Cycloaromatization and DNA Cleavage of Novel Enyne-allene Systems

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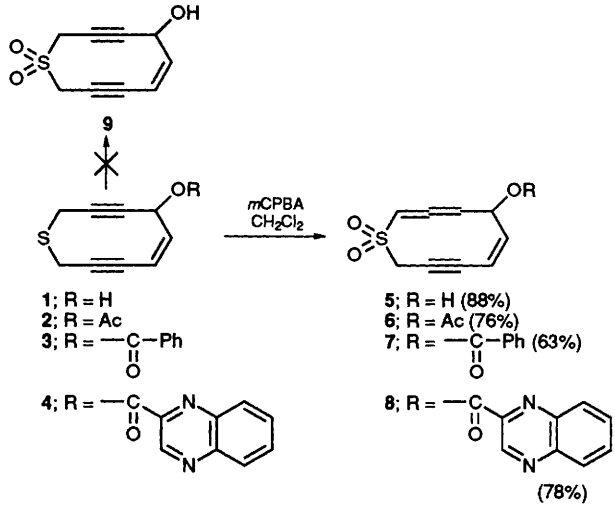
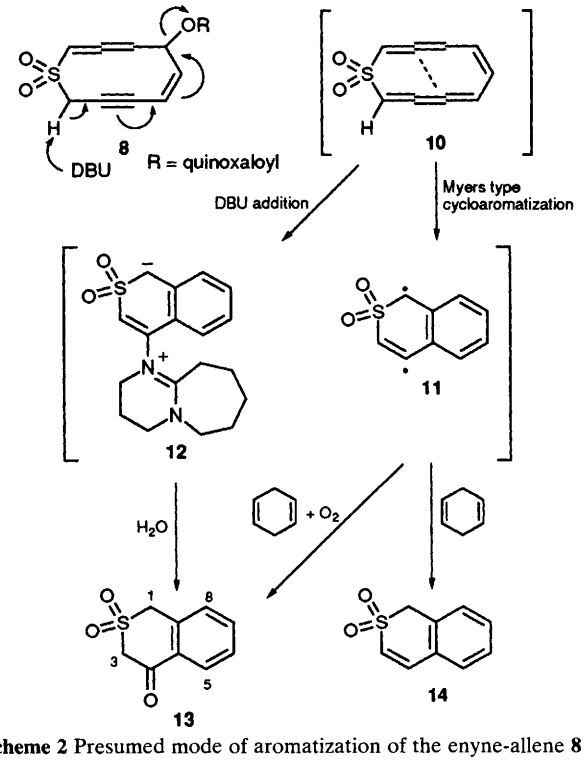
The novel enyne-allene sulfones **5–8** were prepared by *m*-chloroperbenzoic acid oxidation of the corresponding enediyne sulfides **1–4**; the enyne-allene sulfones **6–8** having a leaving group at the allylic position were aromatized by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) *via* the allene-ene-cumulene intermediate **10** and showed DNA-cleaving activities under basic conditions without any additive.

Over recent years DNA-cleaving molecules including enediyne antitumour antibiotics have been the subject of considerable interest in bioorganic chemistry, molecular biology and pharmacology, as well as in organic synthesis.[1] We have recently reported that the simple and stable 10-membered heterocyclic enediyne sulfides **1–4** showed DNA-cleaving activities[2] reminiscent of the neocarzinostatin chromophore which is an active site of the anticancer antibiotic, neocarzinostatin.[3] In this communication, we report the mode of cycloaromatization and DNA-cleaving properties of the novel enyne-allene sulfones **5–8** which were readily prepared from **1–4**,[2] respectively.

During our studies of development of new DNA-cleaving molecules related to the neocarzinostatin chromophore,[4] we expected that the new enediyne sulfone **9** would be obtained by *m*-chloroperbenzoic acid (*m*CPBA) oxidation of the corresponding enediyne sulfide **1**. However, **1** was oxidized by 2.5 equiv. of *m*CPBA in CH_2Cl_2 at 25 °C for 2 h to give only the unexpected enyne-allene sulfone **5**† in 88% yield.[5] Several acylated derivatives **6–8**† were also prepared from the corresponding enediyne sulfides **2–4** by the same method‡ (Scheme 1). Notably, these enyne-allene sulfones are stable when handled at ambient temperature even though they are highly strained. Our attention next turned to the mode of cycloaromatization of these novel compounds. Treatment of the representative enyne-allene sulfone **8** possessing a quinoxaloyl group as a leaving group at the allylic position with 1.2 equiv. of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in cyclohexa-1,4-diene–benzene (1:10) at 25 °C for 1 h under aerobic conditions afforded two cycloaromatization products **13**[6]† and **14**[6]† in 9.3 and 8.0% yields, respectively. The reaction under anaerobic conditions also gave **13** and **14** in 9.8 and 7.6% yields, respectively. These results strongly suggested the following mechanism for this cycloaromatization reaction as shown in Scheme 2. Deprotonation of the propynylic position of **8** with DBU along with elimination of the ester group first generated the allene-ene-cumulene intermediate **10**. The intermediate **10** immediately underwent Myers type cyclization[7] to afford the benzenoid diradical **11** and nucleophilic addition[4a,8] of DBU to give the ionic product **12**. The keto-product **13** was produced both by trapping of **11** with O_2 and H radical from cyclohexa-1,4-diene and by the hydrolysis of **12**. The 3,4-unsaturated compound **14** was produced by trapping of the diradical **11** with H radicals from cyclohexa-1,4-diene. The present novel cycloaromatization reaction involves diradical formation in analogy with the case of the neocarzinostatin chromophore.[7] On the other hand, treatment of the enyne-allene sulfone **5** possessing a hydroxy group at the allylic position with DBU under same conditions afforded neither **13** nor **14** owing to the lack of a leaving group, and gave a complicated reaction mixture.



Scheme 1 Synthesis of novel enyne-allene compounds **5–8**



Scheme 2 Presumed mode of aromatization of the enyne-allene **8**

† All compounds were purified by silica-gel column chromatography and were fully characterized by spectroscopic means. ^{1}H NMR (270 MHz, $CDCl_3$) (δ, $SiMe_4$; *J* Hz), **8**: δ 4.13 (1H, dd, *J* 16.4 and 1.8, $-SO_2CH_2CC-$), 4.23 (1H, dd, *J* 16.4 and 3.6, $-SO_2CH_2CC-$), 5.85 (1H, dd, *J* 9.6 and 6.0, $-SO_2CHCCH-$), 6.00 (1H, dddd, *J* 11.0, 3.6, 2.0 and 1.8, $-CCCH=CH-$), 6.20 [1H, ddd, *J* 9.6, 5.8 and 2.0, $-CH$(O-quinoxaloyl-], 6.40 (1H, d, *J* 6.0, $-SO_2CHCCH-$), 6.58 (1H, dd, *J* 11.0 and 5.8, $-CCCH=CH-$), 7.85–8.35 (4H, Ar), and 9.55 (1H, s, Ar); **13**: δ 4.25 (2H, s, 1-H), 4.55 (2H, s, 3-H), 7.37 (1H, br d, *J* 8.0, 8-H), 7.56 (1H, br dd, *J* 8.0 and 8.0, 6-H), 7.68 (1H, ddd, *J* 8.0, 8.0 and 1.6, 7-H) and 8.23 (1H, dd, *J* 8.0 and 1.6, 5-H); **14**: δ 4.41 (2H, s, 1-H), 6.63 (1H, d, *J* 10.4, 3-H or 4-H), 7.16 (1H, d *J* 10.4, 3-H or 4-H) and 7.25–7.45 (4H, m, Ar). IR($CHCl_3$), **8**: ν_{max}/cm^{-1} 3031, 3003, 2361, 2340, 1952, 1730, 1337, 1150, 1124 and 1101.

‡ In the case of **2** and **3**, the corresponding enediyne sulfones were also produced by *m*CPBA oxidation in 9 and 15% yields, respectively.

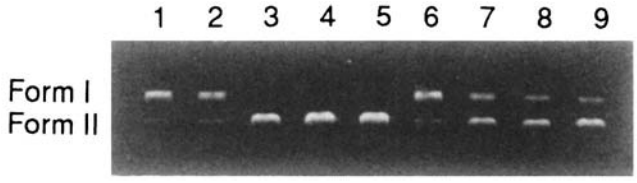


Fig. 1 ΦX174 form I DNA (50 μmol dm^{-3} per base pair) was incubated for 24 h at 37 °C with various compounds in 20% dimethyl sulfoxide in tris-acetate buffer (pH 8.5, 50 mmol dm^{-3}) and analysed by electrophoresis (1% agarose gel, ethidium bromide stain). Lane 1, DNA alone; lanes 2–5 correspond to compounds **5–8** (100 μmol dm^{-3}), respectively; lanes 6–9 correspond to compounds **5–8** (10 μmol dm^{-3}), respectively.

DNA-cleaving activities of the enyne-allene sulfones **5–8** were assayed with supercoiled ΦX174 DNA in pH 8.5 buffer.§ As expected, **6–8** (>10 μmol dm^{-3}) possessing a good leaving group at a suitable position cleaved DNA and caused a single strand break, leading to the nicked open circular DNA (form II) as shown in Fig. 1. Furthermore, it was found that the DNA-cleaving activities were significantly independent of the ester group and 10–100 times higher than those of the corresponding enediyne sulfide derivatives.[2]

In summary, our present work provides a new and promising entry to formation of a benzenoid diradical which is an active species for DNA damage. Details of the DNA cleavage mechanism and the base selectivities of the novel enyne-allene sulfones are now under investigation.

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§ DNA-cleavage experiments were repated more than twice and a similar trend for DNA-cleaving pattern was observed.

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