Synthesis and properties of azulene-containing 1,3-dioxanes

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Abstract

[1,3]Dioxane-4,6-diones with (azulen-1-yl)methylene attached to position 5 were obtained by condensation of azulene-1-carbaldehydes with Meldrum's acid. The reaction was performed either neat or in absolute ethanol using a base as a catalyst. The involvement of the generated C=C bond either in electrophilic or radical reactions appears to be restricted. The advanced molecular polarization of the obtained products can account for the low reactivity of this bond. With the electrophilic reagents only the 3-position of azulenyl moiety was substituted. The azulene acylation with acetylsalicyloyl chloride occurred with rearrangement of the acyl chloride and, the formed products are 4*H*-1,3-benzodioxin-4-ones where azulen-1-yl moiety occupies the position 2 of the heterocyclic system.

Keywords: Azulene, [1,3]dioxane-4,6-dione, 4*H*-1,3-benzodioxin-4-ones, Meldrum's acid

Introduction

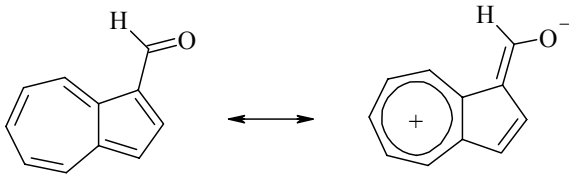
The wide use of redox molecular receptors, for example in analytical chemistry,[1] stimulated the interest on their synthesis and properties. The reported results showed that, generally, the structure of such compounds should contain three elements with specific functions: a C=C double bond which polymerizes on electrode, a chelating group and one with reversible redox property. The good redox property of the azulene compounds suggested us to use this system for the synthesis of molecular receptors. Due to the low stability of unsubstituted vinylazulenes,[2] the C=C bond must be substituted with stabilizing groups, such as carboxyl or cyan.[3] The group with chelating function can be attached to azulene before or after generation of the double bond. As part of our research in this field, we report here two classes of 1,3-dioxanes which are substituted with azulene-1-yl group, compounds that appear to be possible synthones for generation of redox molecular receptors.

Results and Discussion

1,3-Dioxane-4,6-diones

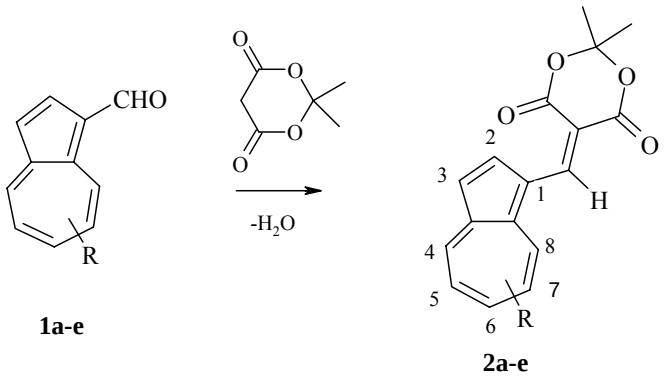
Meldrum's acid is known as an efficient synthon, largely used for the generation of the C=C double bonds.[4] Generally, the condensation of carbonyl compounds with Meldrum's acid can be performed in relatively mild conditions and the results depend on the nature of the carbonyl derivative, the used solvent, or the presence of dehydrating agents. The reactions occur in a basic medium,[5] a neutral medium in the presence of the molecular sieves,[6] in the presence of Lewis acids, such as $TiCl_4$ and pyridine,[7] acetic acid,[8] a buffered medium of piperidine acetate,[9] or even in water.[10] The condensation product, 2,2-dimethyl-[1,3]dioxane-4,6-dione, substituted with an arylmethylene moiety attached at position 5, can be easily converted into the corresponding arylmethylene malonic or arylacrylic acids.

We were pleased to find that, despite the high polarization of the 1-azulenic aldehydes (Scheme 1) which lowers their reactivity compared to common aromatic aldehydes, their condensation with Meldrum's acid occurs smoothly. Thus, by mixing the acid with oily azulen-1-carbaldehyde, **1a**, (Scheme 2) in the absence of solvent and condensation agent, the product **2a** results in more as 90% (Table 1).



Scheme 1

The driving force of this reaction is in the time crystallization of the product from the oily mixture with the retention of the resulting water into the crystalline lattice.[11] The separation from the reaction mixture of the condensation product and aldehyde via column chromatography occurs with difficulty due to similar retention times of these compounds. Additional difficulty arises from the partial hydrolysis of the product to starting aldehyde on a silica gel support. Therefore, the reaction conditions were optimized (Table 1) in the aim to increase the aldehyde conversion and hence, to shorten the separation time.



1a-e **2a-e**

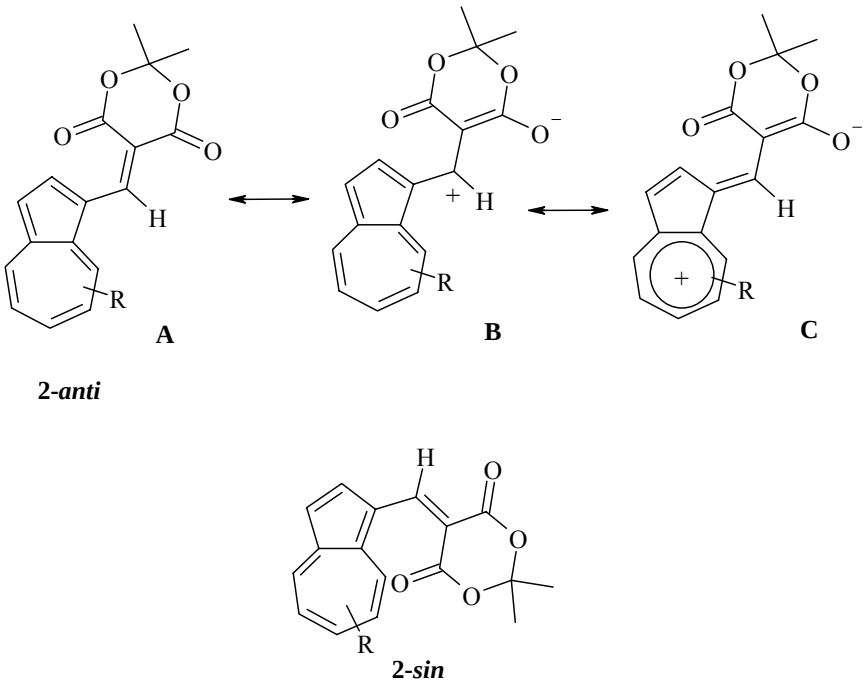
a R=H, **b** R= 4,6,8-Me_3, **c** R= 3,8-Me_2-5-iPr
d R= 3-COOMe, **e** R= 3-COOH

Scheme 2

The electron releasing property of the alkyl groups attached to the seven membered azulene ring deactivates the carbonyl group. Furthermore, when the substitution takes place at C8, as in compounds **1b** and **1c**, the condensation is even more sterically hindered. From the electronic reasons, the presence of CO_2H or CO_2Me groups at C3 lead to a decrease in the reactivity of carbonyl group for the compounds **1e** and **1d**. Therefore, for the condensation of aldehydes **1b-e**, the reaction mixture with Meldrum's acid was melted at 70-100^{o}C. As data in Table 1 indicate, even in these severe conditions the products **2b-e** are formed in lower yields than that starting with **1a**. Because ketones are less reactive than aldehydes, 1-acetylazulenes do not react with Meldrum's acid.

In order to increase the conversion of the aldehydes that do not react significantly only by heating of reagents mixture, we turn our attention towards possible condensation in absolute ethanol using diethylamine as catalyst. In these conditions a considerably increase in condensation yield, till 85%, was observed in the case of compound **2d**. However, starting with the steric hindered compound **1b** the reaction yield remains at 25%.

As previously shown, during the chromatography on silica gel the hydrolysis of condensation compounds was observed. It is a direct relationship between the extent of hydrolysis and the calculated values[12] for dihedral angle α between azulene and CH=heterocycle moieties. Whereas the compound **2a,** with the α angle (Table 2) of 11^{o}, elutes from the silica gel column almost without hydrolysis, only 15% of the compound **2b**, with α = 28^{o}, was collected along to 80% aldehyde **1b**. This could be explained by the loss in stability of the starting reagents **2** when the extension of π electronic system (Scheme 3) is reduced due to deviation from coplanarity. It is notable that, from the two possible isomers for the compounds **2**, namely, *syn* and *anti*, the isomer **2**-*sin* can be rejected due to the high steric hindrance.



Scheme 3

Table 2. Dihedral angle, α (in degrees), between azulenyl and methylene-heterocycle moieties for compounds **2**-*anti* and **2**-*syn*

R	H	4,6,8-Me_3	3,8-Me_2-5-iPr	3-Br	3-COOH
α (*anti*)	11	28	28	10	14
α (*syn*)	38	53	48	40	39

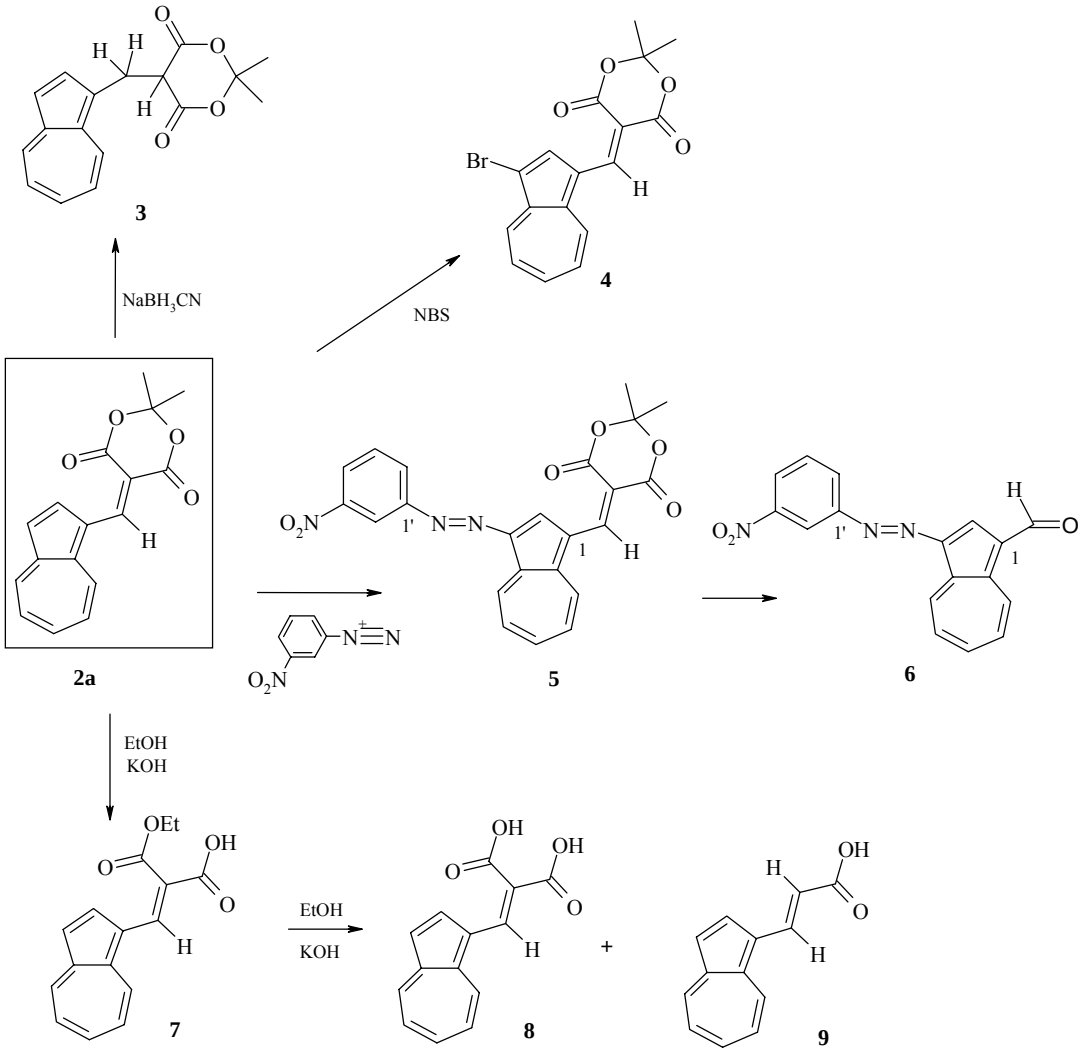
The variation of α value influences also the polarization of the compounds **2** depicted in Scheme 3. As a consequence, the chemical shift in the ^{1}H-NMR spectra of ethylenic proton changes with the change in charge at neighboring carbon atom as well as with the direction of magnetic field of the surrounded systems (δ_H for **2a**, 9.13, for **2b**, 9.32 and for **2c** 9.34 ppm). Another change in the ^{1}H-NMR spectra caused by modification of angle α was observed for the proton attached to C2 in azulenyl group. Thus, this proton is strongly deshielded at 9.42 ppm by the neighbor C=O group of heterocycle in **2a**. The deshielding effect decreases with the increase in α value for **2b** and **2c**, at 8.69 and 8.72 ppm respectively.

The important contribution of structures **B** and **C** to the molecular ground state of compounds **2** decreases the reactivity of the double bond towards either radical or, especially, electrophilic reagents.[13] The classical catalyzed hydrogenation with hydrogen gas, on palladium, yields only tar. Moreover, even using the specific reduction reagent for the polar double bonds,[14] sodium

cyanoborohydride, starting from the compound **2a**, only 12% of the normal hydrogenated product was obtained, together with 6% unsubstituted azulene (Scheme 4).

The reaction of compound **2a** with *N*-bromosuccinimide occurs selectively at C3 of the azulene moiety and affords only the brominated compound **4**, without any trace of the addition product at the double bond.

The coupling of **2a** with the reactive diazonium salts, such as *m*-nitro-benzenediazonium chloride, takes place also at C3. Accordingly, the diazene **5** was obtained from **2a** in acetic acid-acetate buffer after a long reaction time. Our attempt to obtain an analytical sample by separation on column chromatography failed due to the significant hydrolysis of the diazene **5** to the aldehyde **6**.



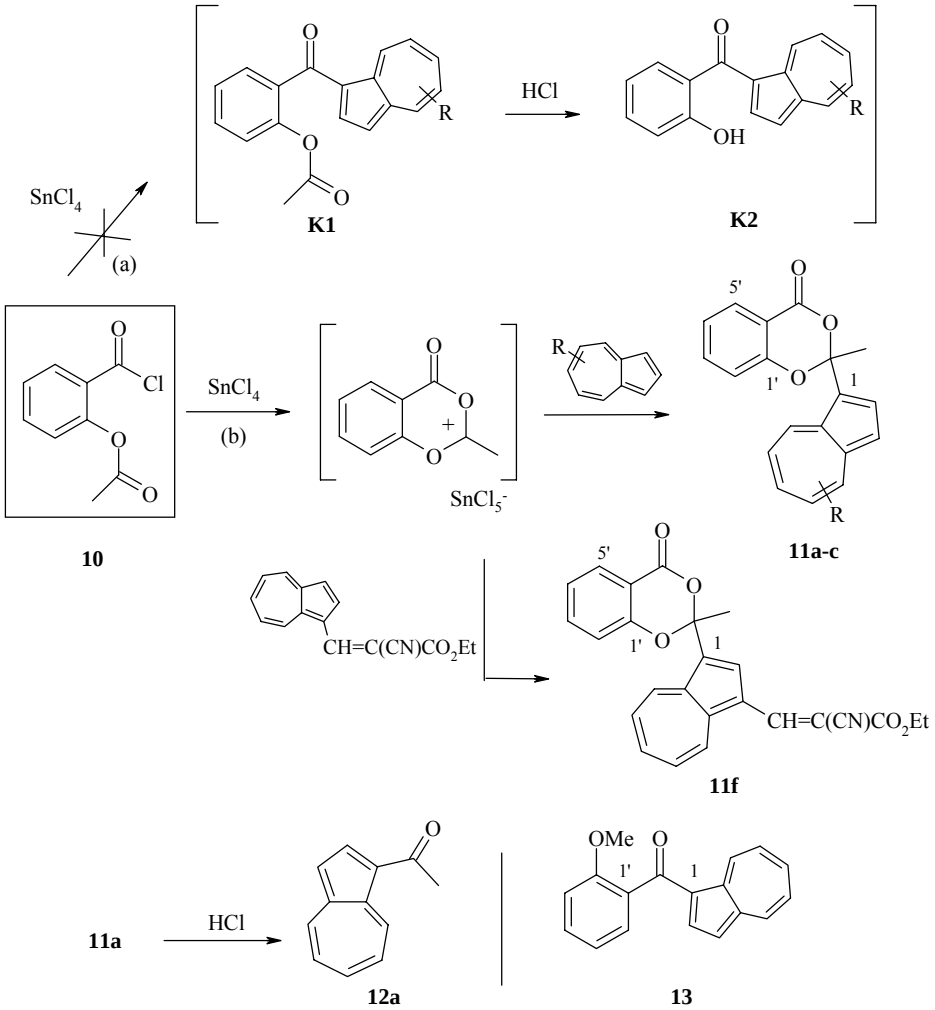
Scheme 4

Under acid hydrolysis, compound **2** affords only tar, probably due to the double decarboxylation of the acid **8** and the subsequent polymerization of the obtained vinylazulene.[2,3a]

However, the compounds **2** successfully hydrolyses in alkaline medium (alcoholic potassium hydroxide) to the monoethyl ester **7**. Even the dicarboxylic acid **8**, along to the side product, the acrylic acid **9**, was obtained in more severe reaction conditions.[3] It is interesting to observe that using the same reaction conditions, but starting with isopropylen arylmethylene-malonates, where aryl is 1-furyl or 2-thienyl, the strong nucleophiles attacks the α-C that belongs to the double bond.[15]

4*H*-1,3-Benzodioxin-4-ones

Another access route to a precursor for redox receptors consists in the substitution of the azulene moiety with the chelating system in the aim to subsequently introduce the double bond C=C. For this purpose, the salicyloyl moiety was chosen as chelating system and the synthesis was directed to afford the hydroxyl-ketones **K2** (Scheme 5).



The same signification for R in **11a-c** as in Scheme 2

Scheme 5

In order to obtain this compound, the azulenes are treated with acetylsalicyloyl chloride, **10**, under Friedel-Crafts reaction conditions ($SnCl_4$ in benzene), route (a). Instead of desired compounds **K1**, other products, **11**, with the same molar weight, were formed in good yields (Table 3). The structure of the compounds **11** was assigned based on the analytical data and it has been confirmed by different properties of the ketone **13**. Generation of the products **11** instead of the compound **K1** is not surprising since the rearrangement of acetylsalicyloyl chloride in the presence of Lewis acids is known.

Table 3. The reaction of acetyl acetylsalicyloyl chloride, **10**, with azulenes

Obtained 2-azulene-1-yl-2-methyl-benzo[1,3]dioxin-4-one	**11a**	**11b**	**11c**	**11f**
Yield (%)	50	70	60	72

The reaction with acetylsalicyloyl chloride was also successfully extended to azulene that contains a double bond with polymerization potential, $CH=C(CN)CO_2Et$, attached at C1.

Conclusions

Several [1,3]dioxane-4,6-diones with (azulen-1-yl)methylene attached at position 5, compounds **2**, were obtained by condensation of substituted or unsubstituted azulen-1-carbaldehydes with Meldrum's acid. The reaction was performed either neat or in absolute ethanol using a base as catalyst. The reaction without solvent represents an improvement of the condensation protocol. Attempts to involve the obtained double bond C=C in electrophilic or radical reactions failed. The preferential attack of electrophilic reagents occurred at C3 position of the azulene moiety. Only a small amount of hydrogenated product was obtained by reduction with $NaBH_3CN$. The alkaline hydrolysis of the compounds **2**, lead to the corresponding derivatives of malonic or acrylic acids. In the aim to acylate the azulenes with acetylsalicyloyl chloride, $SnCl_4$ was used as catalyst. In these conditions the reaction occurred with the rearrangement of acyl chloride and 4H-1,3-benzodioxin-4-ones with azulen-1-yl at the position 2 in heterocyclic system were formed as products.

Acknowledgements

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Experimental Section

General Procedures. Melting points: Kofler apparatus (Reichert Austria). Elemental analyses: Perkin Elmer CHN 240B. UV/VIS spectra were recorded in methanol and dichloromethane using a Varian Cary 100 Bio spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Gemini 300 (^{1}H NMR: 300 MHz, ^{13}C NMR: 75.45 MHz) as well as on Bruker Avance DRX4 (^{1}H NMR: 400 MHz, ^{13}C NMR: 100.62 MHz); δ are expressed in ppm, *J* in Hz, TMS was used as internal standard in $CDCl_3$ at room temperature; ^{1}H-^{1}H and ^{1}H-^{13}C COSY correlation experiments were used for the structure assignment. Mass spectra were recorded on Varian 1200L Quadrupole/MS/MS spectrometer using direct injection in ESI. Column chromatography: alumina [activity BII-III (Brockmann)] and silica gel [70-230 mesh (ASTM)]. Dichloromethane (DCM) was distilled over CaH_2 and ethyl acetate over anhydrous sodium carbonate. Azulen-1-carbaldehydes were obtained using known protocols. The nomenclature was obtained by use of the ACD/I-Lab web service (ACD/IUPAC Name Free 7.06). The numbering of the atoms is presented in the Schemes 2, 4 and 5.

Condensation with 2,2-dimethyl-[1,3]dioxan-4,6-dione (Meldrum's acid)

(a) Without solvent. Azulen-1-carbaldehyde (1 mmol) was mixed with Meldrum's acid (1 mmol) and kept at room temperature for the time indicated in Table 1. If the aldehyde is solid the reagents were dissolved in a little amount of absolute ethanol which then was removed in vacuum and the mixture was heated under a week vacuum for the time reported in Table 1. The reaction occurred easier and in higher yields for small amount of reagents. At larger scale, the reaction mixture was heated under vacuum for water removing. Finally, the solid reaction mixture was separated by column chromatography on silica gel using a mixture of DCM-ethanol (with gradient 0-10%). The separation between the product **2** and the starting aldehyde is difficult because both compounds have very close R_f and colors, therefore, if the conversion is low more column separation are necessary.

(b) Condensation in solvent. The solution of Meldrum's acid (1.5 mmol), azulen-1-carbaldehyde (1 mmol) and diethylamine (5 mmol) in absolute alcohol (10 ml) was stirred at room temperature over night. A brown product, which partially separates from the liquid, is formed. The alcohol was evaporated and the mixture was separated by chromatography on silica gel using as eluent mixture petroleum ether-DCM (1:2), then DCM-ethyl acetate (with gradient).

2-Azulen-1-ylmethylene-5,5-dimethyl-[1,3]dioxane-4,6-dione, **(2a).** Red-brown crystals; mp 180 ^{o}C (170 ^{o}C-phase tr); UV-Vis (MeOH), λ_{max}, (log ε): 223 (4.27), 288 (3.89), 341 (4.04), 455 (4.57); ^{1}H-NMR ($CDCl_3$): 1.81 (s, 6 H, Me), 7.56 (d, ^{3}J = 4.4 Hz, 1 H, 3-H), 7.67 (t, ^{3}J = 9.6 Hz, 1 H, 5-H), 7.73 (t, ^{3}J = 9.7 Hz, 1 H, 7-H), 7.95 (t, ^{3}J = 9.9 Hz, 1 H, 6-H), 8.51 (d, ^{3}J = 9.6 Hz, 1 H, 4-H), 8.94 (d, ^{3}J = 9.9 Hz, 1 H, 8-H), 9.13 (s, 1 H, CH), 9.46 (d, ^{3}J = 4.4 Hz, 1 H, 2-H); ^{13}C-NMR ($CDCl_3$): 27.41, 103.6, 104.2, 122.8, 123.2, 129.7, 130.8, 134.4, 138.5, 140.1, 144.0, 145.1, 147.1, 148.2, 161.7, 165.7; GC-MS [ESI]: m/z 283 [M+1]. Anal. calcd. for $C_{17}H_{14}O_4$ (%): C, 72.33; H, 5.00. Found: C, 72.35; H, 5.06.

5,5-Dimethyl-2-(4,6,8-trimethyl-azulen-1-ylmethylene)-[1,3]dioxane-4,6-dione (2b). Red-brown crystals; mp 165 °C**;** UV-Vis (MeOH), λ_{max}, (log ε): 228 (4.24), 306 (4.03), 335 (4.06), 348 (4.05), 466 (4.50); ^{1}H-NMR ($CDCl_3$): 1.80 (s, 6 H, Me), 2.65 (s, 3 H, Me_6), 2.83 (s, 3 H, Me_4), 3.13 (s, 3 H, Me_8), 7.27 (d, ^3J = 4.2 Hz, 1 H, 3-H), 7.39 (s, 1 H, 5-H), 7.41 (s, 1 H, 7-H), 8.69 (d, ^3J = 4.9 Hz, 1 H, 2-H), 9.32 (s, 1 H, CH); ^{13}C-NMR ($CDCl_3$): 26.04, 27.57, 28.45, 30.70, 102.3, 103.4, 117.3, 119.5, 134.7, 136.0, 140.6, 142.3, 145.6, 147.8, 149.0, 149.2, 152.4, 162.0, 165.4; GC-MS [ESI]: m/z 325 [M+1]. Anal. calcd. for $C_{20}H_{20}O_4$ (%): C, 74.06; H, 6.21. Found: C, 74.01; H, 6.26.

5,5-Dimethyl-2-(3,8-dimethyl-5-isopropyl-azulen-1-ylmethylene)-[1,3]dioxane-4,6-dione (2c). Brown crystals; mp 105 °C; UV-Vis (MeOH), λ_{max}, (log ε): 230 (4.38), 310 (3.99), 333 (4.01), 371 (3.84), 492 (4.50); ^{1}H-NMR ($CDCl_3$): 1.40 (d, ^3J = 6.8 Hz, 6 H, Me_2CH), 1.80 (s, 6 H, Me), 2.38 (heptet, ^3J = 7.0 Hz, 1 H, C*H*Me_2), 2.56 (s, 3 H, Me_3), 3.21 (s, 3 H, Me_8), 7.54 (d, ^3J = 10.9 Hz, 1 H, 5-H), 7.63 (dd, ^3J = 10.9 Hz, ^4J = 2.1 Hz, 1 H, 6-H), 8.22 (d, ^4J = 2.2 Hz, 1 H, 4-H), 8.72 (s, 1 H, 2-H), 9.34 (s, 1 H, CH=); ^{13}C-NMR ($CDCl_3$): 13.20, 24.34, 27.36, 29.82, 38.25, 101.3, 103.2, 122.8, 129.8, 134.8, 136.1, 137.1, 142.9, 145.2, 147.2, 148.3, 150.2, 150.7, 162.3, 165.7; GC-MS [ESI]: m/z 353 [M+1]. Anal. calcd. for $C_{22}H_{24}O_4$ (%): C, 74.98; H, 6.86. Found: C, 74.91; H, 6.92.

Methyl 3-(5,5-dimethyl-4,6-dioxo-[1,3]dioxan-2-ylidenemethyl)-azulene-1-carboxylate (2d). Red-brown crystals; mp 210 °C; UV-Vis (MeOH), λ_{max}, (log ε): 220 (4.44), 304 (4.30), 333 (4.05), 346 (4.05), 437 (4.51); ^{1}H-NMR ($CDCl_3$): 1.82 (s, 6 H, Me), 3.99 (s, 3 H, OMe), 7.90 (t, ^3J = 9.6 Hz, 1 H, 7-H), 7.93 (t, ^3J = 9.6 Hz, 1 H, 5-H), 8.10 (t, ^3J = 9.6 Hz, 1 H, 6-H), 8.99 (d, ^3J = 9.9 Hz, 1 H, 8-H), 9.09 (s, 1 H, CH), 9.86 (s, 1 H, 2-H), 9.87 (d, ^3J = 9.6 Hz, 1 H, 4-H); ^{13}C-NMR ($CDCl_3$): 27.57, 51.68, 104.0, 106.9, 120.4, 131.7, 133.5, 135.5, 139.7, 141.6, 145.6, 146.1, 146.9, 148.7, 161.3, 165.1; GC-MS [ESI]: m/z 341 [M+1]. Anal. calcd. for $C_{19}H_{16}O_6$ (%): C, 67.05; H, 4.74. Found: C, 67.01; H, 4.76.

3-(5,5-Dimethyl-4,6-dioxo-[1,3]dioxan-2-ylidenemethyl)-azulene-1-carboxylic acid (2e). Red-brown crystals; mp 212 °C; UV-Vis (MeOH), λ_{max}, (log ε): 235 (4.18), 278 (4.09), 305 (4.14), 442 (3.87); ^{1}H-NMR ($CDCl_3$): 1.82 (s, 6 H, Me), 8.00 (t, ^3J = 9.6 Hz, 1 H, 7-H), 8.10 (t, ^3J = 9.6 Hz, 1 H, 5-H), 8.19 (d, ^3J = 9.9 Hz, 1 H, 6-H), 9.10 (d, ^3J = 9.2 Hz, 1 H, 8-H), 9.12 (s, 1 H, CH), 9.91 (s, 1 H, 2-H), 9.91 (d, ^3J = 9.6 Hz, 1 H, 4-H); GC-MS [-ESI]: m/z 325. Anal. calcd. for : C, 66.26; H, 4.32 (%). Found: C, 66.17; H, 4.38.

Reactions of the condensation products 2

(a) Reduction reaction. To the stirred solution of condensation product **2a** (0.2 mmol) in absolute ethanol (3 ml), sodium cyanoborohydride (0.3 mmol) was added at 0 °C and the reaction mixture was stirred for 1 hour while the color turns from brown to blue. Then HCl 5% was added for neutralization of the reaction mixture and the product was extracted with DCM. The organic layer was washed with water and dried on sodium sulfate and the solvent was removed under vacuum. The product was separated by column chromatography on silica gel

using a mixture of petroleum ether-DCM (with gradient). The reduced product **3** was formed in 20% yield. The other, more polar, colored fractions were not analyzed.

2-Azulen-1-ylmethyl-5,5-dimethyl-[1,3]dioxane-4,6-dione (3). Blue oil. ^{1}H-NMR ($CDCl_3$): 1.26 (s, 6 H, Me), 3.84 (bt, ^3J = 4.7 Hz, 1 H, CH), 4.00 (bd, ^3J = 4.7 Hz, 1 H, CH_2), 7.32 (d, ^3J = 3.9 Hz, 1 H, 3-H), 7.67 (t, ^3J = 9.6 Hz, 1 H, 5-H), 7.15 (t, ^3J = 9.7 Hz, 1 H, 7-H), 7.61 (t, ^3J = 9.8 Hz, 1 H, 6-H), 8.29 (d, ^3J = 9.6 Hz, 1 H, 4-H), 8.38 (d, ^3J = 9.7 Hz, 1 H, 8-H), 7.90 (d, ^3J = 4.4 Hz, 1 H, 2-H); ^{13}C-NMR ($CDCl_3$): 24.63, 27.54, 48.51, 105.4, 117.3, 122.8, 123.1, 125.1, 134.3, 137.0, 138.0, 138.5, 166.1; GC-MS [ESI]: m/z 285 [M+1]. Anal. calcd. for $C_{17}H_{16}O_4$ (%): C, 71.82; H, 5.67. Found: C, 71.79; H, 5.86.

(b) Bromination. To the solution of condensation product **2a** (0.2 mmol) in DCM (3 ml), N-bromosuccinimide (0.2 mmol) was added and the reaction mixture was stirred at room temperature for 2.5 hours. The solvent was removed and the reaction mixture was separated by column chromatography on silica gel using a mixture of DCM-ethanol. The reddish-brown fraction represented the brominated product **4**; the yield was 95%.

2-(3-Bromo-azulen-1-ylmethylene)-5,5-dimethyl-[1,3]dioxane-4,6-dione (4). Red-brown crystals; mp 174 ^{o}C; UV-Vis (MeOH), λ_{max}, (log ε): 225 (4.29), 293 (3.95), 340 (4.05), 356 (4.03), 463 (4.44); ^{1}H-NMR ($CDCl_3$): 1.81 (s, 6 H, Me), 7.76 (bt, ^3J = 10.0 Hz, 2 H, 5-H, 7-H), 8.01 (t, ^3J = 9.8 Hz, 1 H, 6-H), 8.60 (d, ^3J = 9.6 Hz, 1 H, 4-H), 8.88 (d, ^3J = 9.6 Hz, 1 H, 8-H), 9.48 (s, 1 H, 2-H), 9.01 (s, 1 H, CH). ^{13}C-NMR ($CDCl_3$): 27.56, 104.0, 105.4, 111.4, 121.5, 130.2, 131.0, 134.6, 138.2, 141.4, 143.5, 143.7, 144.2, 146.0, 149.5, 161.6, 165.4; GC-MS [ESI]: m/z 361/363 [M+1]. Anal. calcd. for: $C_{17}H_{13}O_4Br$ (%): C, 56.53; H, 3.63; Br, 22.12. Found: C, 56.49; H, 3.69; Br, 22.09.

(c) Hydrolysis to mono ester-acid 7. The solution of condensation product **2a** (0.2 mmol), potassium hydroxyde (1.8 mmol) in ethanol (2.5 ml) and water (2.5 ml) was stirred at room temperature for 1 hour while the color change from brown to blue. The reaction mixture was extracted with DCM and the blue, basic, aqueous solution was treated with HCl 10%. The ester-acid **7** was extracted in DCM and the organic layer was washed with water and dried over sodium sulfate. After the solvent elimination, the mixture was separated by column chromatography on silica gel using DCM-ethanol (gradient 0-100%). The blue fraction represented the desired product **7** in 81% yield.

2-(1-Azulen-1-yl-methylidene)-malonic acid monoethyl ester (7). Green crystals, mp 152 ^{o}C; UV-Vis (MeOH), λ_{max}, (log ε): 223 (4.27), 283 (4.11), 314 (4.34), 397 (4.15); ^{1}H-NMR ($CDCl_3$): 1.40 (t, ^3J = 7.0 Hz, 3 H, CH_3), 4.44 (q, ^3J = 7.0 Hz, 2 H, CH_2), 7.47 (d, ^3J = 4.3 Hz, 1 H, 3-H), 7.50 (t, ^3J = 9.6 Hz, 1 H, 5-H), 7.56 (t, ^3J = 9.7 Hz, 1 H, 7-H), 7.84 (t, ^3J = 9.6 Hz, 1 H, 6-H), 8.37 (d, ^3J = 4.3 Hz, 1 H, 1 H, 2-H), 8.43 (d, = 9.9 Hz, 1 H, 4-H), 8.79 (d, ^3J = 9.9 Hz, 1 H, 8-H), 9.02 (s, 1 H, CH); GC-MS [-ESI]: m/z 269 [M-1]. Anal. calcd. for: $C_{16}H_{14}O_4$ (%): C, 71.10; H, 5.22. Found: C, 71.05; H, 5.30.

(d) Hydrolysis to dicarboxylic acid 8. The solution of condensation product **2a** (0.4 mmol) and potassium hydroxide (9 mmol) in ethanol (12.5 ml) and water (12.5 ml) was stirred at 60 ^{o}C for 2 hours. The alcohol was removed in vacuum and the aqueous solution was extracted with DCM.

The blue aqueous layer was washed with DCM and then was acidified. It results a brown precipitate which is filtrated and dried leading to a mixture of dicarboxylic acid, **8**, in 46% yield and 2-(azulen-1-yl)acrylic acid, **9**[3] in 5% yield.

2-(1-Azulen-1-yl-methylidene)-malonic acid, (8). Green crystals; mp 238 ^{o}C (dec); UV-Vis (MeOH), λ_{max}, (log ε): 224 (4.27), 286 (4.11), 315 (4.34), 396 (4.15); ^{1}H-NMR (DMSO-d_6): 7.47 (t, ^{3}J = 9.6 Hz, 1 H, 5-H), 7.52 (t, ^{3}J = 9.4 Hz, 1 H, 7-H), 7.52 (d, ^{3}J = 4.3 Hz, 1 H, 3-H), 7.88 (t, ^{3}J = 9.8 Hz, 1 H, 6-H), 8.17-8.19 (m, 2 H, 2-H, CH), 8.52 (d, ^{3}J = 9.4 Hz, 1 H, 4-H), 8.78 (d, ^{3}J = 9.8 Hz, 1 H, 8-H); ^{13}C-NMR (DMSO-d_6): 120.4, 120.8, 122.3, 126.3, 126.9, 130.2, 134.4, 138.4, 139.5, 139.7, 140.0, 143.3, 166.2, 169.3; GC-MS [-ESI]: m/z 241 [M-1]. Anal. calcd. for: $C_{14}H_{10}O_4$ (%): C, 69.42; H, 4.16. Found: C, 69.38; H, 4.25.

(e) Coupling reaction with diazotized *m*-nitroaniline. *m*-Nitroaniline was dissolved in HCl 35% (2 ml) and water (1 ml). Sodium nitrite (2 mmol) was added and the reaction mixture was stirred at 0 ^{o}C for 15 minutes. Then, the solution of diazonium salt was added to the solution of product **2a** (2 mmol) dissolved in methanol (50 ml) and potassium acetate (20 mmol) and the mixture was stirred for 1 day at room temperature then was heated 24 hours at 50 ^{o}C. After cooling of the reaction mixture, another equivalent of diazonium salt was added and the reaction was continued at room temperature for another day. A mixture of DCM-water is added for the good separation of the organic and aqueous layers. The reddish-brown organic layer was washed with water, and dried over sodium sulfate. The solvent was removed and the mixture was separated by column chromatography on silica gel with DCM-ethyl acetate. It was collected a reddish-brown fraction, which contains a mixture of the coupling product, **5**, and the corresponding**,** aldehyde **6**. After a new chromatography the aldehyde, **6** was isolated as pure product in 30% yield. The attempts to obtain a pure sample of diazene **5** failed and for the characterization of this product only ^{1}H-NMR signals were used.

5,5-Dimethyl-2-[3-(3-nitro-phenylazo)-azulen-1-ylmethylene]-[1,3]dioxane-4,6-dione (5). (in mixture with aldehyde **6**). ^{1}H-NMR ($CDCl_3$): 1.82 (s, 6 H, Me), 7.73 (t, ^{3}J = 8.0 Hz, 1 H, 5'-H), 7.95 (bt, ^{3}J = 9.7 Hz, 2 H, 5-H, 7-H), 8.14 (t, ^{3}J = 9.7 Hz, 1 H, 6-H), 8.31 (dt, ^{3}J = 8.1 Hz, ^{4}J = 1.7 Hz, 1 H, 4'-H), 8.36 (dt, ^{3}J = 7.8 Hz, ^{4}J = 1.6 Hz, 1 H, 6'-H), 8.80 (bt, ^{4}J = 1.9 Hz, 1 H, 2'-H), 8.99 (d, ^{3}J = 9.3 Hz, 1 H, 4-H), 9.15 (s, 1 H, CH), 9.58 (d, ^{3}J = 9.9 Hz, 1 H, 8-H), 9.71 (s, 1 H, 2-H).

3-(3-Nitro-phenylazo)-azulene-1-carbaldehyde (**6)**. Brown crystals; mp 197 ^{o}C; UV-Vis (MeOH), λ_{max}, (log ε): 210 (4.29), 233 (4.32), 290 sh (4.27), 311 (4.36), 409 (4.33); ^{1}H-NMR ($CDCl_3$): 7.72 (tt, ^{3}J = 8.2 Hz, ^{4}J = 0.8 Hz, 1 H, 5'-H), 7.83 (t, ^{3}J = 9.9 Hz, 1 H, 5-H), 7.88 (tt, ^{3}J = 9.9 Hz, ^{4}J = 0.8 Hz, 1 H, 7-H), 8.10 (tt, ^{3}J = 9.9 Hz, ^{4}J = 1.1 Hz, 1 H, 6-H) 8.27-8.33 (m, 2 H, 2'-H, 4'-H), 8.67 (s, 1 H, 2-H), 8.79 (s, 1 H, 6'-H), 9.58 (d, ^{3}J = 9.9 Hz, ^{4}J = 1.3 Hz, 1 H, 4-H), 9.79 (d, ^{3}J = 9.6 Hz, ^{4}J = 1.3 Hz, 1 H, 8-H), 10.43 (s, 1 H, CHO); ^{13}C-NMR ($CDCl_3$): 115.7, 123.9, 126.1, 129.9, 130.0, 130.9, 131.8, 132.7, 137.7, 140.5, 142.0, 142.3, 143.9, 154.2, 188.4; GC-MS [ESI]: m/z 306 [M+1]. Anal. calcd. for: $C_{17}H_{11}N_3O_3$ (%): C, 66.88; H, 3.63; N, 13.76. Found: C, 66.80; H, 3.72; N, 13.68.

Synthesis of 2-azulene-1-yl-2-methyl-benzo[1,3]dioxin-4-ones,11

To the solution of acetylsalicyloyl chloride, **10**, (1.15 mmol) and the azulenic derivative (1 mmol) in dry benzene (1.5 ml), under nitrogen atmosphere, a solution of $SnCl_4$ (0.2 ml) in benzene (1 ml) was added dropwise ower 5 minutes. The reaction mixture was maintained at room temperature with stirring 20 minutes and then a solution of HCl 5 N was added with strong stirring while the color changes from yellow to blue. The organic phase was washed with saturated sodium bicarbonate solution, dried on sodium sulfate and the solvent was removed. The chromatography on alumina column of the crud mixture, using petroleum ether as eluent afforded the unreacted azulene derivative and with a mixture of petroleum ether-benzene: 1-2 the elution of product **11** was accomplished. The yields are reported in Table 3.

For the synthesis of product **11f** to the solution of ethyl (*E*)-3-azulen-1-yl-2-cyano-acrylate[3] (2 mmol) and acetylsalicyloyl chloride (10 mmol) in DCM (40 ml), under nitrogen, $SnCl_4$ (2.1 mmol) was added and the reaction mixture was stirred for 24 hours at room temperature while the mixture color turns to orange. The work-up was similar to that presented for other compounds **11** and the yield is reported in Table 3.

2-Azulen-1-yl-2-methyl-4*H*-1,3-benzodioxine-4-one (11a). Blue crystals; mp 95 ^oC; UV-Vis (MeOH), λ_{max}, (log ε): 235 (4.46), 278 (4.65), 340 (3.64), 356 (3.38); ^{1}H-NMR ($CDCl_3$): 2.23 (s, 3 H, Me), 6.93 (dt, ^3J = 7.8 Hz, ^4J = 1.0 Hz, 1 H, 8'-H), 7.07 (d, ^3J = 8.2 Hz, 1 H, 6'-H), 7.18 (d, ^3J = 4.1 Hz, 1 H, 3-H), 7.20 (t, ^3J = 9.6 Hz, 1 H, 5-H), 7.32 (t, ^3J = 9.9 Hz, 1 H, 7-H), 7.42 (dt, ^3J = 7.4 Hz, ^4J = 1.7 Hz, 1 H, 7'-H), 7.65 (t, ^3J = 9.9 Hz, 1 H, 6-H), 7.76 (dd, ^3J = 7.7 Hz, ^4J = 1.7 Hz, 1 H, 5'-H), 7.90 (d, ^3J = 4.1 Hz, 1 H, 2-H), 8.26 (d, ^3J = 9.6 Hz, 1 H, 4-H), 8.91 (d, ^3J = 9.9 Hz, 1 H, 8-H); ^{13}C-NMR ($CDCl_3$): 30.00, 107.5, 115.1, 116.8, 116.9, 122.8, 124.2, 124.3, 127.3, 129.8, 135.4, 135.7, 136.2, 136.9, 137.9, 138.5, 142.1, 156.9 158.9, 162.1; GC-MS [ESI]: m/z 291 [M+1]. Anal. calcd. for: $C_{19}H_{14}O_3$ (%): C, 78.60; H, 4.86. Found: C, 78.56; H, 4.94.

2-Methyl-2-(4,6,8-trimethylazulen-1-yl)-4*H*-1,3-benzodioxin-4-one (11b). Violet crystals; mp 170 ^oC; UV-Vis (MeOH), λ_{max}, (log ε): 245 (4.48), 290 (4.62), 347 (3.72), 365sh (3.40); ^{1}H-NMR ($CDCl_3$): 2.26 (s, 3 H, Me_2), 2.46 (s, 3 H, Me_{Az}), 2.67 (s, 3 H, Me_{Az}), 3.09 (s, 3 H, Me_{Az}), 6.83 (dt, ^3J = 7.8 Hz, ^4J = 1.0 Hz, 1 H, 8'-H), 6.90 (dd, ^3J = 8.4 Hz, ^4J = 0.7 Hz, 1 H, 6'-H), 6.92 (s, 1 H, 5-H), 7.04 (d, ^3J = 4.5 Hz, 1 H, 3-H), 7.06 (s, 1 H, 7-H), 7.32 (ddd, ^3J = 7.4 Hz, ^3J = 7.2 Hz, ^4J = 1.7 Hz, 7'-H), 7.66 (dd, ^3J = 7.8 Hz, ^4J = 1.5 Hz, 1 H, 5'-H), 7.72 (d, ^3J = 4.3 Hz, 1 H, 2-H); ^{13}C-NMR ($CDCl_3$): 26.29, 28.39, 29.79, 30.46, 108.1, 114.7, 115.1, 117.0, 122.5, 126.7, 128.5, 129.6, 131.1, 135.8, 135.9, 136.2, 139.1, 146.1, 146.6, 147.7, 156.5, 162.1; GC-MS [ESI]: m/z 333 [M+1]. Anal. calcd. for $C_{22}H_{20}O_3$ (%): C, 79.50; H, 6.06. Found: C, 79.56; H, 6.12.

2-(3,8-Dimethyl-5-isopropylazulen-1-yl)-2-methyl-4*H*-1,3-benzodioxin-4-one, (11c). Blue crystals; mp 80 ^oC; UV-Vis (MeOH), λ_{max}, (log ε): 244 (4.59), 289 (4.66), 348 (3.69), 371 (3.78); ^{1}H-NMR ($CDCl_3$): 1.24 (d, ^3J = 6.9 Hz, 6 H, C*H*Me_2), 2.25 (s, 3 H, Me), 2.44 (s, 3 H, Me_3), 2.94 (heptet, ^3J = 6.9 Hz, 1 H, CH*Me_2*), 3.12 (s, 3 H, Me_8), 6.88 (dt, ^3J = 7.6 Hz, ^4J = 1.1 Hz, 1 H, 8'-H), 6.94 (d, ^3J = 8.0 Hz, 1 H, 6'-H), 7.07 (d, ^3J = 11.0 Hz, 1 H, 5-H), 7.30 (dd, ^3J = 11.5 Hz, ^4J = 1.8 Hz, 1 H, 6-H), 7.36 (ddd, ^3J = 7.4 Hz, ^3J = 7.2 Hz, ^4J = 1.9 Hz, 7'-H), 7.72 (dd, ^3J = 8.0 Hz, ^4J = 1.4 Hz, 1 H, 5'-H), 7.72 (s, 1 H, 2-H), 8.01 (d, ^4J = 2.2 Hz, 1 H, 4-H); ^{13}C-NMR ($CDCl_3$):

13.25, 24.68, 28.89, 30.87, 37.61, 107.99, 115.2, 117.0, 122.6, 123.8, 129.7, 134.2, 135.6, 136.3, 139.5, 146.3, 156.5, 162.1; GC-MS [ESI]: m/z 361 [M+1]. Anal. calcd. for $C_{24}H_{24}O_3$ (%): C, 79.96; H, 6.72. Found: C, 79.92; H, 6.80.

Ethyl (*E*)-2-cyano-3-[3-(2-methyl-4-oxo-4*H*-benzo[1,3]dioxin-2-yl)-azulen-1-yl]-acrylate (11f). Red crystals; mp 183 °C; ^{1}H-NMR ($CDCl_3$): 1.42 (t, ^3J = 7.2 Hz, 3 H, *Me*CH_2), 2.77 (s, 3 H, Me), 4.40 (q, ^3J = 7.1 Hz, 2 H, Me*C*H_2), 7.16 (dd, ^3J = 8.1 Hz, ^4J = 1.2 Hz, 1 H, 8'-H), 7.35 (dt, ^3J = 7.7 Hz, ^4J = 1.3 Hz, 1 H, 6'-H), 7.58 (dt, ^3J = 7.5 Hz, ^4J = 1.8 Hz, 1 H, 7'-H), 7.65 (t, ^3J = 10.0 Hz, 1 H, 5-H), 7.68 (t, ^3J = 10.0 Hz, 1 H, 7-H), 8.05 (t, ^3J = 9.8 Hz, 1 H, 6-H), 8.25 (dd, ^3J = 7.9 Hz, ^4J = 1.7 Hz, 1 H, 5'-H), 8.81 (d, ^4J = 1.3 Hz, 1 H, 2-H), 8.84 (d, ^3J = 9.4 Hz, 1 H, 4-H), 9.47 (s, 1 H, CH), 10.02 (dd, ^3J = 9.9 Hz, ^4J = 1.2 Hz, 1 H, 8-H); ^{13}C-NMR ($CDCl_3$): 14.47, 29.43, 62.44, 115.0, 116.0, 124.5, 126.6, 131.1, 133.0, 133.7, 134.9, 135.6, 141.1, 141.7, 142.1, 144.0, 162.3, 174.4; GC-MS [ESI]: m/z 414 [M+1]. Anal. calcd. for $C_{25}H_{19}NO_5$ (%): C, 72.63; H, 4.63; N, 3.39. Found: C, 72.56; H, 4.68; N, 3.42.

Synthesis of azulen-1-yl(2-methoxyphenyl)methanone (13)

To the solution of azulene (1 mmol) in 10 ml acetonitrile, under nitrogen atmosphere, 2-methoxybenzoyl chloride (2 mmol) and $SnCl_4$ (0.2 ml) were added at room temperature and the mixture was stirred for 30 minutes at room temperature. Then, a solution of HCl 2 N was added till the color becomes reddish-violet. The organic phase was diluted with DCM (50 ml), and the solution was washed with water, dried on sodium sulfate and then the solvents were removed in vacuum. By the column chromatography on an alumina column, the unreacted azulene was eluted with petroleum ether, while the product needs a mixture petroleum ether-DCM : 1-1. The desired product **13**, was obtained as red crystals in yield of 72%.

Azulen-1-yl-(2-methoxyphenyl)-methanone, (13). Red crystals, mp 122 °C; UV-Vis (MeOH), λ_{max}, (log ε): 267 (4.13), 310 (4.56), 381 (4.14), 393 (4.27); ^{1}H-NMR ($CDCl_3$): 3.77 (s, 3 H, Me), 7.02 (d, ^3J = 8.3 Hz, 1 H, 6'-H), 7.05 (dt, ^3J = 8.2 Hz, ^4J = 0.8 Hz, 1 H, 4'-H), 7.22 (d, ^3J = 4.1 Hz, 1 H, 3-H), 7.40-7.60 (m, 2H, 3'-H, 5'-H), 7.51 (t, ^3J = 9.8 Hz, 1H, 5-H), 7.67 (t, ^3J = 9.8 Hz, 1H, 7-H), 7.85 (t, ^3J = 9.8 Hz, 1H, 6-H), 7.87 (d, ^3J = 4.1 Hz, 1H, 2-H), 8.48 (d, ^3J = 9.7 Hz, 1H, 4-H), 9.98 (d, ^3J = 9.9 Hz, 1H, 8-H); GC-MS [ESI]: m/z 263 [M+1]. Anal. calcd. for $C_{18}H_{14}O_2$ (%): C, 82.42; H, 5.38. Found: C, 82.37; H, 5.45.

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