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FACILE CONVERSION OF N^6-BENZOYLADENOSINES INTO 5'-CHLORO-5'-DEOXY-8-HYDROXYADENOSINES BY A REACTION WITH CUPRIC CHLORIDE: A PROMINENT SUBSTITUENT EFFECT OF THE N^6-BENZOYL GROUP

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Facile conversion of N^6-benzoyl-2',3'-*O*-isopropylideneadenosine (**1**) into N^6-benzoyl-5'-chloro-5'-deoxy-8-hydroxy-2',3'-*O*-isopropylideneadenosine (**3**) by a reaction with cupric chloride in acetonitrile provides a new method for the chemical modification of adenosines. This reflects the prominent substitutent effect of N^6-benzoyl group on the chemical reactivity of adenosines.

KEYWORDS adenosine derivative; 5'-*O*,8-cycloadenosine; oxidative cyclization; cupric chloride; imino-ether bond cleavage; 5'-chloro-8-hydoxyadenosine; N^6-substituent effect

In our research to develop methods for the chemical modification of adenosines,[1,2,3,4,5] the metal ion-catalyzed reactions of the adenosines have been examined as an intriguing target from the biochemical viewpoint.[6] This paper describes our discovery of the facile conversion of N^6-benzoyl-2',3'-*O*-isopropylideneadenosine (**1**) into N^6-bezoyl-5'-chloro-5'-deoxy-8-hydroxy-2',3'-*O*-isopropylidineadenosine (**3**) by a reaction with cupric chloride in acetonitrile. This provides a method for a new chemical modification of adenosines and clearly shows the prominent effect of the N^6-benzoyl group on the reactivity of adenosines.

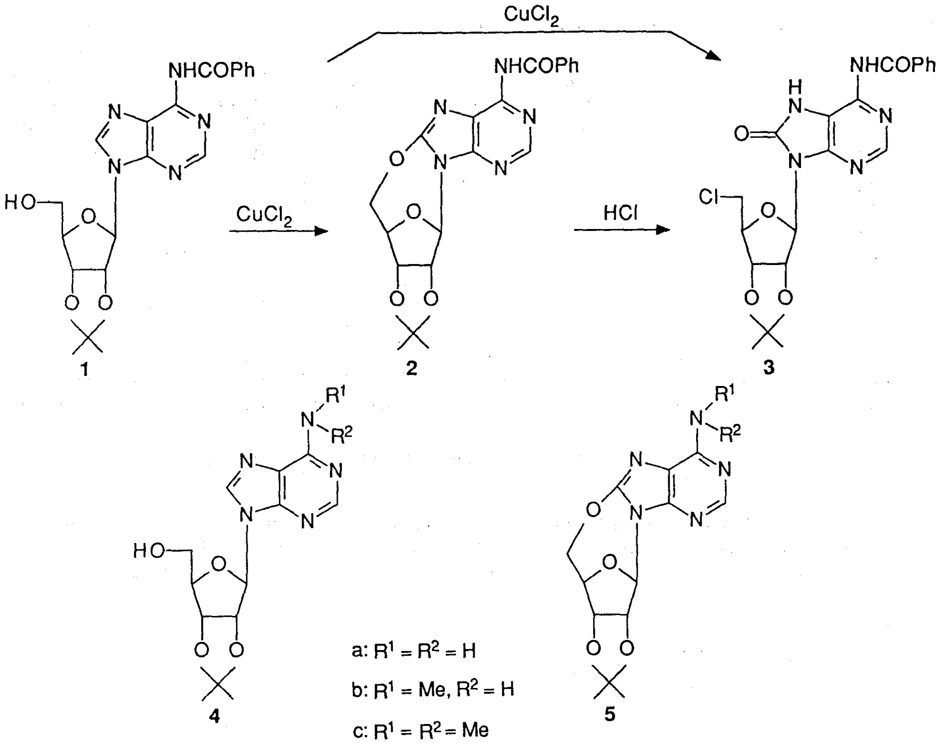

Chart 1

A mixture of **1** [5 mM] and cupric chloride [30 mM] in dry acetonitrile was refluxed under argon for 8 h. After removal of the solvent, the reaction mixture was chromatographed over Florisil (eluent: chloroform-methanol 20:1) to isolate **3** (mp 189-190°C from ethanol) in 90% yield.(7) The stoichiometric study showed that the use of excess cupric chloride is required for the smooth conversion of **1** into **3**. There was no catalytic action of cupric chloride under the aerobic condition. The structure of **3** was fully supported by mass, ^{1}H NMR, UV spectral data and microanalysis.

When the reaction was followed by thin-layer chromatography, a fairly stable intermediate was found. The intermediate was isolated in 35% yield by shortening the reaction time (3 h), together with **3** in 61% yield. The structure of the intermediate was found to be *N*^{6}-benzoyl-5'-*O*,8-cyclo-2',3'-*O*-isopropylideneadenosine (**2**) by spectral comparison with an authentic sample.(2) Analogous treatment of **2** with cupric chloride formed **3**. This was accelerated by adding a small amount of hydrochloric acid to the reaction medium. The above facts clearly show that the formation of **3** occurs *via* the initial oxidative cyclization of **1** to **2** by cupric ion followed by cleavage of the imino-ether bond of **2** by hydrochloric acid in the reaction medium as shown in Chart 1.

Recent works(3,4,5) from our laboratory have demonstrated the new type of the cyclization of 2',3'-*O*-isopropylideneadenosines by oxidation using lead tetraacetate(3) and *N*-bromosuccinimide(5) and photochemical oxidation in the presence of an electron acceptor.(4) The present oxidative cyclization of adenosines promoted by biologically important cupric ions(6) is of mechanistic interest. Cleavage of the imino-ether bond in 5'-*O*,8-cycloadenosines to give 5'-substituted 5'-deoxy-8-hydroxyadenosines by various agents under appropriate conditions has been well demonstrated.(8)

It should be noted that the present conversion easily occurs only when the *N*^{6}-benzoyladenosine (**1**) is the reactant, i.e. under analogous conditions, adenosine (**4a**), *N*^{6}-methyladenosine (**4b**) and *N*^{6},*N*^{6}-dimethyladenosine (**4c**)(9) gave with comparative difficulty the corresponding 5'-*O*,8-cycloadenosines (**5a**), (**5b**),

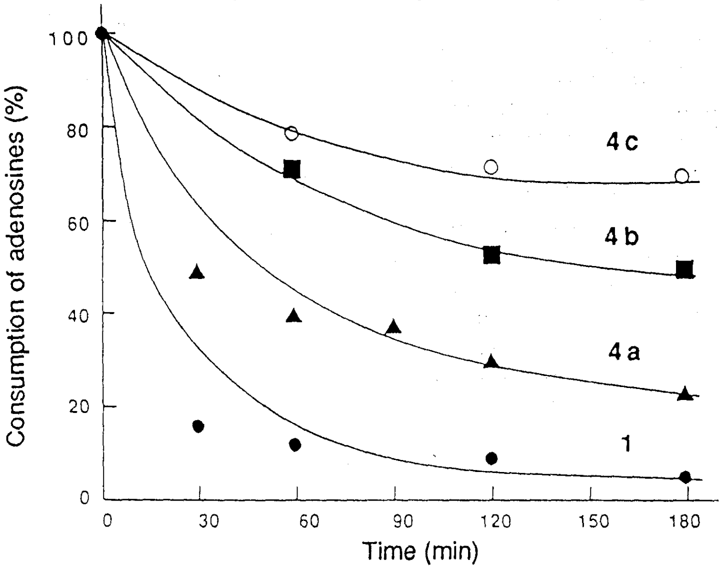

Fig. 1. Consumption of Adenosines, **1** and **4a-c**, in the Reaction with Cupric Chloride as a Function of Reaction Time
Reaction conditions: a mixture of adenosines, **1** and **4a-c**, [5 mM] and $CuCl_2$ [30 mM] in dry MeCN was refluxed under Ar for 3 h.

and (**5c**), without accompanying isolable amounts of 5'-chloro-5'-deoxy-8-hydroxyadenosines. Figure 1 shows the consumption of **1**, **4a**, **4b**, and **4c** in the reaction with cupric chloride as a function of reaction time. It indicates roughly that the ease of the oxidative cyclizations is in the order of **1** > **4a** > **4b** > **4c**. An independent experiment showed that the imino-ether bond of **5a** was almost inert against cupric chloride under the same reaction conditions. Thus, the prominent substituent effect of the N^6-benzoyl group on the present conversion is unequivocal.

It has been proved that the N^6-acyl group in the adenosines relatively increases the nucleophilicity of the imidazole ring nitrogen (N^7), e.g. contrary to the adenosines, protonation and alkylation of N^6-acyladenosines preferentially occurs at the N^7-position rather than the N^1-position.[1)]

In agreement with previous observations, the accelerative effect of N^6-benzoyl group on the present conversion may be explained in terms of preferable coordination of cupric ions at the N^7-position of **1** for the oxidative cyclization (intramolecular oxidative nucleophilic substitution) and by protonation at the N^7-position of **2** essential for the imino-ether bond cleavage.

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5) Y. Maki, M. Sako, T. Saito, and K. Hirota, *Heterocycles*, **27**, 347 (1988).
6) W. Saenger, in '*Principles of Nucleic Acid Structure*,' Springer-Verlag, New York, 1984, ch. 8, p 201.
7) Isopropylidene protection of adenosines and using acetonitrile as a solvent were pre-requisite for the smooth conversion of **1** to **3**. It is known that cupric ion is a weak oxidant in water but relatively strong in acetonitrile (E^0= 1.20 V). Among the cupric salts examined, cupric chloride gave the most satisfactory result for this type of conversion. Some other metal salts may be applicable in place of cupric salts.
8) M. Ikehara, *Acc. Chem. Res.*, **2**, 47 (1969); M. Ikehara and S. Uesugi, *Chem. Pharm. Bull.*, **17**, 348 (1969).
9) The formation of demethylated products (**4b**) and (**5b**) was also observed.

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