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Ligand and Copper Free Sonogashira Coupling to Achieve 2-Alkynyl D-Glucal Derivatives: Regioselective Electrophile Promoted Nucleophilic 5-Endo-dig Cyclization

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ABSTRACT

A general approach for the synthesis of 2-alkynyl-D-glucal derivatives has been achieved through a ligand and copper-free Sonogashira coupling of 2-iodo-3,4,6-tri-O-acetyl-D-glucal and terminal alkynes using palladium acetate in DMF at room temperature with very good to excellent yields. The scope of this reaction is shown by regioselective electrophile promoted nucleophilic (EPN) 5-endo-dig cyclization of these alkynyl-D-glucal derivatives using gold (III) chloride in 1,4-dioxane at reflux.

Introduction

Unlike *C*-1 glycoside derivatives, the synthesis of *C*-2 substituted carbohydrate derivatives is not very common.[1-5] To achieve *C*-2 carbohydrate derivatives some very well-known reactions such as the Suzuki-Miyaura, Wittig and Heck-type reactions have been applied.[6-9] Although it is uncommon, the formation of the *C*-*C* bond at *C*-2 of glucal derivatives has synthetic importance[6-8,10] and it has played a key role in the synthesis of some very interesting and biologically important glycoside derivatives.[11-13]

Sonogashira coupling is among these important and well-studied organic reactions because of recent advances in its use and its flexibility. It has been applied by many groups to synthesize *C*-*C* bonds in complex and delicate organic compounds in natural product synthesis. To make it simpler and more applicable many modifications have been made in Sonogashira coupling; the most common modifications use using copper and/or ligand-free conditions.

Alkyne cyclization is of the utmost importance for making carbocyclic as well as heterocyclic rings in organic synthesis. It has been very often used for the synthesis of three to six membered rings[14] and in several cases[15] for larger rings also. Nucleophilic alkyne cyclization is one of the most well studied and mechanistically developed classes of alkyne cyclizations.[16] It has been determined experimentally that of the two possible pathways for nucleophilic alkyne cyclization the exo-dig pathway is kinetically more feasible[17] unless restricted by thermodynamic factors. The interesting case of 4-exo and 5-endo-dig cyclization exhibits very similar energy barriers despite the clear difference in strain of the two products formed.[18] Thus, the kinetic preference for 4-exo-dig cyclization is somehow balanced by the greater strain in the 4-membered ring product compared with the 5-membered ring.

It has also already been found that using Lewis acid as electrophiles to promote nucleophilic alkyne cyclization changes the kinetic preference in favor of the endo product.[19] For this reason a number of Lewis acids, like Cu, Au, Ag, Zn, W, I_2 have been used by various groups[20] to achieve the 5-endo-dig regioselectivity. Similarly, the use of higher temperatures also favors the formation of the thermodynamically more stable product i.e. 5-endo-dig.

Based in the recent literature regarding the synthesis and structural analysis of 2-iodo-3,4,6-tri-*O*-acetyl-D-glucal[21] derivatives along with that of copper-free Sonogashira coupling,[22-40] a simple ligand and copper-free procedure is applied to synthesize a series of 2-alkynyl D-glucal derivatives, which could further be used as interesting intermediates for the synthesis of potential carbohydrate derivatives. An attempt was then made to cyclize these alkynyl D-glucal derivatives using the hydroxyl at *C*-3 as nucleophile with the alkyne triple bond.

Different Lewis acids were used to achieve the 5-endo-dig regioselectivity applying high reaction temperatures. It was possible to obtain some hydro furan fused glucal derivatives using gold (III) chloride in 1,4-dioxane at reflux. The yields were