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Synthesis of 2,5-diethynyl substituted oxepins from *trans*-1,4-diethynylcyclohexa-2,5-diene-1,4-diols

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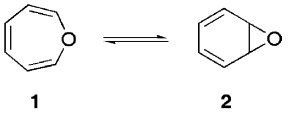
Abstract—Reaction of *trans*-1,4-bis(trimethylsilylethynyl)cyclohexa-2,5-diene-1,4-diol with *n*-BuLi followed by methanesulfonyl chloride resulted in the formation of a dark red solid, which was identified as 2,5-bis(trimethylsilylethynyl)oxepin. Deprotection of the silyl groups resulted in the formation of 2,5-diethynyloxepin, a red, shock sensitive solid. Reaction of a differentially substituted cyclohexa-2,5-diene-1,4-diol gave a mixture of 2,5-diethynyl substituted oxepins.

The reversible thermal valence isomerization of the oxepin **1**–benzene oxide **2** system has been studied in detail (Scheme 1).[1] This system exhibits thermochromism as well as solvatochromism, the benzene oxide form is colorless and the oxepin is yellow.[2] At low temperatures the benzene oxide form is predominant and above room temperature the oxepin form is dominant.

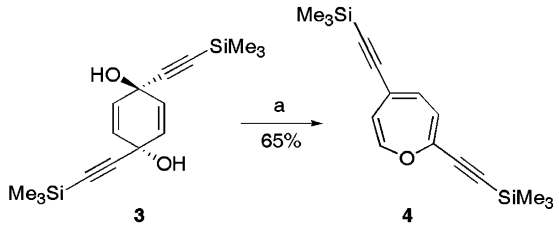
Introduction of functional groups that extend the conjugation of the oxepin π system shifts the electronic absorption maxima well into the visible region.[3] Oxepins bearing functional groups with extended conjugation are potentially useful as thermochromic systems. Ethynyl substituted oxepins are unknown and are potentially useful for the synthesis of oxepins with extended π conjugation and polyacetylene polymers bearing oxepin backbones. The classical methods of oxepin synthesis involve multiple steps.[4] Herein we describe the synthesis of 2,5-diethynyl substituted oxepins in two steps and the application of this method for the synthesis of an oxepin with extended acetylenic conjugation.



Scheme 1. Valence isomerization of oxepin–benzene oxide.

Recently we reported an efficient method for the synthesis of *cis*- and *trans*-isomers of 1,4-diethynyl substituted cyclohexa-2,5-diene-1,4-diols **3** and **6** from *p*-benzoquinone.[5] The *cis*-isomer of **3** was shown to be a useful building block for the synthesis of acetylenic macrocycles.[5] Herein we report the synthesis of 2,5-bis(trimethylsilylethynyl)oxepin from the *trans*-isomer, **3**. Initially our intention was to synthesize the bis-methanesulfonate ester of diol **3**, but to our surprise, treatment of diol **3** with 2 equiv of *n*-BuLi followed by 2 equiv of methanesulfonyl chloride, resulted in the formation of a dark red solid, identified as 2,5-bis(trimethylsilylethynyl)oxepin **4**.

Subsequently the procedure was optimized for the formation of oxepin **4**. It was found that only one equivalent of methanesulfonyl chloride was sufficient to produce oxepin **4** in 65% yield (Scheme 2).



Scheme 2. Synthesis of oxepin **4** from **3**. Reagents and conditions: (a) 2.0 equiv *n*-BuLi, 1.0 equiv CH_3SO_2Cl, THF, −78 °C to rt.

Keywords: Oxepin; Valence isomerization; Extended conjugation; Acetylene; Thermochromism.
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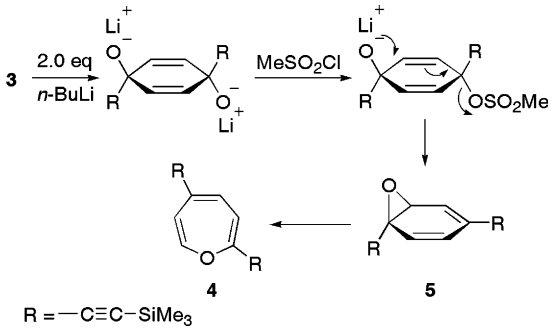
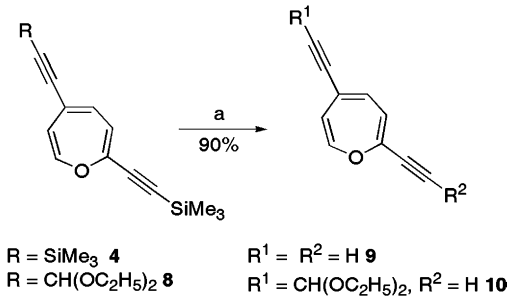


Scheme 3. Mechanism of formation of oxepin **4** from **3**.

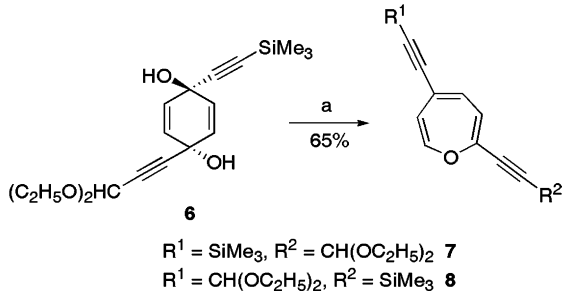


Scheme 5. Deprotection of the TMS group. Reagents and conditions: (a) K_2CO_3, MeOH, rt, 30 min, N_2.

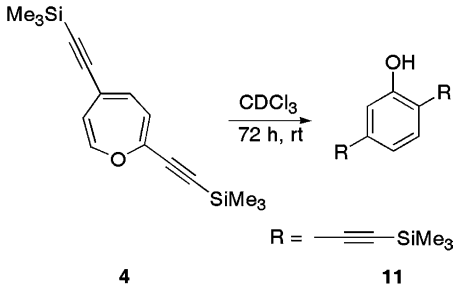
Interestingly the *cis*-isomer of diol **3** under identical reaction conditions failed to yield any oxepin, only the starting diol was recovered after aqueous work up. Based on these observations a probable mechanism of formation of oxepin **4** is shown in Scheme 3. Formation of **4** is explained on the basis of an intramolecular S_N2' substitution reaction of the intermediate mono sulfonate ester which results in the formation of the benzene oxide derivative **5**. Thermal electrocyclic ring opening of **5** leads to the formation of **4** (Scheme 3).[1] The S_N2' substitution reaction is stereoelectronically favored in the case of the *trans*-isomer over the *cis*-isomer which explains the lack of oxepin formation in the latter case.

When a differentially substituted diol was reacted in the same way, a mixture of oxepins were obtained as illustrated in the case of diol **6**. Treatment of *trans* diol **6**[5] with *n*-BuLi followed by CH_3SO_2Cl yielded a 1:1 mixture of oxepins **7** and **8** (Scheme 4). The oxepins were separated by column chromatography and thoroughly characterized by spectroscopic data.[6] The structural assignment of these two regioisomeric oxepins is based on the chemical shift values of the acetylenic carbons from the ^{13}C NMR spectra. In oxepin **7** the chemical shift values of the ethynyl carbons of the trimethylsilylethynyl group are 100.8 and 94.7 whereas that of the diethoxypropynyl group are 88.1 and 84.9, respectively. In the case of oxepins **4** and **8** the chemical shift values of the acetylenic carbons on the 2-position are 105.1 and 97.4 for **4** and 105.5 and 97.4 for **8**, respectively.

Removal of the trimethylsilyl groups in **4** and **8** using K_2CO_3 in MeOH readily yielded the corresponding 2,5-diethynyloxepins **9** and **10**, each in 90% yield (Scheme 5).[6] The red crystalline solid oxepin **4** was stable for several months and no decomposition was observed under ambient conditions. Upon cooling the solid, and the red color of the oxepin **4** gradually changed to yellow below −20 °C and turned to pale yellow at −78 °C. Upon warming the solid back to room temperature the reverse color changes were observed. This thermochromic behavior was observed over several cycles of cooling to −78 °C and warming to room temperature. We attribute the thermochromic behavior of **4** to the well known reversible thermal valence isomerization to **5**, similar to that observed for **1** and **2**. Similarly the dark red solution of oxepin **4** in acetone-d_6 also reversibly changed color to yellow with lowering of the temperature and exhibited thermochromism over several cycles. The solution of **4** in acetone-d_6 was stable for several months and no decomposition could be observed by ^1H NMR spectroscopy and TLC. However a red colored solution of **4** in $CDCl_3$ slowly changed color to pale yellow when stored at ambient temperature and the decomposition of **4** could be followed by ^1H NMR spectroscopy. After 3 days, isomerization of **4** was complete and yielded 2,5-bis(trimethylsilylethynyl)phenol **11** as the only product (Scheme 6). The isomerization of **4** to **11** could be accelerated by the addition of a small amount of trifluoroacetic acid. Repeated cooling and warming of the $CDCl_3$ solution between −78 °C and room temperature also accelerated the isomerization. The ^1H NMR spectrum of **4** was recorded at various temperatures in acetone-d_6 in an attempt to measure the dynamics of the valence isomerization of **4** and **5**. However, the spectra recorded from room temperature to −90 °C did not reveal any changes. The NMR spectral changes due to the valence isomerization of the



Scheme 4. Synthesis of differentially substituted oxepins. Reagents and conditions: (a) 2.0 equiv *n*-BuLi, 1.0 equiv CH_3SO_2Cl, THF, −78 °C to rt.



Scheme 6. Rearrangement of oxepin **4** to phenol **11**.

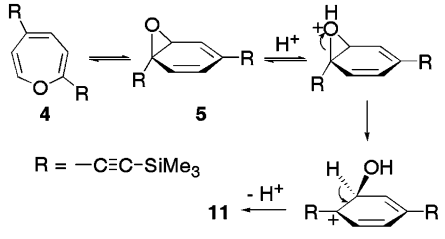
parent oxepin **1** could be observed only below −110 °C.[7] In the present study the NMR spectrum could not be recorded below −90 °C due to poor solubility. The isomerization of **4** to **11** in $CDCl_3$ and also in the presence of acid is due to the acid catalyzed isomerization of the benzene oxide form **5**.

The equilibrium between **4** and **5** is favored toward **5** at low temperatures and hence repeated cooling and warming of the solution in $CDCl_3$ accelerates the isomerization. The trace amount of HCl present in $CDCl_3$ is responsible for the isomerization (Scheme 7).[1,8]

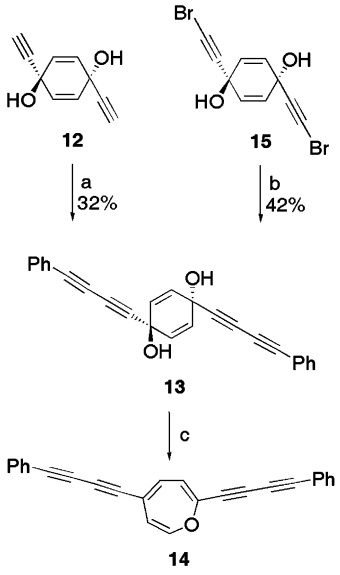
In non-acidic solvents such as acetone, THF, and ether oxepin **4** is quite stable. Oxepin **9** was found to be unstable and shock sensitive. Attempts to remove the solid oxepin using a metal spatula led to exothermic decomposition and formation of smoke. Our attempts to use oxepin **9** as an acetylenic building block for the synthesis of oxepins with extended acetylenic conjugation were unsuccessful as **9** was unstable and slowly polymerized at room temperature both in the solid state as well as in solution to yield a dark red colored polymer. Attempted Sonogashira coupling of **9** with iodobenzene failed to yield 2,5-bis(phenylethynyl)oxepin. Similarly attempted Cadiot–Chodkiewicz coupling of **9** with β-bromophenylacetylene also failed to yield 2,5-bis(phenylbutadiynyl)oxepin **14**. In the above reactions oxepin **9** decomposed to give an intractable polymeric material. Unlike **9**, oxepin **10** was found to be stable in the solid state as well as in solution.

Oxepin **14** could be readily obtained from diol **13** (Scheme 8). The starting diol **13** was obtained by the Cadiot–Chodkiewicz coupling of diol **12**[5] with β-bromophenylacetylene. Alternatively diol **13** was obtained by the Cadiot–Chodkiewicz coupling of the bromodiol **15** with phenylacetylene. The bromodiol **15** was prepared by bromination of **12** using *N*-bromosuccinimide. The availability of diols **12** and **15** makes the methodology shown in Scheme 8 viable and attractive for the synthesis of oxepins with extended acetylenic conjugation.

In conclusion we have reported a new method for the synthesis of the hitherto unknown 2,5-diethynyl disubstituted oxepins from the corresponding 1,4-diethynylcyclohexa-2,5-diene-1,4-diols in a single step. From differentially substituted diols such as **6**, a mixture of isomeric oxepins was obtained that was readily separable by column chromatography. A new methodology for the synthesis of oxepins with extended acetylenic conjugation has also been developed. The effect of ethynyl substituents on the stability and reactivity of various oxepins is currently under investigation.



Scheme 7. Mechanism of rearrangement of **4** to **11**.



Scheme 8. Synthesis of oxepin **14** with extended conjugation. Reagents and conditions: (a) 2.0 equiv β-bromophenylacetylene, CuBr, piperidine, $NH_2OH{\cdot}HCl$, MeOH, rt, 45 min, 32%; (b) same as in (a) but with phenylacetylene, (c) 2.0 equiv *n*-BuLi, 1.0 equiv CH_3SO_2Cl, THF, −78 °C to rt, 30%.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tetlet.2005.03.044. Supplementary material contains experimental procedures and characterization data of all the compounds described in this paper.

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6. General procedure for the synthesis of oxepins: *n*-BuLi (0.04 mol, 25 ml of a 1.6 M solution in hexane) was added at −78 °C to a stirred solution of the *trans*-isomer of the cyclohexa-2,5-diene-1,4-diol (0.02 mol) in THF (100 ml) under a N_2 atmosphere. The resulting solution was stirred for 30 min at the same temperature. Methanesulfonyl chloride (1.55 ml, 0.02 mol) was added and stirring was continued for another 3 h during which time the reaction mixture was allowed to warm to room temperature. It was then cooled to 0 °C and quenched by the addition of ice-cold water (200 ml). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×50 ml). The combined organic extract was washed with ice-cold water (100 ml) and ice-cold saturated brine solution (100 ml). After drying over $MgSO_4$ the solvent was removed and a dark red solid was obtained. The crude product was subjected to column chromatography on silica gel with hexane as the eluant to obtain pure oxepin as a dark red crystalline solid (65%). Oxepin **4**: mp 103–105 °C; IR (KBr) 2957, 2141, 1626, 1595, 1246, 1181 cm^{-1}; UV–vis (hexane) λ_{max} ($\log \varepsilon$) 206 (4.40), 238 (4.30), 284 (4.07), 348 (3.98) nm; ^1H NMR (400 MHz, acetone-d_6) δ 6.43 (1H, d, $J = 6.4$ Hz), 6.04 (1H, d, $J = 6.9$ Hz), 6.01 (1H, d, $J = 5.4$ Hz), 5.61 (1H, d, $J = 5.4$ Hz), 0.15 (9H, s), 0.13 (9H, s); ^1H NMR (400 MHz, $CDCl_3$) δ 6.45 (1H, d, $J = 6.3$ Hz), 5.78 (2H, d, $J = 5.9$ Hz), 5.41 (1H, d, $J = 5.3$ Hz), 0.02 (9H, s), 0.00 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4 (CH), 134.7 (CH), 134.4 (C), 125.8 (C), 121.3 (CH), 118.8 (CH), 105.1 (C), 100.3 (C), 97.4 (C), 94.8 (C), 0.00 (CH_3), −0.21 (CH_3); MS (EI, 70 eV) 286 (M^+, 100), 271 (55), 255 (10), 149 (22), 128 (10), 73 (18); HRMS calcd for $C_{16}H_{22}Si_2O$: 286.1209. Found 286.1197. Oxepin **9**: ^1H NMR (400 MHz, $CDCl_3$) δ 6.42 (1H, d, $J = 6.4$ Hz), 5.95 (1H, d, $J = 6.5$ Hz), 5.92 (1H, d, $J = 5.4$ Hz), 5.58 (1H, d, $J = 5.4$ Hz), 3.05 (1H, s), 2.93 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2 (CH), 134.8 (CH), 133.6 (C), 125.0 (C), 121.5 (CH), 118.6 (CH), 83.4 (C), 79.7 (CH), 79.4 (C), 76.5 (CH); MS (EI, 70 eV) 142 (M^+, 32), 114 (30), 92 (25), 63 (100). (Caution: the solid oxepin **4** appears to be shock sensitive. When the solid was scratched with a metal spatula, in an attempt to remove it from the flask, an exothermic decomposition with the formation of smoke was observed and a black residue was left in the flask. Upon storing the solid at room temperature the oxepin decomposed slowly to an insoluble material over a period of a few days.) Oxepin **10**: (red solid, 92%), IR (neat) 2227 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 6.51 (1H, d, $J = 6.3$ Hz), 6.15 (1H, d, $J = 6.3$ Hz), 6.08 (1H, d, $J = 4.8$ Hz), 5.72 (1H, d, $J = 4.8$ Hz), 5.41 (1H, s), 3.83–3.51 (4H, m), 2.95 (1H, s), 1.18 (6H, t, $J =$ Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 143.2 (CH), 135.4 (CH), 133.8 (C), 125.7 (C), 122.1 (CH), 119.3 (CH), 91.3 (CH), 84.5 (C), 83.9 (C), 81.5 (CH), 80.8 (C), 61.4 (CH_2), 14.4 (CH_3); Oxepin **7**: (red oily liquid, 0.12 g, 13%) IR (neat) 2975, 2931, 2898, 2144 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 6.49 (1H, d, $J = 6.4$ Hz), 6.09 (1H, d, $J = 6.4$ Hz), 6.05 (1H, d, $J = 5.4$ Hz), 5.68 (1H, d, $J = 5.4$ Hz), 5.38 (1H, s), 3.52–3.65 (4H, quartet of AB pattern, $J = 6.83$, 7.33 Hz), 1.16 (6H, t, $J = 6.84$ Hz), 0.10 (9H, s); ^{13}C NMR (100 MHz, acetone-d_6) δ 143.3 (CH), 135.3 (CH), 134.8 (C), 125.1 (C), 121.8 (CH), 119.0 (CH), 100.8 (C), 94.7 (C), 92.1 (CH), 88.1 (C), 84.9 (C), 61.1 (CH_2), 15.1 (CH_3), −0.3 (CH_3); HRMS (ESI, MeOH) calcd for $C_{18}H_{24}O_3SiNa$: 339.1392. Found 339.1422. Oxepin **8**: (red oily liquid, 0.28 g, 30%), IR (neat) 2926, 2936, 2253 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 6.48 (1H, d, $J = 6.4$ Hz), 6.11 (1H, d, $J = 6.4$ Hz), 6.06 (1H, d, $J = 5.4$ Hz), 5.67 (1H, d, $J = 5.4$ Hz), 5.40 (1H, s), 3.56–3.65 (4H, quartet of AB pattern, $J = 9.7$, 6.8 Hz), 1.16 (6H, t, $J = 6.8$ Hz), 0.17 (9H, s); ^{13}C NMR (100 MHz, acetone-d_6) δ 143.2 (CH), 135.1 (CH), 133.9 (C), 126.4 (C), 122.2 (CH), 119.2 (CH), 105.5 (C), 97.4 (C), 91.9 (CH), 84.6 (C), 80.9 (C), 61.4 (CH_2), 15.2 (CH_3), −0.3 (CH_3); HRMS (ESI, MeOH) calcd for $C_{18}H_{24}O_3SiNa$: 339.1392. Found 339.1388. **11**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (1H, d, $J =$ 7.8 Hz), 7.02 (1H, s), 6.94 (1H, d, $J = 7.8$ Hz), 5.82 (1H, br, OH), 0.26 (9H, s), 0.23 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2 (C), 131.3 (CH), 125.1(C), 124.0 (CH), 117.8 (CH), 109.9 (C), 104.2 (C), 98.5 (C), 96.3 (C), −0.11 (CH_3); MS (EI, 70 eV) 286 (M^+, 20), 285 (80), 271 (35), 270 (100), 128 (20), 73 (30).

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