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COMMUNICATION

New synthetic route to substituted dihydroazulene photoswitches†

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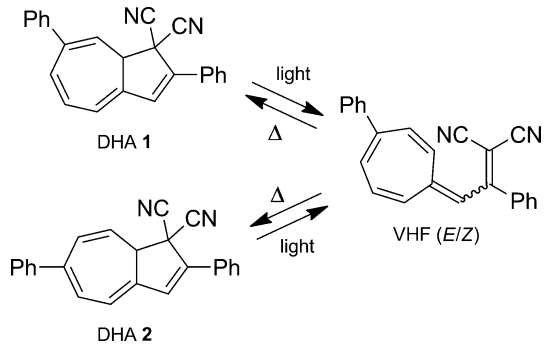
A new procedure for functionalization of the dihydroazulene photoswitch on its seven-membered ring was developed, which has allowed isolation of the first dihydroazulene with a phenyl substituent at position 5 from a mixture of regioisomers. Light-induced ring-opening to the corresponding vinylheptafulvene and the thermal back-reaction was studied in detail.

Molecules that change from one isomer to another upon an external stimulus have attracted interest as components for molecular electronics, information storage, molecular machines, sensors, and as units to control protein folding.[1] We have in recent years turned our attention to the dihydroazulene (DHA)/vinylheptafulvene (VHF) system. DHA undergoes a light-induced ring-opening reaction to VHF, which, in turn, undergoes a thermally assisted ring-closure back to DHA.[2] One advantage of this system is the many possibilities for tuning the properties by suitable functionalization at the different ring positions. Thus, pioneering work by Daub and co-workers[3] has revealed the influence of substituents at positions 2 and 3 of the DHA. As a continuation of this work, we have recently shown that the kinetics of the thermal ring-closure reaction follows Hammett correlations for aryl groups in positions 2 or 7.[4,5] The accessibility to DHAs functionalized at position 7 was accomplished by a regioselective bromination–elimination–cross-coupling protocol.[4–6] Ring-opening of such DHAs to the corresponding *E*/*Z*-isomeric VHFs followed by thermal ring-closure resulted in formation of either the original DHA or of a 6-substituted derivative. Thus, subjecting DHA **1** to one light–heat cycle provided a mixture of the regioisomeric DHAs **1** and **2** (Scheme 1).[5]

Synthetic protocols for obtaining DHA regioisomers in which the substituent group is placed at either position 4, 5, or 8 (or even 8a) have been unknown. Here we present a method that has allowed isolation of the DHA **3** (Fig. 1) containing a phenyl substituent at position 5 from a mixture of phenyl-substituted DHA isomers. Our former method involved direct functionalization of the DHA core. The new method involves incorporation of the substituent before the DHA is obtained in the final step. This strategy, lacking the regioselectivity of the previous one, was in fact our initial and at that time unsuccessful approach for incorporating an ethynyl substituent in the seven-membered ring.[6]



Scheme 1 Conversions between substituted DHAs and VHFs.

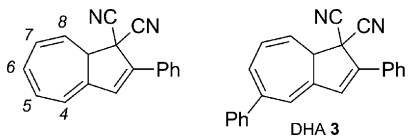


Fig. 1 Numbering of the seven-membered ring of DHA (left) and structure of the new 5-Ph-substituted DHA (right).

The synthesis is shown in Scheme 2. First, the known compound **4**[7] was treated with tritylium tetrafluoroborate ($TrBF_4$) to provide the tropylium tetrafluoroborate salt **5** (96%), which was subsequently treated with compound **6** (made from a Knoevenagel condensation between malononitrile and acetophenone[8]) and triethylamine to furnish an inseparable mixture of the three regioisomers, **7**, **8**, and **9** (yield estimated to be *ca.* 80% based on NMR) together with unreacted **6**. The crude mixture was subjected to hydride followed by proton abstractions in 1,2-dichloroethane (DCE) to give a mixture of VHF regioisomers that upon heating in toluene was converted to the corresponding DHAs. Analysis of the crude reaction mixture by ^{1}H-NMR spectroscopy showed the presence of several DHA regioisomers, most likely **1**, **2**, **3**, and **10**, while **11** seemed absent. By repeated column chromatography, it was possible to isolate one of the DHAs pure, namely DHA **3**.‡ Based on the isolated yield (*ca.* 12%)

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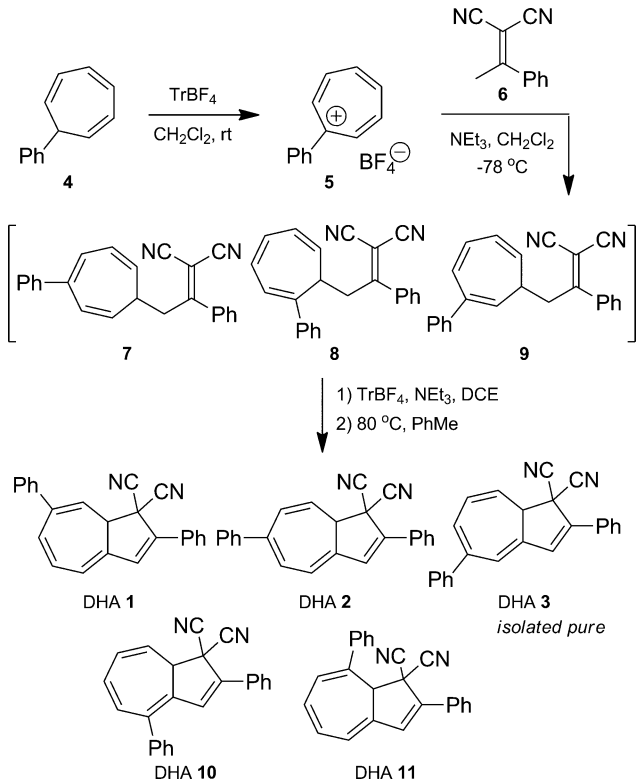


Scheme 2 Synthesis of phenyl-substituted DHA regioisomers. Tr = tritylium; DCE = 1,2-dichloroethane.

and its proportion (according to ^{1}H-NMR spectroscopy) in the original DHA mixture, we can estimate a total yield of DHAs of >33% from **7**, **8**, and **9**. The position of the substituent at position 5 in DHA **3** was confirmed by ^{1}H–^{1}H COSY spectroscopy based on the following proton–proton couplings: H-8a/H-8, H-8/H-7, and H-7/H-6 (see ESI); TOCSY spectroscopy allowed assignment of the protons H-8, H-7 and H-4 as these coupled through-space with H-8a as did H-6. The structure was confirmed ultimately by X-ray crystal structure analysis (Fig. 2).

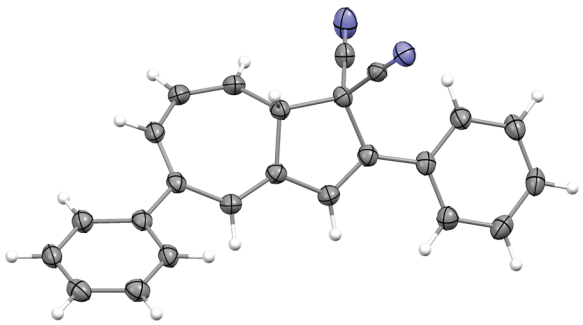
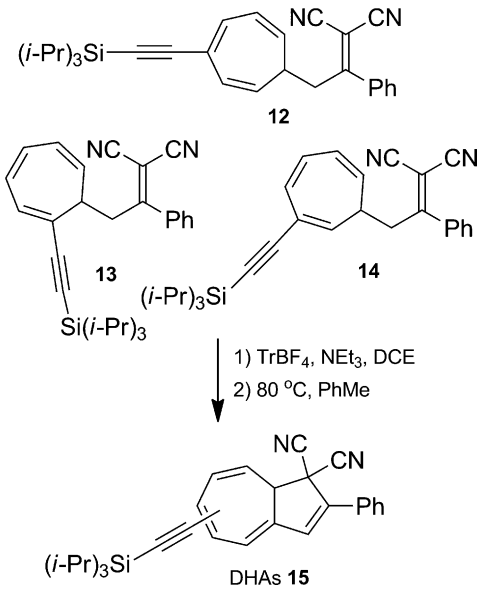


Fig. 2 X-Ray crystal structure of DHA **3** with displacement ellipsoids at 50% probability for non-H atoms. Crystals were grown from heptane/ethyl acetate. CCDC 826860.

By a similar protocol it was possible to prepare a mixture of DHA regioisomers with a triisopropylsilylethynyl substituent in the seven-membered ring from the precursors **12**, **13**, and **14** (Scheme 3), but in this case isolation of a pure DHA regioisomer failed. ^{1}H-NMR spectral analysis did, however, support the presence of the 7-substituted isomer (for which ^{1}H-NMR data



Scheme 3 Synthesis of ethynyl-substituted DHA regioisomers.

were previously obtained[6]) and at least three other DHA isomers. Furthermore, a substantial amount of unreacted **13** was present in the mixture, but not **12** and **14**. It seems that compound **13** is less prone to undergo the conversion in line with previous observations. Thus, in 2009 we reported initial attempts of converting **13** (isolated pure from a mixture of **12**, **13**, and **14**) into a DHA,[6] but only trace amounts were formed.

The UV-Vis absorption spectrum of the DHA **3** is shown in Fig. 3. The compound exhibits a longest-wavelength absorption maximum at 356 nm in MeCN, which is similar to that of **1** (355 nm)[5] Another absorption maximum is observed at 283 nm. Irradiation of a sample in MeCN at the absorption maximum 356 nm resulted in ring-opening to VHF **16** (Fig. 4) exhibiting a characteristic absorption at λ_{max} 488 nm (Fig. 3). A mixture of *E*/*Z* isomers was formed according to analysis by ^{1}H-NMR spectroscopy. The ratio was approximately 2 : 5, but it was not possible to evaluate which isomer was formed in the higher yield. According to NMR, both VHF isomers were thermally converted at 60 °C in CD_3CN to the original DHA **3** as the ^{1}H-NMR spectrum was identical to that of the original one (see ESI). Yet, following by ^{1}H-NMR spectroscopy the ring-closure of an *E*/*Z* mixture of **16** at room temperature revealed signals from formation of an additional DHA, which we reasonably assign to the 8-phenyl-substituted one (**11**). Fig. 5 shows that while the ratio between

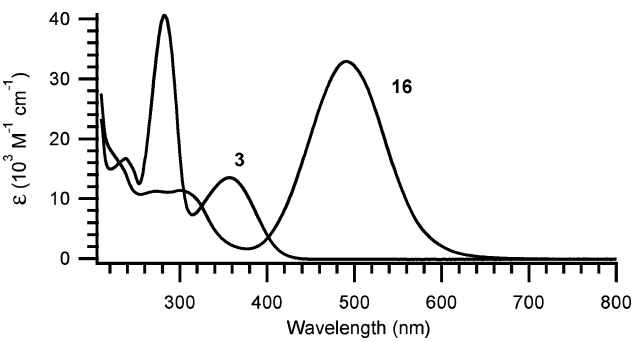


Fig. 3 UV-Vis absorption spectra of DHA **3** and *E*/*Z*-VHFs **16** in MeCN.

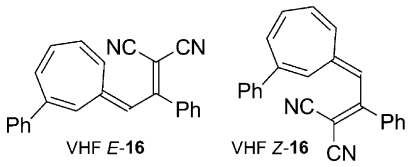


Fig. 4 VHF isomers formed upon ring-opening of DHA **3**.

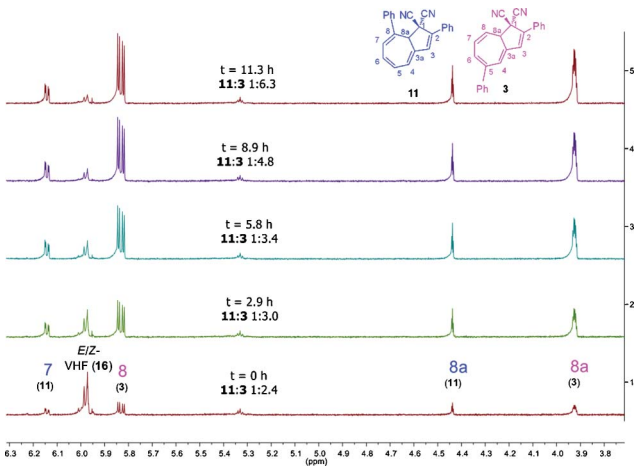


Fig. 5 Conversion of *E*/*Z*-VHFs **16** into DHAs **3** and **11** followed by ^{1}H-NMR (CD_3CN, 25 °C). Assignment of H-7 on **11** was done on the basis of coupling constants.

E- and *Z*-VHF isomers remained constant during their decay (at least in the beginning while it is more difficult to judge after some time where the signals have decreased in intensity), there is a steady build-up of DHA **3** relative to DHA **11** in time. Moreover, we find that after *ca.* 4 days at room temperature in the dark, DHA **11** is almost fully converted to DHA **3** (see ESI). Thus, altogether the experiments show that not only are the VHFs converted to DHAs but also that DHA **11** is thermally converted to DHA **3**, most likely *via* a VHF intermediate. Calculations at the B3LYP/6-311++G(2d,p)//B3LYP/6-31+G(d) density functional theory level using the Gaussian 03 program package[9] suggest that DHA **3** is more stable than **11** by 6.7 kcal mol^{-1}. The thermally assisted ring-opening of **11** to a VHF that subsequently ring-closes to form **3** is also in accordance to the absence of this isomer in the original product mixture, which was isolated after heating to 80 °C (albeit in toluene rather than MeCN, *vide supra*). Subjecting an ice-cooled mixture of the DHAs **3** and **11** (in favor of **3**) to irradiation for 1 h from a 365 nm UV lamp revealed complete ring-opening of **3** as judged from ^{1}H-NMR spectroscopy (see ESI), while **11** was not fully converted. Thus, it seems that **3** is more light-sensitive than **11**, although the two compounds may exhibit slightly different molar absorptivities at the wavelength of irradiation.

The thermal back-reaction of the *E*/*Z*-mixture of **16** was also studied by UV-Vis absorption spectroscopy in MeCN. The decay in the absorbance at 488 nm was followed at different temperatures (see ESI). A sum of two exponential functions was required in order to fit the data, which is in accordance to the fact that the thermally induced ring-opening of DHA **11** came into play in time. A single exponential function can, however, be used to fit the data in the beginning of the VHF to DHA conversion, before DHA **11** has formed in substantial amount. From such single-exponential fits, rate constants at different temperatures were obtained (see ESI). At 25 °C a rate constant for the VHF ring-closure of 4.71 × 10^{-5} s^{-1} was obtained (half-life of 245 min). From an Arrhenius plot (see ESI), an activation energy of 93.1 (±0.7) kJ mol^{-1} and a preexponential factor of 9.8 × 10^{11} s^{-1} were determined. Yet, each VHF likely has a different rate constant for forming either one of the two possible DHAs at any specific temperature. What we have estimated is a net rate constant of ring-closure, assumed identical for each VHF isomer, but which for each VHF is the sum of two unknown rate constants. As the temperature variation of this net rate constant satisfies an Arrhenius plot, the two individual rate constants must differ in their preexponential factors only (the sum of which is reported above), while their activation energy terms must be identical. A similar data analysis was previously performed for the kinetics of formation of 6/7-substituted DHAs by ring-closure of corresponding isomeric VHFs, but here the data satisfied a single exponential decay during the entire time span.[4–6]

In conclusion, we have developed a new procedure for functionalizing dihydroazulenes in the seven-membered ring. The lack of regioselectivity renders purification tedious and is a major drawback of the protocol, but, nevertheless, it has allowed isolation of the first DHA that incorporates a phenyl substituent at position 5. Light-induced ring-opening followed by ring-closure at room temperature provided a mixture of 5- and 8-phenylsubstituted DHAs. The 8-phenyl-substituted DHA is, however, equilibrating in the dark to the more stable 5-phenyl-substituted one. This is the first example of a thermally induced ring-opening of the DHA system.

Acknowledgements

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Notes and references

‡ *1,1-Dicyano-2,5-diphenyl-1,8a-dihydroazulene* (***3***): A crude mixture of the three regioisomers **7, 8**, and **9** (1.63 g, 4.87 mmol) was dissolved in CH_2ClCH_2Cl (10 mL). Then tritylium tetrafluoroborate (1.63 g, 4.95 mmol) dissolved in CH_2ClCH_2Cl was added under an argon atmosphere. The mixture was heated to 80 °C, by which it turned dark red in color. Toluene (110 mL) was added and the solution was cooled on an ice bath for 1.5 h. Then Et_3N (0.52 g, 5.15 mmol) was added and the solution was cooled for 10 min. Stirring at 80 °C for 1 h followed by concentration *in vacuo* yielded a mixture of DHAs (and by-products). By repeated column chromatography (SiO_2, 1. column: EtOAc/heptane 1 : 9; 2. column: CH_2Cl_2/heptane 2 : 1), it was possible to isolate **3** (195 mg, 12%) as a fine, yellow powder. M.p. 128–129 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.77 (dd, *J* 8.2, 1.5 Hz, 2H), 7.53–7.32 (m, 8H), 6.95 (s, 1H), 6.79 (d, *J* 6.5 Hz, 1H), 6.58 (s, 1H), 6.41 (ddd, *J* 10.1, 6.5, 2.0 Hz, 1H), 5.89 (dd, *J* 10.1, 3.6 Hz, 1H), 3.88 (dt, *J* 3.6, 2.0 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 143.5, 142.1, 141.5, 140.8, 132.4, 130.6, 130.3, 129.4, 128.8, 128.3, 128.3, 127.8, 127.1, 126.5, 122.2, 119.9, 115.3, 112.9, 50.9, 45.3.

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