REGIOSELECTIVE PHENYLCARBAMOYLATION OF THE HYDROXYL GROUPS OF PURINE AND PYRIMIDINE RIBONUCLEOSIDES WITH BIS(TRIBUTYLTIN) OXIDE – PHENYL ISOCYANATE[1]

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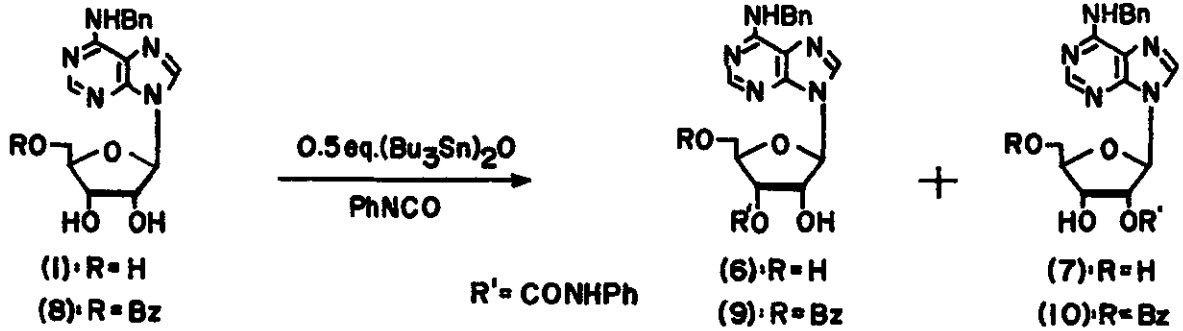
ABSTRACT —— N^6-Benzyladenosine (1) was found to give the corresponding 5'-phenylcarbamate (2)(83% yield) by treating with $(Bu_3Sn)_2O$ in toluene under reflux and then with phenyl isocyanate at room temperature (Procedure A), and to give the corresponding 3'- (73% yield) and 2'-phenylcarbamate (10% yield) by treating with $(Bu_3Sn)_2O$ and PhNCO in toluene – DMF (10:1, v/v) at 0°C (Procedure B). The procedure B was also successful in the partial phenylcarbamoylation of N^6-benzoyladenosine (11), inosine (12) and uridine (13), giving the corresponding 3'-phenylcarbamates (60%, 67%, and 55% yields) and 2'-phenylcarbamates (17%, 31%, and 15% yields), respectively. On the other hand, thymidine (14)(2'-deoxyribonucleoside) afforded the corresponding 5'-phenylcarbamate (93% yield) through the procedure B.

Regioselective 2'-O-deacylation of fully acylated purine and pyrimidine ribonucleosides has successfully been performed with both hydrazine hydrate in acetic acid – pyridine (1:4, v/v)[2] and hydroxyaminium acetate in pyridine[3] in combination with chromatographic separation on a column of silica gel (Wakogel C-300). We were further interested in very facile addition reaction of tin alkoxides, prepared by treating bis(tributyltin) oxide or dibutyltin oxide with an alcohol or its carbonate, to compounds with polar double bond structures; e.g. the reaction of tinalkoxides with isocyanates gives the corresponding carbamates in good yields[4]. As distinct from acetyl and benzoyl groups, the carbamoyl groups are known to be less susceptible to migration even in the cis-diol systems[5]. Therefore, it would be useful for nucleoside chemistry if we could introduce regiose-

lectively the protecting group on the hydroxyl groups of ribonucleosides. The resulting partially carbamoylated ribonucleosides might be versatile synthetic intermediates for derivatizing into useful compounds. We now communicate a novel aspect of regioselective phenylcarbamoylation of some ribonucleosides with bis-(tributyltin) oxide – phenyl isocyanate through two kinds of procedures: i.e., A) The addition reaction of tributyltin alkoxides of nucleosides, prepared by treating with $(Bu_3Sn)_2O$ in toluene under reflux with azeotropic removal of the resulting water, to PhNCO. B) One step treatment of free nucleosides with PhNCO under catalysis with $(Bu_3Sn)_2O$.

In the first place, reaction conditions were scrutinized by use of N^6-benzyladenosine (1). The yields of products were obtained by high performance l.l.c. technique[§]. According to the procedure A, (1)(0.1 mmol) and $(Bu_3Sn)_2O$ (0.05 mmol) were treated in toluene under reflux in a nitrogen atmosphere for 4 h, and the resulting alkoxide solution was then treated with phenyl isocyanate (0.1 mmol) at room temperature for 1 h, to give N^6-benzyl-5'-O-(phenylcarbamoyl)adenosine (2) (83% yield). The reaction on a 10-fold scale afforded (2)(70% isolated yield[†]). On increasing the amount of PhNCO to 0.3 mmol, N^6-benzyl-3',5'-bis- (3)(23% yield), -2',5'-bis- (4)(8% yield), and -2',3',5'-tris-O-(phenylcarbamoyl)adenosine (5)(39% yield) were obtained in addition to (2)(22% yield). Procedure B was performed by treating (1)(0.1 mmol), $(Bu_3Sn)_2O$ (0.05 mmol), and PhNCO (0.2 mmol) together in a solvent at 0°C for 2 h. A striking solvent effect was observed as seen from Entries 1 – 6 in Table 1. In addition to trace amounts of (3) and (4), the corresponding 3'- (6) and 2'-phenylcarbamate (7) were obtained as the main products, and their proportions varied with polarity of the solvent systems used. Toluene – N,N-dimethylformamide (DMF)(10:1, v/v) and toluene – dimethyl sulfoxide (DMSO) (10:1, v/v) brought about the highest regioselectivity with (6) predominating over (7). Incidentally, no (5) was obtained from the reaction described above.

Having obtained excellent regioselectivity in chemical differentiation of 2', 3', and 5' hydroxyl groups of (1), we subsequently attempted to discriminate the 2' and 3' hydroxyl groups of 5'-O-benzoyl-N^6-benzyladenosine (8) in terms of the phenylcarbamoylation reaction. The procedure A proved to be impractical for (8) since a considerable amount of the corresponding 2',3'-bis(phenylcarbamate) was also obtained. In contrast, the procedure B was fruitfully applied to (8), and the results thus obtained as well as the conditions used are summarized in Entries 7 – 10 in Table 1. Among the Entries 7 – 9, the reaction at -78 → -45°C using



(1): R = H
(8): R = Bz

(6): R = H
(9): R = Bz

(7): R = H
(10): R = Bz

TABLE 1. Regioselective Phenylcarbamoylation of N^6-Benzyladenosine Derivatives in the Presence of $(Bu_3Sn)_2O$ [a]

Entry	Substrate	C_6H_5NCO (mol. equiv.)	Solvent	Temp. (°C)	Reaction time (h)	Yield (%) (6) or (9)	Yield (%) (7) or (10)	Recovery (%)
1	(1)	1.8	DMF	0	2	52	46	0
2	(1)	1.8	Toluene – DMF (1:1, v/v)	0	2	55	43	0
3	(1)	2	Toluene – DMF (10:1, v/v)	0	2	73	10	0
4	(1)	2.3	Toluene – DMSO (10:1, v/v)	0	2	76	24	0
5	(1)	2	Acetone – DMF (4:1, v/v)	0	2.5	48	50	0
6	(1)	2	CH_3CN – DMF (7:1, v/v)	0	2	45	51	0
7	(8)	2	Toluene – DMF (4:1, v/v)	Room Temp.	1	25	17	62
8	(8)	2	Toluene – DMF (3:1, v/v)	0	1	47	48	0
9	(8)	Excess	Toluene – DMF (3:1, v/v)	-78 → -48	49	40	60	0
10	(8)	2	Toluene – DMF (10:1, v/v)	0	100	62	34	0

[a] All reactions were performed by use of $(Bu_3Sn)_2O$ (0.5 mol. equiv.) to N^6-benzyladenosine derivatives, and all the yields of the products were obtained through high performance liquid-liquid chromatography (l.l.c.)[5].

excess PhNCO gave the highest but reversed regioselectivity, affording the corresponding 3'- (9)(40% yield) and 2'-phenylcarbamate (10)(60% yield). By reducing the polarity of the solvent system as much as possible (See Entry 10), good regioselectivity, similar to the reactions of (1), was obtained in the formation of (9) and (10) in the yields of 62% and 34%, respectively. Extremely prolonged reaction time was required in this case, (cf. Entry 3); this may reflect the steric effect of the protecting group at the 5' position on phenylcarbamoylation, and the regioselectivity was inferior to that of the reaction of (1). The phenylcarbamoyl group was proved to be not susceptible to migration reaction under the conditions used by treatments of (7) with $(Bu_3Sn)_2O$ (0.5 equiv.) in toluene – DMF (9:1, v/v), and of 5'-O-benzoyl-N^6-benzyl-2',3'-bis(phenylcarbamoyl)adenosine with (8) (1 equiv.) in the presence of $(Bu_3Sn)_2O$ (1 equiv.). The phenylcarbamoyl protecting group of the products was completely removed by treament with either $LiAlH_4$ (2 mol. equiv.) in DMF under reflux for 1 h, with dilute sodium methoxide in methanol under reflux for 3 h, or with 1M sodium methoxide in methanol at room temperature overnight.

On the basis of the above results, we further performed partial phenylcarbamoylation of N^6-benzoyladenosine (11), inosine (12), uridine (13), and thymidine (14). The procedure A was unexpectedly infeasible for these nucleosides. However, the procedure B was successfully applied to (11), (12), and (13), giving the corresponding 3'-phenylcarbamates (60%, 67%, and 55% yields) and 2'-phenylcarbamates (17%, 31%, and 15% yields), respectively. Contrary to these results, 2'-deoxyribonucleoside (14) exclusively gave the corresponding 5'-phenylcarbamate (93% yield).

The procedures A and B were proved to bring about good regioselectivity in the formation of the partially protected ribonucleosides, although a detailed investigation should be required prior to discussing the chemical behavior of the tin species from the mechanistic standpoint. Therefore, the procedures are now being extended to the other nucleosides as well as to C-nucleosides. Moreover, chemical derivatization of the resulting ribonucleoside phenylcarbamates to various useful compounds and the application of the procedure to a variety of glycosyl compounds are now in progress.

† Satisfactory elemental analyses and ^{1}H n.m.r. spectra were obtained with respect to all the compounds described herein.

§ High performance l.l.c. was performed with a Varian LC-9520 apparatus [column of MicroPak Si-5 (30 cm x 4 mm); mobile phase hexane (solvent A) and 40% isopropyl alcohol in dichloromethane (solvent B); detection by u.v. at 270 nm (Variscan apparatus)].

1. Part 5 of the series: Partial Protection of Carbohydrate Derivatives. For Part 4: See ref. 3.

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