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A Novel Route to a Bromo-Cyano-Substituted Azulene and Its Exploitation in the Construction of an Acetylenic Scaffold

Michael Åxman Petersen,[a] Kristine Kilså,[a] Anders Kadziola,[a] and Mogens Brøndsted Nielsen*[a]

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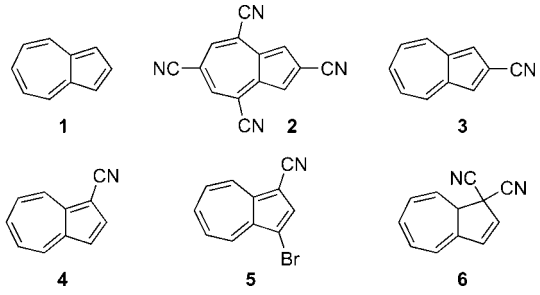
A novel route to functionalized azulenes is devised from a dihydroazulene precursor. Thus, bromination of 1,1-dicyano-2-phenyl-1,8a-dihydroazulene followed by heating in the presence of bromide ions provides an efficient way to generate 3-bromo-1-cyano-2-phenylazulene. Formation of this somewhat unexpected product was confirmed by X-ray crystallographic analysis. It undergoes a palladium-catalyzed cross-coupling reaction with trimethylsilylacetylene, affording a new azulene building block for acetylenic scaffolding. Oxidative homo-coupling hereof provides an azulene dimer, for which the optical and electrochemical properties are compared to the other azulenes.

Introduction

Derivatives of azulene (**1**) are interesting building blocks for advanced materials with electronic and photonic applications.[1] The azulene system has a remarkable polarizability and a tendency to form a stabilized tropylium cation as well as a cyclopentadienyl anion, which may be enhanced by suitable functionalization by donor and acceptor groups.[2] Cyano-substituted azulenes have proven as good electron acceptors that may be employed in organic metals. Thus, Hafner and co-workers[3] showed that the electron donor tetrathiafulvalene forms a charge-transfer complex with 2,4,6,8-tetracyanoazulene (**2**). This compound was prepared from 2-cyanoazulene (**3**) by nucleophilic substitution reactions in the seven-membered ring, followed by hydrolysis and dehydrogenation steps. In contrast, the five-membered ring of azulene is reactive towards electrophiles, and mostly so at the 1- and 3-positions.[4] For example, reaction of cyanogen bromide with azulene (**1**) in the presence of stannic chloride has provided 1-cyanoazulene (**4**).[5] However, with a ten-fold excess of the cyanogen bromide–stannic chloride complex, 1,3-dibromoazulene and 1-bromo-3-cyanoazulene (**5**) were obtained.[5] Interestingly, it was observed that compound **4** was inert to an excess of cyanogen bromide and stannic chloride and thus not able to act as a precursor for **5** under these conditions. Cyanoazulene derivatives such as **5** containing a reactive bromide substituent are potential precursors for larger conjugated electron-accepting scaffolds. Thus, it has recently been shown that halide-functionalized azulenes undergo the Sonogashira cross-coupling reaction[6] with alkynes and that the resulting ethynylazulenes are efficient building blocks for acetylenic scaffolding[7] as well as for metathesis.[8]



1 **2** **3** **4** **5** **6**

We became interested to exploit the possibility for dihydroazulenes, such as **6**, to act as precursors for cyano-bromo-substituted azulenes. Dihydroazulenes have attracted attention as photoswitches as they undergo, after light irradiation, a 10-electron *retro*-electrocyclization to the isomeric vinylheptafulvene compounds, which, in turn, undergo a thermal cyclization back to the dihydroazulene forms.[9,10] Gierisch and Daub[9] showed that dihydroazulenes could in fact also be converted into the corresponding 1-cyanoazulenes, albeit in low yields. We report here a new efficient synthetic procedure for obtaining a 3-bromo-1-cyano-substituted azulene from a dihydroazulene precursor and its further reactivity towards alkynes, providing new electron acceptors and chromophores.

Results and Discussion

Our synthesis starts from a 2-phenyl-substituted derivative of **6**, namely compound **7** (Scheme 1) that was readily

[a] Department of Chemistry, University of Copenhagen, Universitetsparken 5, 2100 Copenhagen Ø, Denmark
E-mail: mbn@kiku.dk
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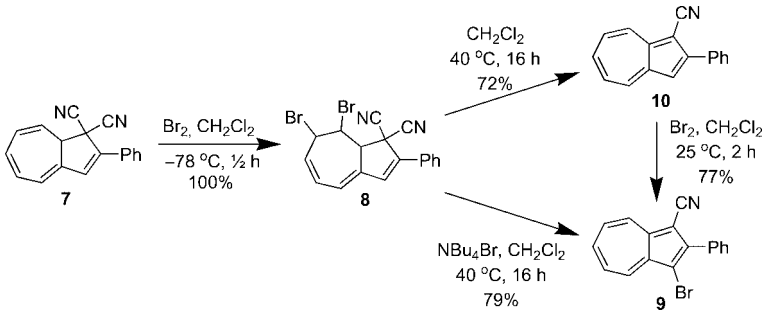


Scheme 1.

prepared according to a general literature protocol.[11] We reckoned from calculations (vide infra) that bromination of this compound should give preferably the 7,8-dibromo compound **8**. Indeed, treating **7** with bromine gave **8** in quantitative yield.[12] Single crystals of **8** were grown from CH_2Cl_2/pentane and subjected to an X-ray crystallographic analysis, which confirmed the proposed structure (Figure 1). When a 0.05 M solution of **8** in CH_2Cl_2 was left overnight at 40 °C, it was converted to a mixture of the two azulenes **9** and **10**[13] formed in a ratio of 4:7 and in a total yield of 61%. In contrast, heating simply the dihydroazulene **7** overnight at 40 °C in CH_2Cl_2 caused no azulene formation. Heating **8** in the presence of one equivalent of bromide (Bu_4NBr) gave solely compound **9** in a yield of 79%.[14] Yet, running the reaction under more dilute conditions (0.009 M) and in the absence of Bu_4NBr produced solely the cyanoazulene **10** in a yield of 72%. While exploitation of 1-cyanoazulene (**4**) as a precursor for 1-bromo-3-cyanoazulene (**5**) was previously discarded,[5] we find that treating azulene **10** with a small excess of Br_2 in CH_2Cl_2 resulted in clean conversion to the bromide **9**. These observations suggest that at least two mechanisms can be responsible for the formation of **9** from the precursor **8**: *i*) initial elimination of either HBr or HCN, followed by nucleophilic attack of bromide at C3 with expulsion of either cyanide or bromide (S_N2'), followed by a final elimination reaction, or *ii*) initial formation of **10** after two elimination reactions, followed by electrophilic substitution by attack of either Br_2 or BrCN. The structures of both **9** and **10** were confirmed by X-ray crystallography (Figure 1).[15]

The formation of azulenes **9** and **10** from dibromide **8** can also be promoted by light irradiation. Thus, photolysis at 350 nm of a dilute sample of **8** (0.009 M) in dry CH_2Cl_2 (1.5 mL; without stabilizator) for 1 hour showed complete conversion to the cyanoazulene **10** (as judged from an ^1H NMR spectroscopic investigation of the reaction mixture after evaporation of the solvent), while photolysis for 1 hour of **8** (0.009 M) in the presence of Bu_4NBr (0.05 M) instead provided the bromide **9** (together with a minor unidentified by-product).

The first step of the bromination of dihydroazulene **7** was subjected to a computational study employing the Gaussian 03 program package[16] in order to compare stabilities of possible cations. The isomeric ions were optimized at the semiempirical PM3 level, and on each structure a frequency

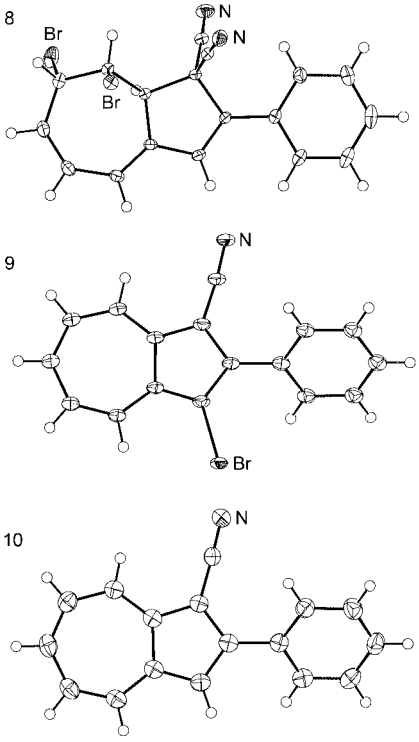
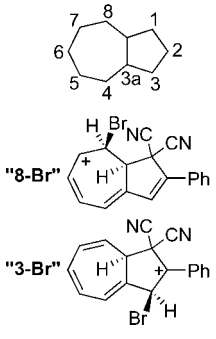


Figure 1. X-ray crystal structures of **8**, **9**, and **10**.

analysis was performed to secure that a real minimum had been obtained. Then single point energy calculations were performed at the B3LYP/6-311+G(2d,p) level. The relative energies (at 0 K) of the ions are depicted in Figure 2. As

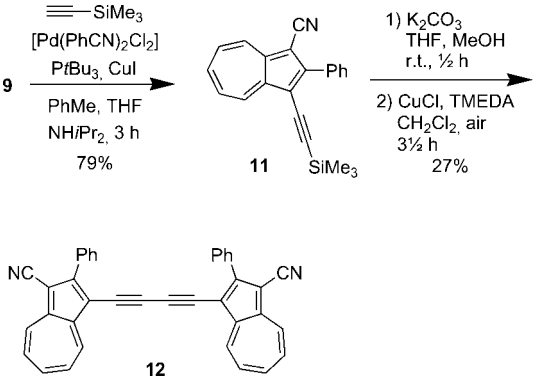


Isomer	Relative energy (kcal mol^{-1})
"8-Br"	0
"7-Br"	+28.1
"6-Br"	+7.8
"5-Br"	+32.2
"4-Br"	+12.2
"3a-Br"	+28.2
"3-Br"	+25.5
"2-Br"	+22.0

Figure 2. Relative cation energies calculated at the B3LYP/6-311+G(2d,p) level on PM3-optimized structures.

expected from simple resonance formulas, an attack at C8 is the most favorable. Electrophilic attack of Br^+ at for example the 2- or 3-positions requires more than 20 kcal mol^{-1} relative to attack at C8. For the subsequent attack of bromide, we find that the kinetic product of addition (assumed so from a proximity effect), namely the 7,8-dibromide **8** (7*S*,8*S*,8a*R* stereoisomer), is also the thermodynamic product as the 2,8-, 3a,8-, and 5,8-dibromides are more energetic by +17.9, +25.3, and +7.1 kcal mol^{-1}, respectively. All in all, the calculations substantiate the exclusive formation of the dibromide **8** from bromination of **7**.

The bromide **9** was subjected to a Sonogashira cross-coupling reaction[6] with trimethylsilylacetylene employing the catalyst system of Hundertmark et al.[17] (Scheme 2). The product **11**[18] was desilylated with K_2CO_3 in MeOH/THF, and the terminal alkyne intermediate was then subjected to an oxidative Hay homo-coupling reaction[19] to give the azulene dimer **12**.[20] Single crystals of **12** were grown from toluene/$CHCl_3$, and the crystal structure is shown in Figure 3. Angles of 22° and 38° are observed between the phenyl and azulene rings.



Scheme 2.

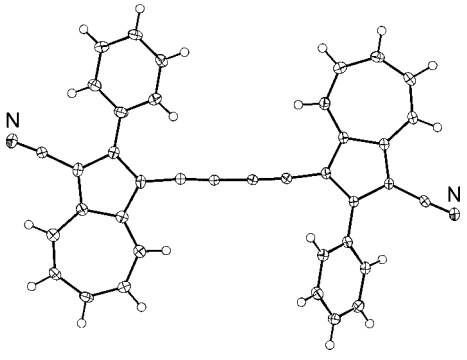


Figure 3. Crystal structure of **12**.

The new azulene derivatives are strong chromophores as is evident from the UV/Vis absorption spectra shown in Figure 4. The azulene monomers **9** and **10** exhibit a bright violet and blue-violet color, respectively, in solution. They are only weakly fluorescent with structured emissions at 433 nm (φ_{fl} = 0.5 ‰) for **9** and 431 nm (φ_{fl} = 0.4 ‰) for **10** in CH_2Cl_2 (λ_{exc} = 322 nm). Compounds **11** and **12** are both green in the solid state, which is also the case in solution for the dimer **12**, while the monomer **11** exhibits a bright blue color in solution. Cyclic voltammetry investigations in CH_2Cl_2 (0.1 M Bu_4NPF_6) show irreversible reductions at –1.23 (**9**), –1.38 (**10**), –1.80 (**11**), and –1.81 (**12**) V vs. Fc^+/Fc. Taking into account the electron-accepting nature of acetylenic scaffolds,[21] it is somewhat surprising that compounds **11** and **12** are the poorest acceptors in the series.

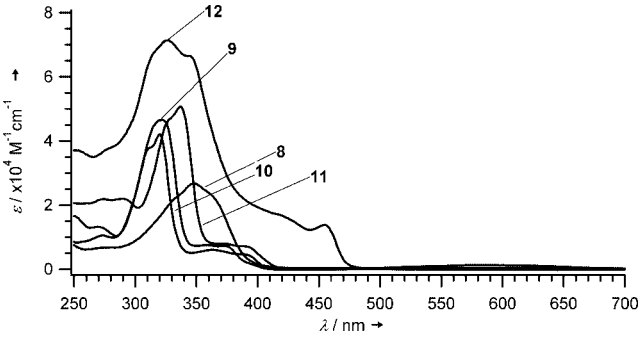


Figure 4. UV/Vis absorption spectra in CH_2Cl_2.

In conclusion, we have developed a new efficient synthesis of a 3-bromo-functionalized azulene. This compound is readily incorporated into new redox-active acetylenic chromophores. We are currently investigating the possibility for controlling the light-induced conversion of **8** into azulenes via a ring-opened intermediate.

Supporting Information (see also the footnote on the first page of this article): A Table containing a summary of general crystallographic data.

CCDC-626060 (for **8**), -626062 (for **9**), -626061 (for **10**), -626063 (for **12**) contain the detailled supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/datarequest/cif.

Acknowledgments

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[12] Dihydroazulene **7** (125 mg, 0.49 mmol) was dissolved in CH_2Cl_2 (4 mL) at –78 °C under N_2. Then a solution of Br_2 in CH_2Cl_2 (0.39 M, 1.25 mL) was slowly added (2 min). Stirring for 1 h at –78 °C followed by evaporation in vacuo yielded **8** (205 mg, 100%) as a yellow-brown foam. An analytical sample was recrystallized from CH_2Cl_2 and pentane. Melting range 170–178 °C, compound turns dark-violet above 95 °C. R_f = 0.36 in EtOAc/heptane, 3:7 v/v, 2D-TLC showed breakdown of main product; decomposition product observed at R_f = 0.075. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, 7.26 ppm): δ = 7.76 (m, 2 H, Ar), 7.48 (m, 3 H, Ar), 6.98 (s, 1 H, CH), 6.27 [dd, ^3J(H,H) = 2.2 Hz, ^3J(H,H) = 7.5 Hz, 1 H, CH], 6.09 [dd, ^3J(H,H) = 7.5 Hz, ^3J(H,H) = 12.2 Hz, 1 H, CH], 5.91 [dd, ^3J(H,H) = 5.6 Hz, ^3J(H,H) = 12.0 Hz, 1 H, CH], 5.32 (m, 1 H, CH), 5.05 (m, 1 H, CH), 4.66 (br. s, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, 77.0 ppm): δ = 144.5, 139.6, 133.9, 130.3, 130.0, 129.3, 128.5, 126.4, 125.7, 121.0, 114.6, 111.7, 53.1, 51.5, 49.0, 44.6 ppm. UV/Vis (CH_2Cl_2): λ_{max} (ε) = 348 nm (26700).

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[14] Dibromide **8** (208 mg, 0.50 mmol) was dissolved in dry, unstabilized CH_2Cl_2 (10 mL) under N_2 atmosphere, whereupon NBu_4Br (171 mg, 0.53 mmol) was added. After stirring at 40 °C for 16 h (***caution:*** HCN evolution expected), the dark-purple reaction mixture was washed with water (2 × 30 mL), dried ($MgSO_4$), and the solvents evaporated in vacuo. Purification by flash column chromatography (EtOAc/heptane, 3:7, v/v, R_f = 0.31) yielded 3-bromo-1-cyano-2-phenylazulene **9** (121 mg, 79%), as a purple solid. M.p. 191–194 °C. Crystals for X-ray crystallography were grown from $CDCl_3$. ^{1}H NMR (300 MHz, 25 °C, $CDCl_3$, 7.26 ppm): δ = 8.65 [d, ^3J(H,H) = 10.0 Hz, 1 H, CH=], 8.62 [d, ^3J(H,H) = 10.8 Hz, 1 H, CH=], 7.93–7.82 (m, 3 H, Ar, CH=), 7.68–7.50 (m, Ar, 5 H, CH=) ppm. ^{13}C NMR (75 MHz, 25 °C, $CDCl_3$, 77.0 ppm): δ = 150.7, 143.5, 140.3, 139.2, 138.2, 136.5, 133.0, 130.2, 129.4, 128.6, 128.5, 128.2, 116.7, 104.4, 96.5 ppm; ES-TOF-MS (neg. mode): *m*/*z* = 308 [H·M$^-$], 339 [MeOH·M$^-$]. UV/Vis (CH_2Cl_2): λ_{max} (ε) = 269 (13000), 321 (46500), 359 (7500), 373 (7500), 588 (500) nm; fluorescence (CH_2Cl_2, λ_{exc} = 322 nm): λ_{em} = 414 (sh), 433 (tail, φ = 0.5 ‰) nm.

[15] Compound **9** crystallizes in the acentric space group *Cc* but does so as a racemic twin with a ratio of 52:48. Moreover, the azulene ring displays disorder, so that the Br and CN substituents are interchanged in 17% of the unit cells. The azulene ring and the phenyl ring form an angle of 41°. Crystals of compound **10** contain two molecules in the asymmetric unit. One of the molecules is all planar (shown in Figure 1), induced by the crystal packing, and disordered. Here 38% of the molecules are rotated 180° with the phenyl ring overlapping the seven-membered ring of the azulene, and the five-membered rings of the azulene partially overlapping. The other molecule is well ordered and displays an angle of 33° between the phenyl ring and the azulene ring.

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[18] Compound **9** (200 mg, 0.65 mmol) was dissolved (with sonication) in dry THF (1.5 mL), dry toluene (1.5 mL), and NH(*i*Pr)$_2$ (0.2 mL) under argon. Then [Pd(PhCN)$_2$Cl$_2$] (33 mg, 0.09 mmol), CuI (20 mg, 0.1 mmol), and P(*t*Bu)$_3$ in hexane (10%, 0.25 mL, 0.08 mmol) were added. Trimethylacetylene (0.4 mL, 2.7 mmol) was added, and the reaction mixture was allowed to stir at room temp. for 3 h. The resulting dark blue solution was diluted with CH_2Cl_2 (25 mL) and washed with water (2 × 50 mL), dried ($MgSO_4$), and the solvents evaporated in vacuo. Purification by flash column chromatography (EtOAc/heptane, 2:8, v/v, R_f = 0.4) gave **11** as a green solid (150 mg, 79%). M.p. 112–113.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, 7.26 ppm): δ = 8.71 [d, ^3J(H,H) = 9.7 Hz, 1 H, CH=], 8.63 [d, ^3J(H,H) = 9.7 Hz, 1 H, CH=], 8.15 (m, 2 H, Ar), 7.85 [t, ^3J(H,H) = 9.8 Hz, 1 H, CH=], 7.64–7.49 (m, 5 H, Ar, CH=), 0.30 (s, 9 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, 77.0 ppm): δ = 153.6, 144.4, 144.1, 140.1, 138.1, 136.4, 133.3, 129.9, 129.6, 129.0, 129.0, 128.5, 117.2, 109.8, 102.3, 99.3, 95.6, 0.0 ppm. HR-ES-TOF-MS (pos. mode): *m*/*z* = 348.1193 [M·Na$^+$]; calcd. for $C_{22}H_{19}NNaSi$: 348.1184. UV/Vis (CH_2Cl_2): λ_{max} (ε) = 273 (22000), 289 (22000), 328 (47000), 337 (51000), 372 (8000), 390 (br. sh, 7000), 601 (500) nm.

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[20] Compound **11** (72 mg, 0.22 mmol) was dissolved in MeOH (3 mL) and THF (1.5 mL). Then K_2CO_3 (160 mg, 1.15 mmol) was added, and the reaction mixture was stirred for 1/2 h at room temp. and then diluted with CH_2Cl_2. The organic phase was washed with water, dried ($MgSO_4$), and the solvents evaporated in vacuo. The dark-blue solid was dissolved in CH_2Cl_2 (15 mL), whereupon Hay catalyst [TMEDA (40 mg, 0.34 mmol) and CuCl (40 mg, 0.40 mmol) in CH_2Cl_2 (1 mL)] was added. After stirring for 31/2 h at room temp., the reaction mixture was washed with water, dried ($MgSO_4$), and the solvents evaporated in vacuo. Purification by flash column chromatography (CH_2Cl_2, R_f = 0.44) followed by two procedures of precipitation, by dissolving in hot $CHCl_3$ followed by addition of heptane, yielded the dimer **12** (30 mg, 27%) as a green solid. M.p. 315–317 °C (dec.). Crystals for X-ray crystallography were grown from toluene/$CHCl_3$. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, 7.26 ppm): δ = 8.79 [d, ^3J(H,H) = 10.0 Hz, 2 H, CH=], 8.66 [d, ^3J(H,H) = 10.0 Hz, 2 H, CH=], 8.13 [d, ^3J(H,H) = 7.6 Hz, 4 H, Ar], 7.90 [t, ^3J(H,H) = 9.4 Hz, 2 H, CH=], 7.69–7.52 (m, 10 H, CH=, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 50 °C, 77.0 ppm): δ = 140.5, 138.4, 136.7, 129.8, 129.7, 129.4, 128.9 ppm, (missing signals due to poor solubility). MALDI-TOF-MS (neg. mode): *m*/*z* = 504 [M$^-$], 1008 [M·M$^-$]. UV/Vis (CH_3Cl): λ_{max} (ε) = 278 (37500), 325 (71500), 345 (66500), 420 (16000), 454 (14000), 583 (1300) nm.

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