π-Allylpalladium Formation from Allylic Amines via N,N-Ditosylimides and N-Tosylamides: Efficient Synthesis of the Antiviral Agent Carbovir

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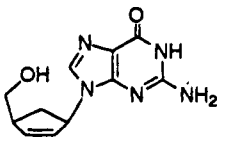
Summary: Allylic amines can be easily converted into their *N,N*-ditosylimides or *N*-tosylamides which are sufficiently good leaving groups to afford π-allylpalladium complexes and, hence, with nucleophiles, new allylic systems with retention of configuration. The synthetic utility of this process has been demonstrated by an efficient synthesis of the antiviral agent (±)-carbovir (**1**) from cyclopentadiene in only seven steps and 13% overall yield.

Due to the efforts of many research groups, foremost among them those of Trost[3a] and Tsuji,[3b] the addition of nucleophiles to π-allylpalladium complexes is one of the most powerful methods for allylic functionalization available today.[4] The substrates in this reaction are predominately allylic esters and carbonates although certain other allylic functionalities, e.g., vinyl epoxides and allyl sulfones,[4] also serve as good leaving groups. In general, however, allylic nitrogen functionality does not prove to be as useful as a leaving group in this process. We wish to report that allylic *N,N*-ditosylimides or *N*-tosylamides, both readily prepared from allylic amines, can serve as substrates in the preparation of π-allylpalladium complexes and demonstrate the usefulness of this process in an efficient total synthesis of (±)-carbovir (**1**) from cyclopentadiene in only seven steps and 13% overall yield.

Carbocyclic analogues of normal purine or pyrimidine nucleosides (having a methylene group in place of the ring oxygen atom) are of interest as potential antiviral and antitumor agents.[5] The recent finding that carbovir (**1**), the carbocyclic analogue of 2′,3′-didehydro-2′,3′-



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dideoxyguanosine, is a selective inhibitor of human immunodeficiency virus (HIV-1) in vitro[6] has further increased interest in this compound and its analogues. Indeed, the hydrolytic stability of carbovir and its ability to inhibit the infectivity and replication of HIV in T-cells at concentrations well below toxic levels make carbovir (**1**) an excellent candidate for development as an antiretroviral agent in treating AIDS.[7] Because of this important biological activity, the search for new general methods for the synthesis of carbovir and its analogues continues apace, with several total and formal syntheses having been reported.[7–9] We report here the formation of π-allylpalladium complexes from allylic amines and the use of this process in a new approach to cycloalkenyl nucleosides which permits an efficient synthesis of carbovir **1**.

The nucleophilicity of palladium in its zero oxidation state is such that it requires a fairly good leaving group on the allyl system in order to afford π-allylpalladium complexes. Thus, allylic halides, esters, carbonates, carbamates, phosphates, sulfones, and selenides generally have been the preferred substrates, with a few other special allylic systems, vinyl epoxides and oxetanes, also having been used.[4] Indeed, one of the best syntheses of carbovir[9a] uses the reaction of a cyclopentenyl carbonate with palladium to generate the π-allylpalladium complex. However, with a few notable exceptions, the allylic nitrogen functionality has generally not been used as a substrate. Several groups have reported that allyltrialkylammonium salts are excellent substrates,[10] while Hegedus described the use of allylic nitro compounds as substrates.[11] However, there has only been one report of the use of an allyldialkylamine as a substrate,[12] and that observation is in doubt[13] since one would not expect allylic amines to be substrates due to the poor leaving group ability of a negatively charged nitrogen atom. Trost and Keinan have reported that dienylic amines were not substrates until they were protonated to give the ammonium salts.[13] We reasoned that if one substituted the allylic nitrogen atom with anion-stabilizing groups, thereby increasing its leaving group ability, they would then serve as good substrates for π-allylpalladium complex formation. If this could be accomplished, it would permit a very rapid synthesis of carbovir from the

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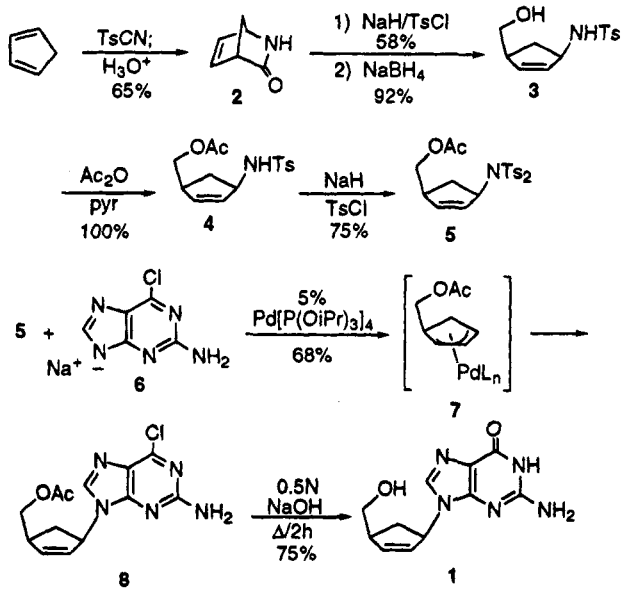
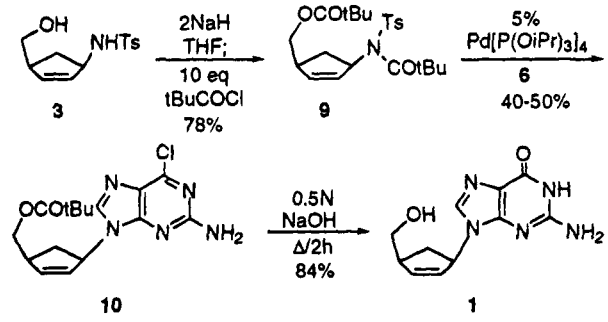
Scheme 1



known product[14] of the Diels–Alder addition of cyclopentadiene and tosyl cyanide followed by hydrolysis, namely the lactam **2**.[15] We now report the successful use of *N,N*-ditosylimides and *N*-tosylamides as substrates for π-allylpalladium complex formation.[16]

The bicyclic lactam **2** (Scheme 1) is prepared by hydrolysis of the Diels–Alder adduct of cyclopentadiene and tosyl cyanide in 65% overall yield.[14] Tosylation of the anion of **2** afforded in 58% yield the *N*-tosyllactam which was reductively opened to the hydroxy sulfonamide **3** in 92% yield. Selective acetylation of the alcohol afforded quantitatively the acetate **4** which was then *N*-tosylated by treatment with sodium hydride and tosyl chloride to give **5** in 75% yield. The key coupling was then effected by treatment of **5** with the sodium salt of 2-amino-6-chloropurine in 1:1 THF:DMSO in the presence of 5% $Pd[P(OiPr)_3]_4$ which furnished (presumably via the π-complex **7**) the desired cis 1,4-disubstituted cyclopentene **8** in 68% isolated yield. Final conversion of **8** to carbovir **1** was done by heating with 0.5 N sodium hydroxide to effect hydrolysis of the acetate and conversion of the imino chloride to amide. This ends a seven-step synthesis of **1** from cyclopentadiene that proceeds in 13% overall yield.

Scheme 2



Other *N,N*-disubstituted systems were also investigated as substrates in this route to **1**. Peracetylation of the hydroxy sulfonamide **3** gave the corresponding acetoxy tosylamide which was treated with **6** under the same conditions as above for **5**. However, the major product was the *N*-deacetylated material **4**, presumably formed from attack of the nucleophile **6** on the *N*-acetyl group. Therefore, we prepared the more hindered bis(pivaloyl) system **9** from **3** (Scheme 2) (78% yield of **9** obtained along with 22% of the simple *O*-pivaloylated material which could be recycled). Reaction of **9** with **6** as before also afforded the desired coupling product, namely the pivalate **10** in an unoptimized yield of 47%. Reaction of **10** with base gave carbovir (**1**) in 84% yield, thereby ending a slightly shorter (six step) synthesis that proceeded in slightly lower yield (11% overall). Further research in both the area of nitrogen leaving groups for π-allylpalladium complex formation and that of carbocyclic nucleoside synthesis is currently underway.

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Supplementary Material Available: Experimental procedures and characterization data (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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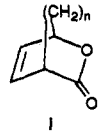
(15) An excellent substrate for this π-allylpalladium complex formation would be the lactone **i** (n = 1) since both strain release and the good leaving group should facilitate the reaction. However, this lactone **i** (n = 1) is unknown due presumably to a very facile retro Diels–Alder reaction to give carbon dioxide and cyclopentadiene. The same reaction sequence that produces the lactones **i** (n = 2, 3) does not afford **i** (n = 1) [Malpass, J. R.; Tweddle, N. J. *J. Chem. Soc., Perkin Trans. 1* **1977**, 874.] Therefore, we chose to use the lactam **2**.



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