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Tandem rearrangement, cyclization and aromatization of sulfur bridged propargylic systems

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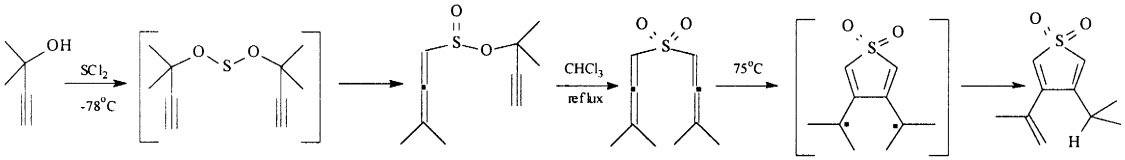
Abstract

The reactivity of some novel π-conjugated bis-propargylic sulfides, sulfoxides and sulfones under basic conditions has been investigated. These compounds undergo isomerization to the corresponding diallenes, followed by a tandem cyclization and aromatization of the latter via a diradical intermediate. Surprisingly, we have found that the rate of the cyclization step was independent of the nature of the bridging functionality.

Keywords: cyclization; diradicals; diynes; diallenes; sulfur compounds.

The [2,3]-sigmatropic rearrangements of propargylic sulfenates[1a] and sulfinates[1b] discovered by us three decades ago have found extensive application in organic synthesis since their publication.[2] In one such application from our own laboratory, a combination of these two rearrangements was used to prepare bis-γ,γ-dimethylallenyl sulfone.[3] Furthermore, this sulfone was found to undergo a quantitative cyclization on heating via a 2,2′-bis-allyl diradical intermediate to the thiophene-1,1-dioxide derivative shown in Scheme 1. Subsequently, this reaction has been used by us as a model for the cycloaromatization of various π and heteroatom bridged diallenic systems.[4] Interestingly, some 15 years later, the same diradical cyclization was used by Nicolaou[5] as a model for the design of a new class of DNA-cleaving molecules that could mimic the activity of the naturally occurring enediynes.[6]



Scheme 1. Preparation and cyclization of bis-γ,γ-dimethylallyl sulfone

The key to the biological activity of the latter postulates a diradical cyclization. However, subsequent mechanistic studies by Nicolaou[7] and others[8] have led to the conclusion that an alternative mechanism,

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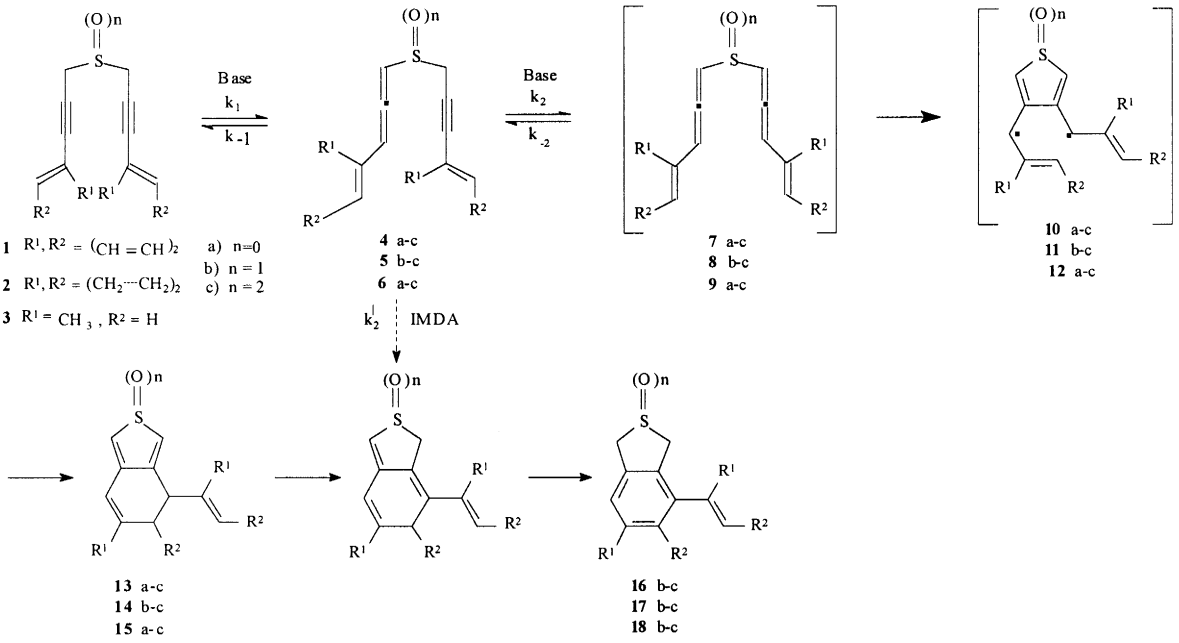
the Maxam–Gilbert[9] mechanism, involving nucleophilic addition of DNA to the diallenic sulfones was responsible for their biological activity. This conclusion is hardly surprising in view of the relatively high temperature required for their cyclization.[3] Consequently, we decided to investigate the effect of tandem cyclization and aromatization on the reactivity of appropriately substituted diallenic sulfones. In addition, we decided to compare the reactivity of such diallenic sulfones with the corresponding sulfides and sulfoxides. The latter have never been investigated before. A study of the behavior of the π-conjugated bis-propargylic systems **1**–**3** under basic conditions has been carried out, and some of the results obtained are presented below.

All starting materials have been prepared by standard procedures.[10] We have found that reaction of bis-γ-phenylpropargyl sulfone (**1c**), a nice crystalline solid, with DBU in $CDCl_3$ at room temperature results in practically spontaneous and quantitative tandem cyclization and aromatization affording the tricyclic naphthalene derivative **16c**. This result may be explained by a series of reactions, as shown in Scheme 2. Interestingly, under the same conditions, the reaction of the corresponding sulfoxide **1b** was considerably slower, but still completed within 1 h, while the corresponding sulfide **1a** remained unchanged even after one day. However, using a more polar solvent such as DMSO led to formation of the expected product **13a** within 24 h. At first glance, these results are rather surprising in view of the greater stability of the thiophene diradical **10a**, comparable to **10b** and **10c**, which are nonaromatic. Our surprise was further enhanced by our finding that no other intermediate except **4b** could be detected.[11] This result has raised the question of cyclization of **4b** via an alternative mechanism involving IMDA of the acetylenic triple bond to the conjugated ene-allene, followed by appropriate fast prototropic shifts to yield **16b** directly. Such a mechanism was initially suggested by Iwai[12] for the base catalyzed cyclization of bis-γ-phenylpropargyl sulfide to the corresponding naphthalene derivative **16a**, but subsequently rejected by Garratt,[4d] who succeeded in isolating intermediate **13a**.



Scheme 2. Tandem isomerization, cyclization and aromatization of bridged dipropargylic systems

In order to prove that the reaction proceeds via a bridged diallenyl sulfoxide **7b** as shown in Scheme 2, the rates of reaction of **1b** with DBU were monitored by NMR: the concentration of **1b**, **4b** and **16b** were

measured as a function of time and numerically fitted to the rate constants shown in Table 1.[13] According to this mechanism, one would expect that both prototropic steps involving conversion of **1b** to **7b** would be sensitive to the base concentration, whereas according to the alternative mechanism involving an internal [4+2]-cycloaddition of **4b**, only the first step would be affected. Consequently, by following the maximal concentration of **4b**, we may distinguish between the two mechanistic alternatives. We have thus found that the maximal concentration of **4b** remained unchanged (Table 1). Furthermore, inspection of the data presented in Table 1 indicates that the two rate constants k_1 and k_2 show the same dependence on base concentration, and that the first step is about three times slower than the second one. Our results can also explain the surprising difference in the rate of reaction of the dipropargyl sulfide **1a**, relative to the corresponding sulfoxide and sulfone, since the rate determining step of all three cyclizations is the prototropic shift from acetylene to allene, which in turn is dependent on the relative acidities of the α-hydrogens of the three systems and slowest in the case of the sulfide **1a**. The cyclization step is thus proceeding at a high rate regardless of the nature of the bridging functionality, nor of the nature of the biradical intermediate **10a–c**. These results may also explain the detection of **4b** but not of **7b**. One should add, that in view of the relative instability of thiophene monoxides in general,[14] the facile and quantitative tandem cyclization and cycloaromatization of **1b** is rather remarkable.

Table 1
Rate constants for the rearrangement of bis-γ-phenypropargyl sulfoxide

[Sulfoxide 1b], M	[DBU], M	10^3k_1, sec^{-1}	10^3k_2, sec^{-1}	[Sulfoxide 4b]$^a_{max}$
0.020	0.006	0.65	2.0	0.21
0.020	0.020	1.70	5.0	0.24
0.020	0.060	3.50	10.0	0.21

a) Molar fraction

Finally, in order to test the generality of the reactions reported above, we have examined the reactivity of the other dipropargylic compounds mentioned in Scheme 2. We have found that while the reactivities of **3a–c** closely resemble those observed with **1a–c**, the cyclization of **2b** and **2c** proceed in moderate yields, and the cyclization of **2a** could not be achieved under various conditions. These results may be explained by the steric hindrance introduced by the bulky cyclohexenyl group. Interestingly, the ^1H NMR spectrum of **17b**, unlike **16b** or **18b**, exhibited structural chirality as a result of the presence of two diastereoisomers which are easily distinguishable by the appearance of two singlets, resulting from the orientation of the cyclohexenyl double bond with respect to the sulfinyl oxygen.[15] The biological activity of the various new compounds is now under examination.

Acknowledgements

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10. All new compounds showed spectral and analytical data in accordance with their structure. Some selected data are as follows: **1b**: mp 99–100°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49–7.46 (m, 4H), 7.35–7.32 (m, 6H), ABq system: 4.13 (d, 2H, J=15 Hz), 3.96 (d, 2H, J=15 Hz); ^{13}C NMR (200 MHz, $CDCl_3$): δ 131.5, 128.7, 128.4, 121.5, 87.7, 77.2, 41.9; IR (neat): 1066, 1442, 1490 cm^{-1}; MS (CI) *m/e* 115 (100%), 147 (71%), 279 (MH^+, 43%); HRMS (elemental composition), calcd ($C_{18}H_{15}OS$) 279.084, obsd, 279.086. Compound **16b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87–7.85 (m, 2H), 7.6–7.26 (m, 8H), ABq system: 4.45 (d, 1H, J=15 Hz), 4.36 (d, 1H, J=15 Hz), 4.17 (d, 1H, J=16 Hz), 4.02 (d, 1H, J=16 Hz); ^{13}C NMR (200 MHz, $CDCl_3$): δ 138.4, 137.9, 133.7, 132.9, 132.3, 132.0, 130.0, 129.5, 128.8, 128.6, 127.9, 126.4, 126.2, 126.1, 125.3, 59.2, 58.6; IR (neat): 1041, 1444, 1492 cm^{-1}; MS (CI) *m/e* 230 (65%), 279 (MH^+, 100%); HRMS (elemental composition), calcd ($C_{18}H_{15}OS$) 279.084, obsd, 279.084.
11. Compound **4b** major diastereoisomer (59%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.75 (d, 1H, J=6 Hz), 6.64 (d, 1H, J=6 Hz), ABq system: 4.06 (d, 1H, J=15.5 Hz), 3.99 (d, 1H, J=15.5 Hz); ^{13}C NMR (600 MHz, $CDCl_3$): δ 102.7, 101.5, 46.2; minor diastereoisomer (41%); ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.71 (d, 1H, J=6 Hz), 6.66 (d, 1H, J=6 Hz), ABq system 4.02 (d, 1H, J=16 Hz), 3.99 (d, 1H, J=16 Hz); ^{13}C NMR (600 MHz, $CDCl_3$): δ 102.8, 102.2, 46.2.
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