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SYNTHESIS OF AZULENEQUINONES FUSED WITH THIOPHENE AND FURAN[1]

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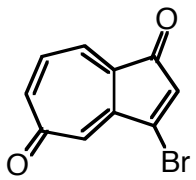
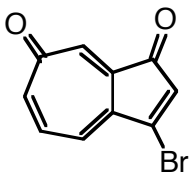
Abstract--- 1,5- And 1,7-azulenequinones fused with a thiophene or furan ring have been synthesized by bromine oxidation of azuleno[1,2-*b*]thiophenes, azuleno[2,1-*b*]thiophene, and azuleno[1,2-*b*]furan in aqueous THF.

Azulenequinones have been of great interest due to not only their physical and chemical properties but also their physiological activities.[2,3] Recently, one of the authors (T. Nozoe) and co-workers have studied in detail concerning the bromination of guaiazulene and other azulene derivatives. As a result of a systematic study, they found a very convenient, standard procedure for an one-pot synthesis of azulenequinones, such as 3-bromo-1,5- and -1,7-azulenequinones (**1** and **2**) (Chart 1).[4,5]



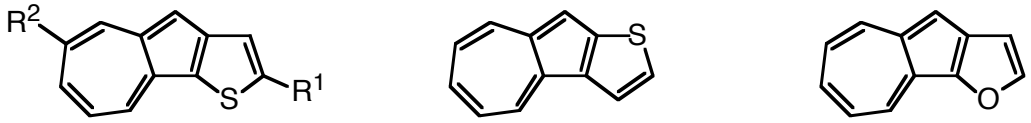
1



2

Chart 1

Now we wish to report on the synthesis of azulenequinones fused with a thiophene or furan ring by the application of the bromine oxidation method to azuleno[1,2-*b*]thiophenes (**3a**-**c**),[6] azuleno[2,1-*b*]thiophene (**4**),[6] and azuleno[1,2-*b*]furan (**5**).[7]



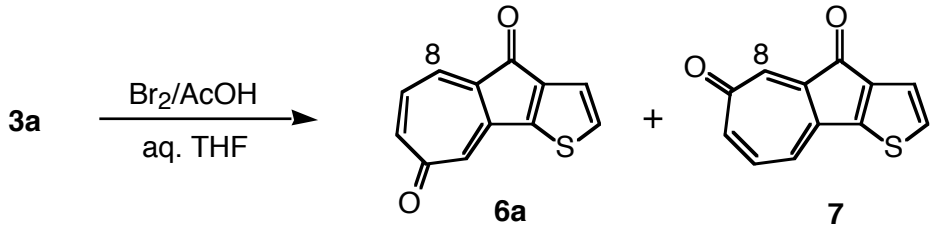
3 **4** **5**

a: $R^1 = R^2 = H$, **b:** $R^1 = CH_3$, $R^2 = H$

c: $R^1 = H$, $R^2 = CH(CH_3)_2$

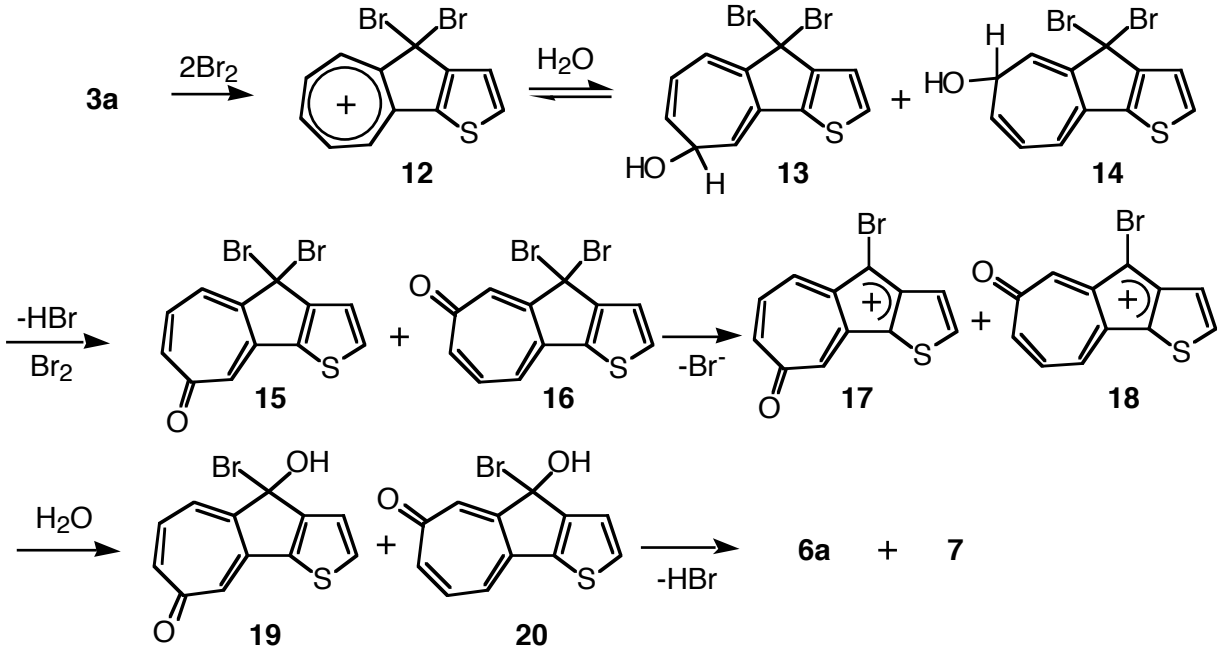
Chart 2

To a stirred solution of **3a** in 5~20% aqueous THF was added 3 molar amounts of bromine in a small amount of acetic acid over a period of a few minutes at 5~10 °C. The reaction mixture was then quenched with water and was allowed to stand overnight at room temperature. Thieno[3,2-*b*][1,5]azulenequinones (**6a)** (30%) and thieno[3,2-*b*][1,7]azulneoquinone (**7**) (35%) were obtained after separation by silica gel column chromatography in the form of stable yellow and orange needles, respectively (Scheme 1). The structures of **6a** and **7** were clearly distinguished by the splitting pattern of the proton at the 8-position on ^{1}H NMR. Namely, H-8 of **6a** was observed at δ = 7.36 as ddd (J= 8.2, 1.2, and 0.7 Hz). On the other hand, H-8 of **7** was observed at δ = 7.34 as dd (J= 2.6 and 0.7 Hz).



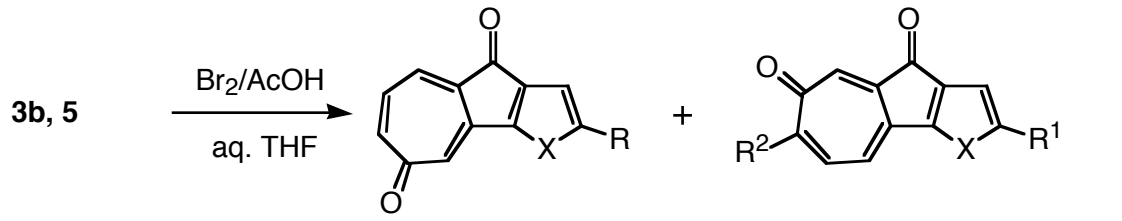
Scheme 1

A possible mechanism for the formation of these two bromoazulenequinones (**6a** and **7**) is shown in Scheme 2.



Scheme 2

Bromine oxidation of 2-methylazuleno[1,2-*b*]thiophene (**3b**) and azuleno[1,2-*b*]furan (**5**) under the same conditions gave also two corresponding azulenoquinones (**8**,**9a** and **10**,**11**), respectively, together with a mixture of minor bromo compounds. On the other hand, oxidation of **3b** with 4.0 molar amounts of bromine afforded 6-bromo-2-methylthieno[3,2-*b*][1,5]azulenequinone (**9b**) together with a small amount of **8** and **9a** (Scheme 3).

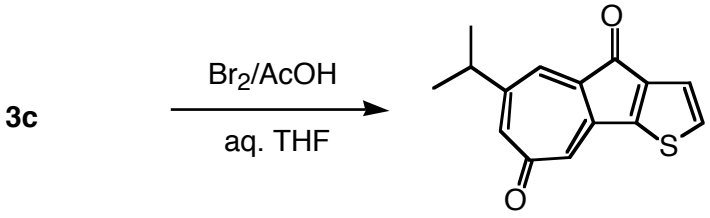


8: X= S, R= CH_3
10: X= O, R= H

9a: X= S, R^1= CH_3, R^2= H
9b: X= S, R^1= CH_3, R^2= Br
11: X= O, R^1= R^2= H

Scheme 3

Further, the bromine oxidation of 7-isopropylazuleno[1,2-*b*]thiophene (**3c**) yielded only 7-isopropylthieno[3,2-*b*][1,5]azulenequinone (**6b**), which was originally expected (Scheme 4).



6b

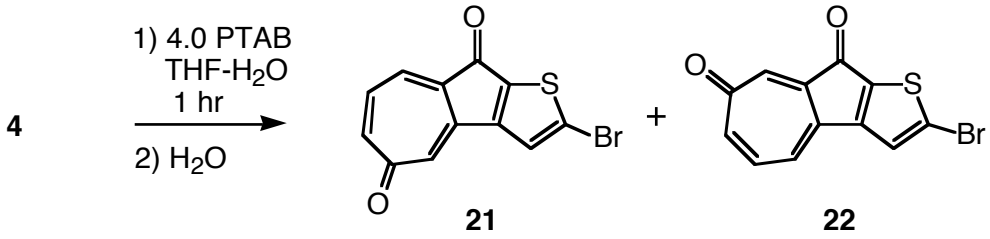
Scheme 4

Oxidation using phenyltrimethylammonium perbromide (PTAB) or pyridinium tribromide (PTB) also afforded azulenequinones (Table 1).

Similar oxidation of azuleno[2,1-*b*]thiophene (**4**) with 4.0 molar amounts of PTAB yielded 2-bromothieno[2,3-*b*][1,5]azulenequinone (**21**) and 2-bromothieno[2,3-*b*][1,7]azulenequinone (**22**) (Scheme 5).

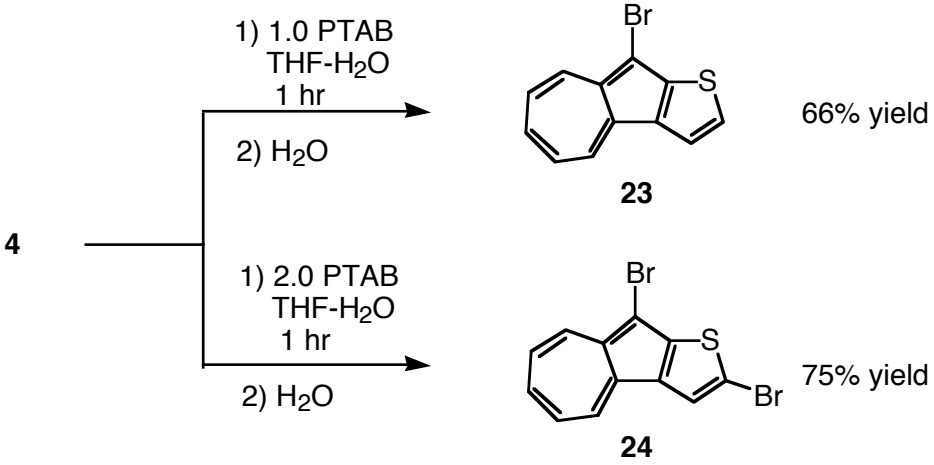
Table 1 Oxidation using PTAB or PTB

Compounds	**Reagents**	**Products** (yield %)	
3a	**PTAB**	**6a** (31)	**7** (33)
3a	**PTB**	**6a** (24)	**7** (28)
3b	**PTAB**	**8** (24)	**9a** (27)
3c	**PTAB**	**6b** (46)	
5	**PTAB**	**10** (7)	**11** (3)

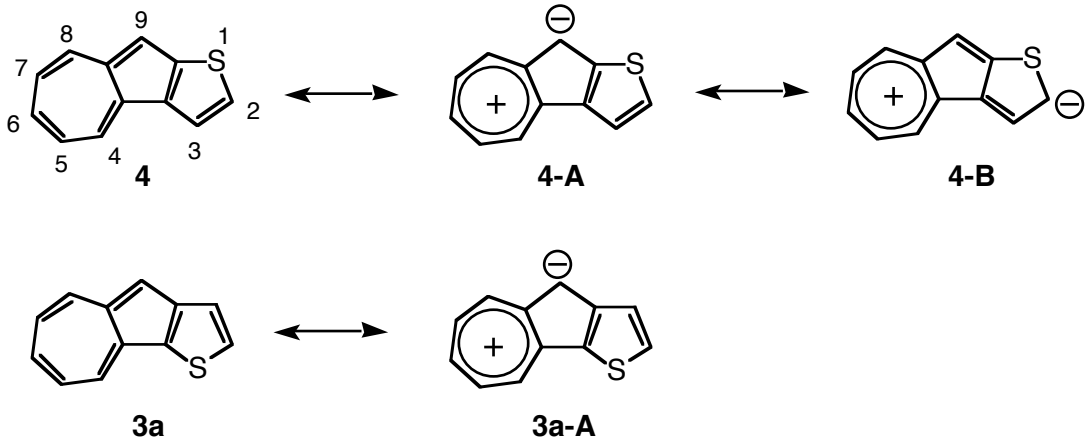


Scheme 5

When **4** was treated with 1.0 and 2.0 molar amounts of PTAB, 9-bromoazuleno[2,1-*b*]thiophene (**23**) and 2,9-dibromoazuleno[2,1-*b*]thiophene (**24**) were obtained in 66 and 75% yields, respectively (Scheme 6). These experimental facts suggest that the 2- and 9-positions of **4**, which is distinct from **3a**, readily undergo bromination due to the contribution of resonance structures **4-A** and **4-B**, as shown in Scheme 7.



Scheme 6



Scheme 7

X-Ray crystallographic analysis of 6a: The ORTEP drawing of **6a** is shown in Figure 1 together with the bond distances, which indicate the bond alternation between single and double bonds in the azulenequinone moiety. The distances corresponding to the five double bonds in **6a** are within a close

range of their average lengths (1.351 Å), which is slightly longer than the distances observed for C2=C3 of *p*-benzoquinone (1.344 Å) and slightly shorter than their average lengths (1.364 Å) of 1,7-guaiazulenequinone.[8] However, the distances corresponding to the C-C single bonds in **6a** appreciably varies between 1.416 Å and 1.503 Å; in particular, the C4-C5 distance (1.503 Å) is characteristically longer than the average of the seven C-C single bond distances (1.469 Å), which is slightly shorter than C1-C2 of *p*-benzoquinone (1.481 Å). The C4=O (1.225 Å) and C9=O (1.232 Å) distances coincide with the C=O distances of *p*-benzoquinone (1.225 Å) and 1,4-naphthoquinone (1.232 Å). Those have been also observed in the X-Ray analysis of 1,7-guaiazulenequinone.[8]

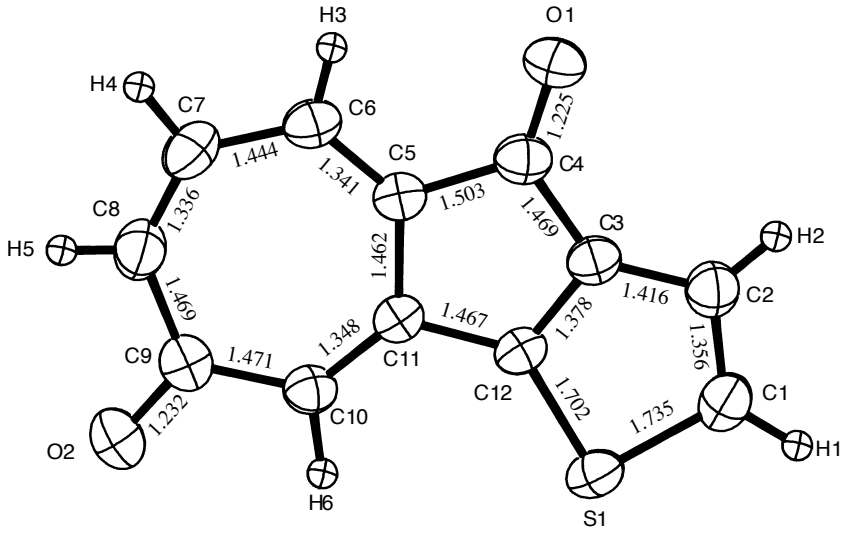


Figure 1 An ORTEP drawing of **6a** with the numbering scheme and the bond distances (Å)

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. Spectral data were obtained on the following instruments: ^{1}H-NMR: JEOL-JNM-LA300 (300 MHz) and –LA400 (400 MHz); ^{13}C-NMR; JEOL-JNM-LA300 (75.5 MHz) and –LA400 (100 MHz); IR: JEOL JIR-Diamond20 and Hitachi model 345; MS spectroscopy: Shimadzu GCMS-QP1000EX; UV-VIS: Hitachi model 200. Elemental analyses were performed on a Perkin-Elmer model 240.

General procedure for preparing azulenequinones fused with thiophene and furan

a) **Bromine oxidation in aqueous THF** To a solution of azulenes (azulenothiophene or azulenofuran) in tetrahydrofuran(THF) and water (THF : H_2O = 5 : 1), cooled in an ice/water bath, were added 3.0 molar amounts of bromine in a small amount of acetic acid over a period of a few minutes. The mixture was stirred at rt for 1 h and water (10 mL) was added. The reaction mixture was allowed to stand over night, diluted with excess water (150 mL), and extracted with dichloromethane. The organic layer was washed with a saturated solution of sodium carbonate, dried with anhydrous sodium sulfate, and

concentrated in vacuo. The residue was purified by column chromatography on silica gel to afford the corresponding azulenequinones.

b) **Oxidation using PTAB or PTB** A solid of PTAB or PTB (3.0 molar amounts) was added to a solution of azulenes in THF and water (5 : 1) at 0 °C. The mixture was stirred for 1 h at rt and water was added. The reaction mixture was allowed to stand over night and worked up in a similar manner as described for a). The residue was purified by column chromatography on silica gel to afford the corresponding azulenequinones.

Thieno[3,2-*b*][1,5]azulenequinone (6a) Pale yellow needles, mp 203-204 °C (from benzene). Yield 30% (bromine oxidation). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 6.95 (1H, ddd, *J*= 12.6, 2.6, 1.1 Hz, H-6), 6.96 (1H, dd, *J*= 2.6, 0.7 Hz, H-4), 7.09 (1H, dd, *J*= 12.6, 8.2 Hz, H-7), 7.32 (1H, d, *J*= 5.1 Hz, H-1), 7.36 (1H, ddd, *J*= 8.2, 1.1, 0.7 Hz, H-8), 7.54 (1H, d, *J*= 5.1 Hz, H-2). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 121.9 (C-1), 128.6 (C-4), 129.4 (C-8), 134.2 (C-7), 134.8 (C-2), 140.8 (C-4b), 142.3 (C-8a), 144.0 (C-6), 147.4 (C-1b), 161.5 (C-3a), 182.9 (C-9), 186.3 (C-5). IR (KBr): 1712, 1645, 1596, 1574, 1267 cm^{-1}. UV-VIS (MeCN): λ_{max}(log ε) 293 (4.13), 302 (4.17). MS (m/z) 214 (M^+-CO, 100), 158 (M^+-2CO, 33). Anal. Calcd for $C_{12}H_6O_2S$: C, 67.28; H, 2.82. Found: C, 67.02; H, 3.15.

7-Isopropylthieno[3,2-*b*][1,5]azulenequinone (6b) Pale yellow needles, mp 152-153 °C (from benzene). Yield 48% (bromine oxidation). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.26 (6H, d, *J*= 6.8 Hz, -CH(C<u>H</u>$_3$)$_2$), 2.78 (2H, sept, *J*= 6.8 Hz, -C<u>H</u>(CH$_3$)$_2$), 6.86 (1H, d, *J*= 2.0 Hz, H-6), 6.87 (1H, d, *J*= 2.0 Hz, H-4), 7.32 (1H, d, *J*= 4.9 Hz, H-1), 7.33 (1H, s, H-8), 7.54 (1H, d, *J*= 4.9 Hz, H-2). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 22.2, 38.2, 121.7, 128.2, 131.6, 134.6, 139.6, 140.1, 140.9, 147.2, 154.8, 161.5, 183.2, 186.7. IR (KBr): 1708, 1641, 1621, 1589 cm^{-1}. MS (m/z) 256 (M^+, 2), 228 (M^+-CO, 50), 213 (100). Anal. Calcd for $C_{15}H_{12}O_2S$: C, 70.28; H, 4.72. Found: C, 70.30; H, 4.75.

Thieno[3,2-*b*][1,7]azulenequinone (7) Orange needles, mp 221-223 °C (from benzene). Yield 35% (bromine oxidation). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.95 (1H, ddd, *J*= 12.1, 2.6, 0.7 Hz, H-6), 6.86 (1H, dm, *J*= 8.4 Hz, H-4), 7.05 (1H, dd, *J*= 12.1, 8.4 Hz, H-5), 7.30 (1H, *J*= 5.1 Hz, H-1), 7.34 (1H, dd, *J*= 2.6, 0.7 Hz, H-8), 7.47 (1H, d, *J*= 5.1 Hz, H-2). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 121.7, 122.0, 133.6, 134.9, 136.0, 138.9, 139.5, 142.9, 145.8, 162,7, 183.4, 1876. IR (KBr): 1713. 1646. 1582, 1588 cm^{-1}. MS (m/z) 214 (M^+, 22), 186 (M^+-CO, 100), 158 (M^+–2CO, 35). UV-VIS (MeCN): λ_{max} (log ε) 286 (4.10), 295 (4.12), 352 (3.91), 407 (sh, 3.41). Anal. Calcd for $C_{12}H_6O_2S$: C, 67.28; H, 2.82. Found: C, 67.05; H, 3.10.

2-Methylthieno[3,2-*b*][1,5]azulenequinone (8) Pale yellow needles, mp 263 °C (decomp) (from

benzene). Yield 13% (bromine oxidation). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.59 (3H, d, *J*= 1.1 Hz, -C<u>H</u>$_3$), 6.82 (1H, dd, *J*= 2.6, 0.7 Hz, H-4), 6.90 (1H, ddd, *J*= 12.1, 2.6, 1.1 Hz, H-6), 6.98 (1H, q, *J*= 1.1 Hz, H-1), 7.05 (1H, dd, *J*= 12.1, 8.1 Hz, H-7), 7.29 (1H, ddd, *J*= 8.1, 1.1, 0.7 Hz, H-8). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 16.6, 119.5, 127.5, 128.8, 134.1, 141.2, 141.9, 143.6, 147.6, 151.4, 160.0, 183.1, 187.0. IR (KBr): 1714, 1648, 1615, 1586 cm^{-1}. MS (m/z) 228 (M^+, 15), 200 (M^+-CO, 100), 172(M^+-2CO, 18). Anal. Calcd for $C_{13}H_8O_2S$: C, 68.40; H, 3.53. Found: C, 68.32; H, 3.20.

2-Methylthieno[3,2-*b*][1,7]azulenequinone (9a) Orange needles, mp 220 °C (decomp) (from benzene). Yield 11% (bromine oxidation). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.58 (3H, d, *J*= 1.1 Hz, -CH_3), 6.72 (1H, dm, *J*= 8.4 Hz, H-4), 6.76 (1H, ddd, *J*= 12.5, 2.9, 0.7 Hz, H-6), 6.95 (1H, q, *J*= 1.1 Hz, H-1), 7.01 (1H, dd, *J*= 12.5, 8.4 Hz, H-5), 7.28 (1H, dd, *J*= 2.9, 0.7 Hz, H-8). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 16.5, 119.4, 121.0, 134.4, 136.1, 138.8, 139.3, 142.5, 146.0, 150.0, 161.4, 183.5, 187.8. IR (KBr): 1712, 1648, 1629, 1585 cm^{-1}. MS (m/z) 228 (M^+, 41), 200 (M^+-CO, 100), 172 (M^+-2CO, 20). Anal. Calcd for $C_{13}H_8O_2S$: C, 68.40; H, 3.53. Found: C, 68.10; H, 3.23.

6-Bromo-2-methylthieno[3,2-*b*][1,7]azulenequinone (9b) Orange needles, mp 233°C (decomp) (from benzene). Yield 3% (bromine oxidation). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.98 (1H, d, *J*= 9.5 Hz, H-5), 7.39 (1H, s, H-8), 6.95 (1H, q, *J*=1.1 Hz, H-1), 6.54 (1H, d, *J*= 9.5 Hz, H-4), 2.58 (3H, d, *J*= 1.1 Hz, -CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 16.6, 118.4, 119.6, 130.3, 138.7, 139.2, 139.4, 141.7, 146.2, 150.9, 160.6, 180.6, 182.9. MS (m/z) 308 (M^++2, 46), 306 (M^+, 48), 280 (M^++2-CO, 91), 278 (M^+-2CO, 100). IR (KBr): 2954, 2924, 2852, 1705, 1635, 1595 cm^{-1}.

Furo[3,2-*b*][1,5]azulenequinone (10) Pale yellow needles, mp 225 °C (decomp) (from benzene). Yield 17% (bromine oxidation). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.72 (1H, d, *J*= 1.8 Hz, H-1), 6.89 (1H, ddd, *J*= 12.1, 2.6, 1.1 Hz, H-6), 6.93 (1H, dm, *J*= 2.6 Hz, H-4), 7.05 (1H, dd, *J*= 12.1, 8.1 Hz, H-7), 7.36 (1H, dm, *J*= 8.1 Hz, H-8), 7.69 (1H, d, *J*= 1.8 Hz, H-2). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 107.3, 125.5, 129.5, 131.0, 134.1, 134.7, 143.4, 143.7, 152.2, 174.0, 180.6, 186.9. IR (KBr): 1723, 1655, 1646, 1592, 1577 cm^{-1}. MS (m/z) 198 (M^+, 13), 179 (M^+-CO, 100), 142 (M^+-2CO, 18). Anal. Calcd for $C_{12}H_6O_3$: C, 72.73; H, 3.05. Found: C, 72.49; H, 3.14.

Furo[3,2-*b*][1,7]azulenequinone (11) Yellow needles. mp 183 °C (decomp) (from benzene). Yield 7% (bromine oxidation). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.71 (1H, d, *J*= 1.8 H, H-1), 6.78 (1H, ddd, *J*= 12.5, 8.1, 1.1 Hz, H-6), 6.85 (1H, dm, *J*= 8.1 Hz, H-6), 7.04 (1H, dd, *J*= 12.5, 8.1 Hz, H-5), 7.35 (1H, dm, *J*= 2.6 Hz, H-8), 7.65 (1H, d, *J*= 1.8 Hz, H-2). MS (m/z) 198 (M^+, 40), 170 (M^+-CO, 100), 142 (M^+-2CO, 24). Anal. Calcd for $C_{12}H_6O_3$: C, 72.73; H, 3.05. Found: C, 72.43; H, 2.75.

2-Bromothieno[2,3-*b*][1,5]azulenequinone (21) Yellow micro needles, mp >300°C (from benzene). Yield 25% (oxidation using PTAB). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.96 (1H, d, *J*= 2.4 Hz, H-4), 6.96 (1H, dd, *J*= 12.7, 2.4 Hz, H-6), 7.11 (1H, dd, *J*= 12.7, 7.8 Hz, H-7), 7.37 (1H, s, H-3), 7.40 (1H, d, *J*= 7.8 Hz, H-8). IR (KBr): 1703, 1687, 1641, 1581, 1564 cm^{-1}. MS (m/z) 294 (M^++2, 7), 292 (M^+, 7), 266 (M^++2-CO, 100), 264 (M^+-CO, 99), 238 (M^++2-2CO, 11), 236 (M^+-2CO, 14). Anal. Calcd for $C_{12}H_5O_2BrS$: C, 49.16; H, 1.72. Found: C, 48.86; H, 1.42.

2-Bromothieno[2,3-*b*][1,7]azulenequinone (22) Yellow micro plates, mp 224 °C (decomp) (from benzene). Yield 10% (oxidation using PTAB). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.83 (1H, dd, *J*= 12.2, 2.7 Hz, H-6), 6.87 (1H, d, *J*= 8.3 Hz, H-4), 7.07 (1H, dd, *J*= 12.2, 8.3 Hz, H-5), 7.37 (1H, s, H-3). IR (KBr): 1709, 1643, 1574 cm^{-1}. MS (m/z) 294 (M^++2, 20), 292 (M^+, 18), 266 (M^++2-CO, 97), 264 (M^+-CO, 100), 238 (M^++2-2CO, 18), 236 (M^+-2CO, 17). Anal. Calcd for $C_{12}H_5O_2BrS$: C, 49.16; H, 1.72. Found: C, 48.96; H, 1.52.

9-Bromoazuleno[2,1-*b*]thiophene (23) Green crystals (unstable). Yield 66%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.23-7.30 (2H, m, H-5 and H-7), 7.43 (1H, d, *J*= 5.1 Hz, H-2), 7.40 (1H, dd, *J*= 10.2, 9.3 Hz, H-6), 7.80 (1H, d, *J*= 5.1 Hz, H-3), 8.29 (1H, d, *J*= 10.5 Hz, H-4 or 8), 8.42 (1H, d, *J*= 8.8 Hz, H-8 or 4).

2,9-Dibromoazuleno[2,1-*b*]thiophene (24) Green needles, mp 97 °C (decomp) (from benzene). Yield 75%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.26-7.31 (2H, m, H-5 and H-7), 7.62 (1H, dd, *J*= 10.2, 9.5 Hz, H-6), 7.78 (1H, s, H-3), 8.28 (1H, d, *J*= 10.5 Hz, H-4 or 8), 8.33 (1H, d, *J*= 9.0 Hz H-8 or 4).

X-Ray structural analysis of 6a. A yellow needle crystal having approximate dimensions of 0.06 × 0.16 × 1.0 mm was used for the measurements. The data collections were performed on a Rigaku AFC-5S diffractometer with graphite-monochromated Mo-Kα radiation (λ = 0.71069 Å) using ω–2θ scan technique. A total of 2728 reflections were measured up to 2θ = 55.0°. Crystal data are as follows: $C_{12}H_6O_2S{\cdot}H_2O$, *MW* = 232.25, monoclinic, space group $P2_1/c$, *a* = 12.854(2), *b* = 3.820(2), *c* = 20.414(2) Å, β = 97.29(1)°, *V* = 994.3(6) Å^3, *Z* = 4, D_{calcd} = 1.551 g cm^{-3}. The structure was solved by direct methods. The non-hydrogen atoms were refined anisotropically by full-matrix least-squares method. Hydrogen atoms were refined isotropically. The final R_1 and R_W are 0.049 and 0.058 for 1460 reflections with $I > 3\sigma(I)$. All calculations were performed using teXsan crystallographic software package of Molecular Structure Corporation.

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