Hydroxylation and Amination of Azulenes by Vicarious Nucleophilic Substitution of Hydrogen

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Hydroxylation of azulenes with *tert*-butylhydroperoxide proceeds efficiently at the 6-position when the former contain electron-withdrawing substituents in the five-membered ring. Similarly, VNS amination of azulenes proceeds with 4-amino-1,2,4-triazole; its anion, being an active nucleophile, also reacts with unsubstituted azulene. A variety of transformations of 6-hydroxyazulenes, such as substitution of the corresponding sulfonates with nitrogen, oxygen, sulfur, carbon nucleophiles and halogens, and the Claisen rearrangement of allylic ethers, is reported.

Introduction

α-Halocarbanions react with electrophilic arenes, particularly nitroarenes, by replacing the hydrogen *ortho*- or *para*- to the nitro group with the carbanion moiety.[1] This reaction, known as vicarious nucleophilic substitution (VNS) proceeds via an addition-β-elimination mechanism,[2][3] and is a general method for the nucleophilic alkylation of nitroarenes.[4]

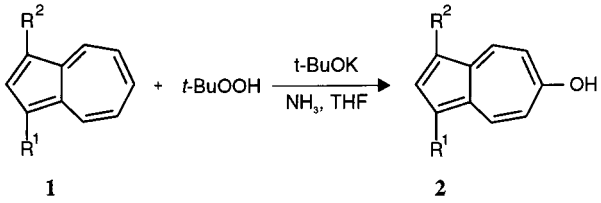
In a previous paper we reported that azulene undergoes the VNS reaction with α-chloroalkanesulfonamides and 4-chlorophenoxyacetonitrile to produce the corresponding azulenes substituted in the seven-membered ring.[5] Thus VNS can be used for the introduction of functionalized carbon substituents into the azulene ring in addition to the previously reported oxidative nucleophilic substitution reactions commonly used for this purpose.[6] Contrary to the large amount of data concerning the introduction of carbon substituents into azulenes,[6][7] practically nothing is known about the synthesis of hydroxyazulenes by the nucleophilic substitution of hydrogen, and only one example of a nucleophilic amination giving 4-aminoazulene has been reported.[8]

Since both OH and NH_2 groups can be efficiently introduced into nitroarene rings by VNS,[9−13] we have attempted to elaborate a synthesis of hydroxy- and aminoazulenes using this reaction.

Results and Discussion

Hydroxylation of Azulenes

The hydroxylation of nitroarenes proceeds smoothly by reaction with *tert*-butyl or cumyl hydroperoxides in the presence of strong bases.[9][10] However, the first attempts at hydroxylation of azulene (**1a**) with *t*BuOOH in the presence of potassium *tert*-butoxide in liquid ammonia gave negative results. Even after prolonged stirring of a reaction mixture containing **1a**, *t*BuOOH and an excess of *t*BuOK, the formation of hydroxyazulene was not observed and compound **1a** was recovered. It appears that due to the low nucleophilic activity of the $tBuOO^-$ anion it does not form a σ^H adduct with the moderately electrophilic azulene (**1a**) in a concentration sufficiently high for the β-elimination, which is the second step in the VNS reaction. On the other hand, reaction with more electrophilic azulenes containing electon-withdrawing substituents in the five-membered ring, when carried out with the *t*BuOOH/*t*BuOK system in liquid ammonia, proceeded satisfactorily (Scheme 1). The higher electrophilicity of the 1-CN (**1b**), 1-NO_2 (**1c**), 1-COPh (**1d**) and 1-CHO (**1e**) azulene derivatives, and azulenes containing two ethoxycarbonyl or chloro substituents in positions 1 and 3 (**1f** and **1g**) ensured a sufficiently high concentration of the σ^H adduct of $tBuOO^-$ to azulene, and thus the subsequent base-induced β-elimination of *t*BuOH gave the 6-hydroxyazulenes **2b−g** in yields between 35 and 86% (Scheme 1).



1 **2**

1,2	a	b	c	d	e	f	g
R^1	H	CN	NO_2	PhCO	CHO	CO_2Et	Cl
R^2	H	H	H	H	H	CO_2Et	Cl
yield	-	60%	70%	86%	35%	83%	63%

Scheme 1

In all these reactions we observed the formation of only one product of the hydroxylation in the 6-position; formation of 4- or 8-hydroxyazulenes was not observed. In the majority of cases the hydroxyazulenes are sufficiently stable

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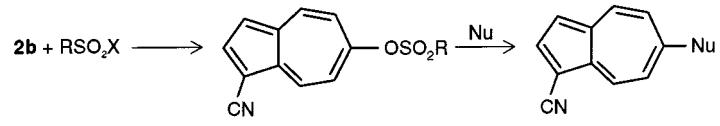


3,4	a	b	c
R	p-Tol	CF_3	n-C_4F_9

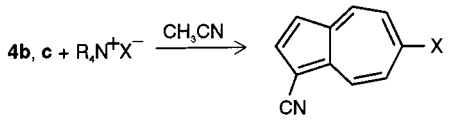
5	a	b	c	d
Nu	O⌒NH	p-$MeOC_6H_4O^-$	p-$MeOC_6H_4S^-$	Ph–C(Me)(CN)$^-$

Scheme 2

to be isolated and purified using standard methods. 1,3-Dichloro-6-hydroxyazulene (**2g**) is relatively unstable in acidic media, although in the pure state it can be kept for months. The sodium salt of 1-formyl-6-hydroxyazulene (**2e**) is much less stable. It was isolated as the corresponding O-tosyl derivative, produced by direct tosylation of the reaction mixture with tosyl chloride immediately after removal of the ammonia. The hydroxylation of 1-formylazulene proceeds in lower yield not only because of the instability of the product but also due to addition of tBuOO$^-$ to the carbonyl group.

We had observed earlier that VNS hydroxylation of 3-nitrobenzophenone proceeded much slower than other nitroarenes, whereas the reaction with 3-nitrobenzaldehyde resulted in its partial oxidation to 3-nitrobenzoic acid without formation of the corresponding nitrophenol.[9b] It appears that in these cases addition of tBuOO$^-$ to the carbonyl group rather than to the ring takes place preferentially, so the VNS proceeds slower and to a moderate extent or not at all. The carbonyl groups at the highly nucleophilic five-membered ring of azulene are less active in nucleophilic addition so the VNS proceeds efficiently with 1-benzoylazulene (**1d**) and in moderate yield with 1-formylazulene (**1e**). All the produced hydroxyazulenes **2b–g** behave as typical phenols, i.e. they can be dissolved in dilute aqueous alkali and recovered upon acidification of these azulenolate solutions. Under standard reaction conditions they form *O*-tosyl, *O*-mesyl and *O*-trifluoromethylsulfonyl derivatives. A facile synthesis of 6-hydroxyazulenes in which the hydroxy group can be subsequently activated by simple conversion into esters of sulfonic acids opens up possibilities for the introduction of a variety of substituents at the 6-position of the azulene ring, since 6-sulfonyloxy groups in the electrophilic azulene ring can be readily replaced with nucleophilic agents by the addition elimination S_NAr process. These possibilities were explored using 1-cyano-6-hydroxyazulene **2b** as an example which, when treated with tosyl chloride under standard conditions, gave the 6-tosyloxy derivative **4a**. This, when treated with such typical N, O and S-nucleophiles as morpholine, 4-methoxyphenolate or 4-methoxythiophenolate, gave the expected substitution products **5a–c** in excellent yields (Scheme 2). However, when **4a** was treated with the carbanion of 2-phenylpropionitrile the expected product of S_NAr was not obtained. Substitution with this carbanion to give **5d** proceeded readily in the reaction with the corresponding ester of trifluoromethanesulfonic acid **4b**.

Of particular interest appears to be the synthesis of 6-haloazulenes which otherwise are not easily available. Attempts to react the tosylate **4a** with tetraalkyl ammonium halides gave negative results. However, treatment of the more active triflate **4b** and nonaflate **4c** of 1-cyano-6-hydroxyazulene with tetraalkylammonium halides leads to the desired 1-cyano-6-chloro- (**6a**), 1-cyano-6-bromo- (**6b**) and 1-cyano-6-iodoazulene (**6c**) in excellent yields. Synthesis of 1-cyano-6-fluoroazulene (**6d**) was, however, problematic as the corresponding tetraalkylammonium fluorides cannot be easily obtained in an anhydrous form; use of the hydrated salts resulted in substantial hydrolysis of the triflate **4b**. On the other hand the corresponding nonaflate **4c** was less sensitive to hydrolysis and even in the reaction with commercial tetraethylammonium fluoride dihydrate gave the expected 1-cyano-6-fluoroazulene **(6d)** in 60% yield. An additional 30% of the hydroxyazulene **2b** was obtained due to hydrolysis of **4c** (Scheme 3).



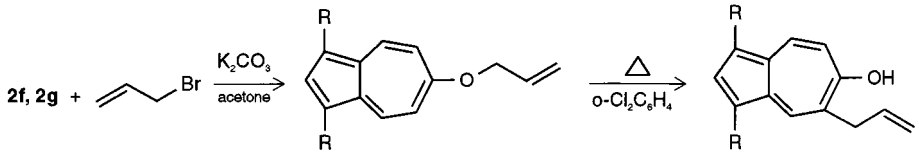
$R_4N^+X^-$; $Et_3\overset{+}{N}CH_2PhCl^-$, $Bu_4\overset{+}{N}Br^-$, $Bu_4\overset{+}{N}I^-$, $Et_4\overset{+}{N}F^-\cdot 2H_2O$

6	a	b	c	d
X	Cl	Br	I	F
yield	96%	94%	91%	60%

Scheme 3

The anions of the 6-hydroxyazulenes **2**, similarly to phenolates, form the corresponding 6-alkoxyderivatives upon treatment with alkyl halides. Particularly interesting was the alkylation with allyl bromide because 6-allyloxy derivatives of azulenes should undergo the Claisen rearrangement to 6-hydroxy-5- (or 7-) allylazulenes as do allylic ethers of phenols. This reaction sequence was performed for 1,3-dichloro-6-hydroxy- **(2g)** and 1,3-diethoxycarbonyl-6-hydroxyazulenes **(2f)** in order to avoid problems due to possible formation of two isomeric products of the Claisen rearrangement of unsymmetrically substituted azulenes. The allylation proceeded satisfactorily under typical conditions

for *O*-allylation of phenols (K_2CO_3 in acetone) to give **7a** and **7b**, respectively. These allyloxyazulenes undergo a facile rearrangement in boiling *o*-dichlorobenzene to give the corresponding 5-allyl-6-hydroxyazulenes **8a** and **8b** in moderate yields (Scheme 4).



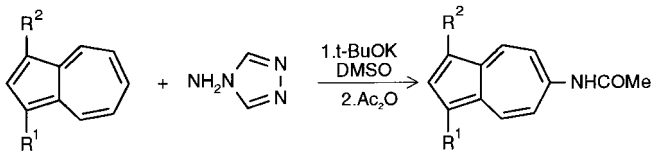
7, 8	a	b
R	CO_2Et	Cl

Scheme 4

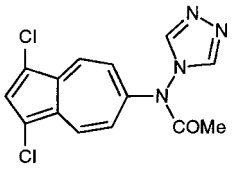
Similarly to 1,3-dichloro-6-hydroxyazulene **(2g),** 1,3-dichloro-5-allyl-6-hydroxyazulene **(7b)** is relatively unstable and decomposed during the rearrangement. When the reaction was carried out in the presence of acetic anhydride the produced hydroxyazulene was directly acetylated and the more stable 6-acetoxyderivative of **8b** was isolated from the reaction mixture. On the other hand the rearrangement product of 1,3-diethoxycarbonyl-6-allyloxyazulene **(8a)** was sufficiently stable to be isolated and purified in a standard way − dissolution in dilute aqueous NaOH and acidification of the obtained phenolate solution. The Claisen rearrangement of 6-allyloxyazulenes provides an efficient pathway for the introduction of carbon substituents at the 5- or 7- positions of the azulene ring.

Amination of Azulenes

For the VNS amination of nitroarenes a variety of aminating agents NH_2X were used, mostly hydrazine[11] and hydroxylamine[12] derivatives. In our laboratory we have found that sulfenamides (R−S−NH_2, R = 2,4,6-trichlorophenyl or *N*,*N*-dialkylthiocarbamoyl) appear to be the most efficient and versatile reactants for this purpose.[13] However attempts at VNS amination of azulene **1a**, 1-cyanoazulene **1b** and 1,3-dichloroazulene **1g** with these sulfenamides gave negative results, the azulenes were recovered and the sulfenamides decomposed. Most probably there are some difficulties in the β-elimination of the RS- group from the σ^H adduct of the sulfenamide anions to azulenes. We have observed earlier that the VNS cyanomethylation of azulene proceeds with the carbanion of $ArOCH_2CN$ but not with carbanions of $ArSCH_2CN$ or $Me_2NCSSCH_2CN$, apparently also because of difficulties in the β-elimination step.[5] These difficulties are rather unexpected because such carbanions containing sulfur-based leaving groups are efficient reagents for the VNS cyanomethylation of nitroarenes.[1,4,14] On the other hand we have found that 4-aminotriazole, proposed by Katritzky for the VNS amination of nitroarenes,[11a] is an efficient aminating agent of azulenes when carried out under argon. In all these cases the substitution took place at the 6-position of the azulene ring and no isomeric products of the amination in the 4- or 8- positions were observed (Scheme 5).



9	a	b	c
R^1	H	CN	Cl
R^2	H	H	Cl
yield	38%	64%	60%



Scheme 5

6-Aminoazulenes are of moderate stability thus they were isolated, purified and characterized as the corresponding acetyl derivatives **9a**, **9b** and **9c**, produced by direct acetylation of the mixture after the reaction. Although the oxidative process leading to 6-triazolyloaminoazulenes was observed in all three cases studied, we have isolated and characterized only the product formed from 1,3-dichloroazulene; this was also isolated and analyzed as the acetyl derivative **9d**. It should be noted that the unsubstituted azulene, which was insufficiently electrophilic for the VNS hydroxylation with $tBuOO^-$, was readily aminated with 4-aminotriazole albeit in moderate yield.

The reported results indicate that VNS is a versatile tool for the introduction of a variety of oxygen, nitrogen, sulfur and halogen substituents directly into azulene or by further conversion of hydroxyazulenes.

Experimental Section

NMR spectra were recorded with a Varian Gemini (200 MHz) spectrometer using TMS as internal standard in solvents as indicated below. Mass spectra were measured with an AMP 604 Interctra spectrometer. Azulenes **1a−g** were prepared according to the following literature procedures: 1a using Hafner's method;[15] **1b** by formylation of **1a** with the Vilsmeier reagent[16] and subsequent dehydration of 1-formylazulene oxime; **1c** via nitration of azulene with copper nitrate;[17] **1d** by a Vilsmeier-type acylation with N,N-dimethylbenzamide and $POCl_3$;[17] **1e** by a Vilsmeier formylation of azulene; **1f** according to the multistep Nozoe synthesis from tropolone[18] and **1g** by chlorination of azulene with N-chlorosuccinimide.[19]

Hydroxylation of Azulene Derivatives: Azulene **1b−g** (1 mmol) in dry THF (3 mL) was added to liquid ammonia (15 mL) and stirred at −50°C. To this solution were added *tert*-butylhydroperoxide (250μL, 80% solution in hexane, 2 mmol) and potassium *tert*-butoxide (560 mg, 5 mmol). The mixture was allowed to warm until the ammonia began to reflux and stirred for 4 hours. The ammonia was then evaporated, the residue acidified with dilute HCl (10%), extracted several times with ethyl acetate and washed with a solution of $K_2S_2O_5$ and brine. The solution was dried with $MgSO_4$ and the solvent was evaporated. The product was chromatographed on silica gel (hexane/ethyl acetate 10:3 to 1:1).

In the case of 1-formylazulene (**1e**) the reaction was carried out as above. After the ammonia was evaporated THF (10 mL) $Et_3N{\cdot}HCl$ (2 g) and Et_3N (1 mL) were added to the residue and then part of the Et_3N was evaporated in order to remove residues of ammonia. To this mixture was added tosyl chloride (0.5 g, 3.2 mmol); an excess of tosyl chloride is necessary because it reacts readily with traces of ammonia present in the mixture. The mixture was stirred for about 12 h, quenched with water (10 mL) and extracted with ethyl acetate. The organic layer was dried with $MgSO_4$ and the solvent was evaporated. The *O*-tosyl derivative of **2e** was chromatographed on silica gel (hexane/ethyl acetate 10:3).

1-Cyano-6-hydroxyazulene (2b): Yield 60%, m.p. 108−109°C. − ^{1}H NMR ($CDCl_3$): δ = 7.06 (dd, *J* = 10.9, 2.5 Hz, 1 H), 7.11 (dd, *J* = 10.9, 2.5 Hz, 1 H), 7.20 (d, *J* = 4.2 Hz, 1 H), 7.80 (d, *J* = 4.2 Hz, 1 H), 8.30 (d, *J* = 10.9 Hz, 1 H), 8.48 (d, *J* = 10.9 Hz, 1 H). − MS (EI) *m/z* (%) 169 (100), 140 (38), 114 (25). HRMS (EI) *m/z* calcd. $C_{11}H_7NO$ (M^+): 169.0528; found 169.0526.

1-Nitro-6-hydroxyazulene (2c): Yield 70%, m.p. 123−124°C. − ^{1}H NMR ([D_6]acetone): δ = 6.84 (dd, *J* = 11.0, 2.3 Hz, 1 H), 6.87 (dd, *J* = 11.0, 2.3 Hz, 1 H), 6.98 (d, *J* = 4.2 Hz, 1 H), 7.69 (d, *J* = 4.2 Hz, 1 H), 8.25 (d, *J* = 11.0 Hz, 1 H), 8.38 (d, *J* = 11.0 Hz, 1 H). − MS (EI) *m/z* (%) 189 (100), 160 (41), 143 (20), 114 (36). HRMS (EI) *m/z* calcd. $C_{10}H_7NO_3$ (M^+): 189.0426; found 189.0431.

1-Benzoyl-6-hydroxyazulene (2d): Yield 86%, m.p. 166−167°C. − ^{1}H NMR ([D_6]acetone): δ = 7.19 (d, *J* = 4.1 Hz, 1 H), 7.26 (dd, *J* = 11.1, 2.0 Hz, 1 H), 7.31 (dd, *J* = 11.1, 2.0 Hz, 1 H), 7.48- 7.60 (m), 7.67 (d, *J* = 4.1 Hz, 1 H), 7.78 7.83(m), 8.49 (d, *J* = 11.1 Hz, 1 H), 9.54 (d, *J* = 11.1 Hz, 1 H). − MS (EI) *m/z* (%) 248 (60), 231 (5), 220 (5), 189 (8), 171 (100), 143 (7), 115 (21). HRMS (EI) *m/z* calcd. $C_{17}H_{12}O_2$ (M^+): 248.0837; found 248.0833.

Diethyl 6-Hydroxy-1,3-azulenedicarboxylate (2f): Yield 83%, m.p. 169−170°C (ref.[20] 171−172°C). ^{1}H NMR ([D_6]acetone): δ = 7.64 (d, *J* = 11.1 Hz, 2 H), 8.76 (1 H,s), 9.6 (d, *J* = 11.1 Hz, 2 H). − MS (EI) *m/z* (%) 288 (100), 259 (32), 243 (51), 215 (27), 186 (72), 141 (31), 113 (10). HRMS (EI) *m/z* calcd. $C_{16}H_{16}O_5$ (M^+): 288.0998; found 288.0996

1,3-Dichloro-6-hydroxyazulene (2g): Yield 63%, m.p. 140−142°C. − ^{1}H NMR ($CDCl_3$): δ = 6.32 (bs), 6.72 (d, *J* = 11.0 Hz, 2 H), 7.35 (s), 8.14 (d, *J* = 11.0 Hz, 2 H). − MS (EI) *m/z* (%) 212 (94), 178 (22), 149 (100), 115 (24). − HRMS (EI) *m/z* calcd. $C_{10}H_6OCl_2$ (M^+): 211.9796; found 211.9793.

1-Formyl-6-tosyloxyazulene: (**2e** *O*-tosylate**)** Yield 35%, m.p. 151−152°C. − ^{1}H NMR ($CDCl_3$): δ = 2.48 (s), 7.14 (dd, *J* = 10.6, 2.5 Hz, 1 H), 7.26−7.41 (m), 7.72−7.84 (m), 8.28 (d, *J* = 4.2 Hz, 1 H), 8.42 (d, *J* = 10.6 Hz, 1 H), 9.42 (d, *J* = 10.6 Hz, 1 H), 10.34 (s). − MS (EI) *m/z* (%) 326 (91), 155 (90), 115 (28), 91 (100), 65 (13). − HRMS (EI) *m/z* calcd. $C_{18}H_{14}O_4S$ (M^+): 326.0613; found 326.0610.

1-Cyano-6-tosyloxyazulene (4a): To a solution of 1-cyano-6-hydroxyazulene **(2b)** (169 mg, 1 mmol) in THF (2 mL) and Et_3N (1 mL) was added *p*-toluenesulfonyl chloride (210 mg, 1.1 mol) and the mixture stirred at room temp. for 3 h. The solvent was evaporated, the residue treated with water (10 mL), the product extracted with dichloromethane and, after evaporation of the solvent, chromatographed (hexane/ethyl acetate 10:3). Yield 290 mg, 90%. − m.p. 122°C. − ^{1}H NMR ([D_6]acetone): δ = 2.48 (s), 7.39 (dd, *J* = 10.9, 2.5 Hz, 1 H), 7.52 (m), 7.57 (d, *J* = 4.2 Hz, 1 H), 7.83 (m), 8.24 (d, *J* = 4.2 Hz, 1 H), 8.60 (d, *J* = 10.9 Hz, 1 H), 8.67 (d, *J* = 10.9 Hz, 1 H). − MS (EI) *m/z* (%) 323 (36), 169 (11), 155 (89), 140 (12), 113 (5), 91 (100), 65 (14). HRMS (EI) *m/z* calcd. $C_{18}H_{13}NO_3S$ (M^+): 323.0616; found 323.0618.

1-Cyano-6-(trifluoromethanesulfonyloxy)azulene (4b): To a solution of 1-cyano-6-hydroxyazulene **(2b)** (85 mg, 0.5 mmol) in THF (5 mL) at −70°C was added Et_3N (0.2 mL) trifluoromethanesulfonyl anhydride (170 mg, 0.55 mmol) and this mixture stirred for 15 min. The THF was evaporated, water (5 mL) was added and the product was extracted with ethyl ether. Organic layer was dried with $MgSO_4$ and the solvent was removed. The residue was chromatographed on silica gel (hexane/ethyl acetate 10:3). Yield 91%, m.p. 98−100°C. − ^{1}H NMR ([D_6]acetone): δ = 7.74 (d, *J* = 4.3 Hz, 1 H), 7.77 (dd, *J* = 11.0, 2.7 Hz, 1 H), 7.83 (dd, *J* = 11.0, 2.7 Hz, 1 H), 8.37 (d, *J* = 4.3 Hz, 1 H), 8.82 (d, *J* = 11.0 Hz, 1 H), 8.88 (d, *J* = 11.0 Hz, 1 H). − MS (EI) *m/z* (%) 3101 (48), 237 (28), 190 (2), 171 (6), 140 (100), 113 (15), 87 (3), 69 (11). − HRMS (EI) *m/z* calcd. $C_{12}H_6NO_3F_3$ (M^+): 301.0021; found 301.0027.

1-Cyano-6-nonafluorobutanesulfonyloxyazulene (4c): To a solution of 1-cyano-6-hydroxyazulene (169 mg, 1 mmol) in THF (10 mL) was added Et_3N (0.5 mL) and nonafluorobutanesulfonylfluoride (362 mg, 1.2 mmol) at room temperature and this mixture was stirred overnight. Water (10 mL) was added and the product was extracted with ethyl acetate. The organic layer was dried with $MgSO_4$ and the solvent was evaporated. The residue was chromatographed on silica gel (hexane/ethyl acetate 10:3). Yield 62%, m.p. 112−113°C. − ^{1}H NMR ([D_6]acetone): δ = 7.72 (d, *J* = 4.2 Hz, 1 H), 7.78 (dd, *J* = 10.9, 2.7 Hz, 1 H), 7.83 (dd, *J* = 10.9, 2.7 Hz, 1 H), 8.35 (d, *J* = 4.2 Hz, 1 H), 8.81 (d, *J* = 10.9 Hz, 1 H), 8.86 (d, *J* = 10.9 Hz, 1 H). − MS (EI) *m/z* (%) 451 (37), 387 (15), 219 (3), 152 (6), 140 (100), 113 (11), 69 (13). − HRMS (EI) *m/z* calcd. $C_{15}H_6NO_3SF_9$ (M^+): 450.9925; found 450.9932.

1-Cyano-6-*N*-morpholinoazulene (5a): A solution of **4a** (33 mg, 0.1 mmol) and morpholine (0.5 mL) in ethanol (2 mL) was stirred at room temp. for 10 min. The solvent and morpholine was evaporated and the residue chromatographed (hexane-ethyl acetate eluent). Yield of **5a**, 96%, m.p. 139°C. − ^{1}H NMR ([D_6]acetone): δ = 3.76−3.90 (8 H, m), 6.99 (d, *J* = 4.0 Hz, 1 H), 7.14 (dd, *J* = 11.4, 2.8 Hz, 1 H), 7.20 (dd, *J* = 11.4, 2.8 Hz, 1 H), 7.48 (d, *J* = 4.0 Hz, 1 H), 8.20 (d, *J* = 11.4 Hz, 1 H). − MS (EI) *m/z* (%) 238 (100),

207 (12), 180 (40), 153 (95), 140 (60), 125 (12), 113 (8). − HRMS (EI) *m/z* calcd. $C_{15}H_{14}N_2O$ (M^+): 238.1106; found 238.1103.

1-Cyano-6-*p*-methoxyphenoxyazulene (5b): To a solution of **4a** (33 mg, 0.1 mmol) and *p*-methoxy phenol (25 m, 0.2 mmol) in ethanol (2 mL) was added 10% aqueous NaOH solution (0.5 mL) and the mixture stirred at room temp. for 15 min. It was then diluted with water (5 mL) and the product extracted with CH_2Cl_2 (3 × 10 mL). The extract was washed with water, dried with $MgSO_4$ and the solvent evaporated. The product was purified by column chromatography (hexane/ethyl acetate 5:1). Yield 92%, m.p. 75°C. − ^{1}H NMR ([D$_6$]acetone): δ = 3.87 (s), 7.07−7.21 (m), 7.24 (dd, *J* = 10.7, 2.8 Hz, 1 H), 7.37 (d, *J* = 4.1 Hz, 1 H), 7.91 (d, *J* = 4.1 Hz, 1 H), 8.55 (d, *J* = 10.7 Hz, 1 H). − MS (EI) *m/z* (%) 275 (100), 260 (7), 247 (10), 232 (26), 204 (27), 152 (25), 123 (20). − HRMS (EI) *m/z* calcd. $C_{18}H_{13}NO_2$ (M^+): 275.0946 found: 275.0942

1-Cyano-6-*p*-methoxyphenylthioazulene (5c): Experimental procedure as above, with *p*-methoxythiophenol instead of *p*-methoxy phenol. Yield 95%, m.p. 66°C. − ^{1}H NMR ([D$_6$]acetone): δ = 3.92 (s, 3 H), 7.17 (ddd, *J* = 9.0, 2.6, 2.6 Hz, 2 H), 7.26 (dd, *J* = 10.5,1.8 Hz, 1 H), 7.31 (d, *J* = 4.2 Hz, 1 H), 7.35 (dd, *J* = 10.5,1.8 Hz, 1 H), 7.62 (ddd, *J* = 9.0,2.6,2.6 Hz, 2 H), 7.94 (d, *J* = 4.2 Hz, 1 H), 8.34 (d, *J* = 10.5 Hz, 1 H), 8.36 (d, *J* = 10.5 Hz, 1 H). − MS (EI) *m/z* (%) 291 (100), 276 (29), 260(21), 183 (5), 152 (18), 139 (10) 125 (17). − HRMS (EI) *m/z* calcd. $C_{18}H_{13}NOS$ (M^+): 291.0718; found 291.0719.

1-Cyano-6-[1-(cyano-1-phenylethyl)]azulene (5d): To a solution of potassium *tert*-butoxide (79 mg, 0.7 mmol) and 2-phenylpropionitrile (66 mg, 0.5 mmol) in DMF (3 mL) at −30°C was added a solution of **4b** (150 mg, 0.5 mmol) in DMF (3 mL). The mixture was stirred at −30°C for 30 min, quenched with aqueous NH_4Cl solution and extracted with dichloromethane. The solvent was evaporated and the residue chromatographed (hexane/ethyl acetate 5:1). Yield of **5d** 78%, m.p. 136−138°C. − ^{1}H NMR ($CDCl_3$): δ = 2.36 (s), 7.39−7.56 (m), 7.80 (dd, *J* = 10.1, 1.9 Hz, 1 H), 7.87 (dd, *J* = 10.1, 1.9 Hz, 1 H), 8.22 (d, *J* = 4.2 Hz, 1 H), 8.69 (d, *J* = 10.1 Hz, 1 H), 8.73 (d, *J* = 10.1 Hz, 1 H). − MS (EI) *m/z* (%) calcd. $C_{20}H_{14}N_2$ (M^+): 282.1157; found 282.1154.

Synthesis of 1-Cyano-4-haloazulenes: A solution of **4b** or **4c** (1 mmol) and the corresponding tetraalkylammonium salt (2 mmol) in acetonitrile (10 mL) was refluxed for 4 hours (chloride), 6 hours (bromide) or 8 hours (iodide). After cooling, the solid salts were filtered off, the solvent was evaporated and the residue chromatographed on silica gel (hexane/ethyl acetate 10:3).

6-Chloro-1-cyanoazulene (6a): Yield 96%, m.p. 153−154°C. − ^{1}H NMR ([D$_6$]acetone): δ = 7.56 (d, *J* = 4.1 Hz, 1 H), 7.81 (dd, *J* = 10.5, 2.1 Hz, 1 H), 7.87 (dd, *J* = 10.5, 2.1 Hz, 1 H), 8.18 (d, *J* = 4.1 Hz, 1 H), 8.55 (d, *J* = 10.5 Hz, 2 H), 8.63 (d, *J* = 10.5 Hz, 2 H). − MS (EI) *m/z* (%) 187 (100), 152 (50), 125 (21), 99 (7), 75 (10), 62 (7), 50 (8). − HRMS (EI) *m/z* calcd. $C_{11}H_6NCl$ (M^+): 187.0189; found 187.0185.

6-Bromo-1-cyanoazulene (6b): Yield 94%, m.p. 150−152°C. − ^{1}H NMR ([D$_6$]acetone): δ = 7.54 (d, *J* = 4.1 Hz, 1 H), 8.00 (dd, *J* = 10.0, 1.9 Hz, 1 H), 8.05 (dd, *J* = 10.0, 1.9 Hz, 1 H), 8.22 (d, *J* = 4.1 Hz, 1 H), 8.43 (d, *J* = 10.0 Hz, 1 H), 8.50 (d, *J* = 10.0 Hz, 1 H). − MS (EI) *m/z* (%) 231 (55), 152 (100), 125 (37), 99 (12), 75 (14), 62 (8), 44 (9). − HRMS (EI) *m/z* calcd. $C_{11}H_6N^{79}Br$ (M^+): 230.9684; found 230.9680, calcd. $C_{11}H_6N^{81}Br$ (M^+): 232.9663; found 232.9643.

1-Cyano-6-iodoazulene (6c): Yield 91%, m.p. 167−168°C. − ^{1}H NMR ([D$_6$]acetone): δ = 7.52 (d, *J* = 4.2 Hz, 1 H), 7.79 (dd, *J* = 10.8, 2.6 Hz, 1 H), 7.84 (dd, *J* = 10.8, 2.6 Hz, 1 H), 8.37 (d, *J* = 4.2 Hz, 1 H), 8.82 (d, *J* = 10.8 Hz, 1 H), 8.88 (d, *J* = 10.8 Hz, 1 H). − MS (EI) *m/z* (%) 272 (52), 152 (100), 125 (27), 99 (10), 75 (11), 57 (12). − HRMS (EI) *m/z*, calcd. $C_{11}H_6NI$ (M^+): 278.9545; found 278.9543.

1-Cyano-6-fluoroazulene (6d): A solution of **4c** (451 mg, 1 mmol) and $Et_4N^+F^-\cdot 2H_2O$ (1.2 mmol) in THF (5 mL) was stirred at room temp. for 15 min. Further procedure as above. Yield 60%, m.p. 132−134°C. − ^{1}H NMR ($CDCl_3$): δ = 7.26−7.45 (m), 8.16 (d, *J* = 4.1 Hz, 1 H), 8.45 (dd, *J* = 11.0, 4.4 Hz, 1 H), 8.63 (dd, *J* = 11.0, 4.4 Hz, 1 H). − MS (EI) *m/z* (%) 171 (100), 153 (93), 149 (34), 144 (25), 126 (25), 100 (7), 74 (12), 63 (14). − HRMS (EI) *m/z* calcd. $C_{11}H_6NF$ (M^+): 171.0484; found 171.0490.

Allylation of Hydroxyazulenes: The 6-hydroxyazulenes **2f** or **2g** (1 mmol), allyl bromide (180 mg, 1.5 mmol) and anhydrous K_2CO_3 (0.5 g) were refluxed in acetone (10 mL) for 5 hours. The inorganic salts were filtered off, washed with acetone and the solvent evaporated. The residue was chromatographed on silica gel (hexane/ethyl acetate 10:3).

Diethyl 6-Allyloxy-1,3-azulenedicarboxylate (7a): Yield 82%, m.p. 191−193°C. − ^{1}H NMR ([D$_6$]acetone): δ = 1.41 (t, *J* = 7.1 Hz, 6 H), 4.38 (q, *J* = 7.1 Hz, 4 H), 4.96 (dt, *J* = 5.2, 1.5 Hz, 2 H), 5.39 (ddt, *J* = 10.5, 1.5 Hz, 1 H), 5.55 (ddt, *J* = 17.3, 1.5 Hz, 1 H), 6.19 (ddt, *J* = 17.3, 10.5, 5.2 Hz, 1 H), 7.56 (d, *J* = 11.6 Hz, 2 H), 8.46 (s), 9.66 (d, *J* = 11.6 Hz, 2 H). − MS (EI) *m/z* (%) 328 (100), 283 (24), 181 (28), 169 (20), 153 (14), 131 (10), 113 (9), 102 (8). − HRMS (EI) *m/z* calcd. $C_{19}H_{20}O_5$ (M^+): 328.1311; found 328.1308.

6-Allyloxy-1,3-dichloroazulene (7b): Yield 70%, m.p. 163−164°C. − ^{1}H NMR ([D$_6$]acetone): δ = 4.68 (dt, *J* = 5.1, 1.3 Hz, 2 H), 5.51 (ddt, *J* = 10.3, 1.3, 1.3 Hz, 1 H), 5.64 (ddt, *J* = 17.1, 1.3, 1.3 Hz, 1 H), 5.82 (ddt, *J* = 17.1, 10.3, 5.1 Hz, 1 H), 7.19 (d, *J* = 10.9 Hz, 2 H), 7.74 (s), 8.32 (d, *J* = 10.9 Hz, 2 H). − MS (EI) *m/z* (%) 252 (100), 216 (10), 181 (36), 153 (12), 131 (9), 113 (10). − HRMS (EI) *m/z* calcd. $C_{13}H_{10}Cl_2O$ (M^+): 252.0109; found 252.0106.

Claisen Rearrangement of 7a: Compound **7a** (0.5 mmol) was dissolved in *o*-dichlorobenzene (5 mL) and refluxed for 2 hours. The mixture was cooled to room temp. A 10% aqueous solution of NaOH (5 mL) and diethyl ether (5 mL) were added. After vigorous shaking the aqueous layer was separated, acidified with 10% HCl, extracted with ethyl acetate, the extract dried with $MgSO_4$ and the solvent evaporated. The residue was chromatographed on silica gel (hexane/ethyl acetate 1:1).

Diethyl 5-Allyl-6-hydroxyazulene-1,3-dicarboxylate (8a): Yield 43%, m.p. 203−205°C. − ^{1}H NMR ([D$_6$]acetone): δ = 1.39 (t, *J* = 7.2 Hz, 3 H), 1.4 (t, *J* = 7.1 Hz, 3 H), 3.77 (dt, *J* = 6.5, 1.7 Hz, 2 H), 4.36 (q, *J* = 7.2 Hz, 2 H), 4.37 (q, *J* = 7.1 Hz, 2 H), 5.13 (ddt, *J* = 11.6, 1.7, 1.7 Hz, 1 H), 5.19 (ddt, *J* = 15.5, 1.7, 1.7 Hz, 1 H), 6.94 (ddt, *J* = 15.5, 11.6, 6.5 Hz, 1 H), 7.58 (d, *J* = 11.4 Hz, 1 H), 8.43 (s), 9.48 (d, *J* = 11.4 Hz, 1 H), 9.80 (s). − MS (EI) *m/z* (%) 328 (100), 283 (52), 255 (47), 228 (10), 211 (12), 184 (16), 153 (6). − -HRMS (EI) *m/z* calcd. $C_{19}H_{20}O_5$ (M^+): 328.1311; found 328.1315.

With compound **7b** the reaction was carried out as above in the presence of acetic anhydride (102 mg, 1 mmol). After the reaction most of the *o*-dichlorobenzene was evaporated under reduced pressure (0.1 Torr), and the residue was treated with water (5 mL) and extracted with ethyl acetate. The organic layer was dried with $MgSO_4$ and the solvent was evaporated. The residue was chromatographed on silica gel (hexane/ethyl acetate 10:3). Yield of 4-acetoxy-5-allyl-1,3-dichloroazulene **(8b)**, *O*-acetate 28%, m.p. 179−180°C. − ^{1}H NMR ([D$_6$]acetone): δ = 2.40 (s), 3.61 (dt, *J* = 6.4, 1.5 Hz,

2 H), 5.13 (ddt, J = 9.7, 1.5, 1.5 Hz, 1 H), 5.19 (ddt, J = 17.0, 1.5, 1.5 Hz, 1 H), 6.01 (ddt, J = 17.0, 9.7, 6.4 Hz, 1 H), 7.19 (d, J = 10.8 Hz, 1 H), 7.76 (s), 8.28 (d, J = 10.8 Hz, 1 H), 8.40 (s). − MS (EI) *m/z* (%) 294 (22), 252 (100), 217 (9), 181 (115), 113 (22), 71 (42), 57 (61). − HRMS (EI) *m/z* calcd. $C_{15}H_{12}Cl_2O_2$ (M^+): 294.0214; found 294.0219.

Amination of Azulenes: Azulene (1 mmol) and 4-aminotriazole (97 mg, 1.15 mmol) were dissolved in DMSO (5 mL) and argon was passed through the solution for 0.5 hour prior to the reaction. To this solution *t*BuOK (560 mg, 5 mmol) was added in a few portions keeping the temperature around 20−25°C. The mixture was stirred for 4 hours, acidified with 10% HCl (2 mL), water (20 mL) and CH_2Cl_2 (20 mL) were added and the aqueous layer containing the aminoazulene hydrochloride was separated. It was made alkaline with a 10% solution of NaOH and the product was extracted with CH_2Cl_2, dried with $MgSO_4$ and concentrated to a volume of about 5 mL. After this acetic anhydride (130 mg, 1.25 mmol) and pyridine (100 mg, 1.3 mmol) were added, the mixture was stirred for 2 hours and treated with water (10 mL). The product was extracted with CH_2Cl_2, dried with $MgSO_4$ and the solvent was evaporated. The residue was chromatographed on silica gel (hexane/ethyl acetate 2:1).

6-Acetamidoazulene (9a): Yield 38%, m.p. 170−171°C (ref. 169−170°C). − ^{1}H NMR ([D$_6$]acetone): δ = 2.59 (s), 7.70 (dd, J = 9.6, 2.0 Hz, 1 H), 7.74 (dd, J = 9.6, 2.0 Hz, 1 H), 7.90 (d, J = 4.2 Hz, 2 H), 8.00 (t, J = 4.2 Hz, 1 H), 8.67 (d, J = 9.6 Hz, 2 H). − MS (EI) *m/z* (%) 185 (63), 143 (100), 115 (29), 72 (14). − HRMS (EI) *m/z* calcd. $C_{12}H_{11}NO$ (M^+): 185.0841; found 185.0838.

6-Acetamido-1-cyanoazulene (9b): Yield 64%, m.p. 125−127°C. − ^{1}H NMR ([D$_6$]acetone): δ = 2.58 (s), 7.29 (d, J = 4.0 Hz, 1 H), 7.50 (d, J = 4.0 Hz, 1 H), 8.11 (d, J = 10.9 Hz, 1 H), 8.17 (d, J = 10.9 Hz, 1 H), 8.50 (d, J = 10.9 Hz, 1 H), 8.55 (d, J = 10.9 Hz, 1 H). − MS (EI) *m/z* (%) 210 (31), 168 (82), 140 (29), 114 (14), 69 (100). − HRMS (EI) *m/z* calcd. $C_{13}H_{10}N_2O$ (M^+): 210.0793; found 210.0797.

6-Acetamido-1,3-dichloroazulene (9c): Yield 60%, m.p. 173−174°C. − ^{1}H NMR ([D$_6$]acetone): δ = 2.22 (s), 7.50 (s), 7.81 (d, J = 11.2 Hz, 2 H), 8.24 (d, J = 11.2 Hz, 2 H), 9.72 (bs). − MS (EI) *m/z* (%) 253 (42), 211 (100), 183 (12), 113 (8). − HRMS (EI) *m/z* calcd. $C_{12}H_9Cl_2NO$ (M^+): 253.0061; found 253.0056.

4-(1,3-Dichloroazulenyl-6-acetamido)-1,2,4-triazole (9d): Experimental procedure as above except that oxygen was bubbled through the reaction mixture during the amination. Yield 32%, m.p. 189−191°C. − ^{1}H NMR ([D$_6$]acetone): δ = 2.87 (s), 7.67 (d, J = 10.9 Hz, 2 H), 7.92 (s), 8.43 (d, J = 10.9 Hz, 2 H), 8.94 (s). − MS (EI) *m/z* (%) 320 (37), 278 (91), 253 (17), 211 (100), 183 (42), 174 (90), 160 (19), 139 (7), 125 (6), 113 (8), 99 (4), 69 (16). − HRMS (EI) *m/z* calcd. $C_{14}H_{10}Cl_2N_4O$ (M^+): 320.0232; found 320.0239.

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