SYNTHESES OF LIGANDS BASED ON AZULENE DERIVATIVES USED AS METALS SENSORS
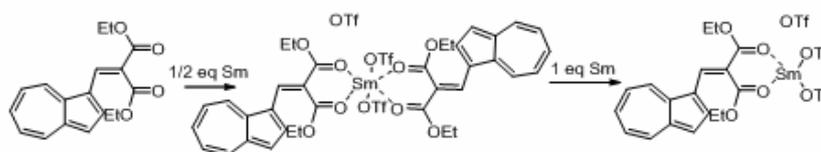
Liviu BIRZAN,[a,*] Mihaela CRISTEA,[a] Victorita TECUCEANU,[a]
Eleonora-Mihaela UNGUREANU[b] and Alexandru C. RAZUS[a]

[a] Institute of Organic Chemistry "C. D. Nenitzescu" of Roumanian Academy, Spl. Independentei 202B,
PO Box 15-258, 71141-Bucharest, Roumania
[b] "Politehnica" University of Bucharest, Faculty of Applied Chemistry and Materials Science,
Gheorghe Polizu 1-7, 011061, Sector1, Bucharest, Roumania

Several synthesis of new 1-vinylazulenes, were reviewed. Knoevenagel condensation of azulene-1-carbaldehyde and its derivatives with compounds containing methylene active groups in the presence of a catalyst represents the main concern. The analyzed redox potentials of synthesized azulene compounds are deeply influenced by the nature of substituents. Some azulene vinyl derivatives interact with metallic cations if they have corresponding auxiliary groups, however, the azulenemethylene thiosemicarbazone have higher ligand effect.

INTRODUCTION

Sensors provide a simple and rapid alternative for the detection of several compounds, which are important in both the chemistry of life and in the technical fields. They avoid the utilization of expensive and complicated devices being miniaturized to rich the development of lab-on-a-chip, which make them portable and very reliable-carrying out analysis in real time. Recent advances in the technological field and the use of new materials with molecular recognition properties, such as carbon nanotubes, micro and nanoparticles, magnetic beads, MIPs, polymers and metal complexes, have led sensor modifications to increase in selectivity, a marked sensitivity and simplification of the analytical devices. In spite of the strong development of the sophisticated materials with molecular recognition properties, the classical ligands with small molecules are still heavily used. Therefore we focused in the preparations of such compounds with azulene-1-yl moiety in molecule. Azulene, being an aromatic hydrocarbon with a strongly polarized electronic system, generates compounds which interact easily with other polar systems and electrodes. Its relatively low stability makes their derivatives able to be oxidized or reduced at low potentials with the formation of films containing diverse functional groups. The purpose of this paper is to present our results in the synthesis and description of the chemical and electrochemical properties of 1-vinylazulene derivatives.

RESULTS AND DISCUSSION

Synthesis of 1-vinylazulene derivatives

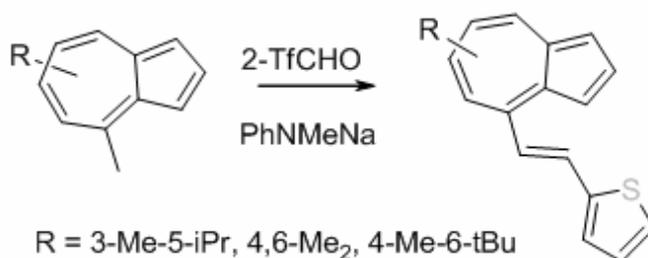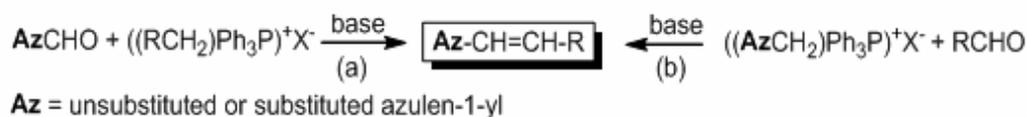One of the earliest procedures for the preparation of 1-vinylazulenes was the Wittig

* Corresponding author: lbirzan@ccocdn.ro, tel: +4021-3167900, fax: +4021-3121601

condensation. There are two alternatives used for Wittig reaction, namely the reaction of azulene-1-carbaldehydes and arylmethylphosphonium salts or the condensation of an azulene-1-methylphosphonium salt with an aromatic aldehyde. With few exceptions, bases used in these condensations led to a mixture of *cis* and *trans* alkenes.
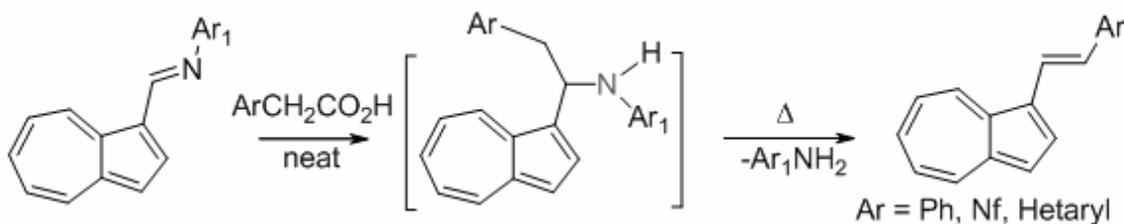
Route (a) occurs with good yields. The alkylated azulenes react depending on the methyl position. While the methyl groups situated on the large cycle are acidic enough for ionization, those attached to the five-membered cycle need an activation group such as Ph_3P^+ or $PO(OEt_2)_2$, to condense with arylaldehydes in the presence of strong bases (Scheme 1)[1]. The condensation on the route (b) is conducted in very strong bases, such as BuLi or LDA.

Some time ago we condensed some azulenic Schiff bases (Scheme 2) with arylacetic acids and a wide variety of 1-(arylvinyl)azulenes were obtained without any catalyst, as trans isomers, with acceptable yields.[2,3,4]
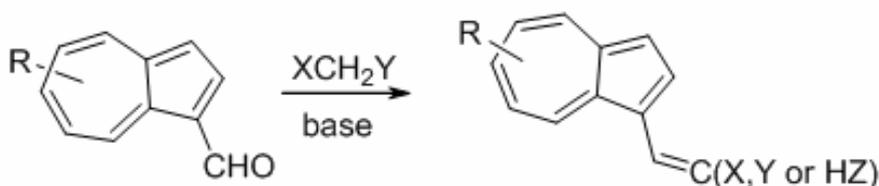
In extension of these outcomes, we have expand the generation of 1-(arylvinyl)azulene series. As was shown above, 1-methyl group at azulene cannot work as an active methylene position in the Knoevenagel condensation, making route b less attractive. On contrary, other compounds with activated methylene groups are easily available being considered in the general reaction with azulene-1-carbaldehydes, as described in Scheme 3. The activating groups X and Y can be either two similar or different EWGs or can be integrated into a heterocyclic system.

AzCHO + ((RCH₂)Ph₃P)⁺X⁻ —base→ **Az-CH=CH-R** ←base— ((AzCH₂)Ph₃P)⁺X⁻ + RCHO
                        (a)   (b)

Az = unsubstituted or substituted azulen-1-yl

R = 3-Me-5-iPr, 4,6-Me₂, 4-Me-6-tBu

Scheme 1

Scheme 2

Scheme 3

Meldrum acid was the first heterocycle used in the condensation with a series of azulenic aldehydes (Scheme 4). Due to the very high acidity of its methylene protons, it reacts with the parent aldehyde neat, without any catalyst.[5] The yields in products **1**R were excellent for R= alkyls and modest when R=COOH or COOMe.

Encouraged by the first results, we used for azulenecarbaldehydes condensations other active heterocyclic systems, such as barbituric and thiobarbituric acids, rhodanine and thiohydantoin (Scheme 5 and Table 1).[6]

However, these heterocycles are less acidic needing harsher reaction conditions for good conversions. More of that, the reaction regioselectivity is reduced by the fact that thiobarbituric acid is not stable in strong basic medium and the azulenic methyls situated on 4-, 6- or 8- positions can interfere generating azulenic self-condensation products. Therefore, pyridine can be used for the condensation of the more reactive barbituric acid, or even for thiobarbituric if no active methyl groups are present on azulene. Diluted HCl is a better catalyst for the condensation of thiobarbituric acid with alkylated azulenes (which do not self-condense in this medium), but the yields are low. The other two heterocyclic systems were condensed in acetic acid/acetate buffer.


R = H, 4,6,8-Me$_3$, 3,8-Me$_2$-5-*i*Pr, COOH, COOMe

Scheme 4
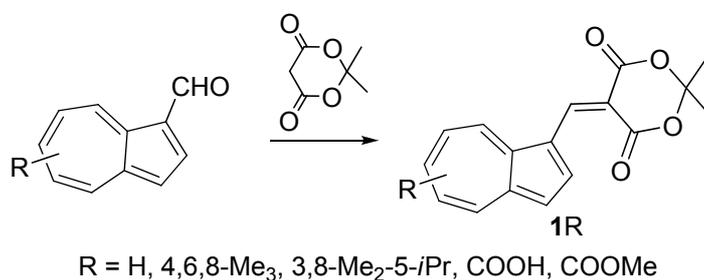
R = H, 4,6,8-Me$_3$
3,5-Me$_2$-5-*i*Pr
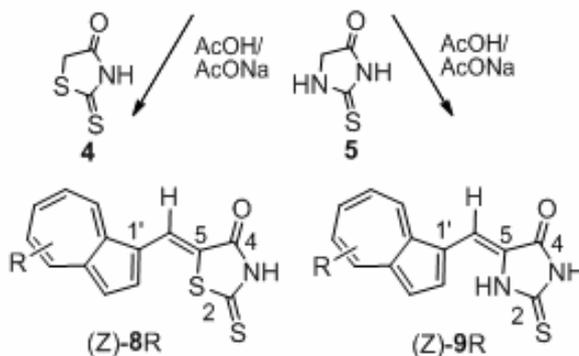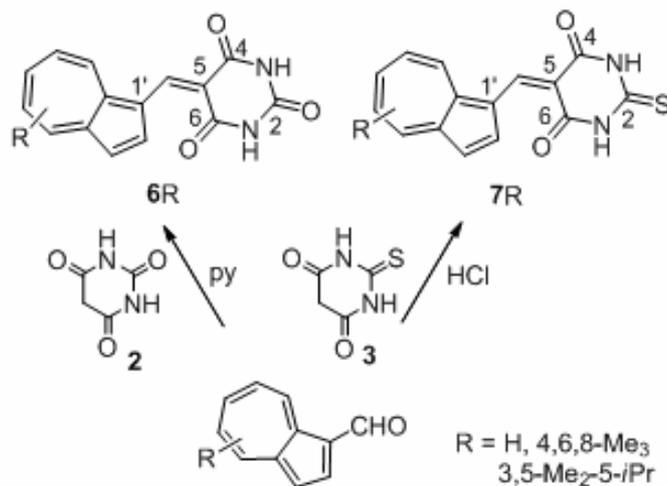
Scheme 5

Table 1

Yields of condensation of azulen-1-carbaldehydes with heterocycles **2–5**

Product	R		
	H	4,6,8-Me$_3$	3,8-Me$_2$-5-iPr
6R (%)	95	95	80
7R (py) (%)	70	-	-
7R (HCl) (%)	69	13	25
(*Z*)-**8**R (%)	36[a]	34[a]	56[a]
(*Z*)-**9**R (%)[b]	57[a]	56[a]	59[a]

[a] In AcOH-AcONa after precipitation and chromatography on alumina column. Without chromatography, raw products were obtained in yield of ~70 % and ~85% for **8** and **9**, respectively. Working with a small amount of piperidine in ethanol at reflux the raw yields were ~50% and ~80%, respectively. [b] Small amount of isomer (*E*) was found in buffered medium.
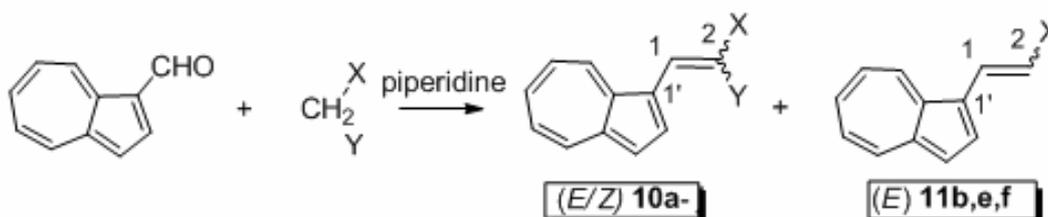
Compounds **10**
a: X=Y=COMe; b: X=Y=CO$_2$Et; c: X=CN, Y=CO$_2$Et; d: X=COMe, Y=CO$_2$Et;
e: X=COCF$_3$, Y=CO$_2$Et; f: X=Y=C(O)SEt; g: X=Y=CONH$_2$; h: X=Y=CONH-nBu;
i: X=Y=CONH(CH$_2$)$_2$OH; j: X=Y=CONH-2py; k: X=NO$_2$, Y=CO$_2$Et

Compounds **11**
b: X=CO$_2$Et; c: X=CN; e: X=COCF$_3$; f: X=C(O)SEt

Scheme 6

Table 2

Condensation yields of azulen-1-carbaldehyde with X(CH$_2$)Y

| Product	**10a**	**10b/4b**	**10c/4c**	**10d/11d**	**10e/11e**	**10f/11f**
Yield in products (%)	51	74/7	58/0	56/0	29/≈2.5[a]	37/44
Recovered **1** (%)	41	2	0	7	39	15

[a] Resulted also compound **4b** (yield ≈2%).

The results of the condensation between azulene-1-carbaldehyde derivatives with compounds containing double activated methylene group (Scheme 6 and Table 2) are next described.[7] The reagents, possessing EWGs groups with different electronegativities, need suitable catalysts. Therefore, the more active are condensed in pyridine, which is compatible with the majority of the activating groups. However, many of them need piperidine in spite of the catalyst reactivity toward some activating groups, due to the very low reactivity of the azulene-1-carbaldehydes. Among the products of side reactions, those obtained by the elimination of C(O)OEt, C(S)OEt or CF$_3$CO groups were detected. However, most of them are not stable and decompose further to polymeric products.

The least reactive derivatives are those of malonamide. To react they must have at least one of nitrogen atoms unsubstituted or only mono substituted in order to generate a cyclic intermediate anion stabilized by strong hydrogen bonds (Scheme 7).

At the same time no competitive azulenic methylene groups attached to the seven-membered ring in positions 4, 6 or 8 should be present. In that case only self-condensation azulenic products are obtained as shown in Scheme 8 or self-polymerization products in the case of 6-substituted aldehydes.
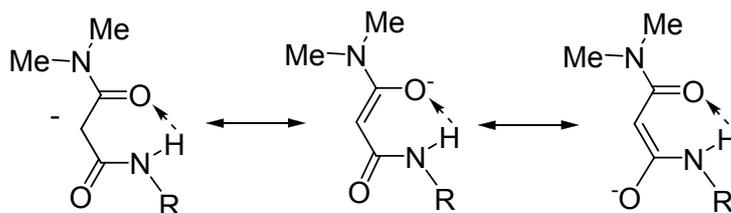
Scheme 7
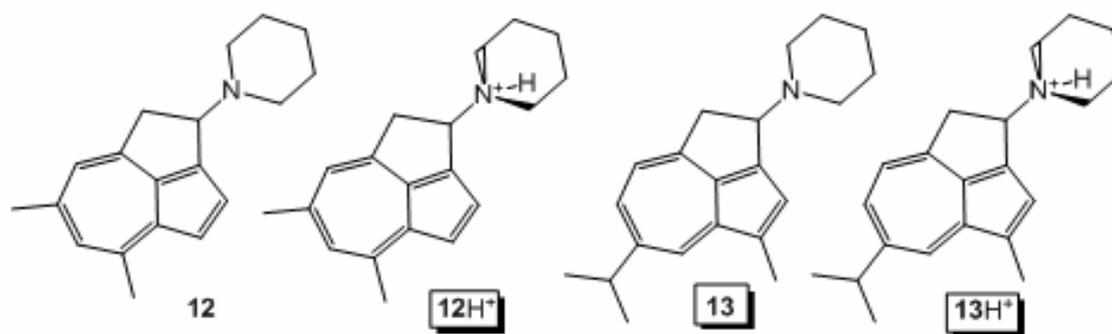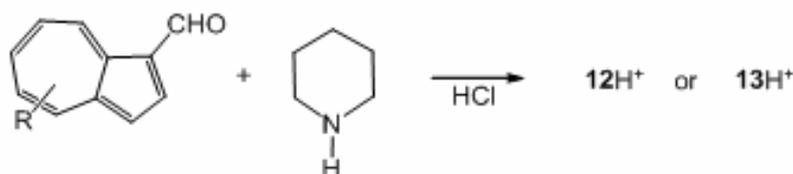
Scheme 8

Scheme 9

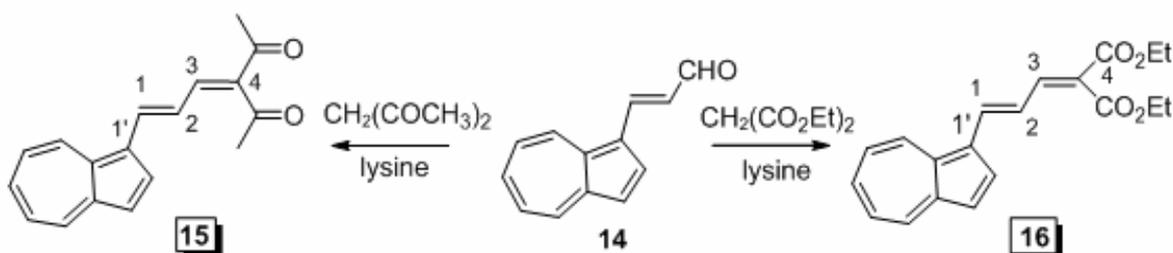Butadiene derivatives, **15** and **16**, are obtained by condensing vinylogated azulene-1-carbaldehyde **14** in a similar manner but in this case a milder catalyst and temperature are used, extending the reactions times (Scheme 9).

Electrochemistry of 1-vinylazulenes

The higher polarization of aromatic azulene, as compared with the normal arylic systems, allows its oxidation and reduction at lower potentials than those needed for classical arylic moieties. These potentials vary widely with the substituents nature; while amide groups as AcNH drop the oxidation

potential to 0.32 V, strong EWG functions, as NO_2 increase it to 1.16 V (Table 3).[8] This behaviour is also found later at 1-azulenediazenes when a large variation of the oxidation and reduction potentials was reported in function of the other aromatic moiety linked by the diazene group.[9]

In this context we have decided to study 1-vinylazulenes, whose redox potentials should also be deeply influenced by the substituents on the vinyl. The highest oxidation potentials are observed for those symmetrically substituted with EWG-s. While the derivative from Meldrum acid is oxidized at 0.87 V,[10] the open correspondent oxidizes at a lower potential of 0.62 V. By replacing COOR with $CONH_2$ group, this potential

falls further to 0.53 V. On the contrary, the condensation compounds of nitroacetate or trifloroacetylacetate esters have higher oxidation potentials, 0.81 V and 0.80 V respectively. These values remain still below that of the compound resulting from Meldrum acid, **1**-H despite the high EWG power of NO_2 or CF_3CO groups, being close to those of barbituric (Z)-**6**H and thiobarbituric (Z)-**7**H condensation products: 0.69 and 0.77 V. The lowest oxidation potentials were determined for the derivatives of rhodanine and thiohydantoin 0.49 and 0.35 V (table 4). The reduction potentials vary in reverse than the oxidation potentials; some peculiar groups, as nitro, trifluoroacetic are reduced at lower potentials. Less expected, in the barbituric series, the thio derivatives are oxidized harder, probably to the electrode passivation by sulfur, and reduced easier than the corresponding oxo derivatives.

Vinylogation reduces significantly the oxidation potential of the compounds but decreases insignificantly the reduction potentials. For example, while the oxidation potential decreases by homologation of the diester from 0.64 V to 0.40 V, the reduction potential remains almost unchanged (-1.65 V to -1.64 V).[7]

Complexation tests with 1-vinylazulenes

The condensation compounds of malonic esters were tested as ligands for lanthanides and heavy metals. Both the electronic spectra and DPV experiments proved the existence of these complexes (Scheme 10). It can be also seen that the absorbance increases with the concentration of Sm(III) ions - a proof that they can be used a sensors.

Table 3

Oxidation potentials of 1R-substituted azulenes (*vs* Fc/Fc[+])

(determined by differential pulse voltammetry (in 0.1 M TBAP, CH_3CN))

R	-NHAc	-Me	-N$_2$Ph	-COOMe	-NO$_2$
E_{ox} (V)	0.32	0.48	0.69	1.27	1.16

Table 4

Redox potentials for azulen-1-ylmethylene compounds **1**H and **6**H - **9**H and for their open corresponding compounds, diamide, **3g**, and bis acetyl derivative, **3a**, (DPV method; in MeCN Fc is 0.070 V)

| Cpd	**1**H	**3g**	**3a**	(Z)-**6**H	(Z)-**7**H	(Z)-**8**H	(Z)-**9**H
E^{ox}, V	0.872	0.535	0.621	0.693	0.768	0.494	0.349
E^{red}, V	-1.371	-1.706	-1.628	-1.420	-1.650	-1.500	-1.600

Table 5

First oxidation potentials for malonic derivatives **10**, E_{a1} (*vs* Fc/Fc[+]) and reduction E_{c1} potentials (determined by differential pulse voltammetry (in 0.1 M TBAP, CH_3CN))

Cpd	**10g**	**10i**	**10h**	**10a**	**10b**	**10d**	**10f**	**10c**	**10e**	**10k**
E_{a1}, V	0.535	0.530	0.540	0.621	0.637	0.639	0.662	0.767	0.797	0.810
E_{c1}, V	-1.706	-1.713	-1.758	-1.628	-1.654	-1.62	-1.563	-1.469	-1.346	-1.210

Table 6

First oxidation potentials for compounds **11**, **15** and **16** E_{a1} (*vs* Fc/Fc[+]) and reduction E_{c1} potentials (determined by differential pulse voltammetry (in 0.1 M TBAP, CH_3CN))

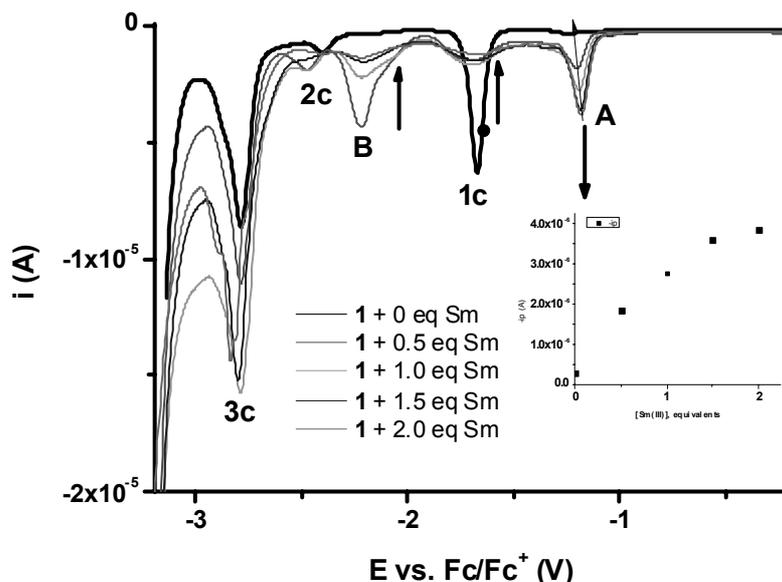| Cpd	**11b**	**11f**	**16**	**15**
E_{a1}, V	0.518	0.553	0.399	0.339
E_{c1}, V	-1.749	-1.691	-1.635	-1.533
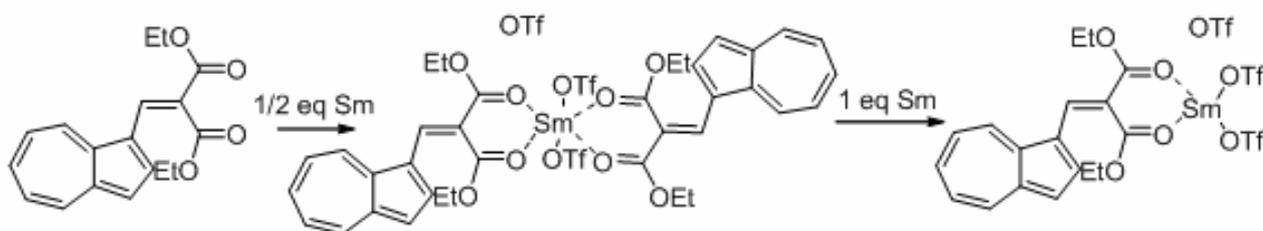
Scheme 10

Fig. 1 – DPV cathodic curves in 0.1M TBAP, CH₃CN on a glassy carbon electrode ($\Phi = 3$ mm) in a solution of **10b** (5×10^{-4} mol / **L**) in the absence (bold black line) and in the presence of increasing amounts of Sm(OTf)₃ (0.5, 1, 1.5, 2 equivalents).
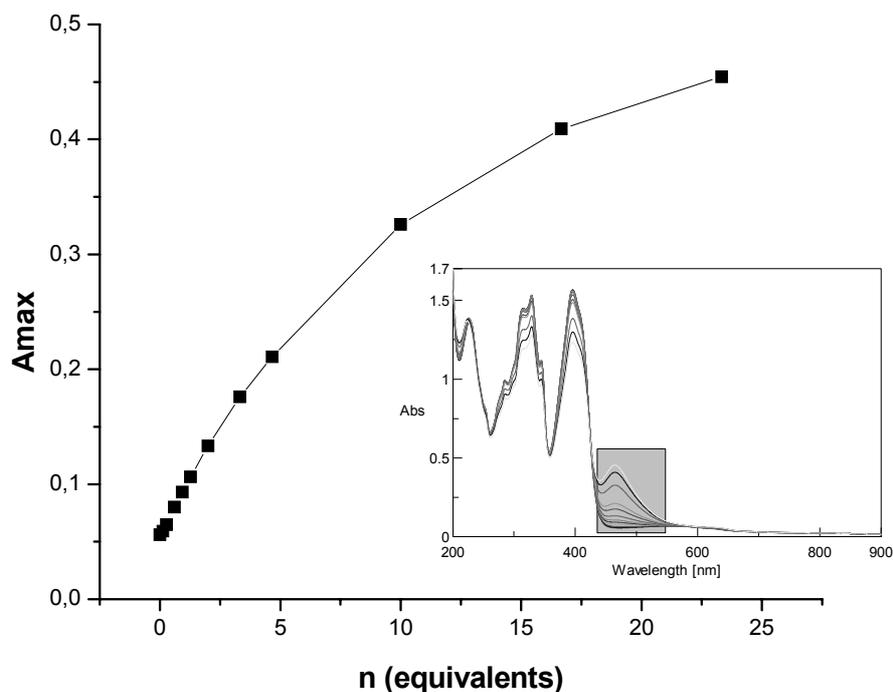

Fig. 2 –Variation of absorbance at $\lambda = 465$ nm with the number of Yb^{3+}equivalents added. Inset: UV-Vis spectra in solutions of **10b** (0.2 mM) containing increasing amounts of Yb^{3+}.

The cathodic part of the voltammogram of diethyl azulen-1-ylvinyliden malonate is deeply influenced by the presence of Sm(III), proving a complexation interaction between Sm(III) and the carboxylate groups of the malonic fragment of **1** (Scheme 10). [11]

After the addition of ½ eq. the samarium (III) salt, a complex 1:2 is formed that reduces in the peak, B (-2.24 V) situated at a higher potential, due to the samarium ion shielding by the ligands. The noncom-

plexed salts is reduced faster at A (-1.17 V), while the ligand is reduced at C (-1.68 V). By adding more amounts of samarium salt the 1:2 complex is destroyed and the 1:1 complex is reduced to the same potential as samarium triflate. Thus, while the peak A increases, the peak B decreases and the small peak C remains almost constant (the free ligand is in equilibrium with the complexes).
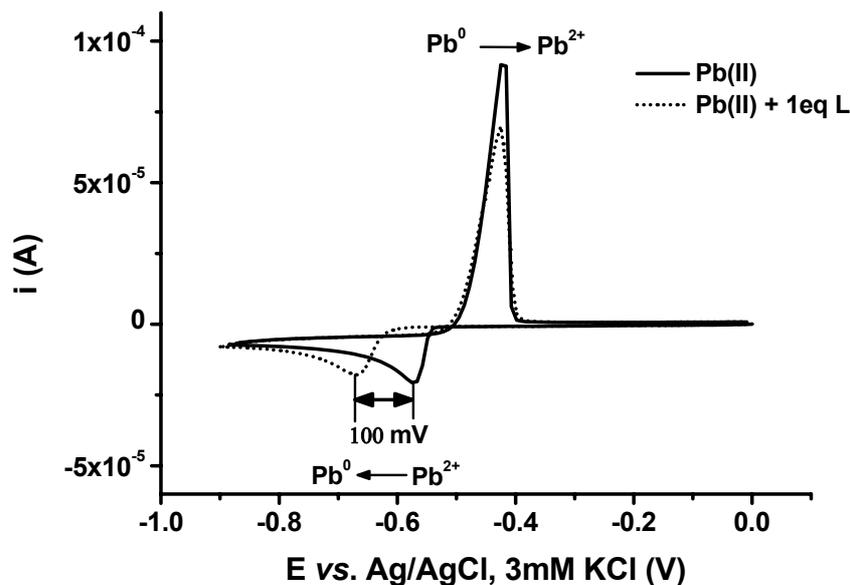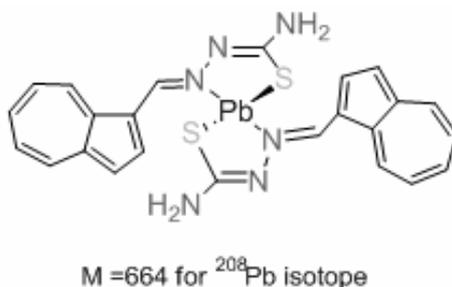
Fig. 3 – Cyclic voltammograms ($25 mVs^{-1}$) at a bare carbon disk electrode (3mm in diameter) recorded in acetate buffer (pH 5.5; M) containing 10^{-4} M Pb(II) in the absence (solid line) and in the presence (dot line) of 1 eq. **L** monomer, **17**.

M = 664 for ^{208}Pb isotope

Scheme 11

The changes of absorbance due to the continuos addition of the $(CF_3SO_3)_3Yb$ solution vary linearly till 2 eq. than they tend to a limiting value around 25 equivalents, behaviour also observed for other triflates of lanthanides, such as Eu, Sm, Tb.

Similar ligands can be used for the identification and/or dozing of transitional metals, such as Pb, Cd, Cu or Hg (Scheme 11). [12]

CONCLUSIONS

New 1-vinylazulenes were prepared mainly by Knoevenagel condensation of azulene-1-carbaldehyde or its derivatives with compounds with methylene active groups in the presence of a catalyst which depends on the acidity of the methylene compound.

From the derivatives of malonic acid, the malonamides are the lowest reactive and need also special condensation conditions. Only the amides containing at least one proton attached at the amidic nitrogen atoms allow the condensation. Azulene-1-carbaldehydes alkylated at the seven-membered ring are harder condensed since they prefer the internal condensation between methyl and carbonyl groups. Similar condensation conditions are used starting from vinylogated 1-azulenecarbaldehydes.

The redox potentials of azulene compounds are deeply influenced by the nature of substituents.

Some azulene vinyl derivatives interact with metallic cations if they have corresponding auxiliary groups; however their affinity is lower than those of the azulenemethylene thiosemicarbazones. However, the formation constants and the shifts in redox potentials show that the new synthesized azulene compounds maybe sufficient to be tested as sensors material.

REFERENCES

1.   A. C. Razus, L. Birzan, V. Tecuceanu, M. Cristea, and C. Enache, *Arkivoc*, **2008**, *xi,* 210-226.
2.   A. C. Razus, C. Nitu, V. Tecuceanu and V. Campeanu, *Eur. J. Org. Chem.,* **2003**, 4601-4610.

3. A. C. Razus, C. Nitu, V. Tecuceanu and L. Birzan, *Rev. Roum. Chim.***, 2005,** *50*, 729-736.

4. A. C. Razus, L. Birzan, V. Tecuceanu, M. Cristea, A. Nicolescu and C. Enache, *Rev. Roum, Chim*., **2007**, *52*, 189-192.

5. A. C. Razus, L. Birzan, L. Cristian and V. Tecuceanu, *Arkivoc*, **2009**, *xi*, 31-44.

6. L. Birzan, M. Cristea, C. Draghici, V. Tecuceanu, M. Maganu, A. Hanganu, A. C. Razus, G. O. Buica, and E.- M. Ungureanu, *Dyes and Pigments*, **2016**, *131*, 246-255.

7. L. Birzan, M. Cristea, C. C. Draghici, V. Tecuceanu, M. Maganu, A. M. Hanganu, A. C. Razus, G.-L. Arnold and E-M Ungureanu, *Tetrahedron,* **2016**, *72*, 2316-2326.

8. E. M. Ungureanu, A C. Razus, L. Birzan, G. Buica, M. Cretu and E. Cristian, *Electrochim. Acta,* **2006,** *52***,** 794-803.

9. E-M. Ungureanu, M.-S. Cretu , G.-O. Buica, A. Razus and L. Birzan, *Electrochim. Acta,* **2008**, *53*, 7089-7099.

10. E.-M. Ungureanu, G.-O. Buica, A. Razus, L. Birzan and E.D. Giol, *Monatshefte fur Chemie*, **2011***, 142*, 243-250.

11. C.-A. Amarandei, G.-O. Buica, G. A. Inel, L. Birzan and E.-M. Ungureanu, *Acta Chem. Slov*. **2014,** *61*, 662-667.

12. G-O. Buica, L.-R. Popescu(Mandoc), A. A. Ivanov, L. Birzan and E.-M. Ungureanu, *J. Solid State Electrochem.*, **2016**, 1-11.