New Benzo- and Dibenzo-Crown Ethers with (Azulen-1-yl)Vinyl Substituents

LIVIU BIRZAN, VICTORITA TECUCEANU, MIHAELA CRISTEA, CONSTANTIN C. DRAGHICI, ANAMARIA HANGANU, ALEXANDRU C. RAZUS*

Romanian Academy, Institute of Organic Chemistry, 202B Splaiul Independentei, 060023, Bucharest, Romania

Abstract: Several 1-azulenyl vinyl crown ethers were synthesized starting from (1-azulennylmethyl) triphenylphosphonium iodide and 4-formylbenzo-crown ethers in the Wittig reaction conditions. The reaction worked in fair conditions and the obtained mixtures of geometric isomers were separated using column chromatography. The isomers were identified using $^1$H-NMR spectra and the mass spectra were recorded using ESI. The UV-vis spectra showed bathochromic effect in Z isomer compared with the E one.

Keywords: azulene, crown ethers, Wittig reaction, NMR spectra

1. Introduction

The benzo- and dibenzo-crown ethers were studied intensively for scientific purposes but also due to their technical importance [1]. The pH-responsive chelation using inserted ionizable moieties [2] or additional functions [3,4], synthesis of supermolecular sensing materials for potentiometric sensing sensors [5], are among their applications. They also can transport cations through cellular membranes into lipid medium as phase transfer catalysts and can be used as chemosensors for metal cations or photosensitive materials [6-8]. However, few compounds belonging to this class were reported containing azulene units. Some results regarding new molecular chromoionophores including in a crown structure azulene moiety, as color-bearing and π-donor system, have been published by Vögtle and all (Scheme 1) [9]. The target compounds were synthesized starting from 1,3-azulenedicarboxylic acids and polyethylene glycol tosylates.

Our interest in the field of crown ethers has already materialized in the research on synthesis and properties of benzo- and dibenzo-crown ethers substituted with (azulen-1-yl)diazenyl [10], (azulen-1-yl)limino and (azulen-1-yl)carbonyl [11] moieties (Scheme 2). It should be emphasized that the coordination of obtained diazenes with heavy metal cations even in very low concentration allows the use of these compounds to detect traces of metals in different media [8]. As pointed above, the presence of azulen-1-yl chromophore in the molecule ensures its color and this feature can provide an increase in the technical importance for such products. Continuing our work in this area, we present in this paper our results on the synthesis and properties of several new benzo-crown ether with (azulen-1-yl)vinyl substituent.

*email: acrazus@yahoo.com
2. Materials and methods

Materials
Melting points (uncorrected): Kofler apparatus (Reichert, Austria). Elemental analyses: COSTECH Automated elemental analyzer CHNS/halogen by catalytic combustion. UV spectra were performed in methanol using a Varian Cary 100 spectrophotometer ($\lambda$ values are given in nm and the molar extinction, $\varepsilon$, in M$^{-1}$cm$^{-1}$units. $^1$H- and $^{13}$C-NMR: Gemini 500 ($^1$H: 500 MHz, $^{13}$C: 125 MHz) and Gemini 300 ($^1$H: 300 MHz, $^{13}$C: 75.47 MHz), $J$ values are given in Hz, TMS was used as internal standard in CDCl$_3$ as solvent; Mass spectra: Varian 310 – MS LC/MS/MS triple quadrupole mass spectrometer fitted with an electrospray ionization interface (ESI). Column chromatography: basic alumina [activity BII-III (Brockmann)] or silica gel [70-230 mesh (ASTM)]. Dichloromethane (DCM) was distilled over calcium hydride and ethyl acetate over anhydrous sodium carbonate.

General procedures for condensation
In the inert atmosphere, to the solution of (azulen-1-ylmethyl)triphenylphosphonium iodide (350 mg, 0.66 mmol) in DCM (40 mL), cooled to -78°C was treated with solid potassium tert-butoxide (896 mg, 8 mmol). To this mixture 4’-formylbenzo-crown-eter (90.6 mmol) was added with stirring. The reaction mixture was stirred for 10 minutes at -78°C and then at room temperature the stirring was continued for 2 ½ hours. Then is added DCM, water and then 10 % HCl solution for base neutralization. The organic layer was separated, washed with water, dried over sodium sulfate and DCM is evaporated. The residue is chromatographed on alumina with petroleum ether-DCM: 1-1. When the starting formyl 3(0) was used, two green bands were separated on column: first allow the isolation of 52 mg (35%) isomer (Z) and the other of 34 mg (31%) isomer (E).

Product characterization
The azulene protons are labeled with numbers and the crown ether protons with Greek letters as in the following model:

(E)-6-(2-(Azulen-1-yl)vinyl)-2,3-dihydrobenzo[b][1,4]dioxine, (E)-4(0), Green oil. UV-Viz (MeOH, $\lambda$ nm/log ($\varepsilon$)): 205 (4.36), 277 (4.22), 318 (4.11), 353 (3.98), 368 (3.98), 399 (3.92). $^1$H-NMR (500 MHz, CDCl$_3$, 25 °C), $\delta$ (ppm): 4.24 (s, 4 H, CH$_2$), 6.84 (d, $^3$J = 8.3 Hz, 1 H, 6-H), 7.00 (d, $^3$J = 9.8 Hz, 1 H, 5'-H), 7.03 (d, $^3$J = 1.9 Hz, 1 H, 3-H), 7.04 (d, $^3$J = 15.8 Hz, 1 H, $^6$CH=), 7.07 (d, $^3$J = 10 Hz, 1 H, 7'-H),
7.07 (dd, $^3$J = 8.3, $^4$J = 1.9 Hz, 1H, 5-H), 7.35 (d, $^3$J = 4.1 Hz, 1H, 3'-H), 7.46 (t, $^3$J = 9.6 Hz, 1H, 6'-H), 7.52 (d, $^3$J = 16.0 Hz, 1H, $^3$CH=), 8.13 (d, $^3$J = 9.3 Hz, 1H, 4'-H), 8.18 (d, $^3$J = 4.4 Hz, 1H, 2'-H), 8.40 (d, $^3$J = 9.8 Hz, 1H, 8'-H) ppm. $^{13}$C-NMR (125 MHz, CDCl$_3$, 25 °C), $\delta$ (ppm): 64.50, 64.58, 114.4, 117.5, 119.0, 119.4, 119.7, 122.6, 123.7, 126.1, 127.6q, 132.4q, 133.3, 133.7, 135.3q, 136.7, 138.3, 142.9q, 143.0q, 143.7q. MS [ESI] = 289 [M+1]. Calcd. for C$_{20}$H$_{16}$O$_2$: C, 83.31; H, 5.59. Found: C, 83.32; H, 5.55.

(Z)-6-(2-(Azulen-1-yl)vinyl)-2,3-dihydropino[b][1,4]dioxine, (Z)-4(0). Green oil. UV-Vis (MeOH, $\lambda$ nm log (e)): 204 (4.46), 279 (4.35), 347 (3.77), 353 (3.74), 358 (3.74), 394 (3.48), 397 (3.48), 401 (3.48). $^1$H NMR (500 MHz, CDCl$_3$, 25 °C), $\delta$ (ppm): 4.17 (d, $^3$J = 1.3 Hz, 2H, CH$_2$), 4.19 (d, $^3$J = 1.3 Hz, 2H, CH$_2$), 6.51 (d, $^3$J = 12.1 Hz, 1H, $^3$CH=), 6.69 (d, $^3$J = 8.3 Hz, 1H, 6-H), 6.83 (dd, $^3$J = 8.3, $^4$J = 2.0 Hz, 1H, 5-H), 6.87 (d, $^3$J = 1.9 Hz, 1H, 3-H), 6.94 (d, $^3$J = 12.1 Hz, 1H, $^3$CH=), 7.04 (d, $^3$J = 9.8 Hz, 2H, $^3$H, $^3$H'), 7.23 (d, $^3$J = 4.1 Hz, 1H, 3'-H), 7.48 (t, $^3$J = 9.8 Hz, 1H, 6'-H), 8.88 (d, $^3$J = 4.1 Hz, 1H, 2'-H), 8.15 (d, $^3$J = 9.5 Hz, 1H, 4'-H), 8.30 (d, $^3$J = 9.8 Hz, 1H, 8'-H). $^{13}$C NMR (125 MHz, CDCl$_3$, 25 °C), $\delta$ (ppm): 64.38, 64.53, 117.0, 117.4, 118.0, 122.0, 122.1, 122.7, 126.2q, 127.9, 132.1q, 136.4, 136.6q, 137.3, 137.9, 141.9q, 142.7q, 143.3q. MS [ESI] = 289 [M+1]. Calcd. for C$_{20}$H$_{16}$O$_2$: C, 83.31; H, 5.59. Found: C, 83.29; H, 5.57.

(E)-4'-(Azulen-1-yl)vinyl)-12-crown-4-ether or (E)-12-(2-(azulen-1-yl)vinyl)-2,3,5,6,8,9-hexahydrobenzo[b][1,4,7,10]tetraoxacyclododecine, (E)-4(2). Green oil. UV-Vis (MeOH, $\lambda$ nm log (e)): 204 (4.46), 278 (4.35), 319 (4.21), 354 (3.97), 368 (3.97), 401 (3.90). $^1$H NMR (300 MHz, CDCl$_3$, 25 °C), $\delta$ (ppm): 3.82 (s, 4H, H-\gamma, H-\delta), 3.89 (s, 4H, H-\gamma, H-\delta). 3.99 (t, $^3$J = 5.1 Hz, 2H, H-\epsilon), 4.21 (t, $^3$J = 4.0 Hz, 2H, H-\Phi), 4.28 (t, $^3$J = 4.1 Hz, 2H, 2H-3), 6.99 (d, $^3$J = 8.2 Hz, 1H, 6-H), 7.07 (d, $^3$J = 15.7 Hz, 1H, $^3$CH=), 7.10 (t, $^3$J = 9.6 Hz, 1H, 5'-H), 7.14 (t, $^3$J = 9.6 Hz, 1H, 2'-H), 7.18 (dd, $^3$J = 8.2 Hz, $^4$J = 1.6 Hz, 1H, 5-H), 7.31 (d, $^3$J = 1.6 Hz, 1H, 3-H), 7.41 (d, $^3$J = 4.4 Hz, 1H, 3'-H), 7.55 (d, $^3$J = 9.6 Hz, 1H, 6'-H), 7.58 (d, $^3$J = 15.7 Hz, 1H, $^3$CH=), 8.20 (d, $^3$J = 10.0 Hz, 1H, 4'-H), 8.23 (d, $^3$J = 4.3 Hz, 1H, 2'-H), 8.45 (d, $^3$J = 9.8 Hz, 1H, 1'-H). $^{13}$C NMR (75 MHz, CDCl$_3$, 25 °C), $\delta$ (ppm): 70.05, 70.10, 70.21, 71.32, 71.80, 72.02, 115.6, 118.2, 119.1, 119.8, 121.1, 122.7, 123.8, 126.2, 127.6q, 133.4, 133.6q, 133.7, 135.4q, 136.8, 138.4, 143.0q, 149.9q, 150.8q. MS [ESI] = 377 [M+1]. Calcd. for C$_{22}$H$_{24}$O$_4$: C, 76.57; H, 6.43. Found: C, 76.55; H, 6.39.
3. Results and discussions

Synthesis

The building of carbon double bond between an aryl and 1 position of azulenes occurs following Wittig condensation [12]. The commercially availability of several 4'-formylbenzo-crown-ethers prompted us to use them as starting materials for the reaction. As active methylene for the Wittig condensation we used the know (azulen-1-ylmethyl)triphenylphosphonium iodide, 1 [13], obtained as in Scheme 3. Because in some cases the arsonium ylides (Scheme 3) are more reactive than phosphonium ylides [14] we tried to prepare this compound and test it in the condensation. Unfortunately, when treating the ammonium salt with triphenylarsine the desired product 2 is not formed. Presumably, the good solubility of arsonium salt allows the reverse reaction with the released amine regenerating the starting ammonium salt (Scheme 3).

The chosen starting ethers for Wittig condensation were 4'-formylbenzo-12-crown-4-eter and 15-crown-5-eter, 3(2) and 3(3) (Scheme 4). Due to the high price of these crown ethers, for the optimization of the reaction conditions several preliminary attempts were made with the cheaper 6-(2-(azulen-1-ylvinyl)-2,3-dihydrobenzo[b][1,4]dioxine, 3(0). Among the reaction conditions described in the literature [10,15], we have chosen tBuOK as base, in dichloromethane (DCM) at -78°C.
Although it is known that in the Wittig reactions the very low temperatures favors the formation of (Z) isomers in kinetic control while the higher temperatures lead to the (E) isomers, mixtures of isomers were usually obtained in almost all our condensation attempts. Treating aldehyde 3(0) with the phosphonium salt 1, in the above mentioned conditions, an almost equimolecular mixture of (Z) and (E) isomers of the desired vinylazulene, 4(0), was obtained with 35% yield (Z) isomer and 31% (E) isomer (Scheme 4). It should be noted that we observed that both isomers are sensitive to the air if they are not pure and crystalized (especially the (Z) one). The identification of isomers was made based on their 1H-NMR spectra, the chemical shifts of vinyl and azulene protons following the model of the same protons in the 1-styrylazulene isomers (Table 1) [16]. An example of such spectrum is presented for the compound (E)-3(2) in Figure 1.

Thus, both vinyl protons belonging to (E) isomer are deshielded compared to (Z) ones, the coupling constants are 12 Hz for (Z) and 16 Hz for (E) isomer. The vinyl proton near azulene is deshielded for both isomers. The existent twist angle between azulene-benzene in (Z) isomer [17], which reduces the molecule polarization due to lower charge conjugation and the coplanarity of (E) isomer, can explain several from the differences noted above. This may also be the reason why the azulene protons H2 and H3 of (Z) isomer are deshielded, while the phenyl protons are shielded. The dimension of the crown ether ring, vinyl and phenyl moieties don’t significantly influence the chemical shifts of the azulene protons.

**Scheme 4.** Wittig reaction between 1-azulenylmethyltriphenylphosphonium iodide and crown ethers aldehydes

**Figure 1.** H-NMR spectrum of (E)-4’-(Azulen-1-ylvinyl)-12-crown-4-eter, (E)-3(2)
Table 1. Chemical shifts for crown ethers 4(0) and (E)-1-styrylazulene (δ in ppm)

| Atom               | H2 | H3 | H4 | H5 | H6 | H7 | H8 | CHAz | CHPh |
|--------------------|----|----|----|----|----|----|----|------|------|
| (Z) 4(0)           | 7.88 | 7.23 | 8.15 | 7.04 | 7.48 | 7.04 | 8.30 | 6.94 | 6.51 |
| (E) 4(0)           | 8.18 | 7.35 | 8.13 | 7.00 | 7.46 | 7.07 | 8.40 | 7.52 | 7.04 |
| E (1)-styrylazulene| 8.25 | 7.40 | 8.20 | 7.07 | 7.52 | 7.11 | 8.48 | 7.71 | 7.19 |

The investigation of crown ethers 3(2) and 3(3) was more complicated due to the small difference between the properties of formed (E + Z) mixture of 4(2) or 4(3). Because of this and, supplementary, due to the low stability of isomer mixtures, their separation and characterization was very difficult. For both products mixture, the first fraction collected by chromatography contains isomers mixture followed by the elution of isomer (E) which crystalize and can be characterized and preserved for days. An additional chromatography allowed the separation of a little amount of isomer (Z) 3(2) which could thus be characterized. Whereas, the yields in Table 2 for reaction of compound 3(0) were calculated for each isomer, for starting 3(2) and 3(3) the reported yields refer to unseparated isomer mixture.

Table 2. Yields for Wittig reaction

| Alkene   | 4(0) | 4(2) | 4(3) |
|----------|------|------|------|
| Yield (%) | (Z) 35 / (E) 31 | 38 | 80 |

Attempts were also undertaken to obtain dibenzo-crown ethers substituted with (azulen-1-yl)vinyl moieties. The synthesis starts with the formylation of available dibenzo-18-crown-6-ether using a Duff protocol described by Jagdale at al. [18] (Scheme 5). Thus, after condensation with hexamethylene-tetramine in presence of trifluoroacetic acid and iminium salt hydrolysis, a mixture of three bis formylated compounds was obtained with 70 % yield [19]. The practically identical properties of the generated isomers did not allow their separation.

Scheme 5. Preparation of the bis (azulenevinylbenzo)-18-crown-6-ether

The next step, Wittig condensation, started from this mixture and, using the reaction conditions described above, a complex mixture of positional and geometric isomers was formed. Once more, the very similar physical properties of these isomers and the tendency to decompose in a relatively short time, made impossible to separate and characterize individually the products. In fact, even the 1H-NMR cannot discriminate between isomers. Fortunately, the first eluted compound on chromatography column, 4,4’-[Z,Z-bis(azulen-1-ylvinyl)]dibenzo-18-crown-6 ether, 7, was enough pure to allow its characterization. More research must be done to improve the separation of the formylated intermediates and Wittig reaction products for their characterization.

Some considerations about MS and UV spectra

Literature points out that, sometimes, in the mass spectra using ESI together with the signal for protonated molecular ion its complexes with sodium or potassium ions may be present due to accidental
contamination of the sample [30]. We found that better spectra are obtained if some ammonia is added to the sample allowing the formation of a strong peak of ammonium complex and very weak peaks of others metal ions. For example, in Figure 2 is presented the mass spectrum of \((E)-4^\prime-(azulen-1-ylvinyl)-15\)-crown-5-eter, \((E)-4(3)\), in the presence of ammonia \((M+NH_4^+ = 438, M + Na^+ = 443, M + K^+ = 459)\).

![Figure 2](image2.jpg)

**Figure 2.** The mass spectrum of \((E)-4^\prime-(Azulen-1-ylvinyl)-15\)-crown-5-eter in the presence of ammonia, \((E)-4(3)\)

The complexes can be decomposed during the signal splitting at low energies as can be seen in Figure 3 (10 eV).

![Figure 3](image3.jpg)

**Figure 3.** The mass peak of \((E)-4^\prime-(Azulen-1-ylvinyl)-15\)-crown-5-eter splitting at 10 eV

It is known from the Curie paper [13] that the *cis* isomers of styrylazulenes are slightly hypsochromic than the *trans* isomers. However, he took in consideration the very weak band S1, which we did not studied being concentration dependent. It can be seen better in a nonpolar solvent and is split to a plethora of bands in polar solvents, such as methanol. For styrylazulene, the *trans-cis* variation in cyclohexane for this band is 626-647 nm, respectively. For the main visible band S2, the variation is much lower 313-317 nm. This behavior was explained by the steric destabilization of the *cis* isomer. In our study, S2 varied in methanol for *cis-trans* isomers from 402-399 nm, the gap being very little influenced by the
size of the crown ether. In this solvent, the $S_1$ band is split into almost 100 bands above 600 nm. However, the color remains bluish-green or green as in the case of other styryl azulenes.

4. Conclusions

Several 1-azulenyl vinyl crown ethers were synthesized starting from (1-azulenylmethyl) triphenylphosphonium iodide and 4-formylbenzo-crown ethers in the Wittig reaction conditions. The reaction worked in fair conditions and allowed mixtures of geometric isomers. The resulted compounds were blue-green oils, which, if pure, crystallized in time as green solids. The oily products are not stable in air for a long time, turning in a black tar. The Z isomers are also not completely stable on column, partially changing to E-isomer. The isomers were easily identified using H-NMR technique. The mass spectra were performed using ESI procedure. However, to obtained good spectra, ammonia must be used to generate a more stable ammonium complex, which can be decomposed by splitting the molecular ion. The Z isomers absorb in visible domain at higher wave lengths than the corresponding E isomers but all compounds are bluish-green or green.

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Manuscript received: 17.07.2020