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Benzo[*cd*]azulene Skeleton: Azulene, Heptafulvene, and Tropone Derivatives

Ingo B. Aumüller and Jari Yli-Kauhaluoma*

Division of Pharmaceutical Chemistry, Faculty of Pharmacy, P.O. Box 56 (Viikinkaari 5 E), FI-00014 University of Helsinki, Finland

jari.yli-kauhaluoma@helsinki.fi

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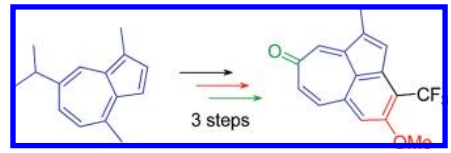
ABSTRACT



Due to our interest in protein kinase modulating compounds, we developed syntheses for benzo[*cd*]azulenes. By using very common catalysts and reagents, such as *t*-BuOK, HCl, and *m*CPBA, the commercially available guaiazulene is converted in three steps into tricyclic tropone derivatives. Electrophilic aromatic substitution reactions of guaiazulene proceed without a catalyst. Complex one-pot reactions convert 1′-hydroxyalkyl azulenes into tricyclic heptafulvenes, and finally, the mild oxidant *m*CPBA cleaves the semicyclic C═C double bonds to furnish tropones.

Azulene is a hydrocarbon consisting of a five- and a seven-membered ring fused to form an unsaturated bicyclic system. Besides their intensive colors, a typical property of azulene derivatives is the ability to undergo redox processes easily. Another important aspect is their polar character, resulting from contributions of charged aromatic partial structures, such as a cyclopentadienyl anion and a tropylium cation. These physicochemical features explain many of their synthetic utilities and have led to the development of interesting modern applications, such as their use as electrochromic materials,[1] near-infrared quenchers,[2] color-tags for the chromophore-supported purification technique,[3] or radical spin-trapping therapeutic agents.[4]

In addition, pure synthetic aspects of these compounds are being studied intensively, more than 70 years after the first synthesis of the parent azulene.[5] It is only recently that new efficient de novo syntheses have been reported,[6] and interesting synthetic modifications are published frequently. Our recent synthetic efforts resulted in three-step transformations of simple azulene precursors into complex tricyclic benzo[*cd*]azulenes,[7,8] which are illustrative with respect to the understanding of azulene chemistry. Benzo[*cd*]azulenes have attracted interest mainly due to their unique theoretical properties as odd nonalternant analogues of phenalene.[7,9] In contrast, the derivatives presented herein are chemically best classified as heptafulvenes or tropones and were prepared with the aim to investigate their properties as inhibitors of protein kinases.[10]

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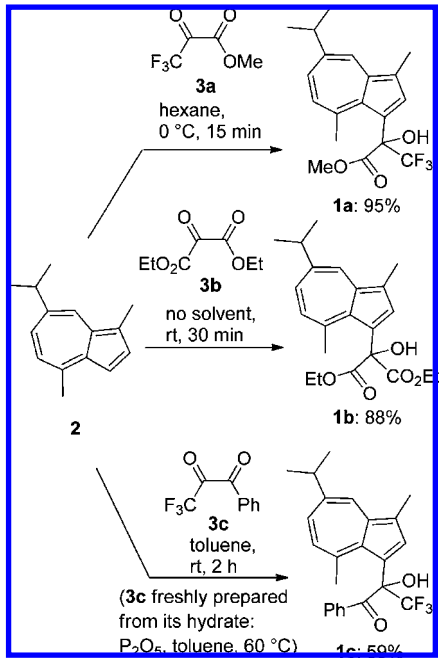
1′-Hydroxyalkyl azulenes are well-known to be acid-sensitive, and this is why such compounds are usually not prepared via electrophilic substitution reactions (S_E) of azulenes with ketones.[11a,12,13] In fact, such structures are primarily formed in these reactions, but the acidic catalyst of S_E reactions typically promotes further reaction steps.[11,12]

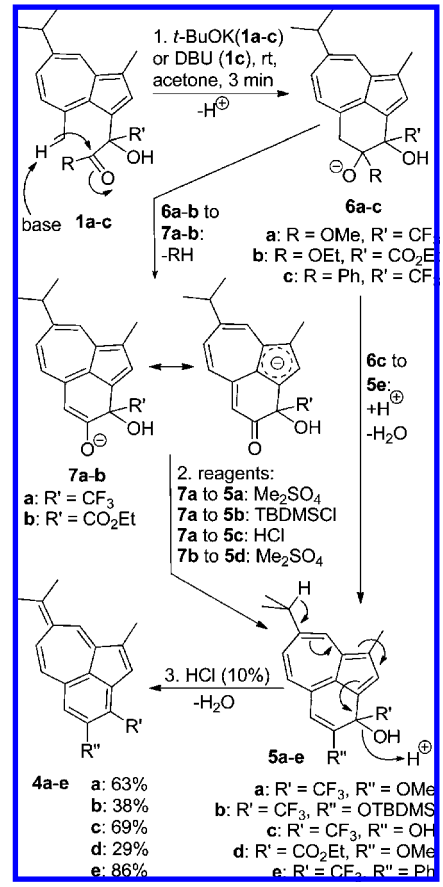
Scheme 1. S_E of Guaiazulene (**2**) to **1a**−**c**, Using the Activated 1,2-Dicarbonyl Electrophiles **3a**−**c**, Which Does Not Require a Catalyst



We found, however, that the specific 1′-hydroxyalkyl azulenes **1a**−**c** are accessible by a S_E, starting from guaiazulene **2** (Scheme 1). Crucial are the structures of the 1,2-dicarbonyl electrophiles **3a**−**c**, which are additionally activated by a second electron-withdrawing substituent (CF_3 (**3a**, **3c**); CO_2Et (**3b**)). The high electrophilicity of the central carbon atom compensates for the need for a catalyst, and the typical S_E side reactions are prevented. Additionally, the particular substituents in **1a**−**c** reduce the electron density on the resulting carbinol carbons, so that these derivatives can be conveniently isolated.

The subsequent transformations of the azulenes **1a**−**c** into the benzo[*cd*]azulenes **4a**−**e** (Scheme 2) are best realized

Scheme 2. One-Pot Reactions for the Synthesis of the Heptafulvenes **4a**−**e** via Elimination Across the Respective Azulene Moieties



as one-pot procedures because the reaction intermediates **5a**−**e** (also 1′-hydroxyalkyl azulenes) are, in particular, prone to elimination of their hydroxy group, due to the concurrent aromatization of the six-membered ring. For this reason, **5a**−**e** were generated in situ from **1a**−**c**, via a reaction path initiated by deprotonation of the methyl group in **1a**−**c**, a common strategy in azulene chemistry.[7d,8c,e,3,14] The intermediate methylene carbanions of **1a**−**c** instantly attack the neighboring carbonyl group to form the benzo[*cd*]azulene skeleton. Accordingly, the ester groups in **1a**,**b** account for the formation of hemiacetals in **6a**,**b**.

The subsequent elimination of the corresponding alcohol gives the enolates **7a**,**b**, which are stabilized by an aromatic cyclopentadienyl anion in the presented resonance forms. When the base catalyst (*t*-BuOK) is used in stoichiometric amounts, **7a**,**b** are reasonably stable in solution, so that modifications of the substitution pattern become possible. Alkylation, silylation, and protonation led to **5a**−**d**, respec-

(10) Some of the benzo[*cd*]azulenes synthesized were preliminarily tested against a panel of 70 kinases, screening for residual kinase activity less than 50%. The most significant inhibitions detected concern serine/threonine kinases, which belong to the CAMK (calcium/calmodulin-regulated kinases) family of kinases. Further work to characterize these bioactivities is now in progress in our and in our collaborators laboratories. An example of our previous work on protein kinase C: Boije af Gennäs, G.; Talman, V.; Aitio, O.; Ekokoski, E.; Finel, M.; Tuominen, R. K.; Yli-Kauhaluoma, J. *J. Med. Chem.* **2009**, *52*, 3969.

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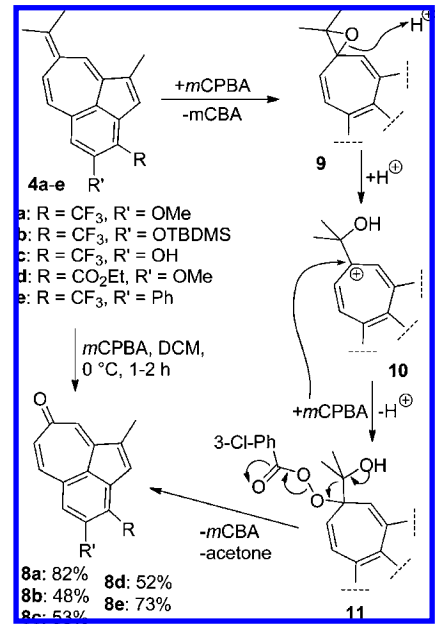
tively. The ketone function in **1c** accounts for a different route to **5e**. In contrast to **6a**,**b**, the cyclized intermediate **6c** is an alkoxide that cannot be converted into an enolate similar to **7a**,**b**. By eliminating water, **6c** directly forms **5e**, a process that accounts for the reprotonation of **6c**. Consequently, the milder base DBU should be used in catalytic amounts only.

Finally, the addition of HCl to the solutions of **5a**−**e** readily initiates an interesting type of acid-catalyzed elimination reaction leading to **4a**−**e**. This reaction starts with the protonation of the hydroxyl oxygens and proceeds via isomerizations of π-bonds across the azulene moieties of **5a**−**e**. Hydroxy eliminations of structurally related 1′-hydroxyalkyl azulenes[11,12] and benzo[*cd*]azulenes[7a−c,15] are known and lead usually to cationic species, in which the positive charge is delocalized predominantly within the seven-membered ring. The unique step in the synthesis of **4a**−**e** is the release of a proton from the alkyl substituents at the 8 position leading to the formation of semicyclic C═C double bonds, which characterize the tricyclic products **4a**−**e** as heptafulvenes.

All in all, these reactions deprive the azulene moieties in **5** of aromaticity by generating the heptafulvenes **4**,[16] containing an aromatic benzene unit. Analogous processes have not been reported previously, but a few azulene-derived heptafulvenes have been characterized as specific oxidation products.[7d,17]

Further, we examined oxidations of the heptafulvenes **4** (Scheme 3). Syntheses of tropones via heptafulvenes are not well documented,[18] but this pathway was quite profitable for the preparation of the tricyclic tropones **8a**−**e**, partly due to the mildness of the oxidant. Although the cleavage of C═C double bonds is unusual for *m*CPBA (*m*-chloroperoxybenzoic acid), this reagent was sufficiently strong for all oxidations. Our hypothetical reaction mechanism suggests that first the epoxide **9** is formed by 1 equiv of *m*CPBA.[19] Presumably, **9** is prone to ring-opening reactions, due to the effective stabilization of the positive charge by the conjugated π-system (especially the seven-membered ring) in the resulting cations **10**. Therefore, even the weak acidity of *m*CPBA or *m*CBA enables catalysis of this step. Subsequently, the acyl peroxides **11** are formed by nucleophilic attack of another equivalent of *m*CPBA. Finally, the exit of the leaving group *m*CBA initiates the fragmentation of **11**, yielding the tropones **8a**−**e** and acetone.

Scheme 3. Oxidations of Heptafulvenes **4a**−**e** to the Corresponding Tropones **8a**−**e**[a]



[a] The suggested reaction mechanism consumes 2 equiv of *m*CPBA (*m*C(P)BA: *meta*-chloro(peroxy)benzoic acid).

In conclusion, we synthesized the tricyclic tropones **8a**−**e**, via three steps from the commercially available guaiazulene. All of the three reactions comprise interesting synthetic aspects. Uncatalyzed S_E reactions of guaiazulene, complex eliminations across azulene moieties, and C═C bond cleavages with the mild *m*CPBA have been uncovered. All the reaction conditions are mild; reaction times are short; and the reagents are easily available, so that broad applicability of these reaction types for similar structures is indicated.

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Supporting Information Available: Experimental procedures, compound characterization data, and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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