

## Synthesis of azulenic compounds with a homo- or hetero-atomic double bond at position 1

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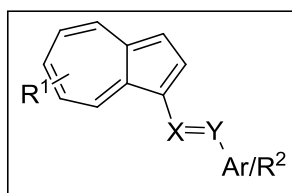
Received 11-17-2017

Accepted 01-21-2018

Published on line 06-09-2018

### Abstract

This work reviews the synthetic routes for the generation of 1-vinylazulenes, azulen-1-yl diazenes and azulen-1-yl imines. The wide range of substituents at the studied double bonds involves varied synthetic routes and a great number of exemplified compounds.



X = Y = CH      X = Y = N  
X = CH; Y = N    X = N; Y = CH  
Ar = aryl or heteroaryl; R<sup>2</sup> = alkyl  
R<sup>1</sup> = H, 4,6,8-Me<sub>3</sub>, 3,8-Me<sub>2</sub>-5-*i*Pr

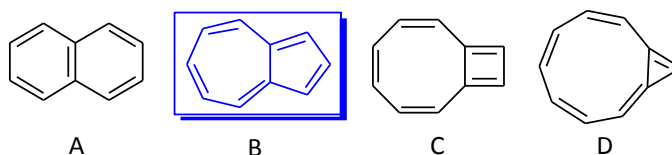
**Keywords:** 1-vinylazulenes, azulen-1-yl diazenes, azulen-1-yl imines

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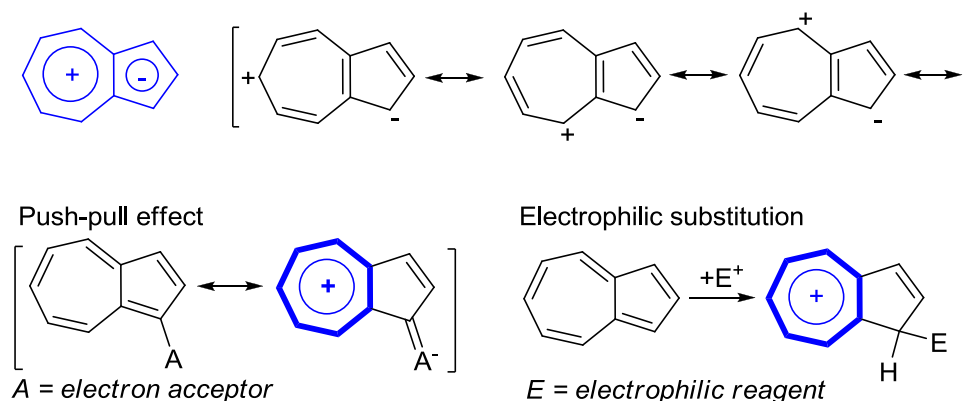
## 1. Introduction

There are four possible bicyclodecapentaene isomers, as represented in Scheme 1. However, whereas the compounds with a naphthalene or azulene core, **A** and **B**, are well known and widely studied for both their scientific and technical importance, the structures **C** and **D** show only scientific interest.<sup>1-3</sup>



**Scheme 1.** Bicyclodecapentaenes.

The benzenoid structure of naphthalene, with its alternating distribution of  $\pi$  electrons over the two rings, contrasts against the non-alternant aromatic azulene where one  $\pi$  electron from the seven-membered ring moves into the five-membered ring. This provides a tropylium aromatic like electron system for the first ring and a cyclopentadienyl anion for the second (Scheme 2). The significant difference between the structures **A** and **B** is reflected in their physicochemical properties starting with the presence of a remarkable dipole moment for azulene ( $\mu \approx 1$  Debye). The azulenic  $\pi$  electron system is, also, easily polarizable, giving the azulen-1-yl group a strong electron donating character, as in the push-pull systems (Scheme 2). At the same time, as implied in Scheme 2, the increased negative charge at C-1 (or C-3) confers on azulenes a good nucleophilic capacity and the intermediate in the electrophilic substitution is stabilized as a tropylium system, facilitating the reaction.



**Scheme 2.** The electronic system of azulene, its electron donating effect and influence on electrophilic substitution.

Insertion of a double bond C=C, N=N or C=N between the azulen-1-yl group and moieties with suitable  $\pi$ -electron systems extends the conjugation of the  $\pi$  electron system. Some compounds with a C=C bond between the azulen-1-yl moiety and an electron acceptor exhibit high hyperpolarizability, offering candidates for NLO systems or to work as building blocks for other molecules with potential technical application.<sup>4-8</sup> The insertion of an azo group, as in the azulen-1-yl diazenes, affords in such products valuable dyeing properties, working as dichroic dyes used in LCD panels,<sup>9</sup> or as chromophores with NLO properties.<sup>10,11</sup> The possible use of azulene compounds as conducting polymers in active battery electrodes, electrochromic displays, electrocatalysts, *etc.*, prompted the study of the electrochemical behavior of a large number of azulenylium diazenes,<sup>12-16</sup> as well as the electrochemical synthesis of azo-azulene films.<sup>17</sup>

Therefore, a review on the routes for the synthesis of the compounds containing azulenes with a double bond in the 1-position, namely, 1-vinylazulenes, (azulen-1-yl)diazenes, and the corresponding azomethines (Schiff bases), seemed to be of interest both in terms of scientific concern and technical utility.

## 2. 1-Vinylazulenes

### 2.1. Introduction

The compounds reviewed in this section contain a C=C bond substituted with one or two azulen-1-yl moieties and hydrogen or other substituents at the ends of the double bond; however, products with two conjugated carbon-carbon double bonds are also considered.

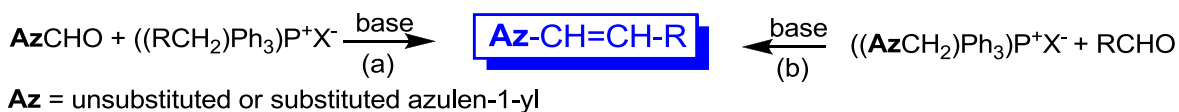
1-Vinylazulenes without any other substituent at the double bond exhibit low oxidation potentials, therefore they are particularly sensitive to air and polymerize quickly.<sup>18,19</sup> When the position 2 of the vinyl bond is substituted by alkyl, aryl or electron withdrawing groups the compounds are somewhat more stable. The isomers of vinylazulene with the C=C bond in another azulene ring position are also quite stable compounds.<sup>20</sup>

Despite the fact that several routes to the synthesis of vinylazulenes have already been summarized in the Houben-Weyl Encyclopedia,<sup>21</sup> the brevity of the reviewed information and the year of its publication (1985) encouraged us to resume and update the routes used for the synthesis of azulenes with C=C double bond in the 1- or 1,3-positions.

## 2.2. Wittig reaction

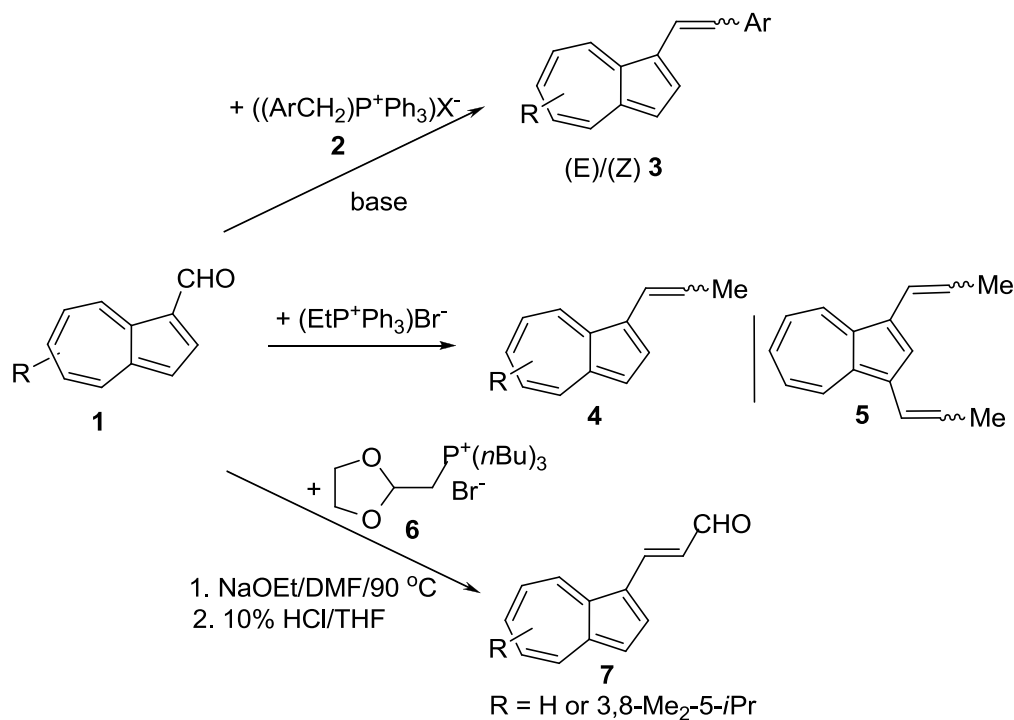
The Wittig condensation occurs between carbonyl compounds and phosphonium salts in the presence of strong bases. Thus, the first attempt to produce the parent 1-vinylazulene started from azulene-1-carbaldehyde and methyltriphenylphosphonium bromide in the presence of *n*-BuLi in anhydrous ether.<sup>19</sup> The unstable oil obtained was not fully characterized; only the IR spectrum of the product and elemental analysis of the trinitrobenzene complex were reported as proof of the structure. An unstable oil was also generated when guaiazulene-3-carbaldehyde reacted with methylmagnesium iodide followed by dehydration of the intermediate alcohol by gentle heating.<sup>18</sup>

There are two options to obtain azulenes with C=C bond in position 1 by Wittig condensation, starting from azulene-1-carbaldehydes or from the phosphonium salt of azulene-1-ylmethyl moiety (route (a) or (b) in Scheme 3). Generally, these routes are suitable for building a symmetrically as well as an unsymmetrically substituted C=C bond with one or even two azulenyl moieties.



**Scheme 3.** Wittig synthesis of 1-vinylazulene.

The lower electrophilic character of a carbonyl group at the 1-position of azulene than that of other aromatic aldehydes prevents reactions such as Cannizzaro or benzoin condensations. However, the Wittig reaction of azulene-1-carbaldehydes occurs smoothly (route a). In addition, these carbonyl derivatives are obtained easily and are among the most stable azulene compounds. Thus, aldehydes **1** react in good yield with benzylphosphonium salts, **2**, to afford a mixture of (*Z*)/(*E*)-1-styrylazulenes, **3** (Scheme 4 and Table 1), regardless of the base or solvent used (*n*-BuLi/ethyl ether,<sup>19</sup> EtONa/EtOH<sup>22</sup> or *t*-BuOK/toluene).<sup>19</sup> It should be emphasized that the phosphonium salt **2** with Ar = MeOC<sub>6</sub>H<sub>4</sub>(*p*) represents also a good alkylating agent for azulene, and, together with the styryl derivative, azulenes substituted in 1(3)-position(s) with ArCH<sub>2</sub> groups were generated as side products (Table 1).



**Scheme 4.** Wittig reactions with azulene-1-carbaldehydes.

**Table 1.** Synthesis of compounds **3** by Wittig reactions with azulene-1-carbaldehydes **1** (Scheme 4)

R	Ar	Base/solvent	Yield (%)	(E)/(Z)	Ref.
H	Ph	<i>n</i> BuLi/EtOEt <sup>a</sup>	74	69/31	19
4,6,8-Me <sub>3</sub>	Ph	EtONa/EtOH <sup>a</sup>	85	70/30	22
	MeOC <sub>6</sub> H <sub>4</sub> ( <i>p</i> )		60 <sup>c</sup>	100/0	
	ClC <sub>6</sub> H <sub>4</sub> ( <i>p</i> )		60 <sup>d</sup>	100/0	
3-Me-7- <i>i</i> Pr	Ph		90	60/40	
3,8-Me <sub>2</sub> -5- <i>i</i> Pr	Ph		90	55/45	
	Me <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> ( <i>p</i> )	EtONa/EtOH <sup>a</sup>	12	100/0	24
	Furan-2-yl	EtONa/EtOH <sup>a</sup>	53	100/0	23
	Thien-2-yl		36	100/0	
	Furan-3-yl		32	100/0	
	Thien-3-yl		46	100/0	
H	O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> ( <i>p</i> )	<i>t</i> BuOK/toluene <sup>b</sup>	92	78/22	9
6-MeO	O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> ( <i>p</i> )		90	82/18	

<sup>a</sup> X = Cl. <sup>b</sup> X = Br. <sup>c</sup> The reaction mixture also contains 1-(4-methoxybenzyl)-4,6,8-trimethylazulene (6.5%) and 1-(4-methoxybenzyl)-[(*E*)-4-methoxystyryl]-4,6,8-trimethylazulene (11%).

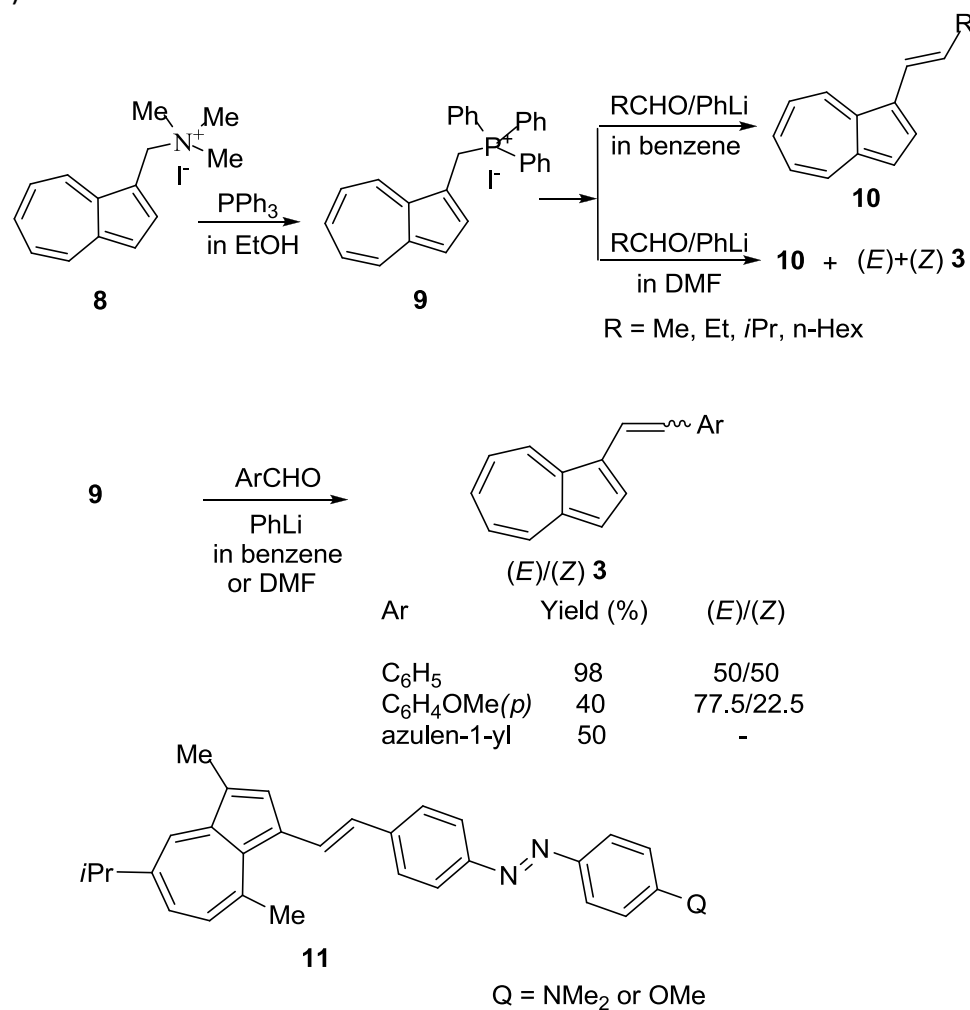
<sup>d</sup> Besides the attempted product, from the reaction mixture 30% of starting aldehyde was recovered together with 7% 4,6,8-trimethylazulene-2-carbaldehyde.

Several phosphonium salts **2** with heteroaromatic Ar were also condensed in moderate to good yields with guaiazulene-3-carbaldehyde (Table 1), affording alkenes only as (*E*)-isomers.<sup>23</sup>

1-Vinylazulenes with an alkyl group in position 2 of the C=C bond were prepared in good yields by Wittig reaction in the presence of very strong bases. However, the products exhibited low stability. For example, guaiazulene-3-carbaldehyde reacts with ethyltriphenylphosphonium bromide in the presence of *n*-BuLi in THF giving 1-(prop-1-enyl)azulene in 64% yield.<sup>25</sup> Such compounds proved to be good radical scavengers, more effective than  $\alpha$ -tocopherol. Later, were reported the results of condensation between azulene-1-carbaldehyde or azulene-1,3-dicarbaldehyde and ethyltriphenylphosphonium bromide, as shown in Scheme 4, however, without information on the yields and with incomplete product characterization.<sup>26</sup> The obtained mixture of geometric isomers of 1,3-di(prop-1-enyl)azulene (**5**) was used subsequently in the olefin metathesis polycondensation to polymers with potential semiconducting properties.

It is interesting to note the procedure followed for the preparation of (azulen-1-yl)acrolein, **7**, by condensation of 1-azulenecarbaldehydes, **1** where R = H, 3,8-Me<sub>2</sub>-5-*i*Pr with [(1,3-dioxolan-2-yl)methyl]-tri(*n*-butyl)phosphonium bromide, **6** (Scheme 4).<sup>27</sup>

The alternative Wittig reaction pathway, postulated in Scheme 3 and detailed in Scheme 5, starts from (azulen-1-ylmethyl)triphenylphosphonium iodide, **9**, obtained from the corresponding trimethylammonium salt, **8**. This salt reacts with aldehydes in the presence of very strong bases as PhLi or *n*-BuLi (the results are shown in Table 2).



**Scheme 5.** Wittig reactions of azulenyl phosphonium salts with alkyl and aryl carbaldehydes.

The reaction products depend on the starting aldehyde and the selected solvent. Thus, the condensation of **9** with aliphatic aldehydes in benzene in the presence of PhLi<sup>28</sup> affords only the isomer (*E*) of alkenes **10**, slightly stable in the presence of air. By working in DMF, the reactions of **9** is less straightforward because PhLi partially reacts with DMF giving benzaldehyde which, in turn, condenses with the phosphonium salt. Thus, alongside the attempted products **10**, a mixture (*Z/E*) of 1-styrylazulenes **3** was generated. In spite of the lower selectivity, the yields in compounds **10** are higher in this solvent, which favors the dissolution of the intermediate ylide salt.

**Table 2.** Wittig reaction of phosphonium iodide **9** with aldehydes RCHO

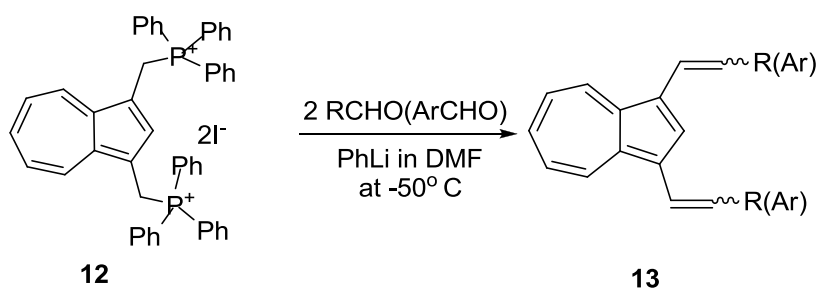
RCHO R	In benzene (%)		In DMF (%)	
	<b>10</b> <sup>a</sup>	<b>10</b>	( <i>Z</i> )- <b>3</b> (Ar = Ph)	( <i>E</i> )- <b>3</b> (Ar = Ph)
Me	50 (68)	-	-	-
Et	25 (37)	59	12	11
iPr	53 (69)	53	30	16
n-Hex	29 (73)	37	23	16

<sup>a</sup> In brackets are the yields of **10** taking in account the recovery of salt **9**

While aliphatic aldehydes react stereoselectively with salt **9** providing (*E*) isomer, a mixture (*Z/E*) resulted starting from benzaldehydes or 1-azulenecarbaldehyde (Scheme 5).<sup>28</sup>

The interesting compounds **11**, possessing simultaneous azo and vinyl bonds (Scheme 5), were obtained from (*E*)-4-(4-methoxyphenyldiazenyl)benzaldehyde or (*E*)-4-[4-(dimethylamino)phenyldiazenyl]benzaldehyde and (3-guaiazulenylmethyl)triphenylphosphonium bromide in ethanol in the presence of sodium ethoxide at 25 °C for 24 h under argon.<sup>29</sup>

The conditions for the condensation of 1,3-bis(triphenylphosphoniummethyl)azulene, **12**, with aliphatic or aromatic aldehydes (Scheme 6 and Table 3) resemble those of monosubstituted azulene ylides and yielded 1,3-divinylazulenes, **13**, as a mixture of geometric isomers.<sup>30</sup>



**Scheme 6.** Preparation of 1,3-divinylazulenes using the Wittig route.

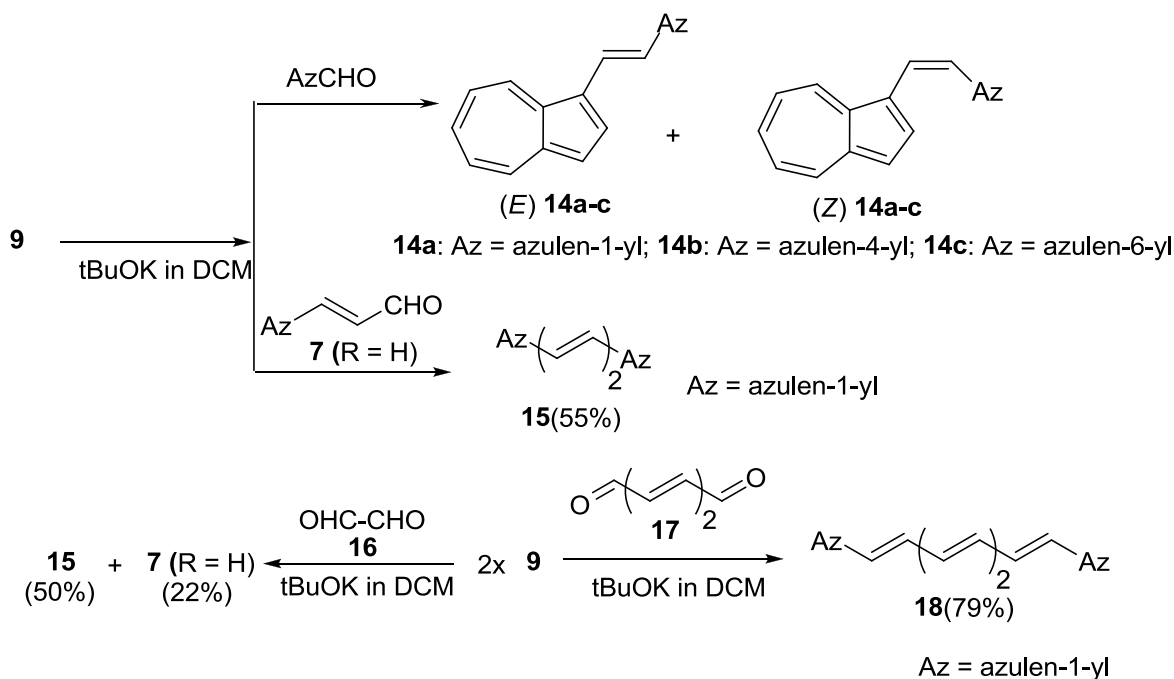
Reactions between the phosphonium salt **9** and acetone or benzophenone in benzene produce the expected condensation products, 1-(2-methylprop-1-enyl)azulene and 1-(2,2-diphenylvinyl)azulene, but in lower yields than those observed with aldehydes. Among the attempted products, when condensation takes place in DMF the reaction also affords styrylazulene, (*Z* and *E*)-**3**Ph, formed through the intermediacy of benzaldehyde generated from PhLi and DMF.<sup>28</sup>

**Table 3.** Synthesis of compound **13** by Wittig reaction of bis-phosphonium salt **12** with aldehydes RCHO or ArCHO

R or Ar	<b>13</b> Yield (%)			
	-	(Z)/(Z) <sup>a</sup>	(Z)/(E) <sup>a</sup>	(E)/(E) <sup>a</sup>
H	65 <sup>b</sup>	-	-	-
C <sub>2</sub> H <sub>5</sub>	15 <sup>c</sup>	-	-	-
C <sub>6</sub> H <sub>5</sub>	-	29	57	12
C <sub>6</sub> H <sub>4</sub> OCH <sub>3</sub> ( <i>p</i> )	-	21	36	20
C <sub>6</sub> H <sub>4</sub> Br( <i>m</i> )	-	21	66.4	8.8
C <sub>6</sub> H <sub>4</sub> I( <i>m</i> )	-	28	56.5	6.3

<sup>a</sup> The structures were assigned on the basis of their absorption maxima and the shielding of protons in the 2-position of azulene. <sup>b</sup> As amorphous solid, mp 60-105 °C (dec); M<sup>+</sup> 180.0926 (calcd. for C<sub>14</sub>H<sub>12</sub> 180.0938). <sup>c</sup> As a mixture with 1-butenyl-3-styrylazulenes

Particular attention has been paid in recent decades to the preparation and properties of the ethenes and polyenes substituted with two azulen-1-yl moieties. Interest is related to the possibility that these compounds may work as a metal due to their very low oxidation potentials. An attempt to produce 1,2-di(azulen-1-yl)ethene by Currie,<sup>30</sup> stimulated Hünig and Ort to undertake a careful study of these classes of compound.<sup>31</sup> (Azulen-1-ylmethyl)triphenylphosphonium iodides were treated with azulencarbonyl aldehydes or their vinylogs, both ylides and carbonyl compounds having substituents at different positions in the azulene moiety (Scheme 7). This results in a large number of products in good yields as mixtures of geometrical isomers. Here we deal only with the preparative route starting from the phosphonium salt **9** containing the azulen-1-yl moiety.

**Scheme 7.** Ethenes and polyenes with azulen-1-yl moieties at the termini.



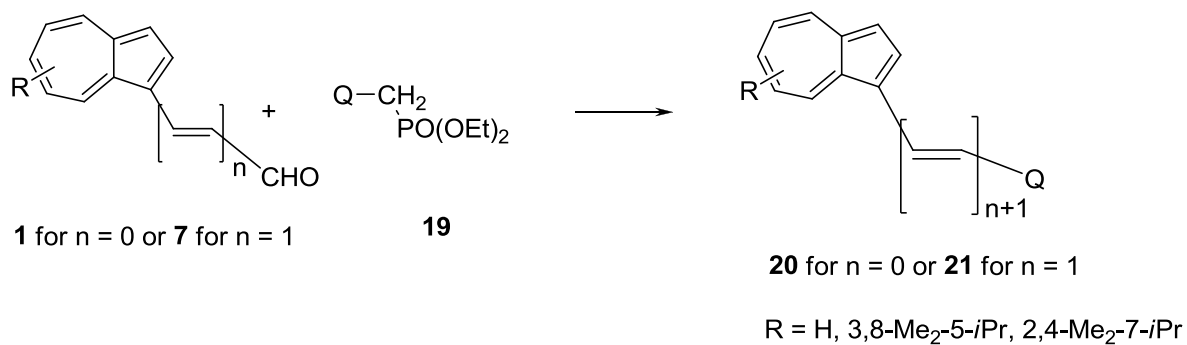
Condensations occur in the presence of *t*-BuOK, more easily to handle than the lithium derivatives used by Currie in the condensation of azulene ylides with azulene carbaldehydes. Working at -78 °C, mixtures of geometric isomers are obtained in good yields (Table 4 shows the condensation of phosphonium salt **9** with several isomers of azulene-1-carbaldehyde). These mixtures can be converted into the more stable (*E*)-isomer under the influence of trifluoroacetic acid or by photo-irradiation.

**Table 4.** Wittig reaction of phosphonium salt **9** with different azulene-carbaldehydes

Product	Yield (%)	
	( <i>E</i> )	( <i>Z</i> )
<b>14a</b>	74	4
<b>14b</b>	23	33
<b>14c</b>	39	26

Diazulenyl substituted polyene are obtained starting from the unsaturated aldehyde as **7** where R = H and the phosphonium salt **9**. Reaction between dialdehyde **16** or **17** and two equivalents of salt **9** (Scheme 7) represents another way to access such compounds. The last procedure affords only symmetric products whereas the route described above can be used also for the asymmetric compounds. The products result as a mixture of geometric isomers. The increase of number of the double bonds between the azulene moieties lowers the stability of *all-Z* isomers, which are isomerized to *all-E* isomers even in daylight.

## 2.3. The reaction of azulene-1-carbaldehydes with phosphonate carbanions



Compound	R	Q	Yield (%)	Ref.
<b>20</b>	H	-C <sub>6</sub> H <sub>4</sub> X; X = H or Me( <i>p</i> ), Cl( <i>p</i> ), Br( <i>p</i> ), NO <sub>2</sub> ( <i>p</i> ), CN( <i>p</i> ) Br( <i>m</i> ), NO <sub>2</sub> ( <i>m</i> ), CN( <i>m</i> ) NO <sub>2</sub> ( <i>o</i> )	2 - 38	32
<b>20</b>	2,4-Me <sub>2</sub> -7- <i>i</i> Pr	-C <sub>6</sub> H <sub>4</sub> X; X = H or Cl( <i>p</i> ), Br( <i>p</i> ), NO <sub>2</sub> ( <i>p</i> ), CN( <i>p</i> ) Br( <i>m</i> ), NO <sub>2</sub> ( <i>m</i> ), CN( <i>m</i> ) NO <sub>2</sub> ( <i>o</i> )	5 - 26	32
<b>20</b>	3,8-Me <sub>2</sub> -5- <i>i</i> Pr	-C <sub>6</sub> H <sub>4</sub> CN( <i>p</i> )	20.5	32
<b>20</b>	3,8-Me <sub>2</sub> -5- <i>i</i> Pr	-C <sub>6</sub> H <sub>4</sub> CN( <i>p</i> )	-	33
<b>20</b>	3,8-Me <sub>2</sub> -5- <i>i</i> Pr	-C <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> Et( <i>p</i> )	49	33
<b>20</b>	H	-CN	89.9	33
<b>21</b>	H		-	33
<b>21</b>	H		58	33
<b>21</b>	3,8-Me <sub>2</sub> -5- <i>i</i> Pr	-CN	56	33
<b>21</b>	3,8-Me <sub>2</sub> -5- <i>i</i> Pr		-	33
<b>21</b>	3,8-Me <sub>2</sub> -5- <i>i</i> Pr		-	33
<b>21</b>	3,8-Me <sub>2</sub> -5- <i>i</i> Pr		31	33

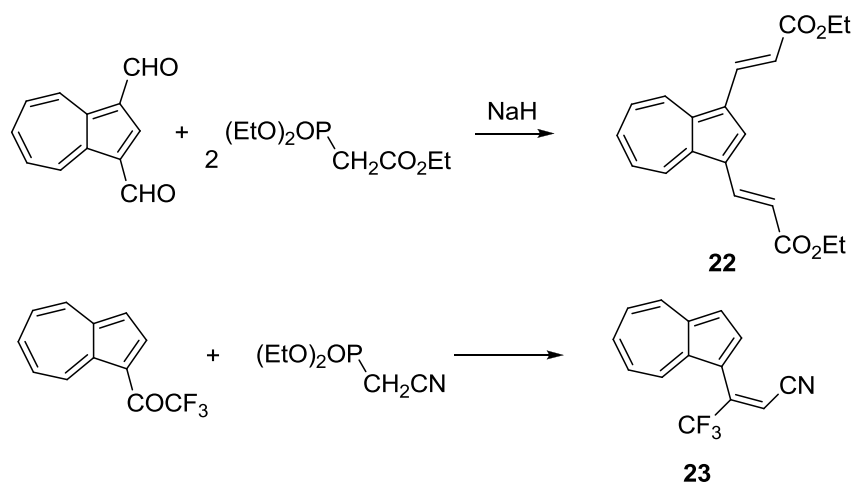
Scheme 8. Reaction of azulene-1-carbaldehydes with the phosphonate carbanions derived from **19**.

The reaction of phosphonate carbanions with the carbonylic reagents, the Horner–Wadsworth–Emmons reaction, is widely used for the preparation of C=C double bond. The phosphonate carbanions have the advantage to be at the same time more nucleophilic and less basic than the carbanions generated from phosphonium salts used in the Wittig reaction.

Scholz *et al.*<sup>32</sup> have prepared several 1-styrylazulenes by reacting 1-azulene-carbaldehydes, **1**, or their vinylogous derivatives **7**, with carbanions obtained from phosphonates **19** (Scheme 8) in the presence of sodium methoxide. Except for benzyl compounds substituted with a cyano group, the condensation products result in very low yields.

Later, Currie *et al.*<sup>28</sup> obtained diethyl azulene-1,3-diacrylate, **22**, from azulene-1,3-dicarbaldehyde and triethyl phosphonoacetate in the presence of sodium hydride (Scheme 9, yield 56%).

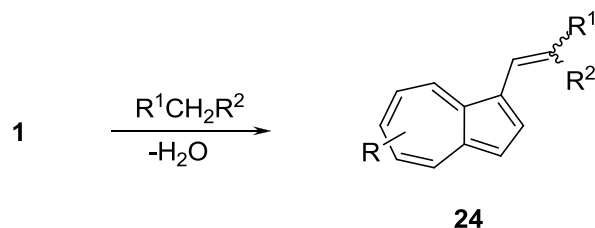
More recently, Asato and Liu found the anti-neoplastic and anti-dermatopathic activity of some azulenic retinoid derivatives with vinylogous structure to products **21** described in a US patent.<sup>33</sup> The access route to these compounds starts from azulene-1-carbaldehyde and guaiazulene-3-carbaldehyde, as well as their derivatives with C=C bond between azulene and carbonyl group, which were condensed in the Horner–Wadsworth–Emmons reaction with phosphonates containing unsaturated organic moieties or even benzyl groups (Scheme 9). The carbanion, generated at low temperature in the presence of butyllithium or lithium diisopropylamine in THF, reacts with aldehydes at room temperature. After work up, the products result as a mixture of (*E/Z*) isomers in which the isomers ratio depends on the structure of the starting compounds. By this route, the authors obtained some products described in Scheme 8. The second example in Scheme 9 starts from a ketone as carbonyl compound for the preparation of a trisubstituted ethylene, **23**. Unfortunately, the yields for several reactions are not reported in the patent.<sup>33</sup>



**Scheme 9.** 1,3-Divinyl and 1-vinyl substituted azulenes functionalized at the double bond.

## 2.4. Condensation between azulene-1-carbaldehydes or their corresponding Schiff bases and compounds with activated methyl or methylene groups

**2.4.1. Condensation of azulene-1-carbaldehydes.** Although azulene-1-carbaldehydes have a lower reactivity than the usual aromatic aldehydes, their easy synthesis and good stability have been strong arguments for further studies on their condensation with compounds with active methyl or methylene groups in base or acid catalysis. In Scheme 10 and Tables 5A and 5B several representative examples of such compounds belonging to different product classes are presented without claiming to be exhaustive.



**Scheme 10.** Condensation of azulene-1-carbaldehydes with compounds with activated methylene groups.

**Table 5A.** Reaction of azulene-1-carbaldehydes **1** with  $R^1CH_2R^2$

R	Compounds <b>24</b>		Yield (%)	Reaction conditions	Ref.
	$R^1$	$R^2$			
H	PhCO	H	76	NaOH; EtOH	34
4,6,8-Me <sub>3</sub>	PhCO	H	- <sup>a</sup>	KOH; EtOH	35
	NO <sub>2</sub>	H	56	Piperidine; EtOH	35
	COOMe	COOMe	66 <sup>b</sup>	Piperidine; EtOH	35
	COMe	COMe	51 <sup>c</sup>		36
	COOEt	COOEt	74 <sup>d</sup>		
	COOEt	CN	58	Piperidine; 60-65 °C	
	COOEt	COMe	56		
	H	COOEt	29 <sup>d</sup>		
H	C(O)SEt	C(O)SEt	37 <sup>e</sup>		
	CONH <sub>2</sub>	CONH <sub>2</sub>	76	Piperidine with water removal as azeotrope at 110 °C	
	CONH-nBu	CONH-nBu	75		
	CONH-2Py	CONH-2Py	68 <sup>f</sup>		

<sup>a</sup> The reported compound was not separated and was used *in situ* for other reaction.

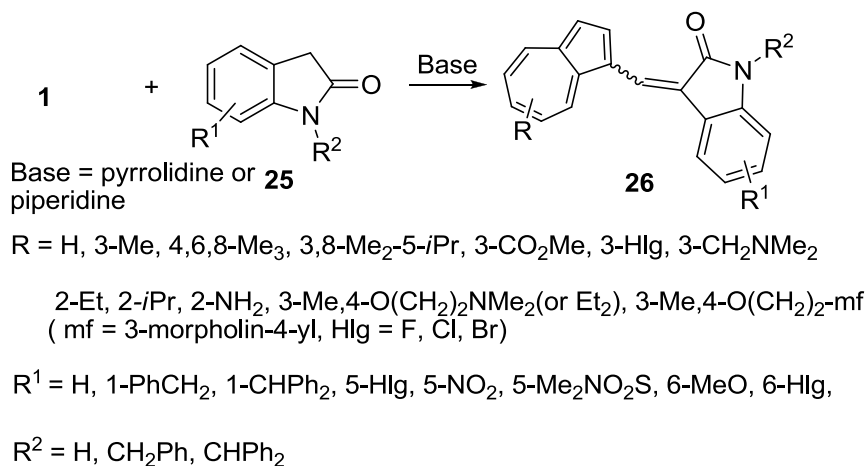
<sup>b</sup> Compound **24** where R = 4,6,8-Me<sub>3</sub>;  $R^1 = R^2 = CO_2Et$  was obtained in good yields starting from the sodium salt of malonic ester and an immonium salt generated from 4,6,8-trimethylazulene and phosphorus oxychloride in DMF.<sup>37</sup> <sup>c</sup> Recovered aldehyde 41%.

<sup>d</sup> A small amount of product generated by the CO<sub>2</sub>Et elimination was also obtained.

<sup>e</sup> Yield for the attempted product, elimination of C(O)SEt group occurred in 44% yield.

<sup>f</sup> Recovered aldehyde 20% (Py = pyridine).

The discovery that numerous condensation products between azulene-1-carboxaldehydes and indolin-2-ones **25** are effective in cancer therapy by inhibiting the activity of protein kinases or phosphatases stimulated research into their synthesis and the obtained results are the subject of a patent.<sup>39</sup> The condensation yields are good and the compounds geometry depends on both the starting reagent and the reaction conditions (the condensation agent was pyrrolidine and the solvent ethanol). Several significances of the claimed products are shown in Scheme 11.

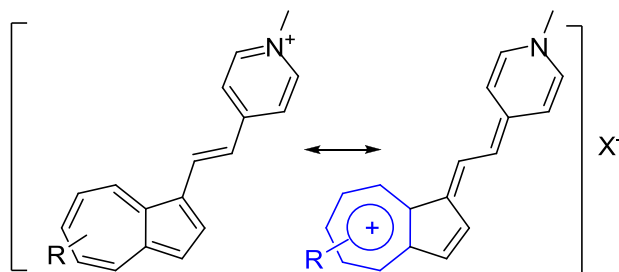


**Scheme 11.** Condensation between azulene-1-carbaldehydes and indolin-2-ones.

**Table 5B.** Reaction of azulene-1-carbaldehydes, **1**, with cyclic derivatives R<sup>1</sup>CH<sub>2</sub>R<sup>2</sup>

Compounds <b>24</b>		Yield (%)	Reaction conditions	Ref.
R	R <sup>1</sup> + R <sup>2</sup>			
H		93		
4,6,8-Me <sub>3</sub>	-C(O)-O-C(CH <sub>3</sub> ) <sub>2</sub> -O-C(O)-	15	One day at room temperature	38
3,8-Me <sub>2</sub> -5- <i>i</i> Pr		82		
3-COOH		52		
H	-C(O)NHC(O)NHC(O)-	95	Pyridine/EtOH at 60 °C	7
4,6,8-Me <sub>3</sub>		95		
3,8-Me <sub>2</sub> -5- <i>i</i> Pr		80		
H	-C(O)NHC(S)NHC(O)-	69	HCl/EtOH+H <sub>2</sub> O at 60 °C	7
4,6,8-Me <sub>3</sub>		13		
3,8-Me <sub>2</sub> -5- <i>i</i> Pr		25		
H	-SC(S)NHC(O)-	34	AcONa in AcOH 4 h at reflux	7
4,6,8-Me <sub>3</sub>		34		
3,8-Me <sub>2</sub> -5- <i>i</i> Pr		56		
H	-NHC(S)NHC(O)-	57		
4,6,8-Me <sub>3</sub>		56		
3,8-Me <sub>2</sub> -5- <i>i</i> Pr		59		
H	-CH=CH-CH=CH-	87	EtONa; EtOH	35
H	-C(Me)=N-O-C(O)-	70	EtOH (24 hours)	36

The possibility of the azulene-1-yl moieties to participate as electron donors in the push-pull systems, as exemplified in Scheme 12, stimulated the investigation of condensation between azulene-1-carbaldehydes and a large number of aromatic heterocyclic salts. In the cation thus formed the positively charged heterocycle acts as an electron acceptor.



**Scheme 12.** Contribution of tropylium structure to the stabilization of pyridinium compounds.

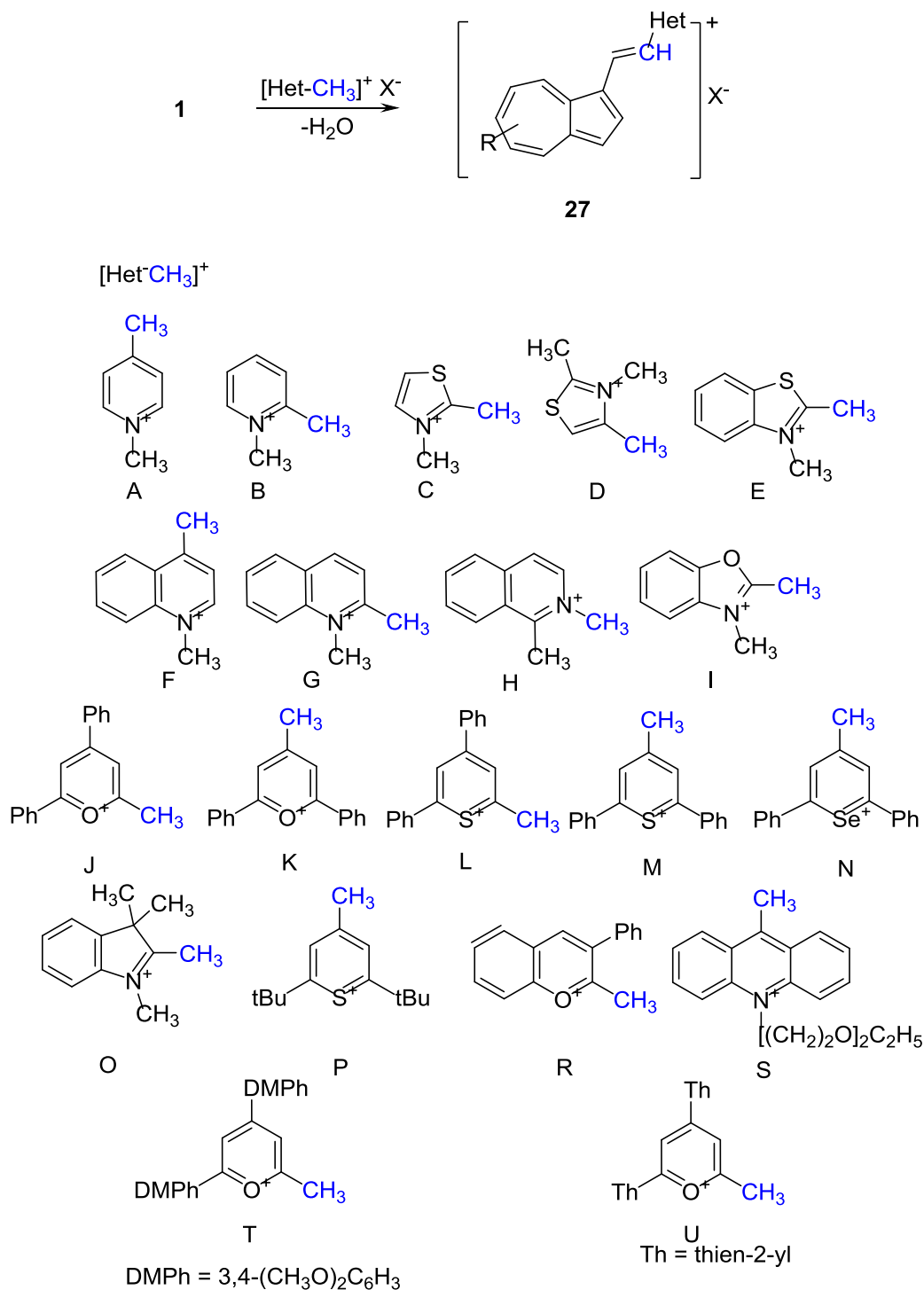
The methyl substituent in the starting salts,  $[\text{Het-CH}_3]^+\text{X}^-$ , when in a 2- or 4-position relative to the positively charged heteroatom, is strongly activated. Some of the salts with heterocycle cations that have been used are illustrated in Scheme 13. The reactions with aldehydes take place in basic, as well as in acidic, media. The condensations in basic medium occur under mild conditions and afford the products in good yields regardless of the azulene substituents (Exp. 1-9 in Table 6).<sup>40</sup>

**Table 6.** Reaction of azulene-1-carbaldehydes, **1**, and heterocyclic salts,  $[\text{HetCH}_3]^+\text{X}^-$  ( $\text{X}^-$  = perchlorate)

No	$[\text{Het-CH}_3]^+\text{a}$	Reaction conditions	Yield in compounds <b>27</b> (%)				Ref.
			R				
			H	3-Me	4,6,8-Me <sub>3</sub>	3,8-Me <sub>2</sub> -5- <i>i</i> Pr	
1	A	Piperidine in ethanol	56 <sup>b</sup>	54	75 <sup>b</sup>	77 <sup>b</sup>	40
2	B		78	44	43	60	
3	C		62	66	56	66	
4	D		55	66	74	-	
5	E		66	66	59	48	
6	F		50 <sup>b</sup>	70 <sup>b</sup>	43 <sup>b</sup>	36 <sup>b</sup>	
7	G		68	96	63	-	
8	H		44	35	-	-	
9	I		36	80	3	-	
10	J	AcOH	-	-	80	85.5	41
11	T	(reflux)	-	-	72.2	64.1	
12	U		-	-	60.3	88.6	
13	K	Ac <sub>2</sub> O	-	-	-	91	40
14	M	AcOH (reflux)	-	-	-	93	40

<sup>a</sup> see Scheme 13. <sup>b</sup>  $\text{X}^-$  = iodide

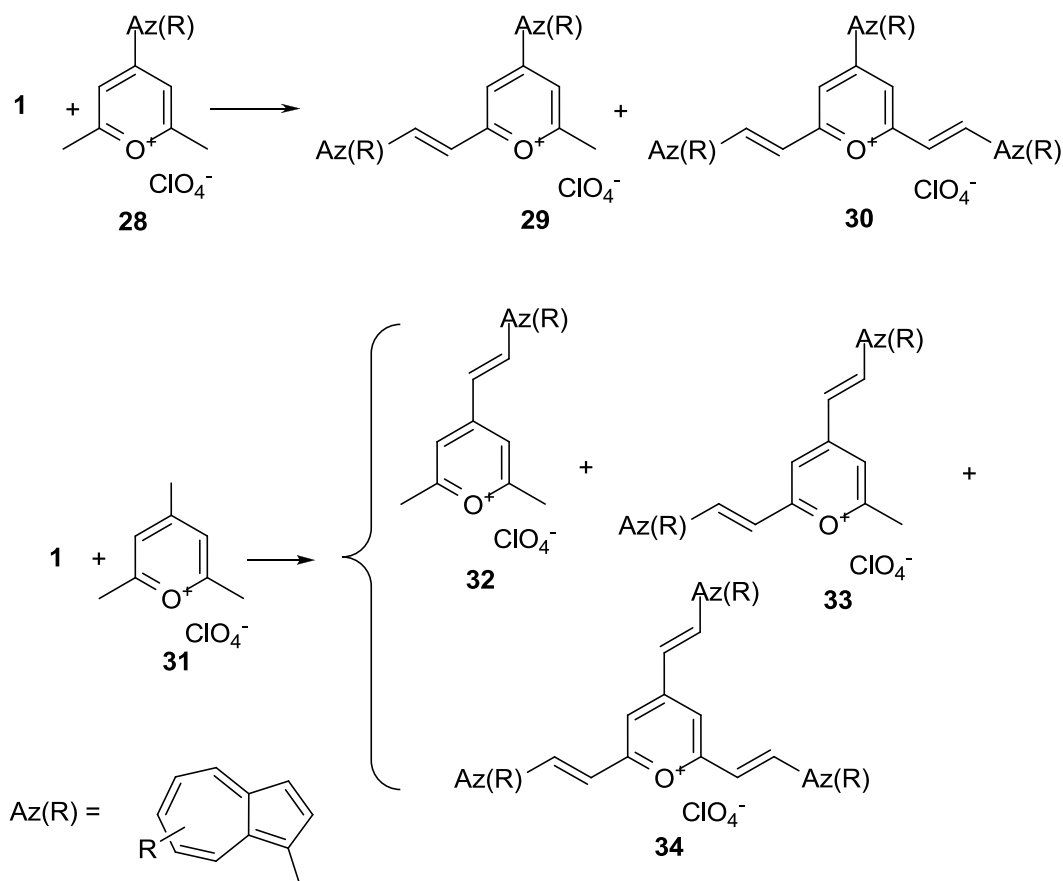
Dorofeenko *et al.*<sup>41</sup> studied the condensation in acidic medium (acetic acid) between azulene-1-carbaldehydes **1** and perchlorates of 2-methyl-pyranium (Exp. 10-12 in Table 6). Several azulenium salts **27** with Het = K-S (Scheme 13) are claimed as suitable for the generation of photoconductive film or as electrophotographic sensitive body. For such products, condensation was promoted also by acetic anhydride or hot acetic acid.<sup>42,43</sup> However, from the numerous compounds claimed in the patents only for the compounds with Het = K and M, the yield and elemental analysis were reported (Exp.13 and 14 in Table 6).



**Scheme 13.** Reaction between azulene-1-carbaldehydes and aromatic heterocyclic salts with a reactive methyl group.

The property of the azulene-1-yl group to accommodate a positive charge as tropylium cation (Scheme 12) encouraged efforts to build molecules where the positive charged heterocycle is suitably stabilized by two or three such groups. The envisaged difficulties for the preparation of the attractive 2,4,6-tri(azulene-1-yl)pyrylium salts led to the idea to insert C=C double bond(s) between the heterocycle and azulene moieties. Razus *et al.* investigated the synthesis of a large number of such compounds (Scheme 14).<sup>44</sup> The first attempts started from 4-(azulene-1-yl)-2,6-dimethylpyrylium perchlorate, **28**. Performing the condensation

with azulene-1-carbaldehydes in conventional conditions (acetic anhydride at high temperature) low yields are obtained; however, the yields significantly increase in microwave-assisted reactions (Table 7). Moreover, whereas conventional heating leads to a reaction mixture of both mono- and bis-condensation products, **29** and **30**, under microwave the bis-condensation product **30** was obtained exclusively and in good yields. There is little difference in yields and in product ratio starting from unsubstituted azulene-1-carbaldehyde or its 4,6,8-trimethyl derivative.



**Scheme 14.** Preparation of the pyrylium salts substituted with azulene-1-vinyl moieties.

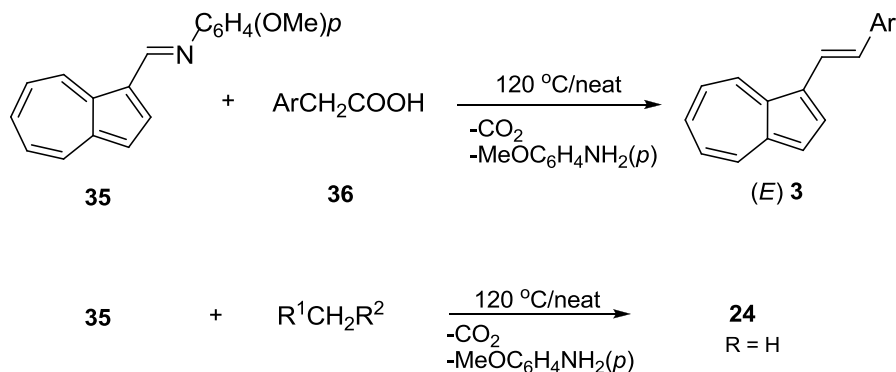
Another synthesis employs the water elimination between 2,4,6-trimethylpyrylium salt **31** and azulene-1-carbaldehydes in acetic anhydride medium.<sup>45,46</sup> While at high temperature the reaction mixture contained all three possible condensation products **32**, **33** and **34** (Scheme 14), the microwave assisted reaction generated selectively the fully condensed compound **34**.



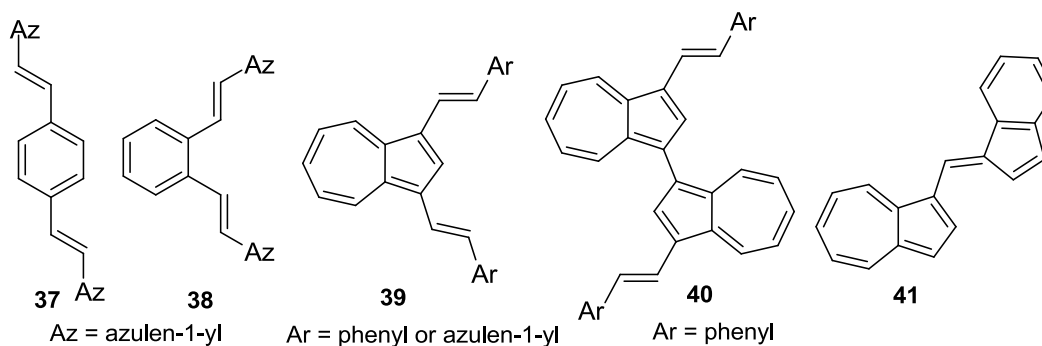
**Table 7.** Reaction of 4-(azulen-1-yl)-2,6-dimethylpyrylium and 2,4,6-trimethylpyrylium perchlorates, **28** and **31** with azulene-1-carbaldehydes

Starting salt	Reaction conditions	Compounds in mixture	R and yields (%)			Ref.
			H	2,4,8-Me <sub>3</sub>	3,8-Me <sub>2</sub> -5- <i>i</i> Pr	
<b>23</b>	100 °C	<b>29</b>	50	47	-	44
	10-15 min	<b>30</b>	traces	traces	-	
	Reflux	<b>29</b>	5-7	5-10	-	
	30 min	<b>30</b>	35-40	45-50	-	
	MW (1 min at 200 °C)	<b>29</b>	0	0	-	
		<b>30</b>	85	78	-	
<b>26</b>	100 °C	<b>32</b>	90-95	90-95	90-95	45,46
	10-15 min	<b>33 + 34</b>	0	0	0	
	160 °C	<b>32</b>	0	0	0	
	30 min	<b>33</b>	50-60	50-60	50-60	
		<b>34</b>	15-20	15-20	15-20	
	MW (1 min at 200 °C)	<b>32 + 33</b>	0	0	0	
	<b>34</b>	50	55	55-58		

**2.4.2. Condensation of Schiff bases.** The literature contains numerous examples of condensation between aromatic azomethines and compounds with active methyl or methylene groups in the molecule in order to build a carbon-carbon double bond. Generally, the reaction occurs in solution, in base or acid catalysis.<sup>47-49</sup> However, in many cases the reaction stops at the intermediate stage without amine elimination. Therefore, until now this route has somewhat rarely been used for the generation of a C=C bond.



The significance of R<sup>1</sup> and R<sup>2</sup> is shown in Table 9

**Scheme 15.** Use of azulenic Schiff bases in the achieving of vinylazulenes.

Whereas some azulene-1-carbaldehydes are liquid and their handling is often cumbersome, the very easy accessibility of azulenic Schiff bases spurred the investigation of this condensation for the generation of 2-substituted 1-(azulen-1-yl)ethenes. The research focused on the synthesis of such compounds with aryl as the second substituent at C=C bond as well as with other functions at this bond.<sup>50,51</sup>

The first reported pathway employed, together with azulenic Schiff base **35**, a large number of arylacetic acids, **36** (Scheme 15). The reaction occurs with very good results in the absence of any solvent or catalyst by melting together the two reagents. Because during the heating of the mixture, both CO<sub>2</sub> and amine are eliminated, the final processing was very simple and the proposed procedure occurs with reduced pollution and lower costs.

Substitution of 4-position of phenyl with an electron donating group, such as methoxy, increases the basicity of the Schiff bases **35**, promoting the ionization of arylacetic acids, while a strong withdrawing group, such as nitro, reduces its basicity. Therefore in the former case yields are improved and in the latter the reaction is inhibited. The nature of Ar moiety in arylacetic acids was widely varied and the results are shown in Table 8.

**Table 8.** Condensation of Schiff base **35** with arylacetic acids **36**; yields<sup>a</sup> and recovered Schiff base (**35**)

	X in Ar = C <sub>6</sub> H <sub>4</sub> X			
	H	<i>p</i> -NO <sub>2</sub>	<i>o</i> -NO <sub>2</sub>	<i>p</i> -Cl
Yields(%)	95	95	90	94
Rec. <b>35</b>	18	3	17	13

	Ar					
	1-Nf <sup>b</sup>	2-Nf <sup>b</sup>	2-Th <sup>c</sup>	3-Th <sup>c</sup>	4-Py <sup>d</sup>	1-Az <sup>e</sup>
Yields(%)	76	86	98	90	82	81
Rec. <b>35</b>	32	15	9	20	26	40

<sup>a</sup> The yields were calculated taking into account the unreacted **35**.

<sup>b</sup> Nf = Naphthyl. <sup>c</sup> Th = Thienyl. <sup>d</sup> Py = Pyridyl. <sup>e</sup> Az = azulenyl.

Following the same route, but starting from aromatic dicarboxylic acids, products **37** – **39** were obtained in good yields. Sometimes, together with compounds **39** and **40**, the products of monocondensation are separated from the reaction mixture.

**Table 9.** Condensation of Schiff base **35** with compounds R<sup>1</sup>CH<sub>2</sub>R<sup>2</sup>; yields and recovered Schiff base (**35**)

Starting R <sup>1</sup> CH <sub>2</sub> R <sup>2</sup>		Products <b>24</b> (R = H)		Rec. <b>30</b> (%)	Yields (%)
R <sup>1</sup>	R <sup>2</sup>	R <sup>1</sup>	R <sup>2</sup>		
COOH	COOH	COOH	H	0	47 <sup>a</sup>
COOH	CN	COOH	CN	0	64 <sup>b</sup>
CN	CN	CN	CN	0	100
CH <sub>3</sub> CO	COOEt	CH <sub>3</sub> CO	COOEt	24	57 <sup>c</sup>
CH <sub>3</sub> CO	CH <sub>3</sub> CO	CH <sub>3</sub> CO	CH <sub>3</sub> CO	77	32

<sup>a</sup> First eluted fraction contained a great amount of material which polymerized before the analysis; perhaps, 1-vinylazulene generated by complete decarboxylation polymerizes spontaneously. <sup>b</sup> Both **24** and the decarboxylated nitrile were obtained as mixtures of *E* and *Z* isomers. <sup>c</sup> A mixture of *E* and *Z* isomers.

The reaction of azulenic Schiff bases **35** with compounds containing active methylene  $R^1CH_2R^2$ , described in Scheme 15 and Table 9, provides products in good yields and represents an alternative synthetic route for that described in Scheme 10 and Table 5A. When one of the substituents  $R^1$  or  $R^2$  was the carboxyl group, the reaction occurs with decarboxylation.

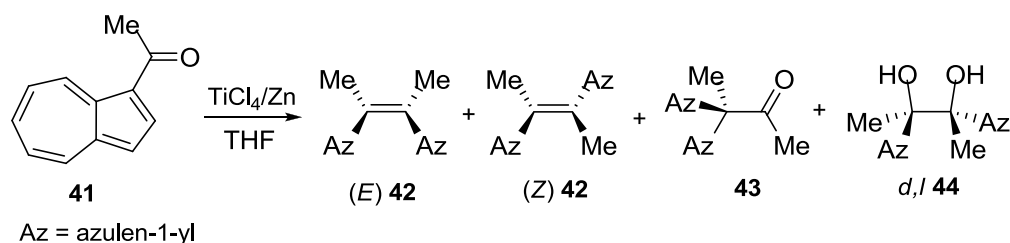
It is interesting to note that the acidity of the methylene group of the hydrocarbon indene is high enough to react with the azulenic Schiff base, affording, after a long condensation time, the product **41** (Scheme 15).

## 2.5. McMurry reductive condensation

In the 1970s several research teams simultaneously found that two carbonyl derivatives may react in a reductive coupling under action of low-valent titanium (e.g. obtained from  $TiCl_3/Mg$ ,  $TiCl_4/Zn$ ,  $TiCl_3/LiAlH_4$ ) to generate a C=C double bond.<sup>52,53</sup> Unlike pinacol condensation, which usually occurs at room temperature, the reductive coupling, generally called the McMurry reaction, requires higher temperatures. Nevertheless, most of the reductive condensations are accompanied by pinacolization. Moreover, the proposed reaction mechanism for McMurry condensation involves as intermediate titanapinacolate.<sup>53</sup> Numerous synthetic applications have attracted a great interest in this reaction and, therefore, an extensively investigation in this research field. Thus, to obtain low-valent titanium from Ti(IV) or Ti(III) species, various reducing reagents were used and different reaction conditions were tested. The addition of pyridine or another auxiliary was tried in order to change the nature and the ratio of the reaction products.<sup>54</sup> The activation of reductive coupling was sometimes successful in the microwave (MW) field.<sup>55</sup> Unfortunately, McMurry coupling can be used only for the preparation of symmetrical products because mixtures of ketones give all possible condensation products. Exceptionally, and under special conditions, this route was used to get unsymmetrically substituted alkenes.

The peculiarity of the azulen-1-yl moiety stimulated research on the McMurry reaction of azulenes substituted with a carbonyl function mainly at the 1-position. Hünig and Ort<sup>31</sup> reported the reactions of azulencarbaldehydes **1**, where  $R = H$ , 4,6,8-Me<sub>3</sub> and 3,8-Me<sub>2</sub>-5-*i*Pr, with low-valent titanium obtained by reduction of  $TiCl_3$  with Li. The reactions yielded 1,2-di(azulen-1-yl)ethenes with (*E*) geometry in 68%, 40% and 70% yields, respectively. They also condensed (*E*)-3-(azulen-1-yl)acrolein, yielding 1,6-di(azulen-1-yl)hexa-1,3,5-triene (33%).

Recently, attention has been paid to the reductive McMurry coupling of 1-acetylazulene, **41** (Scheme 16).<sup>56</sup> The reduction system was  $TiCl_4/Zn$  in THF and the reaction conditions were widely varied (Table 10).



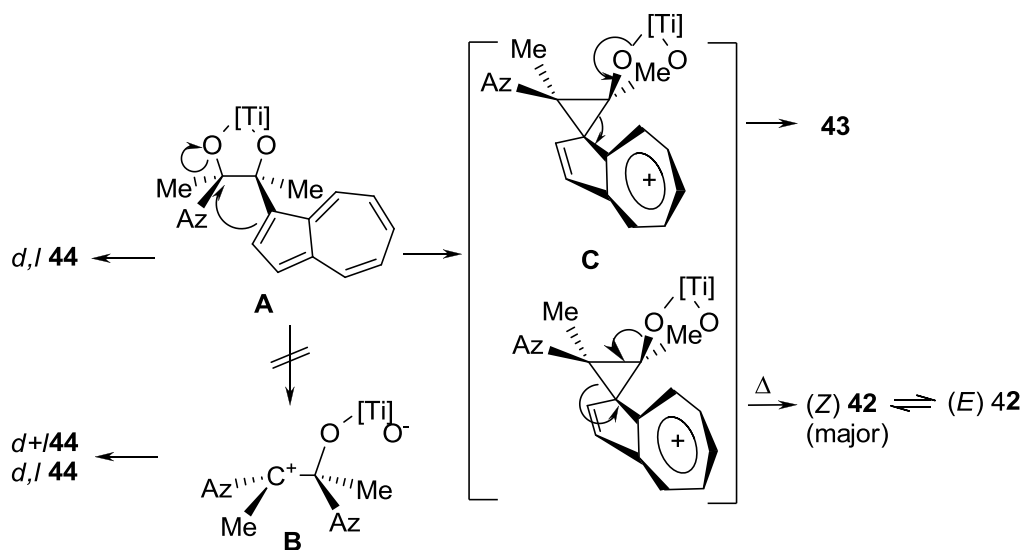
**Scheme 16.** McMurry reductive condensation.

**Table 10.** McMurry reaction of 1-acetylazulene, **41** (TiCl<sub>4</sub>/Zn; THF)

Reaction conditions	<b>42</b>		<i>d,l</i> <b>44</b>	<b>43</b>
	Yield (%) <sup>a</sup>	( <i>E</i> ):( <i>Z</i> )	(%)	(%)
0 °C, 1 h	trace	-	89	3
0 °C, 30 min; then 40 °C, 1.5 h	5	20:80	11	9
py; 0 °C, 30 min; then 40 °C, 1.5 h	35	12:88	38	7
MW; 0 °C, 30 min; then 40 °C, <sup>b</sup> 45 min	19	5:95	20	16
MW+py; 0 °C, 30 min; then 40 °C, <sup>b</sup> 45 min	34	7:93	12	44
MW+py; 0 °C, 30 min; then 60 °C, <sup>b</sup> 20 min	30	5:95	0	43

<sup>a</sup>After separation on chromatography column. <sup>b</sup>MW heating at 80W.

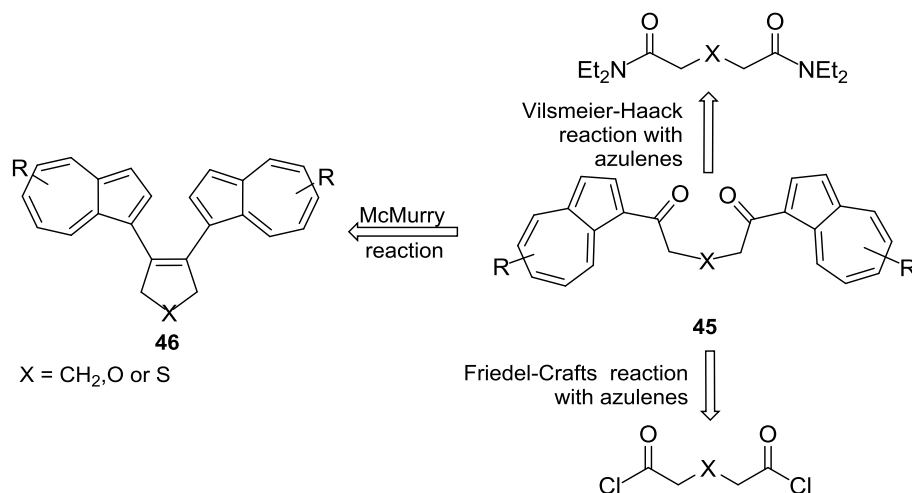
The first interesting finding consists of the presence in the reaction mixture of pinacol **40** and mainly of pinacolone **43**, along the (*Z*+*E*) alkene **42**. Until now, there are only three examples of the McMurry condensation where the attempted unsaturated compound was accompanied by pinacol and its pinacol→pinacolone transposition product. This behavior was adopted by [3]ferrocenophan-1-one<sup>57</sup>, (η<sup>5</sup>-acetylcyclopentadienyl)cobalt-(η<sup>4</sup>-tetraphenylcyclobutadiene)<sup>58</sup> and 1,*n*-bis-(5-acetyl-2-methoxyphenyl)alkanes.<sup>59</sup> It has been assumed that the presence of a moiety that strongly stabilizes the carbonium ions represents the common structural feature for these three ketones and 1-acetylazulene. The reaction mechanism, which explains the products generation, (Scheme 17) involves as key intermediate the cyclic titanapinacolate **A**. Its conversion into the intermediate **C** benefits from the participation of 1-azulenyl group and explains the migration aptitude in titanapinacolate **A**.

**Scheme 17.** The McMurry reductive condensation route.

Data given in Table 10 show that, at low temperature, the major product is a pinacol and, by increasing the temperature, the yields in all products collapse. The yields both in pinacol and in alkene can be improved by adding pyridine. The MW heating levels the products ratio. However, the addition of pyridine in these conditions increases the yields in pinacolone and alkene until the disappearance of pinacol. It should be noted that, regardless of the reaction conditions, the pinacol resulted only as a racemic mixture<sup>60</sup> and the (*Z*)-isomer

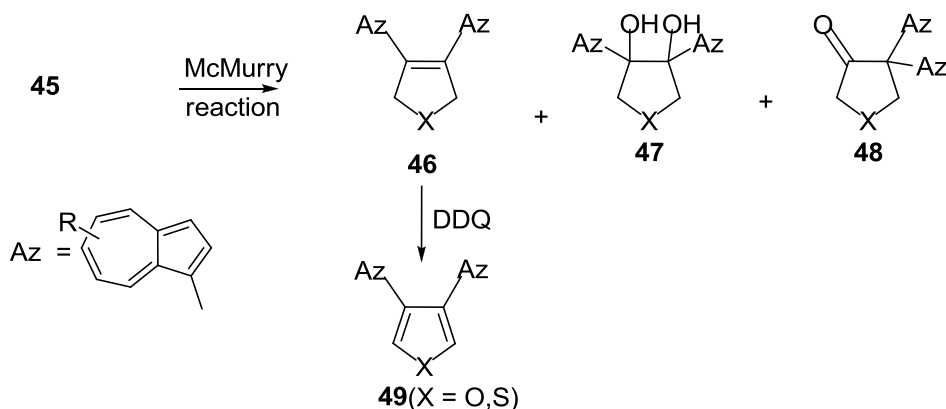
of alkene **42** always exceeds the isomer (*E*). Both of these results are consistent with the mechanism depicted in Scheme 17.

In connection with the results of McMurry reaction of (1-azulenyl)ketones, an investigation on the intramolecular condensation of 1,ω-di(azulen-1-yl)-1,ω-diketones was also undertaken.<sup>61,62</sup> The possibility to obtain by this route unsaturated carbocyclic and heterocyclic derivatives containing azulen-1-yl moieties at the C=C bond (compounds **46** in Scheme 18) is attractive due to the potential technical properties of these compounds with applications in the field of π-conjugated materials (modified electrodes, photochromic materials, etc.).



**Scheme 18.** Intramolecular Vilsmeier-Haack reaction.

For the synthesis of starting diketones **45**, Vilsmeier-Haack or Friedel-Crafts reactions are employed (Scheme 18). The subsequent McMurry reaction of diketones generates, along desired cyclic alkene **46**, as side products, the pinacol **47** and its rearranged product, ketone **48** (Scheme 19) in a ratio depending on the starting diketone and the reaction conditions. Therefore, several conditions for the increase of the reaction selectivity in each product were tested and the results are shown in Table 11.



**Scheme 19.** Products in intramolecular Vilsmeier-Haack reaction.

**Table 11.** McMurry reaction of di(azulen-1-yl)-diketones **41**

Diketone <b>45</b> X; R	Conditions	Products (%)			Overall yield (%)
		<b>46</b>	<b>47</b>	<b>48</b>	
CH <sub>2</sub> ; H	TiCl <sub>4</sub> /Zn, 0 °C, 1 h	77	22	0	99
	TiCl <sub>4</sub> /Zn, -45 °C, 0.5 h	18	0	9	27
	TiCl <sub>4</sub> /Zn, py, 0 °C, 1 h	88	10	0	98
	TiCl <sub>4</sub> /Zn, py, catch., 0 °C, 1 h	61	0	0	61
CH <sub>2</sub> ; 4,6,8-Me <sub>3</sub>	TiCl <sub>4</sub> /Zn, 0 °C, 1 h	87	0	0	87
	TiCl <sub>4</sub> /Zn, py, 0 °C, 1 h	87	0	0	87
CH <sub>2</sub> ; 3,8-Me <sub>2</sub> -5- <i>i</i> Pr	TiCl <sub>4</sub> /Zn, 0 °C, 1 h	93	0	0	93
	TiCl <sub>4</sub> /Zn, py, 0 °C, 1 h	95	0	0	95
O; H	TiCl <sub>4</sub> /Zn, 0 °C, 1 h	47	34	trace	81
	TiCl <sub>4</sub> /Zn, -45 °C, 0.5 h	8	0	13	21
	TiCl <sub>4</sub> /Zn, py, 0 °C, 1 h	86	9	3	98
	TiCl <sub>4</sub> /Zn, py, catechol, 0 °C, 1 h	35	3	45	83
S; H	TiCl <sub>4</sub> /Zn, 0 °C, 1 h	25	50	5	80
	TiCl <sub>4</sub> /Zn, -45 °C, 0.5 h	6	0	30	36
	TiCl <sub>4</sub> /Zn, py, 0 °C, 1 h	48	8	19	75
	TiCl <sub>4</sub> /Zn, py, catechol, 0 °C, 1 h	27	6	53	86

The electronic, as well as the steric effects, of the azulene-1-yl substituents substantially modifies the reaction pathway. When the azulenyl moiety is not substituted, alkene **46** was accompanied by ketone **48** in 22% yield. However, bulky methyl groups situated in position 8, as in **45** where X = CH<sub>2</sub>, R = 4,6,8-Me<sub>3</sub> or 3,8-Me<sub>2</sub>-5-*i*Pr do not allow the azulenyl migration and, therefore, no ketones are formed. The presence of heteroatom in cycle forces the hydroxyl and azulenyl groups to stay in the eclipsed configuration increasing the energy of pinacolic structure. Therefore, elimination of the hydroxyl groups becomes easier than in the case of 1-acetylazulene which, under the same reaction conditions, forms a stable pinacolic derivative with a staggered structure in 89% yield. Starting from **45**, the hydroxyl elimination occurs even at the working temperature of 0 °C that is unusual for common McMurry reactions, which require higher temperatures and longer reaction times.<sup>63</sup> Therefore, to avoid the OH removal in order to obtain a larger amount of pinacol, the reaction temperature is decreased to -45 °C. However, even under these conditions, the pinacol **47** (where R = H) was generated in a small amount together with the alkene **46**, which is formed even at this low temperature as the main product.

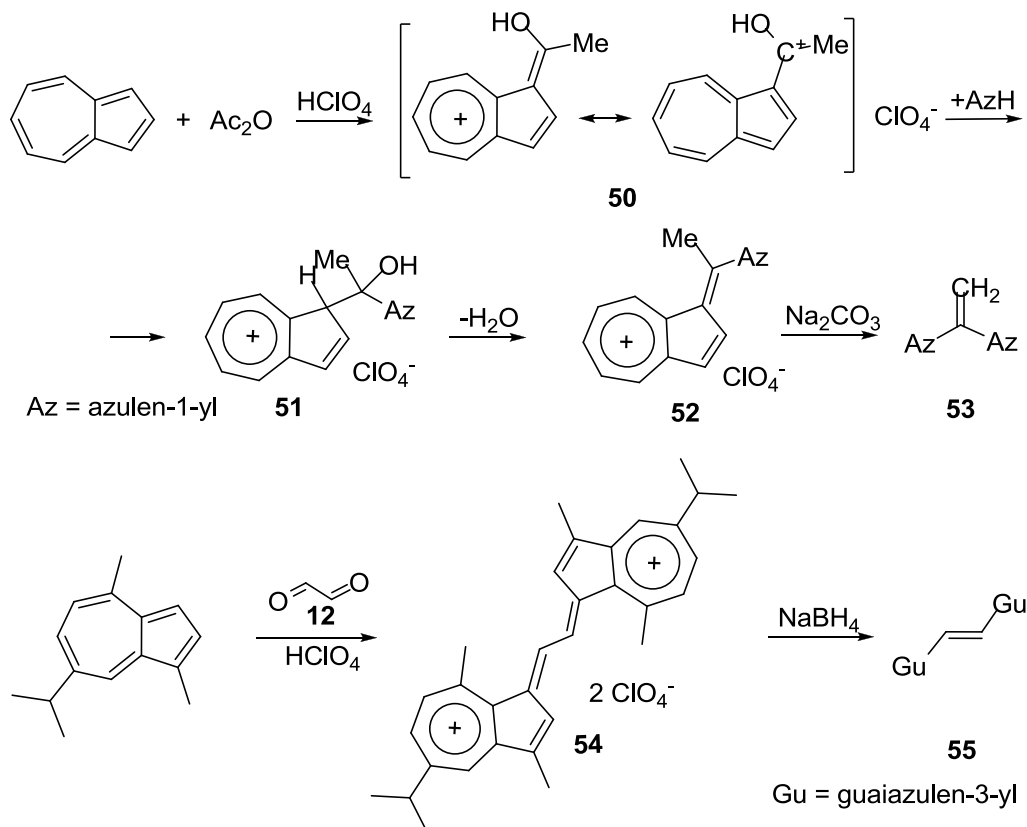
The low-valent titanium reagent is obtained by the action of zinc dust on TiCl<sub>4</sub> without or in the presence of pyridine and eventually also by catechol as an auxiliary system (Table 11). Addition of pyridine increases the alkene/ketone ratio and improves, to some extent, the yield in pinacol. Literature data show that the presence of chelating agents, such as catechol, stops the McMurry reaction to the pinacol stage<sup>54</sup> what can be also observed to some extent in the results in Table 11.

Replacement of CH<sub>2</sub> group in the diketone **45** by a heteroatom influences in a decisive way the McMurry cyclization. While alkene **46**, and sometimes the ketone **48**, represents the sole products when X = CH<sub>2</sub>, working with diketones **45** where X = O or S, the alkene always results together with pinacol and sometimes with pinacolone (Table 10).

The alkenes **46** (X = O or S, R = H) represent valuable sources for aromatic heterocycles **49** (Scheme 17), difficult to obtain by other routes.

## 2.6. Other methods for synthesis of 1-vinylazulenes

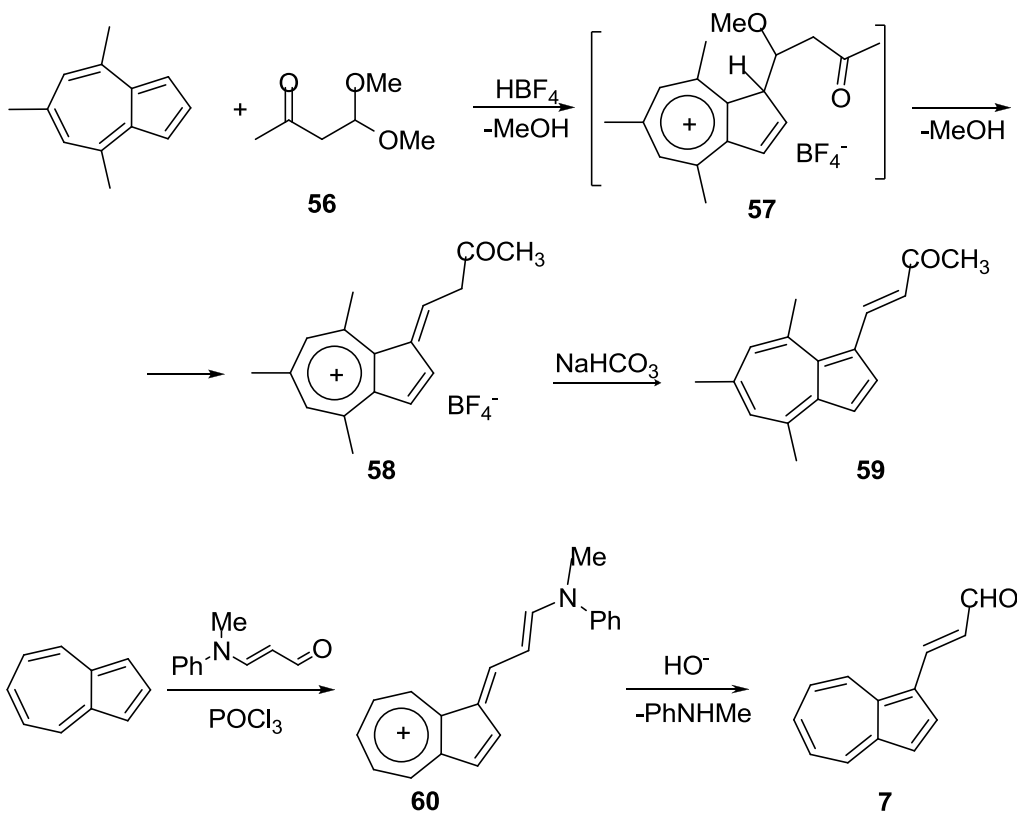
**2.6.1. Electrophilic substitution of azulenes.** The polarized  $\pi$ -electron system of azulene, as well as the low energy of the aromatic tropylium cation, can stop the electrophilic reaction of the relatively stable intermediate 1-alkylidene-1*H*-azulonium salts (e.g. cation **50**, Scheme 20).



**Scheme 20.** Electrophilic substitution of azulenes in strong acidic medium, using acetic anhydride and glyoxal.

However, under special conditions, the obtained cation can again react with suitable nucleophilic species, as for example with azulene, in the sequence shown in Scheme 20. Subsequent water elimination provides 1,1-bis(azulen-1-yl)ethene, **53**.<sup>64</sup> The more basic guaiazulene reacts with acetic anhydride even in the presence of acetic acid instead of strong perchloric acid forming 1,1'-bis-(3,8-dimethyl-5-isopropylazulen-1-yl)ethene.<sup>65</sup> A similar route is involved in reaction of guaiazulene with glyoxal in the presence of perchloric acid (Scheme 20) with the stabilization of the intermediate dication as 1,2-disubstituted ethene **54**.<sup>66,67</sup>

A 1-alkylidene-1*H*-azulonium salt can also be obtained by eliminating another small molecule, as in the condensation of 4,6,8-trimethylazulene with acetal **56** in the presence of tetrafluoroboric acid (Scheme 21). From the first intermediate salt **57** a new azulonium salt **58** was obtained in 96% yield by methanol elimination. After treatment with base compound **59** results, with the double bond stabilized by extended conjugation (41% yield).<sup>68</sup> A molecule of *N*-methylaniline is also eliminated in the electrophilic synthesis of 2-(azulen-1-yl)acrolein, **7**, by the route described in Scheme 21.<sup>69</sup>

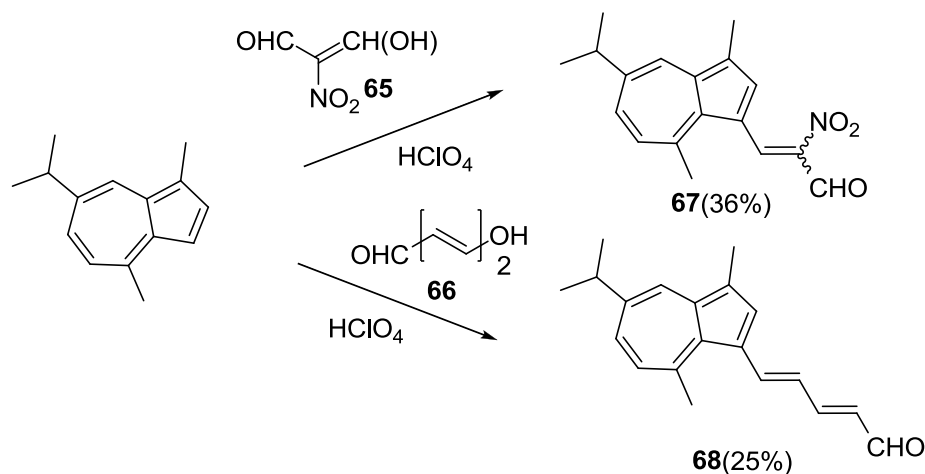
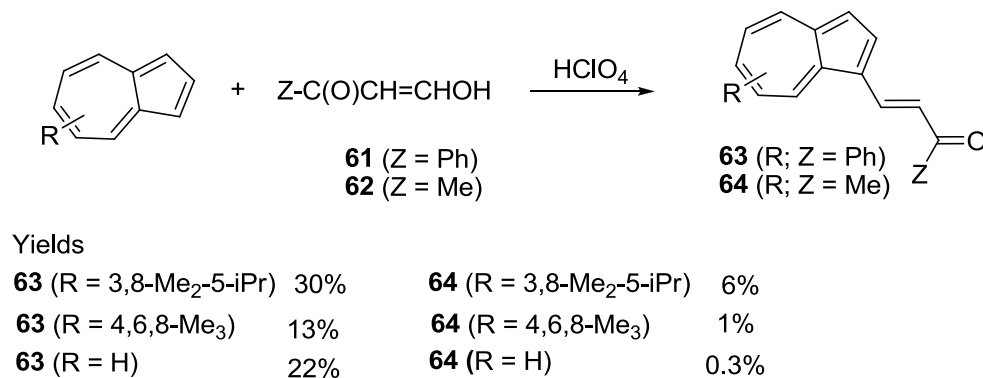


**Scheme 21.** Electrophilic synthesis of (*E*)-3-(azulen-1-yl)acrolein.

Reaction of enols **61** or **62** with azulenes in the presence of perchloric acid was proposed by Kirby and Reid<sup>66</sup> as a route for the synthesis of vinylazulenes (Scheme 22). While the benzoylated compounds **63** resulted in good yields, for acetylated derivatives **64** the yields decreased dramatically. The same reaction conditions were used to generate alkenes **67** and **68** in moderate yields starting from enols **65** and **66** (Scheme 22).

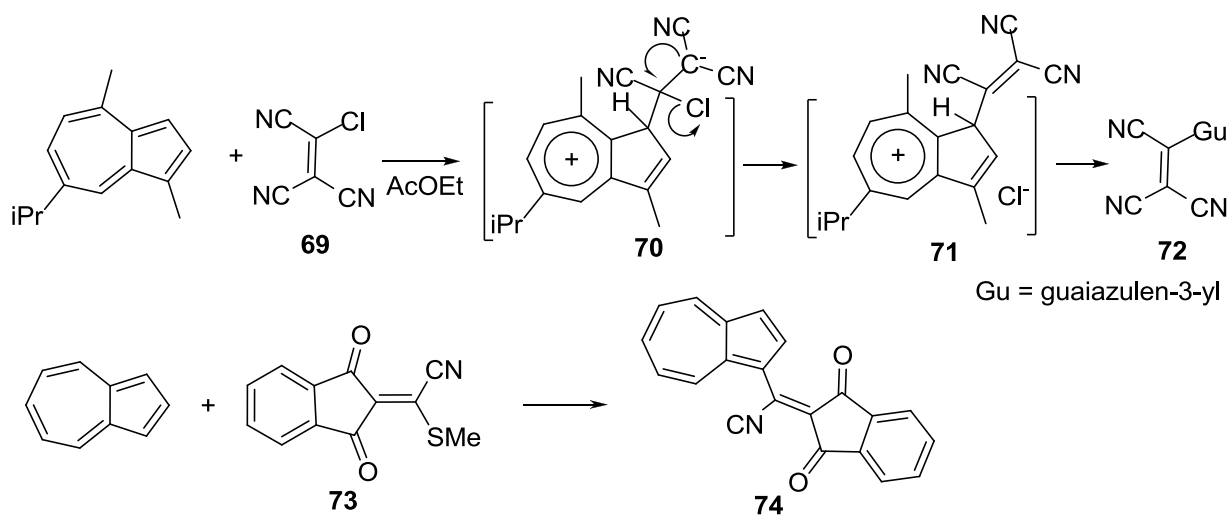
The low stability of unsaturated sp<sup>2</sup> or sp carbocations creates difficulties in the electrophilic attack of such cations on azulenes to give vinylazulenes. Nevertheless, when the multiple bond is deficient in electrons, substitution to nucleophilic azulenes can occur. Thus, with tetracyanoethene, the azulenes first form a charge transfer complex that eliminates a cyanide ion under severe conditions. Yields are low for easily oxidizable azulenes; however, the yield increases to 70% for azulene itself.<sup>70</sup> When the multiple substitution of a C=C bond with CN groups is associated with the presence of a good nucleophilic leaving group, such as halogen, the reaction occurs even in the absence of any catalyst. Thus, from the reaction between chlorotricyanoethene **69** and guaiazulene, product **72** results in 75% yield, as shown in Scheme 23.<sup>71</sup>





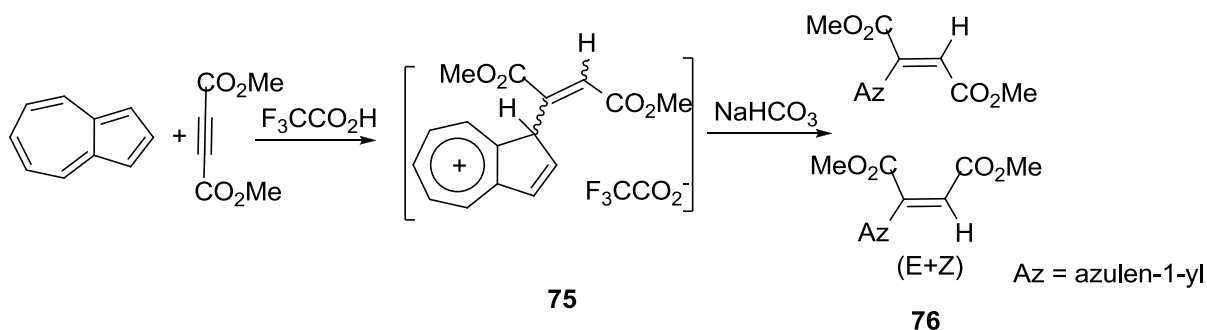
**Scheme 22.** Electrophilic substitution of azulenes with enols in strong acid medium.

The activated double bond of (1,3-dioxindan-2-ylidene)(methylsulfanyl)acetonitrile, **73**, reacts with azulene by displacement of the MeSH, forming azulene-1-yl-(1,3-dioxindan-2-ylidene)acetonitrile (**74**) (Scheme 23).<sup>72</sup>



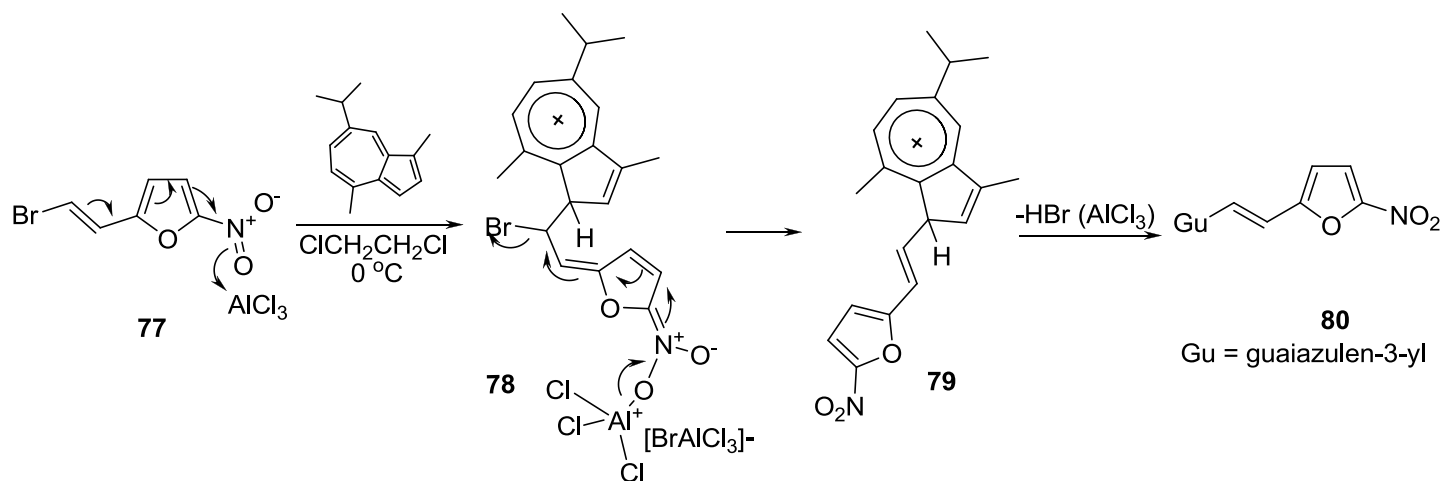
**Scheme 23.** Reaction of azulenes with acrylonitrile derivatives.

Another example in this respect is provided by the triple bond of acetylenedicarboxylic ester, which reacts with azulenes in the presence of trifluoroacetic acid (illustrated in Scheme 24 for azulene; the reaction occurring also with 4,6,8-trimethylazulene) giving an equimolar mixture of azulenyl-maleic and -fumaric esters **76** (35% yield in products starting from azulene and 50% using 2,4,6-trimethylazulene).<sup>73</sup>



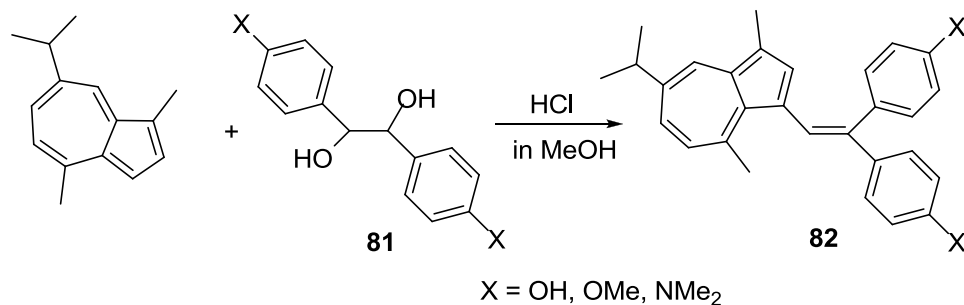
**Scheme 24.** Reactions of azulenes with dimethyl acetylenedicarboxylate.

The destructive effect of aluminum chloride on azulene moiety limits the valuable Friedel-Crafts reaction for azulene chemistry. However, it was used in the peculiar reaction between the 2-(2-bromovinyl)-5-nitrofurans, **77**, and guaiazulene in 1,2-dichloroethane at 0 °C (48% yield).<sup>74</sup> In this case, the effect of the nitro group is transmitted through the  $\pi$ -electronic system of the furan ring, as indicated in Scheme 25.



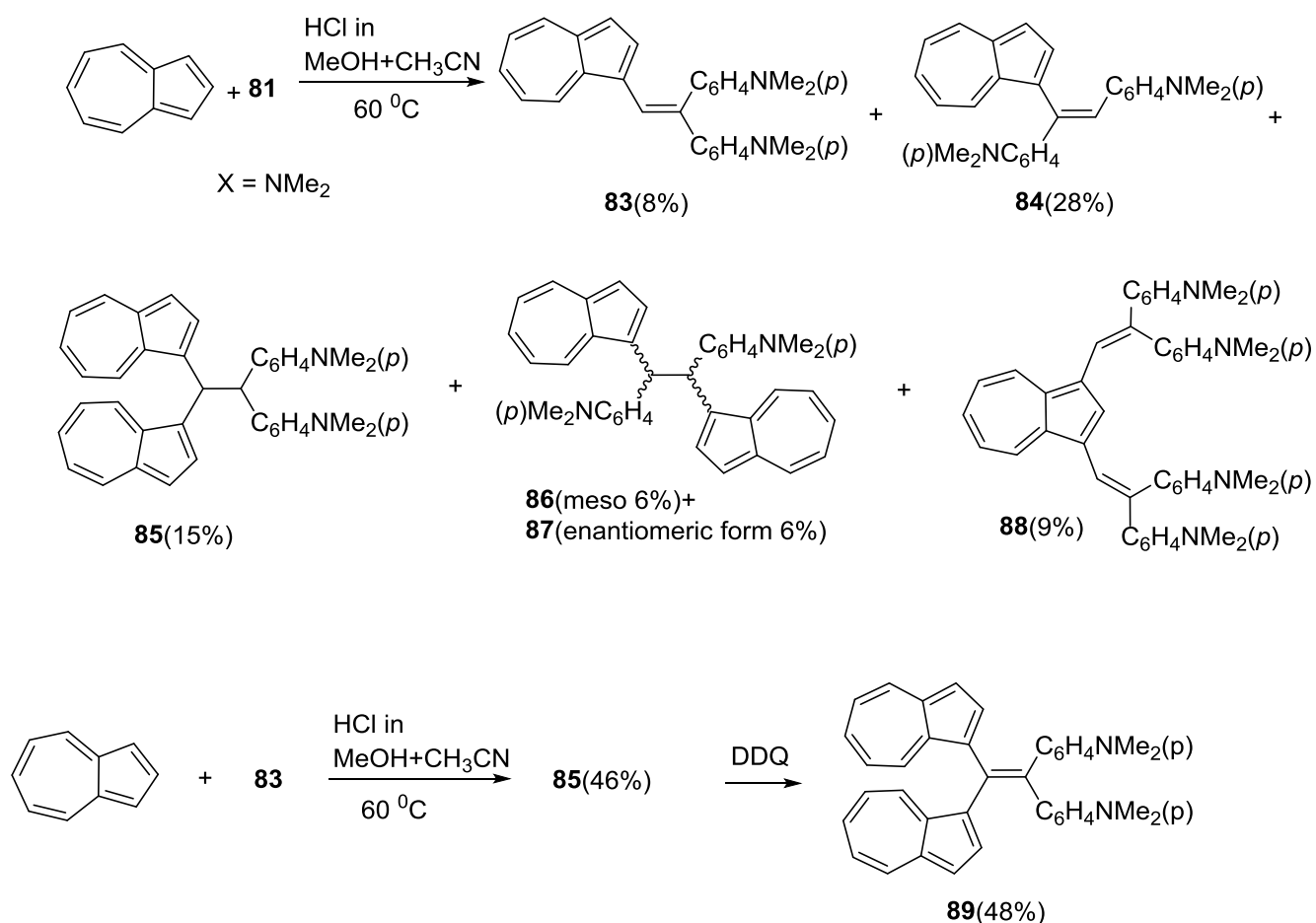
**Scheme 25.** Example of Friedel-Crafts substitution of guaiazulene.

More recently was reported the electrophilic reaction of 1,2-diphenylethane-1,2-diols in which the phenyl groups are substituted in position 4 with OH, OMe or NMe<sub>2</sub> groups, with azulenes in the presence of concentrated hydrochloric acid in methanol.<sup>24,75</sup> As it is illustrated for guaiazulene in Scheme 26, the reaction leads to the product of pinacol rearrangement, **82**. While good yields are obtained for guaiazulene and 1-chloroazulene, azulene reacts in lower yield and methyl azulene-1-carboxylate gives no product.



**Scheme 26.** Reaction of guaiazulene with 1,2-diols in acidic medium (methanol as solvent).

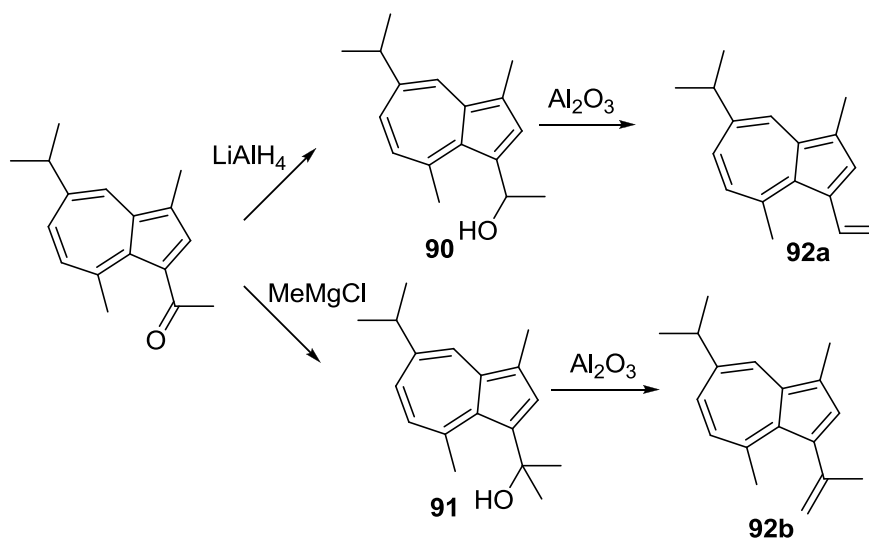
Changing the solvent and working in a mixture of methanol and acetonitrile instead of methanol, the reaction becomes not regioselective and several products were formed.<sup>76</sup> Starting from diol **81** where X = NMe<sub>2</sub> and azulene the targeted product 1-(azulen-1-yl)-(E)-1,2-bis-[4-(dimethylamino)phenyl]ethylene, **84**, and the rearranged alkene **83** result in 28% and 8% yield, respectively (Scheme 27). Alongside of these “primary derivatives”, three isomers of di(azulen-1-yl)-bis-[4-(dimethylamino)phenyl]ethanes, **85-87** are formed in amount of almost 30% from the reaction mixture to the “addition” of azulene to alkenes **83** and **84**. The presence of 1,3-disubstituted azulene **88** has also been signaled. Making compound **85** by the electrophilic substitution of azulene with alkene **83**, under the same reaction conditions, confirms the reaction route. The dehydrogenation of compound **85** produces alkene **89** (Scheme 27).



**Scheme 27.** Reaction of azulene with 1,2-diols in acidic medium (in mixture of MeOH+CH<sub>3</sub>CN).

It is likely that the bulky methyl group situated in position 8 of the guaiazulenyl moiety prevents the presence of a guaiazulenyl and an aryl or two guaiazulenyl groups at the same alkene carbon and explains why the reaction stops at the product **82**. This supposition is confirmed by the unusual reaction which takes place between **82** where X = NMe<sub>2</sub> and azulene, when the guaiazulenyl moiety is partially replaced by azulenyl.

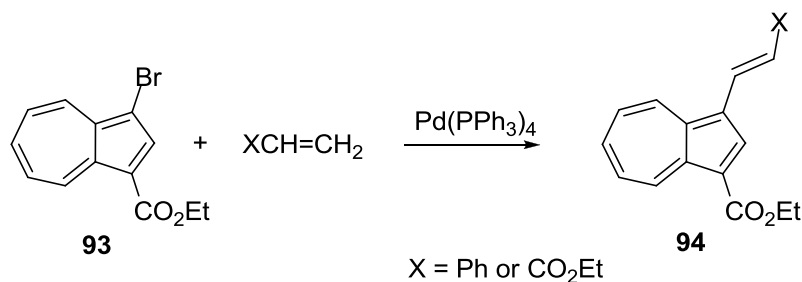
**2.6.2. Dehydration of 2-(azulen-1-yl)ethanols.** Water removal is one of the most well-known ways to form a C=C bond. Difficulties for the preparation of azulenic alcohols and the modest yields in dehydrated products limit this route. However, β-hydroxyethyl substituted azulenes (or their derivatives) have been dehydrated to the corresponding vinylazulenes either in the presence of strong acids, such as tetrafluoroboric acid, at 60-70 °C, in fair yields<sup>77</sup> or under basic condition with poorer results.<sup>18</sup> Passage through an alumina column was also used for water elimination from the alcohols **90** and **91**, obtained from 3-acetylguaiazulene (Scheme 28), but the reported yields for alkenes **92a** and **92b** are low.<sup>79</sup>



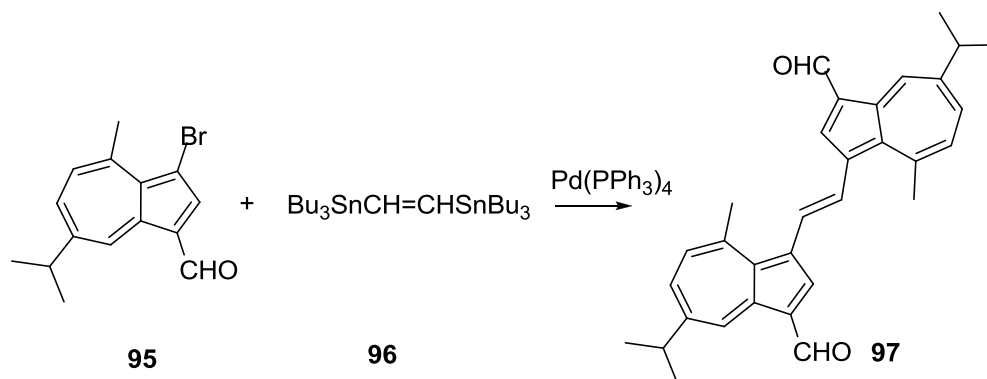
**Scheme 28.** Dehydration of 2-(azulen-1-yl)ethanols.

**2.6.3. Radical and concerted reactions.** Coupling of azulene derivatives with readily accessible reagents in the presence of transition metal catalysts, such as in the Heck reaction, represents an attractive route towards a number of 1-vinylazulenes that can then be used as building blocks of different interesting molecules. Thus, the reaction of many halogen-azulenes with monosubstituted ethenes in the presence of Pd(PPh<sub>3</sub>)<sub>4</sub>/(NEt<sub>3</sub>) was reported.<sup>79</sup> However, a drawback of this synthesis is the difficulty encountered in the monohalogenation of the parent azulene as compared with its 1,3-dihalogenation. Therefore, the use of this pathway has been limited to 1,3-disubstituted azulenes. Halogenation of position 3 becomes almost quantitative when the azulenes are already substituted with electron withdrawing groups at the 1-position. Therefore, good yields are reported in the Heck reaction of ethyl 3-bromo-1-azulenecarboxylate, **93** with styrene or methyl acrylate (yields 66% and 88%, respectively). The vinylation occurs regioselectively only at the carbon substituted with halogen (Scheme 29).

Ethenes are not always reactive enough to participate in the Heck reaction. Therefore, they can be activated as an organostannic derivative, **96**, which reacts with the bromo compound **95**, as represented in Scheme 30, leading to compound **97** in 81% yield.<sup>80</sup>

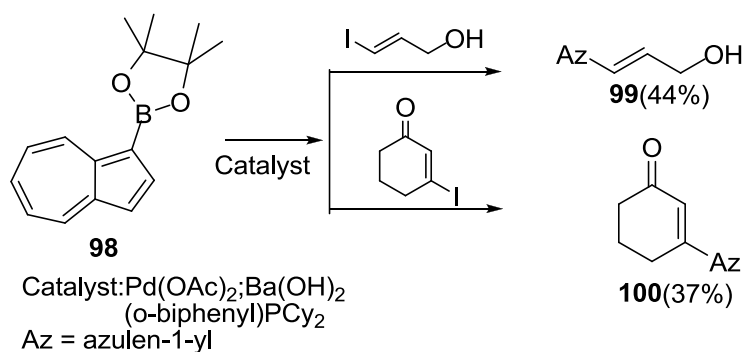


**Scheme 29.** Heck reaction of 1-halogenated azulene with monosubstituted alkenes.



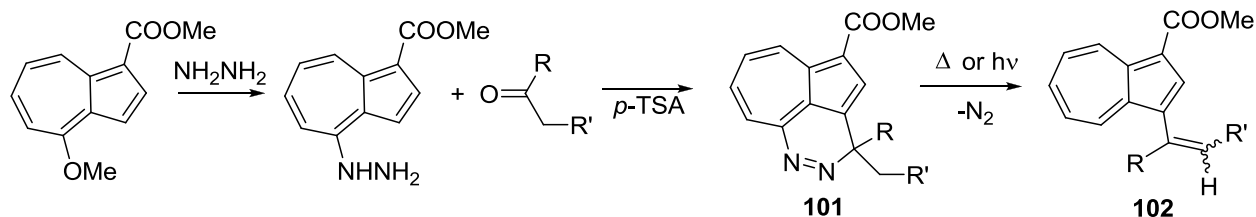
**Scheme 30.** Stille reaction of 1-halogenated azulene with activated double bond.

The bond between the azulene and vinyl moieties can be created also by Suzuki coupling starting from the azulene system activated with the boronic group. In this way it becomes more reactive than the alkenic bond, avoiding the alkene polymerization.<sup>80,81</sup> The dark purple solid boronate **98** reacts with 3-iodoallyl alcohol or with 3-iodocyclohex-2-enone providing compounds **99** or **100** in moderate yields (Scheme 31).



**Scheme 31.** Suzuki coupling starting from the azulene system activated with a boronic group.

The pyrolytic or photochemical elimination of nitrogen from 3*H*-azuleno[8,1-*cd*]pyridazines, **101**, was also proposed for the preparation of 1-alkylated vinylazulenes (Scheme 32), which are difficult to be obtained using classical methods. Although the synthesis of compound **102** occurs in several steps, these reactions are quite regioselective and the starting reagents are available.<sup>82</sup>



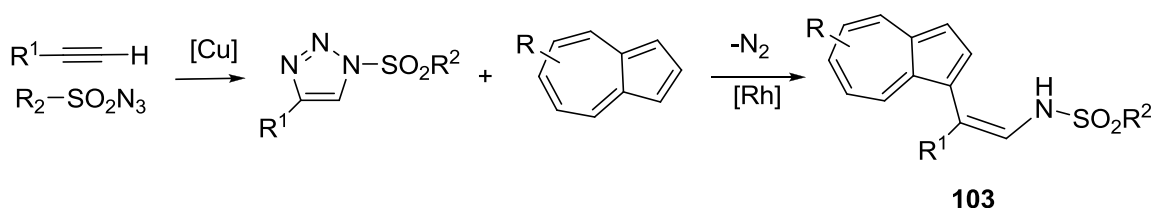
**Scheme 32.** Pyrolytic or photochemical elimination of nitrogen from 3*H*-azuleno[8,1-*cd*]pyridazines.

**Table 12.** Synthesis of 1-vinylazulenes **102** starting from compounds **101**

Entry	R	R'	Yields (%)	
			Thermal process	Photochemical process
1	Me	H	96	72
2	Me	Me	96 (E/Z = 0.9/1)	73 (E/Z = 0.9/1)
3	Me	<i>i</i> Pr	91 (E/Z = 1/0.8)	60 (E/Z = 1.0/0.8)
4	Et	Me	98 (E/Z = 0.4:1.0)	73 (E/Z = 0.8:1.0)
5	Me	COOEt	73 (E/Z = 0.8:1.0)	73 (E/Z = 0.8:1.0)
6	Ph	H	86	74

Unfortunately, the nitrogen elimination is not stereoselective; moreover, in the case of the photochemical reaction, an important isomerization of double bond position takes place and therefore side products are formed. The reaction mechanism proves to be radicalic. Thus, after nitrogen elimination, the intermediate diradical suffers a 1.5-hydrogen shift from one of the alkyl groups toward the 8-position of azulene via a six-membered ring transition state affording the normal or rearranged alkene structures.

An unusual synthesis was recently been accomplished for the generation of compounds **103** by the diastereoselective *N*-sulfonylaminoalkenylation of azulene or its derivatives using alkynes and *N*-sulfonylazides *via* a three-component semi-one-pot process with copper and rhodium as catalysts (Scheme 33).<sup>83</sup>



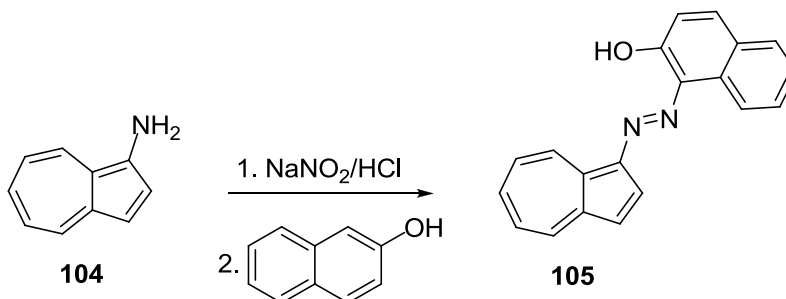
**Scheme 33.** Three-component semi-one-pot process catalyzed by copper and rhodium for vinylation of azulenes.

### 3. Azulen-1-yl Diazenes

#### 3.1. Introduction

The synthesis of azulen-1-yl diazenes can be accomplished by two main routes: the electrophilic azo coupling or the substitution of already obtained azulen-1-yl diazenes. The azo coupling of azulene under radical conditions has also been tried, but it proceeds with low efficiency.

The azo coupling starting from (azulen-1-yl)diazonium salts is prohibited due to the high instability of 1-aminoazulene, **104**, and to the very low reactivity of its diazonium salt with the positive charge at tropylium moiety. This diazonium salt, which is obtained and right away reacted *in situ*, was involved only in a few coupling reactions and even those with low yields such as, for example, reaction with the highly reactive coupling component 2-hydroxynaphthalene (Scheme 34).<sup>84</sup>



**Scheme 34.** Diazotization + coupling starting from 1-aminoazulene.

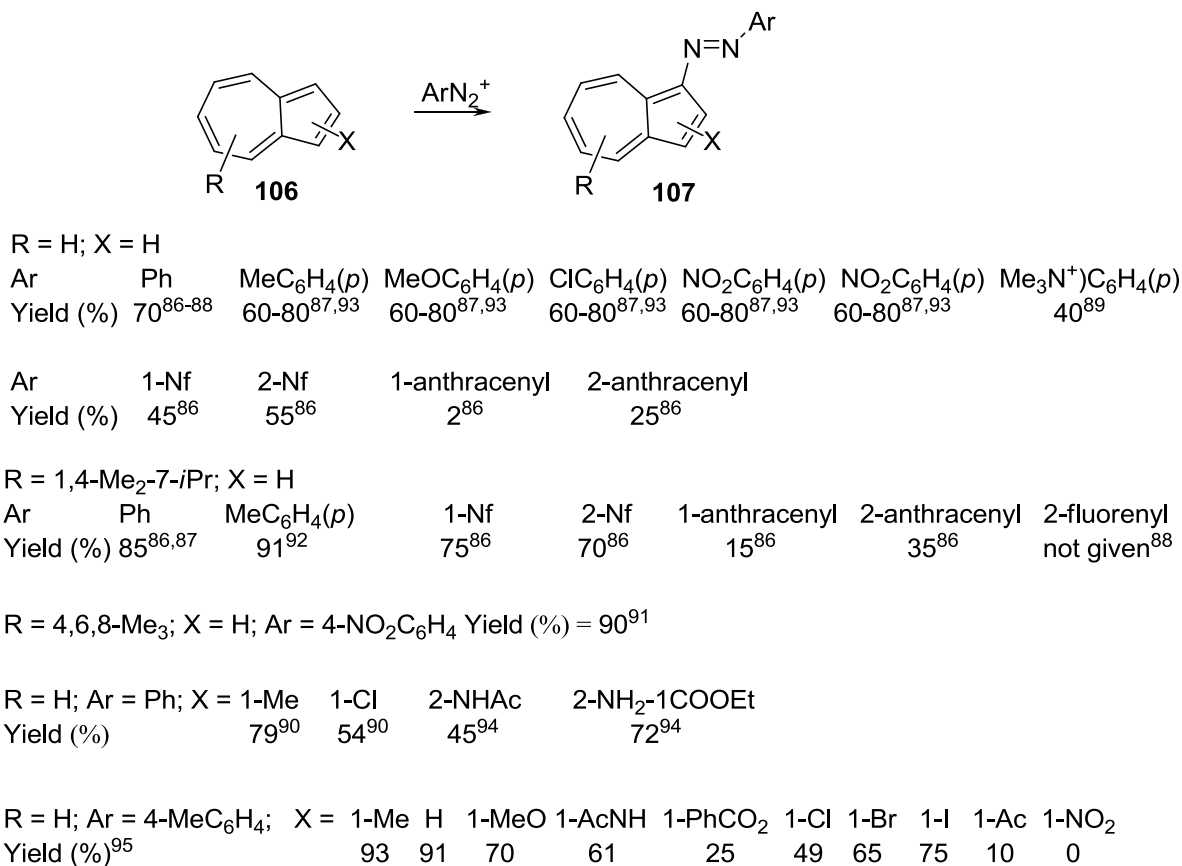
The prominent nucleophilic character of the azulene system, mainly at the 1-position, allows attack at this position by the relatively weak electrophilic aryldiazonium cation. This represents an impressive exception to common experience because only a small number of aromatic hydrocarbons (e.g. 1,3,5-trimethylbenzene) react in this way with diazonium salts and then only when these salts are derived from amines with strongly electron-withdrawing groups in their structure (e.g. 2,4,6-trinitroaniline). This valuable property allows a very wide variety of diazenes with an N=N bond in the azulene 1-position to be obtained, starting from azulene and other substituted azulenes with a free 1-position.

The alternative used route that affords the azulene-1-yl diazenes, namely the electrophilic substitution in position 3 of the already obtained diazene, occurs to be difficult due to the deactivating influence of pre-existing azo group. Nevertheless, for azulene derivatives where the azo coupling is difficult or impossible for some reason this route remains the only accessible pathway.

### 3.2. Azo coupling reactions

**3.2.1. Synthesis of azulene-1-yl diazenes starting from benzenoid amines.** It was only in the 1950s that the first coupling of azulene was achieved, by Anderson *et al.* in diethyl ether/acetic acid with an aqueous solution of phenyldiazonium chloride, in 70% yield.<sup>85</sup> However, over a relatively short period a large number of couplings between azulene derivatives and various aryldiazonium salts had been performed (several examples are reviewed in Scheme 35).<sup>86-93</sup>

All described couplings are regioselective occurring in 1(3) position of azulenes. Substitution with a second arylazo group at 3-position is not possible, except when starting from the electron rich 2-aminoazulene.<sup>94</sup> Limited information is related in the older literature on the coupling conditions, as the reaction medium and temperature or on the used anion for diazonium salts. Absence of yields for most of the reported azo couplings makes it difficult to ascertain the role played by starting reagents on the reaction route and to establish a rule in this regard. Many variations in reported yields are rather a result of the low solubility of diazenes, which hinders their processing and purification. Usually, in buffered alcoholic medium (acetic acid/acetate), the reaction occurs in 0.5 - 1 hour,<sup>93</sup> while in acetic acid–diethyl ether it needs several hours.<sup>89</sup> Anhydrous solvents were occasionally used for special diazonium salts.<sup>92</sup>



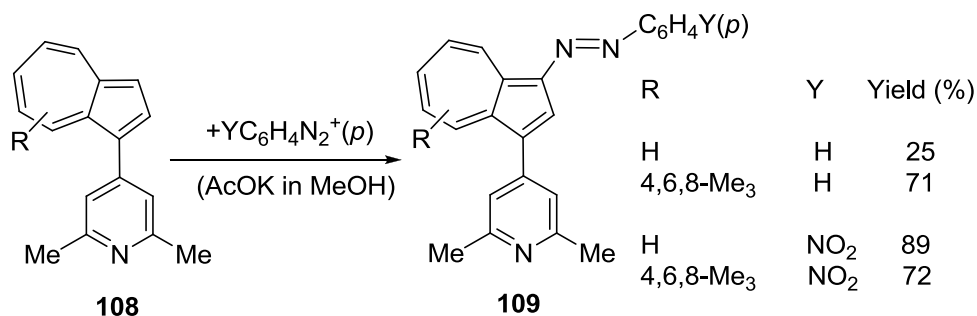
**Scheme 35.** Azo coupling of azulene derivatives with aryldiazonium salts.

A notable decrease in product yield is observed either when Ar represents a phenyl group possessing a strongly electron-withdrawing group such as Me<sub>3</sub>N<sup>+</sup> in the *para*-position, or when Ar is an aromatic polycyclic radical, such as 2-anthracenyl or even 1-naphthyl. The resulted diazonium salts starting from aniline substituted with strong electron donating groups, as for example NMe<sub>2</sub>, are too stable to interact with the azulene moiety. They can, however, react with activated azulenes that contain strong electron donating group, NH<sub>2</sub> or OH, as in ethyl (2-amino)- or (2-hydroxy)- azulene-1-carboxylate.<sup>97</sup>

Substitution of azulene with alkyl groups improves the product yield due to the electron-repelling effect of these groups, which enhances the azulene nucleophilicity (e.g. when Ar = 1-naphthyl in Scheme 35, the coupling yield raises from 45% for azulene to 70% for guaiazulene). The influence of other groups in position 1 of azulene on the coupling reaction with diazotized 4-toluidine was investigated using substituents with varying electron demand (Scheme 35).<sup>95</sup> Thus, despite the electron donor properties of groups such as MeO, PhCO<sub>2</sub>, AcNH or halogen, their low ionization potential can promote the product oxidation with concomitant decrease of yield. Further decrease in yield occurred with the substituent PhCO<sub>2</sub> due to its hydrolysis during the coupling. As attempted, the electron acceptors (Ac or NO<sub>2</sub>) limit or prevent coupling. In the case of formyl or acetyl groups, small amounts of the coupling products can be obtained depending on the reactivity of the diazonium salts.

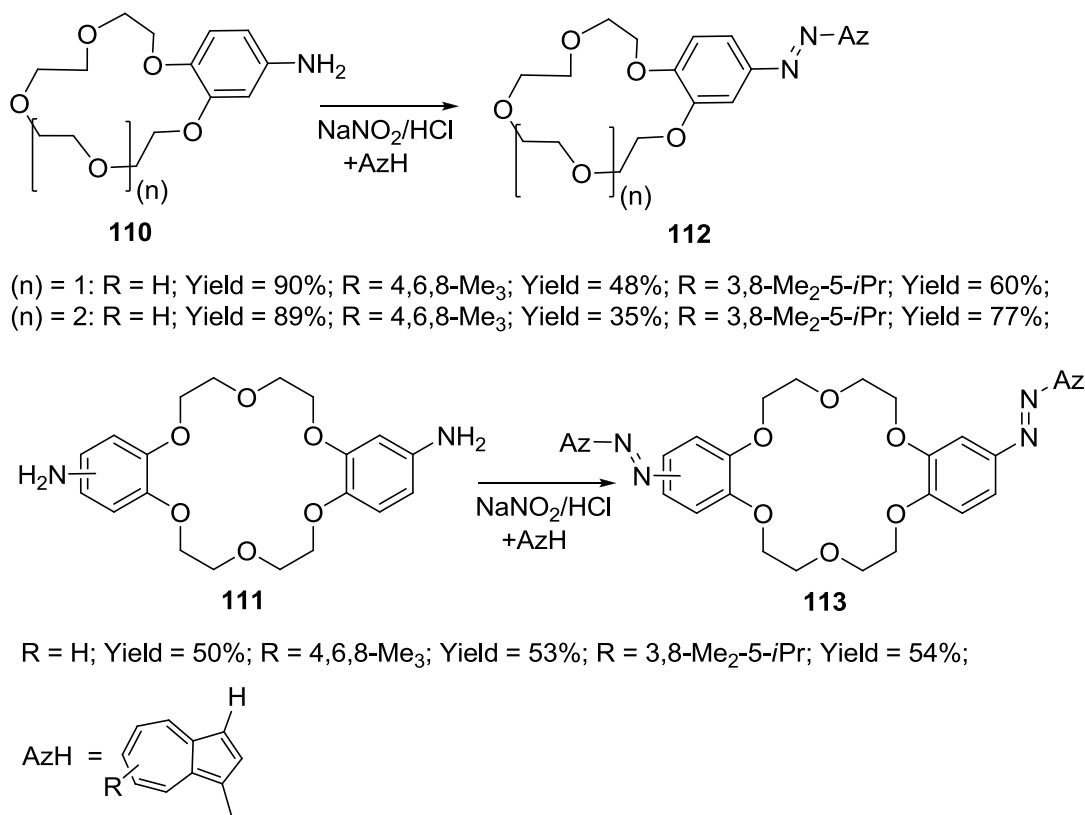
The 4-(azulen-1-yl)-2,6-dimethylpyridines, **108**,<sup>96</sup> were used as building blocks for the synthesis of highly conjugated diazenes with valuable dye properties. In spite of the electron-withdrawing character of the pyridine moiety, these compounds were converted into the diazenes **109** (Scheme 36).<sup>15</sup>





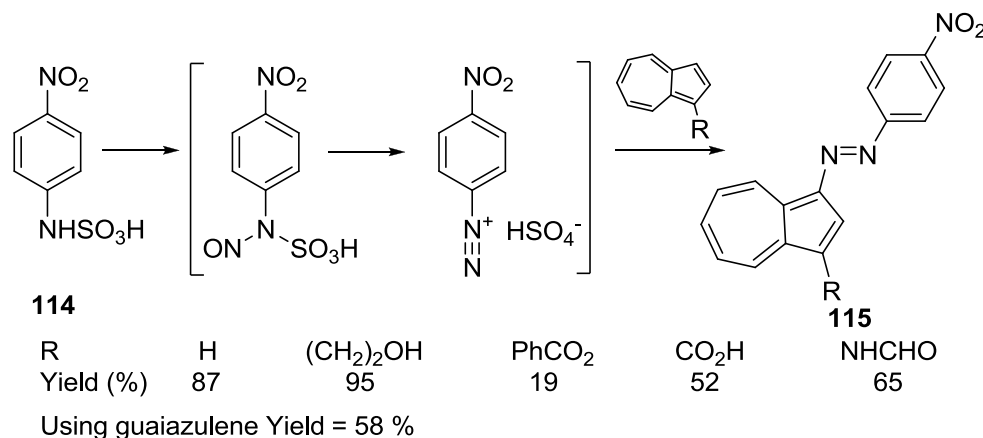
**Scheme 36.** Azo coupling of 4-(azulen-1-yl)-2,6-dimethylpyridines.

The crown ethers are colorless compounds, however, some of their technical uses require the presence of a chromophore in the molecular structure. Therefore, the (azulen-1-yl)azo moieties were attached to several crown ethers in the aim to obtain such colored materials.<sup>97</sup> Thus, the crown ethers with one or two (azulen-1-yl)azo chromophores, **112** or **113** were generated in good or moderate yields (Scheme 37) from commercially available 3-aminobenzo-crown ethers, **110** or from diaminodibenzo-18-crown-6 ether, **111**. The low reactivity of the diazonium salts favors the electron transfer between the diazonium salts and guaiazulene, therefore, the yields in products **112** where R = 3,8-Me<sub>2</sub>-5-*i*Pr fall below those of the products with azulen-1-yl group. At the same time, the yields of trimethylazulene derivatives, **112** where R = 4,6,8-Me<sub>3</sub>, decrease due their poor solubility.



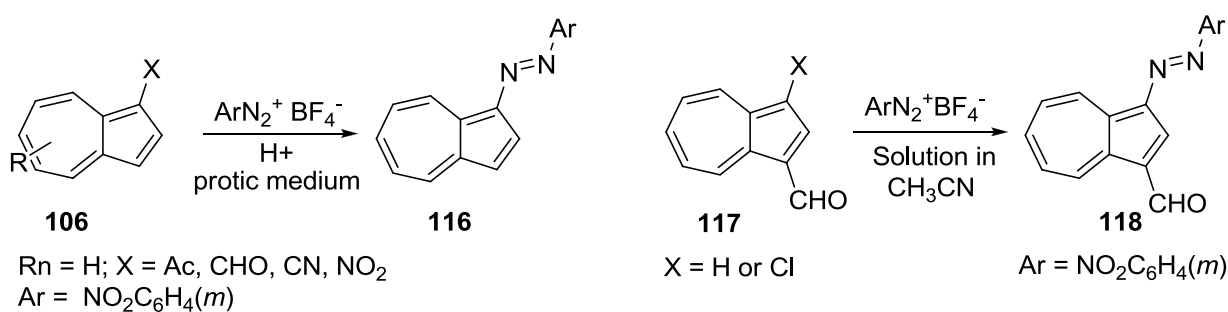
**Scheme 37.** Generation of chromophores containing crown ethers with one or two (azulen-1-yl)diazenyl moieties.

To avoid the partial diazotization when weakly basic aromatic amines (such as 4-nitroaniline) were used, they were dissolved in a little amount of concentrated  $\text{H}_2\text{SO}_4$  with the rising of the temperature and were transformed in the corresponding sulfamic acid **114**. This intermediate is more soluble than the amine and the diazonium salt was obtained at  $0^\circ\text{C}$  and was coupled in good yields with a number of 1-substituted azulene at room temperature with the generation of the compounds **115** (Scheme 38) (see also the next section).<sup>98</sup>



**Scheme 38.** Azo coupling of the azulene derivatives with diazotized weak bases (in the presence of  $\text{H}_2\text{SO}_4$ ).

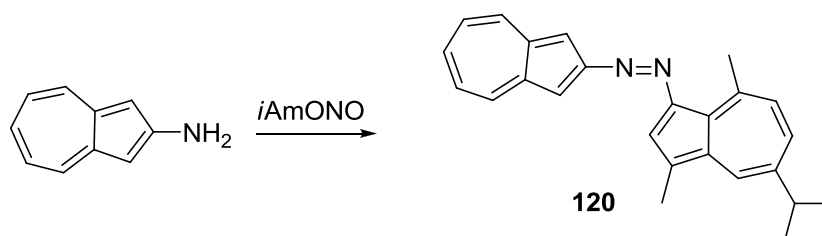
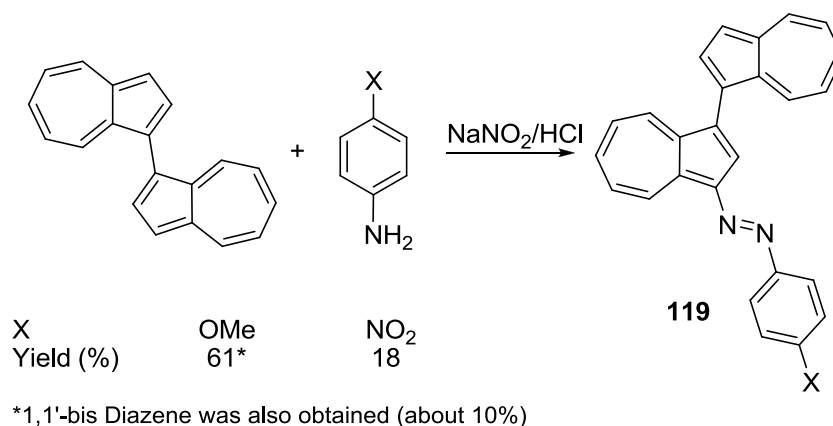
As mentioned above, the presence of electron withdrawing groups in 1-position of azulenes significantly reduces their reactivity toward electrophiles. Compounds **106** where  $\text{X} = \text{Ac}$ ,  $\text{CHO}$ ,  $\text{CN}$  or  $\text{NO}_2$  (Scheme 39) are coupled under severe conditions and only with reactive diazonium salts, such as 3-nitrobenzenediazonium tetrafluoroborate with the removal of the  $\text{X}$  substituent.<sup>99,100</sup> This substitution probably takes place because these groups are good electrophilic leaving groups and are eliminated in acidic medium ( $\text{H}_3\text{PO}_4$ ), with the generation of azulene, which is further azo-coupled generating diazenes **116**. 1,3-Diacetylazulene reacts in good yield with 3-nitrobenzenediazonium salt with the substitution of an acetyl group.<sup>92</sup>



**Scheme 39.** Behavior of azulene derivatives with different reactivity by azo coupling.

Formyl group shows a specific behavior being removed in the protic medium. At the same time, it is retained if an aprotic solvent, such as acetonitrile and an anhydrous tetrafluoroborate aryldiazonium salt are used for coupling. However, in the latter case, coupling requires a longer reaction time to substitute selectively the proton. Under these conditions, the bond of azulene to formyl becomes even stronger than that with chlorine. Therefore, in 3-chloroazulene-1-carbaldehyde, the chlorine atom was replaced by the diazonium ion whereas  $\text{CHO}$  group was preserved as in compound **118** in Scheme 39.<sup>98,99</sup>

The deactivating influence of the azo group in 1-position of azulene on a second azo coupling can be signaled even for [1,1]biazulene, which can be substituted only at one azulenic moiety (compound **119** in Scheme 40). However, by coupling with an electron rich diazonium salt, such as 4-methoxybenzenediazonium chloride, small amounts of disubstituted product are also obtained.<sup>101</sup>

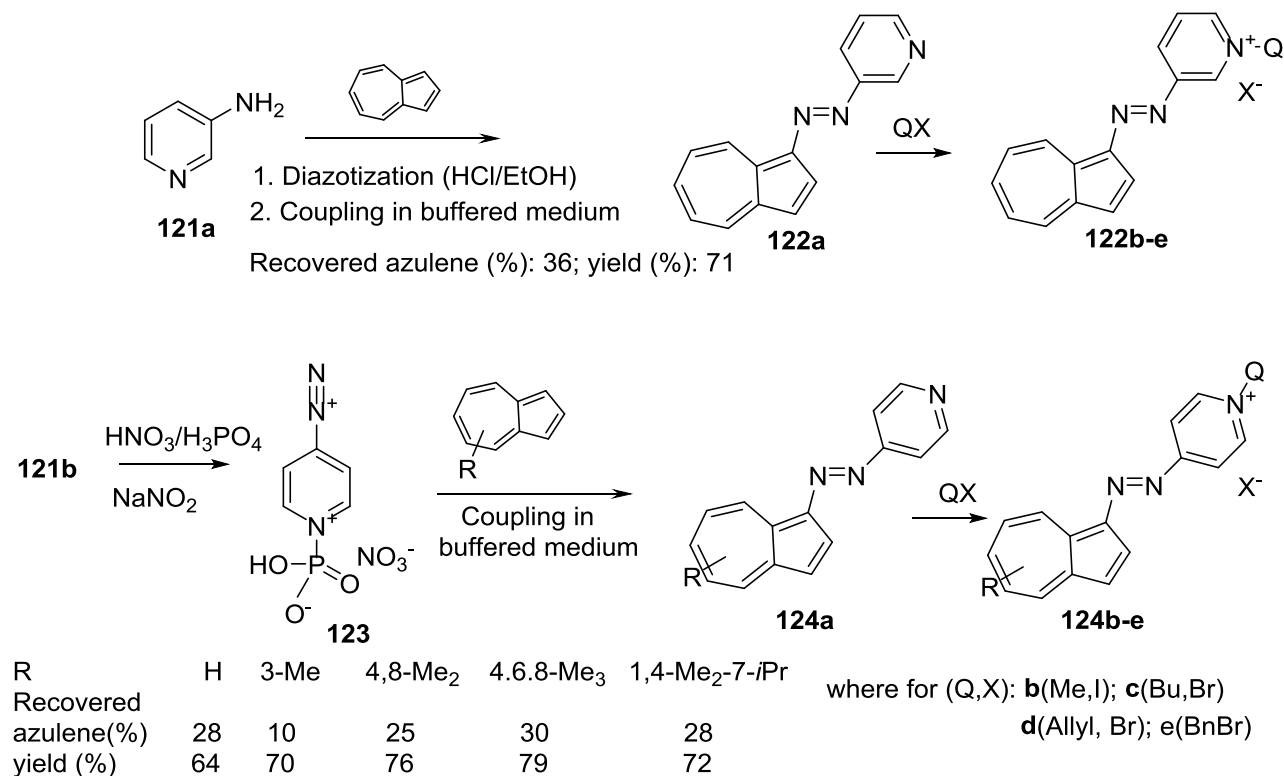


**Scheme 40.** Azo coupling with 1,1'-biazulene and the coupling of guaiazulene with 2-azulene diazonium salt

The resulted salts at the diazotization of 2-aminoazulenes are unstable due to the very fast reaction of the azulene moiety of these salts with nucleophiles, however, curiously, they can be coupled with guaiazulene affording 1-(azulen-2-yl)-2-(guaiazulen-3-yl)diazene, **120** (Scheme 40).<sup>102</sup>

**3.2.2. Synthesis of (azulen-1-yl)diazenes starting from heteroaromatic amines.** As in the case of 1-vinylazulenes, the powerful push-pull electronic effect developed by diazenes where azulene-1-yl, as electron donor, is coupled to a withdrawing heteroaromatic group, stimulated a careful investigation of the synthesis and properties of 1-(azulen-1-yl)-2-heteroaromatic diazenes. The difficulties encountered in their synthesis were related either to the resistance of many heteroaromatic amines to the diazotization or to the low selective reactivity or stability of their diazonium salts. Moreover, it is known that the coupling of these diazonium salts was possible only with basic aromatics and the reaction occurred slowly. For example, the 4-pyridine-diazonium salt, obtained mainly in strong acidic medium, reacts with difficulty with aromatic amines,<sup>103</sup> or with veratrole.<sup>104</sup>

**3.2.2.1. Synthesis starting from aminopyridines.** The satisfactory basicity of 3-aminopyridine allows the successful coupling of the corresponding diazonium salts with azulene in the presence of HCl, in ethanolic buffered medium (azulene conversion 64% and yield 71%, Scheme 41).<sup>105</sup> The yield increases by a further 10% when the reaction was performed in concentrated H<sub>2</sub>SO<sub>4</sub> or in tetrafluoroboric acid.

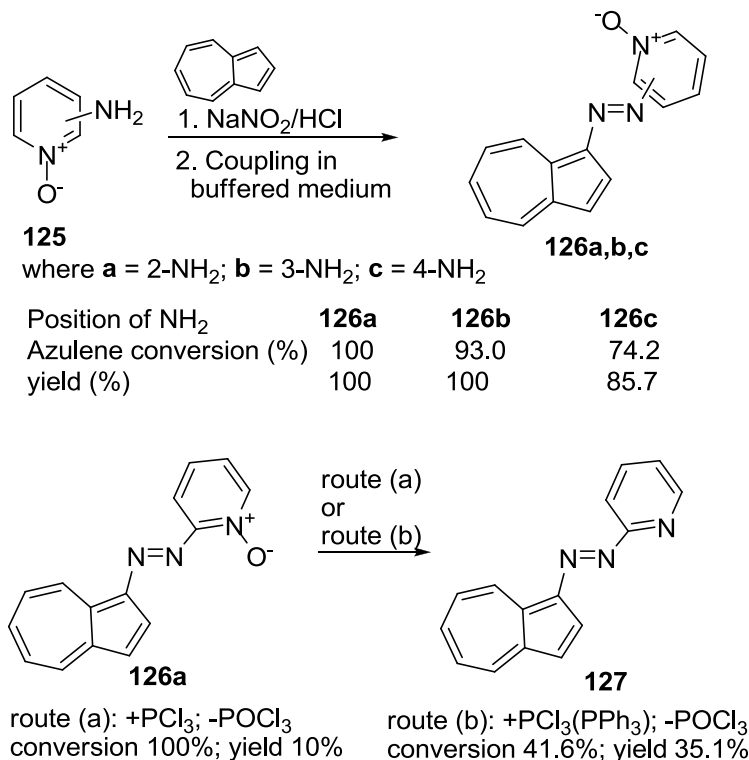


**Scheme 41.** Diazotization and coupling starting from pyridinamines.

Unfortunately, the electronic system of the diazenes, such as **122**, obtained from 3-aminopyridine, does not provide the optimal push-pull activity as the corresponding 2- or, mainly, 4-isomer. Developing a protocol for the preparation of azo dyes from the last two amines represented a challenging task due to the low basicity of 2- or 4-aminopyridine. In addition, the resulting diazonium salts are unstable in acidic medium due to the *ipso*-nucleophilic elimination of a nitrogen molecule prompted by the positive charge on the pyridine nitrogen in position 2 or 4.<sup>106</sup>

Relatively good yields are obtained when the diazotization of 4-aminopyridine **121b** is accomplished in the mixture of  $\text{HNO}_3$  (65%) with a polybasic acid, e.g.  $\text{H}_3\text{PO}_4$  (85%), followed by coupling with azulenes in buffered medium (Scheme 41).<sup>105</sup> These results can be assigned to the formation of a complex **123** where the positive charge on 4-C is reduced by the polybasic acid which, thus, increases the stability of the azo group. Other polybasic acids, such as  $\text{H}_2\text{SO}_4$  or  $\text{H}_3\text{BO}_3$  have been also used, however, with lower success.

An alternative and general route to obtain (azulen-1-yl)diazenylpyridines starts from aminopyridine-1-oxides, **125**, and is depicted in Scheme 42.<sup>107</sup> This is the sole procedure for the synthesis of diazenes with an azo bond in the 2-position of pyridine, as in compound **127**. The diazotization of aminopyridine-1-oxides is suitably performed in aqueous acidic media and occurs with high yields.<sup>108</sup> However, the problem to be solved remains the removal of the oxygen atom from the coupled product without disturbing the reducible azulene moiety and even the azo bond. The method most often used for the oxygen elimination, namely using  $\text{PPh}_3$ , produces in this case only tar and the reaction with  $\text{PCl}_3$  gives the product in only 10% yield. However, a mixture of  $\text{PCl}_3$  and  $\text{PPh}_3$  proves to be effective in the N-O bond breaking (Scheme 42). Despite the very good results from the diazotization-coupling sequence, this pathway remains useful only for generation of 2-(azulen-1-yl)diazenylpyridine, **127**, due to the low yield obtained at the oxygen elimination.

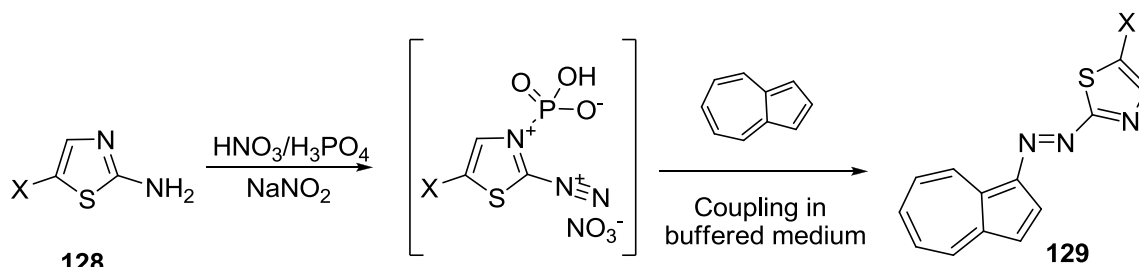


**Scheme 42.** Diazotization and coupling starting from pyridinamine oxides.

Both 3- and 4-(azulen-1-yl diazenyl)pyridines, **122** and **124**, are selectively alkylated in refluxing chloroform on the pyridine nitrogen atom in good yields,<sup>105</sup> using various halides such as those of methyl, butyl, allyl or benzyl (Scheme 41). 1, $\omega$ -Dihalogenated alkanes and di(halogenomethyl)benzenes were also used as difunctional alkylating agents and afforded some bis-azulenylazo derivatives.<sup>109</sup>

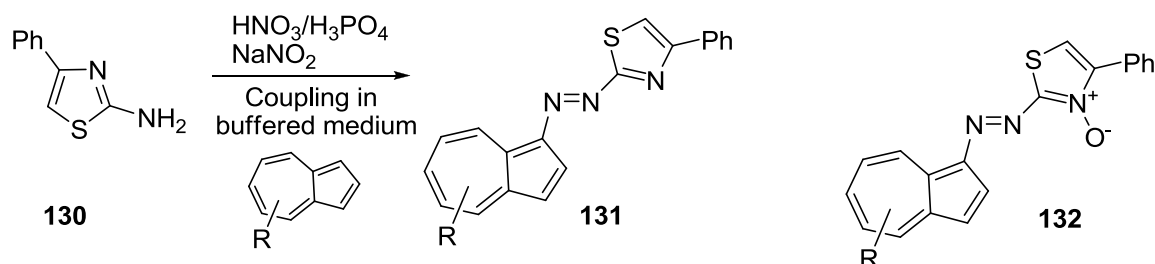
**3.2.2.2. Synthesis starting from 2-aminothiazole or 2-aminobenzothiazole.** The similarity between the electronic density of pyridine and thiazole, as well as the known high  $\beta$ -hyperpolarizability of 2-thiazolyldiazenes with a NO<sub>2</sub> group in the 5-position,<sup>110,111</sup> has stimulated interest in the synthesis and behavior of 2-(azulen-1-yl diazenyl)thiazoles, **129**. The procedure described above for the 4-aminopyridine has also been applied for the tandem diazotization-coupling of 2-aminothiazoles, **128** (Scheme 43).<sup>112</sup> Various substituents X were introduced in the 5-position of the thiazole ring with the intention to influence the dyeing properties of the resulted azulene diazenes. The procedure was then extended to the coupling of diazonium salts arising from 2-amino-4-phenylthiazole, **130** leading to several new diazenes **131**.<sup>112</sup>

It can be pointed out that the synthesis of compounds **132** by diazotization/coupling of 2-amino-4-phenylthiazole *N*-oxide (Scheme 43)<sup>112</sup> represents the first example which starts from an amine with a five-membered nitrogenous heterocycle moiety with *N*-oxide group, thus opening a way for the generation of other derivatives with interesting properties. At the same time, the N<sup>+</sup>-Me derivatives were obtained by alkylation of the compounds **129** with MeI.<sup>112</sup>



X	H	Cl	Br	CO <sub>2</sub> Me	NO <sub>2</sub>	SCN *	SO <sub>3</sub> H
Azulene conversion (%)	100	97.0	64.0	80.4	68.3	54.0	100
Yield (%)	90.0	88.0	98.0	96.3	67.1	56.3	80.0

\*Bis[2-(azulen-1-yl)diazenyl]-1,3-thiazole-5-thio] was also formed in trace

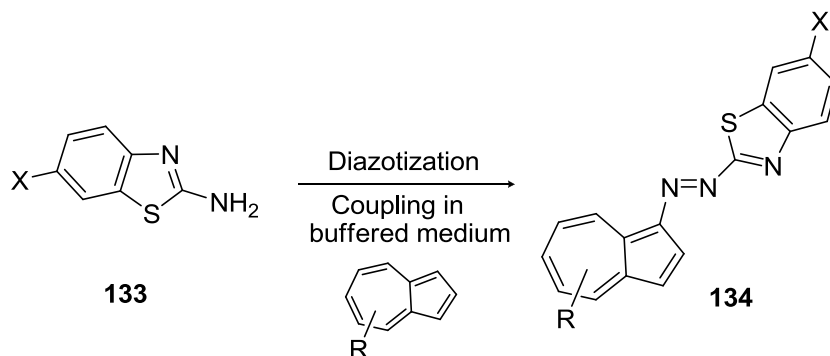


R	H	4,8-Me <sub>2</sub>	4,6,8-Me <sub>3</sub>	1,4-Me <sub>2</sub> -7- <i>i</i> Pr	R	H	4,6,8-Me <sub>3</sub>	1,4-Me <sub>2</sub> -7- <i>i</i> Pr
Recovered azulene(%)	46	52	43	33	Recovered azulene(%)	50	49	33
yield (%)	77	35	30	36	yield (%)	74	77	12

### Scheme 43. Diazotization and coupling starting from 2-thiazolamines and their N-oxides.

Only benzothiazol-2-amine or its derivatives with poor electron donor or withdrawing groups in the 6-position, **133**, can be diazotized and coupled with azulenes. The same protocol as for the thiazole-2-amines was used providing 2-(azulen-1-yl)diazenylbenzothiazoles, **134**, in good yields (Scheme 44).<sup>113</sup> The nitrosation step in the diazotization of 2-amino-6-nitrobenzothiazole is reversible and favors the generation of the unstable 1-nitrosoazulene, resulting in severe reduction of the diazene yield (to 4 %) with the formation of a large amount of tar. The use of nitrosyl sulfate as the diazotization reagent and an excess of both sulfate and amine produces enough diazonium ions to react with azulene and the yield in diazene increases to 84 %. When a methoxy group is present in position 6, it assists the nitration of all positions of the benzo ring by the nitric acid present in the diazotization medium. Therefore, taking into account the stronger basicity of 2-amino-6-methoxy-benzothiazole, the diazotization was performed in phosphoric acid instead of nitric acid with a very good yield (over 80 %).

Because the push-pull effect in 2-(azulen-1-yl)diazenylbenzothiazoles can be improved by the substitution of the azulene moiety with alkyl groups, several alkylazulenes were used, as shown in Scheme 44.



Azulene conversion (%) / yields in products (%)

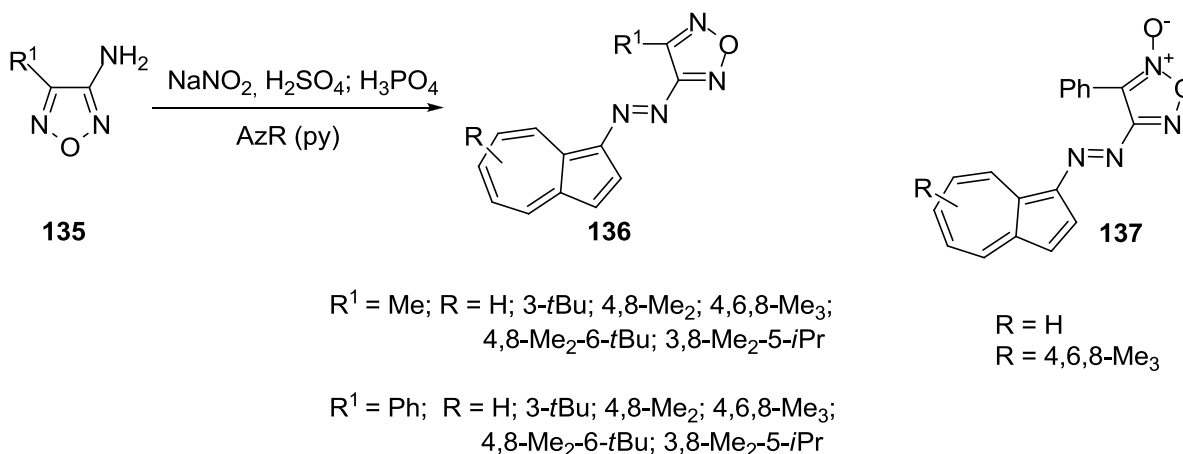
X:	Me	H	Cl	NO <sub>2</sub>
R: H	74/72*	64/83*	64/75*	60/4*; 100/84**
R: 4,6,8-Me <sub>3</sub>	-	-	100/82**	79/33**
R: 3,8-Me <sub>2</sub> -5- <i>i</i> Pr	-	-	100/75**	100/46**

\*Diazotization with NaNO<sub>2</sub> in HNO<sub>3</sub>/H<sub>3</sub>PO<sub>4</sub>

\*\*Diazotization with nitrosyl sulfate in dichloroacetic acid-acetic acid and coupling in the same solvent.

**Scheme 44.** Diazotization and coupling starting from 2-benzothiazolamines.

**3.2.2.3. Synthesis starting from 3-amino-furazans or -furoxan (3-amino-1,2,5-oxadiazoles or 4-amino-3-phenyl-1,2,5-oxadiazole 2-oxide).** Recently, new (azulen-1-yl diazenyl)-heteroaromatic compounds containing 1,2,5-oxadiazol-3-yl moieties and their N-oxides, **136** and **137**, have been prepared, starting from aminofurazan and aminofuroxan (Scheme 45).<sup>114</sup> In spite of the known low stability of the diazonium salts formed from these amines, the reactivity of azulene allows the coupling in yields of between 40-45% for compounds R<sup>1</sup> = Me and 20-40 % for R<sup>1</sup> = Ph; the N-oxide results only in *ca.* 10% yields.



**Scheme 45.** Diazotization and coupling starting from 3-aminofurazan or 3-aminofuroxan.

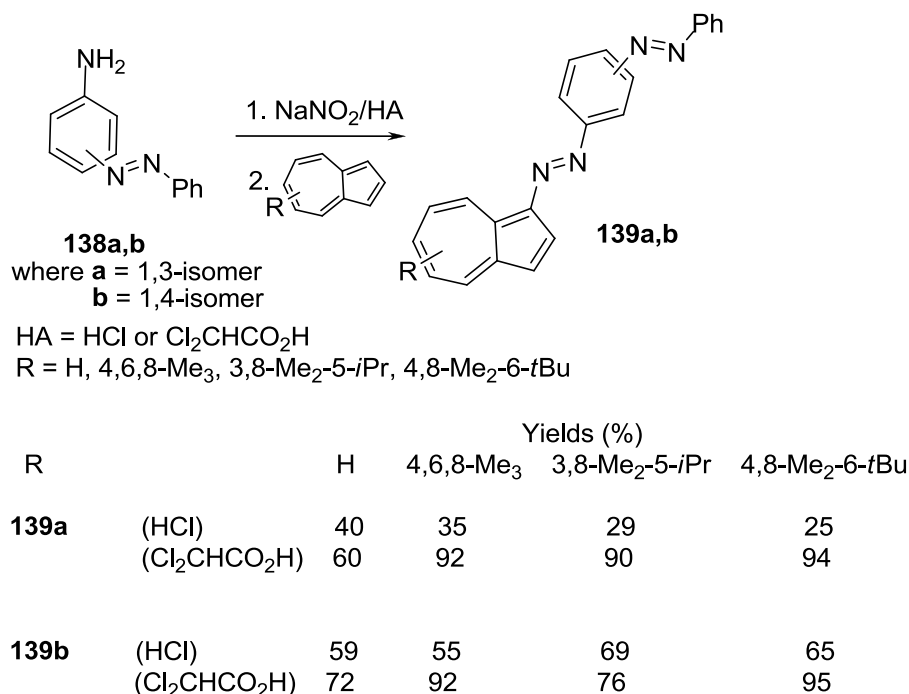
**3.2.3. Synthesis of bis and tris diazenes containing one or two azulene-1-yl moieties.** The direct relationship between the extension of the electron system conjugation and the dyes features, as well as of other properties of the *bis* and *tris* diazenes with phenylene moiety as a spacer between the azo linkages with the azulene-1-yl and phenyl group(s), have stimulated a broad investigation of these compound classes.

**3.2.3.1. Synthesis of bis diazenes with azulene and phenyl at the ends of the system.** Commercially available 3- and 4-(phenyldiazenyl)anilines, **138**, were diazotized and the diazonium salts coupled with azulenes.<sup>115</sup> As shown in Scheme 46, diazotization occurs with difficulty in aqueous HCl due to the low solubility in water of

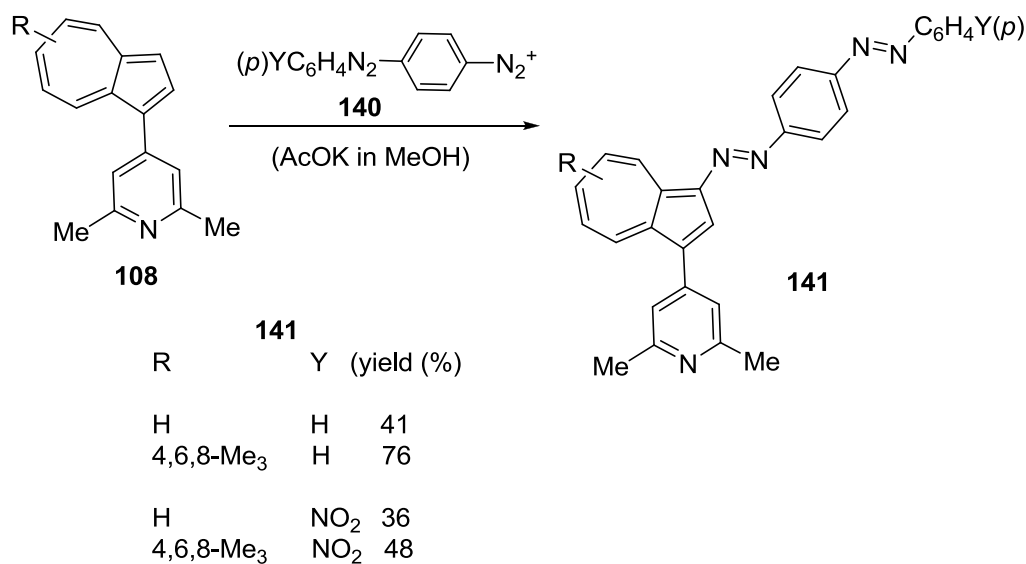
the (phenyldiazenyl)aniline hydrochlorides; however, the yields in products **139** increase considerably working in dichloroacetic acid with a higher solvent power.

Proximity between amino and azo groups in 2-(phenylazo)aniline promotes undesired reactions instead of diazotization; therefore, this starting material cannot be used for generating of bis-diazenes.

Conjugation of the  $\pi$ -electron system was further extended in compounds **141** obtained from (azulen-1-yl)pyridines, **108** and the diazonium salt **140** in methanol buffered with AcOK, as shown in Scheme 47.<sup>115</sup>



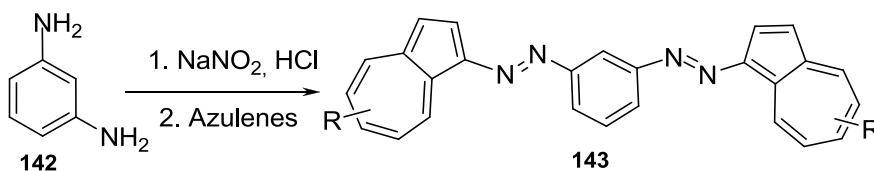
**Scheme 46.** Diazotization and coupling starting from 3- and 4-phenylazoanilines.



**Scheme 47.** Extended conjugation of the  $\pi$ -electron system of bis-diazenes by substitution of the terminal azulene with pyridin-4-yl moiety.

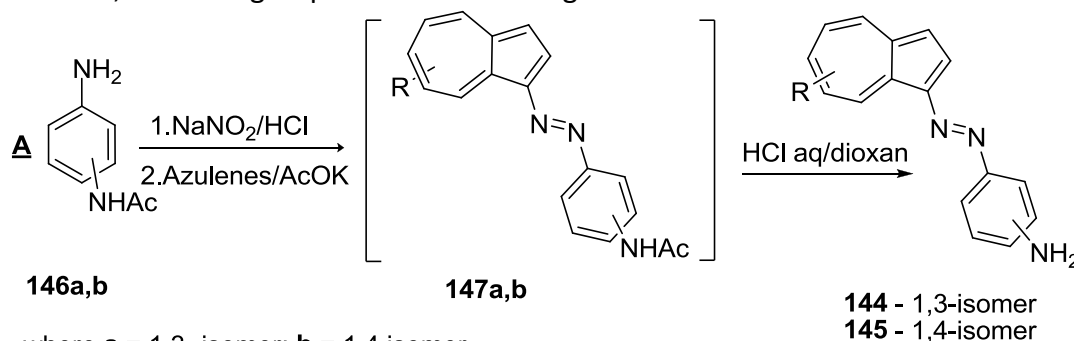


**3.2.3.2. Synthesis of bis-diazenes with two azulen-1-yl groups at the ends of the system.** The attempts to couple bis-diazonium salts, obtained from phenylenediamines, with two equivalents of azulenes succeeded only starting from the 1,3-isomer **142** (Scheme 48); however, even in this case, the yields in the desired compounds, **143** were below 20%, the products being accompanied by a large amount of tar.<sup>116</sup>



**Scheme 48.** Diazotization and coupling starting from 1,3-phenylenediamine.

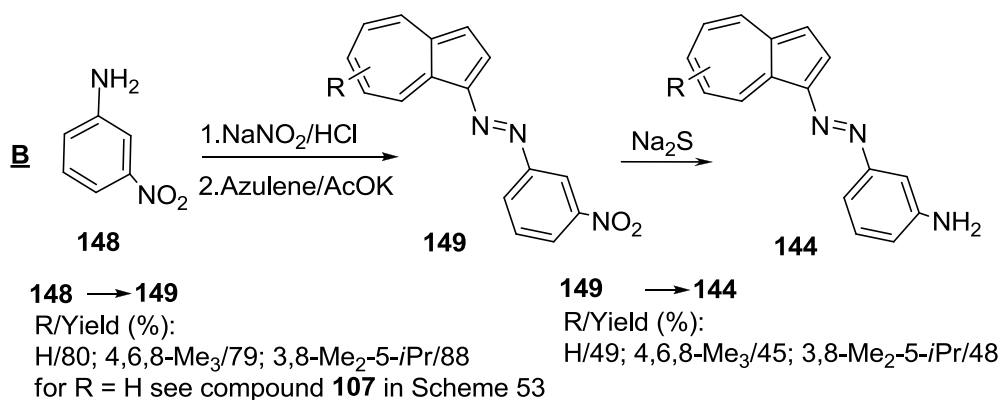
Two routes were developed for obtaining bis-diazenes with two azulen-1-yl groups at the ends of the system, both using as intermediates the (azulen-1-yl diazenyl)anilines **147** or **149** (Scheme 49).<sup>116</sup> One route (pathway A) consists in the hydrolysis of the acetyl group belonging to the intermediates **147** resulted in the coupling of *p*-acetylaminobenzendiazonium salts with azulenes. The alternative route (pathway B) starts from 3-nitroaniline which was normally diazotized in HCl(aq) and coupled with azulenes. Although good yields were obtained for **149**, the nitro group reduction for the generation of amines **144** occurred in lower yields.



where **a** = 1,3- isomer; **b** = 1,4 isomer

**146a** → **144** R/yield (%): H/56; 4,6,8-Me<sub>3</sub>/74\*; 3,8-Me<sub>2</sub>-5-*i*Pr/90\*  
\*in dichloroacetic acid/AcOK

**146b** → **145** R/yield in aniline (%): H/55; 4,6,8-Me<sub>3</sub>/51; 3,8-Me<sub>2</sub>-5-*i*Pr/50

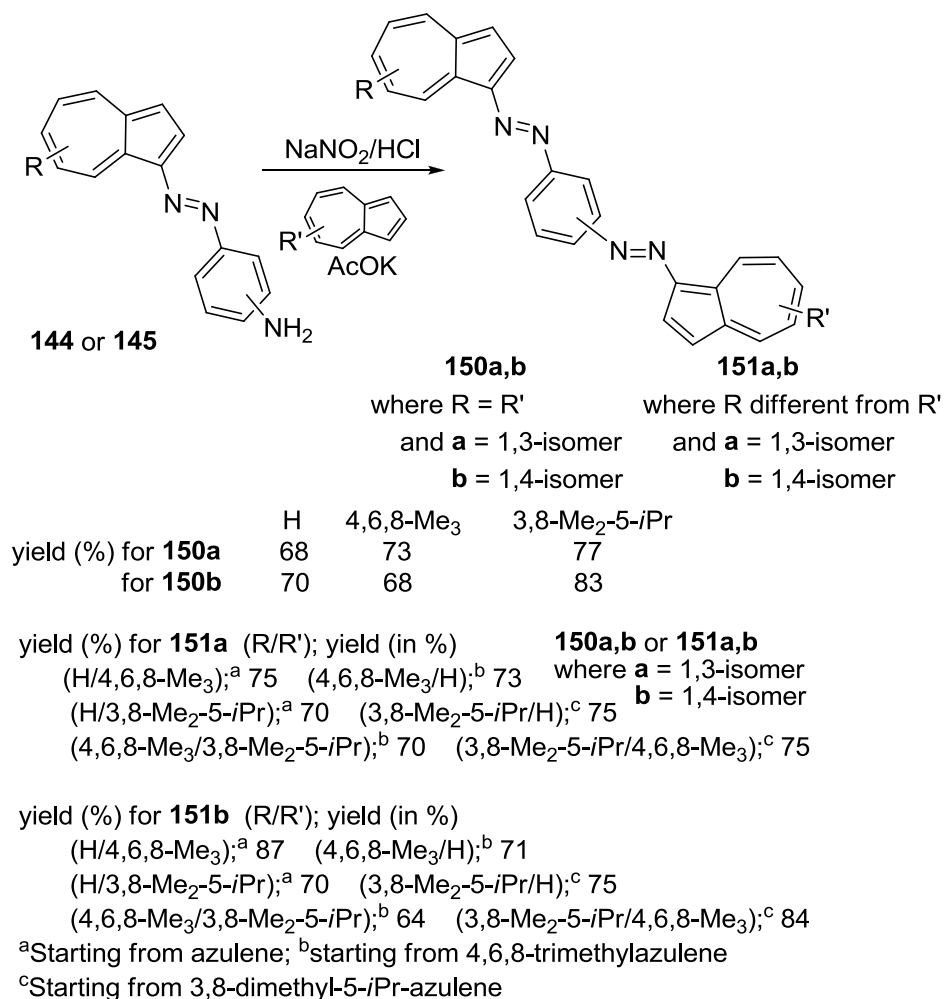


**148** → **149**  
R/Yield (%):  
H/80; 4,6,8-Me<sub>3</sub>/79; 3,8-Me<sub>2</sub>-5-*i*Pr/88  
for R = H see compound **107** in Scheme 53

**149** → **144**  
R/Yield (%):  
H/49; 4,6,8-Me<sub>3</sub>/45; 3,8-Me<sub>2</sub>-5-*i*Pr/48

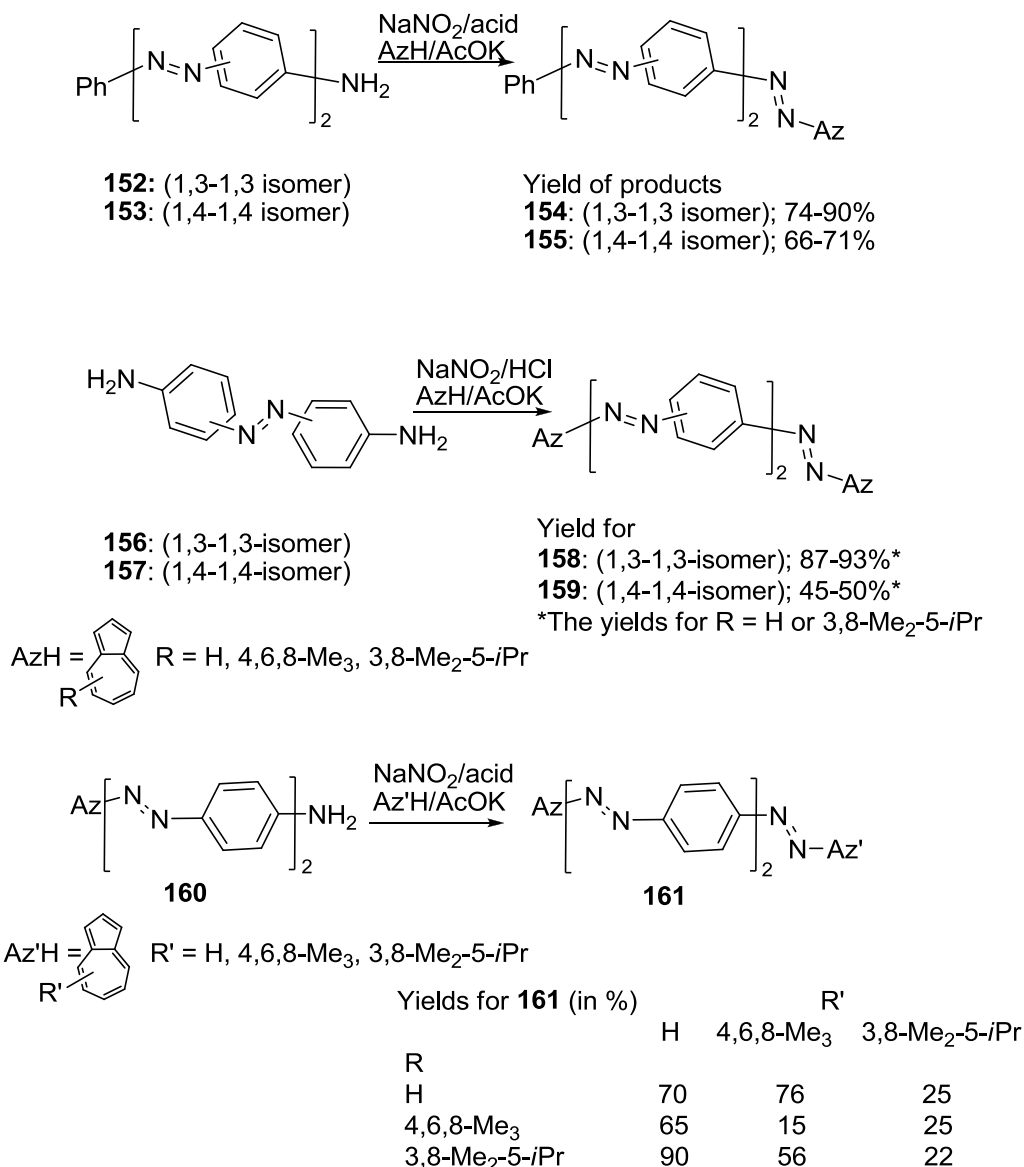
**Scheme 49.** Synthesis of (azulen-1-yl diazenyl)anilines.

Subsequent diazotization of amines **144** and **145** followed by coupling with azulenes affords the bis-diazenes in yields of between 65 and 85%, as shown in Scheme 50.<sup>116</sup> On this pathway it is possible to obtain compounds with two identical or different azulen-1-yl moieties at the end of molecule, **150** or **151**. In the last case, it is possible that the differences between the obtained yields depend on the reaction sequence adopted.



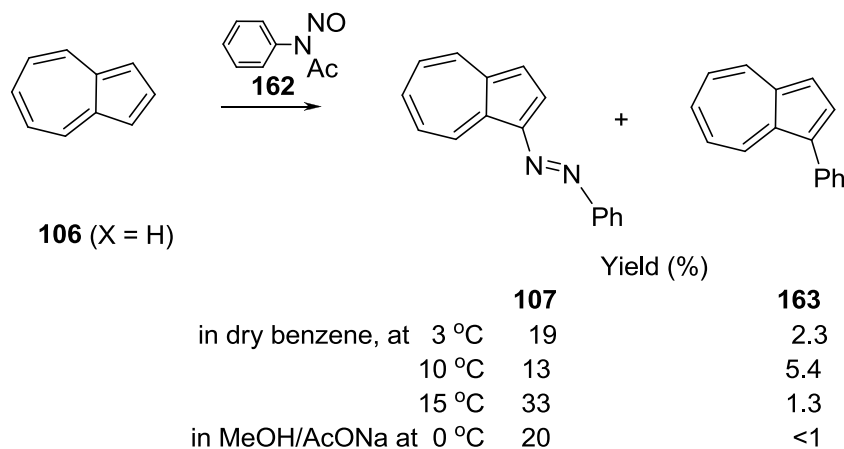
**Scheme 50.** Diazotization and coupling starting from (azulen-1-yl)anilines.

**3.2.3.3. Synthesis of polydiazenes.** Further, investigations were extended into azulene compounds containing three azo groups.<sup>117</sup> The molecules contain a “chain” with two –N<sub>2</sub>–C<sub>6</sub>H<sub>4</sub>– groups with *meta*- or *para*-substituted phenylenes. To one side of the “chain” is attached the phenyl or azulen-1-yl moiety, and on the other side, the (azulen-1-yl)azo group with the same or with different azulen-1-yl moieties (Scheme 51). Their synthesis follows the same route as indicated above, namely diazotization of the suitable amines and coupling of the diazonium salts with azulene in buffered medium. For the compounds **154** and **155** ending with phenyl and azulen-1-yl, anilines **152** and **153** were used. Starting from “azoanilines” **156** and **157** and two moles of azulene, the tris-azo derivatives **158** and **159** with two identical azulenes attached at the system were obtained. It is interesting that, if working with 4,6,8-trimethylazulene, only one amino group was diazotized and coupled. The compounds with two identical or different azulen-1-yl moieties at the ends of molecules **161** were prepared from anilines **160**. As can be seen from Scheme 51, the obtained yields are generally good; however, with the more substituted azulen-1-yl moiety, lower yields were obtained.



**Scheme 51.** Synthesis of *tris* azo derivatives with terminal azulene-1-yl moieties.

**3.2.4. Azo coupling of azulene by radical route** Out of curiosity, the azo coupling of azulene under radical conditions was also performed, however in very low yields. The reaction of *N*-nitrosoacetylaniline, **162**, with azulene affords, together with the desired diazene, the product of arylation, **163** (Scheme 52) and the ratio of the products depends on the conditions.<sup>118</sup>

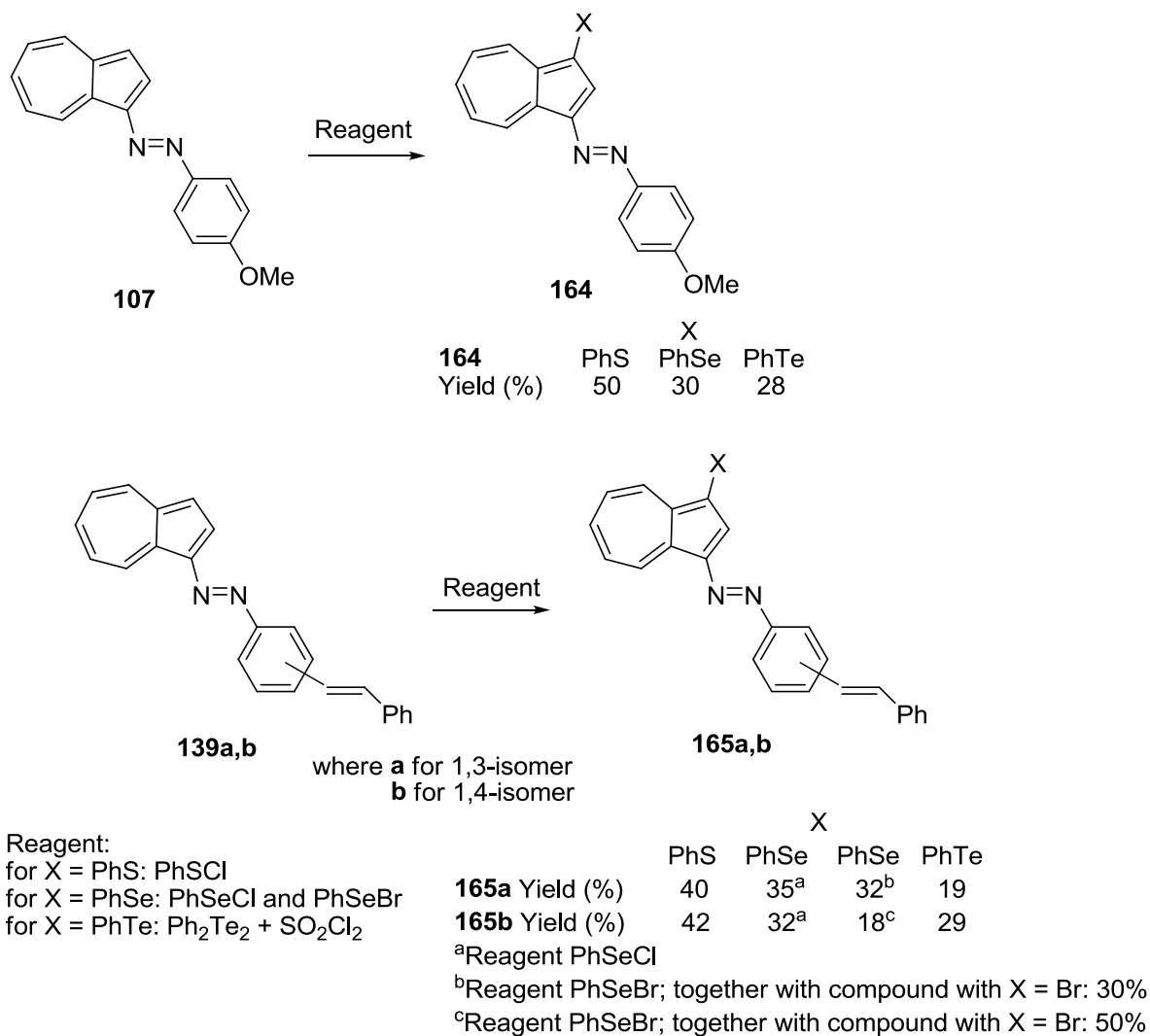


**Scheme 52.** Azo coupling *versus* phenylation of azulenes under radical conditions.

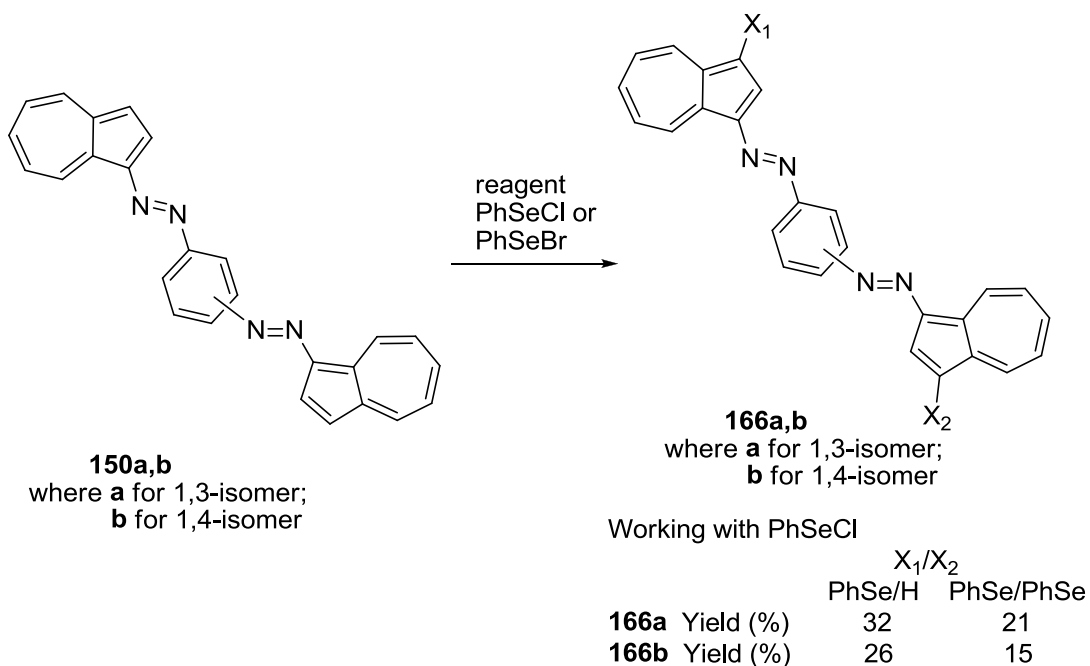
### 3.3. Substitutions of azulene-1-yl diazenes

Despite the deactivating effect of the azo group at position 1 of azulenes, several substitutions of azulene-1-yl diazenes in position 3 still proceeded in acceptable yields affording products which could not be accessed on other routes or for which the synthesis was too difficult. One of the recent examples in this regard is represented by obtaining of chalcogen substituted azulene-1-yl diazenes.<sup>119</sup> Diazenes with PhS in position 3 could be obtained by the diazotization/coupling of 1-phenylthioazulenes, however in poor yields. Due to the difficulties encountered in the synthesis of azulenes possessing PhSe and PhTe in position 1, for the generation of these chalcogen-containing diazenes the substitution of diazenes represents the only practicable route. This pathway was applied for the substitution of diazenes with one or two azo bonds in molecule, **107** and **139** (Scheme 53). As expected, the electrophilic substitution occurs in moderate or reduced yields and together with the targeted products, by-products were also isolated in several reactions. For example, the reaction with PhSeBr produced also a brominated product, probably in a radical process.

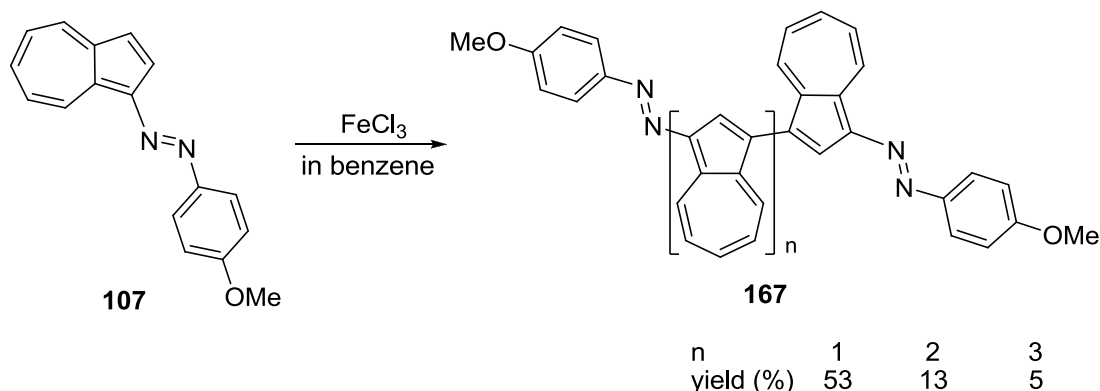
The bis-diazenes with two azulene-1-yl moieties at the end of the molecule, **150** were also reacted with PhSeCl and PhSeBr.<sup>119</sup> With the first reagent, the reaction mixture contained mono- and bis-substitution products, **166** (Scheme 54). The second reagent produced a very complex reaction mixture composed of the products **166** along with the compounds with  $X_1/X_2 = \text{PhSe/Br}$ ,  $\text{Br/Br}$  and  $\text{Br/H}$ .



Scheme 53. Generation of diazenes with phenylchalcogen-substituted azulenes.

Scheme 54. Synthesis of *bis* diazenes with terminal azulenes substituted with phenylselenanyl moiety.

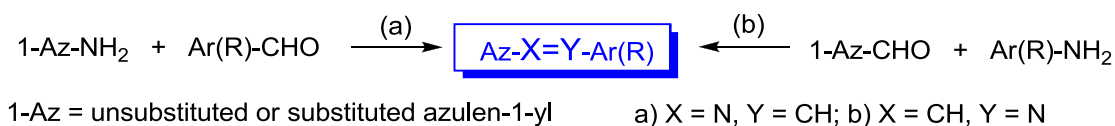
Another peculiar radical reaction takes place at position 3 of azulene-1-yl diazenes under oxidative conditions. As represented in Scheme 55, under the action of ferric chloride, the dimerization of the starting diazenes was observed together with the secondary reactions. When azo group possesses an unsubstituted phenyl moiety, the position 4 of phenyl was linked to the position 3 of azulene belonging to another diazene molecule. Generation of the radical cation of azulene-1-yl diazene was proposed as a reaction intermediate.<sup>120</sup>



**Scheme 55.** Radical linking in position 3 of azulene-1-yl diazenes under oxidative conditions.

#### 4. Azulene-1-yl imines (azomethines or Schiff bases)

The known routes to the synthesis of aryl imines can produce also azulene-1-yl imines starting from 1-azulenamines (route (a)) or azulene-1-carbaldehydes (route (b)).

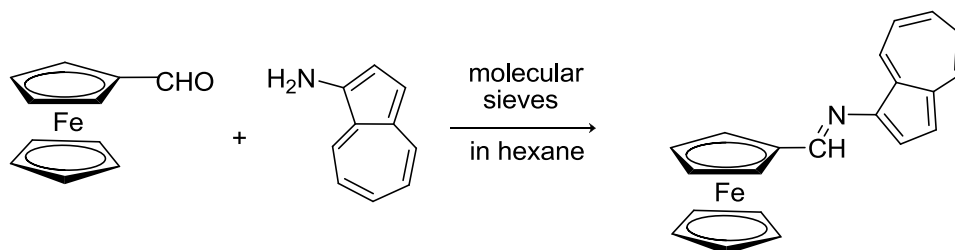


**Scheme 56.** General routes to azulene-1-yl imines.

##### 4.1. Synthesis starting from 1-azulenamines

About the compounds belonging to this class the literature is scarce. Hafner *et al.* reported the condensation of 1-amino-4,6,8-trimethylazulene with 4,6,8-trimethylazulene-1-carbaldehyde or with 4-nitrobenzene carboxaldehyde in pyridine but in relatively low yields.<sup>68</sup>

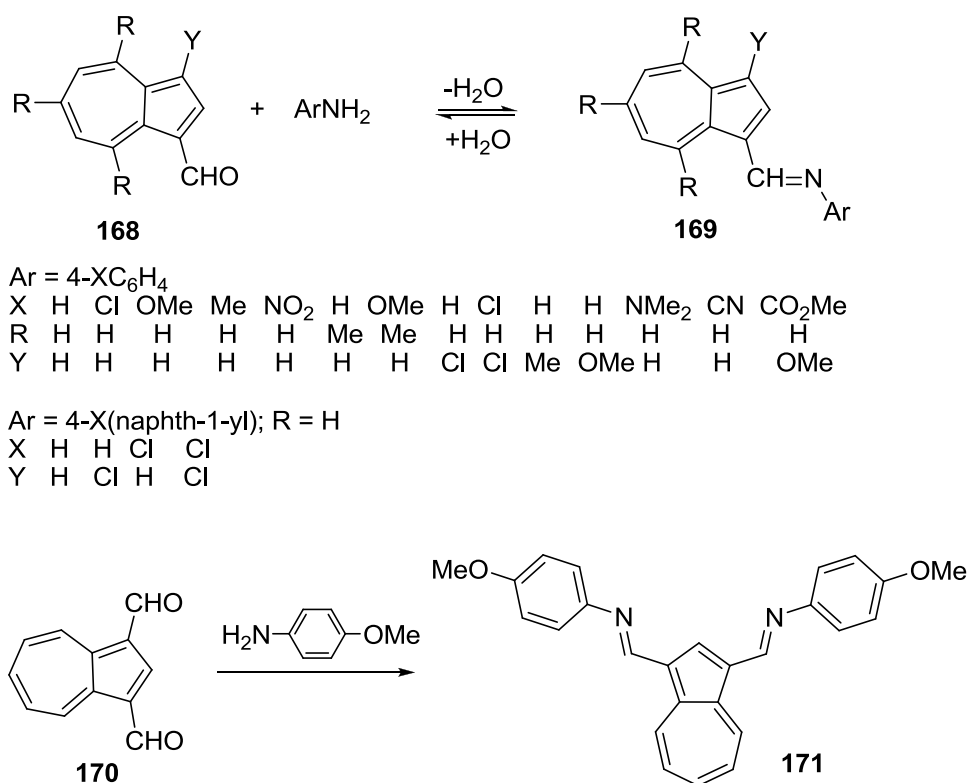
More recently the condensation 1-azuleneamine with ferrocenecarbaldehyde in hexane on molecular sieves was achieved, producing a highly hyperpolarizable compound, as shown in Scheme 57.<sup>5</sup>



**Scheme 57.** Synthesis of azulene-1-yl imines starting from 1-azulenamines.

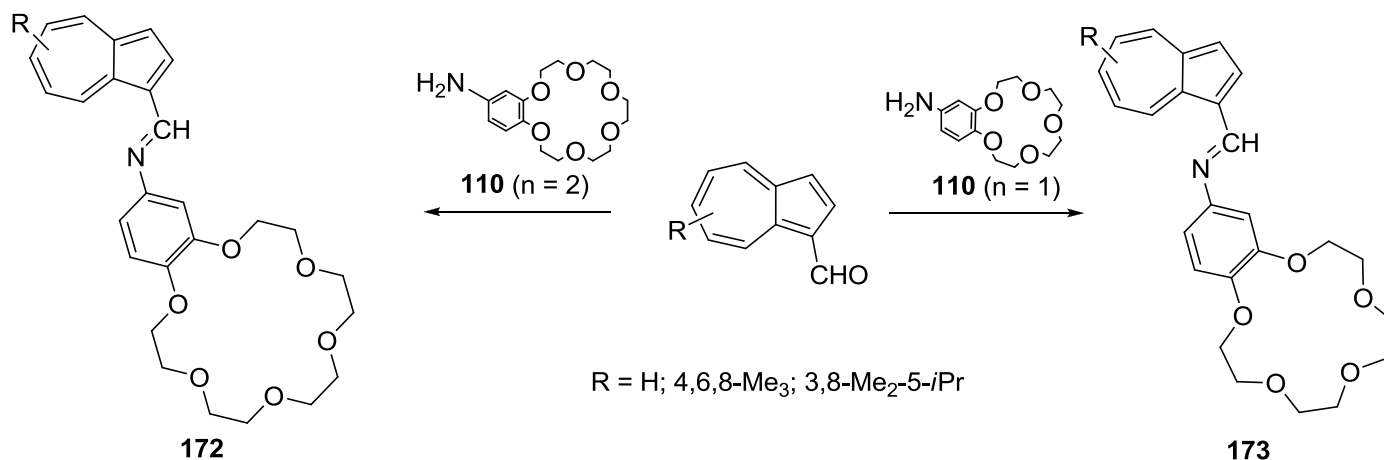
## 4.2. Synthesis starting from azulene-1-yl carbaldehydes

Until 2001 a few references described the condensation between azulene carbaldehydes and amines (e.g. in high excess of amine,<sup>121</sup> in pyridine with amine in excess,<sup>68</sup> in benzene, with ZnCl<sub>2</sub> as condensation agent (with elimination of water as azeotrope),<sup>122</sup> and in dimethylformamide at 70-80 °C).<sup>123</sup> However, the product purification on alumina takes place with significant losses due to hydrolysis of the imines. Several products of condensation between guiazulene-3-carbaldehyde and ammonium salts were reported in a doctoral thesis.<sup>124</sup> The reaction occurred in methanol at reflux and the imines were obtained from their salts after sodium carbonate treatment. In this way 3-(N-tetraacetylglucosylaminomethyl)-guiazulene and azulenimines with substituted phenyl were prepared. Special attention was given to these compounds with the idea of their being used as building blocks in the synthesis of vinylazulenes (see above). Therefore, a great number of such bases have been obtained starting from both 4-substituted anilines and naphthylamines.<sup>125</sup> The condensation between aldehydes and amines is reversible with the equilibrium usually in favor of the starting reagents; therefore, the problem to be resolved remains the water elimination. Just by mixing the starting reagents for a determined time and eventually at a lower pressure, the condensation took place with near quantitative yield (Scheme 58). Even azulene-1-carbaldehydes containing -E groups, such as CN or COOEt, at the position 3 can be condensed with the generation of corresponding imines.<sup>126</sup> The reaction can be applied also for the azulene-1,3-dicarbaldehyde, **170**, as shown in Scheme 58.



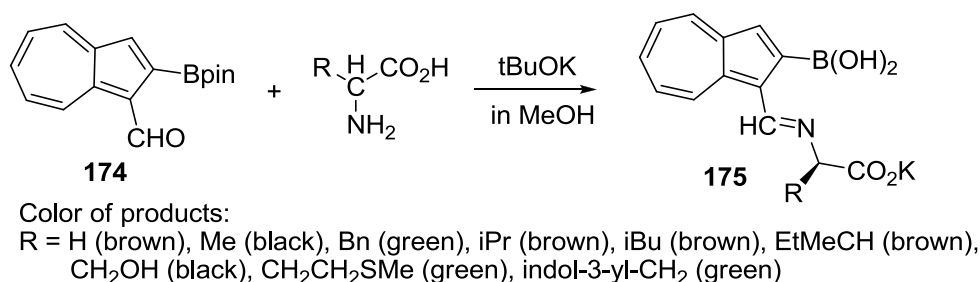
**Scheme 58.** Synthesis of azulene-1-yl imines starting from azulene-1-carbaldehyde.

Several 1-azulenimines **172** and **173** were prepared from the aminobenzo-crown ethers, **110**. These amines are very electron-rich and react easily with azulene-1-carbaldehyde or its alkylated derivatives (Scheme 59).<sup>127</sup>



**Scheme 59.** Preparation of 1-azulenimines starting from aminobenzo-crown ethers.

Not only aromatic amines are used for the generation of 1-azulene azomethines. The finding that some special amino acids can be used to generate photo-functional molecules stimulated the investigation of compounds as those described in Scheme 51.<sup>128</sup> The obtained azomethines **177** present different colors in solid state, depending on the structure of the starting amino acid.



**Scheme 60.** Preparation of 1-azulenimines starting from amino acids.

## 5. Conclusion

The present review is intended as an overlook of the literature data, including our own contributions, to the preparation of azulene compounds with the most common and technically useful double bond at 1-position, namely vinyl, azo and imine bonds. The most used routes for building C=C bonds are: (a) Wittig synthesis starting from azulene-1-carbaldehydes or the phosphonium salt of an azulene-1-ylmethyl moiety, (b) Horner–Wadsworth–Emmons reaction of phosphonate carbanions with azulene carbonylic reagents, (c) condensation between azulenic aldehydes and compounds containing an active methylene group and (d) McMurry synthesis between the carbonyl derivatives of azulene. The substitution of the carbonyl by imine function to the azulene for a milder condensation with compounds containing active methylene, was also described. The next section deals with the synthesis of azulene-1-yl diazenes by azo coupling starting from benzenoid aromatic and heteroaromatic amines and with the synthesis of bis and tris diazenes. A short section presents the preparation of azulene-1-imines. For all classes of the compounds several unusual synthetic procedures have been mentioned.



## 6. Acknowledgements

A. C. R. is thankful to the Humboldt Foundation, and special gratitude is due to Prof. Klaus Hafner for helpful suggestions and discussions during and after the scholarship of the author.

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## Authors Biographies



**Alexandru C. Razus**, after graduating from the Polytechnic Institute of Bucharest, worked three years as engineer in the pharmaceutical industry. Afterwards, based on the results obtained in the Polytechnic Institute, he was asked to come to the Institute of Organic Chemistry of the Academy as scientific researcher. Here he became a PhD in organic chemistry under the supervision of Prof. Costin D. Nenițescu. In the Institute he worked as researcher, senior researcher and from 1990 till 2007 as Scientific Director. He is active also as associate professor in the Department of Organic Chemistry of the Polytechnic Institute of Bucharest and as supervisor of PhD students. He is Humboldt scholar and received the Award of the Romanian Academy. His interest areas are: (a) Friedel-Crafts and related reactions, (b) synthesis and properties of some strained systems containing a cyclopropane ring, (c) synthesis, properties and technical use of azulenic compounds belonging to several classes of compound. (Current address of Dr. A.C. Razus: [acrazus@yahoo.com](mailto:acrazus@yahoo.com))



**Liviu Birzan** was born in 1960 in Bucharest, Romania. He receives his B.S. in Organic Chemistry Engineering in 1985 (five years) from the Polytechnic Institute of Bucharest and M.S. in Chemistry at the University of Rochester, New York, U.S.A in 1995 under the supervision of Dr. Andrew S. Kende. In 2000 he received his Ph.D. degree under the supervision of Dr. Alexandru C. Razus at the Institute of Organic Chemistry "C. D.

Nenițescu” of the Romanian Academy, where he works at present as senior researcher. His work in the USA concerned the synthesis of roquefortine C, and, after returning in Romania, in azulene chemistry, synthesizing numerous derivatives containing alkene, azo or imino pull-push systems, heterocyclic moieties (pyrylium salts, pyridinium salts, pyridine, thiazoles, benzothiazoles, oxadiazoles, thiadiazoles, etc), and heavy elements (Se, Te). He has preoccupations also in compound characterization both as NMR, Uv-Vis, IR, MS spectra and in its electrochemical behavior (CV, DPV).