Efficient Synthesis of Carbovir and Its Congener *via* π-Allylpalladium Complex Formation by Ring Strain-Assisted C−N Bond Cleavage

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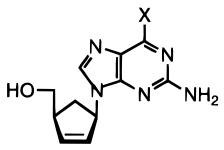
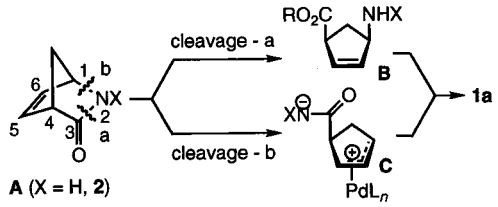
The recent finding that modified nucleosides such as dideoxynucleosides are potentially effective therapeutic agents for the treatment of the acquired immune deficiency syndrome (AIDS) has triggered explosive new developments in the chemistry of these compounds and their analogs.[1] To date, AZT (3′-azido-3′-deoxythymidine), ddI (2′,3′-dideoxyinosine), ddC (2′,3′-dideoxycytidine), d4T (2′,3′-didehydro-3′-deoxythymidine), and 3TC (β-L-(−)-2′-deoxy-3′-thiacytidine) belonging to dideoxynucleosides are the approved drugs for the treatment of AIDS. However, a number of other modified nucleosides have gone through at least preliminary clinical studies. For example, carbovir (**1a**),[2] carbocyclic 2′,3′-didehydro-2′,3′-dideoxyguanosine, has been found to show significant anti-HIV activity, and its congener (**1b**) having a higher oral bioavailability than carbovir is currently undergoing clinical trials for the treatment of HIV infection.[3]



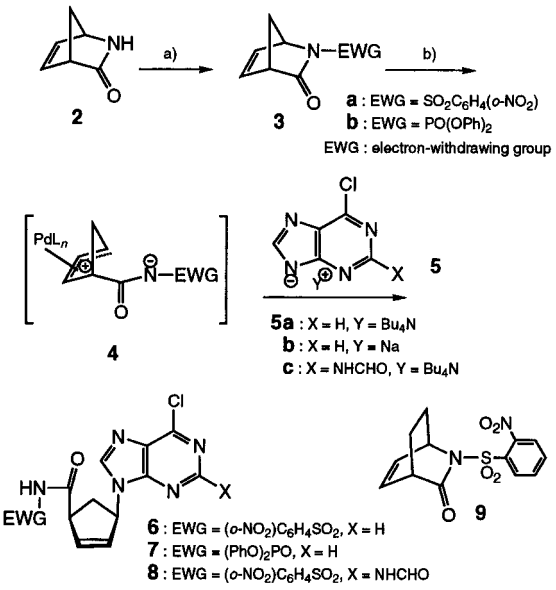
1 a : X = OH (carbovir)
b : X = NH-cyclopropyl (1592U89)

Although considerable literature is available concerning the synthesis of **1a**, most of these papers deal with synthetic methods *via* cyclopentene derivatives as synthetic precursors.[4] 2-Azabicyclo[2.2.1]hept-5-en-3-one (**2**, ABH)[5] produced industrially is one of the most versatile reagents for the synthesis of **1a** as well as other carbocyclic nucleosides. All previous synthetic methods of **1** from **2** (= **A**) involve cyclopentenylamines (**B**) as intermediates formed by 2,3-bond fission (Scheme 1, cleavage-a).[2,6] Previously, we reported a synthesis of cyclopentenylamine from **2** by $NaBH_4$-mediated reductive amido bond cleavage reaction (cleavage-a) and a conversion of the cyclopentenylamine to carbocyclic nucleosides.[7] However, these reported methods have a crucial drawback because of their time-consuming reaction steps concomitant with purine ring construction resulting in low total yield.

Scheme 1



Scheme 2[a]



[a] Key: (a) (i) ^{n}BuLi, THF, −78 °C, (ii) (*o*-NO_2)$C_6H_4SO_2Cl$ or $(PhO)_2POCl$; (b) (i) $Pd[P(O^iPr)_3]_4$ (0.1 equiv), THF or NMP, rt, (ii) 6-chloropurine (Na^+ salt or Bu_4N^+ salt) or 2-(formylamino)-6-chloropurine (Bu_4N^+) salt.

In this paper, we report an efficient synthesis of **1** from **2**, which involves a novel π-allylpalladium complex formation (**C**) by ring strain-assisted 1,2-bond fission (cleavage-b) of **2**, and would provide a more practical method for the synthesis of **1**.

To facilitate the cleavage of the 1,2-bond by Pd^0, an electron-withdrawing group was introduced to the 2-position of **2**. Compound **2** was treated with BuLi followed by *o*-nitrobenzenesulfonyl chloride in THF at −78 °C to give the desired compound **3a** (mp 94 °C) in 83% yield (Scheme 2). In a similar manner, a diphenylphosphoryl group was also introduced to the 2-position by using diphenyl chlorophosphate to give **3b** (mp 51 °C) in almost quantitative yield.

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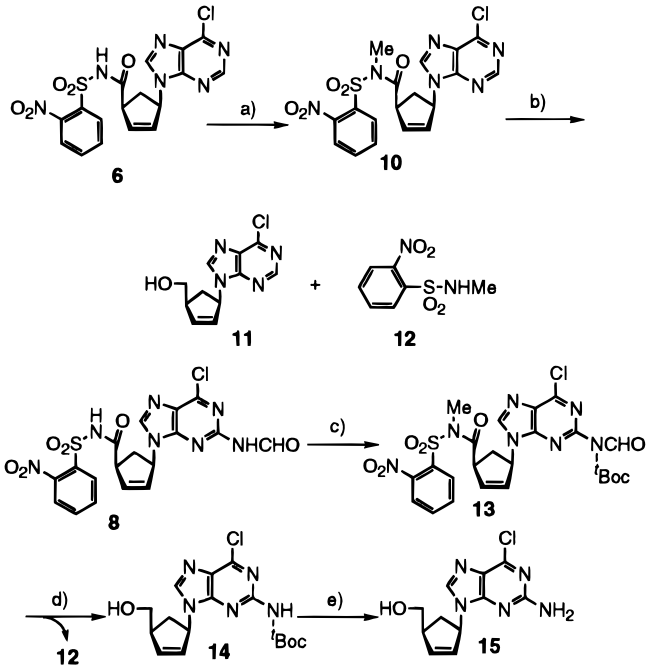
Next, we carried out the coupling reaction of **3** with 6-chloropurines (**5**) in the presence of Pd^0. Compound **3a** was reacted with 6-chloropurine tetrabutylammonium salt (**5a**)[8] in the presence of $Pd[P(O^iPr)_3]_4$ (0.1 equiv) in THF at rt for 1 h to give **6** (mp 212 °C) in 60% yield.[9] The fact that **6** was obtained as the major product in this reaction shows that the Pd^0 catalyst approaches from the *exo*-side of **3a** to form the π-allylpalladium complex (**4**), which reacted stereoselectively with **5a** to give **6**. Compound **3b** did not react with **5a** under the same reaction conditions. Therefore, **3b** was treated with the sodium salt (**5b**) instead of **5a** under the same catalyst in NMP (*N*-methylpyrrolidone) at rt for 1 h to give **7** (mp 187 °C) in 55% yield. In order to obtain a synthetic intermediate of **1**, we then examined the reaction of **3a** with 2-(formylamino)-6-chloropurine tetrabutylammonium salt (**5c**). The reaction was performed under the same reaction conditions for the preparation of **6** to give the required coupling product **8** in 55% yield.

The synthesis of carbocyclic nucleosides by direct introduction of purine bases to cyclopentene derivatives *via* a π-allylpalladium complex was initially pioneered by Trost and his co-workers.[10] Later, this method was applied by several other groups to the synthesis of carbocyclic nucleosides including **1**.[11] In these reactions, cyclopentenyl carbonates, and the epoxide,[10a] were used as efficient substrates for the formation of the π-allylpalladium complex because the allylic oxygen functional group is a good leaving group for the nucleophilicity of palladium in its zero oxidation state.[12] Recently, Jung and his co-worker have reported the synthesis of **1a** *via* a π-allylpalladium complex formed by the reaction of the 3-(*N*,*N*-ditosylimido)cyclopentene derivative obtained from **2** in four steps with Pd^0, in which the ditosylimido group acts as a leaving group.[13] In our reaction, it is noteworthy to mention that π-allylpalladium complex (**4**) is formed by C−N bond cleavage (cleavage-b in Scheme 1) in the ring of bicyclic amide **3**, in which the *N*-sulfonyl- or *N*-phosphorylamido group behaves as an intramolecular leaving group. This may be due to the 5-membered bicyclic ring strain. The fact that 6-membered bicyclic compound **9**[14] no longer reacts with 6-chloropurine in the presence of Pd^0 and results in the quantitative recovery of the starting material may be additional proof of this mechanism.

Next, to obtain **1** and its congener **11** from **8** and **6**, respectively, we investigated conversion of the sulfonyl amide groups of **6** and **8** to the hydroxymethyl group. The direct conversion by using reductive reagents such as $NaBH_4$ in the presence of a metal salt was unsuccessful. Therefore, compound **6** was transformed to the N-methylated derivative **10** (mp 215−217 °C) by the Mitsunobu reaction (Scheme 3). **10** was then treated with $NaBH_4$ to give the known hydroxymethyl product **11**[15] in almost quantitative yield, concomitant with the formation of *N*-methyl-*o*-nitrobenzenesulfonamide. The transformation of **8** to **15** was carried out as follows. That is, **8** was treated with NaH (2 equiv) and reacted with $^tBoc_2O$ and MeI successively to give **13**, which was subjected to reductive amido bond cleavage reaction by $NaBH_4$ to form the hydroxymethyl derivative **14**. Finally, removal of the ^{t}Boc group by acetic acid at 50 °C for 8 h gave the known compound **15** (mp 160−162 °C (lit.[2a] mp 145−147 °C) for $C_{11}H_{12}ClN_5O\cdot 3/4H_2O$) in 72% total yield from **8** leading to **1a** and **1b**.

Scheme 3[a]



[a] Key: (a) MeOH, PPh_3−DEAD, THF−CH_2Cl_2 (1:1), rt; (b) $NaBH_4$, MeOH, 0 °C; (c) (i) NaH (2.2 equiv), THF, 0 °C, (ii) $^tBoc_2O$, rt → 50 °C, (iii) MeI, rt; (d) $NaBH_4$, MeOH, 0 °C → rt; (e) AcOH, 50 °C.

In summary, we have found that formation of the π-allylpalladium complex from the 2-azabicyclo[2.2.1]-hept-5-en-3-one having an electron-withdrawing group at the 2-position in the presence of Pd^0 leads to an efficient synthesis of carbovir (**1a**) and its congener (**1b**). Since chiral **2** is now commercially available, our method is also applicable to the synthesis of optically active **1a** and **1b**.

Supporting Information Available: Experimental procedures for compounds **3a,b, 6**−**8**, **10**, **11**, and **15** and ^{1}H-NMR spectra for compounds **3a,b, 6**−**8**, **10**, **11**, 1**3**, and**15** (13 pages).

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(14) Compound **9** (mp 138−139 °C) was obtained in 66% yield by the same procedure given for the preparation of **3a**.

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