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6-Isobutyrylaminopurine: A Convenient Building Block for the Synthesis of Carbocyclic Adenosine Analogs

Jinglan Zhou, Kamal Bouhadir, Thomas R. Webb and Philip B. Shevlin*

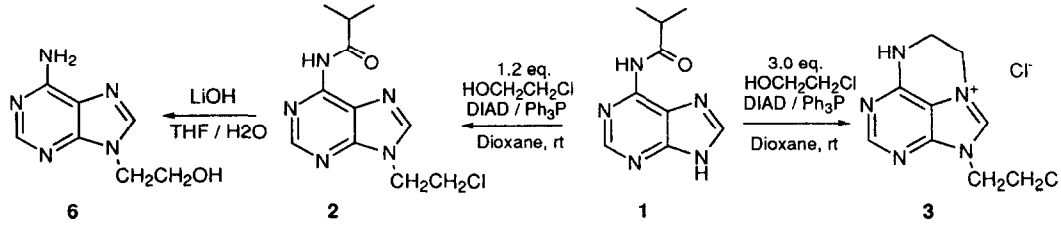
Department of Chemistry, Auburn University, Auburn, AL 36830

Abstract: Readily available 6-isobutyrylaminopurine can replace either a primary or secondary OH group under Mitsunobu conditions and provide an efficient synthesis of carbocyclic analogs of adenosine. X-ray data indicates that only the desired N^9- substituted derivatives of adenine are formed. © 1997 Published by Elsevier Science Ltd.

Carbocyclic analogs of nucleosides have been synthetic targets in many laboratories due to their potential value as anti-tumor and anti-viral agents.[1] Among various reactions which have been developed to introduce nucleoside-base substituents into carbocyclic skeletons, Mitsunobu coupling, in which a secondary hydroxy group of a carbocyclic compound is replaced by a nucleoside base, has proved to be especially effective and convenient.[2]

In most previous syntheses of carbocyclic adenosine analogs, 6-chloropurine was reacted with a carbocyclic alcohol under Mitsunobu conditions and later converted to the adenine derivative.[3] Though it is commercially available, 6-chloropurine is quite expensive. Moreover, vigorous reaction conditions, which may not be compatible with certain functional groups in the molecule, are usually required for the amination of substituted 6-chloropurine to the desired adenine derivatives.[4] We have found that 6-isobutyrylaminopurine, **1**, which is readily prepared in large scale from adenine, is a much more convenient building block for the synthesis of adenine derivatives. When adenine was stirred with a 3-fold excess of isobutyric anhydride in DMF at 160°c for 5 hrs, it was converted into 6-isobutyrylamino-9-isobutyrylpurine. After evaporation of the solvent, the residue was taken up in EtOH/H_2O and the mixture heated under reflux for 30 mins to afford 6-isobutyrylaminopurine, **1**, in 85% yield.

Treatment of **1** with 1.2 eq 2-chloroethanol in the presence of diisopropyl azodicarboxylate (DIAD) and triphenylphosphine in dioxane at room temperature gave 9-(2-chloroethyl)-6-isobutyrylaminopurine **2** in 87%

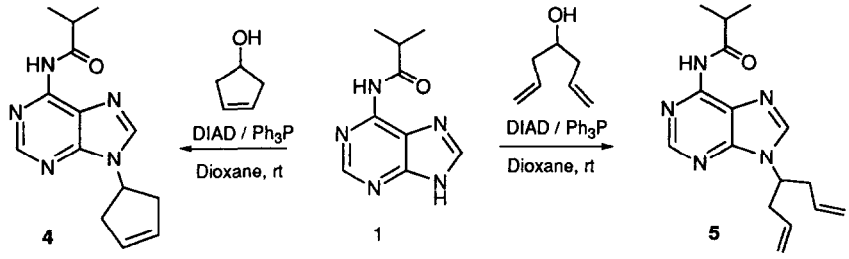


6 **2** **1** **3**

isolated yield. Unexpectedly, when **1** was treated with larger excess (3.0 eq) of 2-chloroethanol under similar reaction conditions, a water soluble product **3** was isolated in 84% yield. The formation of **3** indicates that the

initial Mitsunobu reaction is followed by a coupling between the protecting amide and the primary alcohol. Subsequent cyclization and loss of the isobutyryl group generates **3**. The structure of **3** was confirmed by both NMR (^1H & ^{13}C) and ES-MS. This coupling-deprotection sequence under Mitsunobu conditions may offer a useful way to derivatize the 6-amino group of 9-substituted adenines.

In a synthesis of a potentially useful functionalized carbocyclic adenosine analog, **1** was reacted with 4-hydroxycyclopentene[5] under Mitsunobu conditions to give 9-(4-cyclopentenyl)-6-isobutyrylaminopurine, **4**, in 75% isolated yield. Only the desired N^9- substituted purine was formed as demonstrated by its X-ray crystal structure. An acyclic analog **5**, with the potential for undergoing free radical cyclization to a carbocycle, was isolated in 35% yield upon reaction of **1** with 4-hydroxy-1,6-heptadiene.



4 **1** **5**

The protecting isobutyryl group can be easily removed by mild base hydrolysis. Treatment of **2** with lithium hydroxide at room temperature gave 9-(2-hydroxyethyl)adenine **6** (80%) which was identical to the product of hydroxyethylation of adenine **1** with ethylene carbonate in DMF.[6] The carbocyclic adenosine analog 9-(4-cyclopentenyl)adenine was obtained in 90% yield from **4** under the same conditions.

These reactions, which can effect the replacement of a primary or secondary hydroxyl group by readily available **1**, appear to offer an efficient way to synthesize carbocyclic analogs of adenosine.

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