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Palladium mediated cycloisomerization of sugar alkynols: synthesis of cyclic enol-ethers and spiroketals

C. V. Ramana,* Rosy Mallik, Rajesh G. Gonnade and Mukund K. Gurjar

National Chemical Laboratory, Dr. Homi Bhabha Road, Pune 411 008, India

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Abstract—Functionalized bicyclic enol-ethers and spiroketals are prepared by Pd catalyzed cycloisomerization of 3-*C*-alkynylfuranosyl derivatives. Cycloisomerization of differently substituted alkyne derivatives revealed a preference for 6-*endo*-dig cyclization over 5-*exo*-dig if the substituent is not sufficiently electron withdrawing. The scope of these cycloisomerizations has been further extended by integrating with conjugate addition.

Construction of architecturally complex molecules from simple building blocks has emerged as a powerful tool in synthetic organic chemistry because of the increasing demand for molecules with unprecedented diversity. Designing effective routes to construct complex cyclic structures through organotransition-metal catalyzed reactions provides many attractive possibilities, which by conventional procedures would need a large number of synthetic transformations. A great deal of focus has been directed towards sugar based molecular diversity as these molecules offer inherent rigidity and molecular asymmetry.[1]

Cycloisomerization of alkynols is utilized as a tool to synthesize oxygen-containing heterocycles encompassing functionalized furan, pyran, benzopyran and spiroketal skeletons.[2] Many of these cyclization studies occur via transition metal reactions of palladium, platinum, tungsten, molybdenum, ruthenium, rhodium, gold or iridium catalysts.[3] It is pertinent to mention that the metal mediated hydroalkoxylation reactions of carbohydrate precursors have been less explored and mainly confined to glycals, *exo*-glycals and related derivatives.[4] In this article we describe a novel strategy of tandem cycloisomerization of 3-*C*-acetylenic sugar derivatives and also present the trapping of intermediary alkenylpalladium species [5] with acrolein to derive novel bicyclicspiroketals and cyclic enol-ether derivatives (Fig. 1). The key issue in our intended strategy is the mode of cyclization, that is, 5-*exo*-dig versus 6-*endo*-dig.[6] There are several instances in the literature to indicate that the obtuse angle of 120–127° for the approach of a nucleophile to a triple bond triggers the dominance of 5-*exo*-dig over 6-*endo*-dig for electronically unbiased acetylenes.[7] However, the majority of theoretical and experimental studies reported to understand 5-*exo*-dig versus 6-*endo*-dig cyclizations involve, mainly, the base mediated cyclization with hard nucleophiles,[8] investigations dealing with metal catalyzed cyclizations[9] are, however, rare.

The requisite model 3-*C*-alkynylfuranosyl derivatives **7**–**10** were prepared from the easily accessible 3-ulose derivatives **1** and **2**, by reaction with the lithiated salts

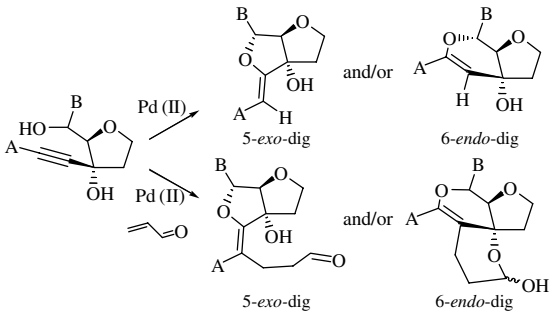

Figure 1. Pd-mediated cycloisomerization and subsequent conjugate addition.

Keywords: Palladium; Cycloisomerization; *C*-alkynylfuranose; Spiroketal; Enol-ether.
* Corresponding author. Tel.: +91 20 25902577; fax: +91 20 25893614; e-mail: vr.chepuri@ncl.res.in

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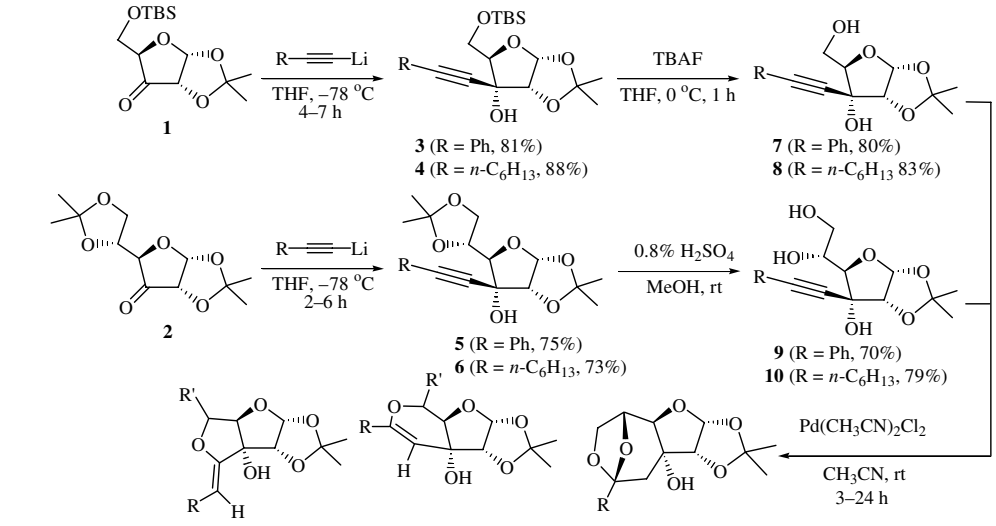
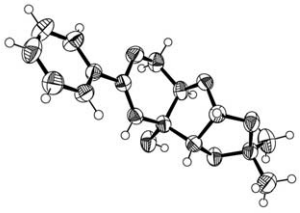
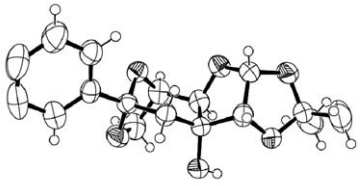


R = Ph, R' = H	**11** (29%)	**12** (59%)	----
R = *n*-C_6H_{13}, R' = H	----	**13** (51%)	----
R = Ph, R' = CH_2OH	**14** (30%)	----	**15** (65%)
R = *n*-C_6H_{13}, R' = CH_2OH	----	----	**16** (55%)



ORTEP Structure of **12**



ORTEP Structure of **15**

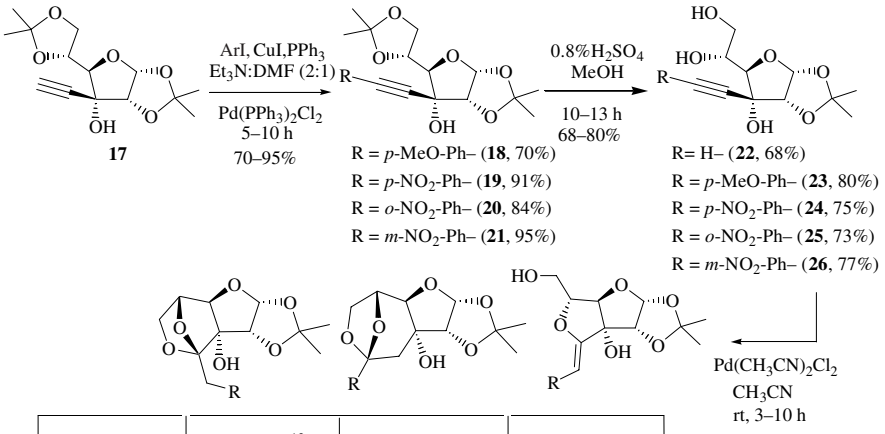
Scheme 1. Synthesis of alkynols **7**–**10** and their Pd-mediated cycloisomerization.

of phenyl acetylene and 1-octyne (Scheme 1). The TBS protecting groups present at *O*-5 of **3** and **4** were subsequently removed using TBAF–THF to give **7** and **8**. Selective hydrolysis of the 5,6-acetonide group of **5** and **6** with cat. H_2SO_4 in methanol gave **9** and **10**, respectively. The cycloisomerization reaction of **7** in the presence of $Pd(CH_3CN)_2Cl_2$ in MeCN at room temperature gave the *exo*-product **11** (29%) and the *endo*-product **12** (59%). The structure of the *exo*-product **11** was proposed based on ^1H, ^{13}C, mass and elemental analysis. The single crystal X-ray study (Scheme 1) of *endo*-product **12** unambiguously proved its structure.[10,11]

The palladium-catalyzed cycloisomerization of **8** gave exclusively the *endo*-product **13**, whose structure was supported by spectral and elemental analysis. The characteristic signal of the enolic proton was observed as a singlet at 4.40 ppm in the ^1H NMR spectrum of **13**. The cycloisomerization of alkynol **9** resulted in a mixture of the *exo*-enol-ether **14** and bicyclic ketal derivative **15**, whose structure was proved by single crystal X-ray structural analysis (Scheme 1). We believe that although the formation of **15** occurred via an *endo*-dig path as noted for **7**, the free hydroxyl group at C-6 underwent further cyclization to furnish the stable ketal structure. Cycloisomerization of **10** similarly gave **16**.

The exclusive formation of **13** and **16** showed, as expected, the favorable 6-*endo*-dig cyclization that could be attributed to the −I effect of the furanose ring over the alkyl chain. With a view to understand the nature of the phenyl ring on the regiochemical outcome, we opted to prepare some specific alkynols containing functional groups on the phenyl ring. Thus, the Sonogashira coupling[12] reactions of **17**[13] with substituted aryl iodides provided a series of compounds **18**–**21**. Selective hydrolysis of the 5,6-acetonide group of **17**–**21** furnished the alkynols **22**–**26**, respectively.

The results of the $Pd(CH_3CN)_2Cl_2$ catalyzed cycloisomerizations of the alkynol derivatives **22**–**26** are given in Scheme 2. These studies revealed that the presence of a +M substituent on the aromatic ring favoured 6-*endo*-dig while −M groups favored 5-*exo*-dig modes of cyclization. Thus, there existed an electronic effect, particularly a competitive balance between −I and +M effects. The information is significant when compared to the base mediated cycloisomerization reactions. Padwa[8c,d] has extensively investigated the base-induced cycloisomerization of several (phenylethyny1)aryl-substituted alcohols modulating one of the phenyl ring substituents (Fig. 2), where the 5-*exo*-dig mode of cyclization was exclusively independent of the nature of the aryl substituent. Along similar lines, Hiroya



R = H	**27** (87%)[13a]	--	--
R = *p*-MeO-Ph-	--	**28** (82%)	--
R = *p*-NO_2-Ph-	--	--	**29** (87%)
R = *o*-NO_2-Ph-	--	--	**30** (72%)
R = *m*-NO_2-Ph-	--	**32** (18%)	**31** (65%)

Scheme 2. Synthesis of alkynols **22**–**26** and their Pd-mediated cycloisomerization.

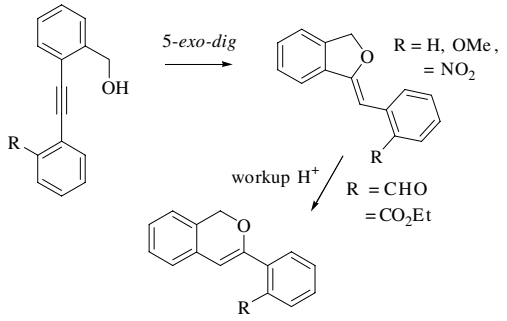
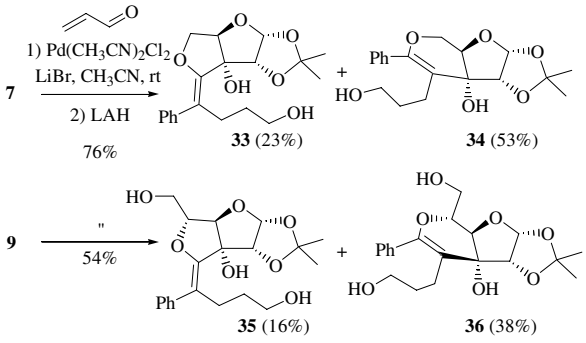


Figure 2. Cycloisomerization of (phenylethynyl) benzyl alcohols.[8c,d]

et al.[8a] concluded that regioselectivity in base mediated cycloisomerization reactions is not influenced by the electronic nature of the functional group on the triple bond, but by the steric bulkiness.

We next investigated our second objective, the two component reactions involving palladium catalyzed cycloisomerization as described above and subsequent conjugate addition of the carbopalladium intermediates with acrolein.[5] To circumvent the problems associated with the stability of the resulting aldehyde derivatives, we chose to reduce them with LAH before isolation and characterization (Scheme 3).

Thus, the successive cycloisomerization of **7** with $Pd(CH_3CN)_2Cl_2$, conjugate addition with acrolein and LAH reduction in one-pot gave a mixture of compounds **33** (23%) and **34** (53%). NMR, mass and elemental analysis, supported their structures. Similar results were obtained with the substrate **9**, giving the products **35** (16%) and **36** (38%). Surprisingly, no conjugate addition reactions were observed with **8** and **10**, however, the expected *endo*-products **13** and **16** were recovered, respectively.



Scheme 3. Cycloisomerization and conjugate addition of alkynols **7** and **9**.

In summary, the regioselectivity of cycloisomerization of sugar acetylene derivatives depends on electronic factors influencing 5-*exo*-dig versus 6-*endo*-dig modes of cyclization, which is in contrast with base-promoted cycloisomerizations. The two-component cycloisomerization and conjugate addition gave highly functionalized compounds.

Acknowledgements

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Supplementary data

NMR Spectra of compounds **11**, **12**, **15**, **33** and **34**, and crystallographic files for **12** and **15** are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.03.143.

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10. (a) X-ray intensity data of compounds **12** and **15** were collected on a Bruker SMART APEX CCD diffractometer with omega and phi scan mode, $\lambda_{\mathrm{Mo\,K\alpha}} = 0.71073$ Å at $T = 297(2)$ K. All the data were corrected for Lorentzian, polarization and absorption effects using Bruker's SAINT and SADABS programs. The crystal structure was solved by direct methods using SHELXS-97 and the refinement was performed by full matrix least squares of F^2 using SHELXL-97. Hydrogen atoms were included in the refinement as per the riding model except for the hydroxyl group, which is located in difference the Fourier map; (b) Sheldrick, G. M. SHELX-97 *program for crystal structure solution and refinement*; University of Göttingen: Germany, 1997.
11. The crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as deposition Nos. CCDC 296444 (**12**) and CCDC 296445 (**15**). Copies of the data can be obtained, free of charge, on application to the CCDC,12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (1223)336033; e-mail: deposit@ccdc.cam.ac.uk].
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