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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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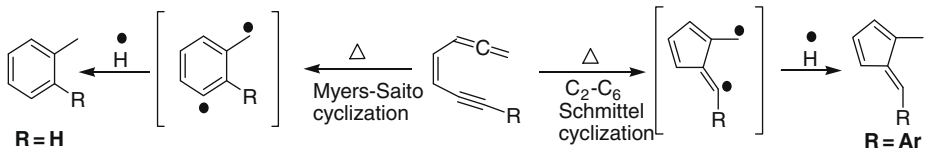
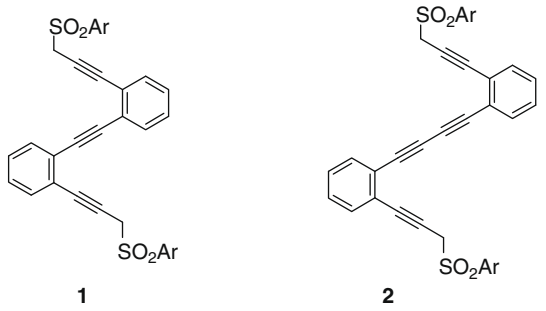
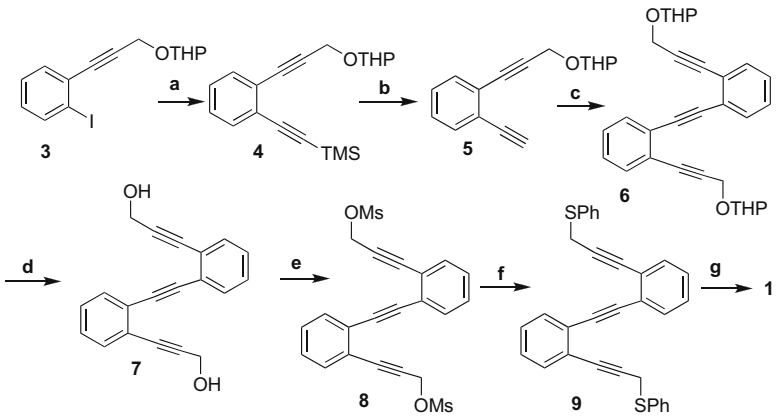


Scheme 1. Cyclization mode of eneyne allene.

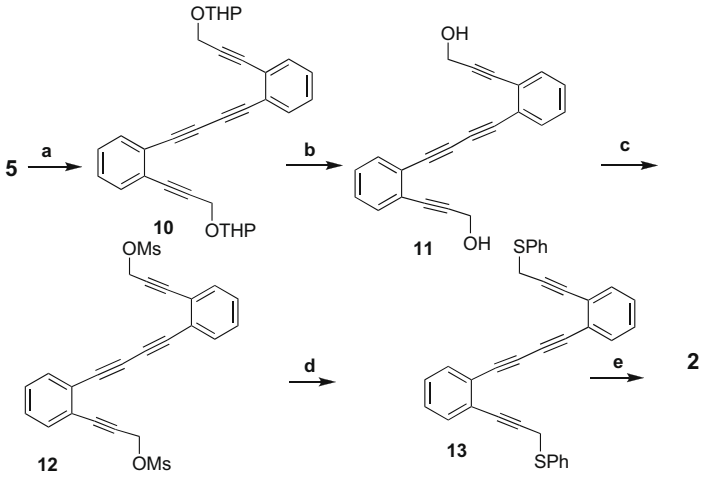


Scheme 2. The target bispropargyl bissulfones.

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$_3$N, 85%; (b) KF/MeOH, 88%; (c) **3**, Pd(PPh$_3$)$_4$, CuI, Et$_3$N, 55%; (d) PPTS/EtOH, 75%; (e) MsCl/Et$_3$N, DCM, 0 °C, 90%; (f) PhSH/Et$_3$N/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$_3$N, DCM, 0 °C, 88%; (d) PhSH/ET$_3$N, DCM, 82%; (e) *m*-CPBA, DCM, rt, 77%.

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