2-[1,3-BIS(ETHOXYCARBONYL)AZULEN-6-YL]ETHYNYLTRIPHENYLPHOSPHONIUM BROMIDE†

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Abstract – 2-[1,3-Bis(ethoxycarbonyl)azulen-6-yl]ethynyltriphenylphosphonium bromide was prepared from diethyl 6-ethynyl-1,3-azulenedicarboxylate. Its NMR spectroscopic property was made clear. Furthermore, its reactivity with o-substituted aniline was studied, comparing with 1- and 2-ethynyl azulene derivatives. We found that 2-[3-(methoxycarbonyl)azulen-1-yl]ethynyltriphenylphosphonium bromide also reacted with o-substituted anilines in CHCl₃ to give corresponding 2-[1,3-bis(ethoxycarbonyl)azulen-6-yl]benzoazoles. However, in DMSO another products were obtained.

INTRODUCTION
During the investigation of reaction of phenylethynyltriphenylphosphonium bromide with vicinal dinucleophiles such as o-phenylenediamine, o-aminobenzenethiol, o-aminophenol, and 1,8-diaminonaphthalene, we found nucleophilic addition of these nucleophiles to β-alkyne carbon of phenylethynyltriphenylphosphonium bromide which attached to the phenyl ring, proceeded and followed

†Dedicated to Professor Dr. Albert Eschenmoser, ETH Zürich on his 85th birthday.
by secondary nucleophilic attack to the same carbon by another functional group to give a corresponding phenyl benzazole or related heterocyclic compound along with methyltriphenylphosphonium bromide. Azulene is characterized as an aromatic hydrocarbon with polarity. In its derivatives, the electronic contribution of azuleny ring depends on the position of connecting to its functional group. As part of our effort to design novel scaffolds for polyfunctionalyzed azulenes, syntheses and reactivities of similar azulene derivatives to phenylethynyltriphenylphosphonium bromide were carried out. Syntheses of 1- and 2-substituted azulene derivatives such as 2-(2-azulenyl)ethynyltriphenylphosphonium bromide (6) and 2-[3-(methoxycarbonyl)azulen-1-yl]ethynyltriphenylphosphonium bromide (9) from the corresponding formylazulene and their reactivity with o-substituted anilines and a related compound have been reported. Therefore, we have investigated on the corresponding 6-substituted azulene as a part of syntheses of a variety of azulenyethynyltriphenylphosphonium bromides and 2-azulenylbenzoazoles. 6-Ethynyl-1,3-diethoxycarbonylazulene (1) could be easily prepared by the palladium-catalyzed coupling reaction of diethyl 6-bromoazulene-1,3-dicarboxylate with trimethylsilylacetylene, followed by desilylation with KF. We will report herein about the preparation and some interesting properties of 2-[1,3-bis(ethoxycarbonyl)azulen-6-y]ethynyltriphenylphosphonium bromide (3).

RESULTS AND DISCUSSION

Synthesis and spectral data of 2-[bis(1,3-ethoxycarbonyl)azulen-6-yl]ethynyltriphenylphosphonium bromide (3)

Due to prepare 6-(2-bromoethynyl)azulene by bromination of corresponding ethynylazulene, C-1 and C-3 positions in azulene ring need to be protected. In addition to this from the synthetic point of view, we select 6-ethynyl-1,3-bis(ethoxycarbonyl)azulene (1) as a starting material. The compound 1 was treated with NBS in the presence of silver nitrate to give 6-(2-bromoethynyl)-1,3-bis(ethoxycarbonyl)azulene (2) in 68% yield. It was treated with triphenylphosphine in diethyl ether at room temperature for 3 days to give 2-[1,3-bis(ethoxycarbonyl)azulen-6-y]ethynyltriphenylphosphonium bromide (3) in 99.6% yield.

![Scheme 1](image)

The IR spectrum of 3 exhibits a strong characteristic absorption of the triple bond at 2174 cm⁻¹. Its wave number is the highest among these of 2-(2-azulenyl)ethynyltriphenylphosphonium bromide (6) (2160 cm⁻¹) and 2-[3-(methoxycarbonyl)azulen-1-yl]ethynyltriphenylphosphonium bromide (9) (2139 cm⁻¹).
The total polarity of its molecule is the lowest because the azulenyl group works as an electron-withdrawing group. The chemical shifts in $^1\text{H}$- and $^{13}\text{C}$-NMR spectra of compounds 1, 2, and 3 are shown in Tables 1 and 2, respectively. As expected, the chemical shifts of azulene ring protons in 3.

**Table 1.** Chemical shift in the $^1\text{H}$NMR spectrum of diethyl 6-ethynylazulene-1,3-dicarboxylate derivatives

<table>
<thead>
<tr>
<th>X</th>
<th>H</th>
<th>Br</th>
<th>PPh$_3$ Br</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>8.79</td>
<td>8.81</td>
<td>8.98</td>
</tr>
<tr>
<td>4 and 8</td>
<td>9.64</td>
<td>9.65</td>
<td>9.79</td>
</tr>
<tr>
<td>5 and 7</td>
<td>7.85</td>
<td>7.82</td>
<td>8.23</td>
</tr>
<tr>
<td>CH$_2$</td>
<td>4.43</td>
<td>4.43</td>
<td>4.43</td>
</tr>
<tr>
<td>CH$_3$</td>
<td>1.45</td>
<td>1.45</td>
<td>1.44</td>
</tr>
<tr>
<td>Ph</td>
<td></td>
<td></td>
<td>7.78-7.88</td>
</tr>
<tr>
<td>$\equiv$C–H</td>
<td>3.48</td>
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</tbody>
</table>

**Table 2.** Chemical shift in the $^{13}\text{C}$ NMR spectrum of diethyl 6-ethynylazulene-1,3-dicarboxylate derivatives

<table>
<thead>
<tr>
<th>X</th>
<th>H</th>
<th>Br</th>
<th>PPh$_3$ Br</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 and 3</td>
<td>117.13</td>
<td>117.18</td>
<td>118.76</td>
</tr>
<tr>
<td>2</td>
<td>144.09</td>
<td>143.98</td>
<td>147.07</td>
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<tr>
<td>3a and 8a</td>
<td>143.61</td>
<td>143.54</td>
<td>144.46</td>
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<tr>
<td>4 and 8</td>
<td>137.50</td>
<td>135.32</td>
<td>137.69</td>
</tr>
<tr>
<td>5 and 7</td>
<td>133.50</td>
<td>133.44</td>
<td>133.45</td>
</tr>
<tr>
<td>6</td>
<td>134.68</td>
<td>137.41</td>
<td>127.90(J=8.8)</td>
</tr>
<tr>
<td>–C=–C–X</td>
<td>82.28</td>
<td>60.20</td>
<td>71.87(J=190.95)</td>
</tr>
<tr>
<td>–C=–C–X</td>
<td>86.20</td>
<td>83.16</td>
<td>118.43(J=28.9)</td>
</tr>
<tr>
<td>p-Ph-</td>
<td></td>
<td></td>
<td>136.35(J=3.0)</td>
</tr>
<tr>
<td>m-Ph-</td>
<td></td>
<td></td>
<td>133.02(J=12.1)</td>
</tr>
<tr>
<td>o-Ph-</td>
<td></td>
<td></td>
<td>131.14(J=14.5)</td>
</tr>
<tr>
<td>ipso-Ph-</td>
<td></td>
<td></td>
<td>117.34(J=99.7)</td>
</tr>
<tr>
<td>CH$_3$-CH$_2$O-</td>
<td>14.52</td>
<td></td>
<td>14.49</td>
</tr>
<tr>
<td>CH$_3$-CH$_2$O-</td>
<td>60.20</td>
<td>60.61</td>
<td></td>
</tr>
<tr>
<td>–CO$_2$CH$_2$CH$_3$</td>
<td>164.74</td>
<td>164.23</td>
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</table>
comparing with those of 1 and 2 were shifted to lower field character by 0.14–0.41 ppm. Triphenylphosphonium moiety works as an electron withdrawing group. Especially ring protons of C-5,7 characteristically shifted to lower field by 0.38–0.41 ppm. A similar result has been obtained in 2-(3-methyloxycarbonylazulene-1-yl)ethynyltriphenylphosphonium bromide. The $^{13}$C NMR spectrum shows beside C-6 and C-P lower field shifts compared with 1 was observed. These observations were due to the contribution of resonance structures 3b and 3c. Electron density of C-2 (C$\beta$) acetylenic carbon is the lowest among azulenylethynyltriphenylphosphonium bromides. We expect compound 3 was attacked the most easily by nucleophiles.

**Table 3.** Chemical shifts of acetylenic carbons (C$\alpha$ and C$\beta$) of compounds 1-9

<table>
<thead>
<tr>
<th></th>
<th>C$\alpha$</th>
<th>C$\beta$</th>
<th>C$\alpha$</th>
<th>C$\beta$</th>
<th>C$\alpha$</th>
<th>C$\beta$</th>
<th>C$\alpha$</th>
<th>C$\beta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>X=H</td>
<td>82.28, 86.20</td>
<td>83.02, 81.80</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>2</td>
<td>X=Br</td>
<td>60.20, 83.16</td>
<td>55.77, 78.53</td>
<td>7</td>
<td>X=H</td>
<td>81.58, 78.87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>X=P+(Ph)3Br$^-$</td>
<td>71.87, 118.43</td>
<td>6</td>
<td>X=P+(Ph)3Br$^-$</td>
<td>72.42, 117.67</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>X=H</td>
<td></td>
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</tr>
<tr>
<td>5</td>
<td>X=Br</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>6</td>
<td>X=P+(Ph)3Br$^-$</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>7</td>
<td>X=H</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>8</td>
<td>X=Br</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>9</td>
<td>X=P+(Ph)3Br$^-$</td>
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<td></td>
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</tr>
</tbody>
</table>

**Figure 1.** The resonance structures of compound 3
Reaction of 1,3-diethoxycarbonylazulen-6-yethyltriphenylphosphonium bromide (3) with \( o \)-phenylenediamine and its related compounds in CHCl\(_3\)

Compounds 3 reacts with \( o \)-phenylenediamine in dry CHCl\(_3\) at refluxing temperature to give a nucleophilic adduct 11a quantitatively which is easily crystalized. Other nucleophilic adducts in the reaction of azulenylethynyltriphenylphosphonium bromides with \( o \)-substituted aniline salts were not crystallized. Azulene ring peaks in NMR spectrum of 11a show little broadening at ca. 30 °C due to the contribution of 11a”. When the temperature was raised to 50 °C, broadening peaks become sharp due to increasing the contribution of 11a and 11a’. When the refluxing was continued for 50 hrs without isolation of 11a, 11a underwent intramolecular cyclization to give a 6-(1\( H \)-benzimidazol-2-yl)azulene derivative (12a) in 34% yield.

\[
\begin{align*}
\text{EtO}_2C & \quad \text{CO}_2Et \\
\text{Ph}_3P & \quad \text{Br} \\
\text{3} & \\
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2C & \quad \text{CO}_2Et \\
\text{X} & \quad \text{H} \\
\text{11} & \\
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2C & \quad \text{CO}_2Et \\
\text{Ph}_3P & \quad \\
\text{12} & \\
\end{align*}
\]

Scheme 2

The investigation of the reaction of 3 with \( o \)-aminothiophenol (10b) to be expected to give a 6-(benzothiazol-2-yl)azulene derivative (12b) was carried out. Consumption of the starting material was observed by thin layer chromatography, but the generation of 12b and methyltriphenylphosphonium bromide could not be observed. On the contrast to 10b, \( o \)-aminophenol (10c) gave a
6-(benzoxazol-2-yl)azulene derivative (12c) in 29% yield along with 6-acetylazulene (13) in 13% yield. By the treatment of the intermediate of the first nucleophilic addition product with sodium hydride or Et₃N, we succeeded to improve a yield of 12c (44-48%). The phosphonium salt 3 reacts with 1,8-diaminonaphthalene the most smoothly in refluxing CHCl₃ under Ar to give diethyl 6-(1H-perimidin-2-yl)azulene-1,3-dicarboxylate (14) in 87% yield.

![Figure 2](image-url)

**Figure 2**

**Cyclic voltammetry of heteroaryl azulenes**

To clarify the effect to electrochemical behavior of azulene ring by the benzoazol, by using cyclic voltammetry (CV) and differential pulse voltammetry (DPV), obtained heteroaryl azulenes 12a, 12c, and 14 were examined. One reversible reducing waves of the azulene itself exhibits at -1.54 V at should correspond to one single-electron transfers. 6,6’-Biazulenyl exhibits two half-waves at -1.09 and -1.32 V. Although the CV spectrum in 12a could not be observed a clear redox wave, 12c and 14 exhibited the reduction potentials E₁/₂ (1) at -1.15 and -1.23 V, respectively. They also exhibit irreversible reduction potential higher voltage at -1.73 (12c), -1.59 and -1.90 volt (14), respectively. That is there is a possibility of stable anion radicals in compounds 12c and 14.

**Reaction of 3 with 10a in DMSO**

In order to investigate the cyclization of 11a over the temperature 60 °C, dimethylsulfoxide was used as a reaction solvent. After mixing 3 and 10a in DMSO, a heterocyclic product was not observed until 80 °C on the TLC. After heating at 100 °C for 2h, three compounds were isolated by column chromatography on silica gel and GPC. One of them is recovered compound 3 (6%). Although the other products could not be purified completely, we assigned compounds 15 (7%) and 16 (18%) as these structures shown in Figure 3 on the basis of their ¹H NMR spectra as shown in Experimental section. Heating was carried out higher temperature at 120°C for 2 h to give known diethyl 6-methylazulene-1,3-dicarboxylate (17) in 8% yield. These observations suggested that nucleophilic attack of 10a to 3 occurred at different acetylene carbon C₃ in DMSO.
Since the contribution of resonance structure 3e in DMSO increases, we could suppose that there is a possibility of following reaction as shown in Scheme 4. The strong nucleophile 10a attacks to Cα of 3 followed by the second attack to the same Cα to give 19 or isomerization to 18 then nucleophilic attack at the same carbon to give 19. Elimination of triphenylphosphonium part from 19 along with oxidation directly or via 20 gives 16. Then the elimination of benzimidazole part from 19 or via 16 or 20 gives 17. At least compound 3 undergoes another reaction with 10a in DMSO compared with the experiment in CHCl₃.

Scheme 4
CONCLUSION
2-[1,3-Bis(ethoxycarbonyl)azulen-6-yl]ethynyltriphenylphosphonium bromide was prepared from corresponding 6-ethynylazulene by two steps in an excellent total yield. Michael type adducts could be isolated for the first time in azulene derivatives. We find that reaction of 3 with 10a is depends on the solvent effect. The position of nucleophilic addition is different between the case of CHCl₃ and DMSO. We supposed that the polarity of azulene regulates the position of nucleophilic addition in DMSO. The yield of cyclized products increases by the addition of sodium hydride or Et₃N to reaction intermediate. The some obtained compounds exhibit a reversible reduction wave. This procedure is applicable for the synthesis of heteroarylazulenes.

EXPERIMENTAL
General Information. Melting points were determined on a Yanaco micro melting point apparatus and are uncorrected. IR spectra were taken on a Shimadzu FTIR-8100M or a Hitachi 270-30 spectrophotometer and UV spectra were measured on a Hitachi U-3410 spectrophotometer. ¹H NMR spectra (¹³C NMR spectra) were recorded on JEOL LAMBDA 400 (100 MHz) and 600 (150 MHz). MS spectra were measured on a JEOL HX-110 or a Hitachi M-2500 instrument usually at 70 eV. Voltammetry measurements were carried out with a BAS 100B/W electrochemical workstation equipped with Pt working and auxiliary electrodes and a reference electrode formed from Ag/AgNO₃ (0.01 M) in acetonitrile containing tetrabutylammonium perchlorate (0.1 M). These results were described in Results and Discussion. Elemental analyses were performed at the Instrumental Analysis Center of Chemistry, Faculty of Science, Tohoku University.

Diethyl 6-(2-bromoethynyl)azulene-1, 3-dicarboxylate (2)
To a stirred solution of diethyl 6-ethynylazulene-1,3-dicarboxylate (1) (1.0 mg, 3.37 mmol) in acetone (85 ml), AgNO₃ (688 mg, 4.05 mmol) was added at rt under Ar and the solution was stirred for 30 min under Ar. The solution of N-bromosuccinimide (721 mg, 4.05 mmol) in acetone (170 mL) was added and stirred for 5 h. After addition of Et₂O (40 mL) to the suspension, precipitates were removed by filtration and the residue was washed with acetone until the washing was no longer colored. The ice water (40 mL) was added to the filtrate with stirring and extracted with 200 mL portion of Et₂O twice, then dried with anhydrous MgSO₄, evaporated under reduced pressure. Purification of resulting residue by column chromatography (silica gel, CH₂Cl₂) gave diethyl 6-(2-bromoethynyl)azulene-1,3-dicarboxylate (2) as purple crystals (858 mg, 68%).

2: Violet needles (CH₂Cl₂/n-hexane); mp 165.8-166.9 °C; ¹H NMR (400 MHz, CDCl₃) δ 9.65 (2H, d, J =
11.2 Hz, H-4, 8), 8.81 (2H, d, J = 11.2 Hz, H-5, 7), 4.43 (4H, q, J = 7.2 Hz, -CO₂CH₂CH₃), 1.45 (6H, t, J = 7.2 Hz, -CO₂CH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 164.76 (CO₂Et), 143.98 (Az-2), 143.54 (Az-3a, 8a), 137.41 (Az-6), 135.32 (Az-4, 8), 133.44 (Az-5, 7), 117.18 (Az-1, 3), 83.16 (Az-CCBr), 60.20 (Az-CCBr), 57.14 (CO₂CH₂CH₃), 1.45 (6H, t, J = 7.2 Hz, -CO₂CH₂CH₃)); IR (KBr) νmax 2974 (w), 2187 (m), 1699 (s), 1686 (s), 1583 (w), 1568 (w), 1543 (w), 1477 (w), 1464 (m), 1433 (s), 1414 (w), 1390 (m), 1377 (w), 1356 (w), 1307 (w), 1240 (s), 1207 (s), 1186 (s), 1107 (w), 1089 (m), 1082 (m), 1045 (m), 1032 (w), 981 (m), 871 (w), 852 (w), 763 (w), 661 cm⁻¹ (w); MS (EI, 70eV) m/z 376 (M⁺+1, 100%), 375 (M⁺, 19.64), 374 (99.5), 331.9 (48.7), 329.9 (47.7), 304 (16.7), 303 (48.7), 302 (18.5), 301 (39.8), 296 (10.5), 285 (7.9), 257 (9.2), 251.2 (6.5), 230 (6.4), 218.9 (6.8), 216.9 (8.3), 150 (8.9), 138.1 (7.8); ES (CH₂Cl₂) 218.6 (log ε 4.85), 220.9 (4.89), 227.0 (4.50), 263.8 (4.25) sh, 270.2 (4.25) sh, 328.1 (4.87), 347.0 (4.30), 358.8 (4.27) sh, 367.1 (4.28), 380.9 (3.61), 539.0 (2.78), 574.2 (2.70) sh, 626.0 nm (2.20); Anal. Calcd (%) for C₁₈H₁₅BrO₄: C, 57.62, H, 4.03, Br, 21.30. Found: C, 57.76, H, 4.15, Br, 21.53.

2-[1,3-Bis(ethoxycarbonyl)azulen-6-yl]ethynyltriphenylphosphonium bromide (3)
A suspension of diethyl 6-bromoethynylazulene-1,3-dicarboxylate (2) (416 mg, 1.11 mmol) and triphenylphosphine (349 mg, 1.33 mmol) in absolute Et₂O (20 mL) was stirred for 3 days at rt under Ar. The green precipitate was collected by filtration, washed with Et₂O and dried thoroughly in vacuo to give pure 3 (705.5 mg, 99.6%).

3: Green powder; mp 129.3-132.9 °C (decomp.); ¹H NMR (400 MHz, CDCl₃) δ 9.79 (2H, d, J = 10.0 Hz, Az-4, 8), 8.98 (1H, s, Az-2), 8.23 (2H, d, J = 10.0 Hz, Az-5, 7), 7.78-7.88 (15H, m, Ph-H), 4.43 (4H, q, J = 7.2 Hz, -CO₂CH₂CH₃), 1.44 (6H, t, J = 7.2 Hz, -CO₂CH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 164.23 (CO₂Et), 147.07 (Az-2), 144.46 (Az-3a, 8a), 137.69 (Az-4, 8), 136.35 (d, J = 3.0 Hz, p-Ph), 133.02 (d, J = 12.1 Hz, m-Ph), 131.14 (d, J = 14.5 Hz, o-Ph), 133.45 (Az-5 or 7), 127.90 (d, J = 8.8 Hz, Az-6), 118.76 (Az-1, 3), 118.43 (d, J = 28.9 Hz, Az-C=C-P), 117.34 (d, J = 99.7 Hz, ipso-Ph), 71.87 (d, J = 190.95 Hz, Az-C=C-P), 60.61 (CO₂CH₂CH₃), 14.49 (CO₂CH₂CH₃); IR (KBr) νmax 3055 (w), 2984 (w), 2174 (s), 1693 (s), 1583 (w), 1568 (w), 1543 (w), 1477 (w), 1464 (w), 1437 (s), 1406 (w), 1390 (m), 1236 (m), 1213 (s), 1188 (s), 1111 (s), 1068 (w), 1037 (m), 995 (w), 850 (w), 827 (m), 762 (m), 727 (m), 688 (m), 571 (w), 542 (w), 524 (s), 482 cm⁻¹ (w); ES (CH₂Cl₂) λmax 219.3 (log ε 4.15), 226.3 (5.21), 261.8 (4.44) sh, 269.5 (4.34) sh, 315.3 (4.77) sh, 327.8 (5.01), 350.5 (4.15) sh, 351.0 (4.22), 369.4 (4.26), 591.1 (2.67), 640.1 (2.55) sh, 720.4 nm (1.97) sh; Anal. Calcd (%) for C₁₈H₁₅BrO₄P·4/5H₂O: C, 66.33, H, 4.89. Found: C, 66.50, H, 5.13.
2-(2-Aminophenylamino)-2-[1,3-di(ethoxycarbonyl)azulen-6-yl]ethynyl]triphenylphosphonium bromide (11a)

To a stirred solution of 3 (100 mg, 0.157 mmol) in CHCl₃ (10 mL), o-phenylenediamine (10a) (22.8 mg, 0.211 mmol) was added and stirred for 1 h at rt. The reaction mixture was evaporated under reduced pressure. Resulting residue was dissolved in a small portion of CH₂Cl₂ and Et₂O was added. Aroused brown precipitate was collected by filtration and dried in vacuo to produce 11a (122.9 mg, 94%).

11a: Brown powder (CH₂Cl₂ / Et₂O), mp 146-147.5 °C (decomp.), ¹H NMR (400 MHz, CDCl₃) δ 9.07 (2H, d, J = 10.4 Hz, Az-4, 8), 8.73 (1H, s, Az-2), 7.27-7.75 (21H, m), 4.38 (4H, q, J = 7.2 Hz, -CO₂CH₂CH₃), 1.43 (6H, J = 7.2 Hz, -CO₂CH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 164.67, 164.39, 144.47, 143.55, 143.26, 138.05, 137.31, 135.01, 33.51, 133.27, 133.16, 133.12, 130.39, 130.26, 129.59, 129.46, 124.10, 121.03, 119.47, 118.59, 117.80, 116.66, 60.16, 14.43; IR (KBr) νmax 3400 (m), 3206 (w), 3058 (w), 2980 (m), 2938 (s), 1690 (s), 1624 (m), 1578 (m), 1560 (m), 1541 (m), 1512 (m), 1483 (m), 1435 (s), 1412 (m), 1391 (m), 1364 (w), 1352 (w), 1341 (w), 1314 (w), 1238 (m), 1212 (s), 1161 (w), 1076, 1036 (m), 997 (w), 988 (w), 930 (w), 907 (w), 853 (w), 820 (w), 750 (m), 721 (m), 693 (m), 669 (w), 633 (w), 615 (w), 572 (w), 556 (w), 542 (w), 519 (m), 498 (w), 478 (w), 409 cm⁻¹ (w); ES (CH₂Cl₂) λmax 268 (log ε 4.49), 314 (4.61), 382 (4.06), 430 (3.05) sh, 466 (2.99) sh, 523 (2.88) sh, 565 nm (2.70); Anal. Calcd (%) for C₄₂H₃₈N₂O₄P·4½H₂O: C, 66.47, H, 5.37, N, 3.73. Found: C, 66.37, H, 5.25, N, 3.69.

Diethyl 6-(IH-benzimidazol-2-yl)azulene-1,3-dicarboxylate (12a)

To a stirred solution of 3 (200 mg, 0.314 mmol) in CHCl₃ (10 mL), 10a (40.8 mg, 0.377 mmol) was added and refluxed for 50 h under Ar. The reaction mixture was evaporated under reduced pressure and small portion of THF was added. The resulting suspension was filtered and the filtrate was evaporated under reduced pressure. The resulting residue was purified by column chromatography (silica gel, AcOEt), followed by GPC (CHCl₃) afford crude cyclized compound diethyl 6-(IH-benzimidazol-2-yl)azulene-1,3-dicarboxylate (12a). Recrystallization of this crude product from toluene gave 12a (41.1 mg, 34%).

12a: Brown crystals (toluene); mp 256.8-259.2 °C; ¹H NMR (400 MHz, DMSO-d₆) δ 13.47 (1H, br, NH), 9.71 (2H, d, J = 11.2 Hz, Az-4, 8), 8.80 (2H, d, J = 11.2 Hz, Az-5, 7), 8.60 (1H, s, Az-2), 7.78 (1H, d, J = 6.4 Hz, Benzo-H₃), 7.63 (1H, d, J = 6.8 Hz, Benzo-H₃), 7.33-7.28 (2H, m, Benzo-H₃), 4.36 (4H, q, J = 7.2 Hz, CO₂CH₂CH₃), 1.38 (6H, t, J = 7.2 Hz, CO₂CH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 163.76 (CO₂Et, 151.31, 144.08, 142.60, 142.42, 141.40, 137.96, 135.88, 128.91, 124.30, 122.77, 119.77, 115.99, 112.07,
51.90 (-CO₂H₂CH₃), 14.34 (-CO₂CH₃CH₃); MS (EI, 70eV) m/z 389.1 (M⁺+1, 7.77 %), 388.1 (M⁺, 100), 343 (31.5), 316.1 (12.8), 315 (14.9), 270.9 (5.7), 242 (5.3); IR (KBr) ν max 3544 (w), 3333 (m), 3056 (w), 2984 (m), 2940 (w), 2905 (w), 2872 (w), 1696 (s), 1661 (s), 1590 (s), 1520 (s), 1435 (s), 1393 (s), 1364 (w), 1350 (w), 1262 (w), 1213 (s), 1148 (w), 1084 (m), 1040 (s), 995 (w), 866 (w), 801 (w), 766 (m), 654 (w), 604 (w), 505 (w), 450 cm⁻¹ (w); ES (THF) λ max 354 (log ε 4.52), 261.8 (4.18) sh, 307.0 (4.28), 359.1 (4.52), 374.8 (4.50), 404.2 (4.43), 567.4 (2.83), 630.5 nm (2.15) sh; Anal. Calcd (%) for C₂₃H₂₀N₂O₄: C, 71.12, H, 5.19, N, 7.21. Found: C, 71.27, H, 5.34, N, 7.21.

**Diethyl 6-(benzoxazol-2-yl)azulene-1,3-dicarboxylate (12c)**

To a stirred solution of 3 (100 mg, 0.157 mmol) in CHCl₃ (10 mL), o-aminophenol (10c) (20.6 mg, 0.188 mmol) was added and refluxed for 13 days under Ar. The reaction mixture was evaporated under reduced pressure. The resulting residue was purified by column chromatography (silica gel, AcOEt) and GPC (CHCl₃) to give diethyl 6-(benzoxazol-2-yl)azulene-1,3-dicarboxylate (12c) (17.4 mg, 29 %) and diethyl 6-acetylazulene-1,3-dicarboxylate (13) (6.3 mg, 13%).

**12c:** Brown-purple needles (CH₂Cl₂/n-hexane); mp 207.2-210.1 °C; ¹H NMR (400 MHz, CDCl₃) δ 9.88 (2H, d, J = 10.4 Hz, Az-4, 8), 8.89 (1H, s, Az-2), 8.82 (2H, d, J = 10.4 Hz, Az-5,7), 7.86 (1H, d, J = 7.6 Hz, Benzo-Ha), 7.67 (1H, d, J = 7.6 Hz, Benzo-Ha), 7.46-7.41 (2H, m, Benzo-Hb), 4.46 (4H, q, J = 7.2 Hz, CO₂C₂H₃CH₃), 1.48 (6H, t, J = 7.2 Hz, CO₂C₂H₃CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 164.75 (-CO₂Et), 163.11 (Az-C=N), 151.54, 145.29, 144.17, 142.27, 138.14, 136.87, 128.63, 126.67, 125.37, 120.89, 117.43, 111.60, 60.31 (-CO₂C₂H₃CH₃), 14.56 (-CO₂C₂H₃CH₃); IR (KBr) ν max 3544 (w), 3333 (m), 3056 (w), 2982 (w), 2940 (w), 2905 (w), 2872 (w), 1696 (s), 1661 (s), 1590 (s), 1520 (s), 1435 (s), 1393 (s), 1364 (w), 1350 (w), 1262 (w), 1213 (s), 1148 (w), 1084 (m), 1040 (s), 995 (w), 866 (w), 801 (w), 766 (m), 743 (m), 654 (w), 604 (w), 505 (w), 450 cm⁻¹ (w); ES (THF) λ max 240.4 (log ε 4.54), 271.1 (4.09), 311.1 (4.32) sh, 352.4 (4.59), 372.6 (4.52), 395.0 (4.35), 498.6 (2.76) sh, 547.3 (2.83), 591.8 nm (2.71) sh; MS (EI, 70eV) m/z 389.0 (M⁺, 100), 345.0 (9.99), 344.1 (38.12), 317.0 (16.02), 316.0 (29.58), 272.0 (7.51), 232.0 (4.57), 185.0 (4.23); Anal. Calcd (%) for C₂₃H₂₀N₂O₄: C, 70.94, H, 4.92, N, 3.60. Found: C, 70.94, H, 4.99, N, 3.63.

**13:** mp 129-130 °C (from EtOH); ¹H NMR (400 MHz, CDCl₃) δ 9.87 (2H, d, J = 11.0 Hz, Az-4, 8), 8.94 (1H, s, Az-2), 8.33 (2H, d, J = 11.3 Hz, Az-5, 7), 4.46 (4H, q, J = 7.2 Hz, CO₂C₂H₃CH₃), 2.82 (3H, s, COCH₃), 1.47 (6H, t, J = 7.2 Hz, CO₂C₂H₃CH₃); MS (EI, 70eV) m/z 314.1 (M⁺, 100), 270.1 (10.7), 269.0 (59.8), 242.1 (18.0), 241.1 (31.6), 197.1 (9.6), 170.1 (5.9).


**Reaction of 3 and 10c in presence of sodium hydride**
To a stirred solution of 3 (50 mg, 0.079 mmol) in CHCl₃ (10 mL), 10c (10.5 mg, 0.094 mmol) was added and refluxed for 2 h under Ar. To the reaction mixture, after cooling to rt, was added sodium hydride (50%, 4.6 mg, 0.096 mmol) and refluxed for 8 h. Reaction mixture was evaporated under reduced pressure and resulting residue was purified by column chromatography (silica gel, AcOEt) and GPC (CHCl₃) to give 12c (13.3 mg, 44%).

**Reaction of 3 and 10c in the presence of triethylamine**
To a stirred solution of 3 (50 mg, 0.079 mmol) in dry CH₂Cl₂ (10 mL), 10c (10.3 mg, 0.094 mmol) was added and refluxed for 1 h under Ar. To the reaction mixture, after cooling to rt, triethylamine (9.4 mg, 0.095 mmol) was added and refluxed for 22 h. Reaction mixture was evaporated under reduced pressure and resulting residue was purified by column chromatography (silica gel, AcOEt) and GPC (CHCl₃) to give 12c (14.8 mg, 0.038 mmol, 48%).

**Diethyl 6-(1H-perimidin-2-yl)azulene-1,3-dicarboxylate (14)**
To a stirred solution of 3 (100 mg, 0.157 mmol) in CHCl₃ (10 mL), 1,8-diaminonaphyhalene (29.8 mg, 0.188 mmol) was added and refluxed for 1 h under Ar. The reaction mixture was evaporated under reduced pressure and small portion of THF was added. The resulting suspension was filtered and the filtrate was evaporated under reduced pressure. The resulting residue was purified by column chromatography (silica gel, CH₂Cl₂), to give diethyl 6-(1H-perimidin-2-yl)azulene-1,3-dicarboxylate (14) (59.9 mg, 0.137 mmol, 87%).

14: Deep green crystals (CH₂Cl₂/n-hexane) mp 129.0-131.7 °C; ¹H NMR (400 MHz, DMSO-d₆) δ 9.74 (2H, d, J = 11.2 Hz, Az-4, 8), 8.67 (1H, s, Az-2), 8.40 (2H, d, J = 10.8 Hz, Az-5, 7), 7.19-7.07 (4H, m, perimidine-H₁ b, c), 6.61 (2H, br, perimidine-H₃), 4.37 (4H, q, J = 7.2 Hz, CO₂CH₂CH₃), 1.38 (6H, t, J = 7.2 Hz, CO₂CH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 163.68 (-CO₂Et), 154.73, 145.11, 143.41, 143.10, 138.02, 134.99, 129.63, 128.51, 121.46, 119.20, 116.00, 59.95 (-CO₂CH₂CH₃), 14.32 (-CO₂CH₂CH₃); MS (EI, 70 eV) m/z 438.0 (M⁺, 100%), 365.1 (3.69), 292.0 (6.25), 291.0 (3.88), 182.5 (14.89); IR (KBr) ν_max 3366 (w), 3052 (w), 2980 (w), 2932 (w), 2905 (w), 1694 (s), 1678 (s), 1657 (m), 1636 (m), 1595 (s), 1566 (w), 1526 (w), 1478 (m), 1435 (s), 1410 (m), 1393 (m), 1374 (m), 1354 (w), 1339 (w), 1291 (w), 1240 (m), 1211 (s), 1165 (w), 1098 (w), 1073 (w), 1042 (m), 1034 (m), 986 (w), 871 (w), 837 (w), 824 (w), 764 (m), 719 (w), 666 (w), 648 (w), 586 cm⁻¹ (w); ES (THF) λ_max 235.9 (log ε 4.79), 270.2 (4.30), 320.7 (4.78), 350.2 (4.42) sh, 377.0 (4.06) sh, 553.4 nm (3.41); Anal. Calcd (%) for C₂₇H₂₂N₂O₄: C, 73.96, H, 5.06, N, 6.39. Found: C, 73.66, H, 5.34, N, 6.35.
Reaction of 3 with 10a in DMSO at 100 °C

To a stirred solution of 3 (100 mg, 0.157 mmol) in DMSO (10 mL), 10a (20.4 mg, 0.188 mmol) was added and stirred at 100 °C for 8 h. The reaction mixture was poured into the water and extracted with AcOEt. The extract was dried with anhydrous MgSO$_4$ and evaporated under reduced pressure. The resulting residue was purified by column chromatography (silica gel, AcOEt), followed by GPC (CHCl$_3$). However, we could not get pure 15 and 16 enough for elemental analysis. Crude 1-(2-aminophenylamino)-2-(1,3-diethoxycarbonylazulen-6-yl)vinyltriphenylphosphonium bromide (15) (8 mg, 6%) and cyclized compound 16 (13 mg, 17%).

15: $^1$H NMR (400MHz, CDCl$_3$) δ 9.80 (2H, d, $J$ = 10.8 Hz, Az-4,8), 8.80 (1H, s, Az-2), 8.20-8.23 (1H, m, vinyl-H), 7.99 (2H, d, $J$=10.8 Hz, Az-5,7), 7.52-7.75 (19H, m, Benzo-H, Ph-H), 5.27 (br, NH or NH$_2$), 4.43 (4H, q, $J$ = 7.2 Hz, CO$_2$CH$_2$CH$_3$), 1.45 (6H, t, $J$ = 7.2 Hz, -CO$_2$CH$_2$CH$_3$).

16: $^1$H NMR (400MHz, CDCl$_3$) δ 9.95 (2H, d, $J$ = 11.2 Hz, Az- 4, 8), 9.45 (1H, s, vinyl-H), 8.92 (1H, s, Az-2), 8.51 (2H, d, $J$ = 11.2 Hz, Az-5, 7), 8.38 (1H, s, NH), 8.20-8.27 (1H, m, Benzo-H), 8.11 (1H, d, $J$=9.0 Hz, Benzo-H), 7.95 (1H, d, $J$ = 8.8 Hz, Benzo-H), 7.84-7.91 (1H, m, Benzo-H); MS (EI, 70eV) m/z 481 (M$^+$+1, 27.5%), 480.1 (M$^+$, 100), 479.2 (27.8), 478.1 (98.5), 435.0 (30.4), 432.8 (28.4), 407.8 (13.2), 406.9 (22.2), 406.0 (13.4), 404.8 (20.8), 401.1 (19.5), 400.1 (75.2), 355.1 (24.5), 328.0 (10.9), 327.0 (16.7), 253.1 (10.6).

Reaction of 3 with 10a in DMSO at 120 °C

To a stirred solution of 3 (100 mg, 0.157 mmol) in DMSO (10 mL), 10a (20.4 mg, 0.188 mmol) was added and stirred at 120 °C for 2 h. The reaction mixture was poured into the water and extracted with AcOEt. The extract was dried with anhydrous MgSO$_4$ and evaporated under reduced pressure to give 27.3 mg of reaction mixture. It was purified by short column chromatography (silica gel, AcOEt) to give diethyl 6-methyl-1,3-azulenedicarboxylate (17) (3.7 mg, 8%).

17: MS (EI, 70eV) m/z 287.0 (M$^+$+1, 18.1 %), 286.1 (M$^+$, 100), 271 (2.6), 258 (5.4), 242 (12.4), 241.1 (68.8), 215.1 (3.7), 214.1 (24.1), 213.1 (50.9), 187 (1), 186 (6.5), 169 (10.3), 142.1 (5.1), 139 (11.1).

REFERENCES


