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Synthesis of 1,3,6-trisubstituted azulenes based on the 1-acyloxyazulene scaffold

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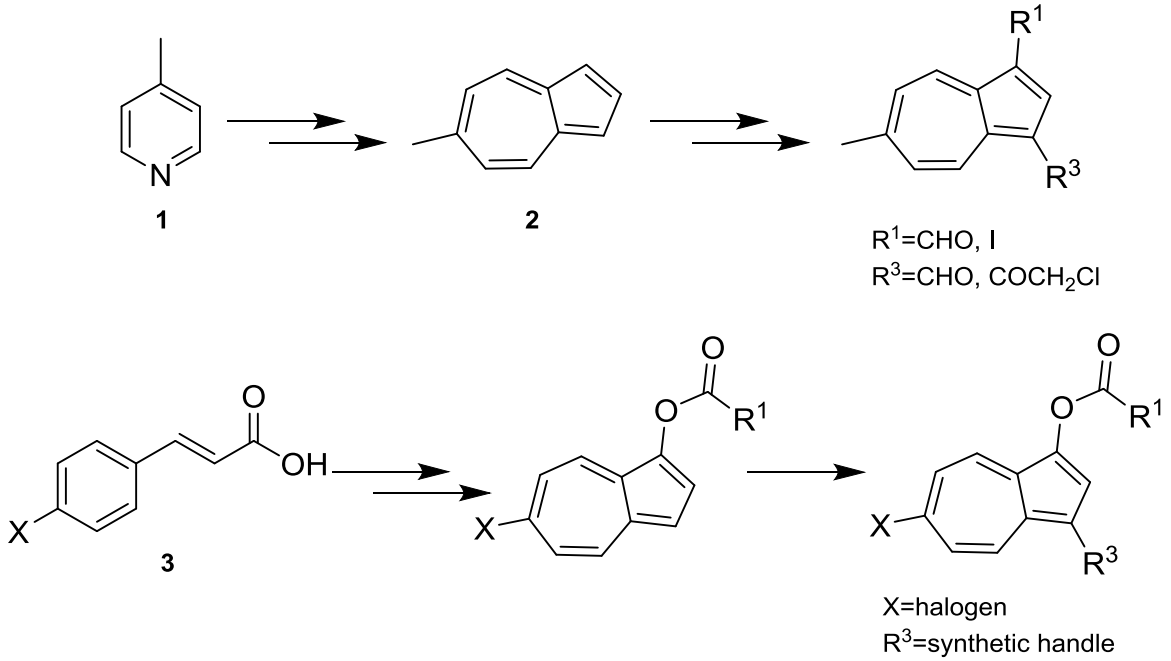
Abstract: An efficient synthetic route to access 1,3,6-trisubstituted azulenes based on the 1-acyloxyazulene scaffold was developed. Position 1 in azulene was substituted in the ring formation step with a functionalized acyloxy group. Additionally, the 3- and 6-positions of azulene were functionalized by versatile synthetic handles, a halogen atom and a formyl group.

Introduction

Azulene is a bicyclic nonbenzenoid aromatic structure and it has a dipole moment between its electron-rich five-membered ring and electron deficient seven-membered ring.[1],[2] The five-membered ring readily reacts with electrophiles at its 1- and 3-positions,[3] but the seven-membered ring is most easily substituted via a synthetic handle such as a halogen atom or a methyl group. Azulene has not been an intensively studied ring structure in medicinal chemistry, unlike its structural isomer naphthalene or isostere indole (aromatic molecule with a similar shape and dipole moment). The only azulene-based drug on the market is the antiulcer agent egualen sodium.[4] In addition, azulene-based compounds have been reported to have e.g. anticancer[5] and antidiabetic[6] activities as well as an application in erectile dysfunction.[7] General synthetic routes for multiple-substituted azulenes will be needed to study azulene as a scaffold in medicinal chemistry.

Aiming at developing a general synthetic route to 1,3,6-trisubstituted azulenes, we have been studying different possibilities to introduce synthetic handles on the azulene scaffold in these positions. The synthetic handles can then be used to introduce a wide variety of substituents in the selected positions and allow a facile generation of a series of new compounds for structure-based drug design or biological screening studies.

We have reported a general and efficient synthetic route to obtain 1,3,6-trisubstituted azulenes from 6-methylpyridine (**1**) (Scheme 1).[8] However, with this procedure we did not succeed in introducing a halogen atom in position 6 by changing the starting material from 6-methylpyridine to 6-chloropyridine. A halogen atom is highly desired as it can be exploited in many palladium-mediated coupling reactions.[9]-[14] Unfortunately, most of the reported synthetic routes to 6-haloazulene derivatives include multiple steps with low overall yields.[15]-[18]



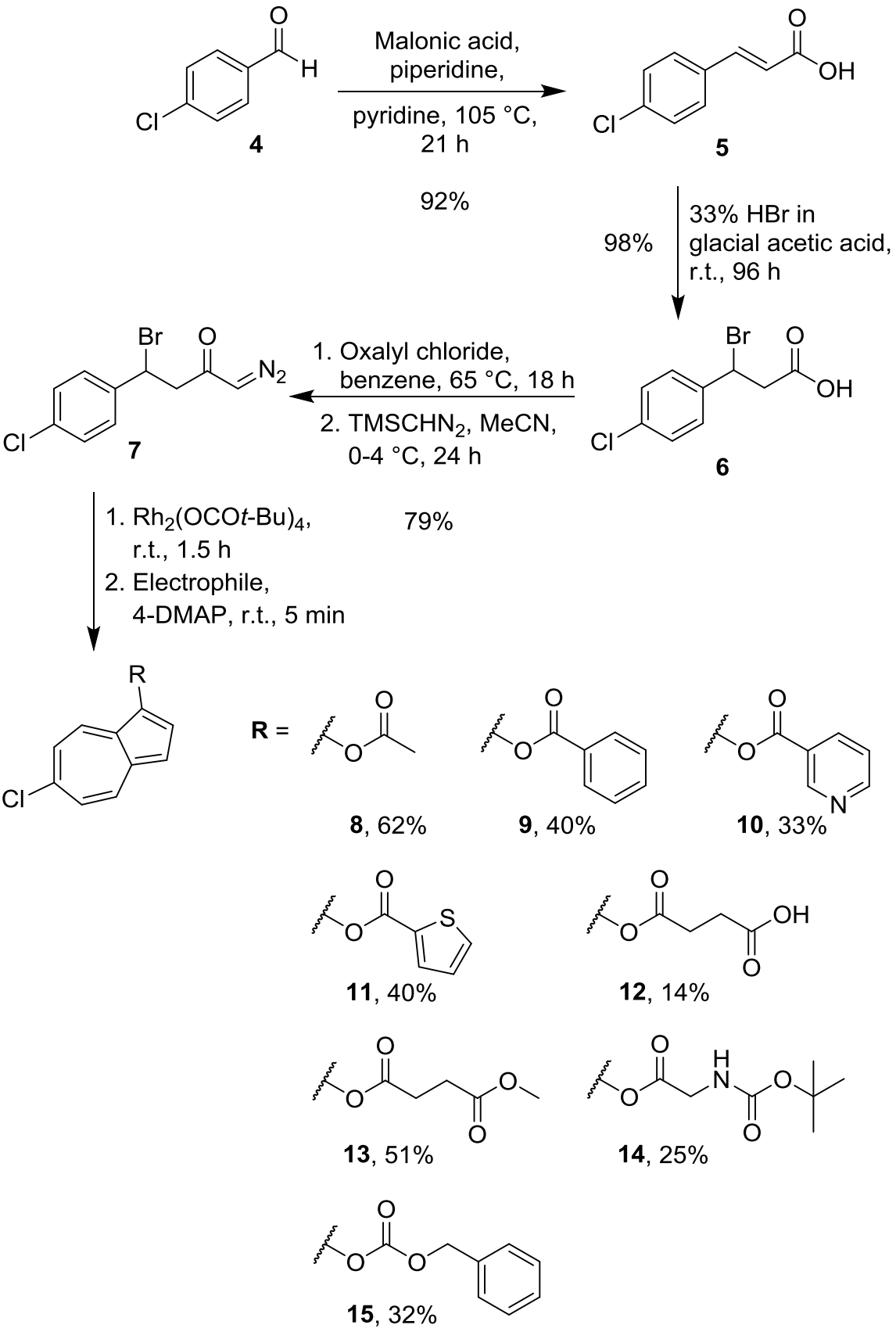
Scheme 1. Two different approaches of synthesizing 1,3,6-trisubstituted azulenes.

We decided to study an alternative method to assemble the azulene ring presented by Kane et al.[19] In this method the halogen atom at the 6-position in azulene is derived from a para-halogenated cinnamic acid **3** (Scheme 1). Furthermore, this method gives directly an ester-linked substituent on the hydroxy group in the 1-position on the azulene scaffold. The previously reported substituents in the 1-position are acetoxy, trimethylacetoxy and triflate.[14] The triflate group has been demonstrated to react by a Suzuki coupling reaction. However, there is a severe selectivity problem in Pd-mediated coupling reactions with the combination of a triflate group in the 1-position and a chlorine atom in the 6-position as both are equally reactive under Suzuki coupling conditions.

We were interested in studying what kind of substituents could be introduced in the 1-position of azulene by a linking ester bond and whether functional groups capable of serving as synthetic handles could also be introduced in this position. In the other positions, a halogen atom was investigated as the synthetic handle in the 6-position and the formyl group in the 3-position.The obtained 1,3,6-trisubstituted azulenes are in fact 1,3,6-trisubstituted azulenes based on the 1-acyloxyazulene scaffold.

Results and Discussion

A Knoevenagel condensation between 4-chlorobenzaldehyde (**4**) and malonic acid gave 4-chlorocinnamic acid (**5**) in 92% yield (Scheme 2). The double bond of **5** was hydrobrominated with HBr in glacial acetic acid at room temperature to give compound **6** in 98% yield. A reaction time of 4 days was needed to reach a high conversion. We replaced gaseous HBr, which was used in the reported procedure,[19] with more practical and commercially available HBr in glacial acetic acid. Treatment of **6** with oxalyl chloride provided the corresponding acid chloride, which was allowed to react with trimethylsilyldiazomethane to generate the diazoketone **7** modifying a method from the literature.[20] Diazoketone **7** was obtained from **6** by this synthetic procedure in 79% yield. Diazomethane was used previously by Kane et al.,[19] but we replaced it with the less explosive trimethylsilyldiazomethane. In addition to the use of safer reagents compared to the reported method, the optimization of the reaction conditions improved the yield. The overall yield from cinnamic acid **5** to diazoketone **7** was 77% with our method, compared with the 61% yield reported in literature.[19]

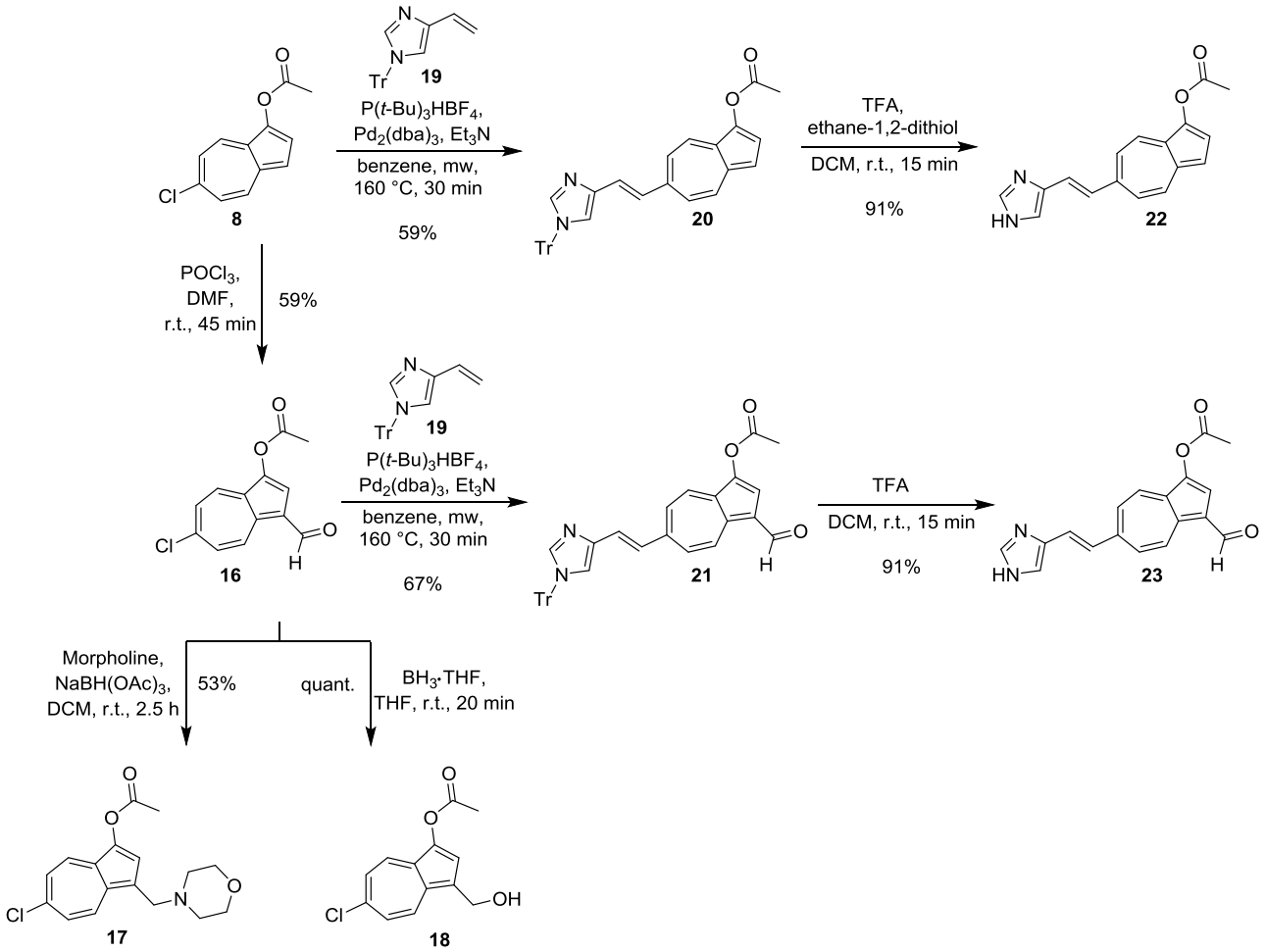


Scheme 2. Synthesis of the azulene scaffold with different 1-acyloxy groups.

1-Acetoxy-6-chloroazulene (**8**) was synthesized from diazoketone **7** in 62% yield, which is consistent with the previously reported yield. Different activated carboxylic acid derivatives were used as electrophiles to demonstrate possible substitutions on the 1-position of azulene during this step. When using benzoyl chloride, nicotinoyl chloride and 2-thiophenecarbonyl chloride, compounds **9**, **10** and **11** were obtained in 40%, 33% and 40% yield, respectively. Carboxylic acid derivative **12** was synthesized from succinic anhydride. The reaction was first carried out using the same method as in the case of **8**, in which five equivalents of the electrophile was added. However, this led to formation of an insoluble residue and the desired product could not be isolated from the reaction mixture. The reaction was repeated with one equivalent of succinic anhydride to get **12** in 14% yield. The result suggests that the excess of anhydride reacts further with the carboxyl group of **12** to form insoluble residue. Compound **12** was turned out to be unstable after purification, which might also account for the low yield.

In addition to anhydrides and acid chlorides, mixed anhydrides made from pivaloyl chloride were used. Compound **13** and *t*-Boc-protected glycine derivative **14** were synthesized by this method in the yields of 51% and 25%, respectively. As **13**, the methyl ester of **12**, is a stable compound, it implies that the free carboxyl group causes the instability of **12**. In the case of **14** the amount of the mixed anhydride resulting from pivaloyl chloride activated *N*-(*tert*-butoxycarbonyl)glycine was reduced from five to two equivalents, as five equivalents formed many side products and they were not separable from the desired product. The reaction of diazoketone **7** with benzyl chloroformate as an electrophile gave the carbonate **15** in 32% yield. The use of various activated carboxylic acid derivatives enables introduction of different ester and carbonate linked substituents in the 1-position. These substituents can carry different functionalities to be introduced in this position of the azulene scaffold.

Introduction of the third substituent in the 3-position on the azulene scaffold was demonstrated using 1-acetoxy-6-chloroazulene (**8**) as a starting material (Scheme 3). Formylation of the 3-position of azulene was optimized by changing reaction temperatures (rt or 90 °C) or the amount of $POCl_3$ (1.5–4 equiv), when preparing the Vilsmeier-Haack reagent from $POCl_3$ and DMF in situ. Yields of the trisubstituted azulene **16** varied from 31% to 59%. There was some variation in the yields when applying the same method, which was likely caused by ester hydrolysis. To avoid this, $NaHCO_3$ was used in the work-up instead of NaOH. The highest yield was observed in the method, in which the reaction was carried out at room temperature using two equivalents of $POCl_3$. Additionally, the formylation was carried out with a commercial Vilsmeier-Haack reagent in DCM at 0 °C providing **16** in 44% yield. The applicability of the formyl group was demonstrated by reductive amination, in which the reaction with morpholine and sodium triacetoxyborohydride gave **17** in 53% yield. The reduction of the formyl group with borane-THF complex to the corresponding alcohol **18** was quantitative. However, **18** is unstable and decomposes in course of a few days at room temperature.



Scheme 3. Functionalization of the 3- and 6-positions of azulene.

Since imidazoles are important heterocycles in medicinal chemistry, we decided to introduce the moiety to the azulene scaffold. 1-Trityl-4-vinyl-1*H*-imidazole (**19**) was synthesized following a method reported in the literature.[21] The Heck reaction was carried out for both disubstituted azulene **8** and trisubstituted azulene **16** by heating the starting material and **19** with microwaves at 160 °C for 30 min in the presence of palladium catalyst, phosphorous ligand and base. The reaction gave **20** and **21** in 59% and 67% yield, respectively. Trityl groups were removed with trifluoroacetic acid in DCM in yields exceeding 90%.

Conclusions

In our current work, we showed it is possible to include different functionalities at positions 1, 3 and 6 on the azulene scaffold. The azulene ring was formed with a halogen atom in the 6-position and an acyloxy group in the 1-position. The third substituent in the 3-position was a formyl group. The halogen atom and the formyl group are versatile synthetic handles for further functionalization of the azulene scaffold. Additionally, we improved the reported synthetic route of the azulene scaffold and successfully replaced the hazardous reagent diazomethane with less explosive trimethylsilyldiazomethane. We have demonstrated the efficiency of the developed route synthesizing the 1,3,6-trisubstituted azulene derivative **23** in seven synthetic steps in overall yield of 16%.

Experimental Section

General information. All synthesized compounds were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy using Varian Mercury 300 MHz spectrometer. NMR spectra are reported in chemical shifts in parts per million (ppm) relative to the residual solvents: $CDCl_3$ 7.26 and 77.16 ppm, acetone-d_6 2.05 and 29.84 ppm, DMSO-d_6 2.50 and 39.52 ppm for ^{1}H and ^{13}C NMR, respectively. The progress of the reactions was monitored by thin-layer chromatography on silica gel 60-F_{254} plates. When the product was purified by flash chromatography, silica gel (SiO_2) 60 (230–400 mesh) or silica gel with a Biotage SP1 purification system (SNAP 10 g, 25 g or 50 g cartridges) was used. Microwave reactions were conducted

in sealed reaction vessels using a Biotage Initiator+ instrument equipped with an external IR-sensor to detect the reaction temperature. Mass spectrometric analyses were executed with Waters Synapt G2 HDMS mass spectrometer with ESI. Compounds **17**, **20** and **21** were ionized with direct APPI/APCI ion source in positive, resolution ion mode, due to fragmentation and no efficient ionization during the HRMS analyses with ESI. Compounds **17**, **20** and **21** were analyzed as Na-adducts and exact masses were corrected with progesterone as a lock mass compound.

4-Chlorocinnamic acid (5). 4-Chlorobenzaldehyde (5.00 g, 35.6 mmol) and malonic acid (5.55 g, 53.4 mmol) were dissolved in pyridine (10 mL) and piperidine (0.50 mL) was added. The reaction mixture was heated at 105 °C for 21 h and poured into a 4 M aqueous solution of HCl (40 mL). The resulting white precipitate was filtered, washed several times with a small amount of a 0.01 M aqueous solution of HCl and evaporated under reduced pressure to give **5** as a white, amorphous solid (5.99 g, 92%). ^{1}H NMR (DMSO-d_6) δ 12.41 (s, 1H), 7.74–7.69 (m, 2H), 7.58 (d, J = 16.2 Hz, 1H), 7.49–7.44 (m, 2H), 6.54 (d, J = 15.9 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 167.3, 142.4, 134.7, 133.2, 129.8, 128.8, 120.1. HRMS (ESI-TOF): calcd for $C_9H_6O_2Cl$ [M - H]$^-$ 181.0056; found 181.0057.

3-Bromo-3-(4-chlorophenyl)propanoic acid (6). Compound **5** (2.01 g, 11.0 mmol) was suspended in a 33% solution of HBr in glacial acetic acid (40 mL) under argon. The red-orange suspension was stirred at room temperature and after 24 h of stirring more 33% HBr in glacial acetic acid (20 mL) was added. In total the reaction mixture was stirred at room temperature for 4 d. The solvents were evaporated and the orange residue was dissolved in Et_2O (100 mL). The organic phase was washed with a 0.05 M aqueous solution of HCl (10 × 40 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to give **6** as a white, amorphous solid (2.85 g, 98%). ^{1}H NMR (DMSO-d_6) δ 7.59–7.54 (m, 2H), 7.44–7.40 (m, 2H), 5.54–5.49 (m, 1H), 3.36–3.22 (m, 2H). ^{13}C NMR (DMSO-d_6) δ 170.6, 140.2, 133.0, 129.3, 128.6, 48.8, 43.6.

4-Bromo-4-(4-chlorophenyl)-1-diazobutan-2-one (7). Oxalyl chloride (0.57 mL, 6.6 mmol) was added to a suspension of **6** (1.5 g, 5.5 mmol) in anhydrous benzene (20 mL) under argon. The reaction mixture was stirred at 65 °C for 18 h. The suspension turned to a clear solution after 45 min of stirring. The clear solution was allowed to cool to room temperature and the solvents were evaporated. The resulting brown oil was dissolved in anhydrous MeCN (17 mL) under argon and it was added dropwise over 25 min to a solution of $TMSCHN_2$ (2 M in Et_2O, 5.5 mL, 11 mmol) in anhydrous MeCN (11 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 3 h and it was allowed to react at 0–4 °C for 21 h without stirring. The yellow solution was diluted with Et_2O (80 mL) and it was extracted with a 0.5 M aqueous solution of $NaHCO_3$ (2 × 40 mL) and water (2 × 40 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to provide an orange oil. The crude product was purified by flash chromatography (*n*-hexane/EtOAc 4:1) to give **7** as a yellow, amorphous solid (1.3 g, 79%). ^{1}H NMR ($CDCl_3$) δ 7.37–7.29 (m, 4H), 5.46–5.41 (m, 1H), 5.27 (s, 1H), 3.31–3.07 (m, 2H). ^{13}C NMR (DMSO-d_6) δ 189.8, 139.6, 134.6, 129.1, 128.7, 56.0, 50.0, 47.0. The NMR data is in accordance with the literature.[14]

General procedure for compounds 8–15. Rhodium(II) pivalate (0.005 equiv) was dissolved in anhydrous DCM (6 mL/mmol) under argon. The yellow solution of **7** (1 equiv) in anhydrous DCM (16 mL/mmol) was added dropwise over 1 h to the green rhodium(II) pivalate solution. The greenish brown reaction mixture was stirred for an additional 30 min at room temperature before the appropriate electrophile (1.1–5 equiv) and 4-DMAP (3 equiv) were added. The resulting mixture was stirred at room temperature for 5 min. In the case of **8** and **13**, the reaction mixture was treated with MeOH (1.5 mL/mmol) and stirred for additional 10 min. The reaction mixture was diluted with DCM and it was washed with a 1 M aqueous solution of HCl (**8**, **9**, **11**, **12**, **13**), a 1% aqueous solution of citric acid (**10**, **14**, **15**), a saturated aqueous solution of $NaHCO_3$ (**10**, **14**), water (**15**) and brine, dried over anhydrous Na_2SO_4, filtered, and evaporated to provide a crude product, which was purified by flash chromatography.

1-Acetoxy-6-chloroazulene (8). Compound **7** (1.1 g, 4.0 mmol) and acetic anhydride (1.9 mL, 20 mmol) gave a dark blue oil, which after flash chromatography (*n*-hexane/EtOAc 19:1) afforded **8** as a blue, amorphous solid (0.54 g, 62%). ^{1}H NMR ($CDCl_3$) δ 8.04–8.00 (m, 2H), 7.79 (d, J = 4.5 Hz, 1H), 7.29 (d, J = 4.5 Hz, 1H), 7.24–7.16 (m, 2H), 2.43 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 169.0, 145.7, 139.8, 135.9, 134.0, 130.4, 128.2, 124.8, 122.9, 122.4, 116.2, 21.1. HRMS (ESI-TOF): calcd for $C_{12}H_{10}O_2Cl$ [M + H]$^+$ 221.0369; found 221.0369. The NMR data is in accordance with the literature.[14]

6-Chloroazulen-1-yl benzoate (9). Compound **7** (0.14 g, 0.50 mmol) and benzoyl chloride (0.064 mL, 0.55 mmol) gave a dark green oil, which after flash chromatography (*n*-hexane/EtOAc 19:1) afforded **9** as a blue, amorphous solid (0.057 g, 40%). ^{1}H NMR ($CDCl_3$) δ 8.35–8.31 (m, 2H), 8.12 (d, J = 10.5 Hz, 1H), 8.06 (d, J = 9.9 Hz, 1H), 7.94 (d, J = 4.5 Hz, 1H), 7.71–7.64 (m, 1H), 7.60–7.54 (m, 2H), 7.35 (d, J = 4.2 Hz, 1H), 7.27–7.18 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 164.8, 145.8, 139.9, 136.0, 134.3, 133.8, 130.5, 130.4, 129.7, 128.8, 128.3, 125.1, 123.0, 122.6, 116.4. HRMS (ESI-TOF): calcd for $C_{17}H_{12}O_2Cl$ [M + H]$^+$ 283.0526; found 283.0525.

6-Chloroazulen-1-yl nicotinate (10). Compound **7** (0.14 g, 0.50 mmol) and nicotinoyl chloride hydrochloride (0.098 g, 0.55 mmol) gave a dark green oil, which after flash chromatography (manual gradient of *n*-hexane/EtOAc 4:1 → 1:1) afforded **10** as a green, amorphous solid (0.047 g, 33%). ^{1}H NMR ($CDCl_3$) δ 9.52 (s, 1H), 8.89 (d, J = 4.2 Hz, 1H), 8.54 (d, J = 7.8 Hz, 1H), 8.09 (t, J = 10.8 Hz, 2H), 7.95 (d, J = 4.5 Hz, 1H), 7.51 (dd, J = 7.8, 3.0 Hz, 1H), 7.34 (d, J = 4.5 Hz, 1H), 7.35–7.21 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 163.5, 154.2, 151.5, 146.1, 139.3, 137.7, 136.2, 134.2, 130.4, 128.0, 125.7, 125.0, 123.7, 123.3, 122.8, 116.4. HRMS (ESI-TOF): calcd for $C_{16}H_{11}NO_2Cl$ [M + H]$^+$ 284.0478; found 284.0473.

6-Chloroazulen-1-yl thiophene-2-carboxylate (11). Compound **7** (0.14 g, 0.50 mmol) and 2-thiophenecarbonyl chloride (0.059 mL, 0.55 mmol) gave a dark green oil, which after flash chromatography (*n*-hexane/EtOAc 19:1) afforded **11** as a green, amorphous solid (0.057 g, 40%). ^{1}H NMR ($CDCl_3$) δ 8.13–8.03 (m, 3H), 7.92 (d, J = 4.5 Hz, 1H), 7.71 (d, J = 5.1 Hz, 1H), 7.32 (d, J = 4.2 Hz, 1H), 7.26–7.18 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 160.3, 145.9, 139.4, 136.1, 134.9, 134.1, 133.8, 132.7, 130.6, 128.3, 128.1, 125.0, 123.1, 122.6, 116.3. HRMS (ESI-TOF): calcd for $C_{15}H_{10}O_2SCl$ [M + H]$^+$ 289.0090; found 289.0094.

4-[(6-Chloroazulen-1-yl)oxy]-4-oxobutanoic acid (12). Compound **7** (0.14 g, 0.50 mmol) and succinic anhydride (0.050 g, 0.50 mmol) gave a green solid, which after two flash chromatographic purifications (EtOAc/MeOH 1% + EtOAc/AcOH 1% and *n*-hexane/EtOAc/AcOH 80:18:2) afforded **12** as a blue solid (0.020 g, 14%). ^{1}H NMR (CD_3CN) δ 8.16 (d, J = 9.9 Hz, 1H), 8.10 (d, J = 10.5 Hz, 1H), 7.71 (d, J = 4.5 Hz, 1H), 7.35 (d, J = 4.2 Hz, 1H), 7.31 (dd, J = 10.1, 2.3 Hz, 1H), 7.25 (dd, J = 10.5, 2.1 Hz, 1H), 2.98–2.91 (m, 2H), 2.77–2.73 (m, 2H). ^{13}C NMR (CD_3CN) δ 173.9, 172.2, 146.3, 140.8, 137.3, 135.2, 131.7, 129.5, 125.8, 123.9, 123.3, 117.3, 30.3, 29.4.

6-Chloroazulen-1-yl methyl succinate (13). Mono-methyl hydrogen succinate (0.33 g, 2.5 mmol) was suspended in DCM (8 mL) and Et_3N (0.35 mL, 2.5 mmol) was added. The clear solution was cooled to 0 °C and pivaloyl chloride (0.31 mL, 2.5 mmol) was added dropwise. The resulting white suspension was stirred at 0 °C for 1 h and then it was used as described in the General procedure. Compound **7** (0.14 g, 0.50 mmol) gave a dark green oil, which after flash chromatography (*n*-hexane/EtOAc 4:1) afforded **13** as a blue oil (0.075 g, 51%). ^{1}H NMR ($CDCl_3$) δ 8.05–8.00 (m, 2H), 7.77 (d, J = 4.5 Hz, 1H), 7.27 (d, J = 4.5 Hz, 1H), 7.24–7.17 (m, 2H), 3.75 (s, 3H), 3.02 (t, J = 7.1 Hz, 2H), 2.82 (t, J = 6.8 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 172.7, 170.6, 145.8, 139.6, 136.0, 134.1, 130.5, 128.1, 124.9, 123.0, 122.6, 116.2, 52.1, 29.5, 29.2. HRMS (ESI-TOF): calcd for $C_{15}H_{14}O_4Cl$ $[M + H]^+$ 293.0581; found 293.0583.

6-Chloroazulen-1-yl (*tert*-butoxycarbonyl)glycinate (14). *N*-(*tert*-Butoxycarbonyl)glycine (0.18 g, 1.0 mmol) was suspended in DCM (3 mL) and Et_3N (0.14 mL, 1.0 mmol) was added. The clear solution was cooled to 0 °C and pivaloyl chloride (0.12 mL, 1.0 mmol) was added dropwise. The resulting white suspension was stirred at 0 °C for 1 h and then it was used as described in the General procedure. Compound **7** (0.14 g, 0.50 mmol) gave a dark green oil, which after two flash chromatographic purifications (*n*-hexane/EtOAc 4:1 and toluene/MeOH 1%) afforded **14** as a blue, amorphous solid (0.042 g, 25%). ^{1}H NMR (acetone-d_6) δ 8.22–8.17 (m, 2H), 7.79 (d, J = 4.5 Hz, 1H), 7.37 (d, J = 4.5 Hz, 1H), 7.31 (dd, J = 10.2, 2.1 Hz, 1H), 7.24 (dd, J = 10.5, 2.1 Hz, 1H), 6.56 (s, 1H), 4.25 (d, J = 6.0 Hz, 2H), 1.46 (s, 9H). ^{13}C NMR (acetone-d_6) δ 169.7, 157.1, 146.0, 140.7, 137.1, 135.0, 131.6, 129.1, 125.6, 123.6, 122.9, 117.3, 79.7, 43.3, 28.6. HRMS (ESI-TOF): calcd for $C_{17}H_{19}NO_4Cl$ $[M + H]^+$ 336.1003; found 336.1007.

Benzyl (6-chloroazulen-1-yl) carbonate (15). Compound **7** (0.14 g, 0.50 mmol) and benzyl chloroformate (0.079 mL, 0.55 mmol) gave a dark green oil, which after flash chromatography (*n*-hexane/EtOAc 9:1) afforded **15** as a blue oil (0.050 g, 32%). ^{1}H NMR (acetone-d_6) δ 8.25 (d, J = 10.2 Hz, 1H), 8.16 (d, J = 10.5 Hz, 1H), 7.86 (d, J = 4.2 Hz, 1H), 7.55–7.28 (m, 8H), 5.37 (s, 2H). ^{13}C NMR (acetone-d_6) δ 154.1, 146.0, 140.9, 137.4, 136.3, 134.9, 131.4, 129.5, 129.3, 129.1, 128.6, 125.1, 123.7, 123.2, 117.1, 71.1. HRMS (ESI-TOF): calcd for $C_{18}H_{14}O_3Cl$ $[M + H]^+$ 313.0631; found 313.0631.

6-Chloro-3-formylazulen-1-yl acetate (16). Compound **8** (0.30 g, 1.4 mmol) was dissolved in anhydrous DMF (6 mL) under argon and $POCl_3$ (0.25 mL, 2.7 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 45 min and then diluted with $CHCl_3$ (200 mL). The organic phase was washed with a 0.5 M aqueous solution of $NaHCO_3$ (2 × 100 mL) and water (2 × 100 mL). The aqueous phases were combined and extracted with $CHCl_3$ (2 × 100 mL). All $CHCl_3$ extracts were combined, dried over anhydrous Na_2SO_4, filtered, and evaporated to provide a black oil. The crude product was purified by flash chromatography (*n*-hexane/EtOAc 4:1) to give **16** as a purple, amorphous solid (0.20 g, 59%). ^{1}H NMR (acetone-d_6) δ 10.36 (s, 1H), 9.30 (d, J = 10.5 Hz, 1H), 8.41 (d, J = 10.8 Hz, 1H), 8.22 (s, 1H), 7.78 (dd, J = 10.5, 2.1 Hz, 1H), 7.66 (dd, J = 10.7, 2.3 Hz, 1H), 2.44 (s, 3H). ^{13}C NMR (acetone-d_6) δ 186.6, 169.2, 148.5, 141.2, 137.0, 134.3, 134.0, 132.2, 131.7, 129.5, 128.4, 124.3, 20.9. HRMS (ESI-TOF): calcd for $C_{13}H_{10}O_3Cl$ $[M + H]^+$ 249.0318; found 249.0322.

6-Chloro-3-(morpholinomethyl)azulen-1-yl acetate (17). Compound **16** (0.075 g, 0.30 mmol) and $NaBH(OAc)_3$ (0.13 g, 0.60 mmol) were suspended in anhydrous DCM (1.5 mL) and morpholine (0.029 mL, 0.33 mmol) was added. The purple reaction mixture was stirred at room temperature for 2.5 h. The color of the reaction turned to green. The reaction mixture was treated with a saturated aqueous solution of $NaHCO_3$ (10 mL) and was extracted with DCM (20 mL). Organic phase was washed with a saturated aqueous solution of $NaHCO_3$ (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to provide a green oil. The crude product was purified by flash chromatography (EtOAc) to give **17** as a turquoise, amorphous solid (0.051 g, 53%). ^{1}H NMR (acetone-d_6) δ 8.47 (d, J = 10.2 Hz, 1H), 8.09 (d, J = 10.5 Hz, 1H), 7.76 (s, 1H), 7.25 (dd, J = 10.4, 2.3 Hz, 1H), 7.18 (dd, J = 10.5, 2.1 Hz, 1H), 3.92 (s, 2H), 3.61–3.57 (m, 4H), 2.43–2.38 (m, 7H). ^{13}C NMR (acetone-d_6) δ 169.4, 146.0, 140.1, 134.3, 132.0, 131.3, 130.5, 126.5, 126.1, 122.7, 122.5, 67.5, 56.2, 54.6, 20.9. HRMS (APPI/APCI-TOF): calcd for $C_{17}H_{18}ClNO_3Na$ $[M + Na]^+$ 342.0873; found 342.0878.

6-Chloro-3-(hydroxymethyl)azulen-1-yl acetate (18). Borane tetrahydrofuran complex (1 M, 0.30 mL) was added dropwise to a solution of **16** (0.050 g, 0.20 mmol) in anhydrous THF (1 mL) under argon. The reaction mixture was stirred at room temperature for 20 min and the color of the solution changed from dark purple to blue. The reaction mixture was diluted with EtOAc (15 mL), washed with saturated aqueous solution of $NaHCO_3$ (3 × 10 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to give **18** as a blue, amorphous solid (0.050 g, quant). ^{1}H NMR (acetone-d_6) δ 8.32 (d, J = 10.2 Hz, 1H), 8.08 (d, J = 10.5 Hz, 1H), 7.79 (s, 1H), 7.24 (dd, J = 10.2, 2.1 Hz, 1H), 7.17 (dd, J = 10.5, 2.1 Hz, 1H), 5.06 (d, J = 4.5 Hz, 2H), 4.14 (t, J = 5.3 Hz, 1H), 2.93 (s, 3H). ^{13}C NMR (acetone-d_6) δ 169.4, 145.8, 140.1, 134.0, 131.4, 130.9, 130.5, 129.2, 126.2, 122.7, 122.5, 57.9, 20.9.

(*E*)-6-[2-(1-Trityl-1*H*-imidazol-4-yl)vinyl]azulen-1-yl acetate (20). Compound **8** (0.10 g, 0.45 mmol), **19** (0.15 g, 0.45 mmol), $Pd_2(dba)_3$ (0.013 g, 0.014 mmol) and P(*t*-Bu)$_3$HBF$_4$ (0.016 g, 0.054 mmol) were suspended in anhydrous benzene (4.8 mL) under argon. Et_3N (0.13 mL, 0.91 mmol) was added and the resulting dark blue suspension was heated with microwaves at 160 °C for 30 min. The reaction mixture was filtered through a small pad of Celite® with EtOAc and diluted with EtOAc (30 mL). The green organic phase was washed with water (2 × 25 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to provide a green solid. The crude product was purified by flash chromatography (*n*-hexane/EtOAc 2:1) to give **20** as a green, amorphous solid (0.14 g, 59%). ^{1}H NMR (acetone-d_6) δ 8.19 (d, J = 9.9 Hz, 1H), 8.13 (d, J = 10.5 Hz, 1H), 7.58 (d, J = 4.2 Hz, 1H), 7.48–7.31 (m, 14H), 7.26–7.14 (m, 8H), 2.37 (s, 3H). ^{13}C NMR (acetone-d_6) δ 169.6, 149.2, 143.5, 140.5, 140.3, 139.8, 137.9, 135.2, 132.0, 131.4, 130.6, 129.1, 129.0, 127.6, 126.5, 125.7, 123.0, 122.1, 121.0, 114.9, 76.4, 20.9. HRMS (APPI/APCI-TOF): calcd for $C_{36}H_{28}N_2O_2Na$ $[M + Na]^+$ 543.2048; found 543.2054.

(*E*)-3-Formyl-6-[2-(1-trityl-1*H*-imidazol-4-yl)vinyl]azulen-1-yl acetate (21). Compound **16** (0.25 g, 1.0 mmol), compound **19** (0.41 g, 1.2 mmol), $Pd_2(dba)_3$ (0.028 g, 0.030 mmol) and P(*t*-Bu)$_3$HBF$_4$ (0.035 g, 0.12 mmol) were suspended in anhydrous benzene (12 mL) under argon. Et_3N (0.28 mL, 2.0 mmol) was added and the resulting dark blue suspension was heated with microwaves at 160 °C for 30 min. The reaction mixture was filtered through a small pad of Celite® with EtOAc and diluted with EtOAc (100 mL). The green organic phase was washed with water (2 × 75 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to provide a green solid. The crude product was purified by flash chromatography (*n*-hexane/EtOAc 1:1) to give **21** as a green, amorphous solid (0.37 g, 67%). ^{1}H NMR ($CDCl_3$) δ 10.25 (s, 1H), 9.39 (d, J = 10.2 Hz, 1H), 8.24 (d, J = 10.5 Hz, 1H), 8.02 (s, 1H), 7.69 (dd, J = 10.5, 1.5 Hz, 1H), 7.61 (dd, J = 10.7, 1.7 Hz, 1H), 7.52–7.64 (m, 2H), 7.40–7.34 (m, 9H), 7.29–7.15 (m, 7H), 7.06 (d, J = 1.2 Hz, 1H), 2.43 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 186.1, 168.8, 151.0, 142.2, 140.4, 139.2, 138.9, 137.7, 134.5, 133.5, 131.9, 130.1,

129.9, 128.5, 128.4, 127.6, 127.2, 126.1, 122.8, 122.1, 75.9, 21.2. HRMS (APPI/APCI-TOF): calcd for $C_{37}H_{28}N_2O_3Na$ $[M + Na]^+$ 571.1998; found 571.2004.

(*E*)-6-[2-(1*H*-Imidazol-4-yl)vinyl]azulen-1-yl acetate (22). Ethane-1,2-dithiol (0.1 mL) was added to a solution of **20** (0.072 g, 0.14 mmol) in DCM (4 mL) under argon. Then trifluoroacetic acid (1 mL) was added and the resulting mixture was stirred at room temperature for 15 min. The green reaction mixture was diluted with DCM (80 mL) and it was washed with a saturated aqueous solution of $NaHCO_3$ (3 × 40 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to provide a green oil. The crude product was purified by flash chromatography (manual gradient of DCM → DCM/MeOH 19:1) to give **22** as a green, amorphous solid (0.035 g, 91%). ^{1}H NMR (CD_3CN) δ 8.20 (d, J = 9.9 Hz, 1H), 8.12 (d, J = 10.5 Hz, 1H), 7.64 (s, 1H), 7.54 (d, J = 4.5 Hz, 1H), 7.04–7.33 (m, 4H), 7.26–7.25 (m, 1H), 7.17 (d, J = 4.5 Hz, 1H), 2.37 (s, 3H). ^{13}C NMR (CD_3CN) δ 170.6, 149.4, 139.7, 138.2, 137.7, 135.4, 132.2, 131.7, 130.8, 128.6, 127.9, 125.8, 122.4, 121.2, 115.1, 21.2. HRMS (ESI-TOF): calcd for $C_{17}H_{15}N_2O_2$ $[M + H]^+$ 279.1133; found 279.1143.

(*E*)-6-[2-(1*H*-Imidazol-4-yl)vinyl]-3-formylazulen-1-yl acetate (23). Trifluoroacetic acid (1 mL) was added to a solution of **21** (0.080 g, 0.15 mmol) in DCM (4 mL) under argon. The reaction mixture was stirred at room temperature for 30 min and then it was diluted with DCM (100 mL). The green organic phase was washed with a saturated aqueous solution of $NaHCO_3$ (3 × 60 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to provide a green oil. The crude product was purified by flash chromatography (manual gradient of DCM → DCM/MeOH 9:1) to give **23** as a green, amorphous solid (0.041 g, 92%). ^{1}H NMR (DMSO-d_6) δ 10.27 (s, 1H), 9.30 (d, J = 10.5 Hz, 1H), 8.35 (d, J = 10.5 Hz, 1H), 7.95 (s, 1H), 7.89–7.79 (m, 3H), 7.61 (d, J = 15.9 Hz, 1H), 7.49 (s, 1H), 7.39 (d, J = 15.9 Hz, 1H), 2.43 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 185.4, 168.9, 151.4, 138.8, 137.4, 136.6, 136.4 (br), 133.9, 133.8, 130.8, 128.1, 127.9, 127.8, 127.2, 125.9, 122.1 (br), 121.4, 20.7. HRMS (ESI-TOF): calcd for $C_{18}H_{15}N_2O_3$ $[M + H]^+$ 307.1083; found 307.1088.

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Keywords: synthesis design; aromatic substitution; cross-coupling; azulene; synthetic scaffold

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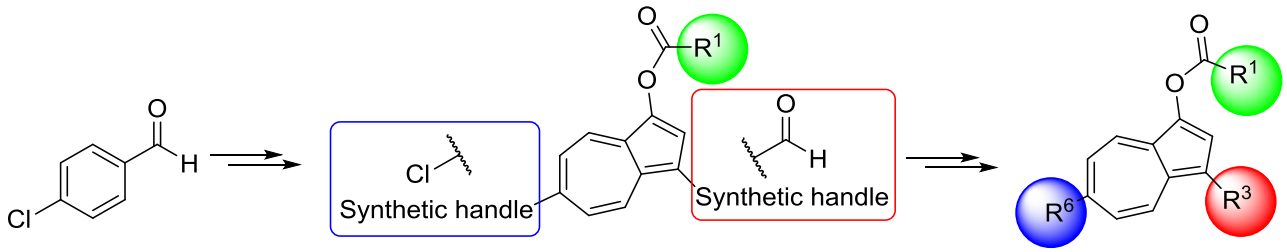
Entry for the Table of Contents

Substituted azulenes



Herein we describe an efficient synthetic approach for 1,3,6-trisubstituted azulenes based on the 1-acyloxyazulene scaffold, in which the 3- and 6-positions of azulene were functionalized by versatile synthetic handles.