Synlett M. D. Kilde et al. Letter

On the Solvent-Dependent Bromination of Dihydroazulenes

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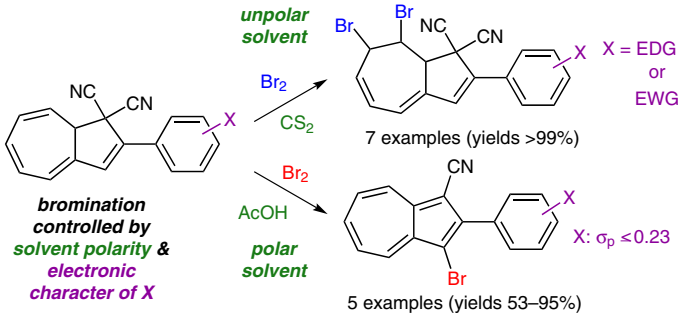
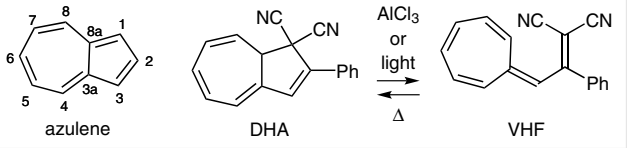


Received: 04.09.2015
Accepted after revision: 29.09.2015
Published online: 13.11.2015
DOI: 10.1055/s-0035-1560823; Art ID: st-2015-d0695-l

Abstract Bromination of 1,8a-dihydroazulene-1,1-dicarbonitriles (DHA) followed by elimination of HBr was previously shown to be an important protocol for functionalizing these molecular photoswitches in the seven-membered ring (at C7). Here we show systematically how the outcome of the bromination reaction depends on the electronic character of an aryl substituent at the C2 position of DHA, and the solvent polarity as the reaction can lead to either the addition product or to the corresponding 2-aryl-1-bromo-3-cyanoazulene.

Key words bromine, conjugation, elimination, solvent effects, cross-coupling

Azulene (Scheme 1) is a nonbenzenoid aromatic molecule with an intense blue color that can be varied depending on the nature and position of substituents on the two fused rings.[1–3] Azulene has a dipole moment of 1.0 D[4] since it has a tendency to form a stabilized tropylium cation together with a cyclopentadienyl anion.[5] Due to these properties, derivatives of azulenes can be utilized for advanced materials such as conducting polymers,[6] nonlinear optical (NLO) materials,[7] charge-transfer complexes,[8] and dye-sensitized solar cells (DSSC).[9] For example, the good electron acceptor 2,4,6,8-tetracyanoazulene was shown by Hafner and co-workers[8] to form a charge-transfer complex with tetrathiafulvalene.



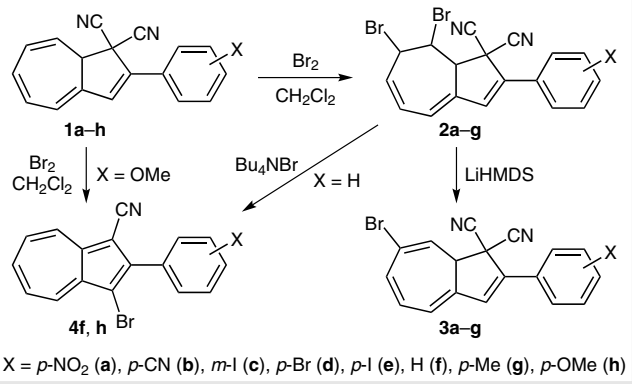
Scheme 1 Left: numbering of the azulene core. Right: dihydroazulene (DHA)/vinylheptafulvene (VHF) photoswitch.

Previously, 2-phenyl-1,8a-dihydroazulene-1,1-dicarbonitrile (DHA), a dihydro derivative of azulene, has proven to act as a precursor for a 1-bromo-3-cyano-substituted azulene, which by palladium-catalyzed reaction with alkynes can give larger conjugated electron-accepting scaffolds.[10] One problem with this procedure is that it cannot be utilized for large-scale preparation of functionalized azulenes, since the workup requires tedious chromatography.

The yellow-colored DHA is a photochromic molecule[11] that can undergo a light-triggered ring-opening to the isomeric, red vinylheptafulvene (VHF), which in turn undergoes a thermally induced cyclization back to the DHA (Scheme 1). The back reaction of VHF to DHA is relatively slow, but enhanced in polar solvents[12] and systematically sensitive to the electronic character of substituents placed at position 2 and/or 7.[12a,13] Hence, the rate of ring-closure obeys linear free-energy relationships.[13]

During the past few years, addition of bromine to the DHA under different conditions has proven to be an effective way to functionalize the DHA (**1** → **2** → **3**; Scheme 2), but also to achieve new azulenes. Thus, in 2007,[10] we showed that an addition of Br_2 over the C7–C8 double bond of DHA in CH_2Cl_2 and treatment of the resulting dibromide **2f** with Bu_4NBr yielded 1-bromo-3-cyano-2-phenylazulene **4f**. Shortly after, in 2009,[14] we reported the regioselective elimination of HBr upon treatment of the dibromide with lithium hexamethyldisilazide (LiHMDS), yielding solely the 7-bromo-substituted DHA **3f**. The procedure is though limited to the presence of phenyl or mostly electron-withdrawing substituents on the 2-position.[15] Thus, in terms of Hammett σ values, *para* substituents on the phenyl should have $\sigma_p \geq -0.17$ (methyl). With the more electron-donating methoxy substituent (corresponding to DHA **1h**; $\sigma_{p,OMe} = -0.27$; Scheme 2) the procedure did not majorly yield the

dibromide **2h**, but instead gave a mixture including the azulene **4h** and starting material. Bromination of **1h** in the polar solvent AcOH gave **4h** in 53% yield.[15]



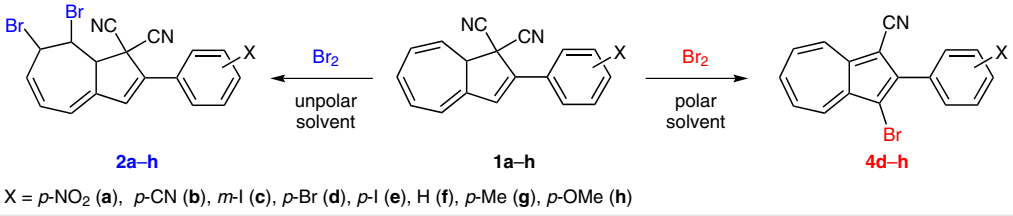
Scheme 2 2-Aryl-1,8a-dihydroazulene-1,1-dicarbonitriles (DHA) as precursors for 1-bromo-3-cyano-substituted azulenes or 7-bromo-substituted DHA

A protocol for the bromination at position C3 of DHA was also developed,[16] employing an $AlCl_3$-induced ring-opening of DHA and a radical bromination of the corresponding VHF with *N*-bromosuccinimide. The procedure is for now limited to only two examples (X = H, Me). For more detailed discussion of the synthesis and functionalization of DHA, we refer to a recently published review.[17] In regard to halogenation of azulenes, electrophilic aromatic substitution occurs at position 1.[18] One recent, convenient protocol deserves particular attention, in which iodination of azulene and heteroazulene derivatives can be achieved with *N*-chlorosuccinimide/NaI.[19]

We believe that azulene formation upon the bromination of **1h** (via an assumed initial attack at C3) in CH_2Cl_2 or AcOH instead of bromination of the C7–C8 double bond originates from the increased electron density at C3 due to the electron-donating methoxy group.

Herein, we demonstrate a solvent-polarity dependence in the bromination reaction of multiple DHA **1a**–**h** with electron-donating and electron-accepting groups on the 2-position, providing either an extended scope for the synthesis of 7,8-dibromo-substituted DHA **2** (important precursor for 7-bromo-substituted DHA **3**) or the opportunity for large-scale synthesis of 1-bromo-3-cyano-substituted azulenes **4** (Scheme 3), with product isolation by simple filtration.

DHA **1a**–**h** were prepared according to our general procedure[15] and were then subjected to bromination reactions. The product yields of the bromination reaction in different solvents are listed in Table 1. Gratifyingly, in AcOH, DHAs **1g**–**d** were converted into the corresponding 1-bromo-3-cyano-azulenes in high yields, like in the case of the methoxy-substituted DHA **1h**. All products precipitated from AcOH and were hence conveniently isolated simply by suction filtration (some further product may even remain in the mother liquor) and washing with heptane, which



Scheme 3 Bromination of DHA in polar and unpolar solvents

Table 1 Outcomes of Bromination of DHA in Different Solvents[a]

Reactant	X	σ_p[22]	Product in CS_2 (0.065[b])	Yield (%)	Product in CH_2Cl_2 (0.309[b])	Yield (%)	Product in AcOH (0.648[b])	Yield (%)
1a	4-O_2N	0.78	**2a**	>99	**2a**	>99[15]	**2a**	77
1b	4-CN	0.66	**2b**	>99	**2b**	>99[15]	**2b**	67
1c	3-I	0.35[c]					**2c**	67
1d	4-Br	0.23	**2d**	>99	**2d**	>99[15]	**4d**	82
1e	4-I	0.18	**2e**	>99	**2e**	>99[15]	**4e**	95
1f	4-H	0	**2f**	>99	**2f**	>99[14]	**4f**	81
1g	4-Me	–0.17	**2g**	>99	**2g**	>99[15]	**4g**	83
1h	4-MeO	–0.27	**2h**	>99			**4h**	53[15]

[a] All listed yields are of pure isolated materials.
[b] Normalized Dimroth–Reichardt E_T^N solvent-polarity parameter.[23]
[c] σ_m

makes the overall synthetic procedure very efficient as the DHA precursors also can be obtained in large scale without the need of chromatographic purification.[15] As a representative example, we prepared the product **4g** on a two-gram scale (in 83% yield).[20] The structure of **4e** was determined by X-ray crystallography, confirming the position of the bromo substituent and the completely planar and conjugated azulene system (Figure 1).

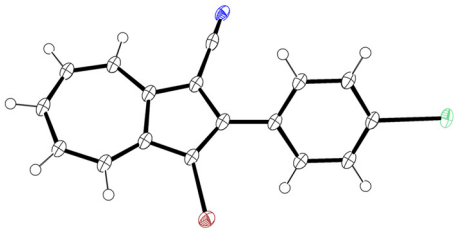
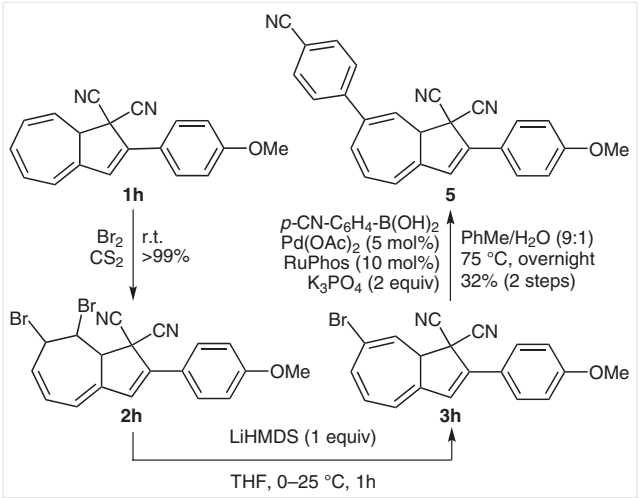


Figure 1 Molecular structure of **4e** (crystals grown from CH_2Cl_2–heptanes, CCDC no. 1421530)[21] with displacement ellipsoids at 50% probability for non-H atoms

For DHA **1a**–**c**, the bromination in AcOH did not lead to the formation of azulene, but instead the DHA were selectively brominated at the C7–C8 double bond, as with our well-established procedure in CH_2Cl_2 at –78 °C. All products precipitated from AcOH and were hence isolated, for characterization, by filtration.

The various outcomes, product **2** vs. **4**, indicate that there is a correlation between the donating and withdrawing strength of the substituents on the 2-position of DHA and the polarity of the solvent in the bromination reaction. To illustrate this, Table 1 includes Hammett substituent constants (σ_p)[22] for the various substituents and normalized Dimroth–Reichardt solvent parameters (E_T^N).[23]

In order to expand the scope of DHA functionalization to also include donating groups such as a methoxy ($\sigma_{p,\,OMe}$ = –0.27) on the phenyl on the 2-position we turned to the very unpolar solvent CS_2 (E_T^N = 0.065). Now, the dibromide **2h** was successfully isolated as a powder in quantitative yield.[24] It was, however, very unstable and could only be kept long enough to allow characterization by ^{1}H NMR spectroscopy. Nevertheless, we managed to convert the dibromide into 7-Br DHA **3h** using our previously reported elimination procedure (Scheme 4).[14] Subsequently, this 7-Br DHA was subjected to a palladium-catalyzed Suzuki cross-coupling[25] with 4-cyanophenylboronic acid to give the donor-acceptor-substituted DHA **5** in 32% yield over two steps. This product was ultimately characterized by X-ray crystallography (Figure 2), showing the characteristic boat-shaped conformation of the seven-membered ring with the C7–C8 double bond out of plane. In addition, the DHA with neutral and electron-withdrawing substituents on the 2-position also underwent a clean conversion into the corresponding 7,8-dibromo-DHA when using CS_2 as solvent (Table 1).



Scheme 4 Synthesis of donor-acceptor-functionalized DHA **5**

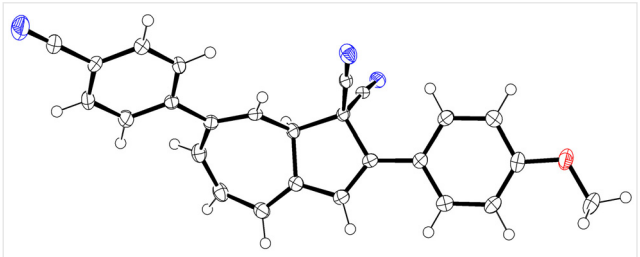


Figure 2 Molecular structure of **5** (crystals grown from EtOAc–heptanes, CCDC no. 1421531)[21] with displacement ellipsoids at 50% probability for non-H atoms

It seems that formation of a 1-bromo-3-cyano-substituted azulene has reached its limit with the bromo-substituted DHA **1d**, *i.e.* that the substituent should not have a σ_p larger than 0.23. Even increasing the solvent polarity from AcOH (E_T^N = 0.648) to MeOH (E_T^N = 0.762) in the bromination of **1c** (X = 3-I, σ_m = 0.35) did not change the outcome as the dibromide **2c** was the only product formed.

With the novel donor-acceptor DHA **5** in hand, we decided to study its photophysical properties in solution. Indeed, this 7-substituted DHA underwent a light-induced (365 nm) ring-opening reaction to form the metastable VHF in MeCN solution. Both the DHA and VHF showed characteristic absorptions with λ_{max} at 369 and 478 nm, respectively (Figure 3, top). The VHF in turn underwent a thermally induced ring-closure to form a mixture of 7- and 6-substituted DHA **5** and **6** (Figure 4) as expected, due to a known *E*/*Z* isomerization around the exocyclic double bond of the VHF.[14,26] This mixture has a redshifted absorption maximum. By plotting the VHF absorption against time (first-order kinetics), the rate constant (VHF → DHA) was determined to be 2.04 ± 0.002·10^{-5} s^{-1} (see Supporting Information). This value is in accordance with our recently published[13] Hammett correlation for the ring-closure of

VHF to DHA with substituents on both the 2- and 7-positions where the difference in substituent constants is used for evaluating the net electronic effect exerted by the substituents. Using this correlation, we estimate a rate constant for the ring-closure of 1.81 ± 0.2·10^{-5} s^{-1} as shown in Figure 3 (bottom), close to the value actually determined.

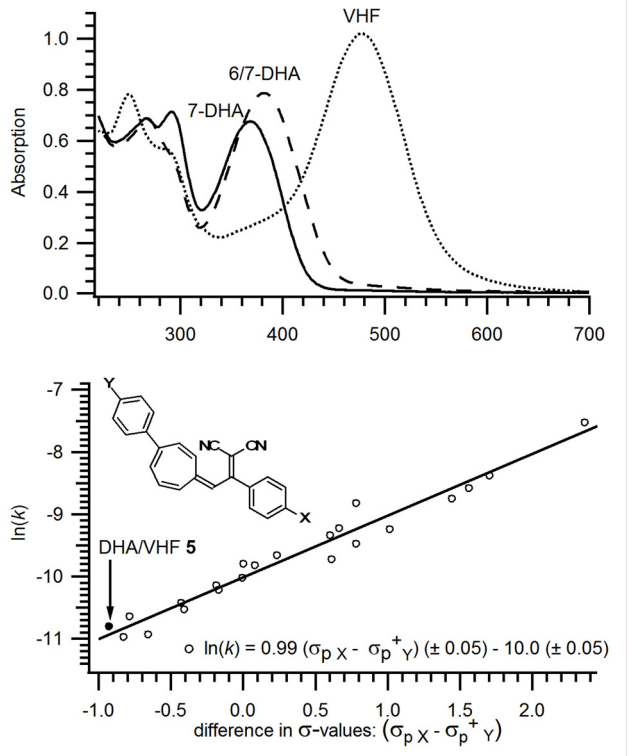


Figure 3 Top: UV-Vis absorption spectra recorded in MeCN at 25 °C of pure 7-DHA **5** (solid), its corresponding VHF (dotted), and a mixture of 7- and 6-substituted DHA **5** and **6** (dashed) resulting after a light/heat cycle. Bottom: Previously published[13] Hammett correlation for the ring-closure of VHF with substituents on both 2- and 7-position (referring to DHA numbering) used for predicting the rate constant for the ring-closure reaction forming a mixture of DHA **5** and **6**. Through-conjugation Hammett substituent constants, σ_p^+, were used for the Y substituents.

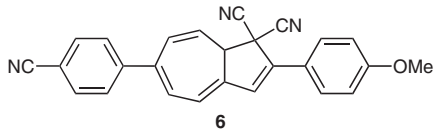


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Figure 4 6-Substituted DHA isomer **6**

In conclusion, we have shown that bromination of 1,8a-dihydroazulenes can give either the addition product in the seven-membered ring or the azulene product with a bromo substituent in the five-membered ring, depending on the electronic character of a substituent group at C2 of the starting material and the polarity of the solvent medium. The conditions were optimized to promote either of these products of which the former acts as precursors for bromo-substituted DHA photoswitches. With the right choice of solvent, the method ultimately allowed us to prepare a donor-acceptor-functionalized DHA with a 4-MeOC$_6$H$_4$ substituent at C2 and a 4-NCC$_6$H$_4$ substituent at C7.

Acknowledgment

The Danish Council for Independent Research | Technology and Production Sciences (#12-126668) and University of Copenhagen are acknowledged for financial support.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560823.

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(20) **3-Bromo-2-(4-methylphenyl)azulene-1-carbonitrile (4g)**
A stirred suspension of methyl DHA **1g** (2.045 g, 7.564 mmol) in AcOH (90 mL) under an argon atmosphere, excluded from light, was warmed to allow dissolution. This solution was allowed to cool to r.t., whereby a solution of Br_2 (9.76 mL, 0.78 M in AcOH, 7.564 mmol) was added dropwise to the dark yellow solution, which after 10 min resulted in a thick blue precipitate. Next day, this precipitation was collected by suction filtration and washed with heptane (300 mL) to afford the title compound as a blue solid (2.023 g, 6.278 mmol, 83%); mp 214.0–215.5 °C. TLC (25% heptanes–CH_2Cl_2): R_f = 0.64. ^{1}H NMR (500 MHz, C_6D_6): δ = 8.24 (d, J = 9.6 Hz, 1 H), 8.15 (d, J = 9.8 Hz, 1 H), 7.84 (d, J = 7.9 Hz, 2 H), 7.09 (d, J = 7.9 Hz, 2 H), 6.92 (app. t, J = 9.8 Hz, 1 H), 6.71 (app. t, J = 9.8 Hz, 1 H), 6.63 (app. t, J = 9.8 Hz, 1 H), 2.09 (s, 3 H). ^{13}C NMR (126 MHz, C_6D_6): δ = 151.2, 143.6, 139.7, 139.4, 139.2, 137.5, 136.2, 130.7, 130.6, 129.7, 127.81, 127.79, 116.5, 104.5, 97.7, 21.3 ppm. Anal. Calcd (%) for $C_{18}H_{12}BrN$ (322.20): C, 67.10; H, 3.75; N, 4.35. Found: C, 67.07; H, 3.41; N, 4.24. HRMS (MALDI$^+$): m/z (%) calcd for [$C_{18}H_{12}BrN^{\bullet+}$ $^{79/81}$Br] 321.0148 (100), 323.0127 (97.3); found: 321.0146 (100), 323.0125 (94.6).

(21) CCDC 1421530 (**4e**) and CCDC 1421531 (**5**) contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

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(24) **2-(4′-Methoxy)-7,8-dibromo-7,8,1,8a-tetrahydroazulene-1,1-dicarbonitrile (2h)**
To a stirred solution of methoxy DHA **1h** (262 mg, 0.915 mmol) in CS_2 (18 mL) under an argon atmosphere, excluded from light, a solution of Br_2 in CS_2 (1.18 mL, 0.915 mmol, 0.78 M) was added dropwise. After 10 min, the solution took upon a dark purple color. The solution was stirred for 80 min after which the solvent was removed with nitrogen gas flow, and the residue was concentrated under reduced pressure, which gave **2h** (408 mg, 0.915 mmol, >99%) as a dark purple solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69 (d, J = 8.8 Hz, 2 H), 6.98 (d, J = 8.8 Hz, 2 H), 6.82 (s, 1 H), 6.20 (dd, J = 7.6, 2.1 Hz, 1 H), 6.08 (dd, J = 12.0, 7.6 Hz, 1 H), 5.88 (dd, J = 12.0, 5.7 Hz, 1 H), 5.35–5.29 (m, 1 H), 5.05–5.00 (m, 1 H), 4.63 (br s, 1 H), 3.88 (s, 3 H).

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