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The Effect of Base and Nucleophile on the Nucleophilic Substitution of Methoxytropone Derivatives: An Easy Access to 4- and 5-Substituted Multifunctional Azulenes

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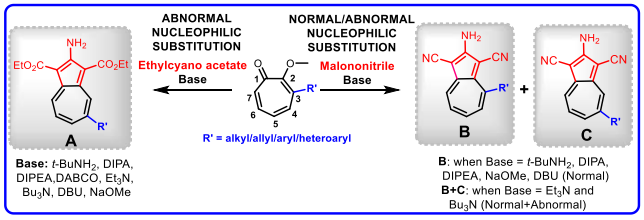


ABSTRACT: The nucleophilic substitution on 3-substituted 2-methoxytropones to form azulenes is dependent on the nucleophile and the base employed. With bulkier nucleophiles (ethyl/methyl cyanoacetate), the reaction proceeds with the abnormal nucleophilic substitution irrespective of the base and with smaller nucleophiles (malononitrile), the reaction follows base dependent normal and abnormal nucleophilic substitution. Thus, the methodologies are developed to selectively obtain 4- and 5-substituted azulenes based on the nature of bases and nucleophile employed.

INTRODUCTION

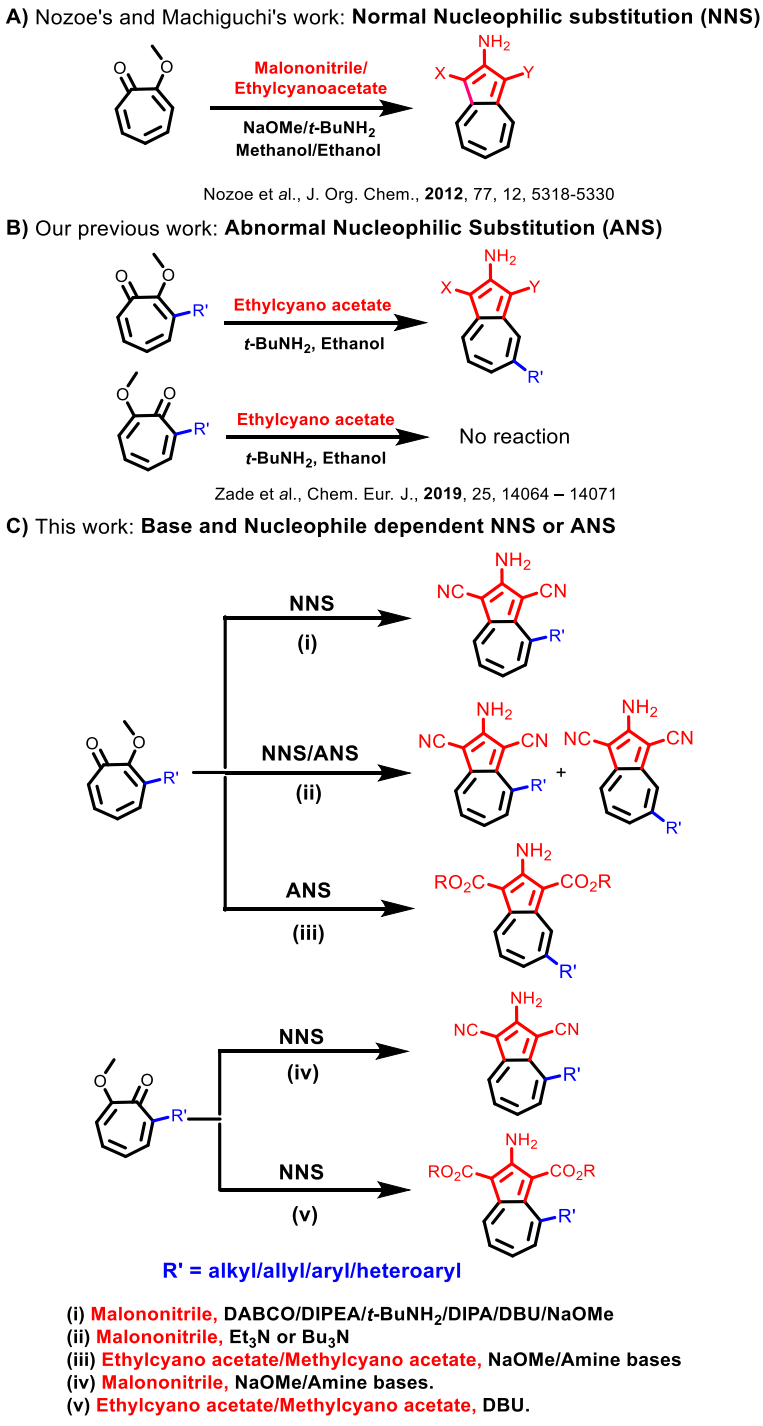
Azulene, an isomer of naphthalene and a non-alternant aromatic hydrocarbon has unique physicochemical characteristics attributed to its large dipole moment, a small gap between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) and its anti-Kasha's rule emission.[1] The design and synthesis of new organic functional materials with improved

performance in devices has always been the quest. There have been several reports in the literature on organic functional materials incorporating azulene unit and such materials have shown remarkable applications in organic electronics.[2,3]

In 1939, Plattner and Pfau[4] reported the first azulene synthesis involving cumbersome dehydrogenation step followed by the Ziegler and Hafner's azulene synthesis, that provided ease for introducing substituents on the seven-membered ring.[5] Nozoe et al. employed troponoids and active methylene compounds for the synthesis of multifunctional azulene in a single step (**Scheme 1A**).[6] Machiguchi et al. provided a detailed theoretical and experimental insight into the mechanism involved in Nozoe's azulene synthesis.[7,8]

Ito and coworkers have contributed significantly to developing azulene derivatives.[9] Other methods of azulene synthesis include (i) Au-catalyzed[10] dimerization of diarylalkynes,[11] (ii) Pt-catalyzed ring expanding cycloisomerization,[12] (iii) Rh-catalyzed ring expansion–annulation of β'-bromo-α-diazo ketones,[13] (iv) [6+4] cycloaddition reactions,[14] and (v) Synthesizing 1,1-dicyanoazulenes and subsequent functionalization to give the bromo-cyano substituted azulene.[15]

Synthesis of functionalized/substituted azulenes has been difficult due to the lack of the appropriate methods for the generation of azulenes from prefunctionalised precursors, and the common strategy towards substituted azulenes has been the post functionalization of the azulene skeleton. In our previous work, we developed a simple steric based strategy for the regioselective synthesis of 5-substituted multifunctional azulenes from 3-substituted 2-methoxytropones which undergo an abnormal nucleophilic attack by the cyanoacetate-enolate at C-7 to form 5-substituted azulene rather than the expected normal attack at C-2 to form 4-substituted azulene (**Scheme 1B**).[16] In this work, we explore the influence of nucleophiles and bases of varying steric bulk and strength on the

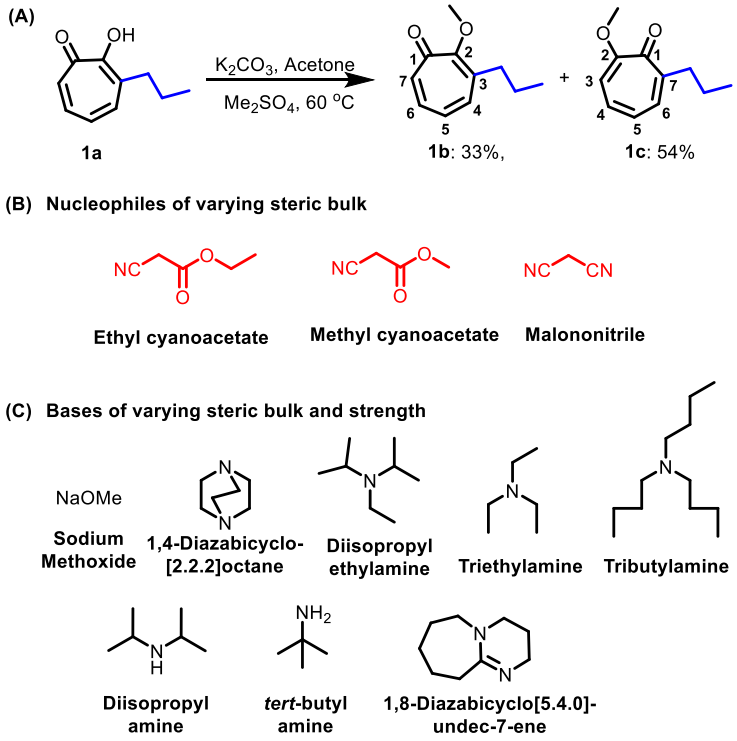


Scheme 1. Synthesis of multifunctional azulenes from 2-methoxytropone

nucleophilic substitution on 3- and 7-substituted 2-methoxytropones (**Scheme 1C**). This study has paved paths for the efficient regioselective synthesis of both 4- and 5-substituted multifunctional azulenes**.**

RESULTS AND DISCUSSION

We chose propyl substituted tropolone[17] **1a** (**Scheme 2A**) as the model substrate and converted it to its methoxy derivative using K_2CO_3 and $(CH_3)_2SO_4$, to give the tautomers 3-propyl-2-methoxytropone (**1b**) and 7-propyl-2-methoxytropone (**1c**). We chose nucleophiles of varying steric bulk as methyl cyanoacetate (MCA), ethyl cyanoacetate (ECA) and malononitrile (MLN) (**Scheme 2B**). Their steric bulk varies in the order MLN<MCA<ECA, and the enolate stability follows the reverse order. Sodium methoxide (NaOMe), 1,4-diazabicyclo[2.2.2]octane (DABCO), diisopropylethylamine (DIPEA), triethylamine (Et_3N), tributylamine (Bu_3N), *tert*-butylamine (*t*-$BuNH_2$), diisopropylamine (DIPA) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were chosen as bases for screening (**Scheme 2C**). The strength of the amine bases follows the following trend DBU>DIPA>*t*-$BuNH_2$>Bu_3N>Et_3N>DIPEA>DABCO. We attempted azulene synthesis reaction with model substrate **1b** using each of MLN/MCA/ECA with the

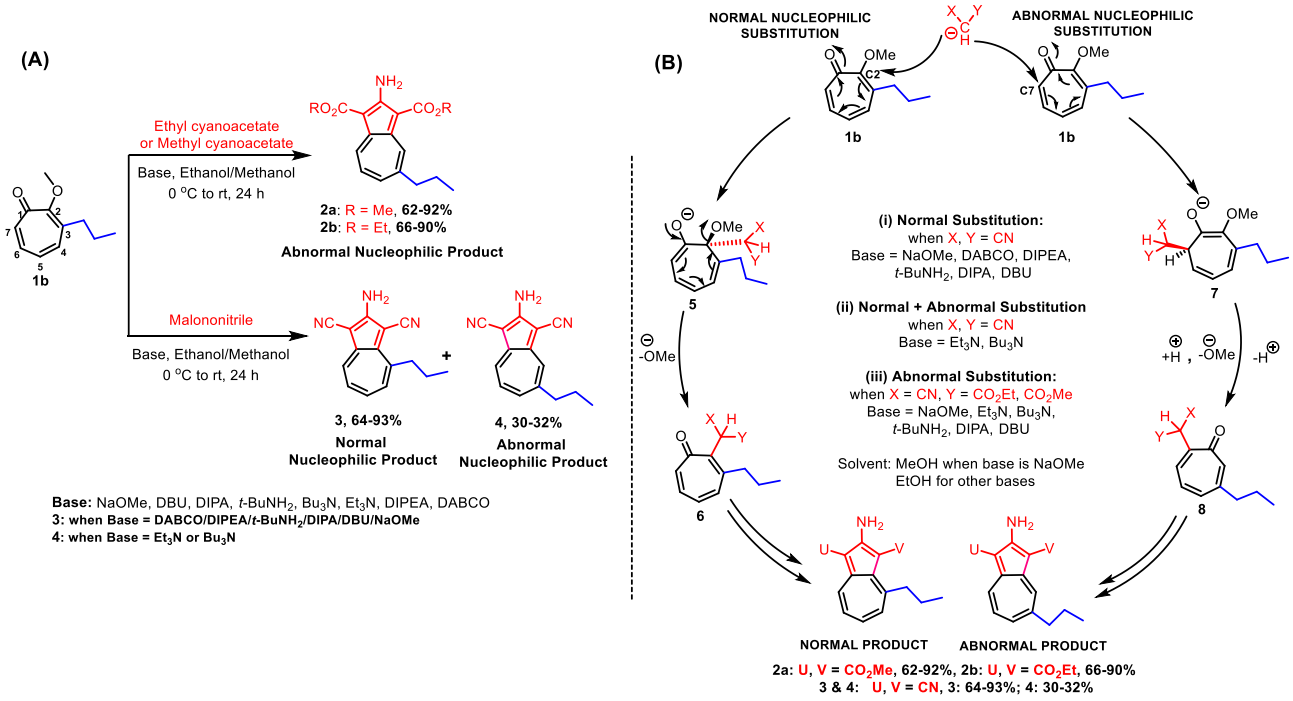


Scheme 2. (A) Synthesis of propyl substituted 2-methoxytropones (B) Nucleophiles of varying steric bulk (C) Bases of varying steric bulk and strength

bases NaOMe/DBU/DIPA/*t*-$BuNH_2$/Bu_3N/Et_3N/DIPEA/DABCO following the general reaction conditions as reported earlier.[7,16]

As discussed by Machiguchi[7] et al., the attack of the nucleophile at C-2 center and C-7 center of 2-methoxytropone are defined as the normal and abnormal nucleophilic attacks, respectively. Theoretical and experimental evidence proved that the attack of nucleophile for 2-methoxytropone takes place at C-2 center. To explore the effect of different nucleophiles and bases, **1b** was subjected to azulene formation reaction. We found that when MCA/ECA were used as nucleophiles, **2a**/**2b** (62-92%/66-90%) were always formed as the product irrespective of the nature of the base (**Scheme 3A**). However, no product was formed when DIPEA and DABCO were used as a base (**Scheme 3B**, entry **iii**). Both MCA and ECA are bulkier nucleophiles, and the presence of substituent at C-3 of **1b** (i.e. propyl group) blocks the attack of the nucleophile at C-2 and the attack occurs at C-7 i.e. the abnormal nucleophilic attack to form anionic intermediate **7** (**Scheme 3B**, right). The next step involves C-H bond formation at C-2, followed by abstraction of H-atom at C-7 to form an anionic intermediate. The final step involves the loss of MeOH molecule to form **8** (**Scheme S4**, ESI). The intermediate **8** then undergoes a series of transformations in the presence of the second molecule of the nucleophile to form 5-substituted azulene (**2a**/**2b**) as per the mechanism proposed by Machiguchi et al.[7] The inactivity of the substrate **1b** when DIPEA and DABCO are used as a base may originate from the weakness of the nucleophile-base (ion) pair as well as the inactivity of the C-7 position for nucleophilic substitution for the particular DIPEA-MCA/ECA or DABCO-MCA/ECA ion pair.

When **1b** was subjected to azulene formation reaction with MLN, in the presence of bases NaOMe, DABCO, DIPEA, *t*-$BuNH_2$, DIPA, or DBU, azulene **3** (64-93%) was formed as the product (**Scheme 3A**). The structure of compound **3** was first confirmed by ^{1}H NMR spectra by the deshielded nature of the -CH_2 protons of propyl chain and then unambiguously by single-crystal X-ray diffraction (SCXRD, **Figure S57, ESI**) analysis. Malononitrile (MLN) is comparatively less bulky than MCA

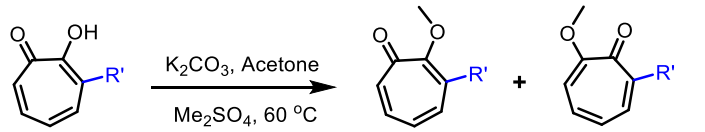


Scheme 3. (A) Effect of nucleophile and base towards nucleophilic substitution on 3-propyl-2-methoxytropones (B) Normal vs. abnormal nucleophilic substitution

and ECA, and the attack of the enolate of MLN is at C-2 of **1b**, unaffected by the propyl group and independent of the sterics of the base employed. When NaOMe/DABCO/DIPEA/*t*-$BuNH_2$/DIPA or DBU was used as a base, the MLN enolate attack the C-2 centre of **1b** (normal nucleophilic attack) to form intermediate **6** via anion **5** (**Scheme3B**, left). The intermediate **6** then undergoes a series of transformations to form compound **3**. However, when Et_3N and Bu_3N were employed as the base, the enolate of MLN ensued a competitive nucleophilic attack at C-2 and C-7 i.e. normal and abnormal nucleophilic attack to form a mixture of products **3** and **4** (**Scheme 3B**, entry **ii**). In both cases, the normal substituted product was formed in a major amount (for Et_3N, 65:35 (percentage of normal and abnormal product) and for Bu_3N, 70:30 (percentage of normal and abnormal product), and these products were easily distinguishable by ^1H NMR spectra. For compound **3**, the signal for -CH_2 proton

attached to the aromatic center was comparatively deshielded 3.37-3.41 ppm than the compound **4** for which the -CH_2 proton was at 2.85 ppm.

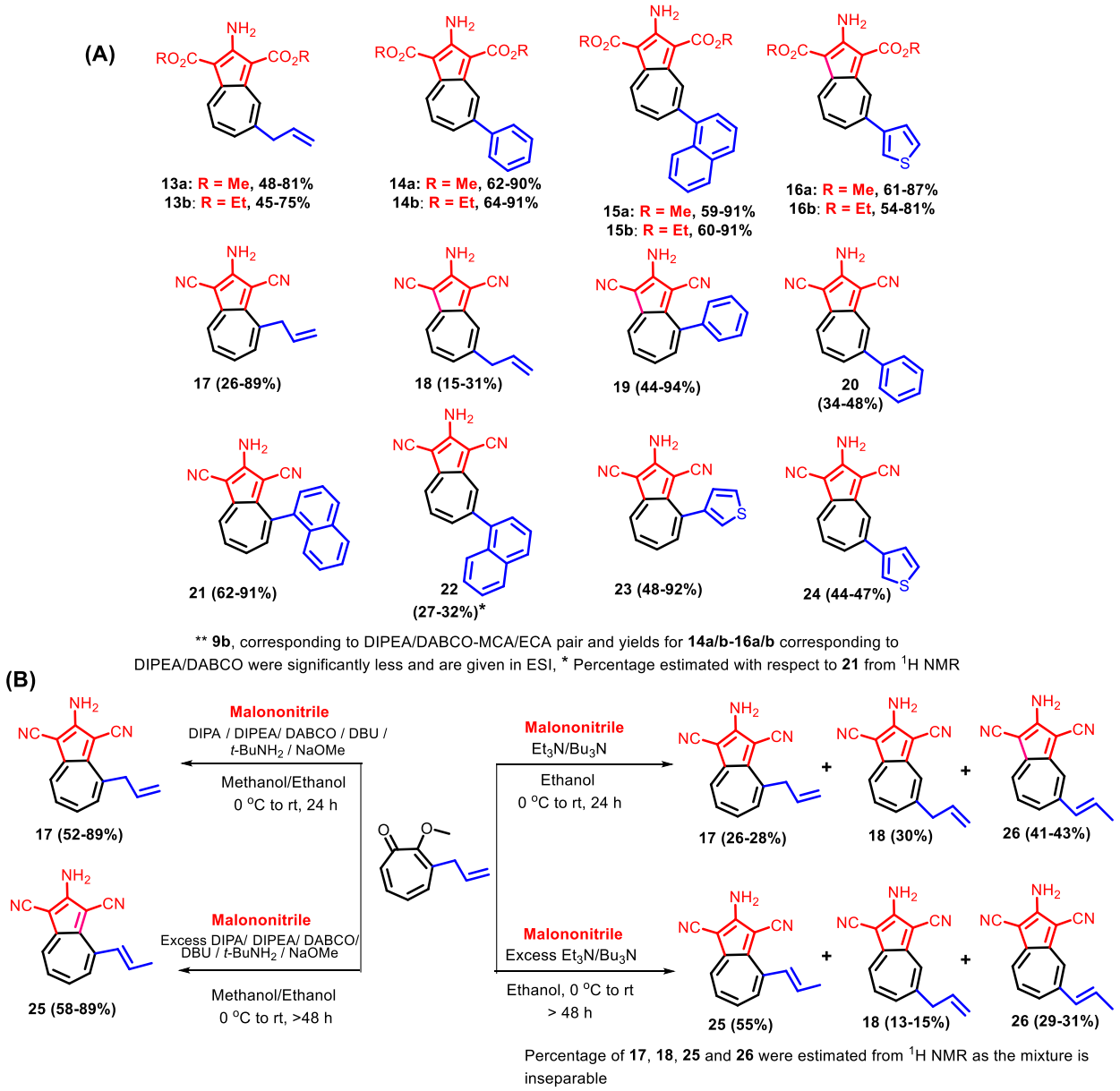
The introduction of a functional group on the five-membered ring of azulene is very well documented in the literature.[18] However, such functionalisation and modification on the 7-membered ring of azulene are dearth owing to the subtle reactivity differences in the positions of the seven-membered ring. There is no report for the regioselective synthesis of 4-substituted multifunctional azulenes from prefunctionalised precursor.



R' = allyl; **9b**: 38%, **9c:** 51%
R' = phenyl; **10b**: 33%, **10c**: 55%
R' = naphthyl; **11b**: 29%, **11c**: 54%
R' = 3-thienyl; **12b**: 37%, **12c**: 58%

Scheme 4. Synthesis of 3- and 7- substituted 2-methoxytropones.

To check the substrate scope of the methodology we synthesized several 2-methoxytropone derivatives with varied substituents at C-3 position. The substituents were varied from alkyl to aryl to heteroaryl (**Scheme 4**).[19] As observed for the propyl isomer, the allyl, phenyl, naphthyl, and 3-thienyl substituted 2-methoxytropones (**9b**-**12b**) when treated with MCA/ECA in the presence of a base (NaOMe/Amine base) gave 5-substituted azulenes (**13a/b-16a/b**, **Scheme 5A**), which was independent of the nature of the base. When the compounds **9b-12b** was treated with malononitrile, as observed for the 3-propyl-2-methoxytropone (**1b**), both normal and abnormal nucleophilic substitution products were formed depending on the base employed. When isomer **9b-12b** were treated with enolate of malononitrile in the presence of base *t*-BuNH_2/DIPA/DIPEA/DABCO/DBU or NaOMe, normal nucleophilic substitution occurred leading to 4-substituted azulene i.e., **17**, **19**, **21** and **23** (**Scheme 5A**). Structure of compound **21** was also confirmed by SCXRD analysis (**Figure S58, ESI**). The practical utility of the



Scheme 5. (A) Scope of the nucleophile and base dependent azulene synthesis (B) Isomerisation of double bond in allyl substituted cyano azulenes.

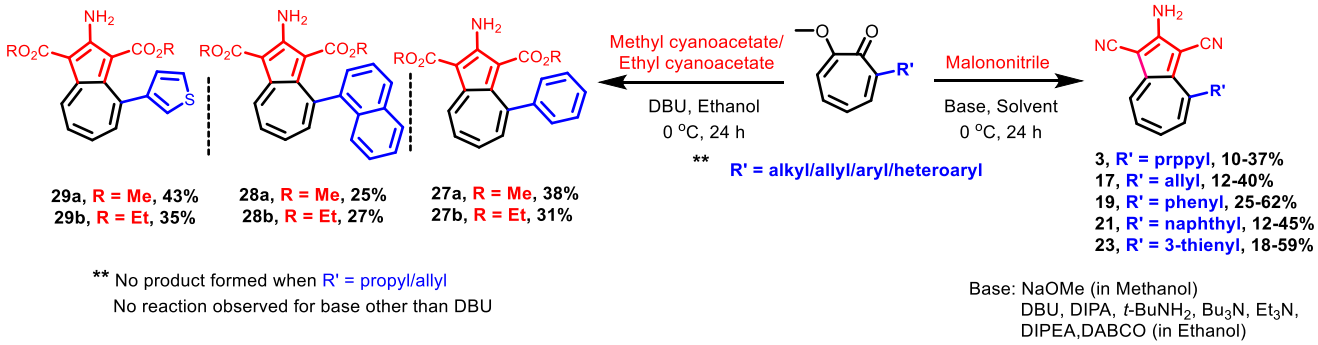
nucleophile and base dependent azulene synthesis was demonstrated by scaling up the reaction to furnish the products **13b** and **19** in 68% and 79% yields, respectively (0.62 g i.e. 68% **13b** obtained from 0.5 g of **9b** using ECA and *t*-$BuNH_2$; 1.18 g i.e. 79% **19** obtained from 1.2 g of **10b** using MLN and DIPA).

When Et_3N/Bu_3N was used as a base with malononitrile, then both normal and abnormal nucleophilic substitution occurred, leading to a mixture of 4- and 5-substituted multifunctional azulenes i.e., **17/18**, **19/20**, **21/22** and **23/24** (**Scheme 5A**) for allyl, phenyl, naphthyl, and 3-thienyl 2-methoxytropones, respectively. On using Et_3N as base the ratio of the percentage of isomers as calculated from ^{1}H NMR were found to be **19:20**~65:35, **21:22**~67.3:32.6, **23:24**~52.1:47.9 and on using Bu_3N as base the ratios were **19:20**~50:50, **21:22**~72.4:27.5, and **23:24**~50.5:49.4. However, 4 and 5-substituted allyl azulene (**17/18**) and 4- and 5- substituted substituted naphthyl azulenes (**21/22**) were obtained as an inseparable mixture.

Interesting results were obtained for the allyl substituted azulenes when malononitrile was used as the nucleophile. When an excess of base i.e., >5 equivalent (DIPA/DIPEA/DABCO/DBU/*t*-$BuNH_2$/NaOMe), was used with malononitrile and the reaction time prolonged, the allyl bond in **17** rearranged to an internal olefin **25**. When 2.3-4.3 equivalent of Et_3N/Bu_3N was used as a base, then in addition to compounds **17** (26-28%) and **18 (**30%**)**, compound **26 (**41-43%**)** was formed, obtained by the rearrangement of allyl bond in **18** (**Scheme 5B**). When an excess of Et_3N/Bu_3N was used, then formation of compounds **25 (**55%**)**, **18 (**13-15%**)**, and **26 (**29-31%**)** was observed (**Scheme 5B**). The isomers obtained in each set of the condition were inseparable by column chromatography and were identified by their characteristic signal in ^{1}H NMR spectra (**17**: -CH_2 protons at 4.15 ppm, **18**: -CH_2 protons at 3.59 ppm, **25**: -CH_3 protons at 1.74-1.76 ppm and **26**: -CH_3 protons at 2.06-2.08 ppm). Such base-catalyzed isomerization is documented in literature[20] and is from a thermodynamically less stable olefin into a more stable one, which means that a terminal olefin affords the internal isomer, a non-conjugated diene the 1,3-diene and a non-conjugated aryl-substituted olefin the corresponding styrene.

In our previous article,[16] we had observed that the 7-substituted 2-methoxytropones were inert to the reaction condition when treated with ECA and *t*-$BuNH_2$ and was attributed to the reversibility of the nucleophilic attack at the C-2 position or at other free conjugate position. Here we further explored

the effect of nucleophile and base on the nucleophilic substitution of 7-substituted-2-methoxytropones (**1c** and **9c-12c**, **Scheme 4**). All the compounds were inert to the nucleophilic substitution by MCA/ECA enolate when NaOMe/DABCO/DIPEA/Et_3N/Bu_3N/*t*-$BuNH_2$/DIPA was used as a base. Surprisingly the isomers bearing aromatic substituents (phenyl, naphthyl, and 3-thienyl) i.e., **10c**, **11c**, and **12c**, lead to 4-substituted azulenes i.e., **27a/b-29a/b** with MCA/ECA enolate and DBU as a base (**Scheme 6**, left). This anomalous reactivity is attributed to the synergistic role of DBU-MCA/ECA (ion) pair, and the aromatic substituent (phenyl, naphthyl, and 3-thienyl) as DBU is one of the strongest amine base (leading to strong ion-pair) and can assist in stabilizing the negative charge (carbanion) generated during the reaction course. We also observed that the 7-substituted isomer reacts with malononitrile irrespective of the nature of the base to give compounds **3**, **17**, **19**, **21**, and **23** in moderate yields. The products obtained in this case also assisted us in the assignment of the products formed on reaction of MLN with compounds **1b** and **9b-12b**. The enolate of MLN is more stable than that of MCA/ECA and hence are their corresponding ion pair with bases that help in driving the azulene formation reaction for compounds **1c** and **9c-12c** in the forward direction.



Scheme 6. Effect of nucleophile and base towards nucleophilic substitution on 7-substituted 2-methoxytropones

CONCLUSION

In summary, systematic investigation of azulene formation from tropolone derivative in the presence of nucleophiles and bases of varying steric bulk and strength led us to develop new selective synthetic strategies for 4- and 5-substituted multifunctional azulenes. The regioselective modification of the seven-membered ring of azulene is difficult due to the subtle reactivity difference among the various positions, and the base and nucleophile dependent azulene synthesis provides easy access to the otherwise difficult to synthesize multifunctional azulenes. The possibility to tune the properties by variation of the substitution on the seven-membered ring and the possibility of functional group modifications on the five-membered ring renders the described regioselective synthesis of 4-and 5-substituted multifunctional azulenes highly interesting in the field of organic synthesis and optoelectronics.

EXPERIMENTAL SECTION

Materials and Instrumentation

All reagents were obtained from commercial sources (Sigma Aldrich, Spectrochem, Merck and Alfa Aesar) and used as received without further purification, unless otherwise specified. Toluene, tetrahydrofuran (THF) and diethyether (Et_2O) were dried over sodium/benzophenone before use. Methanol and ethanol were dried using magnesium turning and iodine. Dry reactions were conducted in oven-dried glassware using a standard Schlenk line under an inert atmosphere of dry nitrogen. Tropolone was obtained from Sigma Aldrich.

^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded at room temperature on a Jeol JNM-ECS 400 spectrometer (400 MHz ^{1}H, 100 MHz ^{13}C) and Bruker Avance 500 (500 MHz ^{1}H, 125 MHz ^{13}C) spectrometer with tetramethylsilane as the internal reference; chemical shifts (δ) are given in parts per

million (ppm). Spectra were processed using Mest ReNova v*5* and referenced to residual protonated solvent signals ($CDCl_3$: ^1H: 7.26 ppm, $^{13}C\{^1H\}$: 77.16 ppm). Mass spectra were recorded on Bruker micrOTOF-Q II spectrometer. FT-IR spectra were recorded by Perkin–Elmer FT–IR Spectrometer. The single crystals of compound **3** and **21** suitable for X-ray diffraction were obtained by slow evaporation of saturated acetone solutions. The measurements on the suitable crystals were done on Agilent SuperNova (Dual, Cu/Mo at zero, Eos) diffractometer. The structure was solved using Olex2[21] and refined with the ShelXL[22] refinement package using Least Squares minimization.

Preparation of methyl ethers of substituted tropolones

Methyl Ethers of propyl, allyl, phenyl, naphthyl and 3-thienyl substituted tropolone (**1b/1c**, **9b/9c**, **10b/10c**, **11b/11c**, and **12b/12c,** respectively) were synthesized using the procedures reported in literature.[16,17,19] ^1H NMR data of all the tropolone derivatives matched with those reported earlier.

General procedure for cyclisation of methyl ethers of substituted tropolones

For reaction with amine bases:

To methoxytropone (1 mmol) dissolved in dry EtOH (10 ml), active methylene compound (2.3 mmol) was added, followed by the slow addition of amine base (2.3 mmol) under ice cooling. The reaction mixture was stirred overnight while the temperature was allowed to rise to room temperature. After completion of the reaction as monitored by thin layer chromatography, the solvent was evaporated and residue extracted with ethyl acetate and dried with Na_2SO_4. The solvent was evaporated and the residue was further purified by column chromatography.

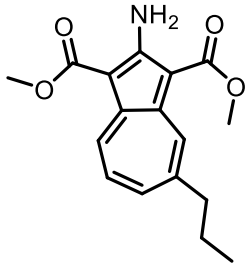
For Sodium methoxide as base:

In a typical case, to a suspension of the sodium salt of Methyl cyanoacetate/Ethyl cyanoacetate [prepared from (2 mmol) of metallic sodium and 2 mmol of the active methylene compound] in 5 mL of

methanol was added dropwise a solution of 1 mmol of substituted 2-methoxytropone in 2 mL of methanol at 0 °C. The reaction mixture was stirred at room temperature overnight. After completion of the reaction as monitored by thin layer chromatography, the solvent was evaporated and residue extracted with ethyl acetate and dried with Na_2SO_4. The solvent was evaporated and the residue was further purified by column chromatography.

Purification procedure and characterization

dimethyl 2-amino-5-propylazulene-1,3-dicarboxylate (2a)

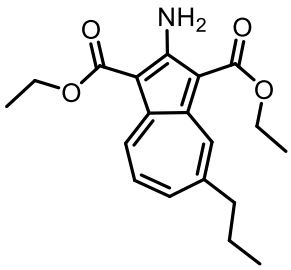


Purification: Column chromatography using silica gel (60-120 mesh), 10% EtOAc/Hexane, orange viscous oil which solidifies in few hours. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (t, 3H, J = 5 Hz), 1.42-1.68 (m, 2H), 2.84 (t, 2H, J = 8 Hz), 3.98 (s, 3H), 3.99 (s, 3H), 7.33-7.46 (m, 4H), 8.94-8.97 (m, 1H), 9.15 (d, 1H, J = 5 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)**:** δ 13.9, 29.8, 43.9, 50.8, 98.7, 125.2, 132.2, 133.3, 135.4, 139.9, 146.1, 148.9, 162.6, 166.9, 167.1. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{19}NO_4Na$ 324.1212; Found: 324.1209. Melting point: 121-123 °C, **IR (ATR)**: υ: 3434, 3301, 2919, 2890, 2826, 1704, 1647, 1565, 1496, 1429, 1360, 1246, 1211, 1167, 1116, 1075, 1009, 841, 784, 686, 626 cm^{-1}.

Product yield: 50 mg of **1b** was used as starting material, amount of **2a** obtained from different bases:

1) NaOMe: 52 mg, 62% 2) DBU: 77 mg, 92% 3) DIPA: 72 mg, 85% 4) *t*-$BuNH_2$: 76 mg, 90% 5) Bu_3N: 62 mg, 74% 6) Et_3N: 68 mg, 81% 7) DIPEA: No product obtained and starting material was recovered 8) DABCO: No product obtained and starting material was recovered.

diethyl 2-amino-5-propylazulene-1,3-dicarboxylate (2b)

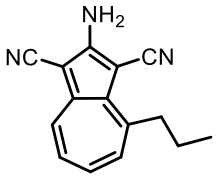


Purification: Column chromatography using silica gel (60-120 mesh), 15% EtOAc/Hexane, orange viscous oil which solidifies in few hours. ^{1}H NMR (400 MHz, $CDCl_3$)**:** δ 1.00 (t, 3H, *J* = 8 Hz), 1.45-1.48 (m, 6H), 1.76-1.80 (m, 2H), 2.82 (t, 2H, *J* = 8 Hz), 4.43-4.47 (m, 4H), 7.31 (d, 1H, *J* = 8 Hz), 7.43 (t, 1H, *J* = 8 Hz), 7.75 (s, 2H), 8.98 (d, 1H, *J* = 8 Hz), 9.17 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)**:** δ 13.8, 14.7, 14.8, 25.6, 43.9, 59.7, 59.8, 98.8, 99.0, 130.1, 132.1, 133.1, 134.2, 145.8, 146.2, 148.4, 162.7, 166.6, 166.7. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{19}H_{23}NO_4Na$ 352.1525; Found: 352.1521. Melting point: 96-98 °C, **IR (ATR)**: υ: 3401, 3288, 2918, 2891, 2825, 1640, 1556, 1491, 1441, 1407, 1352, 1318, 121, 1147, 1107, 1066, 862, 754, 679, 586 cm^{-1}.

Product yield: 50 mg of **1b** was used as starting material, amount of **2b** obtained from different bases:

1) NaOMe: 61 mg, 66% 2) DBU: 79 mg, 86% 3) DIPA: 83 mg, 90% 4) *t*-$BuNH_2$: 81 mg, 88% 5) Bu_3N: 69 mg, 75% 6) Et_3N: 77 mg, 84% 7) DIPEA: No product obtained and starting material was recovered 8) DABCO: No product obtained and starting material was recovered.

2-amino-4-propylazulene-1,3-dicarbonitrile (3)



Purification: Column chromatography using silica gel (60-120 mesh), 20% EtOAc/Hexane, orange solid. ^{1}H NMR (400 MHz,$CDCl_3$)**:** δ 1.13 (t, 3H, J = 10 Hz), 1.82-1.90 (m, 2H), 3.37-3.41 (2H, m), 5.56 (bs, 2H), 7.51-7.52 (m, 3H), 8.18-8.26 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)**:** δ 13.5, 25.4, 40.8, 81.4, 83.4, 115.2, 117.2, 130.9, 132.2, 134.8, 136.3, 141.5, 145.8, 149.3, 160.2. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{13}N_3Na$ 258.1007; Found: 258.1003. Melting point: 227-229 $^\circ$C, **IR (ATR)**: ν: 3285, 3175, 2907, 2830, 2158, 1626, 1498, 1370, 1294, 1170, 971, 885, 719, 685, 562 cm^{-1}.

Product yield:

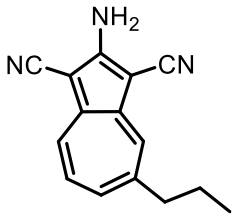
When 50 mg of **1b** was used as starting material, amount of **3** obtained from different bases:

1) NaOMe: 43 mg, 65% 2) DBU: 61 mg, 93% 3) DIPA: 57 mg, 87% 4) *t*-$BuNH_2$: 58 mg, 89% 5) DIPEA: 47 mg, 71% 6) DABCO: 42 mg, 64%

When 100 mg of **1c** was used as starting material, amount of **3** obtained from different bases:

1) NaOMe: 13 mg, 10% 2) DBU: 46 mg, 35% 3) DIPA: 48 mg, 37% 4) *t*-$BuNH_2$: 41 mg, 31% 5) Bu_3N: 35 mg, 27% 6) Et_3N: 26 mg, 20% 7) DIPEA: 31 mg, 24% 8) DABCO: 11 mg, 8%

2-amino-5-propylazulene-1,3-dicarbonitrile (4)



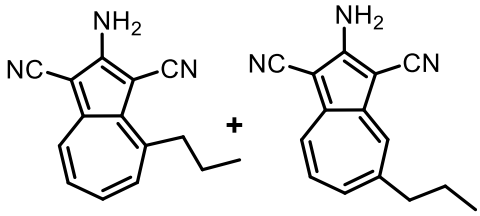
Purification: Column chromatography using silica gel (60-120 mesh), 20% EtOAc/Hexane, orange solid. ^{1}H NMR (400 MHz, $CDCl_3$)**:** δ 1.01 (t, 3H, J = 10 Hz), 1.73-1.82 (m, 2H), 2.85 (t, 2H, J = 10 Hz), 5.55 (bs, 2H), 7.52-7.54 (m, 2H), 8.05-8.08 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)**:** δ 13.8, 25.8, 43.5, 81.8, 81.9, 115.2, 115.3, 129.9, 131.8, 132.9, 136.4, 145.4, 145.8, 148.9, 159.6. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for

$C_{15}H_{13}N_3Na$ 258.1007; Found: 258.1002. Melting point: 182-184 °C, **IR (ATR)**: ν: 3301, 3152, 2923, 2885, 2819, 2176, 1643, 1515, 1407, 1294, 1191, 1075, 857, 775, 598 cm^{-1}.

Product yield: When 100 mg of **1b** was used as starting material, amount of **4** obtained on using Et_3N and Bu_3N as bases:

1) Et_3N: 42 mg, 32% 2) Bu_3N: 39 mg, 30%

2-amino-4-propylazulene-1,3-dicarbonitrile and 2-amino-5-propylazulene-1,3-dicarbonitrile (3+4)

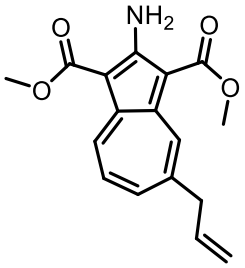


Purification: Column chromatography using silica gel (60-120 mesh), 20% EtOAc/Hexane, orange solid, mixture of **3** and **4**. Characteristic peak: ^{1}H NMR (400 MHz, $CDCl_3$)**:** δ 2.84 (t, 1H, J = 8 Hz) from compound **3** and 3.36-3.40 (m, 2H) from compound **4.**

Product yield: When 100 mg of **1b** was used as starting material, amount of **3** and **4** obtained on using Et_3N and Bu_3N as bases:

1) Et_3N; **3**: 84 mg, 64%, **4**: 42 mg, 32% 2) Bu_3N; **3**: 88 mg, 67%, **4**: 39 mg, 30%

dimethyl 5-allyl-2-aminoazulene-1,3-dicarboxylate (13a)



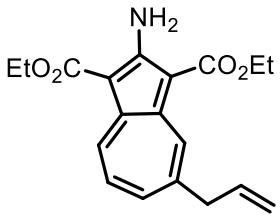
Purification: Column chromatography using silica gel (60-120 mesh), 15% EtOAc/Hexane, orange viscous oil which solidifies in few hours. ^{1}H NMR (400 MHz, $CDCl_3$)**:** δ 3.98 (s, 6H), 5.16-5.21 (m, 2H), 5.99-6.11 (m, 1H), 7.35-7.51 (m, 2H), 7.72 (bs, 1H), 7.79 (bs, 1H), 8.98 (d, 1H, *J* = 8 Hz), 9.14 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)**:** δ 46.0, 50.2, 90.1, 99.3, 116.9, 130.2, 132.1, 133.0, 134.0, 134.4, 137.1, 137.6, 145.3, 146.1, 162.8, 166.8, 167.3. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{17}NO_4Na$ 322.1055; Found: 322.1051.

Melting point: 92-95 °C, **IR (ATR)**: ν: 3418, 3300, 3039, 2910, 2881, 2817, 1708, 1650, 1555, 1487, 1422, 1366, 1165, 1106, 1011, 907, 781, 686 cm^{-1}

Product yield: 50 mg of **9b** was used as starting material, amount of **13a** obtained from different bases:

1) NaOMe: 40 mg, 48% 2) DBU: 66 mg, 78% 3) DIPA: 63 mg, 75% 4) *t*-$BuNH_2$: 68 mg, 81% 5) Bu_3N: 52 mg, 62% 6) Et_3N: 62 mg, 74% 7) DIPEA: No product obtained and starting material was recovered 8) DABCO: No product obtained and starting material was recovered.

diethyl 5-allyl-2-aminoazulene-1,3-dicarboxylate (13b)



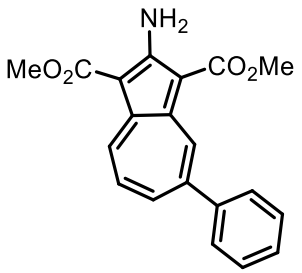
Purification: Column chromatography using silica gel (60-120 mesh), 5% EtOAc/Hexane, orange solid. ^{1}H NMR (400 MHz, $CDCl_3$)**:** δ 1.46-1.50 (m, 6H), 3.63 (d, 2H. *J* = 8 Hz), 4.41-4.47 (m, 4H), 5.15-5.21 (m, 2H), 6.01-6.10 (m, 1H), 7.34 (d, 1H, *J* = 8 Hz), 7.44 (t, 1H, *J* = 8 Hz), 7.79 (bs, 2H), 9.01 (d, 1H, *J* = 8 Hz), 9.16 (d, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)**:** δ 14.6, 14.7, 45.7, 59.8, 99.1, 99.2, 116.9, 130.1, 132.0, 133.9, 133.0, 137.0, 145.3, 145.4, 146.0, 162.7, 166.6. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{19}H_{21}NO_4Na$ 350.3698; Found: 350.3695. Melting point: 68-70 °C, **IR (ATR)**: ν: 3441, 3304, 2944, 2877, 1725, 1642, 1568, 1481, 1403, 1250, 1203, 1140, 1100, 1077, 1014, 904, 783, 692, 645 cm^{-1}.

Product yield: 50 mg of **9b** was used as starting material, amount of **13b** obtained from different bases:

1) NaOMe: 42 mg, 45% 2) DBU: 65 mg, 70% 3) DIPA: 63 mg, 68% 4) *t*-$BuNH_2$: 69 mg, 75% 5) Bu_3N: 60 mg, 65% 6) Et_3N: 64 mg, 69% 7) DIPEA: No product obtained and starting material was recovered 8) DABCO: No product obtained and starting material was recovered.

Half-gram scale synthesis: To 0.5 g (2.83 mmol) **9b** dissolved in dry EtOH (25 ml), ethylcyano acetate (735 mg, 6.5 mmol) was added, followed by the slow addition of *t*-$BuNH_2$ (476 mg, 6.5 mmol) under ice cooling. The reaction mixture was stirred overnight while the temperature was allowed to rise to room temperature. After completion of the reaction as monitored by thin layer chromatography, the solvent was evaporated and residue extracted with ethyl acetate and dried with Na_2SO_4. The solvent was evaporated and the residue was further purified by column chromatography to give **13b** as orange solid (0.62 g, 68% yield).

dimethyl 2-amino-5-phenylazulene-1,3-dicarboxylate (14a)

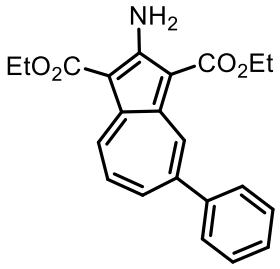


Purification: Column chromatography using silica gel (60-120 mesh), 15% EtOAc/Hexane, orange solid. ^{1}H NMR (500 MHz, $CDCl_3$)**:** δ 3.97 (s, 3H), 4.00 (s, 3H), 7.41-7.70 (m, 9H), 9.05 (d, 1H, *J* = 10 Hz), 9.51 (s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$)**:** δ 51.1, 99.7, 100.2, 125.1, 128.0, 128.6, 129.0, 130.5, 132.3, 132.4, 144.7, 145.5, 146.0, 146.3, 167.0, 167.1. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{17}NO_4Na$ 358.1055; Found: 358.1052. Melting point: 128-129 °C, **IR (ATR)**: ν: 3425, 3304, 2911, 2884, 2816, 1645, 1559, 1470, 1419, 1362, 1260, 1152, 1095, 996, 831, 780, 736, 678 cm^{-1}.

Product yield: 50 mg of **10b** was used as starting material, amount of **14a** obtained from different bases:

1) NaOMe: 49 mg, 62% 2) DBU: 71 mg, 90% 3) DIPA: 66 mg, 84% 4) *t*-$BuNH_2$: 68 mg, 87% 5) Bu_3N: 62 mg, 79% 6) Et_3N: 64 mg, 81% 7) DIPEA: 9 mg, 12% 8) DABCO: 8 mg, 10%.

diethyl 2-amino-5-phenylazulene-1,3-dicarboxylate (14b)

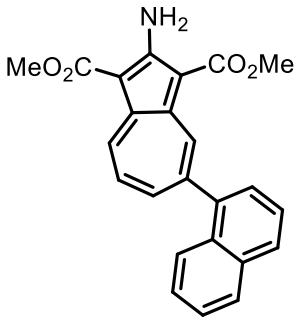


Purification: Column chromatography using silica gel (60-120 mesh), 15% EtOAc/Hexane, orange solid. ^{1}H NMR (400 MHz, $CDCl_3$)**:** δ 1.44-1.50 (m, 6H), 4.41-1.50 (m, 6H), 7.40-7.43 (m, 1H), 7.49 (t, 2H, *J* = 10 Hz), 7.58 (t, 1H, *J* = 10 Hz), 7.69-7.70 (m, 3H), 7.83 (bs, 2H), 9.06 (d, 1H, *J* = 12 Hz), 9.53 (s, 1H, *J* = 1.6 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$)**:** δ 14.6, 14.8, 59.9, 99.7, 100.2, 128.0, 128.5, 128.9, 130.4, 132.1, 132.3, 132.9, 144.4, 145.2, 145.9, 146.0, 162.9, 166.6, 166.7. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{22}H_{21}NO_4Na$ 386.1368; Found: 386.1343. Melting point: 104-106 °C, **IR (ATR)**: ν: 3454, 3307, 2938, 2888, 2822, 1640, 1573, 1479, 1416, 1268, 1141, 1094, 1014, 927, 870, 840, 776, 746, 686 cm^{-1}.

Product yield: 50 mg of **10b** was used as starting material, amount of **14b** obtained from different bases:

1) NaOMe: 54 mg, 64% 2) DBU: 77 mg, 91% 3) DIPA: 71 mg, 84% 4) *t*-$BuNH_2$: 76 mg, 89% 5) Bu_3N: 66 mg, 78% 6) Et_3N: 70 mg, 82% 7) DIPEA: 7 mg, 8% 8) DABCO: 8 mg, 10%.

dimethyl 2-amino-5-(naphthalen-1-yl)azulene-1,3-dicarboxylate (15a)

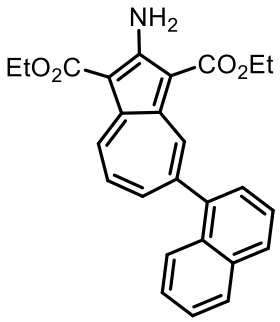


Purification: Column chromatography using silica gel (60-120 mesh), 15% EtOAc/Hexane, orange solid. ^{1}H NMR (500 MHz, $CDCl_3$)**:** δ 3.8 (s, 3H), 4.04 (s, 3H), 7.44-7.65 (m, 6H), 7.83-7.95 (m, 5H), 9.15 (t, 1H, *J* = 10 Hz), 9.36 (s, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)**:** δ 51.0, 51.1, 100.2, 125.1, 125.3, 125.9, 126.1, 126.5, 127.5, 128.4, 128.5, 130.8, 131.5, 131.8, 134.2, 135.3, 135.8, 142.9, 144.8, 145.4, 146.1, 162.8, 166.8. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{24}H_{19}NO_4Na$ 408.1212; Found: 408.1209. Melting point: 157-159 °C, **IR (ATR)**: υ: 3437, 3310, 3011, 2912, 2879, 2814, 1672, 1638, 1549, 1480, 1422, 1360, 1244, 1165, 1107, 1042, 1008, 946, 839, 785, 757, 651 cm^{-1}.

Product yield: 50 mg of **11b** was used as starting material, amount of **15a** obtained from different bases:

1) NaOMe: 43 mg, 59% 2) DBU: 66 mg, 91% 3) DIPA: 61 mg, 84% 4) *t*-$BuNH_2$: 64 mg, 88% 5) Bu_3N: 55 mg, 75% 6) Et_3N: 58 mg, 80% 7) DIPEA: 5 mg, 7% 8) DABCO: 7 mg, 9%.

diethyl 2-amino-5-(naphthalen-1-yl)azulene-1,3-dicarboxylate (15b)



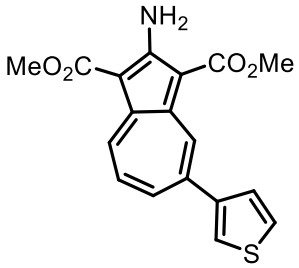
Purification: Column chromatography using silica gel (60-120 mesh), 20% EtOAc/Hexane, orange solid. ^{1}H NMR (400 MHz, $CDCl_3$)**:** δ 1.16 (t, 3H, *J* = 8 Hz), 1.52 (t, 3H, *J* = 8 Hz), 4.26-4.53 (m, 4H), 7.43-7.60 (m,

6H), 7.85-7.92 (m, 5H), 9.16-9.19 (m, 1H), 9.44 (s, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$)**:** δ 14.2, 14.7, 59.7, 59.9, 125.3, 125.9, 126.0, 127.4, 128.3, 128.4, 130.7, 131.4, 131.7, 133.9, 134.4, 135.3, 142.8, 144.8, 145.3, 146.0, 162.9, 166.6. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{26}H_{23}NO_4Na$ 436.1525; Found: 436.1521. Melting point: 102-105 °C, **IR (ATR)**: ν: 3444, 3294, 3015, 2935, 2881, 2820, 1643, 1569, 1479, 1407, 1359, 1147, 1093, 1006, 928, 860, 764, 689, 638, 551 cm^{-1}.

Product yield: 50 mg of **11b** was used as starting material, amount of **15b** obtained from different bases:

1) NaOMe: 47 mg, 60% 2) DBU: 71 mg, 91% 3) DIPA: 69 mg, 88% 4) *t*-$BuNH_2$: 70 mg, 90% 5) Bu_3N: 63 mg, 81% 6) Et_3N: 67 mg, 85% 7) DIPEA: 9 mg, 12% 8) DABCO: 7 mg, 9%.

dimethyl 2-amino-5-(thiophen-3-yl)azulene-1,3-dicarboxylate (16a)

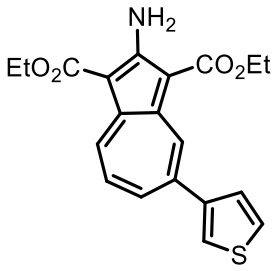


Purification: Column chromatography using silica gel (60-120 mesh), 15% EtOAc/Hexane, orange solid. ^{1}H NMR (400 MHz, $CDCl_3$)**:** δ 4.00 (s, 3H), 4.00 (s, 3H), 7.45-7.58 (m, 4H), 7.63-7.74 (m, 1H), 7.65-7.78 (m, 3H), 8.98 (d, 1H, *J* = 1H), 9.615 (d, 1H, *J* = 4 Hz) $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$)**:** δ 51.1, 51.3, 99.7, 100.1, 123.2, 127.4, 130.3, 131.2, 132.0, 132.3, 140.4, 145.6, 146.1, 162.5, 166.6, 167.2. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{15}NO_4SNa$ 364.0619; Found: 364.0613. Melting point: 152-153 °C, **IR (ATR)**: ν: 3389, 3272, 3064, 2883, 2819, 1254, 1574, 1540, 1483, 1423, 1356, 1319, 1212, 1155, 1075, 1041, 964, 914, 840, 773, 716, 676, 555, 512 cm^{-1}

Product yield: 50 mg of **12b** was used as starting material, amount of **16a** obtained from different bases:

1) NaOMe: 47 mg, 61% 2) DBU: 65 mg, 84% 3) DIPA: 68 mg, 87% 4) *t*-$BuNH_2$: 63 mg, 81% 5) Bu_3N: 56 mg, 72% 6) Et_3N: 61 mg, 79% 7) DIPEA: 8 mg, 10% 8) DABCO: 4 mg, 5%.

diethyl 2-amino-5-(thiophen-3-yl)azulene-1,3-dicarboxylate (16b)

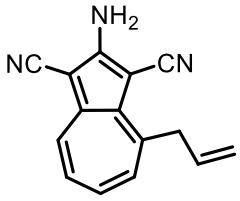


Purification: Column chromatography using silica gel (60-120 mesh), 20% EtOAc/Hexane, orange solid. ^{1}H NMR (400 MHz, $CDCl_3$)**:** δ 1.47-1.52(m, 6H), 4.43-4.49 (m, 4H), 7.41-7.61 (m, 4H), 7.72 (d, 1H, *J* = 8 Hz), 7.81 (bs, 2H), 8.99 (d, 1H, *J* = 12 Hz), 9.61 (d, 1H, *J* = 4 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$)**:** δ 14.8, 59.8, 99.8, 100.0, 123.0, 126.8, 127.4, 130.2, 131.1, 131.7, 132.1, 140.1, 145.4, 145.6, 146.0, 162.9, 166.6, 166.7 HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{19}NO_4SNa$ 392.0932; Found: 392.0925. Melting point: 101-104 °C, **IR (ATR)**: ν: 3445, 3301, 3060, 2883, 2822, 1725, 1637, 1553, 1480, 1421, 1359, 1271, 1139, 1088, 1019, 916, 843, 773, 678, 586, 531 cm^{-1}.

Product yield: 50 mg of **12b** was used as starting material, amount of **16b** obtained from different bases:

1) NaOMe: 45 mg, 54% 2) DBU: 66 mg, 78% 3) DIPA: 68 mg, 81% 4) *t*-$BuNH_2$: 67 mg, 79% 5) Bu_3N: 57 mg, 68% 6) Et_3N: 60 mg, 72% 7) DIPEA: 11 mg, 13% 8) DABCO: 7 mg, 8%.

4-allyl-2-aminoazulene-1,3-dicarbonitrile (17)



Purification: Column chromatography using silica gel (60-120 mesh), 20% EtOAc/Hexane, orange solid. ^{1}H NMR (400 MHz, $CDCl_3$)**:** δ 4.22 (d, 2H, J = 8 Hz), 5.10-5.22 (m, 2H), 5.57 (bs, 2H), 6.11-6.17 (m, 1H), 7.51-7.56 (m, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$)**:** δ 41.8, 81.7, 83.5, 115.2, 117.3, 117.8, 131.3, 132.1, 134.7, 135.2, 136.2, 141.6, 145.6, 146.0, 160.7. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{11}N_3Na$ 256.0851; Found: 256.0848. Melting point: 178-180 °C, **IR (ATR)**: ν: 3287, 3181, 2884, 2815, 2169, 1625, 1504, 1443, 1385, 1301, 1178, 1104, 981, 904, 725, 571 cm^{-1}.

Product yield:

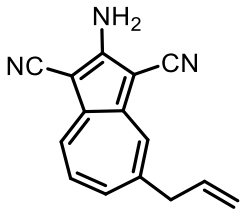
When 50 mg of **9b** was used as starting material, amount of **17** obtained from different bases:

1) NaOMe: 34 mg, 52% 2) DBU: 57 mg, 87% 3) DIPA: 55 mg, 84% 4) *t*-$BuNH_2$: 59 mg, 89% 5) DIPEA: 47, 71% 6) DABCO: 43, 65%

When 100 mg of **9c** was used as starting material, amount of **17** obtained from different bases:

1) NaOMe: 16 mg, 12% 2) DBU: 47 mg, 36% 3) DIPA: 50 mg, 38% 4) *t*-$BuNH_2$: 53 mg, 40% 5) Bu_3N: 33 mg, 25% 6) Et_3N: 27 mg, 21% 7) DIPEA: 39 mg, 30% 8) DABCO: 20 mg, 15%

5-allyl-2-aminoazulene-1,3-dicarbonitrile (18)

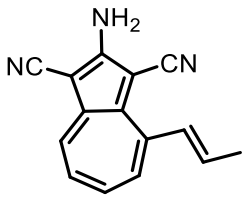


Purification: Column chromatography using silica gel (60-120 mesh), 20% EtOAc/Hexane, orange solid. ^{1}H NMR (400 MHz,$CDCl_3$) The compound was obtained as mixture with **17** and **26** and could not be separated using column chromatography. Characteristic peak for compound **18** is a doublet at 3.64 ppm from the allylic -CH_2 connected to the aromatic centre.

Product yield: Estimated from ^{1}H NMR as the product was inseparable from the mixture

1) Et_3N: 30% 2) Bu_3N: 31% On using excess base: 1) Et_3N: 13% 2) Bu_3N: 15%

(*E*)-2-amino-4-(prop-1-en-1-yl)azulene-1,3-dicarbonitrile (25)

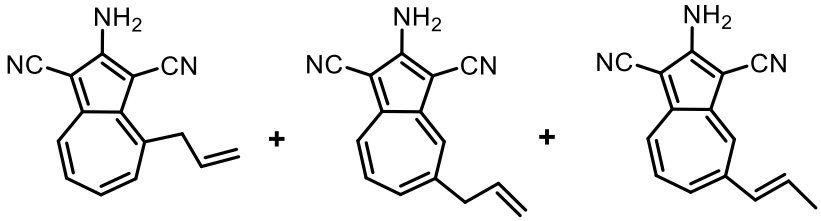


Purification: Column chromatography using silica gel (60-120 mesh), 20% EtOAc/Hexane, orange solid. ^{1}H NMR (400 MHz, $CDCl_3$)**:** δ 1.75 (dd, 3H, *J* = 12 Hz), 5.62 (bs, 2H), 6.19-6.25 (m, 1H), 7.18 (dd, 1H, *J* = 8 Hz), 7.45-7.55 (m, 3H), 8.18-8.21 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$)**:** δ 21.2, 60.5, 83.0, 115.2, 116.8, 129.9, 131.2, 131.8, 132.4, 134.0, 135.4, 141.0, 145.8, 160.4. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{11}N_3Na$ 256.0851; Found: 256.0843. Melting point: 276-278 °C, **IR (ATR)**: ν: 3328, 3280, 3180, 2880, 2816, 2162, 1622, 1502, 1382, 1298, 1178, 1128, 998, 945, 728, 598 cm^{-1}.

Product yield: When 50 mg of **9b** was used as starting material, amount of **25** obtained from different bases:

1) NaOMe: 38 mg, 58% 2) DBU: 55 mg, 84% 3) DIPA: 59 mg, 89% 4) *t*-$BuNH_2$: 53 mg, 81% 5) DIPEA: 51 mg, 78% 6) DABCO: 41 mg, 62%

4-allyl-2-aminoazulene-1,3-dicarbonitrile (17) + 5-allyl-2-aminoazulene-1,3-dicarbonitrile (18) + (E)-2-amino-5-(prop-1-en-1-yl)azulene-1,3-dicarbonitrile (26)

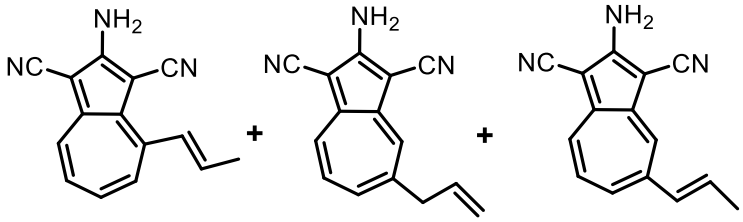


Purification: Column chromatography using silica gel (60-120 mesh), 20% EtOAc/Hexane, orange solid (The compounds were inseparable by column chromatography and were identified by their characteristic peak in ^{1}H NMR) ^{1}H NMR (400 MHz, $CDCl_3$)**:** δ **17**: -CH_2 protons at 4.15 ppm, **18**: -CH_2 protons at 3.59 ppm, **26**: -CH_3 protons at 2.06-2.08 ppm. **IR (ATR) of the mixture (17+18+26)**: ν: 3287, 3178, 2880, 2820, 2165, 1629, 1504, 1396, 1297, 1182, 1140, 993, 958, 904, 786, 757, 728, 581 cm^{-1}.

Product yield: Estimated from ^{1}H NMR as the mixture was inseparable.

1) Et_3N, **17**: 28%, **18**: 30%, **26**: 41% 2) Bu_3N, **17**: 26%, **18**: 31%, **26**: 43%

(E)-2-amino-4-(prop-1-en-1-yl)azulene-1,3-dicarbonitrile (25) + 5-allyl-2-aminoazulene-1,3-dicarbonitrile (18) + (E)-2-amino-5-(prop-1-en-1-yl)azulene-1,3-dicarbonitrile (26)

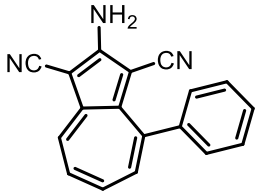


Purification: Column chromatography using silica gel (60-120 mesh), 20% EtOAc/Hexane, orange solid (The compounds were inseparable by column chromatography and were identified by their characteristic peak in ^{1}H NMR) ^{1}H NMR (400 MHz, $CDCl_3$)**:** δ **25**: -CH_3 protons at 1.74-1.76 ppm **18**: -CH_2 protons at 3.59 ppm, **26**: -CH_3 protons at 2.06-2.08 ppm. **IR (ATR) of the mixture (25+18+26)**: ν: 3295, 3174, 2883, 2815, 2167, 1629, 1507, 1397, 1297, 1188, 1139, 943, 899, 759, 715, 571 cm^{-1}.

Product yield: Estimated from ^{1}H NMR as the mixture was inseparable.

1) Et_3N, **25**: 55%, **26**: 31%, **18**: 13% 2) Bu_3N, **25**: 55%, **26**: 29%, **18**: 15%

2-amino-4-phenylazulene-1,3-dicarbonitrile (19)



Purification: Column chromatography using silica gel (60-120 mesh), 20% EtOAc/Hexane, orange solid. ^{1}H NMR (400 MHz, $CDCl_3$)**:** δ 5.53 (bs, 2H), 7.39-7.41 (m, 2H), 7.50-7.59 (m, 6H), 8.28-8.30 (m, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$)**:** δ 83.7, 114.0, 115.1, 128.6, 129.3, 129.4, 131.2, 132.0, 134.0, 135.6, 141.4, 146.5, 147.2, 152.2, 160.6, 163.7. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{11}N_3Na$ 292.0851; Found: 292.0848. Melting point: 306-309 °C, **IR (ATR)**: ν: 3294, 3168, 2889, 2850, 2167, 1630, 1507, 1388, 1172, 1061, 1009, 875, 737, 708, 686, 577 cm^{-1}.

Product Yield:

When 50 mg of **10b** was used as starting material, amount of **19** obtained from different bases:

1) NaOMe: 38 mg, 61% 2) DBU: 59 mg, 94% 3) DIPA: 54 mg, 85% 4) *t*-$BuNH_2$: 58 mg, 92% 5) DIPEA: 50 mg, 79% 6) DABCO: 41 mg, 65%

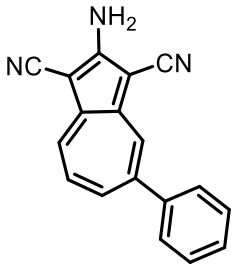
When 100 mg of **10c** was used as starting material, amount of **19** obtained from different bases:

2) NaOMe: 31 mg, 25% 2) DBU: 78 mg, 62% 3) DIPA: 72 mg, 57% 4) *t*-$BuNH_2$: 68 mg, 54% 5) Bu_3N: 57 mg, 45% 6) Et_3N: 59 mg, 47% 7) DIPEA: 46 mg, 40% 8) DABCO: 36 mg, 31%

Gram scale synthesis: To 1.2 g (5.6 mmol) **10b** dissolved in dry EtOH (40 ml), malononitrile (0.85 g, 12.8 mmol) was added, followed by the slow addition of DIPA (1.29 g, 1.8 mL, 12.8 mmol) under ice cooling. The reaction mixture was stirred overnight while the temperature was allowed to rise to room

temperature. After completion of the reaction as monitored by thin layer chromatography, the solvent was evaporated and residue extracted with ethyl acetate and dried with Na_2SO_4. The solvent was evaporated and the residue was further purified by column chromatography to give **19** as orange solid (1.18 g, 79% yield).

2-amino-5-phenylazulene-1,3-dicarbonitrile (20)

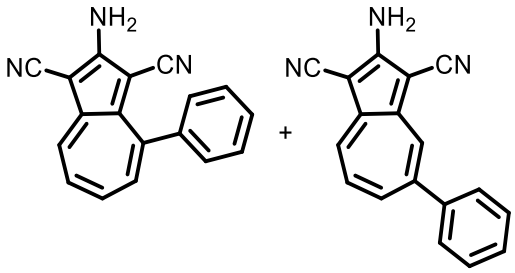


Purification: Column chromatography using silica gel (60-120 mesh), 20% EtOAc/Hexane, orange solid. ^{1}H NMR (400 MHz,$CDCl_3$)**:** δ 5.66 (bs, 2H), 7.48-7.53 (m, 3H), 7.63-7.70 (m, 3H), 7.845 (dd, 1H, *J* = 12 Hz), 8.14 (d, 1H, *J* = 8 Hz), 8.358 (d, 1H, *J* = 4 Hz). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)**:** δ 82.5, 83.4, 108.8, 109.1, 109.8, 115.1, 115.2, 128.6, 128.8, 129.3, 130.2, 131.9, 135.6, 143.0, 145.2, 145.8, 146.6, 159.8 HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{11}N_3Na$ 292.0851; Found: 292.0849. Melting point: 192-194 $^\circ$C, **IR (ATR)**: υ: 3309, 3180, 2890, 2827, 2176, 1642, 1521, 1408, 1362, 1291, 1189, 1068, 992, 864, 792, 743, 682, 550 cm^{-1}.

Product yield: When 100 mg of **10b** was used as starting material, amount of **20** obtained on using Et_3N and Bu_3N as bases:

1) Et_3N: 43 mg, 34% 2) Bu_3N: 61 mg, 48%

2-amino-4-phenylazulene-1,3-dicarbonitrile and 2-amino-5-phenylazulene-1,3-dicarbonitrile (19+20)



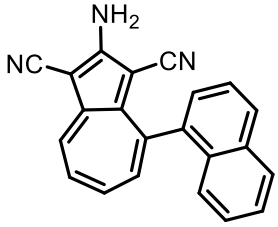
Purification: Column chromatography using silica gel (60-120 mesh), 20% EtOAc/Hexane, orange solid, mixture of **19** and **20**. Characteristic peak: ^{1}H NMR (400 MHz, $CDCl_3$)**:**

Reaction with Et_3N: 5.54 (bs, 2H) for compound **19** and 5.64 (bs, 2H) for compound **20** Reaction with Bu_3N: 5.52 (bs, 2H) for compound **19** and 5.61 (bs, 1H) for compound **20**

Product yield: When 100 mg of **10b** was used as starting material, amount of **19** and **20** obtained on using Et_3N and Bu_3N as bases:

1) Et_3N; **19**: 78 mg, 62%, **20**: 43 mg, 34% 2) Bu_3N; **19**: 55 mg, 44%, **20**: 61 mg, 48%

2-amino-4-(naphthalen-1-yl)azulene-1,3-dicarbonitrile (21)



Purification: Column chromatography using silica gel (60-120 mesh), 20% EtOAc/Hexane, orange solid. ^{1}H NMR (400 MHz, $CDCl_3$)**:** δ 5.44 (s, 2H), 7.22 (d, 1H, *J* = 8 Hz), 7.36 (t, 1H, *J* = 8 Hz), 7.47-7.67 (m, 6H), 7.99 (d, 1H, *J* = *8* Hz), 8.09 (d, 1H, *J* = 8 Hz), 8.35 (d, 1H, *J* = 8 Hz). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)**:** δ 83.7, 84.4, 113.6, 115.1, 124.9, 125.1, 126.4, 126.9, 127.5, 128.9, 130.0, 131.6, 132.0, 132.2, 133.5, 134.0, 138.5, 143.1, 145.2, 146.2, 160.5. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{22}H_{13}N_3Na$ 342.1007; Found:

342.1003. Melting point: 274-276 °C, **IR (ATR)**: ν: 3300, 3148, 3019, 2880, 2173, 1638, 1504, 1381, 1178, 1141, 1003, 887, 753, 713, 586 cm^{-1}.

Product yield:

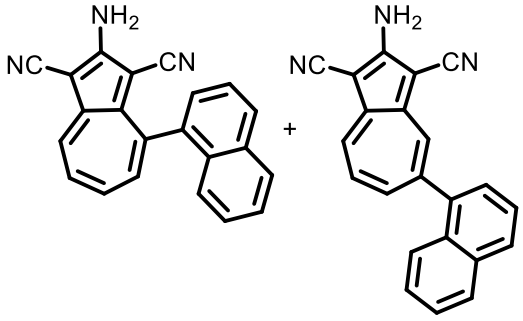
When 50 mg of **11b** was used as starting material, amount of **21** obtained from different bases:

1) NaOMe: 37 mg, 62% 2) DBU: 54 mg, 90% 3) DIPA: 55 mg, 91% 4) *t*-$BuNH_2$: 53 mg, 88% 5) DIPEA: 49 mg, 81% 6) DABCO: 45 mg, 75%

When 100 mg of **11c** was used as starting material, amount of **21** obtained from different bases:

1) NaOMe: 14 mg, 12% 2) DBU: 53 mg, 44% 3) DIPA: 55 mg, 45% 4) *t*-$BuNH_2$: 47 mg, 39% 5) Bu_3N: 37 mg, 31% 6) Et_3N: 45 mg, 37% 7) DIPEA: 35 mg, 29% 8) DABCO: 18 mg, 15%

2-amino-4-(naphthalen-1-yl)azulene-1,3-dicarbonitrile and 2-amino-5-(naphthalen-1-yl)azulene-1,3-dicarbonitrile (21+22)



Purification: Column chromatography using silica gel (60-120 mesh), 20% EtOAc/Hexane, orange solid, mixture of **21** and **22**. Characteristic peak: ^{1}H NMR (400 MHz, $CDCl_3$)**:**

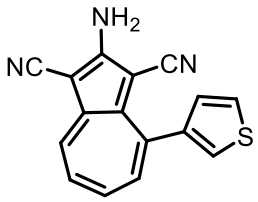
Reaction with Et_3N: 5.48 (bs, 2H) for compound **21** and 5.67 (bs, 1H) for compound **22** Reaction with Bu_3N: 5.49 (bs, 2H) for compound **21** and 5.69 (bs, 0.76H) for compound **22. IR (ATR) of mixture**

(21+22): ν: 3298, 3153, 3016, 2894, 2169, 1636, 1511, 1386, 1314, 1182, 1138, 995, 888, 766, 713, 584 cm^{-1}.

Product yield: Estimated from ^1H NMR, as the mixture were inseparable

1) Et_3N; **21**: 67.3%, **22**: 32.6% 2) Bu_3N; **21**: 72.4%, **22**: 27.5%

2-amino-4-(thiophen-3-yl)azulene-1,3-dicarbonitrile (23)



Purification: Column chromatography using silica gel (60-120 mesh), 20% EtOAc/Hexane, orange solid. ^1H NMR (400 MHz, $CDCl_3$)**:** δ 5.59 (bs, 2H), 7.20 (dd, 1H, J = 4 Hz), 7.43-7.57 (m, 5H), 8.25-8.27 (m, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$)**:** δ 83.8, 84.2, 113.9, 115.0, 126.1, 126.6, 129.2, 131.4, 131.9, 133.8, 135.5, 141.5, 142.4, 143.2, 146.1, 160.5. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{16}H_9N_3SNa$ 298.0415; Found: 298.0411. Melting point: 304-308 °C, **IR (ATR)**: ν: 3386, 3281, 3192, 3055, 2882, 2817, 2157, 1615, 1500, 1379, 1310, 1178, 1137, 1062, 840, 762, 742, 711, 653, 572 cm^{-1}.

Product yield:

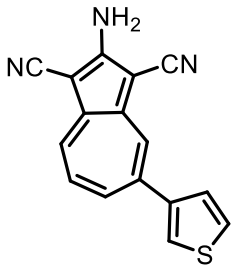
When 50 mg of **12b** was used as starting material, amount of 2**3** obtained from different bases:

1) NaOMe: 37 mg, 59% 2) DBU: 56 mg, 89% 3) DIPA: 58 mg, 92% 4) *t*-$BuNH_2$: 54 mg, 86% 5) DIPEA: 44 mg, 71% 6) DABCO: 47 mg, 74%

When 100 mg of **12c** was used as starting material, amount of **23** obtained from different bases:

1) NaOMe: 22 mg, 18% 2) DBU: 63 mg, 51% 3) DIPA: 67 mg, 54% 4) *t*-$BuNH_2$: 74 mg, 59% 5) Bu_3N: 46 mg, 37% 6) Et_3N: 57 mg, 45% 7) DIPEA: 51 mg, 41% 8) DABCO: 30 mg, 24%

2-amino-5-(thiophen-3-yl)azulene-1,3-dicarbonitrile (24)

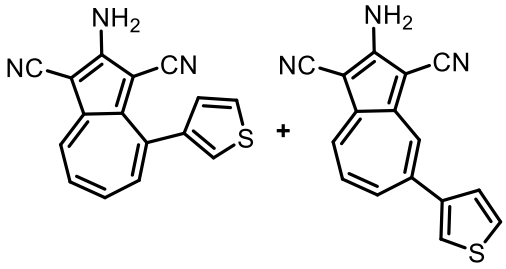


Purification: Column chromatography using silica gel (60-120 mesh), 20% EtOAc/Hexane, orange solid. ^1H NMR (400 MHz, $CDCl_3$)**:** δ 5.59 (s, 2H), 7.47-7.50 (m, 2H), 7.61-7.66 (m, 2H), 7.91 (dd, 1H, *J* = 4 Hz), 8.09 (d, 1H, *J* = 12 Hz), 8.45 (d, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$)**:** δ 102.1, 103.7, 114.9, 115.3, 124.3, 127.2, 127.7, 130.0, 130.7, 131.9, 134.4, 143.8, 145.2, 145.8, 148.5, 159.7. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{16}H_9N_3SNa$ 298.0415; Found: 298.0411. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{16}H_9N_3SNa$ 298.0415; Found: 298.0408. Melting point: 259-261 °C, **IR (ATR)**: ν: 3286, 3187, 3059, 2893, 2820, 2161, 1613, 1499, 1378, 1177, 1144, 843, 752, 710, 655, 569 cm^{-1}.

Product yield: When 100 mg of **12b** was used as starting material, amount of **24** obtained on using Et_3N and Bu_3N as bases:

1) Et_3N: 55 mg, 44% 2) Bu_3N: 59 mg, 47%

2-amino-4-(thiophen-3-yl)azulene-1,3-dicarbonitrile and 2-amino-5-(thiophen-3-yl)azulene-1,3-dicarbonitrile (23+24)



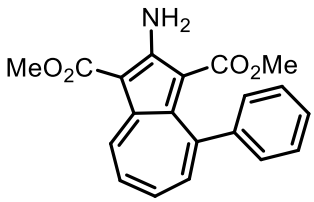
Purification: Column chromatography using silica gel (60-120 mesh), 20% EtOAc/Hexane, orange solid, mixture of **23** and **24**. Characteristic peak: ^{1}H NMR (400 MHz, $CDCl_3$)**:**

Reaction with Et_3N: 5.62 (bs, 2H) for compound **23** and 5.70 (bs, 1.84H) for compound **24** Reaction with Bu_3N: 5.69 (bs, 2H) for compound **23** and 5.79 (bs, 1.96 H) for compound **24**

Product yield: When 100 mg of **12b** was used as starting material, amount of **23** and 2**4** obtained on using Et_3N and Bu_3N as bases:

1) Et_3N; **23**: 60 mg, 48%, **24**: 55 mg, 44% 2) Bu_3N; **23**: 61 mg, 49%, **24**: 59 mg, 47%

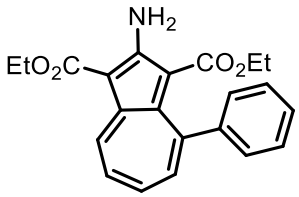
dimethyl 2-amino-4-phenylazulene-1,3-dicarboxylate (27a)



Purification: Column chromatography using silica gel (60-120 mesh), 15% EtOAc/Hexane, orange solid. ^{1}H NMR (500 MHz, $CDCl_3$)**:** δ 3.00 (s, 3H), 4.00 (s, 3H), 7.31-7.52 (m, 8H), 9.21 (d, 1H, J = 10 Hz). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)**:** δ 50.8, 51.1, 98.8, 104.2, 127.5, 128.0, 128.7, 130.8, 131.6, 136.4, 142.3, 144.7, 146.4, 147.2, 161.3, 166.7, 166.9. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{17}NO_4Na$ 358.1055; Found: 358.1053. Melting point: 183-186 $^\circ$C, **IR (ATR)**: ν: 3396, 3280, 2883, 2819, 1644, 1559, 1488, 1427, 1367, 1208, 1157, 1079, 870, 782, 728, 677, 532 cm^{-1}.

Product Yield: 67 mg product obtained from 100 mg starting material (Percentage yield: 38%)

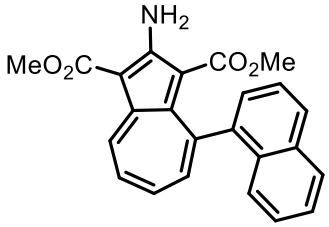
diethyl 2-amino-4-phenylazulene-1,3-dicarboxylate (27b)



Purification: Column chromatography using silica gel (60-120 mesh), 15% EtOAc/Hexane, orange solid. ^{1}H NMR (400 MHz, $CDCl_3$)**:** δ 0.98 (t, 3H, J = 4 Hz), 1.49 (t, 3H, J = 8 Hz), 3.44 (q, 2H, J = 8 Hz), 4.48 (q, 2H, J = 8 Hz), 7.29-7.53 (m, 8H), 9.21-9.24 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)**:** δ 14.2, 14.8, 59.9, 60.1, 98.6, 105.8, 127.5, 128.1, 130.6, 131.4, 136.0, 144.6, 147.3, 151.3, 154.2, 160.9, 165.7, 166.5. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{22}H_{21}NO_4Na$ 386.1368; Found: 386.1361. Melting point: 140-142 $^{\circ}$C, **IR (ATR)**: ν: 3420, 3301, 2933, 2878, 2822, 1644, 1560, 1482, 1385, 1203, 1161, 1087, 1009, 899, 776, 733, 682, 594 cm^{-1}.

Product Yield: 53 mg product obtained from 100 mg starting material (Percentage yield: 31%)

dimethyl 2-amino-4-(naphthalen-1-yl)azulene-1,3-dicarboxylate (28a)

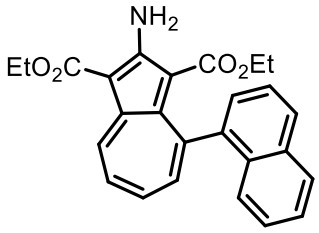


Purification: Column chromatography using silica gel (60-120 mesh), 10% EtOAc/Hexane, orange solid. ^{1}H NMR (500 MHz, $CDCl_3$)**:** δ 2.30 (s, 3H), 4.03 (s, 3H), 7.40-7.54 (m, 7H), 7.805 (d, 1H, J = 5Hz), 7.91 (d, 1H, J = 10 Hz), 8.065 (d, 1H, J = 5 Hz), 9.28 (d, 1H, J = 10 Hz). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)**:** δ 50.1, 51.1, 99.8, 103.3, 125.4, 125.7, 126.0, 126.1, 126.4, 127.8, 128.3, 131.0, 131.2, 131.6, 131.7, 134.2, 137.3,

143.0, 144.0, 144.5, 146.2, 161.2, 166.7, 166.9. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{24}H_{19}NO_4Na$ 408.1212; Found: 408.1207. Melting point: 175-178 °C, **IR (ATR)**: ν: 3418, 3304, 3005, 2890, 2823, 1649, 1561, 1485, 1424, 1369, 1208, 1163, 1099, 1017, 874, 765, 674 cm^{-1}.

Product Yield: 36 mg product obtained from 100 mg starting material (Percentage yield: 25%)

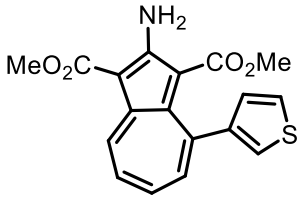
diethyl 2-amino-4-(naphthalen-1-yl)azulene-1,3-dicarboxylate (28b)



Purification: Column chromatography using silica gel (60-120 mesh), 10% EtOAc/Hexane, orange solid. ^1H NMR (500 MHz, $CDCl_3$)**:** δ 0.33 (t, 3H, *J* = 5 Hz), 1.50 (t, 3H, *J* = 5 Hz), 2.23-2.27 (m, 1H), 3.45-3.48 (m, 1H), 4.48-4.52 (m, 2H), 7.35-7.54 (m, 9H), 7.805 (d, 1H, *J* = 5 Hz), 7.91 (d, 1H, *J* = 5 Hz), 8.085 (d, 1H, *J* = 5 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$)**:** δ 13.0, 14.8, 59.8, 60.0, 99.6, 104.7, 125.3, 126.0, 126.1, 126.2, 126.5, 127.8, 128.4, 130.7, 130.9, 131.4, 131.7, 137.0, 142.5, 143.5, 144.0, 145.9, 160.9, 166.5. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{26}H_{23}NO_4Na$ 436.1525; Found: 436.1521. Melting point: 134-136 °C, **IR (ATR)**: ν: 3434, 3301, 3009, 2885, 2822, 1643, 1557, 1481, 1381, 1164, 1093, 1010, 896, 765, 728, 671 cm^{-1}.

Product Yield: 42 mg product obtained from 100 mg starting material (Percentage yield: 27%)

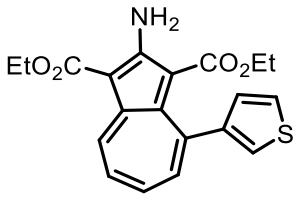
dimethyl 2-amino-4-(thiophen-3-yl)azulene-1,3-dicarboxylate (29a)



Purification: Column chromatography using silica gel (60-120 mesh), 15% EtOAc/Hexane, orange solid. ^{1}H NMR (500 MHz, $CDCl_3$)**:** δ 3.24 (s, 3H), 4.0 (s, 3H), 7.275 (dd, 1H, *J* = 5 Hz), 7.35-7.40 (m, 6H), 7.58 (dd, 1H, *J* = 10 Hz), 9.17 (dd, 1H, *J* = 10 Hz). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)**:** δ 51.0, 51.4, 96.0, 104.2, 122.2, 125.7, 128.0, 130.9, 135.3, 139.3, 142.8, 146.3, 147.8, 161.2, 166.9. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{15}NO_4SNa$ 364.0619; Found: 364.0615. Melting point: 178-181 °C, **IR (ATR)**: ν: 3420, 3302, 3060, 2959, 2902, 2821, 1647, 1558, 1482, 1423, 1371, 1205, 1166, 1092, 883, 843, 770, 730, 665 cm^{-1}.

Product Yield: 67 mg product obtained from 100 mg starting material (Percentage yield: 43%)

diethyl 2-amino-4-(thiophen-3-yl)azulene-1,3-dicarboxylate (29b)



Purification: Column chromatography using silica gel (60-120 mesh), 20% EtOAc/Hexane, orange solid. ^{1}H NMR (400 MHz, $CDCl_3$)**:** δ 1.06 (t, 3H, *J* = 8 Hz), 1.49 (t, 3H, *J* = 8 Hz), 3.67 (q, 2H, *J* = 8 Hz), 4.48 (q, 2H, *J* = 8 Hz), 7.30-7.43 (m, 5H), 7.58 (dd, 1H, *J* = 12 Hz), 9.18-9.20 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)**:** δ 14.3, 14.8, 60.0, 60.6, 98.8, 104.7, 122.4, 125.7, 128.0, 130.7, 135.0, 139.1, 142.5, 146.2, 147.8, 161.1, 166.5, 166.6. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{19}NO_4SNa$ 392.0932; Found: 392.0929.

Melting point: 149-151 °C, **IR (ATR)**: ν: 3443, 3313, 2881, 2821, 1645, 1575, 1481, 1445, 1362, 1246, 1163, 1089, 1009, 961, 836, 765, 666 cm^{-1}.

Product Yield: 60 mg product obtained from 100 mg starting material (Percentage yield: 35%)

ASSOCIATED CONTENT

Supporting Information

Details of the synthesis of tropolone precursors and mechanism of abnormal nucleophilic substitution to form the neutral intermediate **8**, ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra, and crystal structure information (CCDC Number: 1983409 and 1983442)

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Notes

The authors declare no competing financial interest

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REFERENCES

(1) Ou, L.; Zhou, Y.; Wu, B.; Zhu, L. The Unusual Physicochemical Properties of Azulene and Azulene Based Compounds. *Chin. Chem. Lett.* **2019**, *30*, 1903-1907.

(2) (a) Xin, H.; Gao, X. Application of Azulene in Constructing Organic Optoelectronic Materials: New Tricks for an Old Dog. *ChemPlusChem* **2017**, *82*, 945–956. (b) Murai, M.; Iba, S.; Ota, H.; Takai, K. Azulene-Fused Linear Polycyclic Aromatic Hydrocarbons with Small Bandgap, High Stability, and Reversible Stimuli Responsiveness. *Org. Lett.* **2017**, *19*, 5585–5588. (c) Shoji, T.; Ito, S. Azulene-Based

Donor–Acceptor Systems: Synthesis, Optical, and Electrochemical Properties. *Chem. Eur. J.* **2017**, *23*, 16696–16709.

(3) (a) He, Y. Y.; Chen, J.; Zheng, X. L.; Xu, X.; Li, W. Q.; Yang, L.; Tian, W. Q. Spiral Graphene Nanoribbons with Azulene Defects as Potential Nonlinear Optical Materials. *ACS Appl. Nano Mater.* **2019**, *2*, 1648−1654. (b) Yamaguchi, Y.; Ogawa, K.; Nakayama, K.; Ohba, Y.; Katagiri, H. Terazulene: A High-Performance n-Type Organic Field-Effect Transistor Based on Molecular Orbital Distribution Control. *J. Am. Chem. Soc.* **2013**, *135*, 19095–19098. (c) Yamaguchi, Y.; Takubo, M.; Ogawa, K.; Nakayama, K.; Koganezawa, K.; Katagiri, H. Terazulene Isomers: Polarity Change of OFETs through Molecular Orbital Distribution Contrast. *J. Am. Chem. Soc.* **2016**, *138*, 11335–11343. (d) Murfin, L. C.; Weber, M.; Park, S. J.; Kim, W. T.; Lopez-Alled, C. M.; McMullin, C. L.; Caggiano, F. P.; Lyall, C. L.; Köhn, G. K.; Wenk, J.; Bull, S. D.; Yoon, J.; Kim, H. M.; James, T. D.; Lewis, S. E. Azulene-Derived Fluorescent Probe for Bioimaging: Detection of Reactive Oxygen and Nitrogen Species by Two-Photon Microscopy. *J. Am. Chem. Soc.* **2019**, *141*, 19389−19396.

(4) Pfau, A. S.; Plattner, P. Zur Kenntnis der flüchtigen Pflanzenstoffe VIII. Synthese des Vetivazulens. *Helv. Chim. Acta* **1939**, *22*, 202.

(5) (a) Ziegler, K.; Hafner, K. Zu vorstehender Zuschrift. *Angew. Chem*. **1955**, *67*, 301. (b) Hafner, K. Zur Kenntnis Der Azulene I. Eine Neue Azulen-Synthese. *Ann. Chem.* **1957**, *606*, 79–89. (c) Poronik, Y. M.; Mazur, L. M.; Samoc, M.; Jacquemin, D.; Gryko, D. T. 2, 5-Bis(azulenyl) Pyrrole[3,2-*b*] Pyrroles-The Key Influence of the Linkage Position on the Linear and Nonlinear Optical Properties. *J. Mater. Chem. C* **2017**, *5*, 2620–2628.

(6) (a) “Azulenes”: K. P. Zeller in Carbocyclische p-Elektronen-Systeme, Houben-Weyl, Methoden der organischenChemie, Vol. 5/2c (Eds.: Meller, E.; Bayer, O.; Meerwein, H.; Ziegler, K.), *Thieme, Stuttgart*, **1985**, pp. 127–419. (b) Nozoe, T. Recent Advances in the Chemistry of Troponoids and Related Compounds in Japan. *Pure Appl. Chem.* **1971**, *28*, 239–280. (c) Nozoe, T.; Seto, S.; Matsumura, S.; Asano,

T. Synthesis of Azulene Derivatives from Troponoids and Cyanoacetic Ester. *Proc. Jpn. Acad*. **1956**, *32*, 339-343. (d) Nozoe, T.; Seto, S.; Nozoe, S. Synthesis of Azulene and 1-Azaazulanone Derivatives by the Application of Cyanoacetamide to Tropolone and 4-Methyltropolone Methyl Ethers. *Proc. Jpn. Acad.* **1956**, *32*, 472–475. (e) Nozoe, T.; Seto, S.; Matsumura, S.; Murase, Y. The Synthesis of Azulene Derivatives from Troponoids. *Bull. Chem. Soc. Jpn.* **1962**, *35*, 1179–1188. (f) Nozoe, T.; Takase, K.; Shimazaki, N. The Synthesis of Diethyl 2-Hydroxyazulene-1,3-Dicarboxylate from Troponoids and Some Reactions of 2-Hydroxyazulene Derivatives. *Bull. Chem. Soc. Jpn.* **1964**, *37*, 1644–1648. (g) Nozoe, T.; Takase, K.; Fukuda, S. Synthesis of 1-Phenylazulene and 2-Phenylazulene from the Troponoid Compound. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 2210–2214.

(7) Machiguchi, T.; Hasegawa, T.; Yamabe, S.; Minato, T.; Yamazaki, S.; Nozoe, T. Experimental and Theoretical Analyses of Azulene Synthesis from Tropones and Active Methylene Compounds: Reaction of 2-Methoxytropone and Malononitrile. *J. Org. Chem.* **2012**, *77*, 5318–5330.

(8) Carret, S.; Blanc, A.; Coquerel, Y.; Berthod, M.; Greene, A. E.; Depres, J. P. Approach to the Blues: A Highly Flexible Route to the Azulenes. *Angew. Chem. Int. Ed.* **2005**, *44*, 5130; Approach to the Blues: A Highly Flexible Route to the Azulenes. *Angew. Chem.* **2005**, *117*, 5260.

(9) (a) Ito, S.; Terazono, T.; Kubo, T.; Okujima, T.; Morita, N.; Murafuji, T.; Sugihara, Y.; Fujimori, K.; Kawakamia, J.; Tajiri, A. Efficient Preparation of 2-Azulenylboronate and Miyaura-Suzuki Cross-Coupling Reaction with Aryl Bromides for Easy Access to Poly(2-azulenyl)benzenes. *Tetrahedron* **2004**, *60*, 5357–5366. (b) Shoji, T.; Maruyama, A.; Araki, T.; Ito, S.; Okujima, T. Synthesis of 2- and 6-Thienylazulenes by Palladium-Catalyzed Direct Arylation of 2- and 6-Haloazulenes with Thiophene Derivatives. *Org. Biomol. Chem*. **2015**, *13*, 10191–10197. (c) Ito, S.; Shoji, T.; Morita, N. R. Recent Advances in the Development of Methods for the Preparation of Functionalized Azulenes for Electrochromic Applications. *Synlett.* **2011**, 2279.

(10) (a) Asiria, A. M.; Hashmi, A. S. K. Gold-catalysed reactions of diynes. *Chem. Soc. Rev.* **2016**, *45*, 4471-4503. (b) Zhao, X.; Rudolpha, M.; Hashmi, A. S. K. Dual gold catalysis an update. *Chem. Commun*. **2019**, *55*, 12127-12135. (c) Hashmi, A. S. K. Gold Catalyzed Organic Reactions. Chem. Rev. **2007**, *107*, 3180−3211.

(11) Claus, V.; Schukin, M.; Harrer, S.; Rudolph, M.; Rominger, F.; Asiri, A. M.; Xie, J.; Hashmi, A. S. K. Gold-Catalyzed Dimerization of Diarylalkynes: Direct Access to Azulenes. *Angew. Chem. Int. Ed*. **2018**, *57*, 12966–12970; Direkter Zugang zu Azulenen gber eine Gold-katalysierte Dimerisierung von Diarylalkinen. *Angew. Chem.* **2018**, *130*, 13148–13152.

(12) Usui, K.; Tanoue, K.; Yamamoto, K.; Shimizu, T.; Suemune, H. Synthesis of Substituted Azulenes via Pt(II)-Catalyzed Ring-Expanding Cycloisomerization. *Org. Lett.* **2014**, *16*, 4662-4665.

(13) Kane, J. L.; Shea, K. M.; Crombie, A. L.; Danheiser, R. L. A Ring Expansion−Annulation Strategy for the Synthesis of Substituted Azulenes. Preparation and Suzuki Coupling Reactions of 1-Azulenyl Triflates. *Org. Lett.* **2001**, *3*, 1081–1084.

(14) Moiseev, A. M.; Balenkova, E. S.; Nenajdenko, V. G. [6+4] Cycloaddition Reactions of Acceptor Thiophene Dioxides: The Synthesis of Substituted Azulenes. *Russ. Chem. Bull.* **2006**, *55*, 141–146.

(15) (a) Daub, J.; Knochel, T.; Mannschreck, A. Photosensitive Dihydroazulenes with Chromogenic Properties. Angew. *Chem. Int. Ed. Engl.* **1984**, 23, 960–961; Lichtsensitive Dihydroazulene Mit Chromogenen Eigenschaften. *Angew. Chem.* **1984**, *96*, 980–981. (b) Gobbi, L.; Seiler, P.; Diederich, F. Photoswitchable Tetraethynylethene-Dihydroazulene Chromophores. *Helv. Chim. Acta* **2001**, *84*, 743–777. (c) Petersen, M. A.; Kils, K.; Kadziola, A.; Nielsen, M. B. A Novel Route to a Bromo-Cyano-Substituted Azulene and Its Exploitation in the Construction of an Acetylenic Scaffold. *Eur. J. Org. Chem.* **2007**, 1415–1418 (d) Mazzanti, V.; Cacciarini, M.; Broman, S. L.; Parker, C. R.; Magnussen, M. S.; Bond, A. D.; Nielsen, M. B. On the Bromination of the Dihydroazulene/Vinylheptafulvene Photo-/Thermoswitch. Beilstein *J. Org. Chem*. **2012**, *8*, 958–966. (e) Skov, L.; Petersen, M. A.; Broman, S. L.; Bond, A. D.; Nielsen, M. B. New

Synthetic Route to Substituted Dihydroazulene Photoswitches. *Org. Biomol. Chem.* **2011**, *9*, 6498–6501. (f) Petersen, A. U.; Jevric, M.; Elm, J.; Olsen, S. T.; Tortzen, C. G.; Kadziola, A.; Mikkelsen, K. V.; Nielsen, M. B. Azulenium Chemistry: Towards New Derivatives of Photochromic Dihydroazulenes. *Org. Biomol. Chem*. **2016**, *14*, 2403–2412

(16) Kumar, N. R.; Agrawal, A. R.; Zade, S. S. Abnormal Nucleophilic Substitution on Methoxytropone Derivatives: Steric Strategy to Synthesize 5-Substituted Azulenes. *Chem. Eur. J.* **2019**, *25*, 14064-14071.

(17) Bushby, R.; Jarecki, C. Making a Vinyl-Trimethylenemethane Precursor Through the Addition of Diethyl Azodicarboxylate to Tropone. *J. Chem. Soc. Perkin Trans 1*, **1990**, 2335-2343.

(18) (a) Boothe, R.; Dial, C.; Conavay, R.; Pagni, R. M.; Kabalka, G. W. The Iodination of Aromatic Substrates on Alumina. *Tetrahedron Lett.* **1986**, *27*, 2207–2210. (b) Fujinaga, M.; Murafuji, T.; Kurotobi, K.; Sugihara, Y. Polyborylation of Azulenes. *Tetrahedron* **2009**, *65*, 7115–7121.

(19) (a) Thumin, I. T.; Crozet, M. P.; Barrière, J. C. A Convenient Method for the Alkylation of Tropolone Derivatives and Related a-Keto Hydroxy Compounds. *Synthesis* **1999**, *7*, 1149–1154. (b) Ononye, S. N.; VanHeyst, M. D.; Oblak, E. J.; Zhou, W.; Ammar, M.; Anderson, A. C.; Wright, D. L. Tropolones As Lead-Like Natural Products: The Development of Potent and Selective Histone Deacetylase Inhibitors. *ACS Med. Chem. Lett.* **2013**, *4*, 757-761.

(20) (a) Fernandes, I.; Monterde, M.; Plumet, J. On the Base-Induced Isomerization of Cyclic Propargylamides to Cyclic Allenamides. *Tetrahedron Lett.* **2005**, *46*, 6029-6031. (b) Tiwari, V. K.; Tripathi, R. P. Unexpected isomerisation of double bond with DBU: A Convenient Synthesis of Tetrasubstituted α-Alkylidene Tetrahydrofuranoses. *Ind. J. Chem.* **2002**, *41B*, 1681-1685. (c) Humbert, A. J.; Reimlinger, H. The Isomerization of Olefins Part I. Base Catalysed Isomerization of Olefins. *Synthesis, International Journal of Methods in Synthetic Organic Chemistry*, **1969**, *3*, 97-112.

(21) Dolomanov,O. V.; Bourhis,L. J.; Gildea,R. J.; Howard, J. A. K.; Puschmann,H.OLEX2: A Complete Structure Solution, Refinement and Analysis Program. *J. Appl. Cryst.* **2009**, *42*, 339-341.

(22) SHELXL, Sheldrick,G. M. A Short History of *SHELX*. *Acta Cryst.* **2008**, *A64*, 112-122.