Cyclobutadiene Intermediates in Cycloaddition Reactions of 1-Alkynyl Sulfones with 1-Alkynylamines[1]

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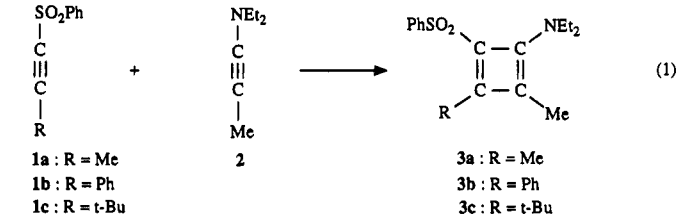
Summary: The initially formed product from ynamines, such as diethyl(1-propynyl)amine, and 1-alkynyl sulfones is in fact the corresponding cyclobutadiene and not the 2-sulfinyl-4-aminofuran proposed by Himbert. The formation of the cyclobutadiene ring has been established by MS, IR, and ^{1}H NMR data, as well as by chemical trapping experiments.

Almost ten years ago, we reported that a wide variety of α,β-unsaturated sulfones readily enter into a [2 + 2]-cycloaddition reaction with ynamines to produce carbocyclic intermediates in high yields.[2] The cycloadducts from vinylic sulfones proved to be readily hydrolyzed to the synthetically useful, corresponding cyclobutanones. In the only instance of a 1-alkynyl sulfone then studied, we also suggested that phenyl 1-propynyl sulfone (**1**) reacted with diethyl(1-propynyl)amine (**2**) exothermically to yield the corresponding cyclobutadiene (**3**). Well-aware that the cyclobutadiene system is antiaromatic and generally unstable,[3] we judged that the observed mass spectral, infrared, and ^{1}H NMR data justified the conclusion that cyclobutadiene **3** (eq 1) had indeed been formed as a metastable intermediate.[4] That a cyclobutadiene bearing simultaneously both electron-donating and electron-withdrawing substituents could be stabilized by such "push–pull" electron delocalization has become clear from the pioneering studies of Gompper and co-workers.[5]



(1)

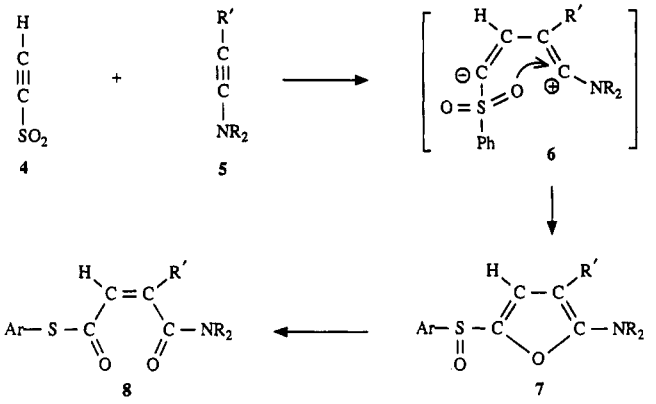
1a : R = Me
1b : R = Ph
1c : R = t-Bu

2

3a : R = Me
3b : R = Ph
3c : R = t-Bu

Subsequent studies of the addition reactions possible between 1-alkynyl sulfones (**4**) and ynamines (**5**) by Himbert and co-workers have revealed that higher temperatures produce an unusual series of redox reactions (**7** and **8**, Scheme I). Because of these observations, Himbert has expressed deep skepticism that any cyclobutadiene-like intermediate is formed in such ynamine–alkynyl sulfone interactions. He preferred to suggest that **4** and **5** react directly via **6** to form **7** and ultimately **8**.[6-8]

Scheme I



In light of the studies and the tenuous speculations of Himbert, we now present cogent evidence that a cyclobutadiene, such as **3**, is the first metastable intermediate formed from the reaction of an ynamine with a 1-alkynyl sulfone. The available evidence consists of the following: (1) mass spectral, infrared, and ^{1}H NMR data that is in agreement with structure **3**; (2) the trapping of structure **3** as complexes with transition metal carbonyls; and (3) the chemical trapping of **3** as a Diels–Alder adduct with dimethyl acetylenedicarboxylate.

In separate experiments each of the following sulfones was allowed to interact neat with diethyl(1-propynyl)amine (**2**) at low temperatures:[4,9] 1-propynyl phenyl sulfone (**1a**), phenyl phenylethynyl sulfone (**1b**), and *tert*-butylethynyl phenyl sulfone (**1c**). Spectral examination of each adduct revealed the following: (1) a parent ion for the cyclobutadiene adduct (**3**) of moderate intensity; (2) the presence of strong infrared bands at 1130 ± 10 and 1300 ± 5

(1) Part 8 of the series Sulfone Reagents in Organic Synthesis. For the previous part, see: Eisch, J. J.; Dua, S. K.; Behrooz, M. *J. Org. Chem.* **1985**, *50*, 3674.

(2) Eisch, J. J.; Galle, J. E.; Hallenbeck, L. E. *J. Org. Chem.* **1982**, *47*, 1608.

(3) Liehr, A. D. *Z. Physik. Chem.* **1956**, NF9, 338.

(4) In our original report (ref 2) we mentioned that **1** reacted exothermically with **2**. Already at that time we noticed that if such an exotherm were not gradually dissipated, but led to a sharp temperature rise, product **3** was extensively contaminated with other products, such as probably **7** and **8**. In order to avoid this further reaction, ynamine **2** was admixed with the alkynyl sulfone at −78 °C and the mixture slowly brought to 0 °C.

(5) Gompper, R.; Seybold, G. *Aromaticity, Pseudo-Aromaticity and Anti-Aromaticity*; Bergmann, E. D., Pullman, B., Eds.; Israel Academy of Sciences and Humanities: Jerusalem, 1971; p 215.

(6) Himbert, G.; Kosack, S.; Maas, G. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 321.

(7) Kosack, S.; Himbert, G. *Chem. Ber.* **1987**, *120*, 71.

(8) Himbert, G.; Kosack, S. *Chem. Ber.* **1988**, *121*, 2163.

(9) As a representative procedure followed for these cycloaddition reactions, the formation of 1-(diethylamino)-2,3-dimethyl-4-(phenylsulfonyl)cyclobutadiene (**3a**) is given. The starting addends were synthesized by known procedures. (1) Diethyl(1-propynyl)amine (**2**): Hubert, A. J.; Viehe, H. G. *J. Chem. Soc. C* **1968**, 228. (2) Phenyl 1-propynyl sulfone (**1a**): Truce, W. E.; Onken, D. W. *J. Org. Chem.* **1975**, *40*, 3200. A 1.0-g sample (5.60 mmol) of **1a** was cooled to −78 °C under an argon atmosphere, and then 0.78 mL (5.70 mmol) of **2** was added slowly by means of a gas-tight syringe. After 2 h the cold bath was removed and the mixture allowed to stir for 16 h. The unreacted **2** was then removed in vacuo to leave a pale brown, viscous product, **3a**: ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 6 H, J = 7.0 Hz), 1.88 (s, 3 H), 2.25 (s, 3 H), 3.1 (q, 4 H, J = 7.0 Hz), 7.3–7.7 (m, 5 H); IR (deoxygenated mineral oil) ν 3000–2800, 1630, 1600, 1550, 1300, 1260, 1220, 1150, 1130, 1080; LRMS calcd for $C_{16}H_{21}NO_2S$ 291, found 291 (M^+); other intense peaks at 143 ($PhSO_2H_2^+$), 141 ($PhSO_2^+$), and 74 ($Et_2NH_2^+$, 100). Since the ^{1}H NMR spectrum is exceptionally clean, especially in the Me group region (1.5–2.5 ppm), no significant contaminant was present at this stage. By a similar procedure 1-(diethylamino)-2-methyl-3-phenyl-4-(phenylsulfonyl)cyclobutadiene (**3b**) was prepared from **2** and phenyl phenylethynyl sulfone (**1b**) (prepared according to Schrock, R. R.; Williams, I. D.; Blum, L. *J. Am. Chem. Soc.* **1984**, *106*, 8316). The pale brown oil displayed the following spectral properties: ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 6 H, J = 7.0 Hz), 2.0 (s, 3 H), 3.0 (q, 4 H, J = 7.0 Hz), 7.0–8.3 (m, 10 H); IR (deoxygenated mineral oil) ν 1300, 1130; LRMS calcd for $C_{21}H_{23}NO_2S$ 353, found 353 (M^+). Again, the ^{1}H NMR spectrum is consistent with there being >95% of one product.

(10) As with open-chain enamines, cycloaddition by dimethyl acetylenedicarboxylate would be expected to occur selectively at the Me—C≡C—NEt_2 side of the cyclobutadiene ring (**3a–c**).

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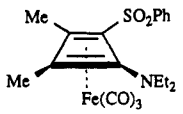
cm^{-1}, characteristic of a sulfone group, and the absence of bands in the region of 1045 ± 10 cm^{-1}, characteristic of a sulfoxide group; (3) broad, intense bands at 1620–1650 cm^{-1}, expected for C=C stretching absorptions; and (4) appropriate ^1H NMR signals for Me, Et, *t*-Bu, and $PhSO_2$ groups in the correct ratio. All such data accord with the presence, in each case, of a sulfonyl- and amino-substituted cyclobutadiene, such as **3**; conversely, such data are not consistent with the presence of a 2-sulfinyl-4-aminofuran such as **7** in the reaction product at this stage.

Furthermore, by treating cyclobutadiene **3a** with $Fe(CO)_5$ or by exposing cyclobutadiene **3b** to $Mo(CO)_6$, the corresponding complexes, **3a**·$Fe(CO)_3$ (**9**) and **3b**·$Mo(CO)_4$ (**10**), were obtained. Both complexes displayed mass fragments for their cyclobutadiene subunits, **3a** and **3b**, in their mass spectra, had characteristic metal carbonyl bands in the 1800–2000 cm^{-1} region and sulfonyl bands at 1140 ± 10 and 1335 ± 10 cm^{-1} in their infrared spectra, and showed proton absorptions and splittings in their ^1H NMR spectra only slightly shifted over those shown by uncomplexed **3a** and **3b**.



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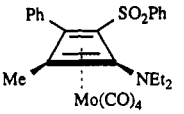

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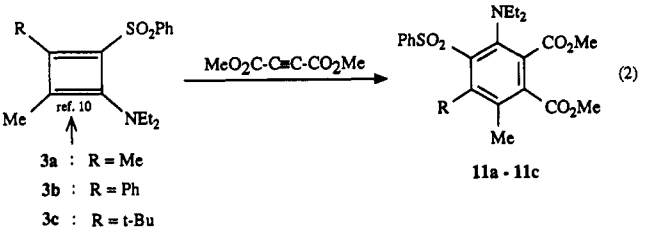
Finally, depending upon how soon 1 equiv of dimethyl acetylenedicarboxylate is added to cyclobutadiene **3a**, **3b**, or **3c** after its formation from ynamine **2** and the appropriate alkynyl sulfone **1a**, **1b**, or **1c**, modest to good yields of the Diels–Alder adduct, **11a**, **11b**, and **11c**, were isolated (eq 2). These products **11a–c** displayed weak parent ions, as well as intense fragment ions at $M^+ - PhSO_2$, in their mass spectra, infrared bands at 1150 and 1310 cm^{-1} consistent with the presence of the sulfonyl group, and ^1H NMR spectra appropriate for the expected substituents.

In conclusion, we have adduced compelling evidence that ynamines and 1-alkynyl sulfones combine initially with



(2)

3a : R = Me
3b : R = Ph
3c : R = t-Bu

11a - 11c

each other to provide metastable cyclobutadiene intermediates and that such cyclobutadienes can be chemically trapped, as metal complexes (**9** and **10**) or as Diels–Alder adducts (**11a–c**), in a potentially useful manner. In opposition to Himbert's contention (Scheme I), furans such as **7** are not formed directly from ynamines and alkynyl sulfones. Rather, at this point in our studies it appears that the initially formed cyclobutadiene eventually may isomerize to the furan **7** and, ultimately, to the enedione **8**.[11]

Acknowledgment. This research was supported, in part, by the National Science Foundation under Grant CHE-87-14911. Professor Marek P. Boleslawski and Ms. Gabriela Blaich provided valuable technical assistance.

Supplementary Material Available: Experimental details and data for the discussed reactions and their products (8 pages). Ordering information is given on any current masthead page.

(11) Himbert and co-workers repeated our reported interaction of **1a** with **2** and found that they "could confirm most of the ^1H NMR data quoted" in our work.[6] However, they were unable to "give a definite statement about the structure of the adduct or the new compound formed from it on distillation". We have not actually isolated furans or enediones of types **7** and **8** from this reaction either, but we do observe spectral changes in **3a**, upon standing, that are consistent with its isomerization into a furan like **7**: the ^1H NMR spectrum shows two new singlets as "shadows" on the methyl peaks at 1.88 and 2.25 ppm and the triplet and the quartet at 0.95 and 3.1 ppm display more complex splittings; the neat IR spectrum begins to develop new bands, especially one or more bands in the 1030–1045-cm^{-1} region, ascribable to the sulfoxide group.

Synthesis of the Mannosidase II Inhibitor Mannostatin A

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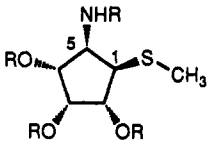
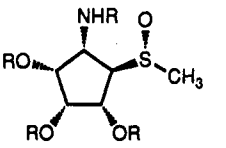
Summary: The synthesis of mannostatin A (**1**), a new inhibitor of glycoprotein processing, has been accomplished in stereocontrolled fashion starting from D-ribonolactone, **7** (~32% overall yield).

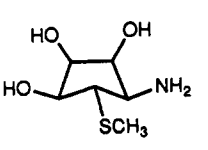
Two unusual aminocyclopentanetriols containing sulfur have recently been isolated from *Streptoverticillium verticillus* var. *quintum* and found to competitively inhibit the α-mannosidase from rat epididymus.[1] Dubbed mannostatin A and B, they were reported to have the sulfide and sulfoxide structures **1** and **3**, respectively, based on ^1H NMR, ^{13}C NMR, and mass spectroscopy, and on crystallographic analysis of mannostatin B tetraacetate (**4**).[2] Further biological evaluation by Elbein et al. led to the discovery that **1** powerfully and selectively inhibited Golgi processing mannosidase II, and in cell culture altered viral



1: R = H (mannostatin A)
2: R = Ac



3: R = H (mannostatin B)
4: R = Ac



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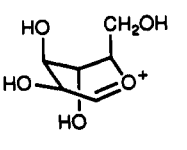

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glycoprotein processing so as to cause an increase in hybrid-type glycoproteins at the expense of complex type.[3] There is currently widespread interest in glycosidase inhibitors not only as biochemical tools for probing the

(1) Aoyagi, T.; Yamamoto, T.; Kojiri, K.; Morishima, H.; Nagai, M.; Hamada, M.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1989**, *42*, 883–889.
(2) Morishima, H.; Kojiri, K.; Yamamoto, T.; Aoyagi, T.; Nakamura, H.; Iitaka, Y. *J. Antibiot.* **1989**, *42*, 1008–1011.
(3) Tropea, J. E.; Kaushal, G. P.; Pastuszak, I.; Mitchell, M.; Aoyagi, T.; Molyneux, R. J.; Elbein, A. D. *Biochemistry* **1990**, *29*, 10062–10069.

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