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Synthesis and reactivity of azobenzene-based bispropargyl sulfones: Interesting comparison between cyclic and acyclic systems

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Abstract—Azobenzene-based bispropargyl bissulfone **3** containing stable *E*-azo moiety has been synthesized. Upon irradiation with long wavelength UV it isomerized to the *Z*-form **4**, which can be thermally reisomerized to the *E*-isomer. Reactivity towards isomerization to the allenic system as well as DNA-cleaving efficiency under basic conditions was found to be significantly lower as compared to the previously synthesized cyclic sulfones **1** and **2**. This lowering of reactivity can be explained in terms of low conversion to the allenic form and hence the lower extent of alkylation of DNA-bases, the only possible DNA-cleavage pathway for **3** and **4**.

An important aspect of development of anticancer drugs that target DNA and bring about its destruction is to enhance the efficiency of cleavage of the genetic material.[1] There can be various mechanisms by which DNA can be cleaved; amongst these the radical mediated H-abstraction from the sugar moiety followed by oxidative cleavage[2] as well as alkylation of DNA bases[3] cover a wide range of molecules. Recently,[4] we have developed a novel photochemical way to enhance the DNA-cleaving efficiency of bispropargyl cyclic sulfones. The process involved photoconversion of the thermally stable *E*-form **1** into the *Z*-form **2**, which by virtue of higher chemical reactivity towards isomerization into bisallenic sulfone brings about greater extent of DNA-cleavage (Fig. 1). Interestingly, bisallenic sulfone[5] offers two pathways for DNA-cleavage namely, the Garratt–Braverman rearrangement[6] as well as alkylation (Michael pathway).[7]

In order to strengthen the above rationality, we undertook a project which involved the synthesis of azo benzene-based bispropargyl bissulfone **3**. We were curious to know its reactivity, both in terms of isomerization to the allene and subsequent DNA-cleavage. We expected lower DNA-cleavage efficiency as the cleavage can take place only via alkylation; cleavage via

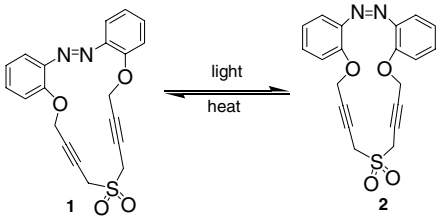

Figure 1. Cyclic sulfones **1** and **2**.

Garratt–Braverman rearrangement in this case is not possible. In this communication, we describe our results.

The synthesis of the target sulfone **3** was straight forward and was accomplished in four steps starting from 2,2′-dihydroxyazobenzene (**5**). Bis O-alkylation with butyn-1,4-diol mono tosylate (2 equiv) in the presence of K_2CO_3/DMF followed by treatment with mesyl chloride and triethylamine gave the bismesylate **7**. Displacement with thiophenol followed by oxidation with m-CPBA produced the target sulfone **3** (Scheme 1). No isomerization to the allene could be seen as judged from the ^{1}H NMR spectrum (Scheme 2).

The sulfone **3** was in the thermally more stable *E*-form as determined from the λ_{max} which was at 360 nm, characteristic of the *E*-configuration.[8] Photo irradiation from a high pressure Hg-lamp for 5 h produced a 3:1 mixture of *Z*- and *E*-isomers with the *Z*-isomer showing a new λ_{max} at 410 nm. In the ^{1}H NMR spectrum, new peaks at δ 6.6 (2,2′-aromatic Hs) and δ 4.6 (OCH_2)

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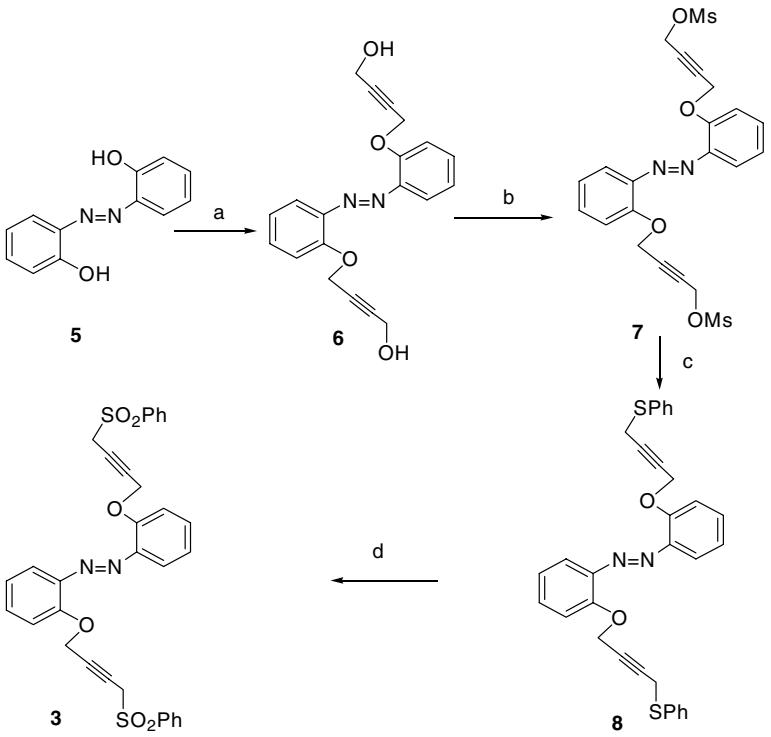
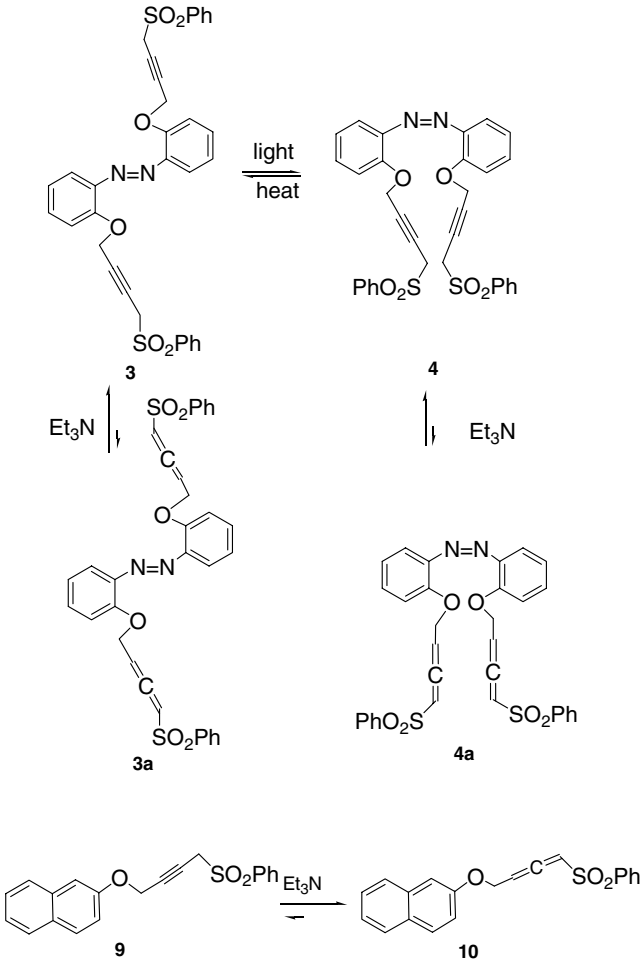


Scheme 1. Synthesis of bispropargyl bissulfone. Reagents and conditions: (a) 2-butyn-1,4-diol mono tosylate, K_2CO_3, DMF, rt, 12 h, 90%; (b) MsCl, Et_3N, CH_2Cl_2, 0 °C, 15 min, 95%; (c) PhSH, Et_3N, CH_2Cl_2, 0 °C, 30 min, 20%; (d) m-CPBA, CH_2Cl_2, 0 °C, 1.5 h, 90%.

appeared besides signals for aromatic hydrogens which were assigned to the *Z*-isomer (Fig. 2). The kinetics of thermal reisomerization was followed by monitoring the ^{1}H NMR at different time points at a temperature of 25 °C. Interestingly, the thermal reisomerization was significantly slower as compared to the cyclic sulfone **2** where strain as well as π–π repulsion[9] obviously play major roles in speeding up the reisomerization.

The kinetics of isomerization of the propargyl to allene system was then studied. As described before, the isomerization was followed by recording the ^{1}H NMR in presence of triethylamine (3 equiv) at 25 °C in $CDCl_3$. Within 10 min, the equilibrium was reached between the bispropargyl and the bisallenic bissulfone; however, the equilibrium favoured the bispropargyl system (6:1). Similar result was also obtained in case of isomerization for the *cis* sulfone **4**. The formation of allene moiety was indicated by the appearance of new peaks at the olefin region at δ 6.28 and δ 6.09. The ratio of propargyl to allene did not change even after keeping the solution for 12 h at 25 °C. This result is in sharp contrast to the isomerization of the monopropargyl sulfone **9**. In this case also, the equilibrium was reached within 15 min, however, the allene **10** was favoured under equilibrium condition (ratio of allene to propargyl was 2:1). The allene could be trapped with methanol[10] to provide the mono methoxy derivative. In case of isomerization of sulfone **3** or **4**, the formation of bisallene was confirmed by trapping with methanol to produce the dimethoxy derivative detected by mass spectrometry (631, MH^+ peak). Peak corresponding to the monoallene could not be observed. The ^{1}H NMR spectrum is also consistent with the bisallene. Similarity of environment for the two propargylic arms may be the reason for the failure to observe the monoallene which is fast converted into the bisallene. Regarding the inversion of allene–propargyl ratio for **3/3a** or **4/4a** pair as compared to the **9/10** pair, it is possible that the steric strain as imposed by the peri-hydrogen (Fig. 3) to the methylene is less in the propargyl form than that in the allene form for **3/3a** and **4/4a** pair. For **9/10** pair the greater conformational flexibility allows the formation of more stable allene form in excess. The aryl-O bond length is possibly more in the propargyl form because of higher electronegativity of sp-carbon which reduces the participation of oxygen lone pair for resonance with the aromatic π-cloud.

Thus, it can be concluded that although the better thermal stability of the *Z*-isomer **4** in comparison to the corresponding cyclic sulphone analogue **2** would allow us to study the DNA-cleavage by carrying out the incubation for a longer time, the low extent of allene formation should reduce the efficiency of DNA-cleavage. As a matter of fact, both the *E*-isomer **3** and the 3:1 mixture of *Z*- and *E*-isomers (**4** and **3**) are both poor DNA-cleaving agents[11] even at 100 μM concentrations (Fig. 4). The mixture however, showed ~20% better cleavage efficiency as compared to the pure *E*-isomer. This can probably be attributed to the greater cleavage efficiency of *Z*-isomer, possibly because of better binding with the DNA due to greater complimentarily[12] in shape between the two. The monopropargyl sulfone **9** also showed slightly higher cleavage activity (~15%) as compared to the sulfone **3**. The greater extent of allene formation is perhaps the reason for its better efficiency.



Scheme 2. Base mediated isomerization to allene.

However, both these acyclic sulfones were much inferior as compared to the cyclic sulfone **2**.

These results clearly indicated the importance of having a sulfone in a cyclic network in order to develop highly efficient DNA-cleaving agent. The inherent strain, the greater acidity of the Hs α- to the sulfone moiety and the possibility of occurrence of Garratt–Braverman rearrangement can be exploited in the cyclic system as compared to an acyclic counterpart where alkylation remains as the only possible pathway leading to DNA-cleavage. Moreover, the greater strain in the cyclic sulfone makes it more reactive towards alkylation via conversion of sp^2 carbons to sp^3 state. These parameters need to be considered while designing sulfone-based DNA-cleaving agents.

Selected spectral data. For **6**: δ_H (200 MHz, $CDCl_3$) 7.7–7.6 (2H, m), 7.5–7.4 (2H, m), 7.2–7.1 (4H, m), 4.96 (4H, t, $J = 2$ Hz,), 4.28 (4H, t, $J = 2$ Hz); δ_C (50 MHz, $CDCl_3$) 154.4, 142.7, 131.6, 121.2, 116.9), 114.9, 86.9, 78.4, 57.2, 49.3; Mass (ES^+) *m/z* 351 (MH^+).

For **7**: δ_H (200 MHz, $CDCl_3$) 7.64–7.60 (2H, m), 7.44–7.40 (2H, m), 7.19–7.06 (4H, m), 5.0 (4H, t, $J = 1.7$ Hz), 4.87 (4H, t, $J = 1.7$ Hz), 2.99 (6H, s); Mass (ES^+) *m/z* 507 (MH^+).

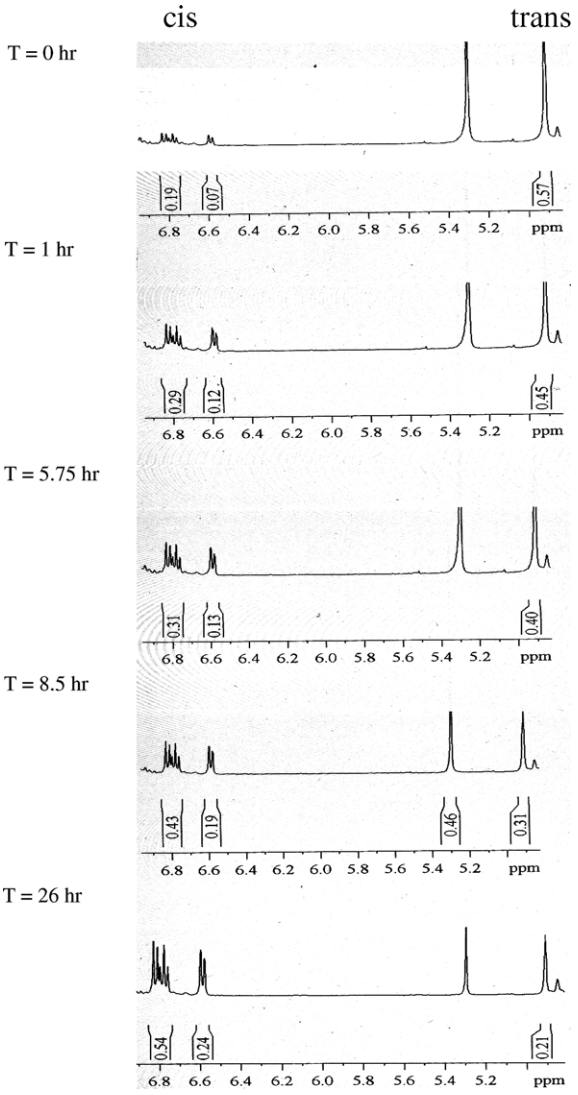


Figure 2. ^1H NMR spectra for thermal *Z*- to *E*-isomerization in $CDCl_3$.

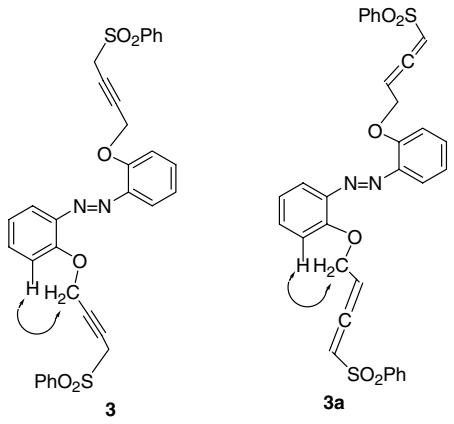


Figure 3. The steric interaction with the peri-hydrogens.

For **8**: δ_H (400 MHz, $CDCl_3$) 7.6 (2H, m), 7.26 (6H, m), 7.18 (6H, m), 7.04 (2H, d, $J = 4$ Hz), 6.96 (2H, $J = 7.6$ Hz), 4.83 ($2 \times CH_2$, s), 3.56 ($2 \times CH_2$, s); δ_C (100 MHz, $CDCl_3$) 155.0, 143.4, 132.0, 130.0, 128.9,

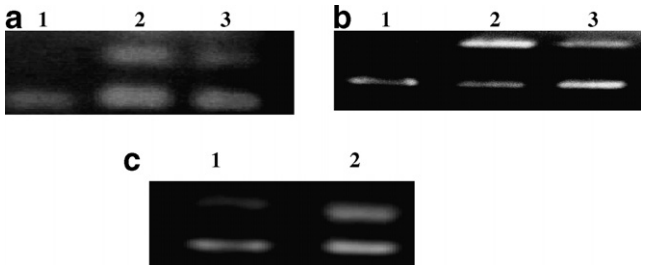


Figure 4. (a) pBR322 DNA-cleavage experiment of compounds **3** and **4** after 2.5-h incubation at 37 °C; lane 1: control DNA in TAE buffer (pH 8.5, 7 μL) + CH_3CN (5 μL); lane 2: DNA in TAE buffer (pH 8.5, 7 μL) + *Z*-sulfone **4** (0.16 mM) in CH_3CN (5 μL); lane 3: DNA in TAE buffer (pH 8.5, 7 μL) + *E*-sulfone **3** (0.16 mM) in CH_3CN (5 μL); (b) DNA-cleavage experiment of compounds **2** and **1** after 1.5-h incubation at 37 °C; lane 1: control DNA in TAE buffer (pH 8.5, 7 μL) + CH_3CN (5 μL); lane 2: DNA in TAE buffer (pH 8.5, 7 μL) + *Z*-sulfone **2** (0.02 mM) in CH_3CN (5 μL); lane 3: DNA in TAE buffer (pH 8.5, 7 μL) + *E*-sulfone **1** (0.02 mM) in CH_3CN (5 μL); (c) DNA-cleavage experiment of compound **9** after 2.5-h incubation at 37 °C lane 1: control DNA in TAE buffer (pH 8.5, 7 μL) + CH_3CN (5 μL); lane 2: DNA in TAE buffer (pH 8.5, 7 μL) + sulfone **9** (0.16 mM) in CH_3CN (5 μL).

126.8, 121.8, 117.6, 115.4, 83.9, 78.1, 57.8, 22.8; Mass (ES^+) *m*/*z* 535 (MH^+).

For **3**: δ_H (400 MHz, $CDCl_3$) 7.85 (4H, d, $J = 7.6$ Hz), 7.59 (4H, m), 7.43 (6H, m), 7.08 (4H, m), 4.91 ($2 \times CH_2$, m), 3.99 ($2 \times CH_2$, m); δ_C (100 MHz, $CDCl_3$) 134.3, 134.2, 132.2, 129.2, 129.1, 128.6, 122.1 (CH), 117.6, 115.2, 82.6, 75.6, 57.4, 42.6; Mass (ES^+) *m*/*z* 599 (MH^+).

For **9**: δ_H (200 MHz, $CDCl_3$) 7.86–7.72 (5H, m), 7.50–7.26 (5H, m), 7.17–7.10 (2H, m), 4.79 (2H, t, $J = 2$ Hz), 4.01 (2H, t, $J = 2$ Hz). Mass (ES^+) *m*/*z* 337 (MH^+).

Acknowledgments

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11. The DNA used for the present study is pBR322 plasmid DNA in mainly the supercoiled form. The identity of the bands has been ascertained from the control DNA which has Form I as a major band. The cleavage efficiency was determined by checking the relative UV-absorbance of the bands at 260 nm. The cleavage efficiency was also measured by densitometry using image processing software (Kodak 1D version V.3.6.3) and similar results were obtained. It is to be noted that the control DNA specimen is usually contaminated with some nicked form (form II). The reason for having an alkaline pH of 8.5 was to aid the propargyl to allene isomerization.
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