Facile One-pot Synthesis of A Novel Propargyl-Azulene Hybrid Derivative: Cycloaddition Reaction and Some Spectroscopic Properties

Musa ERDOĞAN[1*]

ABSTRACT: Guaiazulene, *1,4-dimethyl-7-isopropylazulene*, is one of the non-benzenoid aromatic compounds consisting of fused of the seven- and the five-membered ring. Guaiazulene is an important natural product and having great potential due to its unique optical and electronic properties. In this study, a method for propargyl insertion into the C-4 methyl group of the guaiazulene is developed. A one-pot reaction of the guaiazulene, LDA, and propargyl bromide in THF affords the corresponding a new propargyl-azulene hybrid derivative. Additionally, Diels-Alder cycloaddition reaction between the propargyl-GA and tetraphenylcyclopentadienone was performed, and the cycloadduct was obtained with excellent yield. The structures of new compounds were elucidated on the basis of extensive spectroscopic (IR, NMR, and UV-vis) data analysis. This approach may be potentially useful for the development of the new azulene derivatives.

Keywords: Azulene, guaiazulene, propargylation, alkynylation, one-pot synthesis, Diels-Alder, cycloaddition

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INTRODUCTION

Azulene (**1**) is a non-alternant aromatic hydrocarbon that has fascinated chemists for many years due to its excellent blue color and high dipole moment (Cowper et al., 2016; Narita et al., 2018). Azulene skeleton is one of the bicyclic aromatic systems containing 10π-electron (Kiriazis et al., 2017) (Figure 1). The azulene (**1**) one of the isomer of colorless naphthalene and displays a blue color that has fascinated people since medieval times (Amir et al. 2011; Woodward et al., 2016). In general, naturally occurring derivatives can be obtained from plant sources (Gordon, 1952). The most typical features of azulene derivatives are the ability to have redox processes easily. It has also a polar character due to the contributions of charged aromatic scaffold structures such as cyclopentadienyl anion and tropylium cation (Aumüller and Yli-Kauhaluoma 2009). The fused two-ring system contributes to the dipolar nature of the molecule with a high, 1.08 D dipole moment and increased reactivity. Five-membered cyclopentadienyl unit of the azulene carries a partial negative charge, so electrophilic aromatic substitution reactions (S_EAr) occur at the C1 and C3 positions of this unit (Székely et al., 2017). Therefore, substituted azulene reported in the literature relates to the positions, which are the most reactive in S_EAr reactions.
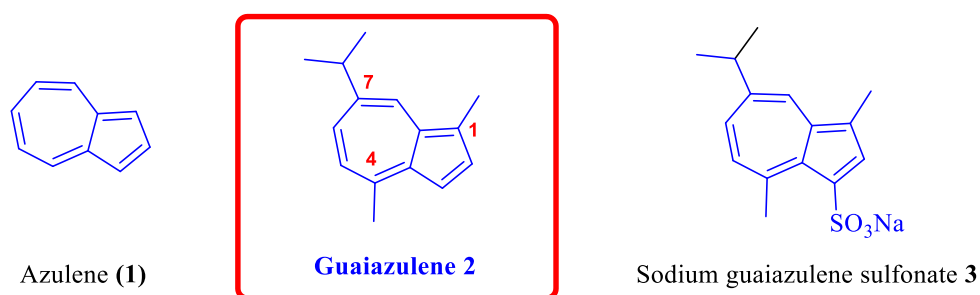

Figure 1. Structures of azulene (**1**), guiazulene **2** and sodium guiazulene sulfonate **3**.

With their unique chemical and electronic properties, the substituted azulenes have diverse applications in medicinal chemistry (as antiulcer (Yanagisawa et al., 1988), antidiabetic (Imamura et al., 2012), anticancer (Asato et al., 1993), antiarrhythmic (Tanaka and Shigenobu, 2001) and anti-erectile-dysfunction (Shoji et al., 2020) agents, and as TXA2 receptor antagonists (Tomiyama et al., 1993)), in photosensitizers (Ghasimi et al., 2016), multistate switches (Vlasceanu et al., 2016), as metal-organic frameworks for hydrogen storage (Barman et al., 2010), chromophores (Wang et al., 1999; Zadeh et al., 2015).

Guaiazulene (GA) **2** is a natural derivative of the azulene (**1**) and can be extracted from plants. It is found in nature as a component of the pigments of mushrooms, guaiac wood oil, and some marine invertebrates, and these natural resources currently serve as commercial sources. The GA **2** is an FDA approved cosmetic color additive and has potential applications as an anti-inflammatory, pain reliever, antioxidant, antiviral, and anti-ulcer drug. Due to its rose-like scent, it is used as a fragrance in some formulations. Because of these multiple uses, the discovery of simple access to guaiazulen derivatives would be very useful (Zhao et al., 2013). The GA **2** is the main active ingredient of the plant '*Matricaria chamomilla L.*', and displays alluring pharmacological properties, including antipepsin, antiinflammatory, antianaphylaxis and promoting mucosa's metabolism (Zhang et al., 2011; Cao et al., 2016). Sodium guaiazulene sulfonate **3**, a hydrophilic derivative of GA **2** with its excellent anti-inflammatory effect, is the main component of *Compound Glutamine Granules* which used in gastric ulcer treatment (Seo et al., 1996; Chen et al., 2012). Among the known natural pigments, the GA **2** has recently gained popularity due to its interesting physical and electronic properties. As a non-toxic natural

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product found in *Guajacum Officinale and Matricaria chamomilla* oils and lively blue mushroom Lactarius indigo, the GA **2** is approved by the FDA as a cosmetic color additive. GA core exhibits a relatively large permanent dipole moment because it contains a fused electron-rich cyclopentadiene and electron-poor heptathrine skeleton, which causes aromatic delocalization energy to be 5 times lower than that of benzene (Zhao et al., 2013; Ghazvini et al., 2015) (Figure 2).
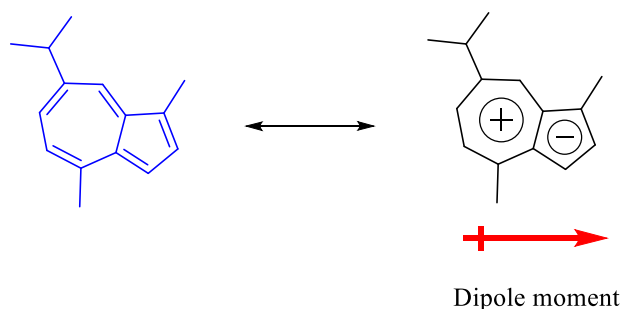

Dipole moment

Figure 2. Resonance structures of the guiazulene **2**.

The GA core has low transition energy to the S1 state and an unusually large S1-S2 gap, where S1 and S2 refer to the first and second electronically excited states, respectively. As a result of the high electron density in the C-3 position, the GA **2** can easily participate in the S_EAr. In fact, the treatment of GA **2** with strong acids leads to protonation at the C-3 position and the formation of a resonance-stabilized 6π-electron tropilium cation. Conjugated systems, resulting from hybridization of the GA nucleus with different conjugated units, show significant optical, electrochemical, and electrochromic properties (Zadeh et al., 2015). These systems have diverse applications such as modular building blocks for the construction of conducting polymers, as cathode modification layers in bulk-heterojunction solar cells, and in electrochromic and nonlinear optical materials (Takekuma et al., 2012; Ghazvini et al., 2015). Despite all this, these fascinating and electronic approaches often suffer from excessively long, low efficiency, or general lack. Access to most of azulens' replacement templates is still difficult (Crombie et al., 2004; Carret et al., 2005). Therefore, the development of efficient synthetic methods of these compounds from the easily available starting materials is in constant demand. In this context, it is important to hybridize the GA with an important functional group due to the preparation of azulene derivatives (Park et al., 2014).

There is a limited number of synthesis related to derivatives from 4 positions of the GA in the literature (Kurokawa, 1983; Razus et al., 2008; Aumüller et al., 2011; Zhao et al., 2013; Cao et al., 2016; Woodward et al., 2016). There is also only one study in the literature that is about directly the propargylation from the 3-position of GA core (Székely et al., 2017) [8]. Herein, we focus on the placed of propargyl into the 4-position on the seven-membered ring of the GA scaffold. This approach offered the possibility of synthesizing a new propargyl-azulene hybrid derivative. We also examined the Diels-Alder cycloaddition reaction between the obtained propargyl-GA **4** and tetraphenylcyclopentadienone **5**.

MATERIALS AND METHODS

Materials

The reaction was carried out under nitrogen atm. and monitored by TLC and/or ^{1}H-NMR spectroscopy. THF, used as a solvent, was dried and distilled before use. Column chromatography was performed on silica gel (60 mesh, Merck) or on neutral alumina. TLC was carried out on silica gel 60 HF254 aluminum plates (Fluka). The one and two dimensional ^{1}H spectra were recorded on a Varian-

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400 or a Bruker-400 spectrometer in $CDCl_3$ using tetramethylsilane as the internal reference. All spectra were recorded at 25 °C and coupling constants (J values) are given in Hz. Chemical shifts are given in parts per million (ppm). Abbreviations used to define the multiplicities are as follows: s = singlet; d = doublet; dd = doublet of doublets; td = triplet of doublets. IR spectra were recorded on an Perkin Elmer FT-IR spectrometer. Absorption spectrometry was performed using a Perkin Elmer Lambda 35 spectrophotometer. Absorbance spectroscopy measurement was kept in CH_2Cl_2 (5 µM).

Experimental procedure

Synthesis of the propargyl-GA 4: Under nitrogen atm., a solution of *n*-BuLi in hexane (2.5 M, 2.52 mL, 6.30 mmol) was added to a solution of dry diisopropylamine (1.24 mL, 8.82 mmol) in dry THF (10 mL) cooled at -78 °C. After 40 min, a solution of guaiazulene **2** (0.50 g, 1.31 mmol) in dry THF (15 ml) was added and the mixture was maintained at the same temperature for 30 min. The solution is allowed to warm to -10 °C. During this time the color changes from blue to brown-yellow. Then, the solution is cooled again to -78 °C and the propargyl bromide (0.30 mL, 2.77 mmol, 80 wt. % in toluene) is added dropwise. The solution is stirred for 30 min at -78 °C and then allowed to warm to rt slowly. The resulting mixture was stirred at the same temperature for 12 h. Meanwhile, a color change from brown-yellow to black-blue is observed. The final mixture was diluted with water (50 mL) and extracted with EtOAc (3 × 50 mL). Combined EtOAc extracts were dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (25% EtOAc/*n*-hexane). The obtained solid was recrystallized from CH_2Cl_2/*n*-hexane (9:1) to give black-blue crystals the propargyl-GA **4** (yield 580 mg, 97%). *4-(But-3-yn-1-yl)-7-isopropyl-1-methylazulene (4)*: Mp. 134 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, J = 1.8 Hz, 1H), 7.66 (d, J = 3.7 Hz, 1H), 7.44 (dd, J = 10.7, 1.8 Hz, 1H), 7.29 (d, J = 3.7 Hz, 1H), 7.05 (d, J = 10.7 Hz, 1H), 3.40 (t, J = 7.5 Hz, 2H), 3.09 (sept, J = 6.9 Hz, 1H), 2.70 (td, J = 7.5, 2.5 Hz, 2H), 2.68 (s, 3H), 2.04 (t, J = 2.5 Hz, 1H), 1.37 (d, J = 6.9 Hz, 6H). IR (cm^{-1}): 3289, 2962, 2928, 2871, 2117, 1695, 1602, 1432, 1384, 1362, 1156, 1067, 1052.

Synthesis of the compound 6: Tetraphenylcyclopentadienone **5** (0.976 g, 2.54 mmol) was added to a solution of the propargyl-GA **4** (0.500 g, 2.12 mmol) in *o*-xylene (30 mL) under N_2 atm. The reaction mixture was heated for 12 h at 160 °C. The resulting reaction mixture was poured into MeOH and the precipitate filtered off. The cycloadduct **6** was obtained by repeated precipitation from EtOH until the red color of the tetraphenylcyclopentadienone **5** had disappeared. The residue was purified via column chromatography on silica gel (100 g) by eluting with 5% EtOAc/*n*-hexane to give the cycloadduct **6** (1.22 g, 97%). *4-(2-(3',6'-Diphenyl-[1,1':2',1''-terphenyl]-4'-yl)ethyl)-7-isopropyl-1-methylazulene (6)*: Mp. 139-141°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, J = 1.8 Hz, 1H), 7.52-7.50 (m, 2H), 7.34 (dd, J = 1.8, 10.6 Hz, 1H), 7.27-7.15 (m, 9H), 6.94-6.81 (m, 11H), 6.77 (d, J = 3.7 Hz, 1H), 6.73 (d, J = 10.6 Hz, 1H), 3.31-3.27 (m, 2H), 3.11-3.04 (m, 3H), 2.64 (s, 3H), 1.35 (d, J = 7.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.43, 142.21, 142.06, 141.08, 140.83, 140.65, 140.30, 140.27, 139.92, 139,43, 138.38, 137.08, 136.62, 136.11, 135.49, 133.38, 131.83, 131.49, 130.88, 130.67, 130.19, 127.93, 127.80, 127.09, 126.77, 126.52, 126.42, 125.71, 125.49, 125.36, 124.78, 112.53, 40.67, 38.47, 36.43, 24.99, 13.13. IR (cm^{-1}): 3054, 3023, 2958, 2928, 2866, 1710, 1600, 1575, 1555, 1526, 1495, 1440, 1387, 1364, 1321, 1263, 1206, 1178, 1154, 1072, 1026, 912, 887, 807.

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RESULTS AND DISCUSSION

Synthesis

Starting from the GA **2**, more that one methyl group can be involved by the nucleophilic addition. Our approach was to extend the guaiazulene carbon framework through nucleophilic addition of the resonance-stabilized anion **2⁻** to propargyl bromide, yielding the propargyl-GA **4**. It is well known that, due to the hyperconjugation of methyl at the 4-positions of a GA **2**, the Cα protons of the alkyl groups can be removed using a strong base such as LDA (Balduzzi et al., 2004). Typically, the resulting azulene carbanions are quite stable due to the presence of an aromatic cyclopentadienyl anionic moiety in their resonance forms. In the literature, the carbanion **2⁻** has a limited number of nucleophilic addition reactions with electrophilic centers (Kurokawa, 1983; Razus et al., 2008; Balduzzi et al., 2004; Aumüller et al., 2011; Woodward et al., 2016). The GA **2**, which was commercially available, became the key structure that allowed us to prepare propargyl-GA **4**.
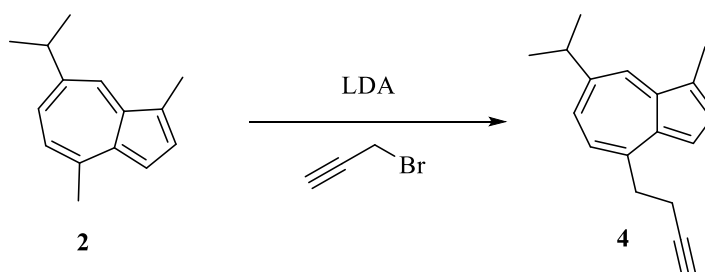

Figure 1. One-pot reaction for the synthesis of the compound **4** via nucleophilic addition.

In this study, we report the one-pot synthesis of the propargyl-GA **4**, and its activation step based on Diels-Alder cycloaddition. Firstly, the compound **4** was synthesized by the nucleophilic addition reaction of the propargyl bromide with GA carbanion **2⁻**, which was obtained *in situ* as a result of the reaction between the acidic H-atom of the methyl group existing in the 4-position of the guaiazulen ring and LDA in THF solution (Figure 1-2), in excellent yield 97%. Then, the compound **6** was obtained by the Diels-Alder cycloaddition between the propargyl-GA **4** and tetraphenylcyclopentadienone **5** in excellent yield 97% (Figure 3).

NMR and FT-IR analysis

The ¹H-NMR spectrum of compound **4** consists of sets of signals appearing in aromatic and aliphatic regions (Figure 4). In comparison with Spectra 1 in Figure 3, Spectra 2 in Figure 4 was observed that the signal of the C-4 methyl group of the guaiazulene scaffold was disappeared. In addition, it was observed that three new signals were formed in the aliphatic region, which is 3.40, 2.70, and 2.04 ppm in Figure 4. The aromatic Ha protons are split into triplet only by the coupling with Hb protons δ=3.40 (t, J = 7.5 Hz, 2Hₐ). Hb protons resonate as a triplet of doublets at 2.70 ppm from the coupling firstly with Ha and then with Hc protons, two different coupling constants of (J = 7.5, 2.5 Hz). In addition, the acetylenic Hc proton, one of the most specific peaks, resonates as a triplet at 2.04 ppm (t, J = 2.5 Hz, 1Hc) due to only by the coupling with Hb protons.

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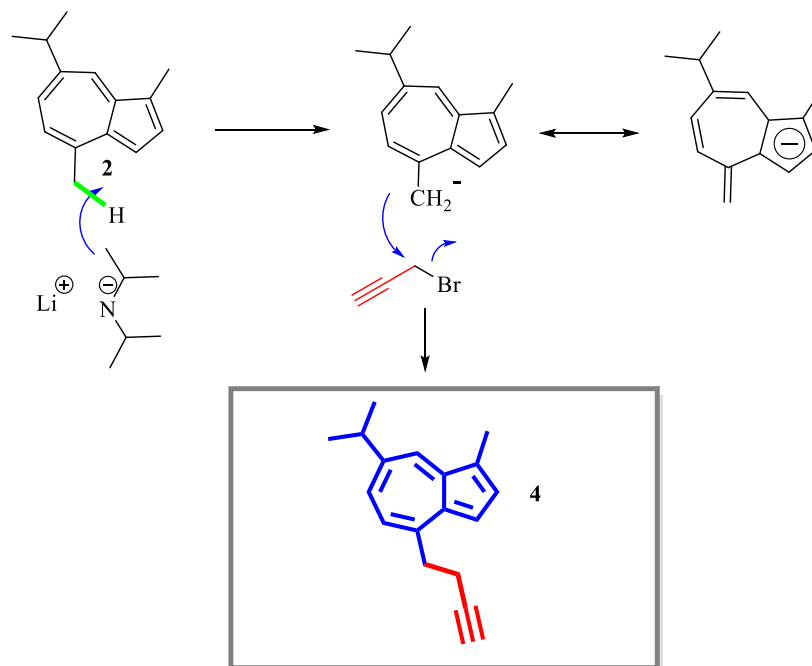Properties**

Figure 2. Synthesis mechanism for the formation of the compound **4.**
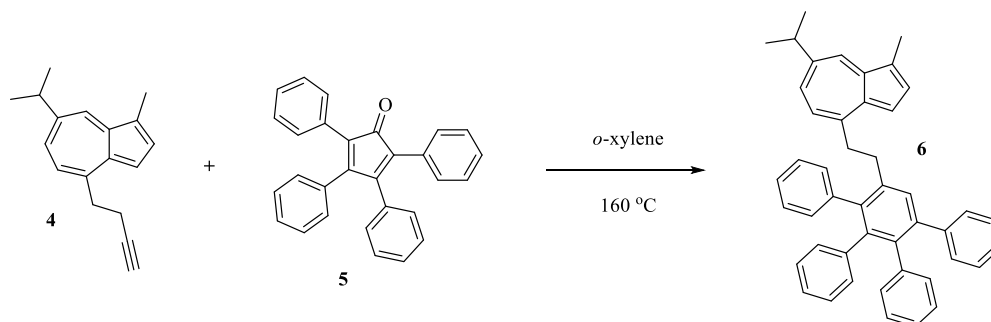
Figure 3. Synthesis of cycloadduct **6**
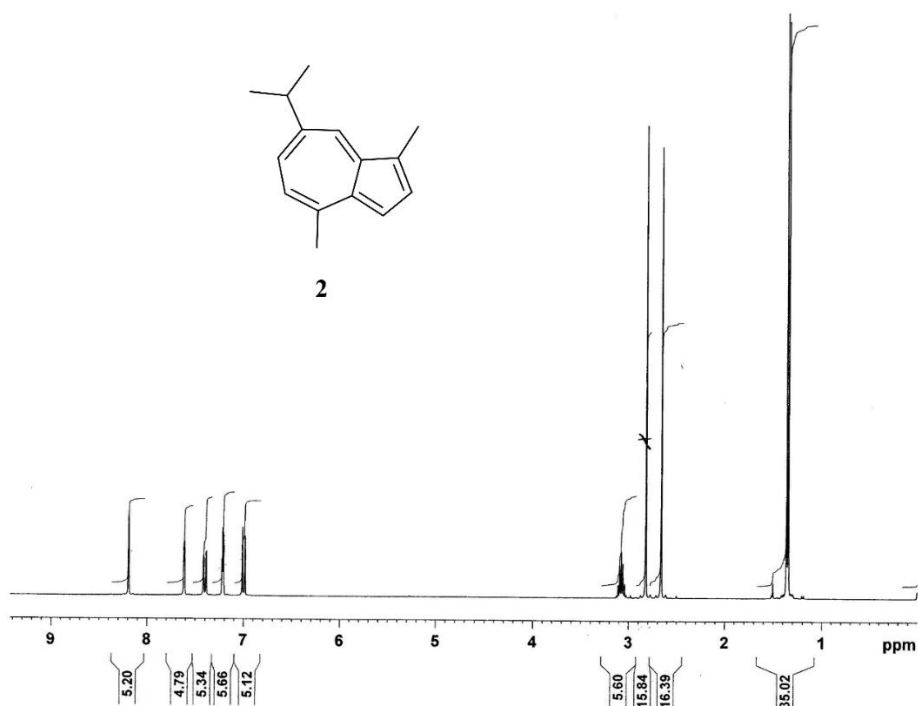
Figure 3. ^{1}H-NMR (400 MHz, CDCl$_3$) spectrum of the compound **2** (Spectra 1).

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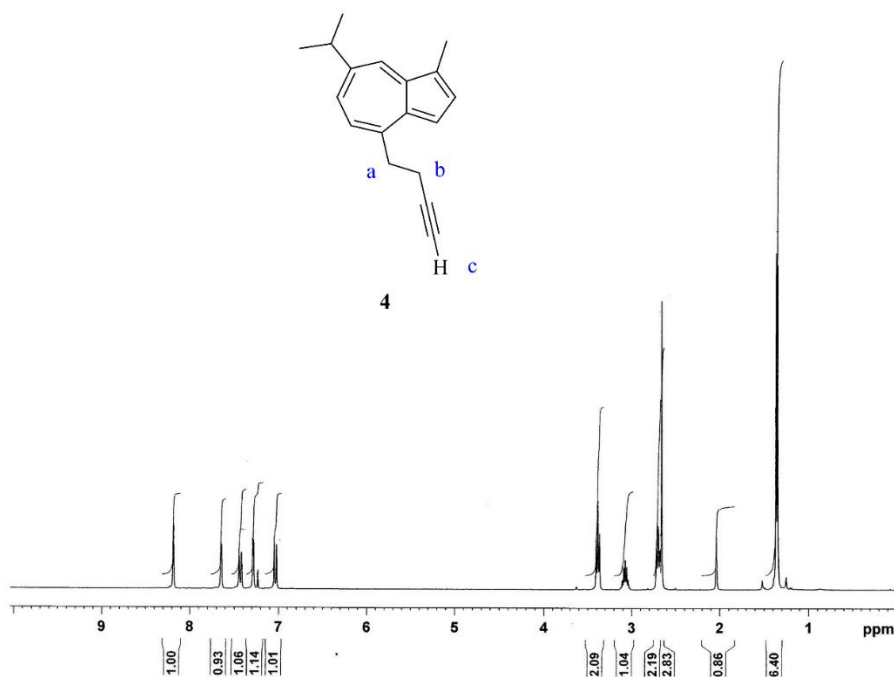
Figure 4. ¹H-NMR (400 MHz, CDCl₃) spectrum of the compound **4** (Spectra 2).

In similar to, the ¹H-NMR and ¹³C-NMR spectrum of cycloadduct **6** consists of sets of signals appearing in aromatic and aliphatic regions (Figure 5-6). In comparison with the Spectra 2 (Figure 4), in the Spectra 3 (Figure 5) was observed that the signal of the propargyl functional group of the propargyl-GA **4** was disappeared. Additionally, the NMR data were in very good agreement with the structure of the cycloadduct **6**.

Figure 5. ¹H-NMR (400 MHz, CDCl₃) spectrum of the compound **6** (Spectra 3).

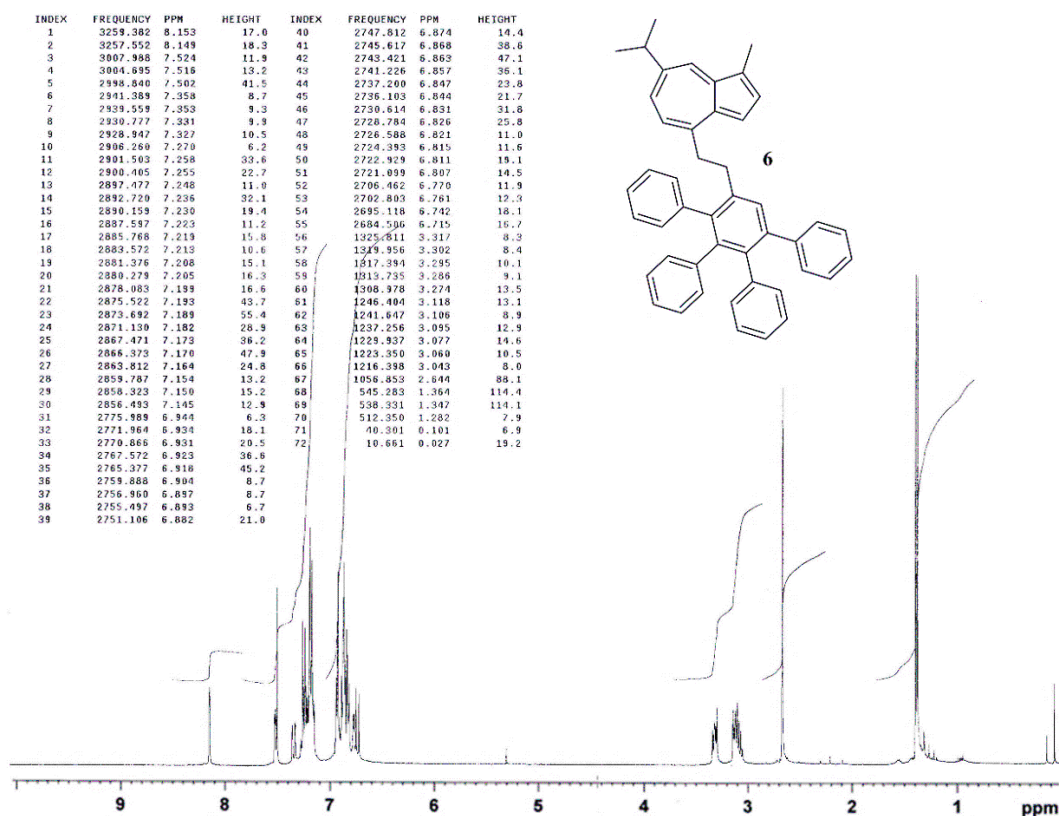Musa ERDOĞAN   10(4): 2747-2758, 2020

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INDEX	FREQUENCY	PPM	HEIGHT	INDEX	FREQUENCY	PPM	HEIGHT
1	14920.545	148.433	16.8	40	1319.971	13.131	32.7
2	14294.915	142.209	7.6				
3	14279.656	142.058	5.6				
4	14181.234	141.079	10.9				
5	14156.056	140.828	9.5				
6	14138.508	140.653	8.4				
7	14103.412	140.304	16.6				
8	14099.597	140.266	11.9				
9	14064.501	139.917	11.7				
10	14015.671	139.431	14.6				
11	13909.619	138.376	7.8				
12	13779.152	137.078	11.5				
13	13732.612	136.615	40.6				
14	13681.493	136.107	14.4				
15	13619.693	135.492	40.0				
16	13407.590	133.382	39.6				
17	13251.182	131.826	86.9				
18	13217.612	131.492	85.5				
19	13156.575	130.885	76.9				
20	13135.212	130.672	45.0				
21	13086.382	130.187	91.0				
22	12859.782	127.932	87.8				
23	12846.812	127.803	79.5				
24	12775.094	127.090	80.1				
25	12743.049	126.771	90.5				
26	12717.871	126.521	42.1				
27	12707.953	126.422	39.9				
28	12636.234	125.708	41.0				
29	12614.108	125.488	43.8				
30	12601.138	125.359	8.3				
31	12543.153	124.782	43.3				
32	11311.731	112.532	37.9				
33	7797.525	77.572	10.9				
34	7765.480	77.253	13.0				
35	7733.436	76.934	13.2				
36	4088.000	40.668	39.0				
37	3866.741	38.467	39.3				
38	3661.504	36.426	37.7				
39	2511.719	24.987	88.8				

Fig. 6. ^{13}C-NMR (100 MHz, CDCl$_3$) spectrum of the compound **6** (Spectra 4).
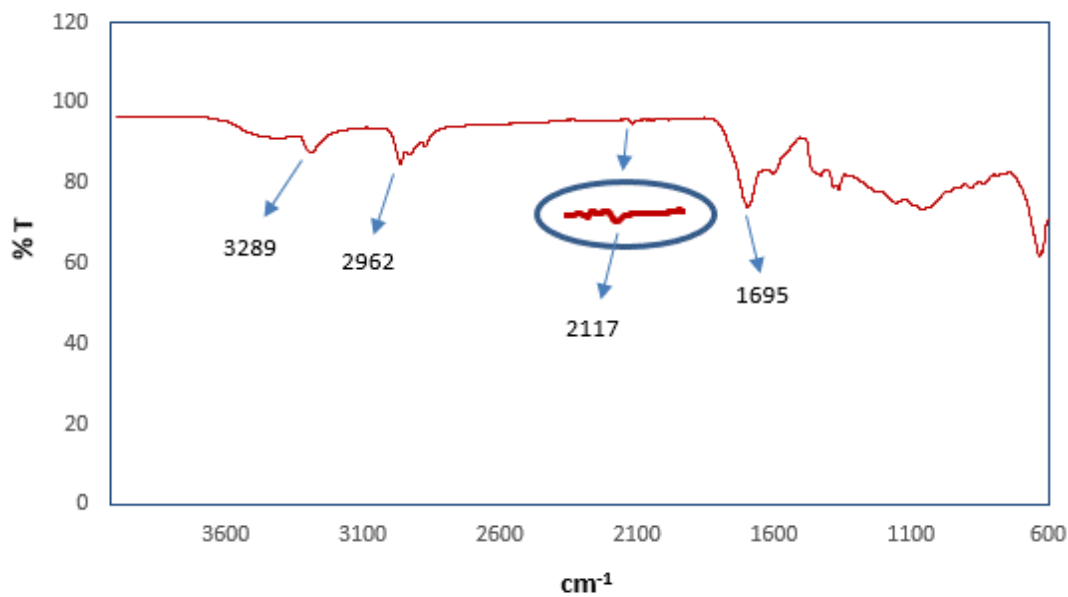
Figure 7. FT-IR spectrum of the compound **4** (Spectra 5).

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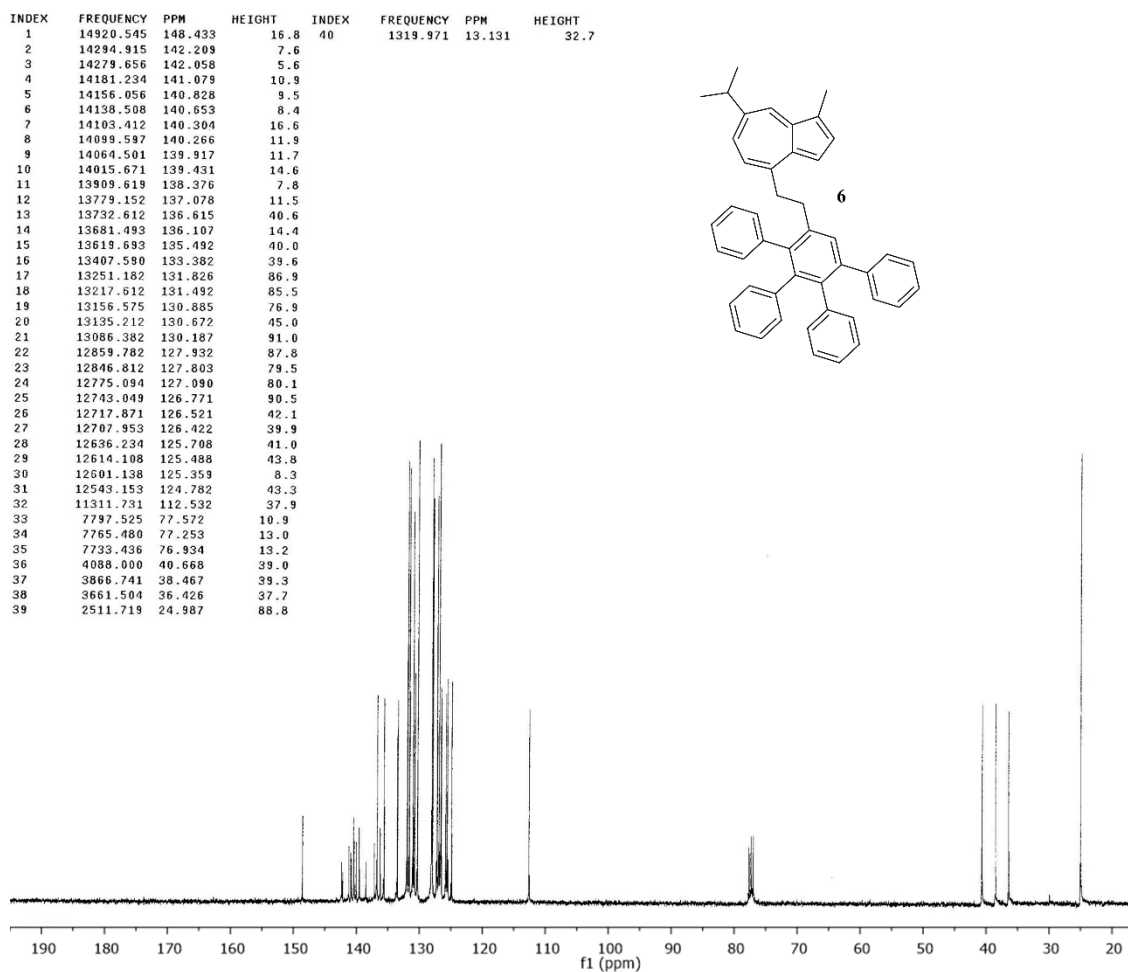

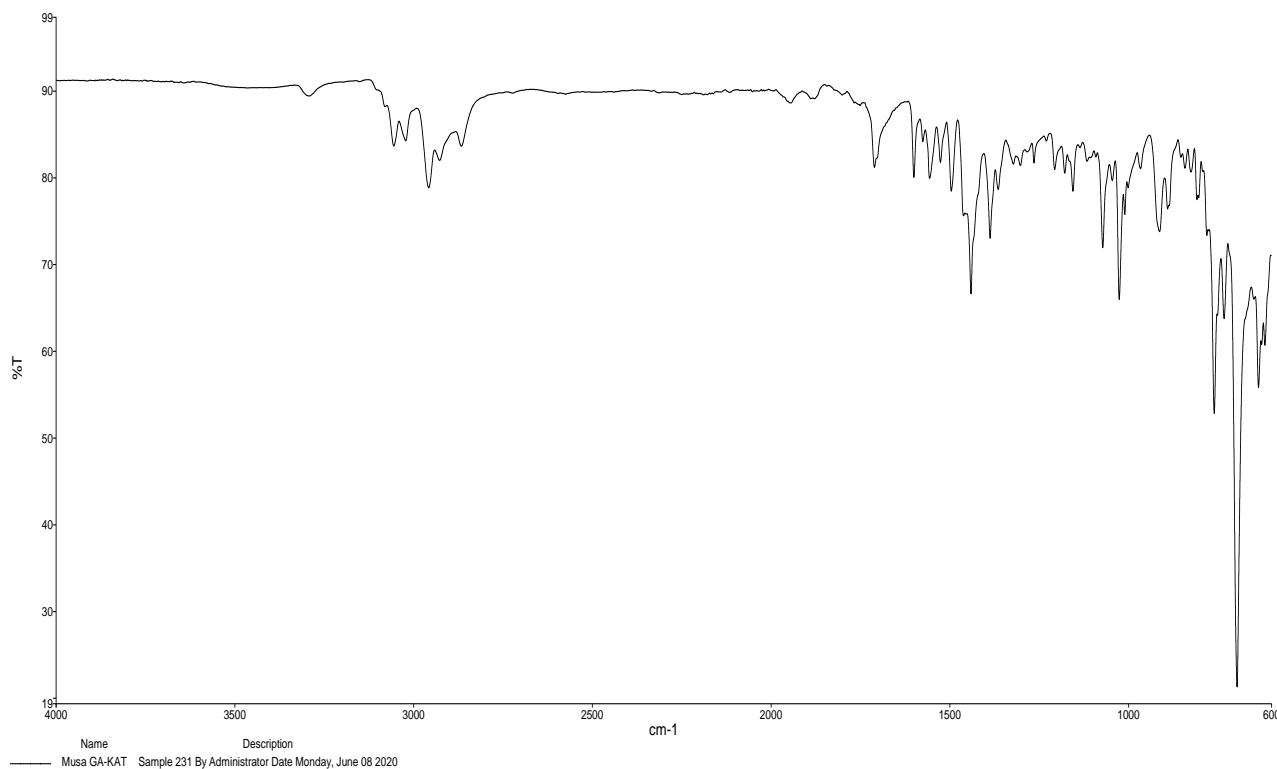**Figure 8.** FT-IR spectrum of the compound **6** (Spectra 6) (see the Experimental part for details).

Figure 7 displays FT-IR spectra of the compound **4**. The IR spectrum of **4** exhibited characteristic absorptions bands for acetylen-H, aromatic C-H, acetylene functional group, and aromatic C=C bonds. The C–H stretch in acetylen-H is observed at 3289 cm^{-1}. The absorption bands at 2962, 2928 and 2871 cm^{-1} are attributed to aromatic C–H bending vibrations of compound **4**. The absorption band at 2117 cm^{-1} is assigned to stretching vibrations of the acetylene functional group, and those at 1695 cm^{-1} are due to the aromatic C=C groups. Figure 8 displays FT-IR spectra of cycloadduct **6**. The IR spectrum of **6** exhibited characteristic absorptions bands for aromatic C-H, and aromatic C=C bonds. The absorption bands at 3054, 3023, 2958, 2928 and 2866 cm^{-1} are attributed to aromatic C–H bending vibration of the compound **6**. The absorption band at 1710, 1600 and 1575 cm^{-1} are assigned to the stretching vibration of the aromatic C=C groups. It was observed that the signal of the propargyl functional group was disappeared in Spectra 6.

UV-vis analysis

The result of the absorbance measurement for the GA **2,** propargyl-GA hybrid derivative **4** and the compound **6** is shown in Figure 9. The UV-vis absorption spectra of the compounds GA **2,** propargyl-GA hybrid derivative **4** and the compound **6** in CH$_2$Cl$_2$ (5 µM) are dominated by absorption bands at **2**; 290, 351, 367, and 396 nm, **4**; 284, 354, 356, and 396 nm and **6**; 396, 369, 352 and 340 nm, respectively. These compounds displayed similar band substructures, because of the π-conjugation is interrupted via methylene or ethylene bridges.
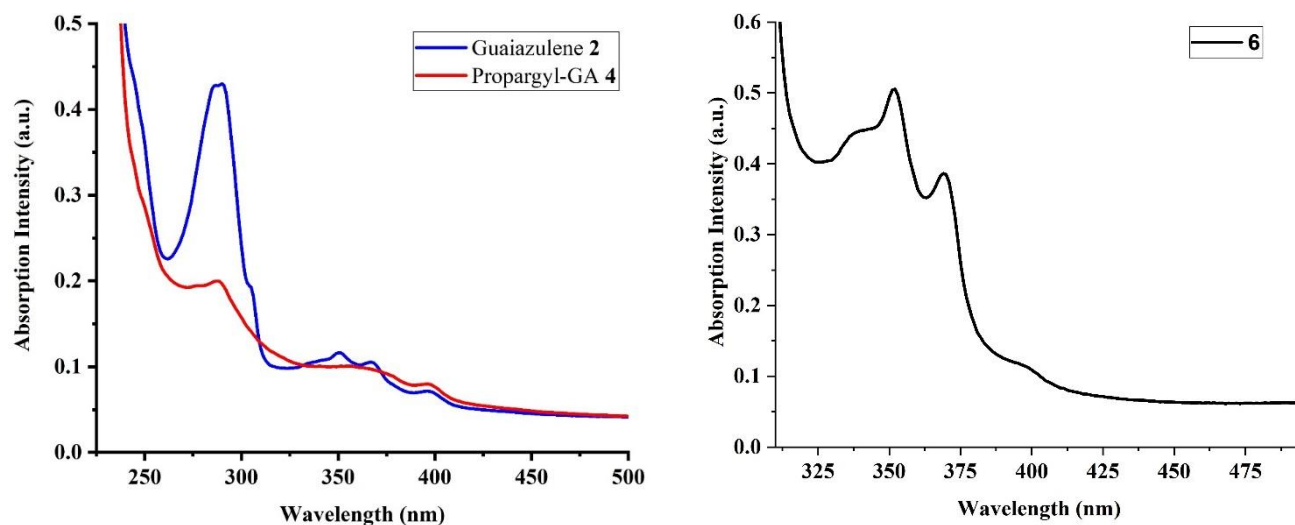
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Figure 9. Absorbance spectra of the compounds **2**, **4** and **6**.

CONCLUSION

A new propargyl-GA hybrid derivatives **4** and **6** have been designed, synthesized and characterized. The absorbance properties of these compounds were also investigated. The compound **4** was synthesized in excellent yield using the nucleophilic addition reaction. Additionally, Diels-Alder cycloaddition reaction between the propargyl-GA **4** and tetraphenylcyclopentadienone **5** was performed, and then the cycloadduct **6** was obtained with excellent yield. We have exhibited that sp^3 direct propargylation of GAs is possible when convenient reaction conditions are occupied. The current study potentially also makes inroads into the construction of novel GA for use of other GA derivatives in different applications since the obtained product **4** contains the propargyl unit.

ACKNOWLEDGEMENT

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