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Biradical Formation from Molecules with (Z)-7-Sulfonyl-3-hexen-1,5-diyne Functionalities

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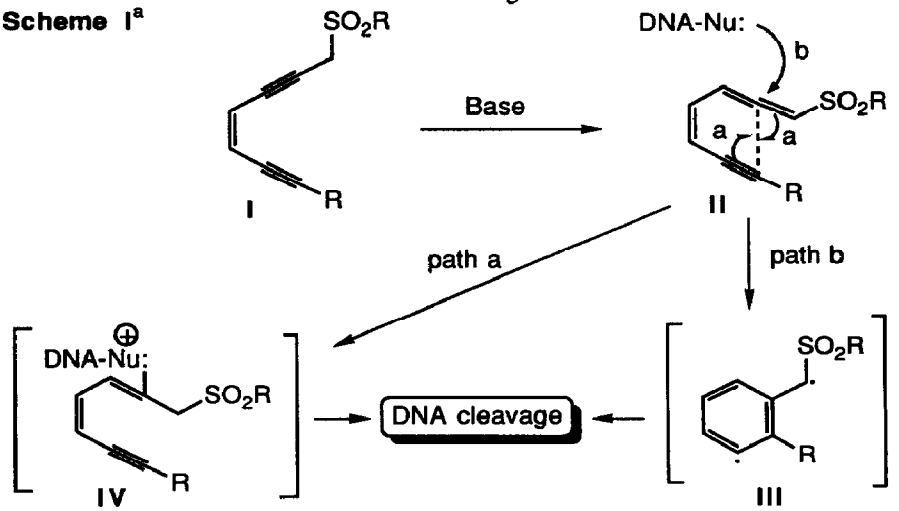
Abstract: Molecule that contains (Z)-7-sulfonyl-3-hexen-1,5-diyne functionalities undergoes base-catalyzed isomerization to (Z)-eneyne-allene-sulfone and subsequent Myers cyclization to form aromatic products, presumably via a biradical intermediate. In the presence of a nucleophile, (Z)-eneyne-allene-sulfone served as a good Michael acceptor.

Among the recent studies on the enediyne antitumor antibiotics[1] related to neocarzinostatin,[2] esperamicin,[3] calichemicin,[4] dynemicin,[5] and most recent kedarcidin,[6] molecules that contain the (Z)-allene-ene-yne functional group have been shown to undergo mild thermal reaction to form aromatic products[7] and exist DNA-cleaving properties.[8] Here, we demonstrate that a simple molecule that contains (Z)-7-sulfonyl-3-hexen-1,5-diyne substructure undergoes Myers cyclization reaction to form biradical under alkaline conditions.

The rationale design of this new class of compounds is based on the base-isomerization of propargyl sulfones to allenyl sulfones.[9] Thus, compound **I** would be converted to allene-ene-yne **II** under an alkaline condition. Structure **II** was then expected to undergo either Myers cyclization reaction to form biradical **III** or nucleophilic attack fron DNA to form **IV** and cause the cleavage of DNA as shown in scheme I.

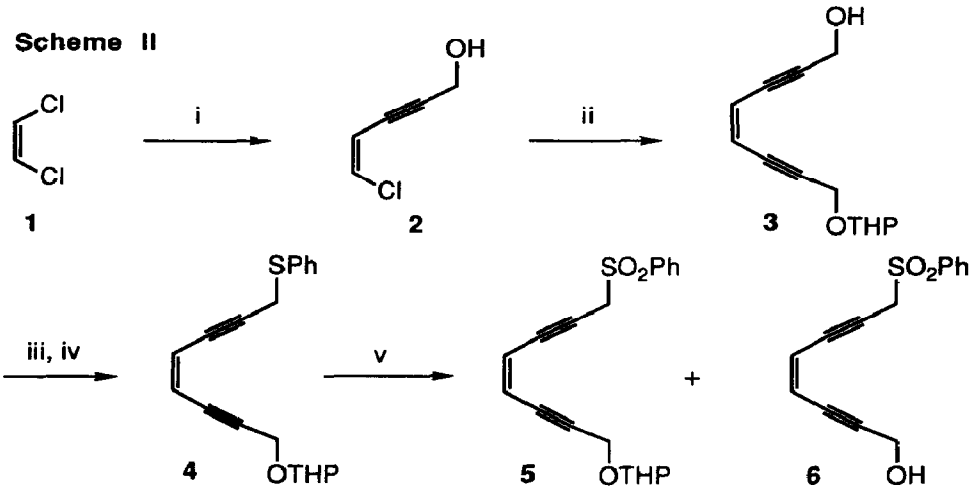
Scheme I[a]



[a]Mechanistic rationale for ene-diyne-sulfones.

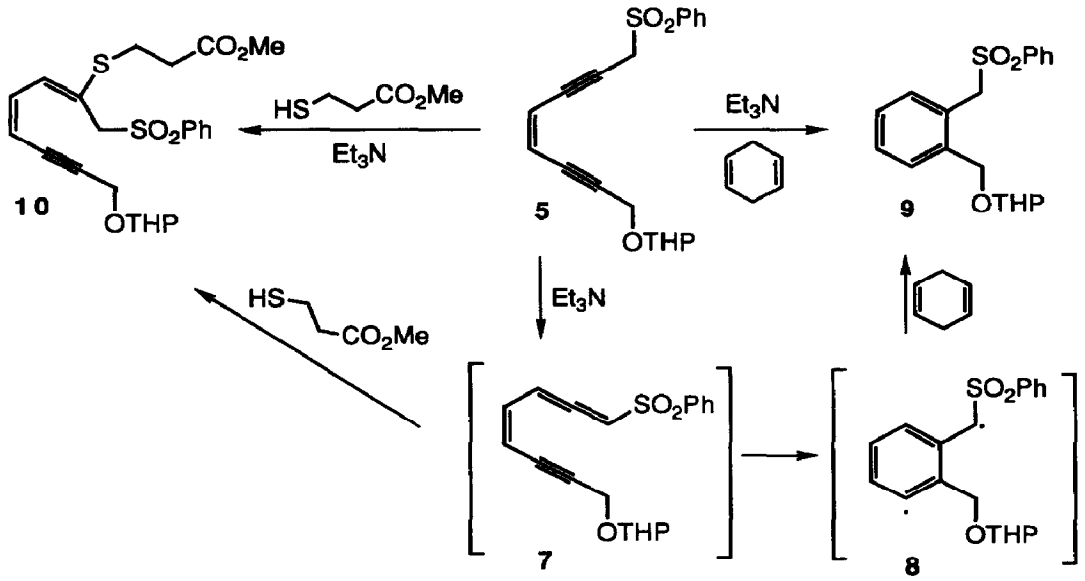
The synthesis of the representative compound **5** is outlined in scheme II. The synthesis of the key intermediate (Z)-enediyne **3** is readily achieved from commercial available (Z)-1,2-dichloroethylene **1** following the precedent of Myers.[7c] Thus, reaction of propargyl alcohol (1 equiv) with (Z)-1,2-dichloroethylene (5 equiv), bis(triphenylphosphine) palladium (II) chloride (0.05 equiv) and cuprous iodide (0.15 equiv) in ethyl ether containing n-butylamine (5 equiv) at 30 °C for 6 h afforded, after isolation with flash column chromatography, the (Z)-vinyl chloride **2** in 65 % yield.[7c] Subsequent coupling of **2** with protected propargyl alcohol (1.5 equiv) using tetrakis(triphenylphosphine)palladium (0) (0.05 equiv) as the catalyst under the same condition gave the (Z)-enediyne **3** in 50 % yield. Compound **3** was then converted into the corresponding mesylate by the standard method (MsCl, Et_3N in CH_2Cl_2). Subsequent reaction of the mesylate with thiophenol (1.0 equiv) under an alkaline condition (NaOH (1.0 equiv) in aqueous THF) afforded sulfide **4** in 44 % yield. Finally, oxidation of sulfide **4** with m-chloroperbenzoic acid (2.2 equiv) provided the sulfone **5** in 45 % yield along with 32 % of the deprotected product **6**.

Scheme II



reagents and conditions: i) $HCCCH_2OH$, $Pd(PPh)_2Cl_2$, Et_2O, CuI, $BuNH_2$, 65 %; ii) $HCCCH_2OTHP$, $Pd(PPh_3)_4$, Et_2O, CuI, $BuNH_2$, 50 %; iii) CH_3SO_2Cl, Et_3N, CH_2Cl_2; iv) HSPh, NaOH, THF-H_2O, 44 %; v) mCPBA, CH_2Cl_2, 45 % of **5** and 32 % of **6**.

In order to confirm whether the enediyne-sulfone **5** undergoes base-catalyzed conversion to eneyne-allene-sulfone **7** and subsequent cyclization to generate biradical **8**, the degased solution of **5** in benzene (0.01 M) in the presence of 1,4-cyclohexadiene (1.5 M) was treated with Et_3N (5 equiv) at 30 °C for 10 h. After extractive isolation and flash column chromatography, the aromatized compound **9** was isolated in 45 % yield as a colorless oil. These results strongly suggested that the eneyne-allene-sulfone **7** and biradical intermediate **8** are actually involved in the transformation of enediyne **5** to aromatized compound **9**. On the other hand, the reaction of enediyne-sulfone **5** with methyl 3-mercaptopropionate (1 equiv) in the presence of Et_3N (5 equiv) in benzene (0.01 M) afforded the nucleophilic addition adduct **10**[10] in 53 % yield. These results also suggested that eneyne-allene-sulfone **7** serves as an excellent Michael acceptor and possibly posseses DNA-cleaving properties.



In conclusion, molecules with (Z)-7-sulfonyl-3-hexen-1,5-diyne functionalities proceeded base-catalyzed conversion to (Z)-eneyne-allene-sulfones and subsequent Myers cyclization to form aromatized products or 1,2-addition reaction with nucleophiles. These results might provide an opportunity to development of a new class of DNA-cleaving antitumor agents.

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10. Some physical properties of **3**, **4**, **5**, **6**, **9**, and **10**. **3**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.87 (s, 2H), 5.07 (t, 1 H, J = 3.1 Hz), 4.47 (d, 2 H, J = 1.0 Hz), 4.43 (d, 2 H, J = 1.0 Hz), 3.78-3.90 (m, 1 H), 3.55-3.64 (m, 1 H), 1.53-1.84 (m, 6 H); **4**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.20-7.50 (m, 5 H), 5.82 (bs, 2 H), 4.88 (t, 1 H, J = 3.1 Hz), 4.42 (t, 2 H, J = 1.1 Hz), 3.80-3.89 (m, 3 H, including one set of doublet at 3.82 (d, 2 H, J = 1.4 Hz)), 3.51-3.59 (m, 2 H), 1.50-1.88 (m, 6 H); **5**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.96-8.08 (m, 2 H), 7.55-7.74 (m, 3 H), 5.91 (dt, 1 H, J = 11.0, 2.0 Hz), 5.76 (dt, 1 H, J = 11.0, 2.0 Hz), 4.84 (t, 1 H, J = 3.5 Hz), 4.41-4.47 (m, 2 H), 4.17 (d, 2 H, J = 2.0 Hz), 3.78-3.90 (m, 1 H), 3.48-3.59 (m, 1 H), 1.49-1.88 (m, 6 H); **6**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.03-8.09 (m, 2 H), 7.55-8.00 (m, 3 H), 5.96 (dt, 1 H, J = 11.0, 2.0 Hz), 5.76 (dt, 1 H, J = 11.0, 2.0 Hz), 4.46 (d, 2 H, J = 2.0 Hz), 4.17 (d, 2 H, J = 2.0 Hz), 2.16 (bs, 1 H); **9**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.95-7.96 (m, 9 H), 4.31-4.70 (m, 5 H), 3.79-3.88 (m, 1 H), 3.48-3.57 (m, 1 H), 1.46-1.82 (m, 6 H); **10**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.49-7.91 (m, 5 H), 6.65 (d, 1 H, J = 11.4 Hz), 6.38 (t, 1 H, J = 11.4 Hz), 5.40 (bd, 1 H, J = 11.4 Hz), 4.83 (bs, 1 H), 4.40-4.48 (m, 2 H), 4.10 (s, 2 H), 3.76-3.92 (m, 1 H), 3.69 (s, 3 H), 3.48-5.10 (m, 1 H), 3.00 (t, 2 H, J = 7.0 Hz), 2.58 (t, 2 H, J = 7.0 Hz), 1.39-1.90 (m, 6 H).

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