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Synthesis and Tautomerization of Benzo[*cd*]azulen-3-ones

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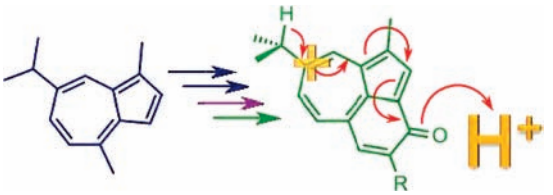
ABSTRACT

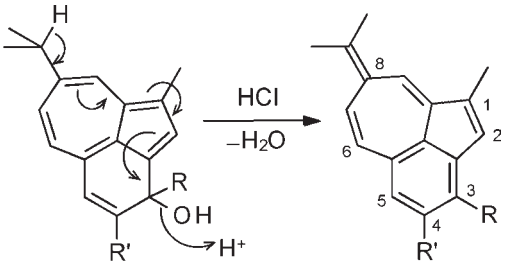


This report describes a type of tautomerization reaction that proceeds via isomerization of π-bonds across the azulene moieties of tricyclic benzo[*cd*]azulen-3-ones. The reaction mechanism shows similarities to an elimination reaction that was recently developed in our group. Furthermore, the facile four-step syntheses of the benzo[*cd*]azulen-3-ones, the starting materials for the tautomerization reactions, and computational analyses of the tautomerization reaction are included.

We recently analyzed heptafulvenes computationally[1,2] and also reported on complex one-pot transformations of azulene derivatives into tricyclic heptafulvenes,[3a] similar to those obtained by McGlinchey *et al.*[3b] The central step of these reaction sequences was an acid-catalyzed elimination of water, proceeding via isomerizations of π-bonds across the azulene moieties of benzo[*cd*]azulenes, rationalized in Scheme 1. By use of hydrochloric acid, the tricyclic benzo[*cd*]azulene **1** is converted to the heptafulvene **2**. The transformation is initiated by the protonation of the hydroxy group in the 3-position, followed by its elimination and the isomerization of π-bonds. Most surprising, however, was the release of a proton from the alkyl substituent in the 8-position, which leads to the formation of an exocyclic double bond. Thereby, the aromaticity of the azulene subunit is lost in favor of the formation of an aromatic benzene moiety.

After elaborating successful reaction conditions for such elimination reactions, we became interested in similar transformations based on a tautomerization reaction mechanism. This idea is outlined in Scheme 2. In the course of such a reaction, the carbonyl group of the benzo[*cd*]azulen-3-ones **3** would undergo an enolization process that gives the heptafulvenic phenols **4**.

Scheme 1. Previously Reported Elimination Reaction of 3-Hydroxy-3*H*-benzo[*cd*]azulenes



1 **2**

R = CF_3, CO_2Et R' = OMe, OTBDMS, OH, Ph

The syntheses of the starting materials **3** for the tautomerization reactions are described in Scheme 3. Some benzo[*cd*]azulen-3-ones, similar to **3**, are known that have different substitution patterns from our compounds, so related synthetic routes to such tricyclic compounds have been published elsewhere. Neidlein and Kramer, for example, obtained 4,5-dihydrobenzo[*cd*]azulen-3-ones by

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(3) (a) Aumüller, I. B.; Yli-Kauhaluoma, J. *Org. Lett.* **2009**, *11*, 5363. (b) Balduzzi, S.; Müller-Bunz, H.; McGlinchey, M. J. *Chem.—Eur. J.* **2004**, *10*, 5398.

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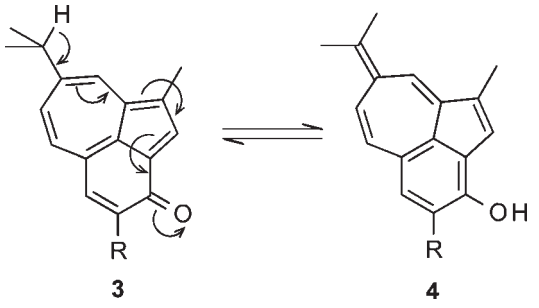
Scheme 2. Proposal for a Tautomerization Reaction of Benzo[*cd*]azulen-3-ones

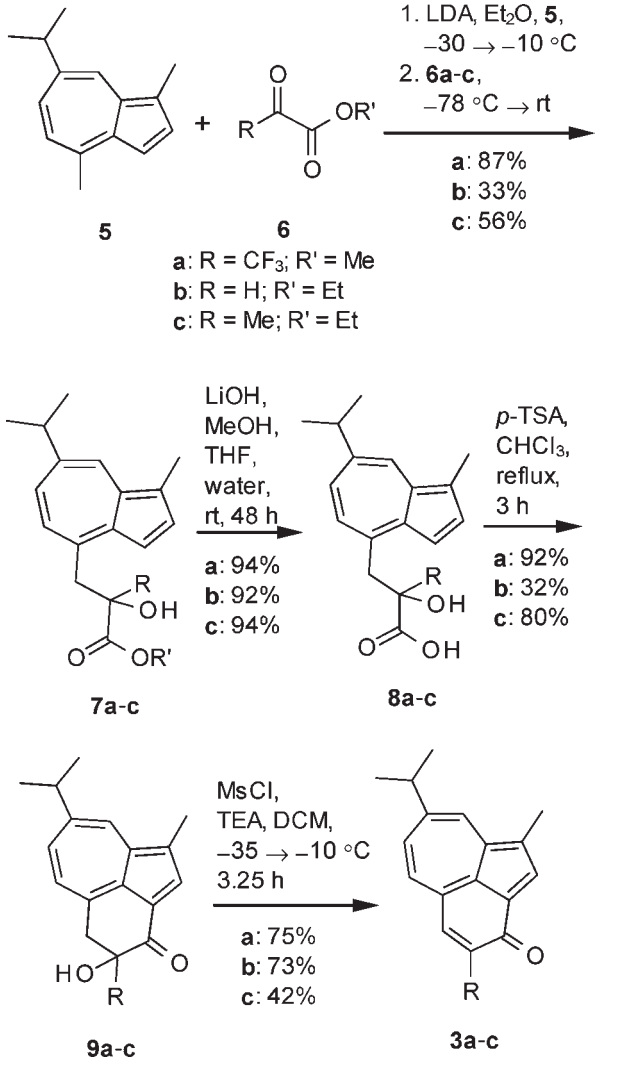


intramolecular acylations of azulene-4-propionic acid derivatives.[4] Our modification of their synthetic pathway allows the introduction of substituents in the 4-position of the resulting benzo[*cd*]azulene skeleton.

A four-step sequence resulted in being preferable. We started from the commercially available guaiazulene **5**. The first synthetic step makes use of the CH-acidity of the 4-methyl group, a procedure that reflects a common strategy in the field of azulene chemistry.[4,7a,b,8] Strong bases, such as lithium diisopropylamide (LDA), facilitate the deprotonation of the 4-methyl group of **5**. Typically, the resulting azulene carbanions are quite stable due to the presence of an aromatic cyclopentadienyl anionic moiety in their resonance forms. Nevertheless, these species react readily with electrophiles.[8] Neidlein and Kramer used bromoacetic acid and obtained a 3-azulenylpropionic acid via nucleophilic substitution.[4]

In contrast, herein we report the use of the α-oxo carboxylic acid esters **6a**−**c** as electrophiles in such reactions. The nucleophilic attack of the guaiazulene-derived carbanion proceeds predominantly at the ketone carbonyl instead of the ester carbonyl. Accordingly, these reagents give the azulene-substituted propionic acid esters **7a**−**c**, which bear a hydroxy group in the α-position to the carboxylic acid ester. The use of **6a**−**c** offers an advantage over the use of bromoacetic acid, as different substituents (R) can be introduced at this step. In contrast, homologous derivatives of bromoacetic acid are prone to take part in elimination reactions instead of substitutions, if they possess hydrogen substituents in the *β*-position. The esters **7a**−**c** could be easily hydrolyzed to the corresponding carboxylic acids **8a**−**c** with lithium hydroxide. The

Scheme 3. Syntheses of the Benzo[*cd*]azulen-3-ones **3a**−**c**



cyclization of **8a**−**c** to the tricyclic benzo[*cd*]azulene skeleton, present in **9a**−**c**, was performed following previous examples of structurally related compounds, which showed that the catalysis with *p*-toluenesulfonic acid (*p*-TSA) in chloroform is preferred for such intramolecular electrophilic acylations.[4] Finally, the 4,5-dihydrobenzo[*cd*]azulen-3-ones **9a**−**c** were converted to the benzo[*cd*]azulen-3-ones **3a**−**c** by mesylation of the hydroxy groups followed by base-assisted elimination of the mesylate in the presence of triethylamine (TEA). Also, this last step deviates from the previously published benzo[*cd*]azulene syntheses that generated the final double bond between C4 and C5 via oxidation instead of elimination.

The benzo[*cd*]azulenes **3a**−**c** were subjected to attempts at tautomerization reactions according to Scheme 2. Indeed, we found that a reaction mechanism, analogous to the previously published elimination reaction, can be applied successfully to these ketones, which converts **3a**−**c** into the tricyclic heptafulvenes as described in Scheme 4. Hydrochloric acid was observed to be a suitable

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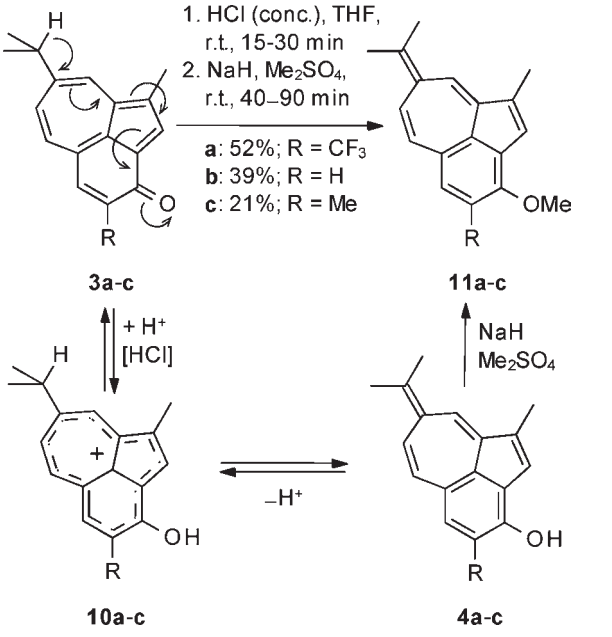
Scheme 4. Tautomerization Reactions Furnishing the Tricyclic Heptafulvenes **11a**−**c** from the Benzo[*cd*]azulen-3-ones



catalyst for the initial step of these isomerizations, leading to a color change from green to orange within 15 to 30 min. Presumably, the initial protonation of the carbonyl oxygens of **3a**−**c** leads to the formation of the cationic benzo[*cd*]azulenium species **10a**−**c**. Subsequently, the positive charge in **10a**−**c** is stabilized by the release of a proton from the alkyl substituent in the 8-position to form the phenols **4a**−**c**. Hereby, the exocyclic double bond is formed that characterizes the reaction products as heptafulvenes.

Although a concerted mechanism instead of the pathway via the intermediates **10a**−**c** has to be considered, a two-step mechanism of such reactions to **4a**−**c** is likely, because similar benzo[*cd*]azulenium ions have demonstrated considerable stability in numerous examples.[4−6] Notwithstanding, it is conceivable that not only the protonated derivatives **10a**−**c** but also predominantly the tautomerized phenols **4a**−**c** are present in the reaction mixture, because the hydrochloric acid was used in catalytic amounts. Thus, in an acidic medium the orange tautomers **4a**−**c** accumulate, possibly due to a higher proton affinity of the carbonyl oxygen in **3a**−**c** compared to the *i*Pr carbon atom in **4a**−**c**, so that the tautomerization of **3** to **4** is faster than the reverse reaction of **4** to **3**.

However the reaction mixture cannot be analyzed by TLC, due to the instability of the orange-colored intermediates. Accordingly, the primary tautomerized products with the general structure of **4** could also not be isolated as phenols. An additional *in situ* derivatization after the acidification with hydrochloric acid was needed, in order to prevent a possible reverse tautomerization during workup. We chose deprotonation with the strong base sodium hydride followed by methylation with dimethyl sulfate. That is why the heptafulvenic reaction products were isolated as the orange phenol ethers **11a**−**c**.

A reverse tautomerization in the last step is prevented as the deprotonation with excess of NaH is fast. Due to the higher electronegativity of oxygen the resulting negative charge is localized predominantly at the oxygen atom, so that an alternative methylation of the *i*Pr carbon could not be observed. So far, we were also not able to obtain heptafulvenes by direct base treatment of **3a**−**c**. Therefore, the initial acid-catalyzed tautomerization seems to be essential for this conversion as it facilitates the proton abstraction from these tricyclic systems.

The energies of the derivatives **3a**−**c** and **4a**−**c** were determined computationally with the Kohn−Sham density functional theory method and the Gaussian03 suite of programs.[9] The M05 functional[10] has been used in combination with Dunning's correlation-consistent plus polarization basis set cc-pVDZ.[11,12] These calculations showed that, with respect to total energies in the gas phase, the ketone tautomers are more stable than the phenol forms. The energy difference is smallest for derivative **a** (3.38 kcal mol^{-1}), bearing an electron-withdrawing substituent at position 4 (CF_3). For derivative **b** it is greater (6.20 kcal mol^{-1}), and for **c** the largest difference of 9.24 kcal mol^{-1} could be determined. These energy differences seem to correlate with the yield of these reactions, so that better yields can be obtained, when the energy difference between the two tautomers is small, as in derivative **a**. Likewise the orange color after addition of the hydrochloric acid was most pronounced in the reaction of **3a** compared to **3b** and **3c**.

In conclusion, benzo[*cd*]azulen-3-ones are available from guaiazulene (**5**) in four steps and are convertible to tricyclic heptafulvenes. The use of α-oxo carboxylic acid esters for the initial derivatization of **5** allows introduction of various substituents at the 4-position of the final tricyclic products. The reaction works best, when the energy difference between the two tautomeric forms is small. The successful application of a tautomerization reaction mechanism shows that the formation of exocyclic double bonds from tricyclic azulene derivatives can be achieved by different reaction types. Common for both, the

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tautomerization and the previously published elimination reaction,[3a] is the isomerization of π-bonds across the tricyclic system, supported by the formation of an aromatic six-membered ring.

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Supporting Information Available. Synthesis procedures and ^{1}H and ^{13}C NMR spectra of all synthesized compounds, as well as Cartesian coordinates and total electronic energies of the geometrically optimized structures. This material is available free of charge via the Internet at http://pubs.acs.org.