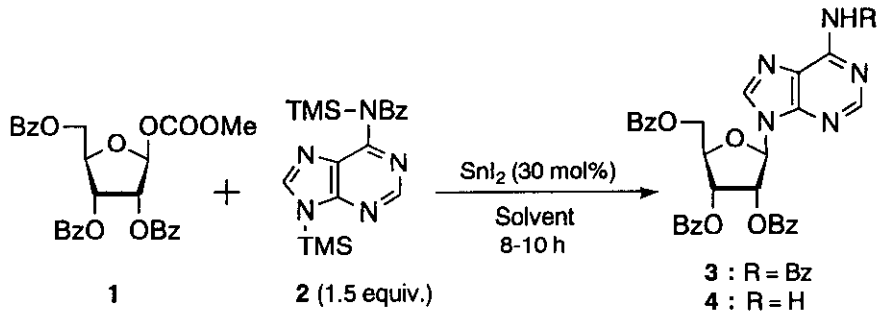
In spite of high efficacies of nucleoside analogs *in vitro*, it is often difficult to use them for therapies because of such disadvantages as low water solubility, low lipophilicity or low stability in human blood. Many derivatives were synthesized in order to improve their properties, and acylation of amino group in nucleoside base moiety sometimes gave successful results. Actually, N^4-behenoyl derivative of 1-β-D-arabinofuranosylcytosine (ara-C) is used in the therapy for leukemia as a prodrug of ara-C, a highly effective antitumor agent.[10]

Table 3. Effect of Tin(II) Salts in N^6-Debenzoylation of N^6,N^6,2',3',5'-Pentabenzoyl-β-D-adenosine (**5**)



Entry	Catalyst	Solvent	Yield / %		
			5	**3**	**4**
1	SnI_2	CH_3CN	17	31	43
2	SnI_2	CH_2ClCH_2Cl	75	18	-
3	SnF_2	CH_3CN	83	9	-
4	$SnCl_2$	CH_3CN	36	26	23
5	$SnBr_2$	CH_3CN	33	33	28
6	$Sn(OTf)_2$	CH_3CN	7	64	13

Table 4. Effect of Nitriles in *N*-Glycosylation of **2** with **1**



Entry	Solvent	Temp. / ℃	Yield / %		
			3	**4**	Total
1	$CH_3(CH_2)_2CN$	105	75	10	85
2	$(CH_3)_2CHCN$	105	80	7	87
3	$(CH_3)_3CCN$	105	81	7	88
4	PhCN	80	84	4	88

Then in order to optimize the reaction conditions in which the *N*-glycosylation proceeds smoothly without accompanying the N^6-debenzoylation, the effect of nitrile solvent was investigated in the presence of 30 mol% of SnI_2 (Table 4). It is noted that the N^6-debenzoylation proceeded slower in isobutyronitrile, pivalonitrile or benzonitrile than in acetonitrile. Though the role of nitrile solvent on the N^6-debenzoylation is still unknown, it became possible to synthesize N^6, 2', 3', 5'-tetrabenzoyl-β-D-adenosine (**3**) as a major product by changing the solvent from acetonitrile to the other nitriles mentioned above even when a catalytic amount of SnI_2 was used.

A typical procedure is described for the reaction of N^6-benzoyl-N^6,N^9-bis(trimethylsilyl)adenine (**2**) with methyl 2, 3, 5-tri-*O*-benzoyl-β-D-ribofuranosyl carbonate (**1**) (Table 2, Entry 6); to a dry acetonitrile suspension (2 ml) of TeI_4 (0.024 mmol) was added **1** (0.120 mmol) in acetonitrile (1.5 ml) and **2** (0.180 mmol) in 1, 2-dichloroethane (0.27 ml) at room temperature under argon atmosphere, and the mixture was refluxed for 8 h. After being cooled down to room temperature, saturated aqueous $NaHCO_3$ was added to the mixture. The resulting suspension was filtered through celite and the filtrate was extracted with dichloromethane. The extract was washed with water and saturated aqueous NaCl, dried over Na_2SO_4, and evaporated. The residue was purified by preparative tlc to afford N^6, 2', 3', 5'-tertabenzoyl-β-D-adenosine (**3**) (93%).

It is noted that, in the presence of 20 mol% of SbI_3 or TeI_4, **3** was synthesized in high yield from **1** and **2** under mild conditions. By using 30 mol% of SnI_2, nearly equal amounts of **3** and **4** were obtained in acetonitrile whereas **3** was obtained as a major product along with a small amount of **4** in other nitrile solvents such as isobutyronitrile, pivalonitrile and benzonitrile. Application to the syntheses of other nucleosides and the clarification of detailed mechanism of N^6-debenzoylation are now in progress.

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