The Novel Selenium Mediated Aromatization of a 1,6-Diyn-3-ene System Related to Neocarzinostatin Chromophore

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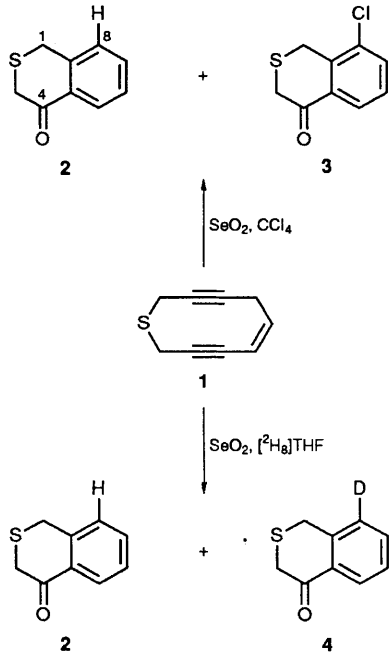
Treatment of 1,6-diyn-3-ene system **1** with SeO_2 caused a Myers type cyclization to produce a biradical **6** through an enyne–allene system **5** which was generated by an ene reaction of **1** with SeO_2, in analogy with the case of neocarzinostatin chromophore.

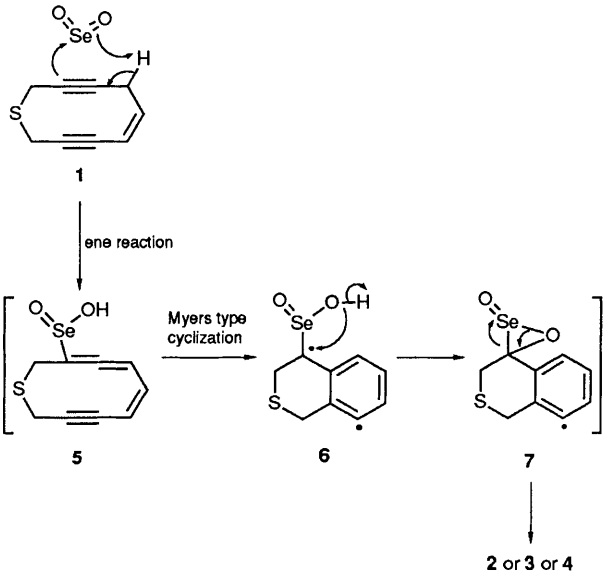
Simple stable molecules that generate benzenoid biradical species by Bergman–Masamune or Myers type cyclizations under specific conditions and then cleave DNA are of considerable current interest in relation to a new class of antitumour antibiotics such as neocarzinostatin, esperamicin, calicheamicin and dynemicin.[1] Also, investigation of new aromatization reactions of enediyne compounds is attractive synthetically. Recently, we demonstrated that two different types of aromatization of the new ten-membered ring, 1,6-diyn-3-ene compound **1**, occur under basic conditions.[1] In this communication we report that a novel selenium mediated cyclization of **1** forms a biradical and then gives substituted isothiochroman-4-one derivatives.

During our studies in connection with design and synthesis of neocarzinostatin chromophore analogues, we expected that the ketone function would be introduced onto the allylic position of **1** by SeO_2 oxidation.[2a–c] However, **1** was found to be aromatized by treatment with SeO_2 in dioxane–H_2O[2c] to give isothiochroman-4-one **2**† as the sole isolated product.



Scheme 1

† All new compounds were purified by silica gel column chromatography and were fully characterized by spectroscopic means including mass spectral analyses. ^{1}H NMR (270 MHz, $CDCl_3$) (δ, $SiMe_4$; *J* Hz), **2**, δ 3.56 (2H, d, *J* 0.7, H-3), 3.93 (2H, d, *J* 0.7, H-1), 7.20 (1H, dd, *J* 7.9 and 0.4, H-8), 7.37 (1H, dt, *J* 7.9 and 0.4, H-6), 7.46 (1H, dt, *J* 7.9 and 1.4, H-7) and 8.08 (1H, dd, *J* 7.9 and 1.4, H-5).



Scheme 2

This surprising phenomenon prompted us to examine the new reaction.

Treatment of **1** (0.1 mol dm^{-3}) with 1.5 equiv. of SeO_2 in carbon tetrachloride (26 °C, 42 h) under anaerobic conditions with Ar caused the aromatization of **1** to produce 8-chloroisothiochroman-4-one **3**[1] and **2** in 8 and 7% yields as shown in Scheme 1. The reaction under aerobic conditions afforded **3** (20% yield) and **2** (11% yield). However, treatment of **1** (0.2 mol dm^{-3}) with 3.4 equiv. of SeO_2 in [$^2H_8$]THF (THF = tetrahydrofuran) (26 °C, 4 h) under anaerobic conditions afforded 8-deuterioisothiochroman-4-one **4**† and **2** in 5 and 13% yields.‡ The reaction under aerobic conditions also gave **4** and **2** in 8 and 16% yields.‡ In these experiments, 4-keto products[1] were obtained under both anaerobic and aerobic conditions. These results strongly suggested the following mechanism for this aromatization reaction. First, an ene reaction[2a] of SeO_2 with the acetylenic function of **1** generated the enyne–allene seleninic acid intermediate **5**.[2b] Further the enyne–allene system immediately underwent a Myers type cyclization[1] to produce a biradical **6** which would subsequently form the three-membered ring, seleninic ester **7**. Finally removal of SeO from **7** gave the ketone function at C-4. In this pathway, another radical at C-8 trapped the resulting *H* radical and Cl or D radicals from CCl_4 or [$^2H_8$]THF as shown in Scheme 2.

The present novel aromatization reaction of **1** involved a biradical formation in analogy with the case of neocarzinostatin chromophore. The results in biological studies of **1** will be published elsewhere in detail.

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‡ Ratio of **2** and **4** was determined by ^1H NMR analysis.