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Design and synthesis of bisenediyne bissulfones and their reactivity under basic condition

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ABSTRACT

A new class of bisenediyne bis sulfones has been synthesized. These molecules underwent cycloaromatization under basic conditions via isomerization to allene and were able to cleave ds-stranded plasmid DNA.

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Apart from Myers–Saito cyclization[1], (*Z*)-allene-ene-yne systems can undergo Schmittel cyclization[2] (as shown in Scheme 1) under certain structural perturbations, especially when the hydrogen at the alkyne termini is replaced by an aryl group or by a bulky substituent. Recently, enediyne sulfones have also emerged as a new class of DNA-cleaving agents.[3] Under alkaline conditions, these can be isomerized to eneyne–allene–sulfone, which spontaneously cyclized to form biradical intermediates following the MSC pathway. Recently, Wu and Lin have exploited the double cycloaromatization of the (*Z*,*Z*)-11-sulfonylundecan-3,7-diene-1,5,9-triyne system through an eneyne–allene–sulfone forming an α,6-didehydro-α-methylnaphthalene.[4]

Much of the current research has paid attention to the design, synthesis and reactivity of molecules that generate new types of dehydroaromatic biradical intermediates at different locations of the molecule.[5] Several workers have reported cyclization behaviour of bis-aryl-triynes and related systems.[6] Based on the pioneering work of Wang[7] on cascade Schmittel cyclization, we have designed and subsequently synthesized novel bis enediyne bis sulfones **1** and **2** (Scheme 2). Their chemical and biological reactivity under basic conditions are also studied.

The synthesis of the representative compound **1** is outlined in Scheme 3. Palladium catalyzed coupling of 1,2-diiodobenzene with protected propargyl alcohol afforded **3** in 70% yield. Another round of Sonogashira coupling[8] of eneyne **3** with TMS–acetylene afforded the enediyne **4** in 85% yield. After removal of silyl group, compound **5** was further coupled with iodo alkyne **3** under Sonogashira conditions to provide the bis THP ether in 55% yield. Treatment of **6** with catalytic amount of PPTS in EtOH produced the bisalcohol **7** which was then converted to the bis sulfide **9** following a reported procedure.[9] Finally, *m*-CPBA oxidation of **9** provided the bis sulfone **1** in 75% yield (Scheme 3).

The synthesis of compound **2** was similar to what was followed for compound **1**. Only difference was a Glaser type of coupling[10] which was performed instead of 3rd Sonogashira coupling. For that, the enediyne **5** was treated with CuI (5 mol %) and *N*,*N*,*N*′,*N*′-tetramethyl ethylenediamine (5 mol %) in acetone under oxygen atmosphere to afford compound **10** in 77% yield. The synthetic scheme for compound **2** is presented below (Scheme 4). All the compounds were characterized by NMR and mass spectroscopic data. In addition, the structure of compound **1** was further confirmed by single crystal X-ray analysis[11] (Fig. 1).

The chemical reactivity of the sulfones **1** and **2** were then evaluated. Under neutral conditions, the compounds are stable with no isomerization occurring. However, treatment of **1** with triethylamine (2 equiv) in diluted degassed benzene solution containing 1,4-cyclohexadiene (20 equiv) at room temperature resulted in slow disappearance of **1** with conmittant production of a mixture of unidentified products after 24 h at room temperature. However, by carefully controlling the reaction for over 4 h at 15 °C, we were able to isolate the monoallene bissulfone **14** (Scheme 5).

The isolation of monoallene **14** strongly suggested that the isomerization to the bisallene is either very slow or may not be

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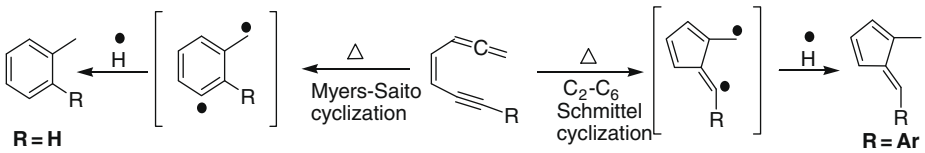
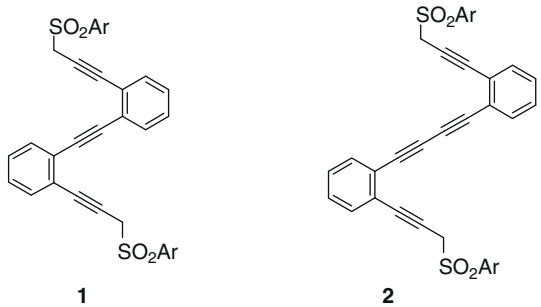
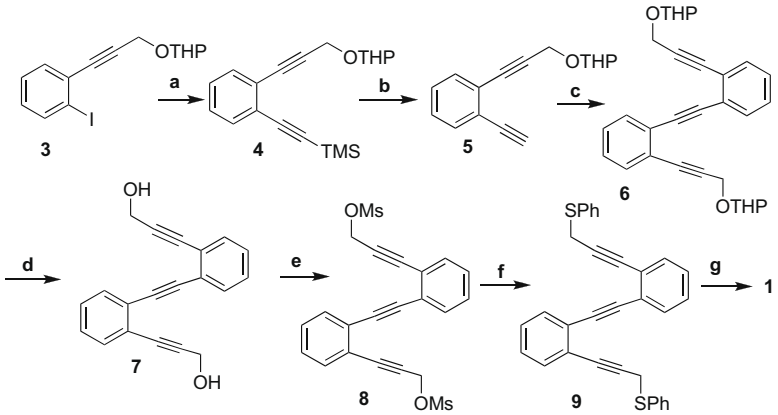


Scheme 1. Cyclization mode of eneyne allene.

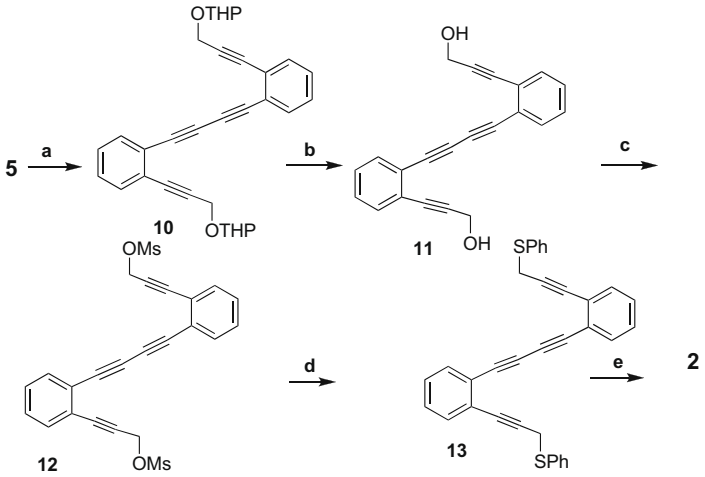


Scheme 2. The target bispropargyl bissulfones.

occurring. If the stirring at 15 °C was continued for 36 h, the monoallene also disappeared and a mixture of two inseparable products was isolated (combined yield ~33%, ratio 2:1). These could not be separated even by HPLC. However, considering all the spectroscopic data, like appearance of four acetylenic carbon signals, four 2H singlets (for both the isomers) and the tendency of 7-phenyl substituted eneyne allenes to undergo Schmittel type cyclization, isomeric structures **17** and **18** were assigned for the two products (Scheme 6). The benzylidine hydrogens in the two isomers appeared as broad singlets at δ 6.59 and 7.17, similar to what has been reported by Wu et al.[5c] in benzfulvene systems. Moreover, the ^{1}H-COSY spectrum also showed the connectivity (allylic coupling) between the benzylidine hydrogen and the methylene hydrogens attached to the sulfonyl moiety. Mass spectrum showed



Scheme 3. Synthesis of sulfone **1**. Reagents and conditions: (a) TMS–acetylene, CuI, $Pd(PPh_3)_4$, Et_3N, 85%; (b) KF/MeOH, 88%; (c) **3**, $Pd(PPh_3)_4$, CuI, Et_3N, 55%; (d) PPTS/EtOH, 75%; (e) MsCl/Et_3N, DCM, 0 °C, 90%; (f) PhSH/Et_3N/DCM, 78%; (g) *m*-CPBA/DCM, rt, 75%.



Scheme 4. Synthesis of sulfone **2**. Reagents and conditions: (a) CuI/O_2, TMED, acetone, 77%; (b) PPTS, EtOH, 70%; (c) MsCl, Et_3N, DCM, 0 °C, 88%; (d) PhSH/ET_3N, DCM, 82%; (e) *m*-CPBA, DCM, rt, 77%.

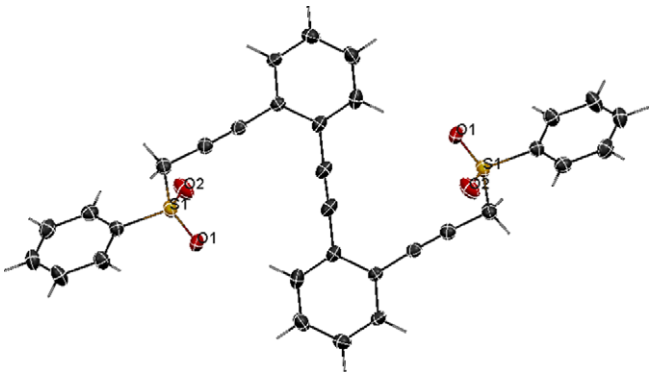
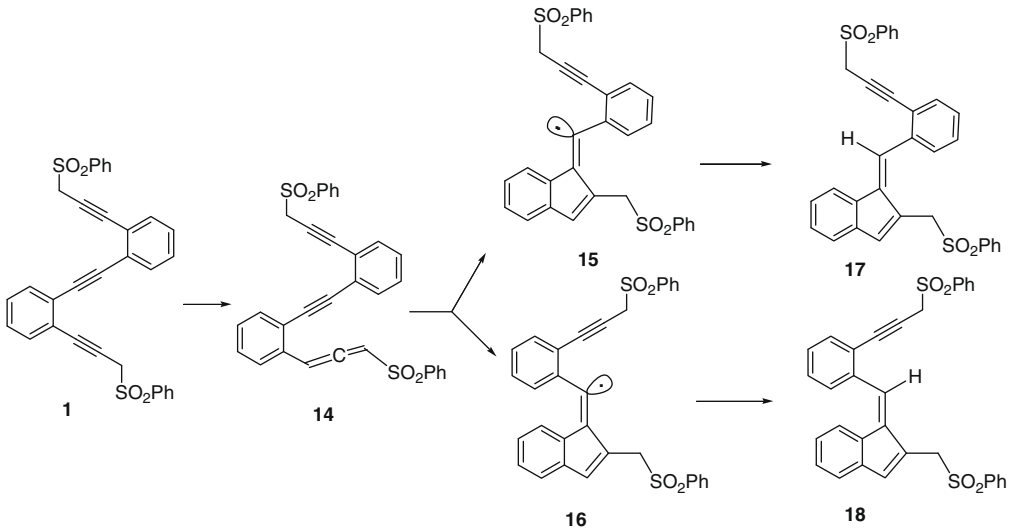


Figure 1. X-ray structure of sulfone **1**.

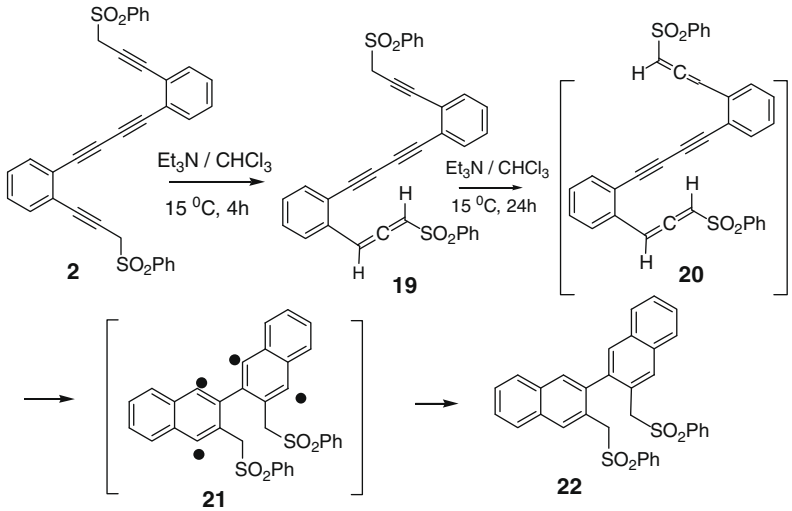
the molecular ion peak at *m*/*z* 537 commensurate with the molecular formula (MH^+). Both the products were produced by Schmittel cyclization of the monoallene. The failure of the intermediate radical to undergo 5-endo-dig cyclization[12] might be due to its rapid quenching of the radical or perhaps due to geometric constrains.[13]

The other sulfone **2**, upon treatment with triethylamine (2 equiv) in presence of 1,4-cyclohexadiene (20 equiv) in benzene at 15 °C temperature for 4 h yielded only a distinct product identified as the monoallene **19**. Thus like the previous one, here also we isolated the monoallene **19** under controlled reaction condition. This monoallene was found to be more reactive than the previous one **14**. Spectral characterization for this mono allene was done in similar fashion as that for **1**. Again, if the stirring was continued for 24 h at 15 °C in $CHCl_3$, a mixture of two inseparable compounds were isolated. One of the structures was identified as a bisnaphthyl derivative **22** produced by double Myers–Saito cyclization of the bisallene **21**. The structure was mainly based on the absence of any vinyl hydrogen in the ^1H NMR, absence of any acetylenic carbon in the ^{13}C NMR and appearance of peak at *m*/*z* 563.2 from mass spectral data.

Since both the sulfones **1** and **2** can isomerize initially to monoallenes in presence of base, it is expected to show DNA cleavage activity via both alkylation as well as oxidative diradical pathway. Based on this, the cleavage experiments were carried out with both



Scheme 5. Reactivity of sulfone **1** in Et_3N.



Scheme 6. Reactivity of sulfone **2** in Et_3N.

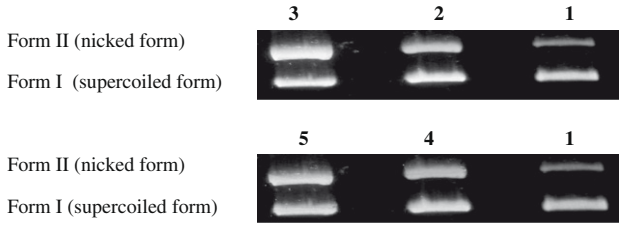


Figure 2. DNA cleavage experiment of compound **1** and **2** after 8 h and 16 h incubation at 37 °C.

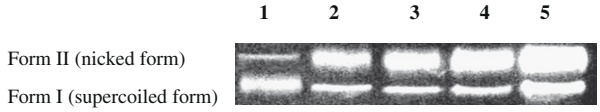


Figure 3. DNA cleavage experiment of compound **14** and **19** after 8 h and 16 h in incubation at 37 °C.

the sulfones at 37 °C using pBR 322 supercoiled plasmid DNA at pH 7.2 in presence of Et_3N (Figs. 2 and 3). The results showed higher cleavage efficiency for sulfone **2** as compared to the other. For the sulfone **2**, the percent cleavage efficiency increased with gradual increase in time of incubation (62% at 16 h and 47% at 8 h). This is because of the increase of concentration of monoallene or diradical intermediates with time. For the sulfone **1**, the efficiency was 45% at 8 h which remained same after 16 h of incubation. Same results were also observed when the monoallene **14** and **19** were incubated with double stranded plasmid DNA (pBR 322) at 37 °C at pH 7.2 without using any base.

Acknowledgments

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13. It may be mentioned here that Alabugin et al. have shown that 6-endo-dig processes involving vinyl radicals in conjugated systems are thermodynamically more favourable as compared to the corresponding 5-exo processes; Alabugin, I. V.; Manoharan, M. *J. Am. Chem. Soc.* **2005**, *127*, 12583. In our case, such substantial aromatic stabilization is lacking (fulvene from 5-endo vs benzene from 6-endo). Wu et al.[5c] have also reported the failure of an aryl radical to undergo 6-endo-dig cyclization involving a cyanide functionality as the dig component.
Selected spectral data: All the ^1H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz respectively in $CDCl_3$.*For* **1** δ_H 4.27 (4H, s), 7.26–7.37 (6H, m), 7.43–7.55 (8H, m), 8.02 (4H, d, *J* = 7.6 Hz); δ_C: 49.5, 80.6, 86.1, 91.6, 123.9, 125.7, 128.2, 128.8, 128.9, 128.9, 128.9, 132.3, 132.5, 134.1, 137.6; Mass (ESI): *m/z* 535 (MH^+).
For **2** δ_H: 4.29 (4H, s), 7.30–7.38 (6H, m), 7.50–7.65 (8H, m), 8.06 (4H, d, *J* = 7.2 Hz); δ_C: 49.6, 77.7, 81.0, 81.4, 85.6, 124.3, 125.1, 128.8, 128.9, 129.0, 129.2, 129.4, 129.4, 132.7, 133.3, 134.3, 137.7, Mass (ESI): *m/z* 559.4 (MH^+).
For **14**: δ_H: 4.22 (2H, s), 6.68 (1H, d, *J* = 6.4 Hz), 7.27–7.36 (3H, m), 7.39–7.57 (10H, m), 7.61–7.63 (1H, d, *J* = 7.6 Hz) 7.96–7.99 (5H, m); δ_C: 49.4, 81.1, 86.3, 90.6, 93.2, 101.4, 104.9, 122.1, 124.0, 125.4, 127.3, 127.6, 128.4, 128.8, 128.8, 128.8, 128.9, 129.0, 129.3, 131.5, 131.9, 132.3, 132.6, 132.7, 133.7, 134.0, 137.6, 208.4; Mass (ESI): *m/z* 535 (MH^+).For **19**: δ_H: 4.22 (2H, s), 6.68 (1H, d, *J* = 6.4 Hz), 7.27–7.65 (14H, m), 7.96–7.99 (5H, m); Mass (ESI): *m/z* 559 (MH^+).
Mixture of compound **17** and **18** δ_H: 3.25 (2H, s, major), 3.29 (2H, s, minor), 3.74 (2H, s, major), 3.82 (2H, s, minor), 6.59 (1H, s, minor), 7.17 (1H, s, major), 7.19–7.39 (26H, m, major + minor), 7.57 (2H, m, minor), 7.84 (2H, d, *J* = 8.2 Hz, major), 8.04 (2H, dd, *J* = 8.8, 2.0 Hz, minor), 8.11 (2H, dd, *J* = 8.8, 2.0 Hz, major), 8.25 (2H, d, *J* = 4.8 Hz, minor), 8.27 (2H, d, *J* = 4.8 Hz, major); δ_C: 49.3, 49.5, 54.2, 54.3, 81.8, 81.9, 85.3, 85.7, 127.6, 127.7, 128.2,, 128.2, 128.5, 128.6, 128.7, 128.8, 128.9, 128.9, 129.0, 129.1, 129.2, 129.3, 129.6, 129.8, 129.9, 132.4, 132.7, 132.7, 132.9, 133.0, 133.4, 133.5, 133.7, 133.9, 134.0, 134.1, 134.3, 145.6, 146.4; Mass (ESI): *m/z* 537 (MH^+); HRMS: calcd for $C_{32}H_{24}O_4S_2 + H^+$ 537.1194 found 537.1197.
For **22** δ_H: 4.66 (4H, br s), 7.39–7.47 (6H, m), 7.53–7.60 (8H, m), 7.67–7.72 (4H, m), 8.09 (4H, d, *J* = 8.0 Hz); Mass (ESI): *m/z* 563.2 (MH^+); HRMS: calcd for $C_{34}H_{26}O_4S_2 + H^+$ 563.1350 found 563.1354.