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# Abnormal Nucleophilic Substitution on Methoxytropone Derivatives: Steric Strategy to Synthesize 5-Substituted Azulenes

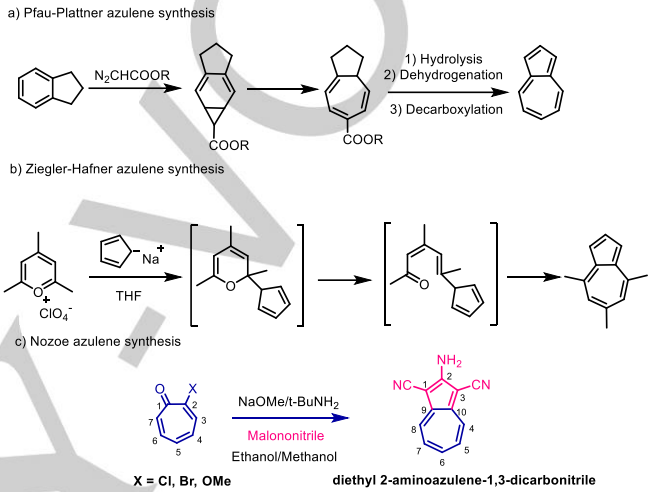
Neha Rani Kumar, Abhijeet R. Agrawal, and Sanjio S. Zade*

**Abstract:** Azulene is a non-alternant non-benzenoid aromatic system, and in turn, it possesses unusual photophysical properties. Azulene-based conjugated systems are receiving increasing interest in recent years as optoelectronic materials. Despite the routes available for the preparation of substituted azulene derivatives, there remain few methods that allow regioselective substitution on seven-membered ring of azulenes due to the subtle reactivity difference among the various positions. This report explores the reactivity of substituted tropolones as the azulene precursors and also provides the new method to create 5-substituted azulenes. The reaction of cyanoacetate enolate with unsubstituted 2-methoxytropone affords azulene via the attack of the nucleophile on C-2 center (normal pathway). We have observed that 3-substituted 2-methoxytropones undergo steric-guided nucleophilic addition at C-7 center (abnormal pathway) to afford 5-substituted azulene derivatives. Based on this observation and DFT calculation, a new synthetic strategy is devised for the regioselective synthesis of 5-substituted multifunctional azulenes, which cannot be accessed by any other method.

## Introduction

Azulene is a non-alternant non-benzenoid aromatic system, and in turn, it possesses unusual photophysical properties such as a large dipole moment and a narrow HOMO-LUMO gap. Although azulene-based conjugated systems remained largely unexplored as optoelectronic materials, however, in the recent few years, they have received increasing interest. Thus, azulenes are explored as active materials in the field of conducting polymers, electronic materials, fluorescence switching materials, and anion receptors.[1] 2,6-Connected azulene oligomers form donor-acceptor conjugated systems by delocalizing the π-electrons along the direction of $C_{2v}$ dipolar axis. Thus, they possess small HOMO-LUMO gaps. This idea has been exploited in recent studies, and 2,6-connected azulene scaffolds have been synthesized and utilized in OFET devices.[2,3]

In 1937, Plattner and Pfau reported azulene synthesis involving troublesome dehydrogenation step (Scheme 1a) thus limiting its practical application.[4] Ziegler-Hafner's azulene synthesis (Scheme 1b) was highly effective for azulene synthesis having substituents on the seven-membered ring.[5] Nozoe *et al.* reported the remarkable single pot synthesis of multifunctional azulenes from troponoids and active methylene compounds that allows easy functional group modification (Scheme 1c).[6]




**Scheme 1.** Various approaches to azulene synthesis.

Tropone and tropolone derivatives are the important precursors for the synthesis of azulenes by easy synthetic route with the scope of functional group modifications. Several natural products featuring tropone and tropolone have been isolated in the past seven decades and shown to possess various bioactivities[7] which have been attributed to the pharmacophore center based on the seven-membered carbocyclic system. Tropolone derivatives are part of synthetically challenging drugs like colchicine[8] and have attracted extensive studies since they possess powerful antibacterial and antifungal activity particularly against antibiotic-resistant bacteria. Their pharmacological properties, in turn, are determined by the nature and position of functional groups in the tropolone ring.[9] Hashmi and group reported the synthesis of several natural products bearing the active unsaturated seven-membered ring.[10]

A wide variety of cycloaddition reactions, photochemical transformations and nucleophilic substitutions on tropolone, 2-methoxytropone and other substituted tropolones have been carried out for the synthesis of biologically active compounds.[11-14] Yamamoto and co-workers have studied the regioselectivity of nucleophilic substitution on 5-bromo-2-methoxytropone with the various nucleophiles, where soft S-nucleophiles preferred the 5-position and the harder O- and N-nucleophiles preferred 2-position for the substitution.[15]

Pietra and Biggi have provided a detailed insight into the normal and abnormal nucleophilic substitution and ring contraction reactions on tropones with a labile α-substituent where the alteration of reactivity was attributed to the nature of

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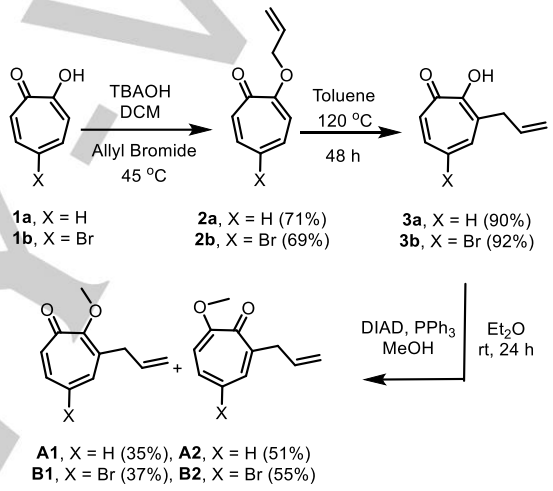
the leaving group, the nucleophile, and the solvent.[16,17] On the other hand, Machiguchi and co-workers[18] have reported a detailed theoretical and experimental study on the mechanism of Nozoe's synthesis of azulene from 2-methoxytropone.

There are limited ways to incorporate substituents on the azulene scaffold, which include (i) Sonogashira coupling of 6-bromoazulene with the terminal alkynes followed by catalytic reduction,[19] (ii) the reaction between fulvene ketene acetal and α-pyrone derivatives to yield the [6+4] cycloaddition adduct leading to azulenols,[20] and (iii) Rh-catalyzed ring expansion-annulation of β′-bromo-α-diazo ketones to afford 1-azulenols.[21] (iv) gold catalysed dimerisation of diaryldialkynes for the synthesis of substituted and modifiable azulenes.[22] (v) the synthesis of 1,1-dicyanoazulenes and subsequent functionalization of the seven-membered ring followed by elimination of HCN to give bromo-cyano substituted azulene.[23] Traditional methods for the construction of an azulene scaffold include long, low-yielding synthetic procedures that in many cases do not afford the desired substitution patterns. Achieving regioselectivity for the substitution on the seven-membered ring of azulene is a challenging task due to very close reactivity of all positions. Although sophisticated synthetic methodologies for the introduction of functional groups on the seven-membered ring have been reported recently,[24] we note that, there is no synthetic strategy to create regioselectively multifunctional 5-substituted azulenes. Hence, the regioselective synthesis of substituted azulenes is highly crucial considering their varied applications. It is imperative to develop facile synthetic methods for novel substitution motifs to extend the applications of azulenes.[25]

In an attempt to introduce allyl chain as a solubilising group on the azulene scaffold at the 4-position, we have synthesized 3-allyltropolone and 3-allyl-5-bromotropolone and subsequently, their methyl ethers. We here elucidate the reactivity difference of allyl substituted isomeric 2-methoxytropone (**A1** and **A2**) and 5-bromo-2-methoxytropone (**B1** and **B2**). We observed an interesting alteration of the reaction pathway of the construction of azulene scaffold to that described by Machiguchi and co-workers merely by the introduction of allyl chain, which led to the formation of diethyl 5-allyl-2-aminoazulene-1,3-dicarboxylate (**14**) rather than 4-allyl-2-aminoazulene-1,3-dicarboxylate (**12**) from the precursor 3-allyl-2-methoxytropone (**A1**). We have further successfully extended this observation to create a new synthetic strategy to synthesize 5-substituted azulenes.

## Results and Discussion

In our initial attempts to create 2,6-halo substituted azulene having solubilizing group on the seven-membered ring, we have synthesized allyl substituted tropolone regioisomers, 3-allyl-2-methoxytropone (**A1**) and 2-allyl-7-methoxytropone (**A2**) and their corresponding bromo analogues i.e. 3-allyl-5-bromo-2-methoxytropone (**B1**) and 2-allyl-4-bromo-7-methoxytropone (**B2**) (Scheme 2). Commercially available tropolone (**1a**) was O-allylated[26] using tetra-butyl ammonium hydroxide solution (TBAOH) in dichloromethane (DCM) and allyl bromide at 45 °C to give 2-allyloxytropone (**2a**) in 71% yield. Claisen rearrangement of **2a** in toluene at 120 °C gave the rearranged product 3-allyltropolone (**3a**) in 90% yield. Compound **3a** was then converted to its methyl ether derivative using Mitsunobu reaction conditions to give isomers **A1** and **A2** in 35% and 51% yields, respectively. 5-Bromotropolone (**1b**), obtained from 1,4-cyclohexadiene in 4 steps using De Shong's method[8] (Scheme S2), was subjected to similar O-allylation, Claisen rearrangement and Mitsunobu reaction to give sequentially compounds **2b** and **3b** in 69% and 92% yields and isomers **B1** and **B2** in 37% and 55% yields, respectively. Structures of **A1**, **A2**, and **B1** were confirmed $^{1}$H NMR.[27] Compounds **B1** and **B2** were characterized by $^{1}$H NMR, $^{13}$C NMR, and HRMS. Structure of **B2** was unambiguously confirmed by single crystal X-ray diffraction (SCXRD) analysis (Figure 1).




**Scheme 2.** Synthesis of allyl substituted methyl ethers of tropolone and 5-bromotropolone

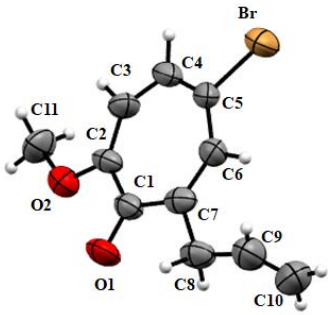
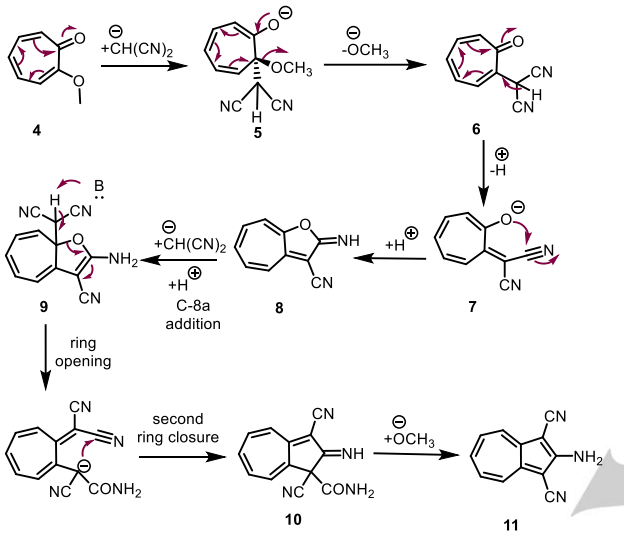



**Figure 1.** Crystal structure of **B2**.

Further, we have attempted the synthesis of azulenes from compounds **A1**, **A2**, **B1**, and **B2** by the reaction with *t*-BuNH$_2$ as a base, ethylcyanoacetate as the active methylene compound and ethanol as solvent at 0 °C. Machiguchi and co-workers in

their report[18] provided detailed theoretical and experimental insight of the mechanism of azulene synthesis from a troponoid precursor (2-methoxytropone) and active methylene compound (Scheme 3). As described,[18] the process consists of the following elementary steps. (a) The initial step includes the nucleophilic attack of malononitrile anion $(HC(CN)_2^-$ on the troponoid substrate, 2-methoxy tropone (**4**), to form Meisenheimer-type complex **5**, which rapidly converts to the intermediate anion **7** via the compound **6**. (b) The first ring closu-




**Scheme 3.** Key steps of Machiguchi's mechanism for azulene formation.

re reaction of anion **7** gives an isolable intermediate, 2-imino-2H-cyclohepta[*b*]furan-3-carbonitrile (**8**).(c) Nucleophilic addition of the second $HC(CN)_2^-$ to the imine **8** at C-8a position produces the second Meisenheimer-type adduct **9**. (d) The second ring closure leads to 1-carbamoyl-1.3-dicyano-2-imino-2,3-dihydroazulene (**10**). A base attacks the imine **10**, which results in the generation of a conjugate base of the final product azulene (**11**) Based on Machiguchi's mechanism, the expected products from the reaction of **A1** and **A2**, with ethylcyanoacetate and *t*-$BuNH_2$ is diethyl 4-allyl-2-amino azulene-1,3-dicarboxylate (**12**), whereas **B1** and **B2** would afford diethyl 4-allyl-2-amino-6-bromoazulene-1,3-dicarboxylate (**13**) (Scheme 4).

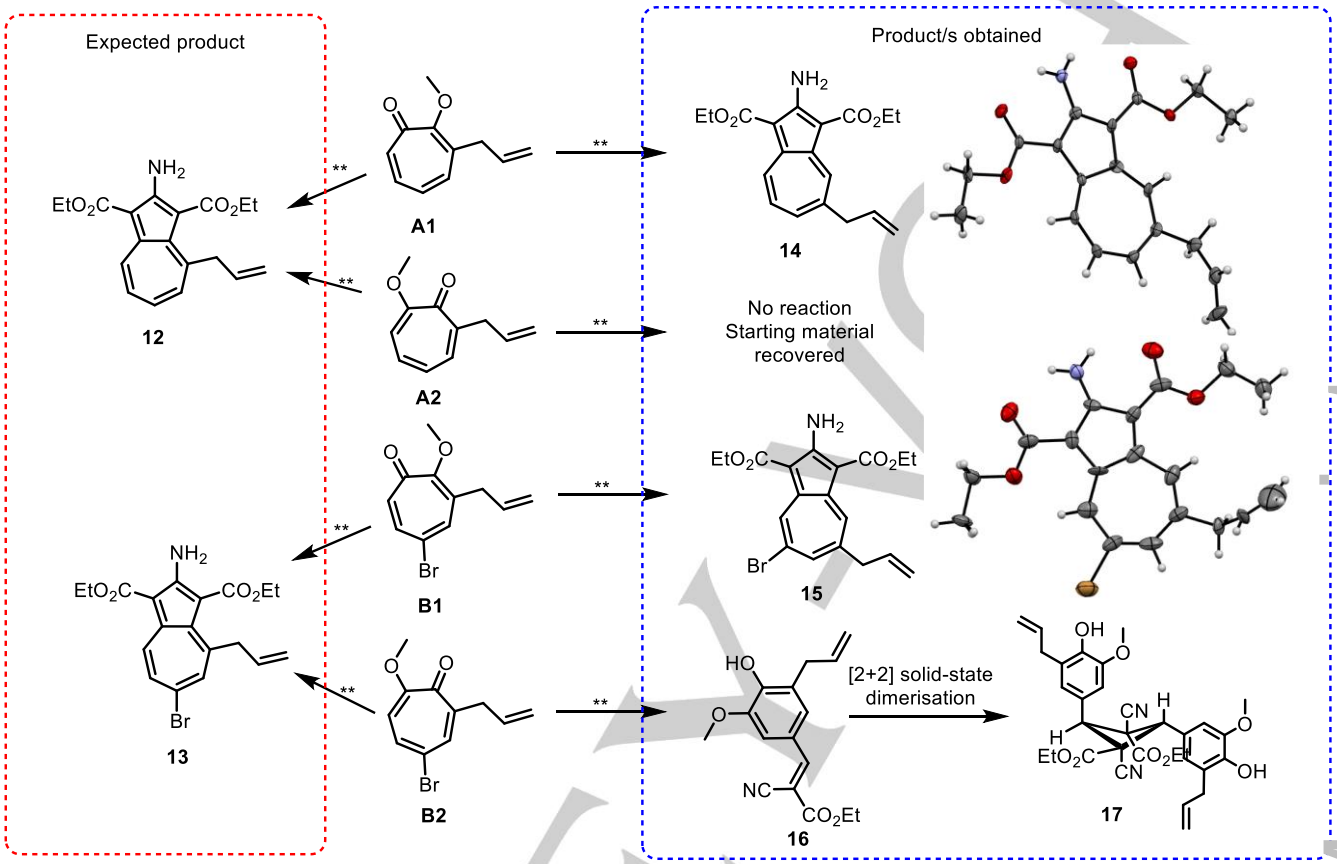
However, all the four reactions resulted in the unexpected outcomes indicating the subtle reactivity of these tropolone derivatives (Scheme 4). Compound **A1** led to formation of diethyl 5-allyl-2-aminoazulene-1,3-dicarboxylate (**14**) instead of diethyl 4-allyl-2-aminoazulene-1,3-dicarboxylate (**12**). Similar to the reaction of **A1**, the reaction of the corresponding bromo-derivative **B1** afforded diethyl 5-allyl-2-amino-7-bromoazulene-1,3-dicarboxylate (**15**) rather than the expected product diethyl 4-allyl-2-amino-6-bromoazulene-1,3-dicarboxylate (**13**). Structures of compound **14** and **15**, as well as the position of allyl chain in both of these compounds, were confirmed by SCXRD analysis (Scheme 4). $^1$H NMR spectra of **14** and **15** also revealed a highly deshielded singlet or a doublet with a very low coupling constant corresponding to the H at C-4. Compound **A2**, on the contrary, was inert when subjected to similar reaction conditions. Unlike the reaction of **A2**, the reaction of isomeric **B2** afforded ethyl (*E*)-3-(3-allyl-4-hydroxy-5-methoxyphenyl)-2-cyanoacrylate (**16**) under similar reaction conditions. Compound **16** was confirmed by $^1$H, $^{13}$C NMR and HRMS data. Compound **16** was topochemically converted to all-trans-cyclobutane derivative **17**.

Machiguchi et al. have reported the formation of intermediate **6** (Scheme 3) by the attack of the nucleophile at C-2 of the active troponoid precursor. This pathway was termed as the normal path and was supported by experimental observations and theoretical calculations. The attack of the nucleophile at C-7 of troponoid system was discussed as the abnormal path (Scheme 6), and their experimental observations confirmed that the reaction proceeded via the normal nucleophilic substitution.

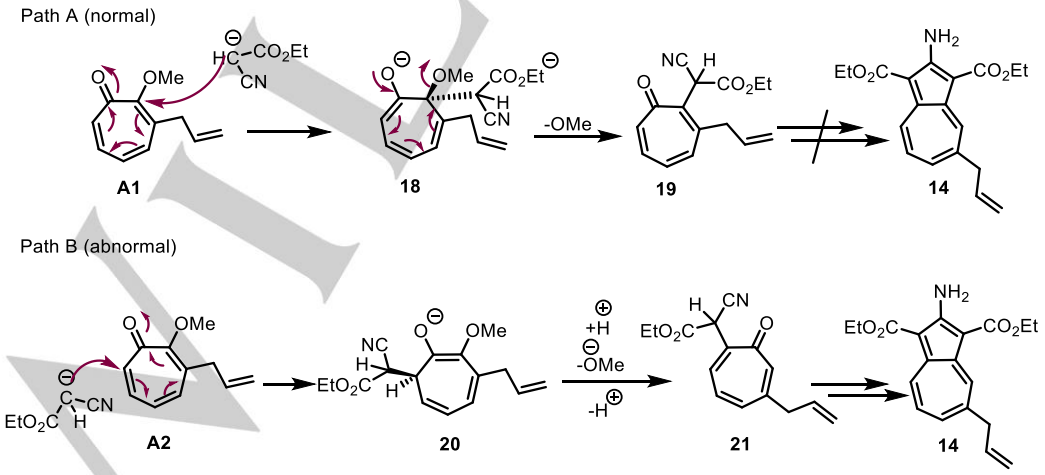
From Scheme 4, we note the following important observations. (a) The allyl chain has occupied C-5 position in azulene derivative **14** and **15** rather than usual C-4 position (as in **12** and **13**). (b) In contrast to the reaction of **A1**, the isomer **A2** was found inert in this reaction under similar reaction conditions. (c) Compound **B1** smoothly underwent the azulene ring formation, whereas **B2** afforded ring-contracted product **16** and subsequently it was converted into **17**.

The following consideration can explain these observations. In the synthesis of azulene scaffold from **A1**, we envision that the first step would be the nucleophilic attack either at C-2 (Path A, normal) or C-7 (Path B, abnormal) of the allyl-substituted active troponoid precursor **A1** as shown in Scheme 5. The reaction will afford **14** if it proceeds via 'Path B', which was earlier considered as the abnormal path. The attack of a nucleophile (ethyl cyanoacetate anion) at the C-2 i.e. methoxy centre via Path A (normal) cannot lead to the formation of **14**. The primary nucleophilic addition of ethyl cyanoacetate anion and elimination are through Path B, i.e. at C-7 on the tropone ring which by the loss of methoxide subsequently forms **21** via the intermediate anion **20**. The attack of the nucleophile at C-2 is sterically unfavoured due to the presence of allyl substituent on the adjacent carbon that hinders the formation of **19** via the sterically unfavored Meisenheimer adduct **18**. Formation of **15** can also be explained by a similar mechanism. The rest of the steps proceed similar to that-described by Machiguchi et al. (Scheme S8).

Unlike **A1** and **B1**, in isomers **A2** and **B2**, the attack of nucleophile cannot occur at C-7 as the allyl group blocks the nucleophilic attack. But, attack of the nucleophile at C-2 is sterically favorable, despite that there is no nucleophilic substitution at C-2. This anomalous behavior of **A2** and **B2** compared to **A1** and **B1** can be explained only by the reversibility of nucleophilic attack either at C-2 position or at the other free conjugate positions of **A2** and **B2**. Inactivity of **A2** and **B2** in the formation of azulene derivatives may also be possible due to the tautomerism as the alternate channel, which is absent



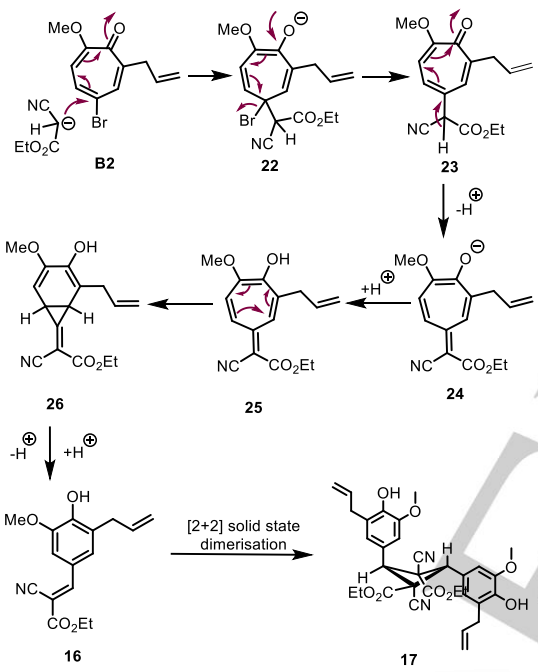

**Scheme 4.** Expected products from cyclisation of allyl substituted active troponoid precursors and the products obtained (Crystal structure of **14** and **15**, Grey: C, Red: O, Blue: N, Yellow: Br, pale grey: H)

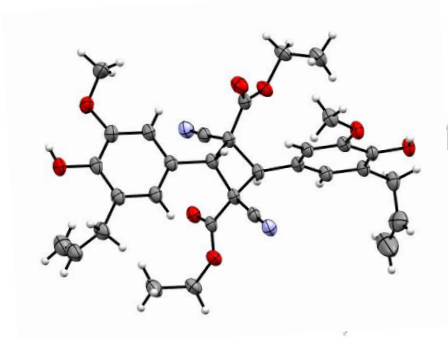



**Scheme 5.** Possibility of the attack of nucleophile in the first stage

in **A1** and **B1** thus favoring the nucleophilic attack on the later isomers.

Compound **B2**, however, undergoes nucleophilic ipso-substitution followed by the electrocyclic reaction and rearrangement to form **16**. The presence of bromo-substituent at C-4 of **B2** enhances the orbital interaction (soft-soft interactions) between the nucleophilic and C-Br center to facilitate the ipso-substitution (Scheme 6).[15] The nucleophilic attack at the C-Br center leads to the formation of **23** via the intermediate anion **22** with bromide as the leaving group. Under the basic reaction conditions, subsequent tautomerism form **25** via intermediate anion **24**. Compound **25** then undergoes intramolecular electro-



**Scheme 6.** Proposed mechanism of nucleophilic substitution at bromo center of **B2** leading to solid state dimerized product **17** (Crystal structure of **17**, Grey: C; Red: O, Blue: N, pale grey: H)

cyclic reaction to form ethyl cinnamate derivative **16** via the intermediate **26**. Compound **16** then undergoes topochemically driven solid-state [2+2] cycloaddition (solid state dimerization) to form the trans substituted cyclobutane isomer **17** under ambient light in ~35% yield in 7 days. Compound **17** was isolated from a mixture of **16** and **17** by column chromatography, and its structure was confirmed by SCXRD analysis (Scheme 6). A $CDCl_3$ solution of compound **16** was found to be stable as monitored by $^1H$ NMR over a long period, confirming its topochemical solid state dimerization.

## Theoretical Calculations

To shed more light on the experimentally observed abnormal nucleophilic substitution, we have carried out DFT calculations at M06-2X/6-311+G(d,p) [SCRF = PCM, solvent = ethanol]//B3LYP/6-31G(d) + ZPVE. For DFT calculation, we have considered the first crucial step of substitution of methoxy group by ethyl cyanoacetate anion for **A1**. We have considered both, normal and abnormal, pathways (nucleophilic attack at the C-2 and C-7 position, respectively), which are important to obtain information about the regioselectivity of the final azulene products (Figure 2).

The 'normal path' and 'abnormal path' involve two and four elementary steps, respectively, as shown in Figure 1. For normal path (the attack of the nucleophile at C-2), the first step is the formation of Meisenheimer adduct **A1-C2-P1** via transition state (TS) **A1-C2-TS1**. From this adduct, the $MeO^-$ group is dissociated via **A1-C2-TS2** to form the product **A1-C2-P2**, which is a neutral intermediate. First step of abnormal pathway (the attack of the nucleophile at C-7) is the attack of the nucleophile to form anionic intermediate **A1-C7-P1** via TS **A1-C7-TS1**. The next step involves C-H bond formation at C-2 to give neutral intermediate **A1-C7-P2** via TS **A1-C7-TS2**. The H-atom on C-7 is sufficiently acidic to be abstracted by the base to form the anionic intermediate **A1-C7-P3** via TS **A1-C7-TS3**. The anionic intermediate **A1-C7-P3** loses a molecule of MeOH under the influence of base to form neutral intermediate **A1-C7-P4** via the transition state **A1-C7-TS4**. The neutral intermediate **A1-C7-P4** would be then converted to azulene skeleton via the intermediates proposed by Machiguchi et al.[17] The activation energy of the first step of the abnormal path is lower by 2.6 kcal/mol than that of the normal path. Overall, the formation of **A1-C7-P4** by the abnormal path was more favorable considering the lower energy barriers of the rate-determining step by 3.6 kcal/mol compared to the formation of **A1-C2-P2** by the normal path. Overall, DFT study indicates that 'abnormal path' is more favarable than 'normal path' in presence of 3-allyl substituent. Thus, DFT study is consistent with the experimental observation and provides the indication of developing a synthetic strategy to synthesize 5-substituted azulene regioselectively from the 3-substituted 2-methoxytropone.

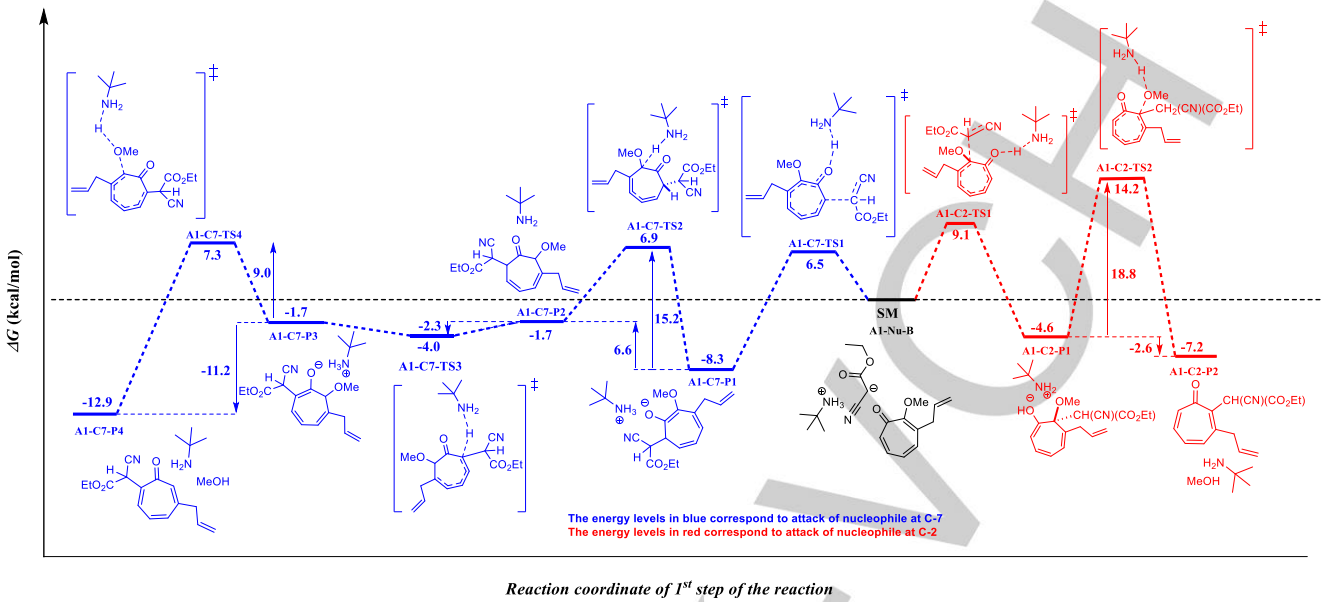


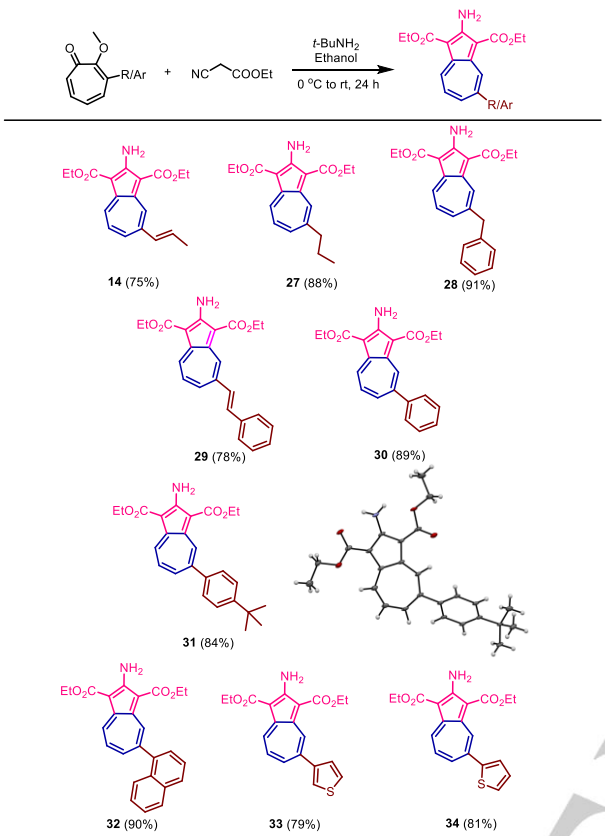

**Figure 2.** Energy profile diagram of nucleophilic substitution on **A1**

## Scope of the Methodology

Based on the experimental results and theoretical calculation, we have proposed a synthetic strategy to obtain regioselectively 5-substituted azulenes. Regioselective substitution on the five-membered ring of azulenes is well documented in the literature.[28] Ito and coworkers also reported the synthesis of 2-azulenyl boronate and direct arylation of 2- and 6-halo azulenes that provide access to a wide variety of substituted azulene derivatives.[29] However, there remain very limited methods that allow regioselective substitution on the seven-membered ring of azulenes because of the small difference in the reactivity of the positions of the seven-membered ring of azulenes. To check the scope of the proposed synthetic methodology, we have synthesized several 2-methoxytropone derivatives with varied substituents at C-3 and subjected to similar reaction conditions. The substituents were varied from alkyl to aryl to heteroaryl. Alkyl substituted tropolone was synthesized by reduction of allyl chain and subsequent conversion of tropolone to its methyl ether (Scheme S4). Benzyl substituted tropolone was prepared by thermal rearrangement of O-benzyl substituted tropolone (Scheme S5). Heck reaction of styrene with 3-iodotropolone gave the styryl substituted tropolone (Scheme S6). Phenyl, 4-*tert*-butyl phenyl, naphthyl, 3-thienyl, and 2-thienyl substituted tropolones were prepared by following the general procedures reported by Ononye and co-workers (Scheme S7), and the substituted tropolones were converted to their methyl ethers by using dimethyl sulfate. In all the cases excellent yields of 5-substituted azulene derivatives **14**, **27**-**34** were obtained from the C-3 substituted 2-methoxytropone (Scheme 7). In all the synthesized azulene derivatives a highly deshielded singlet or a doublet with a very low coupling constant was observed in their $^1$H NMR spectra confirming that the substituents were at C-5 of azulene. Further confirmation was obtained by SCXRD studies in some cases. The C-7 substituted 2-methoxy tropone isomers remained inert to the reaction conditions as observed in the allyl-substituted isomer.

## Conclusions

In summary, we have explored anomalous reactivity of 3- and 7-substituted 2-methoxytropones towards azulene synthesis. The position of the substituents on the 2-methoxytropone dictates the mechanism and hence the product formation. The initial study on allyl substituted 2-methoxy tropone indicates unexpected reactivity difference of the regioisomers. Unsubstituted 2-methoxytropone forms azulene by the attack of the nucleophile at C-2 as the primary step, whereas the presence of a substituent on the carbon adjacent to methoxy group facilitates the attack of the nucleophile at C-7 and leads to the formation of steric guided 5-substituted azulenes. We note that the regioselective modifications of the seven- membered ring of azulenes and tropones are challenging due to the subtle reactivity difference among the various positions. Based on the study on allyl substituted 2-methoxytropone and subsequent DFT calculation, we have devised the synthetic strategy to obtain 5-substituted azulenes regioselectively. Thus, the modification of the precursor tropolone as described here provides easy access to the otherwise difficult to synthesize




**Scheme 7.** Scope of steric guided synthesis of 5-substituted azulenes

5-substituted azulenes where the substituents vary from alkyl, vinyl, aryl to heteroaryl. The multifunctional five-membered ring further broadens the scope of the methodology for the synthesis of 5-substituted azulene derivatives.

## Experimental Section

Detailed experimental procedure for the synthesis of all precursors and the azulene derivatives is given in the supporting information. The references for the compounds reported elsewhere are also included in supporting information.

## Acknowledgements

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**Keywords:** methoxytropone • multifunctional azulene • regioselective • nucleophilic • ipso

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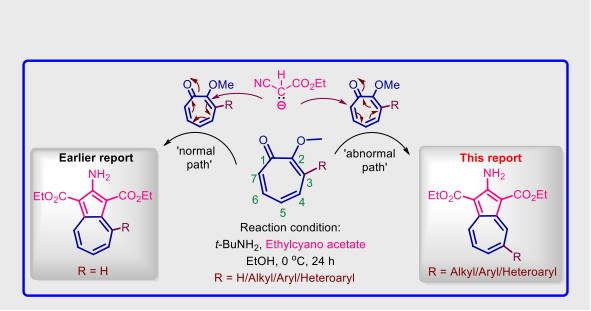


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**Abnormal Nucleophilic Substitution on Methoxytropone Derivatives: Steric Strategy to Synthesize 5-Substituted Azulenes**

Abnormal nucleophilic attack on the 3-substituted 2-methoxytropones, rather than the expected normal nucleophilic attack, leads to a new steric strategy for the synthesis of 5-substituted multifunctional azulenes.