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Pinacol rearrangement of cyclopent-3-en-1,2-diols: Cyclopentenone formation and interrupting reaction

Valerii Z. Shirinian [a,*], Andrey G. Lvov [a], Dmitry V. Lonshakov [a], Anton V. Yadykov [a,b], Vadim V. Kachala [a], Mikhail M. Krayushkin [a]

[a] N. D. Zelinsky Institute of Organic Chemistry, RAS, Moscow 119991, Russia
[b] Higher Chemical College, D.I. Mendeleev University of Chemical Technology of Russia, Moscow 125047, Russia

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ABSTRACT

Cyclopentenyl carbocations formed as a result of the protonation of 3,4-substituted cyclopent-3-en-1,2-diols can give either cyclopent-2-en-1-one derivatives via pinacol rearrangement or interrupted reaction products similar to the Nazarov intermediate.

Functionalized cyclopentenyl cations are key intermediates in a number of chemical transformations: e.g. the Nazarov reaction,[1] Piancatelli rearrangement,[2] [4+3]-cycloaddition,[3] and others.[4] To the best of our knowledge the most developed reaction proceeding with the participation of these charged intermediates is an acid-induced cyclization of divinyl ketones known as the Nazarov reaction. Generally, this transformation leads to substituted cyclopentenones,[1,5] which form *via* elimination of a proton from cyclopentenyl cation **I** (Scheme 1).[6] In 2009 West and co-workers proposed the concept[7] of an "interrupted Nazarov cyclization", which involves the trapping of intermediate **I** by various intra- or intermolecular nucleophiles to form functionalized mono- and polycyclic products instead of the normal Nazarov reaction product **III**.[8]

Unlike intermediates **I**, the reactivity of isomeric cyclopentenyl cation **II** is virtually unexplored. These intermediates can be obtained *via* protonation of the corresponding cyclopent-3-en-1,2-diols, and this process typically initiates the pinacol rearrangement. Despite considerable progress in the study of the pinacol rearrangement and related processes,[9] the reaction of cyclopent-3-en-1,2-diols remains an unstudied transformation, possibly due to the inaccessibility of the starting compounds. The only example of this transformation was reported for compound **IV**, which forms cyclopentenone **V** as a result of pinacol rearrangement and double bond migration.[10] Additionally, several examples of the acid-catalyzed rearrangement of diol derivatives of cyclopentane-annulated aromatics (indane and aceanthrene) without migration of the double bond are described (structural specificity of these compounds makes double bond migration impossible).[11]

As part of our studies on the synthesis of photoactive diarylethene derivatives of cyclopentenones[12] as well as their photochemical properties,[13] herein we report a new method for the preparation of 3,4-substituted cyclopent-3-en-1,2-diols and an examination of their acid-catalyzed reactions.

For the synthesis of substrates **4a,b**, we have developed a method based on previously work in our group[14] utilizing cyclopentenone **1** bearing two thienyl groups at positions 3 and 4 (Scheme 2). In three steps (ketoxime synthesis,[15] hydrolysis by formaldehyde/HCl, and sodium borohydride reduction) diarylcyclopent-2-en-1-one **1** was converted to the key diol as a mixture of diastereomers **4a** (*cis*) and **4b** (*trans*) in an overall yield of 67%. The diastereomers were separated by column chromatography and characterized by NMR spectroscopy and mass-spectrometry.

The reactivity of diols **4a** and **4b** in the presence of catalytic tosylic acid in benzene was examined.[11] The reaction pathway was found to be dependent on the temperature. At 80 °C the acid-catalyzed reaction of both the mixture of diastereomers **4a,b**

* Corresponding author.
E-mail address: shir@ioc.ac.ru (V.Z. Shirinian).

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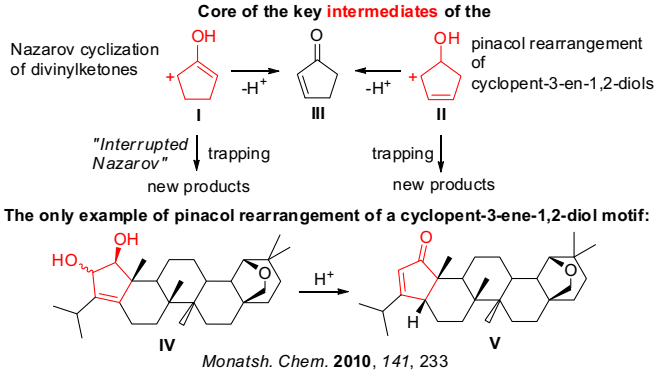


Scheme 1. Reactions of cyclopentenyl cations.

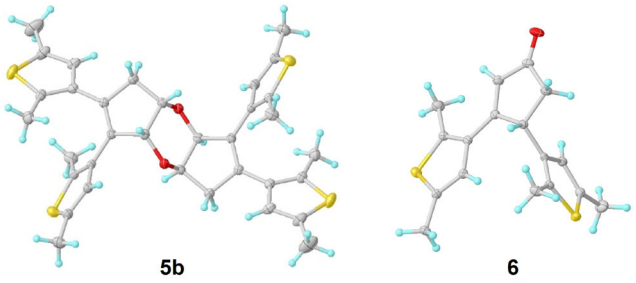


Fig. 1. Single crystal X-ray structures for compounds **5b** and **6**.

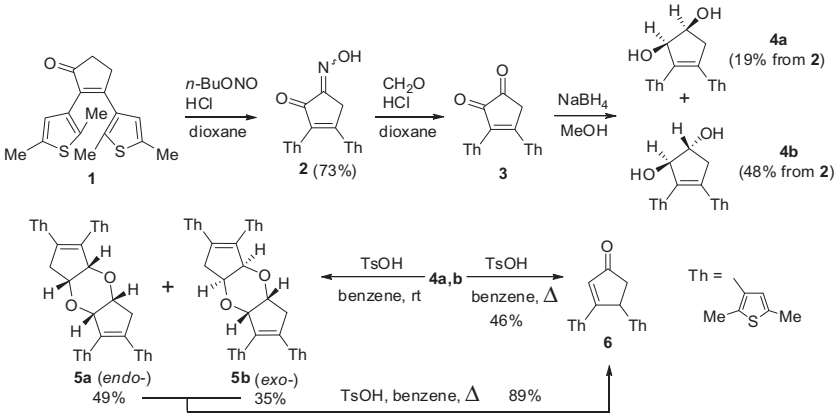
or the individual diols results in cyclopentenone **6** (which is isomeric to the starting compound **1**) as a single product in 46% yield (Scheme 2). The structure of compound **6** was proven by X-ray crystallography (Fig. 1).[16] At the same time, the acid-catalyzed reaction of a mixture of **4a**,**b** at room temperature provided isomeric products **5a** and **5b** containing a central dioxane core in 84% yield. X-ray crystallography of compound **5b** showed the *exo*-conformation of the tricyclic skeleton (Fig. 1).[16] It should be noted that the formation of compounds **5** from the corresponding diols represents the first synthesis of the dicyclopenta[*b*,*e*][1,4]-dioxine core. Compounds **5** are unstable under acidic conditions at high temperature and formed cyclopentenone **6** in 89% yield. It should be noted that the four-step transformation of **1** to **6** made it possible to obtain a less stable 3,4-disubstituted cyclopent-2-en-1-one from a more stable 2,3-isomer (the energy difference is 4.4 kcal/mol[17]).

Interesting results were also obtained for an unsymmetrical 3,4-substituted cyclopent-3-en-1,2-diol bearing different aromatic substituents. Diarylethene **7** comprising of thiophene and oxazole moieties was sequentially converted into the corresponding diol **10** (as a mixture of *cis*- and *trans*-diastereomers[17]) *via* oxime **8** and diketone **9** (Scheme 3). The isomeric ketones **11a** (major) and **11b** (minor) were isolated after acidic treatment of diols **10**. The structures of the isomers were proven by assignment of the NMR signals using two-dimensional NMR methods.[17]

A mechanistic rationalization for this reaction is given in Scheme 4. Obviously, the key intermediate of this acid-catalyzed transformation is carbocation **12**. Note, when cyclopent-3-en-1,2-diols react with acid, a cyclopenten-3-yl cation is formed rather than cyclopenten-4-yl one, which is due to the contribution of the double bond and the aromatic substituent in the stabilization of the positive charge.[18] At room temperature, carbocation **12** undergoes a dimerization reaction to give adducts **5**. Depending on the stereochemistry of the involved cations, two adducts, *endo*- and *exo*- were obtained.

At a higher temperature, carbocation **12** is unstable and undergoes a sigmatropic [1,2]-H shift which is typical for the pinacol rearrangement, leading to protonated ketone **13**. The next step is enolization of the latter resulting in intermediates **14**. Isomerization of the β,γ-unsaturated ketones to the corresponding α,β-unsaturated ketones under acidic conditions by protonation at the γ-carbon atom has been previously reported in several publications.[19] Compounds **14** react similarly, forming terminal products **6** or **11** *via* protonation/deprotonation steps. On the basis of these considerations, the observed selectivity in the formation of cyclopentenones **11a** and **11b** can be explained. This selectivity is determined by the distribution of electron density at the γ-carbon atom in intermediates **14**. As shown by DFT calculations,[17] the electron density at this position is higher for intermediate **14a** (Het^1 = thiophene, Het^2 = oxazole), which leads eventually to the major product **11a**. Although intermediate **14a** is less stable than isomer **14b** (1.3 kcal/mol difference in ground state energy), it does not affect the selectivity of the reaction, possibly due to the reversibility of keto-enol tautomerization.

The mechanism of the above-described acid-catalyzed reaction of 3,4-disubstituted cyclopent-3-ene-1,2-diols has similar stages to the Nazarov cyclization. The key intermediates of both transformations are isomeric cyclopentenyl carbocations, and in both case elimination of the proton leads to the formation of cyclopent-2-en-1-ones. Another similarity is the possibility of carbocation trapping by nucleophiles. For the Nazarov cyclization this transformation is called an interrupted Nazarov cyclization and has been described for a wide range of substrates.[7] In the described reaction, the carbocation formed from the corresponding cyclopent-3-en-



Scheme 2. Synthesis and acid-induced reactions of 2,3-bis (2,5-dimethylthiophen-3-yl) cyclopent-3-en-1,2-diol.