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Published in:
ARKIVOC

DOI:
10.3998/ark.5550190.p008.475

Publication date:
2014

Document version
Publisher's PDF, also known as Version of record

Synthetic protocols for the key functionalizations of the photochromic dihydroazulene scaffold

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DOI: http://dx.doi.org/10.3998/ark.5550190.p008.475

Abstract
1,8a-Dihydroazulene-1,1-dicarbonitrile (DHA) is a photochromic molecule which upon irradiation undergoes ring-opening to a vinylheptafulvene (VHF). The system has many possible sites for functionalization and hence for tuning of its properties. In this account we summarize different synthetic protocols for attaching substituents at the ring carbon atoms of DHA as well as for replacing the cyano groups at position 1. In particular, positions 2 and 7 are most easily accessed, the latter from DHA by a regioselective bromination-elimination protocol.

Keywords: Azulene, bromination, isomerization, photoswitch, tropylium

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1. Introduction

The growing interest in light-harvesting molecular devices for solar energy conversion and storage has increased the attention on systems able to change their status upon excitation.[1-3] Photo- and thermo-activated molecular switches are a family of compounds able to switch from

one molecular structure to another upon light irradiation or changes in temperature, and whose characteristics depend on the nature of the functional groups that reside on the molecules.[4] Thus, a molecule which upon excitation isomerizes to a more energetic metastable isomer, which in time will return to the more stable isomer by releasing energy as heat, may find use in light-harvesting energy storage devices.[3] In this context, the dihydroazulene/vinylheptafulvene (DHA/VHF) system **1/2** (Scheme 1), reported for the first time by Daub and co-workers in 1984,[5,6] is particularly interesting. DHA **1** is a yellow photochromic compound, which undergoes a light-induced 10-electron retro-electrocyclization to the red VHF **2**. The back-reaction to the parent DHA **1** can be realized by a thermally induced ring-closure and, as recently discovered, by treatment with mild Lewis acids that enhance the rate of the thermal conversion,[7] while it is not induced by light. The rate of the back reaction is strongly solvent dependent, increasing with solvent polarity.[8,9] This is in line with a suggested mechanism that involves a zwitterionic transition state, with a positively charged seven-membered ring and a negatively charged malononitrile moiety.[10] The longest-wavelength absorption maxima of DHA **1** and VHF **2** are at 353 and 470 nm, respectively, in acetonitrile (Figure 1).[9] In this solvent, the quantum yield of the ring-opening reaction from **1** to **2** is 0.55[8], and the rate constant for the back-reaction is 5.36 x 10^{-5} s^{-1}.[9] It is worth noting that C-8a of DHA **1** is a stereocenter and the DHA hence exists as a pair of enantiomers. Recent applications of the DHA/VHF system include its use as a chemodosimeter for thiols[11] and as a molecular switch in molecular electronics devices.[12-15]

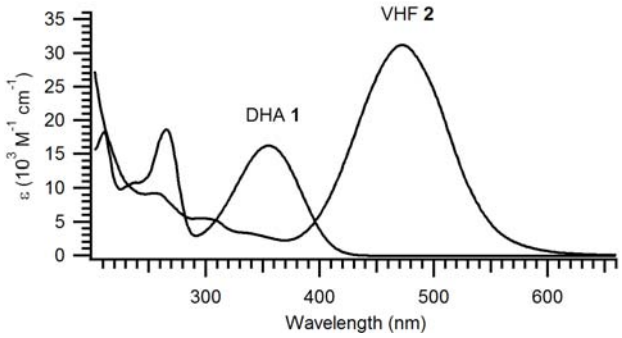
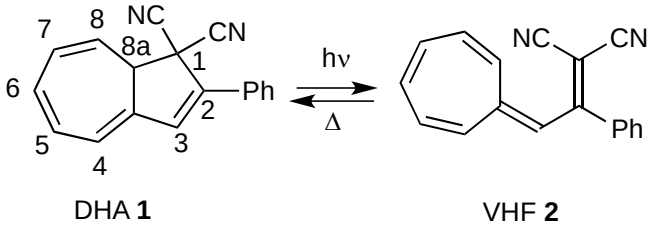


Figure 1. UV-Vis absorption spectra of DHA **1** and VHF **2** in acetonitrile at 25 °C.

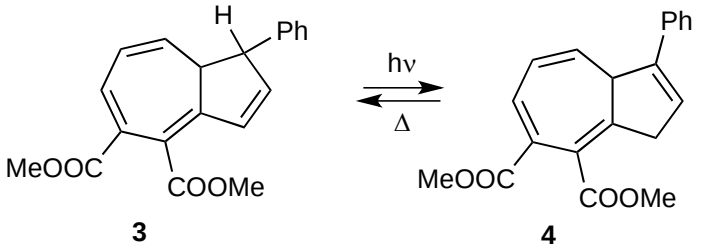


Scheme 1. DHA/VHF photo/thermoswitch system and numbering of the DHA skeleton.

The switching event between the two isomers seems to be dependent on the presence of the two cyano groups in position 1;[16,17] besides, modulation of the optical and switching properties

of the system can be accomplished by introduction of diverse functional groups either on the five-membered or on the seven-membered ring of the skeleton or on both. Therefore, efficient synthetic protocols that allow easy access to new derivatives substituted at various positions of the original scaffold **1** have been explored and will be the focus of this account.

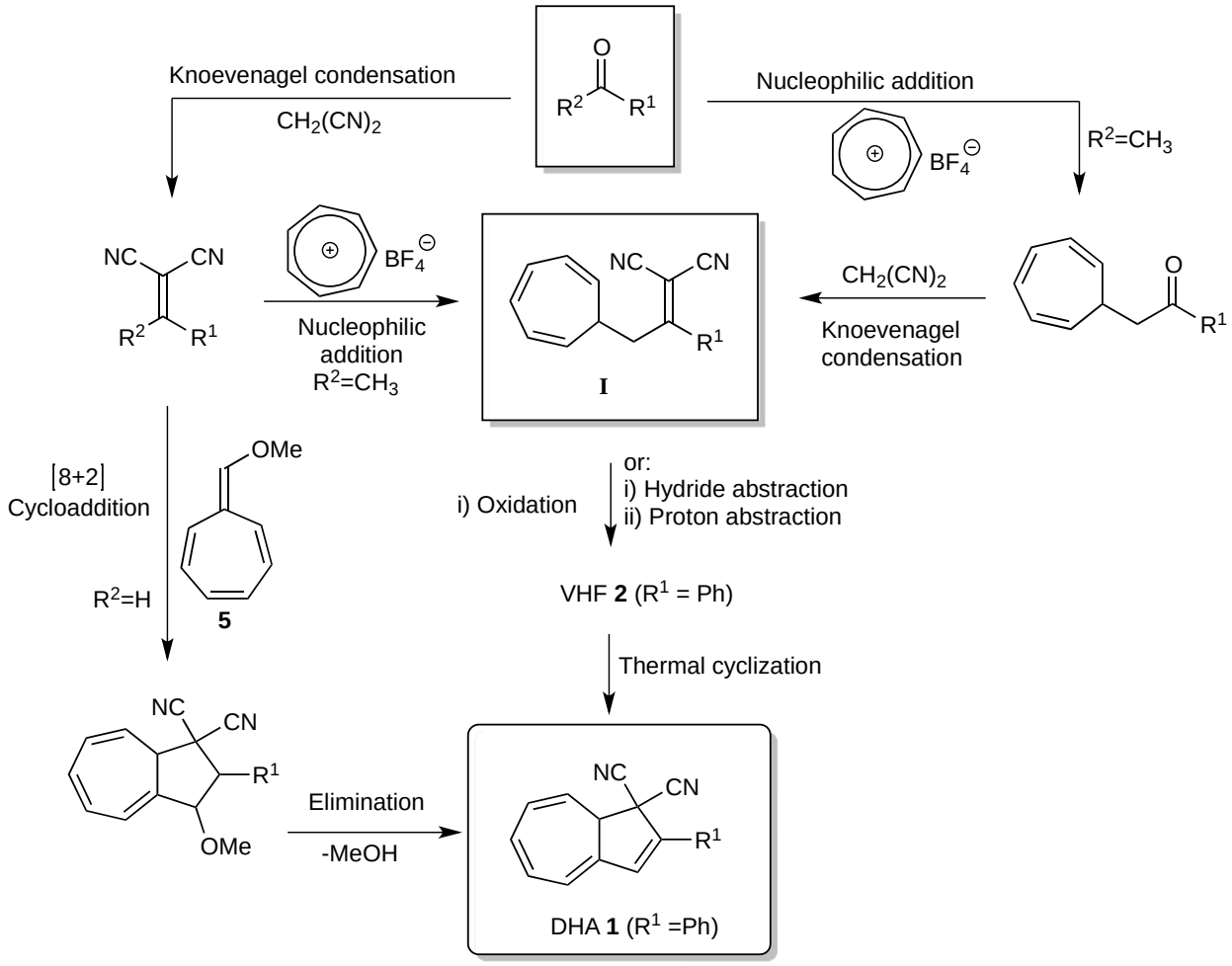
A few other dihydroazulene compounds bearing different groups from cyano at C1 should be mentioned here in the introduction.[18-21] They are mainly 1-phenyl, 1,1-diphenyl or 1,1-dimethyl-3-phenyl derivatives, and in only one example there was evidence of a photo-switching event (Scheme 2).[20] Compound **3** underwent a 1,3-sigmatropic arrangement upon irradiation, furnishing the isomer **4**. Upon heating, the original isomer **3** was regenerated.



3 **4**

Scheme 2. Dihydroazulene undergoing light-induced sigmatropic rearrangement.

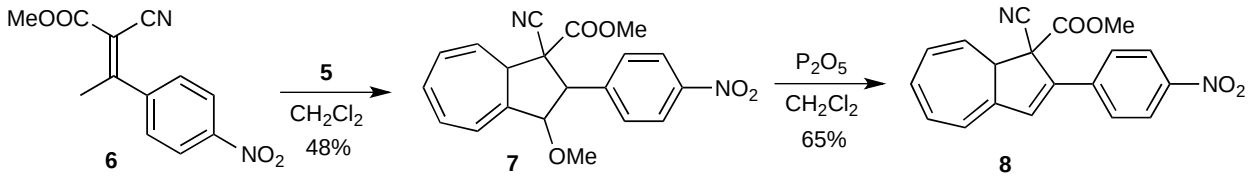
The first procedure for the preparation of DHA skeletons like **1** consisted of a [8+2] cycloaddition reaction between 8-methoxyheptafulvene **5** and the 1,1-dicyanoethylene derivative, obtained by a Knoevenagel condensation between benzaldehyde (R^1 = Ph, R^2 = H) and malononitrile (Scheme 3). Thus, direct formation of DHA **1** (R^1 = Ph) was accomplished by elimination of methanol.[16] This strategy suffered from the need of stoichiometric amounts of toxic mercury(II)acetate in the preparation of 8-methoxyheptafulvene **5**. An alternative and more versatile route identifies **I** as a key intermediate in the synthetic pathway. As a matter of fact, **I** can be prepared either by nucleophilic addition of the enolate of acetophenones to tropylium, followed by a Knoevenagel condensation with malononitrile,[22] or, as later reported,[23] reversing the reaction order (which allows synthesis on a multigram scale),[9] by a Knoevenagel condensation of acetophenones and malononitrile, and then a base-catalyzed nucleophilic addition with tropylium salts. Next, intermediate **I** can be subjected to oxidation, or first to hydride abstraction and then proton abstraction, giving the VHF derivative, which in turn gives the corresponding DHA by thermal isomerization.



Scheme 3. Possible routes to the DHA skeleton.

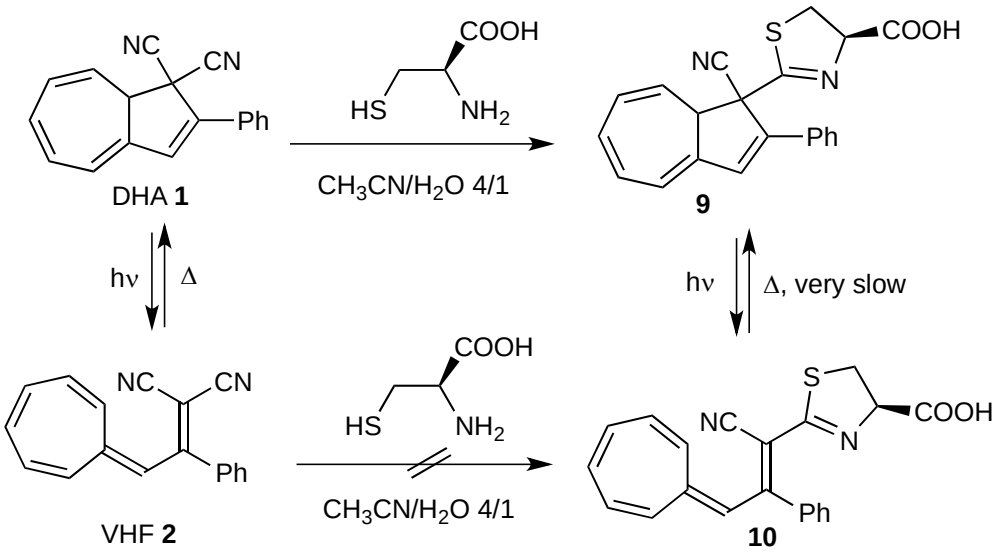
2. Reactivity and Functionalization of the Five-membered Ring of Dihydroazulene

Replacing one or both of the cyano groups on C-1 by esters or amides may have a significant impact on the switching ability. The synthesis of 1-R^1,1´-R^2-DHA derivatives was accomplished by Daub and coworkers following the first strategy described for DHA **1**.[17] A [8+2] cycloaddition reaction between 8-methoxyheptafulvene **5** and **6**, obtained by Knoevenagel condensation, gave the intermediate **7**, which furnished **8** by elimination with phosphorus pentoxide (Scheme 4). The switching properties of **8** and its analogs, however, were not described.[16,17] The two different substituents on C-1 introduce a second stereocenter (C-1) in addition to C-8a, and in consequence diastereomeric mixtures of isomers can be formed.



Scheme 4. Daub's synthesis of a DHA bearing two different groups on C-1.

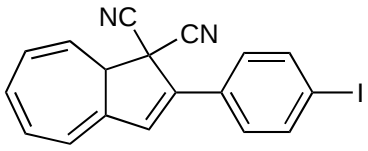
Recently, we have shown that DHA **1** can be used as chemodosimeter for thiols, producing a visible color change from orange to yellow that allows detection of sulfhydryl groups in solution.[11] Thus, DHA **1** reacts quantitatively with L-cysteine or its methyl ester furnishing DHA **9** (Scheme 5) as a mixture of two diastereomers, where one of the cyano groups at C-1 has reacted with the 1,2-aminothiol moiety of cysteine to give a 4,5-dihydro-1,3-thiazole ring. Albeit efforts to perform the reaction on a preparative scale were not successful in terms of the purification of the single diastereomers, a quantitative transformation seemed to occur, as did a switching event to VHF **10**. A very slow conversion back to DHA **9** was observed. Apparently, the 4,5-dihydro-1,3-thiazole ring does not destroy completely the switching ability of the molecule.



Scheme 5. DHA with different substituents on C-1.

Functionalization of position 2 on the DHA skeleton has been most extensively explored.[5,6,9-17,22-28] Aromatic groups are the substituents most widely incorporated, but few examples with methyl group on C-2 or cyclopentyl between C-2/C-3 have also been reported.[22] As described in the introduction (Scheme 3), the syntheses have followed either: (i) the [8+2] cycloaddition protocol, (ii) the route *via* nucleophilic addition of acetophenones to tropylium, followed by a Knoevenagel condensation with malononitrile, or (iii) an initial Knoevenagel condensation

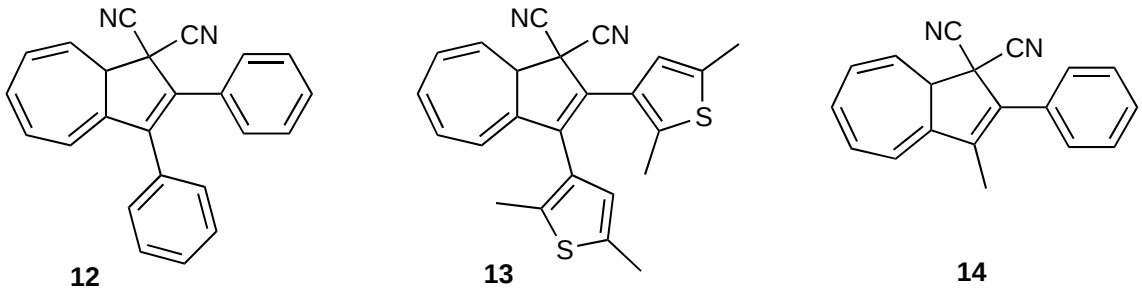
followed by reaction with tropylium species. The last route was particularly convenient for a multigram synthesis of an iodophenyl-substituted DHA **11** (Figure 2).[23] The same procedure was recently employed for synthesis of DHA **1** also in multigram scale.[9] The different routes have in common that a substituent group on the phenyl ring at position 2 of the final DHA is present from the beginning in the starting materials. None direct functionalization in this position of the final DHA skeleton is reported. Among this wide family of 2-substituted DHAs, compound **11** is particularly relevant for further functionalization owing to the halogen substituent, which allows for metal-catalyzed cross-coupling reactions.[14,24-26]



DHA **11**

Figure 2. DHA bearing a iodo substituent, prone to further functionalization.

Functionalization of position 3 has been little explored; a few derivatives are shown in Figure 3.[22,27,28] While the syntheses of **12** and **13** were straightforward, starting from malononitrile by Knoevenagel condensation,[27,28] the 3-methyl derivative **14** was never isolated, because it decomposed to the corresponding cyanoazulene under the reaction conditions.[22]



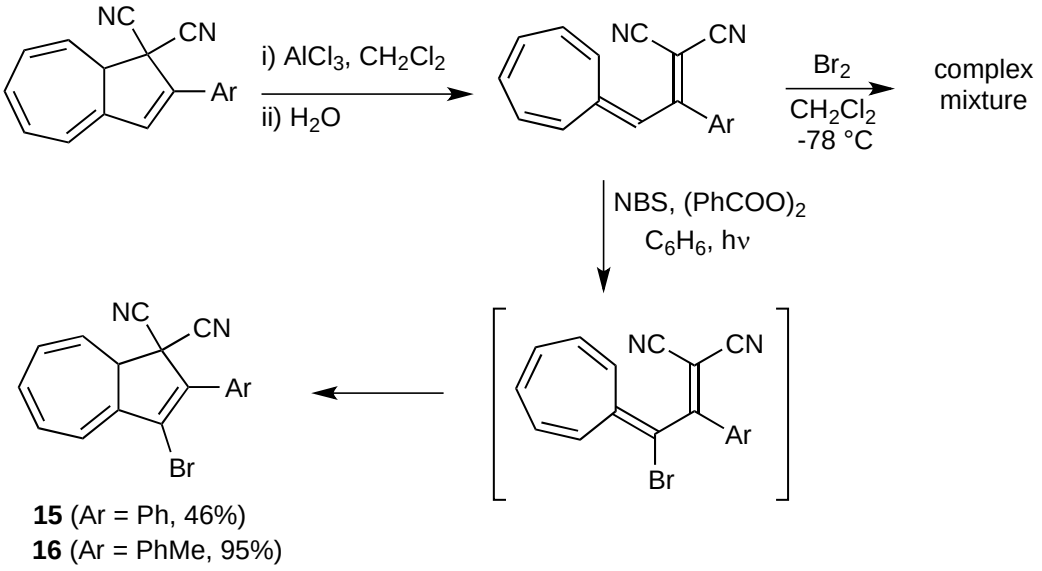
12 **13** **14**

Figure 3. DHAs with varying substituents at position 3.

Besides, a radical bromination of a VHF skeleton was previously reported by Kuroda and Asao,[29] but no thermal conversion to a DHA form was described. We have recently reported a direct functionalization at C-3 starting from the parent and readily available DHA/VHF system.[30] Ionic and radical bromination were both considered and attempted, as shown in Scheme 6, but only the latter was successful. DHA **1** was treated with aluminum chloride and water to furnish quantitatively VHF **2** (*i.e. via* a Lewis acid induced ring-opening of DHA).[7] When VHF **2** was reacted with bromine at low temperature, a complex mixture was detected, while radical bromination of **2** with *N*-bromosuccinimide (NBS) and a radical initiator in the presence of light

gave the 3-bromo derivative **15** in good yield. The procedure has been successfully applied also to a 2-tolyl DHA starting material to furnish **16** in 95% yield (estimated by NMR) over 3 steps. Interestingly, no evidence of benzylic bromination was registered on the tolyl substrate; the reaction hence shows complete regioselectivity.

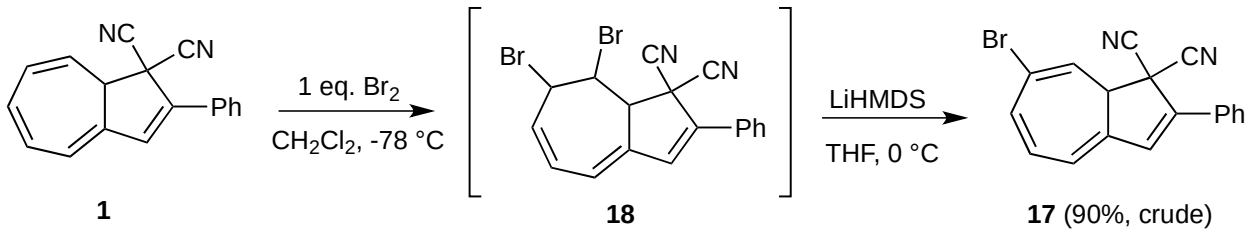
Initial attempts of Sonogashira and Suzuki coupling reactions of compound **15** unfortunately failed and the bromide seems very unreactive. It was instead possible to introduce another bromine in position 7 to give a 3,7-dibromo-substituted DHA through a bromination/elimination protocol, which had already been established for DHA **1** itself (*vide infra*, Section 4).[31-34]



Scheme 6. Functionalization on C-3.

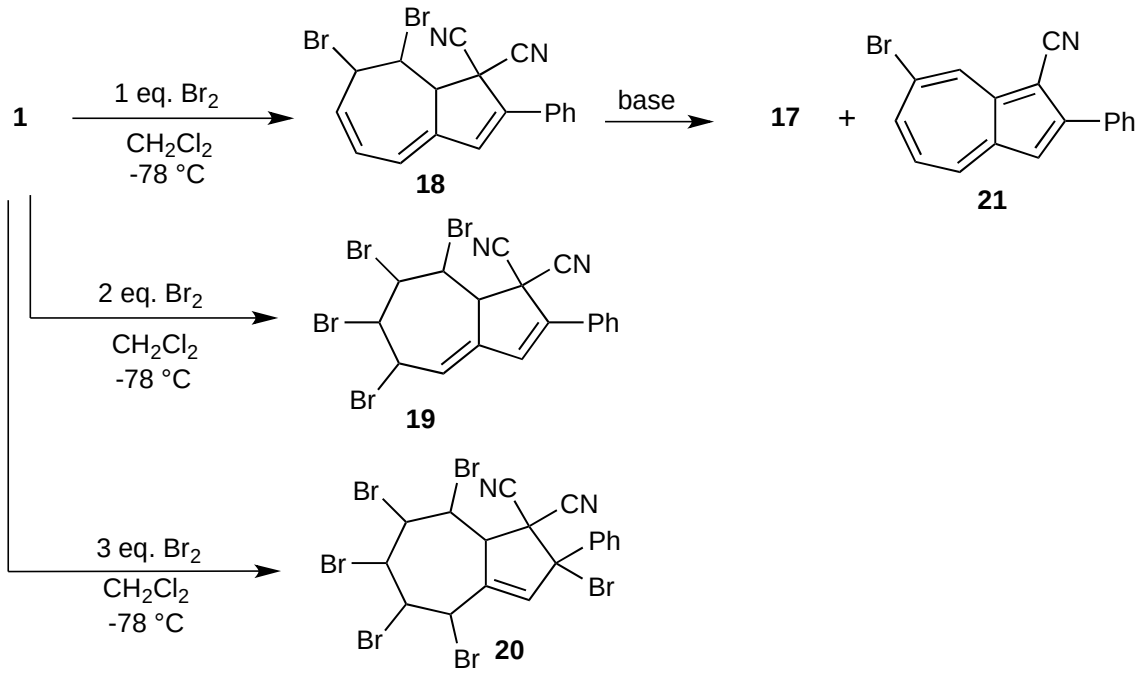
3. Reactivity and Functionalization of the Seven-membered Ring of Dihydroazulene

Recently, we reported the first direct and regioselective functionalization of the seven-membered ring of DHA **1**.[31-34] It consists of a sequential bromination/elimination protocol, which furnished selectively the 7-bromo DHA **17** starting from DHA **1** (Scheme 7).



Scheme 7. Functionalization on C-7.

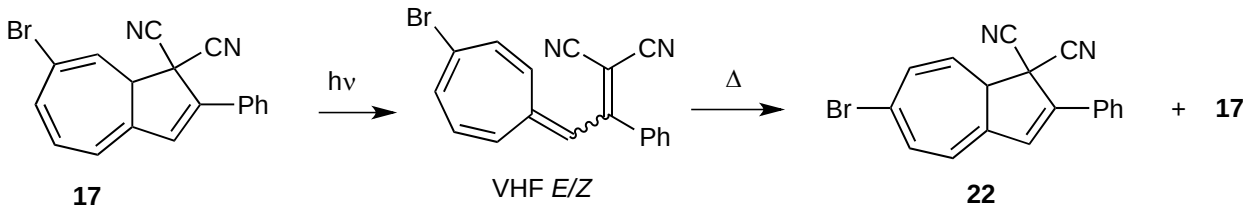
Addition of up to three molar equivalents of elemental bromine was possible in the first step (Scheme 8). Bromination of **1** occurs selectively at the 7,8-positions in quantitative yield to provide the dibromide **18** as a pair of enantiomers when using only one molar equivalent of bromine.[31] Treatment with two molar equivalents of bromine selectively furnished the tetrabromide **19**, while treatment with three (or more) equivalents furnished the hexabromide **20**.[32,34] The elimination step to give the 7-bromo DHA **17** from **18** was accomplished in high yield but was successful only upon treatment with lithium hexamethyldisilazide (LiHMDS) at 0 °C; indeed, raising the temperature or using more common bases, such as KO*t*Bu, pyridine, DBU, triethylamine or Hünig's base, gave azulene **21** and other azulene derivatives, and only in few cases, traces of **17**.



Scheme 8. Addition of bromine (1-3 eq.) to DHA **1.**

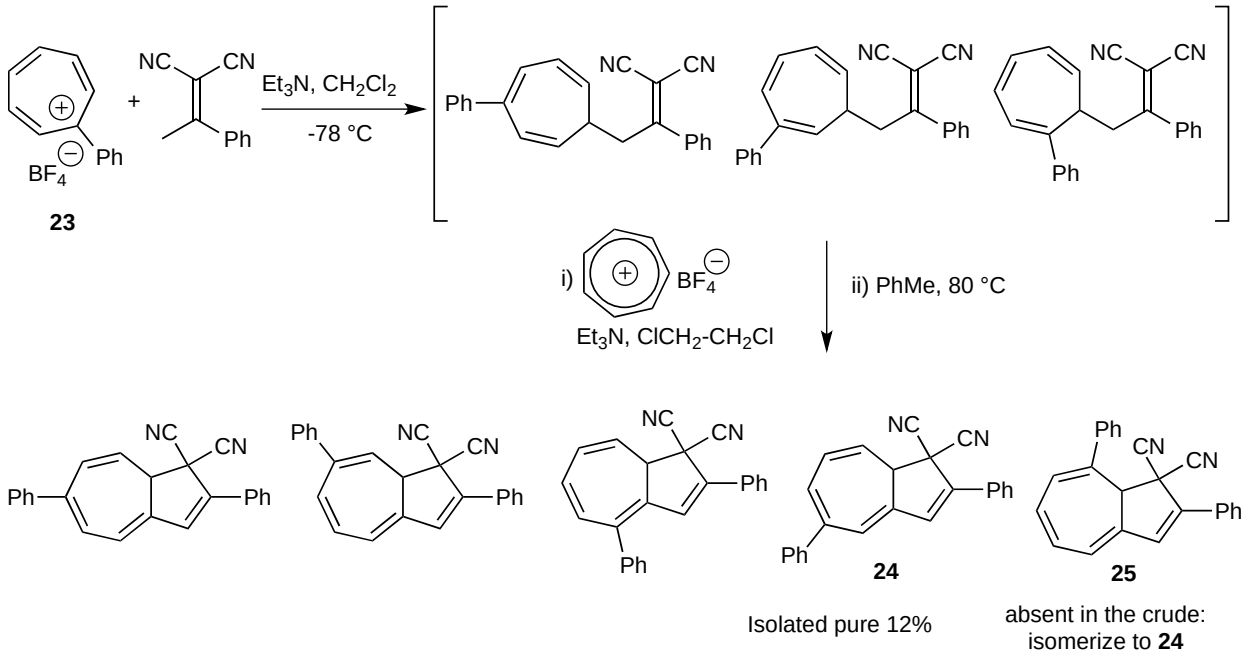
The straightforward access to the 7-bromo DHA **17** has opened the way *via* metal-catalyzed cross-couplings to a wide variety of 7-substituted DHA derivatives.[26,32,33] Thus, while the 3-bromo-derivative **15** described above was unreactive to such coupling conditions, the 7-bromo-substituted DHA is readily functionalized by aryl and alkynyl groups.

Another important step on DHA functionalization was taken while investigating light/heat cycles on **17**. Indeed, light irradiation provoked opening of the five-membered ring of the DHA skeleton and formation of VHF *E/Z*-isomers. Thermal ring-closure hereof gave a mixture of the original 7-bromo DHA **17** and the 6-bromo DHA **22** (Scheme 9).[33] The two DHA regioisomers can be easily distinguished by ^{1}H-NMR spectroscopy, and a COSY spectrum supported the assignment of the new DHA isomer as being the C-6 substituted.



Scheme 9. Isomerization of 7-bromo DHA **17** to 6-bromo DHA **22** *via* VHF.

Regioselective methods for obtaining DHA regioisomers with functional groups at the remaining positions in the seven-membered ring are still unknown. Yet some of these derivatives have been isolated by a nonregioselective method. In this method, a phenyl substituent was incorporated on the seven-membered ring before building the DHA skeleton.[35] Using the phenyltropylium species **23** in the key synthetic step shown in Scheme 10 resulted in a mixture of VHF precursors, from which a mixture of DHA isomers were ultimately obtained. By repeated chromatography it was possible to isolate the 5-phenyl DHA **24** in pure form as confirmed by X-ray crystallographic analysis. Light-induced ring-opening of this DHA to the corresponding VHF followed by thermal ring-closure gave both of the regioisomers **24** and **25**. Yet, after four days in the dark at room temperature, **25** was almost fully converted to **24**, possibly through a VHF intermediate. This result is in agreement with the absence of regioisomer **25** found in the crude mixture of the reaction and has been rationalized by calculations, which confirmed that **24** is more stable than the regioisomer **25** by 6.7 kcal/mol. The results show that **25** undergoes ring-opening without being subjected to light.

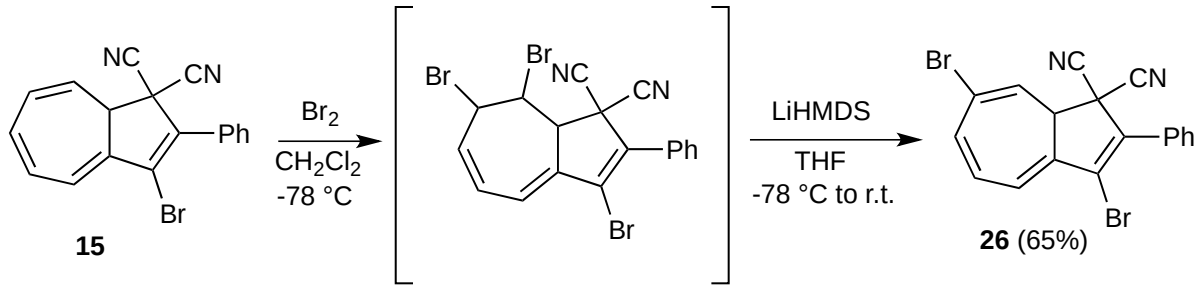


Scheme 10. Incorporation of substituent early in the synthesis of DHA.

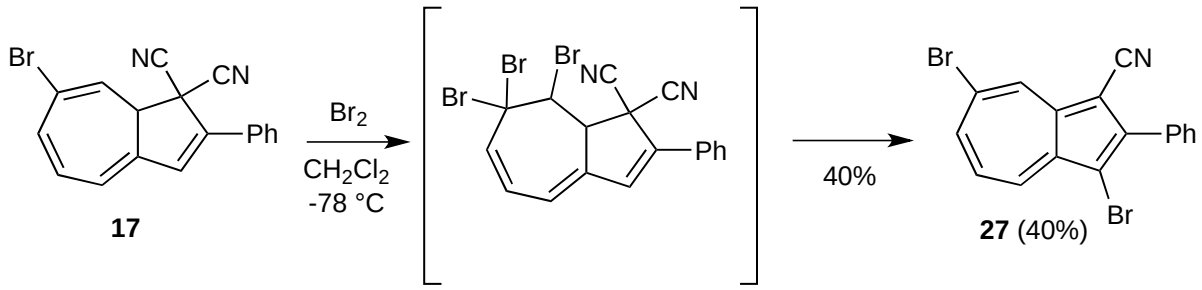
4. Double Functionalization of the Dihydroazulene Skeleton

Double functionalization of the DHA skeleton has been achieved applying the bromination/elimination protocol on 3-substituted DHA **15**,[30] 7-substituted DHA **17**[30] and on a wide variety of 2-substituted DHAs bearing various functional groups on the phenyl ring on C-2.[13,36]

The bromination/elimination protocol described in Section 3 was successfully applied to 3-bromo DHA **15** giving the 3,7-dibromo-functionalized DHA **26** in good yield (Scheme 11).[30] However, when applying the same bromination/elimination sequence to the 7-bromo-substituted DHA **17**, the azulene **27** was obtained (Scheme 12); this product was even formed in the absence of base, showing the lability of the intermediate.[30]

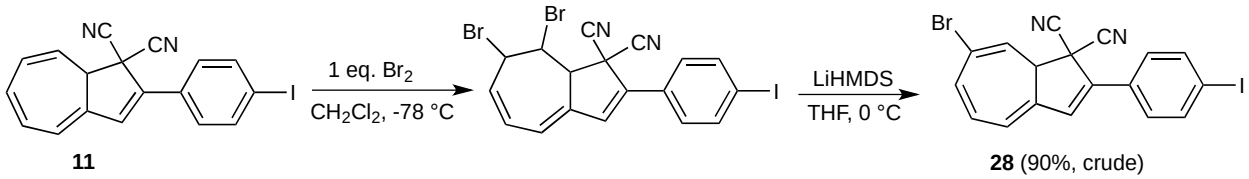


Scheme 11. Second functionalization of 3-bromo DHA **15.**



Scheme 12. Second functionalization of 7-bromo DHA **17.**

When subjecting the iodophenyl-DHA **11** to the bromination/elimination protocol, the doubly-functionalized derivative **28** was obtained (Scheme 13), containing two reactive handles for metal-catalyzed cross-coupling reactions.[13] Such reactions indicate that the iodine on **28** is more reactive than the bromine.



11 **28** (90%, crude)

Scheme 13. Synthesis of DHA with two reactive handles (halogens) for metal-catalyzed cross-coupling reactions.

5. Conclusions

As functionalization of dihydroazulenes can strongly alter their optical and photochromic properties, development of efficient synthetic protocols for functionalizing the system is important. For example, we have found that the kinetics of the thermal ring-closure reaction of aryl-substituted VHFs follows Hammett correlations, with opposite effects of electron-withdrawing/donating aryl groups in the five- and seven-membered rings. Positions 2, 3, and 7 can today be regioselectively accessed by efficient protocols. In particular, the regioselective bromination-elimination protocol, which can be expanded to derivatized DHAs, has offered within the past six years a particularly convenient way of achieving functional DHA derivatives. Ongoing research in our laboratory seeks to develop regioselective methods for functionalizing the other positions, with the prospect of being able to fine-tune the properties of the system.

Acknowledgements

University of Copenhagen is acknowledged for financial support.

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Søren Lindbæk Broman has been an instrumental figure in the developing field of DHA chemistry, from the onset of the research within the Brøndsted group. He has obtained both his undergraduate degree and masters diploma under the supervision of Prof. Mogens Brøndsted Nielsen at the Department of Chemistry at the University of Copenhagen. He is currently due to graduate with PhD specializing in method development in regioselective functionalizations of the 7-membered ring of DHA. His aspirations are to stay involved in the chemistry whilst pursuing research interests in TTF chemistry.

Mogens Brøndsted Nielsen is Professor of organic and sustainable chemistry and heads the Center for Exploitation of Solar Energy at University of Copenhagen. He received his Ph.D. in 1999 from the University of Southern Denmark under the supervision of Prof. Jan Becher in the field of synthetic and supramolecular chemistry. During his Ph.D. he spent one year with Prof. J. Fraser Stoddart at UCLA. He did two years of postdoctoral work with Prof. François Diederich at ETH in Zürich in the field of acetylenic scaffolding, and returned in 2002 to the University of Southern Denmark as Assistant Professor. In 2004 he moved to the University of Copenhagen as Associate Professor and was promoted in 2008 to Professor. His current research focuses on the development of redox-active and photochromic molecules.

