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The influence of electronic factors on Pd-mediated cycloisomerization: a systematic investigation of competitive 6-*exo*-dig versus 7-*endo*-dig cyclizations of sugar alkynols

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ABSTRACT

Pd-mediated cycloisomerization of 3-*C*-propargyl-*ribo*- and *allo*furanose derivatives was investigated in detail to understand the influence of electronic factors on the regioselectivity (6-*exo*- vs 7-*endo*) of alkynol cycloisomerization leading either to a six- or seven-membered ring. In general, the 6-*exo*-dig mode of cyclization is facile and is independent of electronic factors. With some of the alkynols, a regioselective (7-*endo*?) hydration of the alkyne unit was observed and this has been attributed to the participation of *C*(3)–OH. When the *C*(3)–OH was protected as its benzyl ether, cycloisomerization of these alkynols occurred exclusively in a 6-*exo*-dig mode resulting in the corresponding [3.2.1]-bicyclic ketals. Additional control experiments conducted were in support of the participation of *C*(3)–OH in regioselective alkyne hydration.

1. Introduction

The intramolecular addition of *C*- and heteroatom nucleophiles across the alkynes falls under the broad category of cycloisomerization reactions.[1] The cycloisomerization is projected as a tool for synthesis of oxygen-containing heterocycles encompassing functionalized furan, pyran, benzopyran, and spiroketal skeletons.[2] Various transition metals like palladium, gold, platinum, tungsten, molybdenum, ruthenium, rhodium, and iridium have been explored as catalysts in cycloisomerization reactions.[3] The key issue of the cycloisomerization reactions is the mode of cyclization, i.e., *exo*-dig versus *endo*-dig.[4] In this context, recently we reported a systematic investigation dealing with the influence of electronic and steric factors over competitive 5-*exo*-dig versus 6-*endo*-dig cyclizations mediated by the $Pd(CH_3CN)_2Cl_2$ complex.[5,6] Using a large set of substrates for the projected cycloisomerization reaction, we noticed that Pd promoted cycloisomerization reactions were substantially influenced by electronic factors, which is in contrast with the base promoted cycloisomerizations.[6] From the results obtained, we concluded that competitive balance between the $-I$ effect of furanose ring and the +M effect of the aryl substituents influences the mode of cyclization. The presence of a +M substituent (–OMe) on the aromatic ring in general enforced a 6-*endo*-dig while the presence of a −M group ($-NO_2$) favored 5-*exo*-dig modes of cyclization. In the cases where the *exo*-mode of ring closure is disfavored due to ring strain we noticed exclusive 6-*endo* cyclization.[6b]

Compared to the competitive 5-*exo*-dig/6-*endo*-dig case, reports concerning the 6-*exo*-dig/7-*endo*-dig cyclizations are less frequent.[7,8] The seminal publications by Utimoto et al. on the Pd-mediated cycloisomerization of ω-alkynols show that 5-*exo* and 6-*exo*-dig cyclizations are more favored over their competitive *endo*-dig cyclizations.[2f] A one pot Sonogashira coupling and cycloisomerization of 3-, 4-, and 5-alkynols with aryl halides were studied by Santelli and co-workers using the *tedicyp* ligand.[7c] In general, 6-*exo*-dig mode of cyclizations was documented and the cyclizations are favored only with electron deficient aryl halides whereas with electron rich aryl halides, only coupling products were isolated. Results published by Luo et al. showed that oxypalladation and cross-coupling of acetylenic alkoxides generally prefer to undergo 6-*exo*-ring closure.[5h] Liu and de Brabander reported regiochemical control in the cycloisomerization of electronically unbiased internal alkynes by selecting appropriate catalysts and conditions.[7d] While our work was in progress, Ley and co-workers reported the selective

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7-*endo* cyclization of alkyne diols by employing $PtCl_4$ as the catalyst.[7e]

In continuation of our interest in the Pd-mediated cycloisomerization of sugar alkynol and the synthesis of natural products having either bridged- or spiro-bicyclic ketal units, we were interested to learn the control of electronic factors over the competitive 6-*exo*-dig versus 7-*endo*-dig modes of cyclization.[6] Herein we describe our investigations in this direction, employing two sets of 3-*C*-propargylfuranosyl derivatives (Fig. 1) **8**–**12**, and **13**–**17**. With the first set of compounds **8**–**12**, the cycloisomerization should lead either to [3.4.0]- or [3.5.0]-dioxabicyclic enol ether derivatives, whereas the formation of fused [3.2.1]- or [4.2.1]-bicyclicacetal derivatives is possible from the second set of compounds **13**–**17** (Fig. 1).

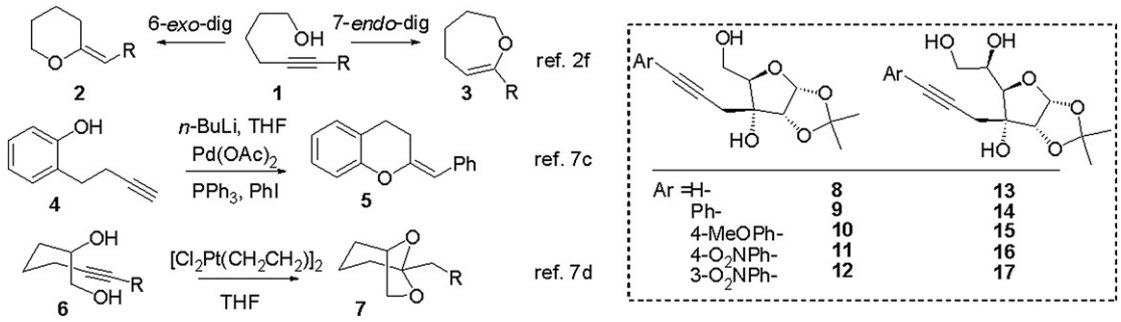


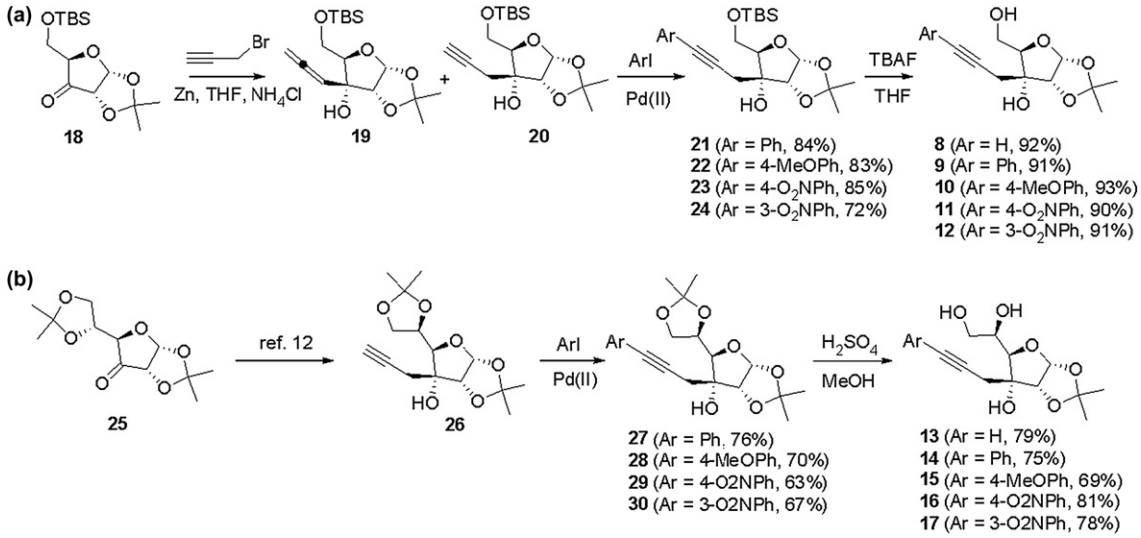
Figure 1. Competitive 6-*exo*-dig versus 7-*endo*-dig cyclizations, some representative examples, and designed substrates **8**–**17**.

2. Results and discussion

The synthesis of the requisite model 3-*C*-propargyl-*ribo*furanose derivatives **8**–**12** started with propargylation of the known 3-ulose derivative **18**[9] under Barbier conditions to afford **20** along with the allene **19** (Scheme 1).[10] The Sonogashira coupling[11] of **20** with different aryl iodides was carried out to obtain compounds **21**–**24**. The TBS group present at *O*-5 of **20**–**24** was subsequently removed by using TBAF/THF to give the first set of cycloisomerization substrates **8**–**12**. The synthesis of the projected cycloisomerization substrates **13**–**17** was carried out in a similar way following the Sonogashira coupling with the 3-*C*-propargyl-*allo*furanose derivative **26** (prepared according to the literature procedure from ulose **25**) (Scheme 1)[12] affording compounds **27**–**30**. The selective hydrolysis of the 5,6-*O*-acetonide group of **26**–**30** with cat. H_2SO_4 in methanol completed the synthesis of the projected cycloisomerization substrates **13**–**17**.

The palladium-catalyzed cycloisomerization reactions of model 3-*C*-propargyl-*ribo*furanose derivatives **8**–**12** were carried out in the presence of $Pd(CH_3CN)_2Cl_2$ in MeCN at room temperature. The results are summarized in Table 1. The parent compound **8** gave exclusively the fused dihydropyran **31** resulting from the double bond isomerization of the intermediate *exo*-methylene derivative.[13] A doublet resonating at 1.79 (d, J=0.8 Hz, 3H) ppm in the ^{1}H NMR spectrum of compound **31** indicated the presence of a methyl group attached to an olefin. There is one additional signal in the downfield region 4.40 (br q, J=0.8 Hz, 1H) ppm along with the sugar ring protons and it was characterized as the internal olefinic proton. The assigned structure of **31** was further supported by the ^{13}C NMR spectrum where signals corresponding to the primary methyl and endocyclic tertiary olefinic-CH and endocyclic quaternary –C appeared at 20.3 (q), 95.0 (d), and 156.2 (s) ppm, respectively.

Cycloisomerization of alkynol **9** (Table 1) afforded the 6-*exo*-product **32** along with small amounts of the hemiketal **33**. The structure of compound **32** was determined with the help of NMR spectroscopy, which shows the characteristic benzylic protons at 3.36 (d, J=16.5 Hz, 1H), 3.40 (d, J=16.5 Hz, 1H) ppm, and endocyclic olefinic proton at 4.40 (br d, J=1.1, Hz, 1H) ppm in ^{1}H NMR (Table 1). Peaks at 40.5 (t) for the benzylic CH_2, at 96.2 (d) for olefinic-CH, and at 158.5 (s) for the quaternary olefinic carbon in ^{13}C NMR indicate the 6-*exo*-dig cyclization with the concomittant isomerization of the double bond. The structure of compound **32** was further confirmed



Scheme 1. Synthesis of (a) 3-*C*-propargyl-*ribo*- (**8**–**12**) and (b) *allo*furanose derivatives (**13**–**17**).