ORGANIC LETTERS

2011
Vol. 13, No. 5
888–891

Selectivity in Garratt–Braverman Cyclization: An Experimental and Computational Study

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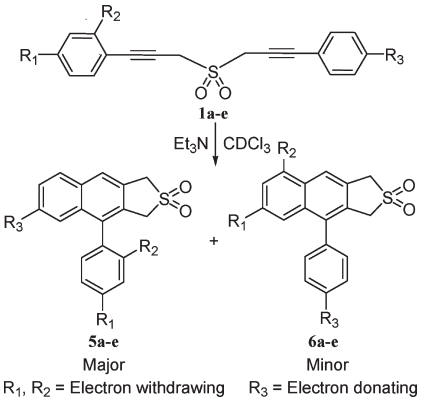
Received December 6, 2010



Bispropargyl sulfones equipped with aromatic rings of dissimilar nature were synthesized. Under basic conditions, these sulfones isomerized to the bisallenic sulfones, creating a competitive scenario between two alternate Garratt–Braverman (GB) cyclization pathways. The observed product distribution ruled out the involvement of any ionic intermediate and supported the diradical mechanism with greater involvement of the electron-rich aromatic ring via the more nucleophilic radical. DFT-based calculations supported the diradical mechanism along with the observed selectivity.

Spontaneous generation of diradical has attracted the attention[1] of the chemical community in the past two decades, triggered by the discovery of enediyne antibiotics in the 1980s.[2] Their role in pharmacology[3] and other aspects such as applications in organic synthesis[4] and preparation of new materials[5] have continued to grow. Not all diradicals are generated spontaneously under ambient conditions and not all of them have the same efficiency of H-abstraction. Diradicals that do not have any mechanism to self-quench become diamagnetic through H-abstraction from external sources. This category includes Bergman cyclization (BC)[6] and related reactions such as Myers–Saito (MS)[7] and Schmittel cyclization (SCM).[8] On the other hand, cyclizations such as Garratt–Braverman (GB)[9] involving conjugated bisallenes (Scheme 1) have a self-quenching mechanism thereby reducing the chances of

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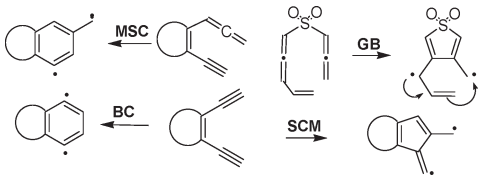
10.1021/ol102861j
Published on Web 02/08/2011

Scheme 1. Various Cyclization Pathways



interaction with external sources. Nicolaou et al.[10] first attempted to utilize the GB cyclization chemistry in bisallenic sulfones. However, the DNA cleavage exhibited by these molecules mostly involved a Michael addition of DNA-base followed by Maxam−Gilbert type cleavage[11] and not through H-abstraction.[10] It is widely believed that the GB pathway involved generation of a diradical, the support for which comes from trapping[9b] with $^3O_2$ and also from the fact that the solvent polarity does not affect the kinetics of the reaction.[9a] In this paper, we provide chemical evidence to support the accepted mechanism and, in the process, disprove the involvement of any ionic intermediate by studying the reactivity of unsymmetrical bispropargyl sulfones with donor and acceptor moieties. The method also demonstrates a strategy for achieving selectivity in GB rearrangement involving unsymmetrical sulfones. The involvement of a diradical intermediate and the overall results are in good agreement with those obtained by computations.

We would like to address the problem by making sulfones of the type **X** equipped with aromatic rings of a different electronic nature (Scheme 2). Under basic conditions, **X** should isomerize to the bisallenic sulfone **A** which can then undergo GB cyclization to produce products represented by **F** and **G**. Our notion is that if ionic intermediates are involved, the product ratio should be dependent upon the stability of the ions (carbocation and carbanion). Thus the ions should be located as shown in structure **B**. The rearrangement then should involve the electron-deficient aromatic ring to produce **F** as the major product. The reactivity of benzyl cations and anions supports such an argument.[12] On the other hand, for a diradical pathway, the radical α to the electron-rich aromatic ring will be nucleophilic in character and hence the major product formed is expected to involve the electron-rich aromatic ring, as is represented by structure **G**.

With this background, we set out our objective to synthesize various unsymmetrical sulfones (**1a**−**e**). The key step in the synthesis is the alkylation of the *in situ* generated thiol [from the corresponding thioacetate (**3i**−**k**)] with the bromide (**4l**−**n**).[13] Both the thioacetate and the bromide

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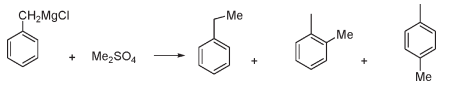
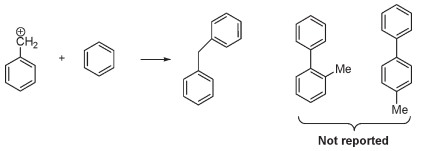
(12) It may be mentioned here that benzyl magnesium chloride, a progenetor of the benzyl anion upon alkylation, produces, in addition to alkyl benzene, *o*- and *p*-substituted products thus indicating the involvement of the ring carbons.[a] On the other hand, Friedel−Crafts reaction of benzene with the benzyl cation yielded only the benzylated product; no toluene derivatives resulting from an *o*- or *p*-carbon acting as the electrophilic center was reported.[b] In this case there was no participation of the ring atoms of the benzyl cation.



(a) Benkeser, R. A.; Johnston, T. E.; Tong, W.-H. *J. Org. Chem.* **1968**, *33*, 2203–2206.



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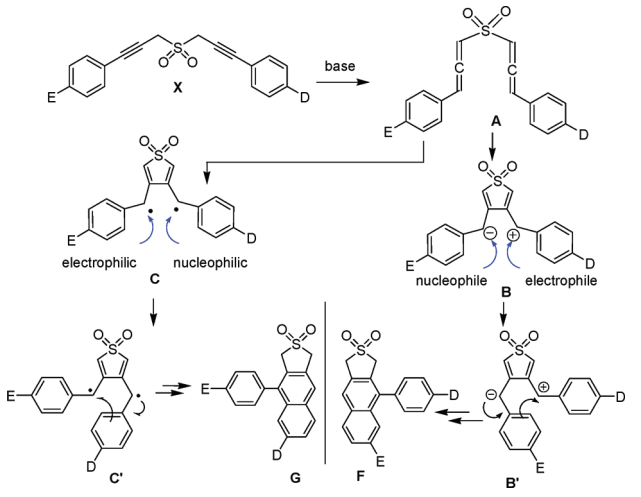
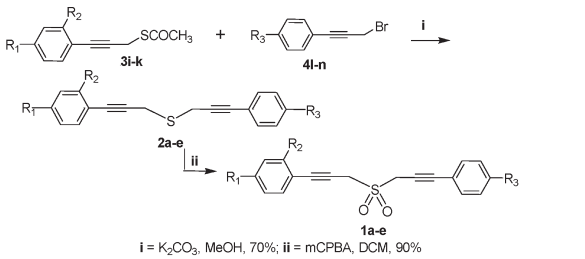
Scheme 2. Possible GB Cyclization Pathways



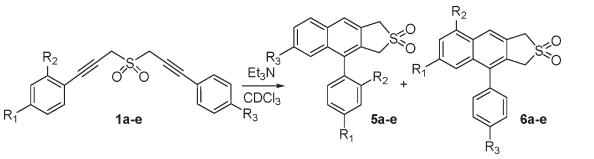
were derived from the aryl substituted propargyl alcohols which were prepared via Sonogashira coupling between the 2- or 4-substituted iodo benzene derivatives and protected propargyl alcohol (Scheme 3).

Scheme 3. Synthesis of Sulfones



To check the reactivity of the various sulfones toward base-mediated GB rearrangement, the compounds were dissolved in $CDCl_3$ and treated with 2 equiv of triethyl amine. A ^1H NMR spectrum was recorded at different time points, and the ratio of the products was determined from the ratio of integration of the doublet for the *o*-coupled aromatic hydrogens (SI, Figure S1). The results are shown in Table 1. The individual products could be separately isolated by column chromatography over Si-gel. The structures were deduced mainly from the NMR and mass spectral analysis. The single-crystal

Table 1. Results of GB Cyclization



entry	starting sulfone	combined yield of products	ratio of products (**5a**−**e**:**6a**−**e**)
1	**1a**	92%	4.7:1
2	**1b**	92%	3.9:1
3	**1c**	95%	2.8:1
4	**1d**	93%	3.4:1
5	**1e**	95%	3.0:1

X-ray structure of one of the products, **5d**, confirmed its assigned structure (SI, Figure S2).[14]

We have carried out Density Functional Theory (DFT) calculations to support the radical mechanism and product distribution.[15,16] The proposed reaction mechanism (Scheme 2) for the cyclization of bisallenic sulfone of **1a** (**A**) was analyzed by computing the stationary points (**A**−**G**).[17] The optimization of **A** using different DFT methods showed that on using methods that account for the dispersive interactions (M06-2X[15c] and DFT-D[15d]), the aryl groups come close to each other (distance between the centers of the aromatic rings is 3.6−3.9 Å). Two geometries, **A1** and **A2**, were optimized which differ in the relative orientation of the aryl groups with each other (SI, Figure S3). The difference in free energy between **A1** and **A2** is very small (ΔG_{A1-A2} = 0.1 kcal mol^{-1}). Interconversion between **A1** and **A2** requires only 4.4 kcal mol^{-1}, and hence we assume that they are in equilibrium with each other.

A free energy profile at the M06-2X/6-31+G* level of theory for the reaction (**A1**/**A2** → **G**/**F**; Scheme 4) is shown in Figure 1. Cyclization of **A1** and **A2** led to the biradical intermediates **C1** and **C2** through the transition states **TS1-1 and TS1-2** respectively. The stability of the wave function was checked for all the species. A restricted approach was used for all the closed-shell structures, whereas an unrestricted broken-spin-symmetry (BS-UM06-2X) approach was used for the open-shell singlet state intermediates (**C1** and **C2**) and transition states (**TS2-1** and **TS2-2**). The broken-spin-symmetry solutions were achieved by feeding the SCF computation with a 50:50 mix (singlet−triplet) initial guess of the HOMO and LUMO orbitals. Activation free energy (ΔG_{act}) for the first cyclization step is 21.0 kcal mol^{-1} for the formation of **C1**, compared to the ΔG_{act} for the formation of **C2** which is 24.2 kcal mol^{-1}. Since the two conformers, **A1** and **A2**, interconvert rapidly

(14) CCDC number of the crystal structure of **5d** is 780945.

(15) (a) All computations were performed using the Gaussian 09 package. The nature of the stationary points was characterized by vibrational frequency calculations. (b) Frisch, M. J. et al. *Gaussian 09*, revision A.02; Gaussian, Inc.: Wallingford, CT, 2009. (c) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215–241. (d) Grimme, S. *J. Comput. Chem.* **2004**, *25*, 1463–1476.

(16) Preliminary EPR studies also supported the involvement of a radical species. Detailed EPR studies are currently under progress and will be reported later.

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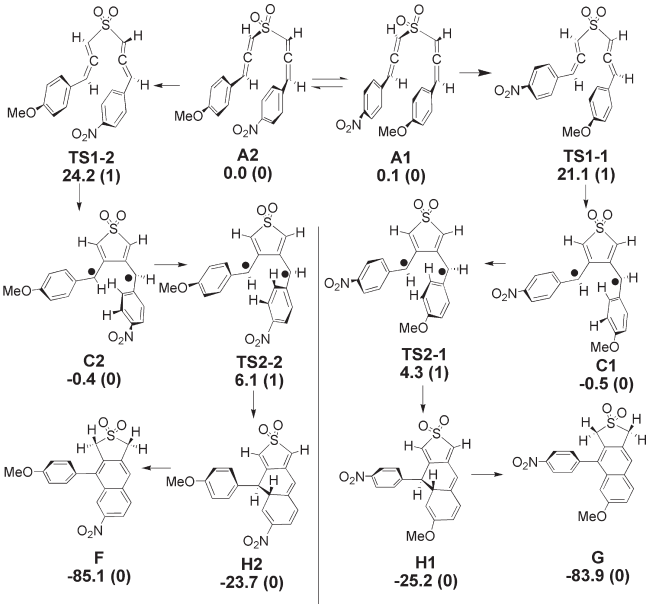
Scheme 4. Relative Free Energies and the Number of Imaginary Frequencies (in Parentheses) at the M06-2X/6-31+G* Level of Theory for the Different Species Involved in the Reaction Pathways



through a low lying transition state, the reaction is under a Curtin−Hammet regime. Hence the formation of **C1** and **C2** which will eventually lead to the products, will depend upon the free energy difference ($\Delta\Delta G^{\ddagger}$) between their corresponding transition states which is 3.1 kcal mol^{-1}. Conversion between **C1** and **C2** requires rotation of two benzylic groups which are unlikely considering the low barriers (Figure 1) for the subsequent quenching steps (**C1**/**C2** → **H1**/**H2**). The activation free energy for the second cyclization step (**C1**/**C2** → **H1**/**H2**) is computed to be 4.8 and 6.5 kcal mol^{-1} respecively for the formation of **H1** and **H2**. The activation energy for the step involving a tautomeric shift of hydrogen (**H1**/**H2** → **G**/**F**) should be a low-energy process (regaining aromaticity) and should not have any bearing on the selectivity. Though the energetics seems to be an insufficient explanation for the product

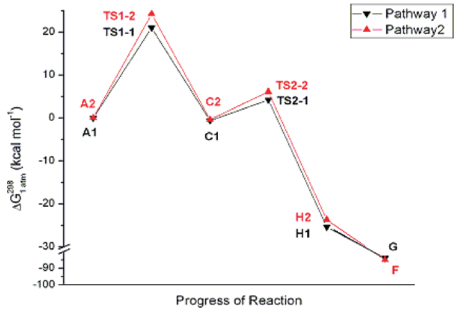


Figure 1. Free energy profile for the cyclization steps (Scheme 4).

ratio quantitatively, it certainly explains the preferential formation of **G** over **F**. It is interesting to note that the solvent calculation (SI, Scheme S1) in $CHCl_3$ using the PCM model[18] at the same level of theory gives a better result ($\Delta\Delta G^{\ddagger}$ = 2.6 kcal mol^{-1}).

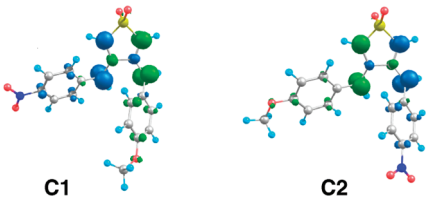


Figure 2. Spin density plot for intermediates **C1** and **C2**.

Considerable spin density at the carbons α to the aromatic rings (Figure 2) is observed in the intermediates **C1** and **C2**, confirming the free radical mechanism. The dipolar (ionic) intermediate **B** is an excited state which is 12.3 kcal mol^{-1} higher in energy than the diradical intermediate at the BS-UM06/6-31G* level of theory. The electronic nature of the aromatic ring causes a slight variation of spin density at the radical centers. In both **C1** and **C2**, the benzylic carbon adjacent to the nitrophenyl carries more spin density than that of the one adjacent to the methoxyphenyl carbon (ρS(nitro) − ρS(methoxy) = 4% in **C1** and 13% in **C2**). Alternately, it can be seen that the spin density at the aromatic carbon meta to the methoxy (22.5%) is more than that at the corresponding position for the nitrophenyl (20.4%) and hence is more likely to react. The capto-dative[19] nature of the *p*-methoxy benzyl radical could be a possible explanation for this greater delocalization (it may be mentioned that the sulfolene is an electron-withdrawing group).

In summary, experimental and computational results support the involvement of diradicals in the GB process and explain the observed selectivity. This strategy also helps to bring selectivity in GB rearrangements.

Acknowledgment. We thank Mr. R. Mukherjee for solving the X-ray structure. M.M. is grateful to CSIR for a fellowship. DST is thanked for funds for the project and 400 MHz NMR facility (IRPHA) and also for the J. C. Bose Fellowship Grant (to E.D.J.). D.M. and E.D.J. thank the SERC, IISc. and the CMSD, UoH, for computational resources.

Supporting Information Available. Experimental procedure, crystallographic data for **5d** (CIF), $^{1}H/^{13}C$ NMR spectra, complete ref 15b, Cartesian coordinates and Computational studies involving methyl substituent **1b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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