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The first Cu- and amine-free Sonogashira-type cross-coupling in the C-6-alkynylation of protected 2′-deoxyadenosine

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ABSTRACT

The Sonogashira cross-coupling reaction offers a convenient route to C(sp)–C(sp^2) bond formation. Although the Sonogashira reaction has traditionally been carried out in the presence of Pd catalyst and a co-catalyst of Cu(I) salt, the use of Cu(I) salt is often not efficient because it leads to the formation of unwanted side-products. This has prompted interest in recent years in the development of Cu-free Sonogashira cross-coupling reaction conditions. In addition, the development of Cu-free Sonogashira cross-coupling conditions for the alkynylation of nucleoside derivatives remains largely unexplored. Herein, we demonstrate that Cu- and amine-free Sonogashira-type cross-coupling lead to successful alkynylation of aryl bromides and heteroaryl bromides. For the first time, we have extended this method for the alkynylation of protected 2′-deoxyadenosine at the C-6 position.

1. Introduction

Alkynes are commonly found in many natural products and biologically active compounds.[1] The versatility of alkynes as important synthetic intermediates has prompted interest in designing efficient methods to incorporate alkynes in organic molecules. One commonly used method for incorporation of alkynes in organic molecules, through the formation of C–C bonds, is the Sonogashira cross-coupling method.[2] The Sonogashira coupling reaction has been extensively studied since its discovery in 1975. The Sonogashira cross-coupling reaction involves the coupling of a terminal alkyne with an aryl or vinyl halide or triflate, using a palladium catalyst and a Cu(I) salt as co-catalyst.[3] The creation of the C(sp)–C(sp^2) bond makes the Sonogashira cross-coupling reaction one of the most important reactions in synthetic organic chemistry. It has been reported that the use of CuI does not always have a positive outcome on effective Sonogashira cross-coupling reactions.[4] This is because the use of CuI results in unwanted side-reactions, such as the oxidative homocoupling of alkynes to form the so-called Glaser product.[5] This side-reaction has driven the modification of the original Sonogashira cross-coupling reaction.[6–9] To date, examples of Pd-free,[6] Cu-free,[10] amine-free,[11] ligand-free,[12] and solvent-free[5b] conditions have been reported. The Sonogashira cross-coupling reaction has also been performed in the presence of water as solvent,[12b,13] or using tetrabutyl ammonium salts as additives.[5b,12b,14] Modifications in the original Sonogashira cross-coupling reaction have resulted in the reaction being easily amenable on a laboratory and industrial scale.

Modified nucleosides play important roles in many biological processes. Nucleoside analogs, substituted at the C-6 position, have been shown to display a broad range of biological activities.[15–18] The Sonogashira cross-coupling reaction provides easy access to 6-alkynylpurine nucleosides, which would otherwise be difficult to synthesize using other conventional coupling reactions. Successful Sonogashira cross-coupling reaction has been reported using 6-chloropurine and 6-iodopurine nucleosides with 1-hexyne, and employing $Pd(PPh_3)_4$/CuI/TEA as the catalytic system.[19] However, only one terminal alkyne was used and there is no evidence that the catalytic system could be extended, with equal success, to other terminal alkynes.

Nucleosides can be covalently modified to form fluorescent analogs.[20] Fluorescent nucleoside analogs can serve as valuable probes in cellular and signal transduction pathways.[21] The synthesis of modified nucleosides by Pd-catalysis has been reported.[3c,22] The alkynylation of nucleosides by Sonogashira cross-coupling has also been reported.[3c,20,23] However, most of the successful alkynylation reactions reported so far have involved 8-bromoadenosine and 8-bromoguanosine with terminal acetylenes. Interestingly, development of a catalytic system for the alkynylation at the 6-position of 6-bromo-2′-deoxyadenosine has not been fully explored. To the best of our knowledge, very limited information exists in the literature on the Sonogashira cross-coupling of 6-bromo-2′-deoxyadenosine with terminal alkynes to generate 6-alkynylated-2′-deoxyadenosine derivatives.

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Most biological activities studies with modified nucleosides have been limited to the 6-arylpurine ribonucleosides, with a few studies on the 6-alkynylpurine ribonucleosides. However, biological studies on the 6-alkynylpurine deoxyribonucleosides remain largely unexplored. One reason why the potential biological activities of 6-alkynylpurine deoxyribonucleosides have not been fully explored could be the difficulty in synthesizing 6-alkynylpurine deoxyribonucleosides through cross-coupling reactions between the labile deoxyribonucleosides and terminal alkynes. Although the common Sonogashira cross-coupling method works well in the cross-coupling of terminal alkynes with aryl halides and heteroaryl halides, this method may not necessarily be extended to deoxyribonucleosides with equal success. Although many different variations of the common Sonogashira cross-coupling methods have been reported in the literature, the application of these methods with protected 2′-deoxyribonucleosides requires a careful and systematic approach; the cross-coupling method must be compatible with the protecting group on the sugar moiety and be tolerant to the lability of the nucleosidic bonds. As a result of our ongoing interest in transition metal-mediated syntheses of modified nucleosides,[24] we decided to evaluate the common Sonogashira cross-coupling method and the modified versions in the coupling of protected 2′-deoxyadenosine with terminal alkynes. Herein, we report a convenient Sonogashira cross-coupling protocol for the alkynylation of aryl bromides, heteroaryl bromides, and 6-bromo-2′-deoxyadenosine.

2. Results and discussion

We envisaged the establishment of a general synthetic route to 6-alkynylpurine deoxyribonucleoside derivatives through a Sonogashira-type cross-coupling reaction of protected 6-bromo-2′-deoxyadenosine with a series of terminal alkynes. The Sonogashira cross-coupling reaction was carried out using 3 mol % Pd species and 2 mol % CuI as the catalytic system. For initial optimization, we chose bromobenzene and phenylacetylene as substrates, $Pd_2(dba)_3$, $PdCl_2(CH_3CN)_2$, and $Pd(PPh_3)_4$ as Pd species, **L-1**, **L-2**, **L-3**, and **L-4** as ligands, and Et_3N and DABCO as bases (Fig. 1). The ligands were chosen because of our previous experience with these ligands,[24] and because Buchwald et al. had shown that biaryl dialkyl phosphine ligands are efficient at catalyzing the Sonogashira cross-coupling reaction.[4] Interestingly, in our hands, the Pd species and ligand that were successful in the coupling of aryl chlorides with terminal alkynes, as reported by Buchwald et al. did not work quite as well in the coupling of aryl bromides with terminal alkynes. We chose the more readily available Pd species, which were more promising. In the optimization experiments, four different solvents were tried at 50 °C, 90 °C, or ambient temperature (see Supplementary data for a comprehensive table of results).

In the course of the optimization experiments, some important lessons were learned. The combination of $Pd_2(dba)_3$/CuI, the ligands **L-1**, **L-2**, **L-3**, or **L-4**, any of the solvents, and either Et_3N or DABCO, at 90 °C, 50 °C, or ambient temperature led to no significant product formation over a 24 h period. However, the use of $Pd(PPh_3)_4$/CuI, the ligands **L-1** or **L-2**, Et_3N or DABCO, and the solvent DMF or toluene led to significant improvement in the yield at 90 °C and 50 °C. Although the use of $PdCl_2(CH_3CN)_2$ gave better results when compared to $Pd_2(dba)_3$, the yields were still lower when compared to $Pd(PPh_3)_4$. Our initial experiments established the combination $Pd(PPh_3)_4$/CuI/**L-1**/Et_3N in DMF at 90 °C as the optimal conditions for the common Sonogashira coupling.

Although results from our optimization studies using Et_3N, DMF, $Pd(PPh_3)_4$, and **L-1** at 90 °C were largely satisfactory, we were still concerned with the occasional appearance of the Glaser product, as judged by GC–MS analysis. To combat the problem of Glaser coupling, Cu-free Sonogashira cross-coupling reactions were explored. Three Pd species, $Pd_2(dba)_3$, $Pd(PPh_3)_4$, and $PdCl_2(CH_3CN)_2$, were used in these Cu-free cross-coupling reactions, with acetonitrile, DMF, and toluene as solvents (Table 1). The $Pd_2(dba)_3$/**L-1** catalytic system provided no coupling under the Cu-free conditions, while the $PdCl_2(CH_3CN)_2$/**L-1** gave a modest 72% yield. However, the $Pd(PPh_3)_4$/**L-1** catalytic system was extremely efficient under these conditions producing a 91% yield of the Sonogashira cross-coupling product. The optimum conditions for the Sonogashira cross-coupling reactions were found to require the use of **L-1** and $Pd(PPh_3)_4$ at 90 °C in acetonitrile (Table 1, entry 2).

In order to study the scope of our optimized reaction conditions, a number of aryl bromides and heteroaryl bromides containing a wide array of functional groups were subjected to Sonogashira cross-coupling with phenylacetylene (Table 2). The yields were good for all substrates; simple aromatic, heteroaromatic, and extended aromatic substrates. Irrespective of the substituents on the aromatic substrates, products were obtained for activated and less activated aryl halides. No significant difference was observed in the reactivity between 2-bromosubstituted and 4-bromosubstituted substrates when the electron-donating group was a methyl group (Table 2, entries 4 and 7). However, there was a significant difference in the reactivity between 2-bromosubstituted and 4-bromosubstituted substrates when the electron-donating group was a methoxy group (Table 2, entries 6 and 8). The reaction with *ortho*-bromoanisole proceeded to afford the desired cross-coupling product in 94% yield (Table 2, entry 6), while the reaction with *para*-bromoanisole gave a modest 69% yield (Table 2, entry 8). In addition, aryl bromides showed selective reactivity in the presence of fluorine and chlorine (Table 2, entries 3 and 5). In the reaction of 4-bromo-2-chlorophenol, selective alkynylation was observed at the 4-bromo position given 53% of the desired product (Table 2, entry 3); there was no evidence of alkynylation at the 2-chloro position.

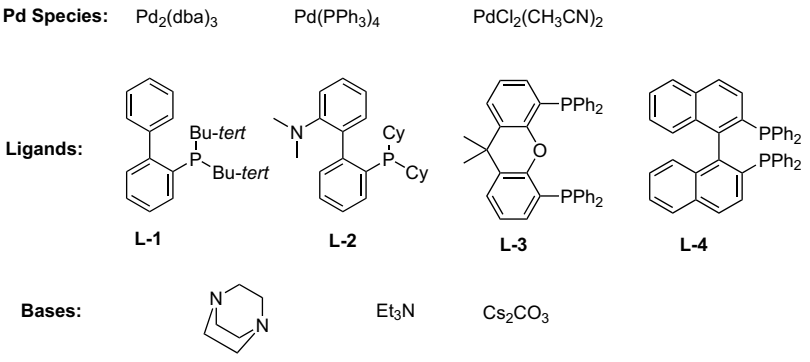

Figure 1. Pd species, ligands, and bases investigated.