Pergamon

Tetrahedron Letters 42 (2001) 2911–2914

TETRAHEDRON LETTERS

Base catalyzed [2,3]-sigmatropic rearrangements of propargylic sulfonium and selenonium salts

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Received 25 January 2001; accepted 21 February 2001

Abstract—The synthesis and reactivity of bis-γ-substituted and unsubstituted propargylic sulfonium and selenonium salts under various basic conditions have been investigated. While the former compounds reacted only by [2,3]-sigmatropic rearrangement of the corresponding sulfur ylides, the latter salts exhibited a wider range of reactivity and showed potent DNA-cleaving properties.
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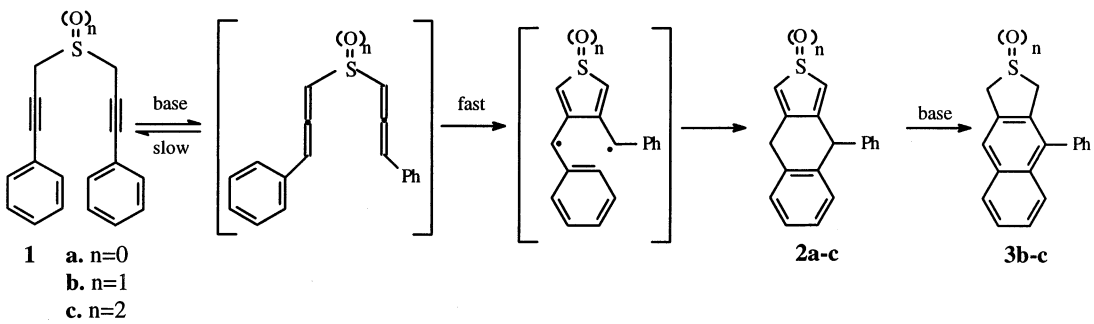
The chemistry of sulfonium[1] and selenonium[2] salts is well documented and reviewed. The well-known stabilized carbanion adjacent to the cationic sulfur/selenium atom is a common intermediate in many reactions involving such species. However, to our knowledge bis-allenic sulfonium salts have not been studied and relatively little attention has been given to the bis-propargylic sulfonium salts.[3,4] Furthermore, as far as we are aware, no bridged propargylic nor allenic selenonium analogues, have been investigated to date. In addition, while [2,3]-sigmatropic rearrangement of allyl sulfonium ylides is well known, the rearrangement of the corresponding selenonium salts has been studied to a smaller extent.[5]

Recently, we became interested in the behaviour of some novel π-conjugated bis-propargylic sulfides, sulfoxides and sulfones. These compounds have been found to undergo facile isomerization to the corresponding diallenes, followed by a tandem cyclization and aromatization via a diradical intermediate, in the presence of various bases at room temperature.[6] Surprisingly, we have found that the rate of the cyclization step was independent of the nature of the bridging functionality (Scheme 1). Interestingly, such a diradical cyclization of bis-γ,γ-dimethylallenyl sulfone, discovered by us in the past,[7] was subsequently used by Nicolaou as a model for the design of a new class of DNA-cleaving molecules that could mimic the activity of



Scheme 1. Tandem isomerization, cyclization and aromatization of bridged dipropargylic systems.

Keywords: sulfur and selenium compounds; allenes; acetylenes; sigmatropic rearrangements.
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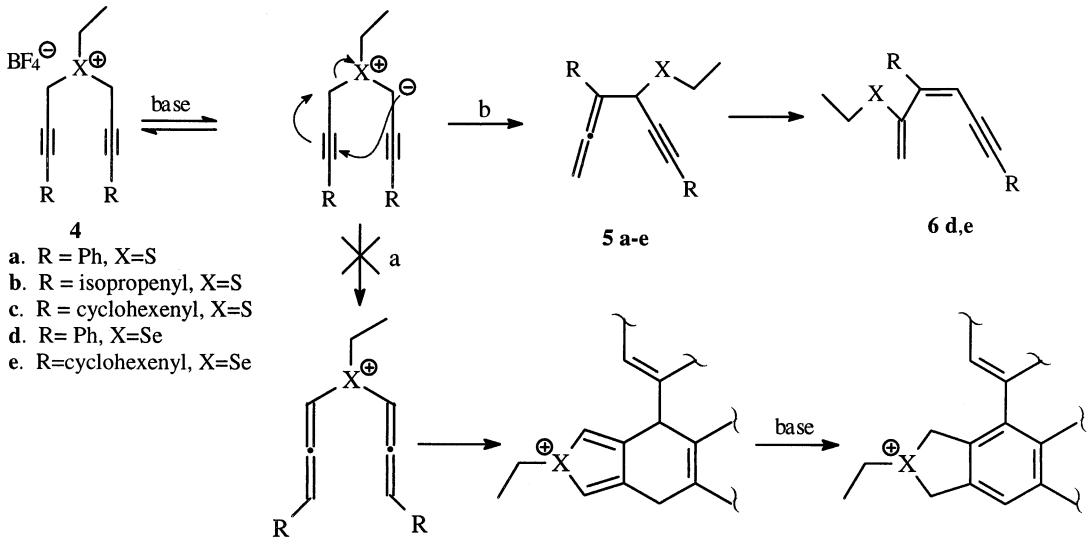
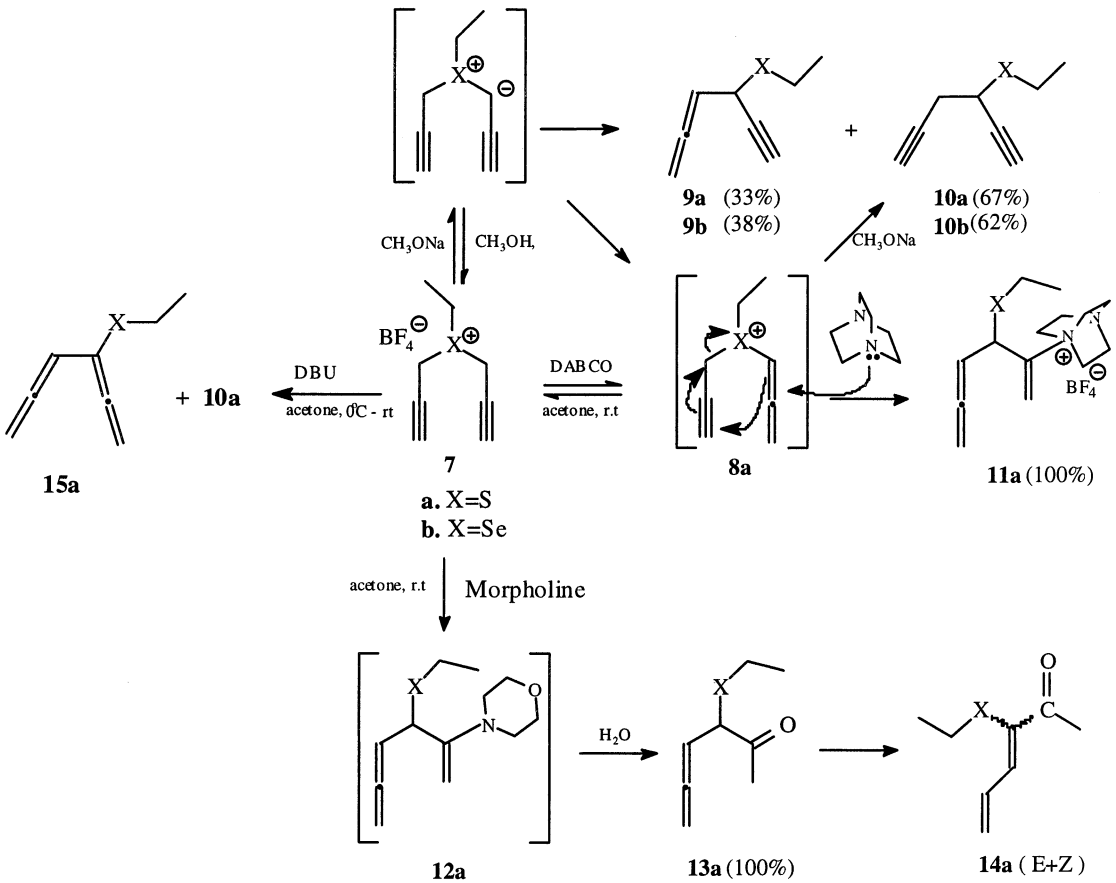
0040-4039/01/$ - see front matter © 2001 Published by Elsevier Science Ltd.
PII: S0040-4039(01)00322-7

the naturally occurring enediynes.[8] However, subsequent mechanistic studies by Nicolaou[9] and others[10] led to the conclusion that an alternative mechanism, the Maxam–Gilbert mechanism,[11] involving nucleophilic addition of DNA to the diallenic sulfone was responsible for its biological activity.

Prompted by the high reactivity of π-conjugated bis-allenyl sulfones and sulfoxides,[6] we decided to investigate the behaviour of the bis-propargylic sulfonium **4a–c** and selenonium **4d,e** analogues. One may expect that these analogues may at least partly cyclize to the corresponding thiophenium and selenophenium salts. Recently, thiophenium salts have received considerable attention.[12] The structural similarities between *S*-alkylthiophenium salts and thiophen-*S*-oxides have prompted the suggestion that these classes are antiaromatic. In addition, and in contrast to the related



Scheme 2. Base catalyzed [2,3]-sigmatropic rearrangement of bis-γ-substituted bridged propargylic systems.



Scheme 3. Rearrangements of unsubstituted bridged propargylic systems **7a,b**.

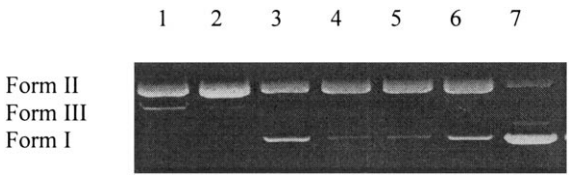


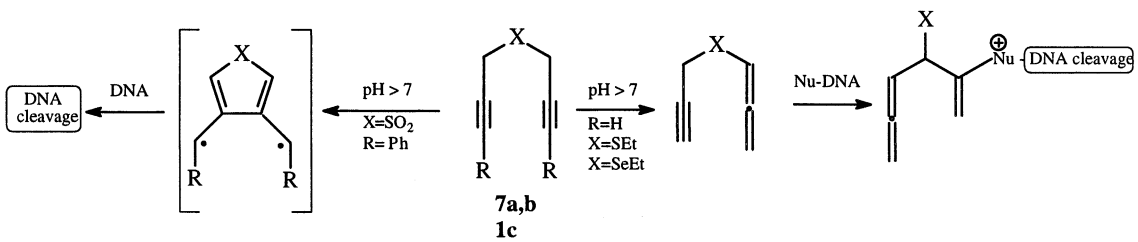
Figure 1. DNA cleavage by sulfonium **7a** and selenonium **7b** salts. ΦX 174 form I DNA (50 μM per base pair) was incubated for 23 h at 37°C with compounds **7a**,**b** in various concentrations in 10% DMSO in tris-HCl buffer (pH 8.5, 50 mM) and analyzed by electrophoresis (1% agarose gel, ethidium bromide stain). Lanes 1–3 correspond to DNA and selenonium salt **7b** at 1000, 500 and 100 μM, respectively; lanes 4–6 correspond to DNA and sulfonium salt **7a** at 1000, 500 and 100 μM, respectively, and lane 7 to DNA alone. Forms I, II and III correspond to supercoiled, relaxed and linear DNA, respectively.

bridged sulfur bis-propargylic systems **1a**–**c**, these onium salts have some water solubility, which in general is necessary for biological activity.

All starting materials were prepared by standard procedures.[13] Despite our expectation for competition between tandem cyclization and aromatization (path a, Scheme 2) and [2,3]-sigmatropic rearrangement (path b), we were surprised to find that these bis-γ-substituted sulfonium/selenonium salts reacted by the latter process exclusively. For example, reaction of ethyl bis-γ-cyclohexenylpropargyl sulfonium tetrafluoroborate (**4c**) with DBU in $CHCl_3$ at room temperature resulted in practically spontaneous and quantitative [2,3]-sigmatropic rearrangement, affording the sulfide derivative **5c**. These results may be partly explained by the steric hindrance introduced by the bulky γ-substituent for isomerization of the propargyl to the allenyl system. It may also be consistent with thermodynamic data which indicate that a nonterminal acetylene is more stable than an isomeric nonterminal allene by 1.0 kcal/mol.[14] In contrast to the stability of sulfides **5a**–**c**, selenides **5d**,**e** underwent a subsequent [1,3]-shift to the appropriate ynedienes **6d**,**e** in $CDCl_3$ at room temperature after 24 h. This result is not surprising in view of the fact that selenoallylic rearrangements[15] occur more readily than their thioallylic analogues.[16] However, whereas the known selenoallylic rearrangements occur at a relatively high temperature, in the case of allenes **5d**,**e** it takes place at room temperature.

In view of the above results, we became interested in investigating the unsubstituted bis-propargyl sulfonium and selenonium salts (**7a**,**b**), which might have a better chance of propargyl–allene isomerization. We have thus found that sulfonium salt **7a** underwent a series of reactions which depend on the nature of the base. These reactions involved prototropic and sigmatropic rearrangements as well as nucleophilic addition and displacement (Scheme 3). For instance, treatment of sulfonium salt **7a** with sodium methoxide in methanol at room temperature afforded sulfides **9a** and **10a**, which mechanistically can be explained by [2,3]-sigmatropic rearrangements of the corresponding ylide.[3] Conversely, the same reaction with *t*-BuOK as base in 85% *t*-BuOH–acetone yielded sulfide **9a** as a single product. On the other hand, when sulfonium salt **7a** reacts with tertiary amine bases such as DABCO or Et_3N, the nucleophilic addition–displacement of the base to allene **8a** is exclusive. The stable crystalline ammonium product **11a** was thus formed in quantitative yield. However, using the secondary base morpholine, sulfonium salt **7a** initially gives the expected eneamine **12a**, which easily hydrolyzed to the corresponding ketosulfide **13a**, followed by slow isomerization to diene **14a**. Finally, the conjugated bis-allene **15a** and diyne **10a** were obtained by the use of DBU as base in the ratio of 7:3, respectively. The formation of **15a** is easily explained by a prototropic isomerization of **9a** in the presence of a strong base. In contrary to these various reactions of sulfonium salt **7a**, the selenonium salt analogue **7b** has been found to undergo only [2,3]-sigmatropic rearrangements to the corresponding selenides **9b** and **10b** in the presence of either DBU or CH_3ONa. Using weaker bases like DABCO leads to mixtures of S_N2 products. This result indicates the relatively high sensitivity of selenonium salts to nucleophilic displacement as compared to sulfonium salts, which may be explained by the relatively higher polarizability of the selenium atom as well as the weaker Se–C bond.[17]

Sulfonium **7a** and selenonium **7b** salts have been found to cleave DNA. Thus, incubation of onium salts **7a**,**b** with ΦX 174 form I DNA aerobically at 37°C led to form II and form III DNA, as shown by gel electrophoresis analysis (Fig. 1). According to the above-mentioned results and in view of our previous work,[6] one may expect two modes of action in the biological activity of sulfur bridged bis-propargyl systems, which depends on the nature of both the bridge and the γ-substituent. The predictable DNA-cleavage by water-soluble onium salts **7a**,**b** may occur by the Maxam–Gilbert mechanism, whereas the bis-γ-phenylpropargyl sulfone **1c** may cleave DNA by the diradical mechanism (Scheme 4).



Scheme 4. Two modes of action for DNA-cleavage by onium salts **7a**,**b** and sulfone **1c**.

Acknowledgements

Financial support of this work by the Israel Science Foundation is gratefully acknowledged.

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13. All new compounds showed spectral and analytical data in accordance with their structure. Some selected data are as follows: (**4c**) ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.27 (quint, $J=2$ Hz, 2H), ABq system: 4.46 (d, $J=17$ Hz, 2H), 4.38 (d, $J=17$ Hz, 2H), 3.49 (q, $J=7.5$ Hz, 2H), 2.1 (m, 8H), 1.63 (m, 11H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 139.4, 118.8, 93.1, 70.9, 34.2, 30.5, 28.5, 25.7, 21.9, 21.1, 9.3. MS (CI) m/e 119 (100%), 181 (21%), 299 (MW, 64%). HRMS (elemental composition): calcd ($C_{20}H_{27}S$) 299.183; found: 299.183. (**5c**) ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.08 (quint, $J=2$ Hz, 1H), 5.97 (m, 1H), ABq system: 5.15 (dm, $J=12$ Hz, 1H), 5.08 (dm, $J=12$ Hz, 1H), 4.53 (bs, 1H), ABq system: 2.78 (dq, $J=12.5$, 7.5 Hz, 1H), 2.68 (dq, $J=12.5$, 7.5 Hz, 1H), 2.09 (m, 8H), 1.61 (m, 8H), 1.3 (t, $J=7.5$ Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 209, 134.4, 129.2, 124.0, 120.5, 107.1, 86.5, 84.6, 80.2, 34.5, 30.2, 29.6, 29.3, 27.4, 25.8, 25.6, 25.5, 22.7, 22.2, 22.1, 14.3. MS (CI) m/e 179 (9.5%), 237 (100%), 299 (MH^+, 35%). HRMS (elemental composition): calcd ($C_{20}H_{27}S$) 299.183; found: 299.182.
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