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Synthesis of a New Class of 5′-Functionalized Adenosines Using a Rh(II)-Catalyzed 1,3-Dipolar Cycloaddition

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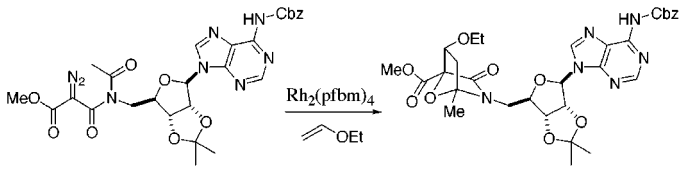
ABSTRACT



Chemically protected adenosine was functionalized at the 5′ position to generate novel dipolarophiles and mesoionic dipoles. These species were found to undergo facile 1,3-dipolar cycloaddition to afford a new series of adenosine derivatives that contain a point of diversification at the 5′ position of adenosine.

Nucleotide-utilizing enzymes such as transferases and synthases have long been recognized as playing a central role in metabolism.[1] More recently, the role of kinases and phosphatases in signal transduction has also been recognized.[2] In response to this finding, small-molecule analogues of both adenosine triphosphate (ATP) and guanosine triphosphate (GTP) have been developed. While small-molecule GTP mimicry remains a mostly underdeveloped area, in many cases ATP analogues have shown high affinity and inhibitory activity.[3]

Many of the traditional ATP-mimetic agents target the hydrophobic subsite of the purine nucleotide pocket, a site that is characterized by high affinity yet low specificity.[4] In the few known cases where inhibitors do access the phosphate-binding region, a greater specificity is achieved.[5] In an effort to develop a molecular scaffold that will both complement the nature of the phosphate binding site and provide a molecular platform from which diversity can be generated, we have developed a 1,3-dipolar cycloaddition strategy for the construction of a series of adenosine-derivatized bicyclic molecules (**1**−**3**). By building this feature at the 5′ end of the adenosine, we hope to create a structure that can replace the phosphate group of a purine nucleotide,[6] thus providing a chemical diversity scaffold that is anchored by a biologically pertinent molecule. Herein, we report the successful rhodium(II)-catalyzed 1,3-dipolar cycloaddition of adenosine-modified dipoles and dipolarophiles for the

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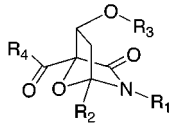
construction of functionalized bicyclic molecules and a computational analysis of their ability to occupy the same relative geometric space as the phosphate portion of ATP.

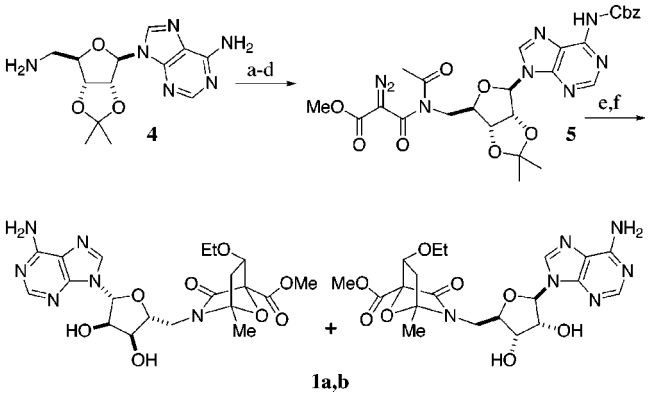


1 R_1=adenosine, R_2=Me, R_3=Et, R_4=OMe
2 R_1=Me, R_2=adenosine, R_3=Et, R_4=OMe
3 R_1=Me, R_2=Me, R_3=adenosine, R_4=NH_2

The 1,3-dipolar cycloaddition reaction is an important transformation for the construction of polyheterocyclic molecules.[7] The concurrent formation of two carbon−carbon bonds, yielding cyclic or even bicyclic heterocycles, makes this reaction a good choice for diversity-oriented synthesis. Examples of the 1,3-dipolar cycloaddition reaction for the construction of nucleoside-like molecules include the synthesis of heterocyclic aromatics such as nucleo-bases,[8] synthesis of nucleoside antibiotic natural products,[9] stereospecific generation of ribose moieties,[10] and functionalization of the 2′, 3′, and 5′ positions of nucleosides.[11] While these thermally initiated cycloadditions have proven useful, the rhodium(II)-mediated cyclization−cycloaddition strategy is subject to side reactivity[12] and its use with molecules of this complexity has remained elusive. We have previously reported a diastereoselective rhodium(II) 1,3-dipolar cycloaddition with a class of mesoionic dipoles known as the isomünchnones.[13] We sought to expand the generality of the process and diversity of potential substrates to include molecules of biological origin. In this example, the generation of nucleoside-derived isomünchnones and dipolarophiles will provide adenosine-derived cycloadducts (**1**−**3**) with the triphosphate of ATP being replaced by a polyoxygenated bicyclic heterocycle.

Synthesis of the dipole precursor for the first adenosine-linked 1,3-dipolar cycloaddition reaction to form scaffold **1** is shown in Scheme 1. Modification to the dipole begins

Scheme 1[a]



[a] (a) $(CH_3CO)_2O$, pyridine, rt, 85%; (b) Rapoport's reagent, CH_2Cl_2, rt, 92%; (c) methyl malonyl chloride, toluene, bubbling N_2, 80 °C, 50%; (d) MsN_3, Et_3N, CH_2Cl_2, rt, 65%; (e) ethyl vinyl ether, $Rh_2(pfbm)_4$, toluene, 60 °C, 70%; (f) TFA/H_2O 10:1, 0 °C; Pd/C, EtOH, NH_4CO_2H, 95%.

with amidation of 5′-aminoadenosine **4**[14] under careful control of both temperature and time, to protect against overacylation of the adenine basic nitrogen. Rapoport's Cbz-transferring reagent,[15] originally developed for deoxy-ribonucleosides, was found to efficiently protect the exocyclic amine. Imidation with methyl malonyl chloride was carried out in refluxing toluene with nitrogen bubbling through the reaction mixture in order to facilitate removal of HCl, which could interfere with reaction progress and prove detrimental to the acid-sensitive nucleoside moiety.[16] The diazotransfer step proceeded smoothly to give α-diazoimide **5** in 25% yield over four steps from amine-nucleoside **4**. Diazoimide **5** was subjected to the tandem Rh(II)-catalyzed carbonyl-ylide formation and cycloaddition with ethyl vinyl ether in toluene at 60 °C. Although the potential Lewis acidity of rhodium(II) perfluorobutyramidate [$Rh_2(pfbm)_4$] raised concerns for possible nucleoside decomposition, the catalyst proved mild enough to allow the reaction at elevated temperatures. While the cycloaddition of ethyl vinyl ether proceeded with high diastereoselectivity, providing only the *endo* cycloaddition product, as previously described,[17] the chiral ribose portion of adenosine provided little facial bias for dipolarophile approach. Deprotection of the purine exocyclic amine and removal of the ribose acetonide furnished a 1:1 mixture of diastereomeric products **1a** and **1b**.

Synthesis of the second adenosine scaffold, **2**, begins with the oxidized adenosine molecule 5′-carboxyadenosine (**6**)

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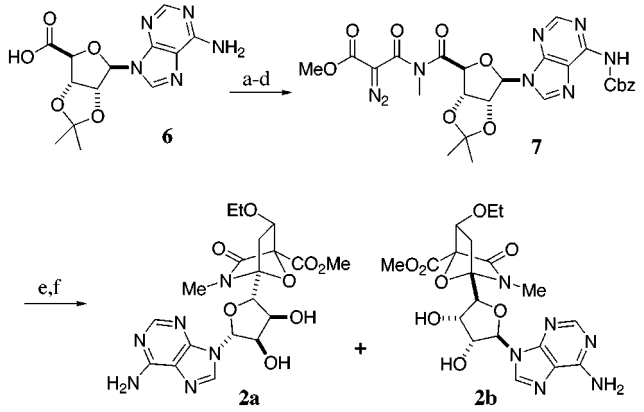
Scheme 2[a]

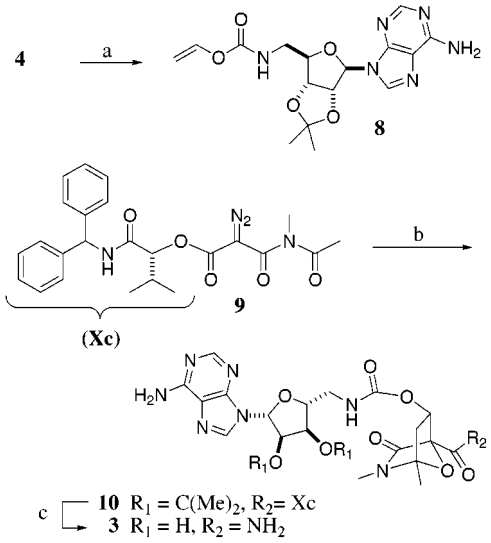


[a] (a) BOP reagent, HOBT, $MeNH_2$, DMF, 84%; (b) Rapoport's reagent, CH_3CN/CH_2Cl_2, rt, 66%; (c) methyl malonyl chloride, toluene, bubbling N_2, 110 °C, 50%; (d) MsN_3, Et_3N, CH_2Cl_2, rt, 86%; (e) ethyl vinyl ether, $Rh_2(pfbm)_4$, chlorobenzene, 130 °C, 37%; (f) TFA/H_2O 10:1, 0 °C; Pd/C, EtOH, NH_4CO_2H, 60−80%.

(Scheme 2). Sufficient quantities of 2′,3′-isopropylidene-adenosine-5′-carboxylic acid (**6**) were obtained by oxidation of acetonide-protected adenosine with a catalytic amount of TEMPO and a stoichiometric amount of bis-acetoxyiodobenzene, as previously reported.[18] Coupling of the carboxyl-adenosine (**6**) with methylamine, followed by Cbz protection, imide formation, and diazotransfer provided α-diazoimide **7**. This dipole precursor behaved similarly in this synthetic sequence as the previous diazoimide, although **7** was not as stable under basic conditions as **5** was. Treatment of **7** with $Rh_2(pfbm)_4$ in the presence of ethyl vinyl ether proved somewhat sluggish, and cycloaddition in this case required higher temperatures and proceeded with a lower yield. This is presumably due to the higher steric congestion near the reactive centers of the dipole. Despite the encumbered nature of the dipole, no diastereofacial selectivity of the dipolarophile was observed, again showing little facial bias from the chiral nucleoside. However, complete *endo* selectivity was observed, as in the cycloaddition of adenosine scaffold **1**. Deprotection of the Cbz and acetonide protecting groups provided the adenosine-linked molecules (**2a** and **2b**) at the second position of the scaffold.

Attaching adenosine to the third position of the scaffold required the use of an adenosine-derived dipolarophile in the cyclization−cycloaddition strategy (Scheme 3). Dipole **8** was synthesized by treating adenosine-amine **4** with vinyl chloroformate. α-Diazoimide **9**[19] was treated with $Rh_2(pfbm)_4$ in toluene at 80 °C to give the facially biased isomünchnone, which underwent subsequent cycloaddition with dipolarophile **8** to give a single product, cycloadduct **10**. This single product arises from an entirely diastereofacial and *endo* selective cycloaddition. It is important to note that the weak nucleophilicity of the free *exo*-amino group on the adenine

Scheme 3[a]



[a] (a) Vinyl chloroformate, Et_3N, CH_2Cl_2, 75%; (b) **8**, $Rh_2(pfbm)_4$, toluene, 80 °C, 69%; (c) NH_3 in methanol; TFA/water 10:1, rt, 52%.

ring does not interfere with the Rh(II) catalyst. In addition, the chiral auxiliary led to high facial selectivity, which was not compromised at the relatively high temperature required for the reaction. Deprotection of the resulting product yielded adenosine scaffold **3** in 27% overall yield from adenosine acid **4**.

With the synthesis of the three modified adenosines in hand, we sought to investigate the spatial potential for this class of adenosine derivatives to replace an enzyme-bound form of ATP. A Monte Carlo conformational search using the MM2* force field, as implemented in Macromodel,[20] was performed on one of the diastereomers (**1**). The nucleoside

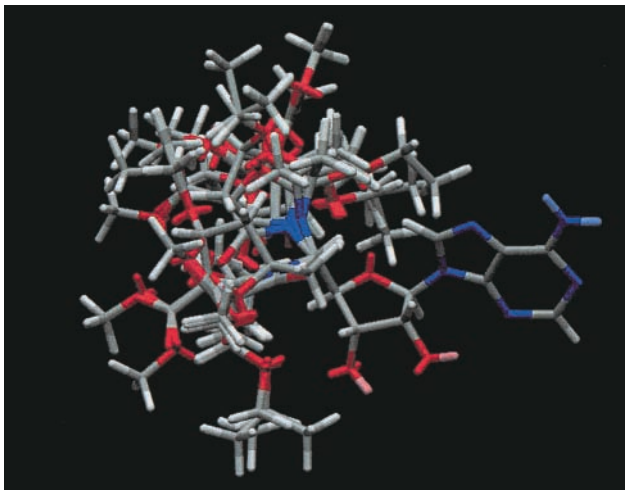


Figure 1. Molecular overlay of the lowest energy conformations of diastereomer (**1**) with the ATP molecule from CDK2, showing the spatial array of the diversity scaffold adjacent to adenosine.

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portion of the molecule was obtained from a crystallographic structure of cyclin dependent kinase 2 (CDK2).[21] The energy minimizations were performed with the GB/SA solvation model for water[22] with the adenosine rigidified. All conformations within 5 kcal/mol of the global minimum conformation were kept, and all other conformers were rejected. Figure 1 shows an atomic overlay of those structures within 3 kcal/mol (MM2 energy) of the global minimum, with the adenosine held constant. It is easy to see that the bicyclic structure is free to sample conformational space adjacent to the adenosine nucleus. To assess the ability of any *individual* isomer to approximate the phosphate backbone, a second conformational analysis was performed, in which the adenosine was also allowed to explore conformational space. Figure 2 shows an overlay of one of these conformers with the enzyme-bound ATP from a cyclin-bound CDK2.[23] Even with a flexible adenosine, the displacement of the scaffold relative to the adenosine can be maintained.

In conclusion, we have shown that the Rh(II)-catalyzed tandem cyclization−cycloaddition sequence can be used in a general and versatile strategy for the synthesis of complex substrates containing adenosine. In addition, we have shown that the synthetic attachment of the diversity core is within the geometric space of the phosphate portion of an enzyme-bound ATP molecule. Evaluation of the biological activity for this new class of molecules and their ability to interact with ATP-binding proteins and ATP-utilizing enzymes is currently underway.

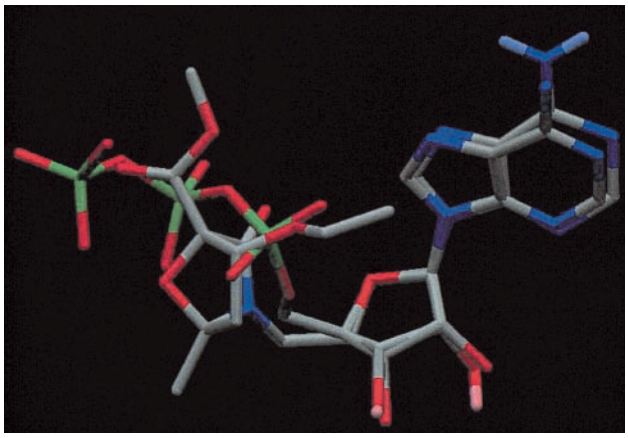

Figure 2. Atomic overlay of a single conformational isomer of diastereomer (**1**) with the bound conformation of ATP in CDK2.

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Supporting Information Available: Experimental details of the synthesis and characterization of compounds **1**−**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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