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Separate Deprotonation Reactions Converge Mechanistically for a New Cyclization of Benzyl 1-Alkynyl Sulfones

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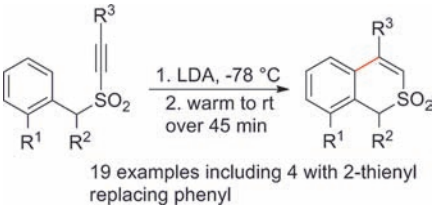
ABSTRACT



A heretofore unknown LDA-induced conversion of benzyl 1-alkynyl sulfones to 1*H*-2-benzothiopyran-*S*,*S*-dioxides is demonstrated. A benzyl carbanion, accessible by two means, is thought to cyclize by temporary disruption of aromaticity. Key intermediates are observed by ReactIR analysis. Thiophene derivatives are also amenable to cyclization, forming 7*H*-thieno[2,3-*c*]thiopyran-*S*,*S*-dioxides.

Acetylenic and allenic sulfones are popular as reactive and functionality rich starting materials for the synthesis of a variety of heterocycles and carbocycles and for the development of synthetic methods.[1] Conjugate additions of selected nucleophiles to alkynyl and allenyl sulfones have been used as crucial starting steps in several methodologies[2] and in the total synthesis of natural products.[3] Another example demonstrates further the flexibility of sulfones. On selected allenyl sulfones possessing remote functionality, deprotonation of the allene brings about intramolecular anion relocation. The new anion is then positioned to effect a cyclization by way of conjugate attack on the unsaturated sulfone.[4]

The anion stabilizing effects of the sulfone functionality are underscored by dearomatizing conjugate additions to create α-sulfonyl carbanions.[5] Such chemistries have been used for medium rings,[6] heterocycles,[7] and functionalized naphthalene derivatives.[8]

Recently we published a paper pertaining to 5-endo cyclizations of transient benzyl allenyl sulfides, using substituted benzyl 1-propynyl sulfides as the starting material.[9] This prompted us to explore the base chemistry of the 1-alkynyl sulfone analog. Hence, using KOBu^t as the base, 2-iodobenzyl 1-propynyl sulfone (**1a**) cyclized not to a five-membered ring but to unexpected product **2a**, a 1*H*-2-benzothiopyran-*S*,*S*-dioxide, in 27% yield (Scheme 1).[10] Given this C−C bond forming process and that relatively

(1) (a) Back, T. G. *Tetrahedron* **2001**, *57*, 5263. (b) Back, T. G.; Clary, K. N.; Gao, D. *Chem. Rev.* **2010**, *110*, 4498.

(2) (a) Xie, M.; Lin, G.; Zhang, J.; Li, M.; Feng, C. *J. Organomet. Chem.* **2010**, *695*, 882. (b) Xie, M.-H.; Xie, F.-D.; Lin, G.-F.; Zhang, J.-H. *Tetrahedron Lett.* **2010**, *51*, 1213. (c) Mukai, C.; Ukon, R.; Kuroda, N. *Tetrahedron Lett.* **2003**, *44*, 1583. (d) Weston, M. H.; Nakajima, K.; Back, T. G. *J. Org. Chem.* **2008**, *73*, 4630. (e) Mukai, C.; Kobayashi, M.; Kubota, S.; Takahashi, Y.; Kitagaki, S. *J. Org. Chem.* **2004**, *69*, 2128.

(3) (a) Zhai, H.; Parvez, M.; Back, T. G. *J. Org. Chem.* **2007**, *72*, 3853. (b) Back, T. G.; Parvez, M.; Wulff, J. E. *J. Org. Chem.* **2003**, *68*, 2223.

(4) (a) Kitagaki, S.; Teramoto, S.; Mukai, C. *Org. Lett.* **2007**, *9*, 2549. (b) Kitagaki, S.; Teramoto, S.; Ohta, Y.; Kobayashi, H.; Takabe, M.; Mukai, C. *Tetrahedron* **2010**, *66*, 3687.

(5) (a) Lopez Ortiz, F.; Iglesias, M. J.; Fernandez, I.; Andujar Sanchez, C. M.; Ruiz Gomez, G. *Chem. Rev.* **2007**, *107*, 1580. (b) Clayden, J.; Kenworthy, M. N. *Synthesis* **2004**, 1721.

(6) Crandall, J. K.; Ayers, T. A. *J. Org. Chem.* **1992**, *57*, 2993.

(7) Padwa, A.; Filipkowski, M. A.; Kline, D. N.; Murphree, S. S.; Yeske, P. E. *J. Org. Chem.* **1993**, *58*, 2061.

(8) Clayden, J.; Kenworthy, M. N.; Helliwell, M. *Org. Lett.* **2003**, *5*, 831.

(9) Motto, J. M.; Castillo, Á.; Greer, A.; Montemayer, L. K.; Sheepwash, E. E.; Schwan, A. L. *Tetrahedron* **2011**, *67*, 1002.

(10) McConachie, L. K. MSc Thesis, University of Guelph, 2000.

(11) (a) Abe, H.; Suzuki, H. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 787. (b) Cao, D.; Kolshorn, H.; Meier, H. *Tetrahedron Lett.* **1995**, *36*, 7069. (c) Himberg, G.; Ruppmich, M.; Schmidt, U. *Phosphorus, Sulfur Silicon Relat. Elem.* **1993**, *74*, 387. (d) Truce, W. E.; Markley, L. D. *J. Org. Chem.* **1970**, *35*, 3275. (e) Truce, W. E.; Onken, D. W. *J. Org. Chem.* **1975**, *40*, 3200. (f) Bouillon, J.-P.; Musyanovich, R.; Portella, C.; Shermolovich, Y. *Eur. J. Org. Chem.* **2001**, 3625. (g) Riddell, N.; Tam, W. *J. Org. Chem.* **2006**, *71*, 1934.

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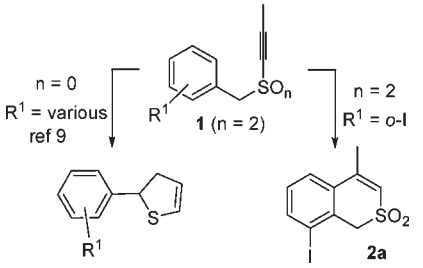
little is known about benzyl alkynyl sulfones, particularly under basic treatment,[11,12] we sought to investigate this reaction and learn about its mechanism.

Scheme 1. KOBu^t Induced Cyclizations of Benzyl 1-Propynyl Sulfides and Sulfones



The cyclization reaction was optimized by way of extensive variation of reaction conditions, including solvent, temperature, time, base identity, and substrate concentration on both 2-iodobenzyl and benzyl 1-propynyl sulfones (**1a**, **1b**, respectively). Only the iodo congener **1a** responded and the formation of **2a** could be optimized to 66%. The eventual conditions proved to be 0.5 M substrate in dry THF, with introduction of 1 equiv of LDA at −78 °C, removing the cold bath and warming under ambient conditions for 45 min before eventual aq. acid quenching.[13]

Given these conditions, other aryl substituted systems were studied as shown in Table 1, but only those substrates with selected ortho-substituted aryl groups provided product. Indeed, the absence of a substituent on the benzylic aryl group (Table 1, entry 2) prevented cyclization, while an additional aryl group at the benzylic position (entry 12) promoted it.

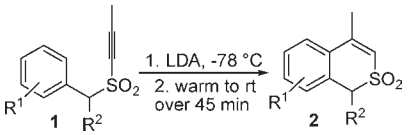
The data seem to indicate that steric crowding around the benzyl position plays at least a partial role in promoting cyclization, presumably because LDA is directed *away* from benzylic deprotonation.[14] With this structural condition in mind, several more substrates were prepared and subjected to cyclization conditions. Generally, the proposed theory held and cyclized products were obtained in yields of 51−91% (Table 2).

This collection of results permits some useful observations. The cyclization tolerated the change from a terminal methyl on the alkyne to a butyl group (Table 2, entries 2−4), and those results portend that a variety of extended chains would be suitable. Also of note is the preferential involvement of the thiophene group when it was positioned to compete with a benzene ring (entry 4).

Some mechanistic information was gained through ReactIR analysis of the reaction progress. Of particular value was the alkynyl/cumulene section of the IR spectrum. Figure 1 is a snapshot of that region during the cyclization reaction of **1a**, with starting material and two proposed intermediates labeled by compound number (see also Scheme 2).

The large absorption beginning at the bottom of the diagram represents the starting material alkyne stretch at 2222 cm^{-1}. Upon introduction of the LDA, the disappearance of that absorption coincides with the immediate,

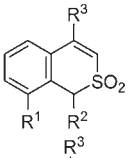
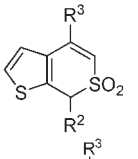
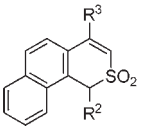
Table 1. LDA Induced Cyclization of Benzyl 1-Propynyl Sulfones



no.	**1**	R^1, R^2	**2** (% yield)[a]
1	**a**	2-I, H	66[b]
2	**b**	H, H	0
3	**c**	4-F, H	0
4	**d**	3-CN, H	0
5	**e**	2-Cl, H	0
6	**f**	2-Me, H	13[c]
7	**g**	2-Br, H	55
8	**h**	2-Et, H	0[d]
9	**i**	2-CF_3, H	51
10	**j**	2-OPr^i, H	47
11	**k**	2-Ph, H	80
12	**l**	H, Ph	71

[a] Scale of reactions is 100−500 mg of **1**. 1.0 equiv of LDA was added to a 0.5 M solution of **1** in THF. All yields are of isolated, purified material, unless otherwise indicated. [b] Yield reaches 75% when reaction is performed on a 1−2 g scale. [c] Calculated by ^{1}H NMR. [d] The cyclization chemistry of **1h** was irreproducible; product was observed on one occasion.

Table 2. LDA Induced Cyclizations of Hindered (Het)Arylmethyl 1-Alkynyl Sulfones[a]

no.		product (**2**)	R^1, R^2, R^3	% yield[b]
1	**m**		2-thienyl, H, Me	69
2	**n**		H, Ph, Bu^n	91
3	**o**		I, H, Bu^n	61
4	**p**		--, Ph, Bu^n	83
5	**q**		--, H, Me	68
6	**r**		--, Ph, Me	51

[a] See Table 1 for reaction conditions. [b] Scale of reactions is 100−300 mg of **1**. All yields are of isolated, purified material.

(12) The use of alkynyl benzyl sulfones removes the availability of addition to the aromatic at a position β to the sulfone and introduces acidic hydrogen(s) for possible deprotonation at the benzylic site.

(13) When the cyclization does not occur, undefined polymeric material is typically obtained, regardless of substrate concentration.

(14) Ortho substituents containing heteroatoms also seem to deter benzylic deprotonation and may be more important in this regard than steric effects.

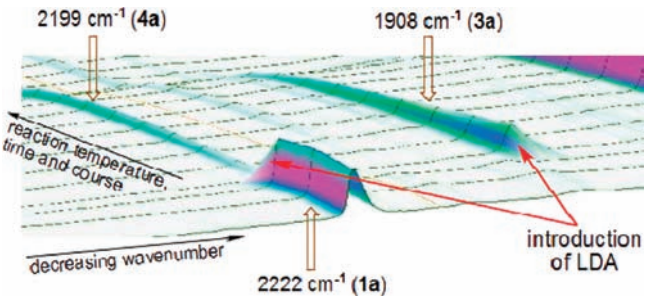


Figure 1. View of cumulene and alkyne region of IR spectrum during cyclization of sulfone **1a**. Key absorptions are assigned to proposed intermediates. See text for discussion.

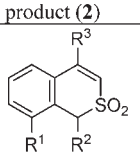
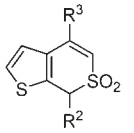
rapid growth of another peak at 1908 cm^{-1}. Over time and with warming, the 1908 cm^{-1} peak disappears, while a longer lived band is evident at 2199 cm^{-1}.

These bands are consistent with a mechanism that involves immediate deprotonation of the terminal methyl of **1a** to produce allenyl anion **3a** (Scheme 2). The observed allenyl stretch of 1908 cm^{-1} is similar to that of calculated and measured allenyl anions as reported by Lambert et al.[15] The attachment of the (primarily inductive) electron-withdrawing sulfone might be expected to move the absorption to higher energy. Compound **3a** slowly disappears, and it is proposed that the longer lived 2199 cm^{-1} peak is indicative of anion **4a**, which arises through bimolecular proton exchange, promoted by the high concentration of substrate.[16]

Anion **4a** then undergoes an intramolecular cyclization, which temporarily sacrifices aromatic stabilization, a cyclization that may be accelerated by the warming temperature. Additional proton transfers relocate the anion position to the benzylic position prior to quenching. Support for this latter claim is found when MeI is used to quench the reaction; the product of monomethylation (**7**) is recovered in 61% yield. The preference for thiophene over benzene participation (Table 2, entry 4) is also consistent with the aromatic disruption portion of the proposed mechanism. The mechanism at hand has features similar to those in the work of Mukai and co-workers that was introduced earlier,[4] including the proton transfer and the counterattack of the anion.

On the basis of the proposed mechanism, it follows that direct deprotonation from the benzylic site should bring about cyclization. As such, a series of compounds possessing blocking groups β to the sulfone were evaluated. The only optimizations performed on these substrates were dilution experiments. Working at a substrate concentration of 0.05 M, cyclization occurred as indicated in Table 3.

Table 3. Direct Induced Cyclizations of (Het)Arylmethyl 1-Alkynyl Sulfones[a]

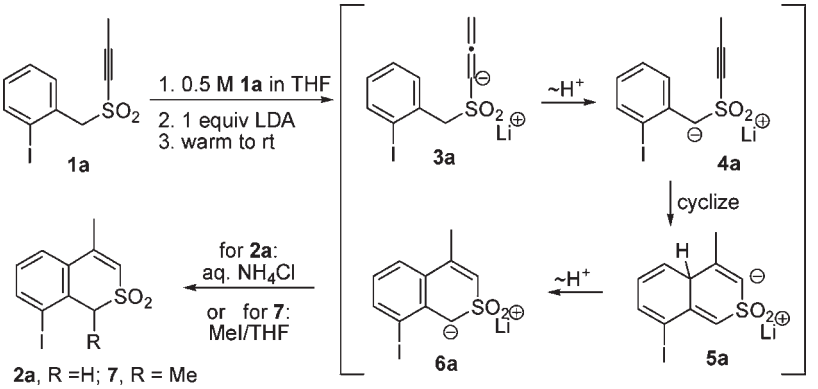
no.		product (**2**)	R^1, R^2, R^3	% yield[b]
1	**s**		H, H, Ph	59
2	**t**		H, Ph, Ph	71
3	**u**		I, H, Ph	59
4	**v**		H, H, Bu^t	0
5	**w**		I, H, Bu^t	0
6	**x**		--, H, Ph	80
7	**y**		--, Ph, Ph	90
8	**z**		--, H, Me	88

[a] See Table 1 for reaction conditions. 1.0 equiv of LDA was added to a 0.05 M solution of **1** in THF. [b] Scale of reactions is 100−300 mg of **1**. All yields are of isolated, purified material.

With phenyl groups on the triple bond, the cyclization occurred readily (entries 1−3, 6, 7), but *tert*-butyl blocking groups hindered cyclization (entries 4,5), presumably for steric reasons. The thiophene-containing cases provided the higher yield of product (entries 6−8), consistent with the relative aromaticity of each ring system.

For sulfone **1a**, the ReactIR data provide an amount of certainty with regard to the initial site of proton removal. Given the cyclizations of Table 3, it is entirely possible that some of the entries in Table 2 arise from initial deprotonation at both the benzylic position and opposite the triple bond. Similarly, 2-thienylmethyl sulfone **1z** (Table 3, entry 8)

Scheme 2. Proposed Mechanism for Cyclization of Benzyl-Hindered Sulfones **1**



may be prone to deprotonation at both positions. The fates of the triple bond of starting sulfones **1s** and **1z** were separately followed by ReactIR analysis. Upon addition of LDA, the IR absorptions of the triple bonds of these substrates display a similar profile for eventual disappearance, one that is noticeably slower than in the reaction of **1a**. Furthermore, no allenyl anion was observed in the spectra (see Supporting Information). Based on these comparisons, proton removal from the site α to the sulfone appears to be the predominating occurrence for thiophene **1z**.

The mechanism proposed above suggests that anions of the type **6a** are the most stable of the various options and are the species that eventually get quenched. Previous reports on cyclic sulfonyl anions including the parent benzothiopyran *S*,*S*-dioxide of **6a** note their stability in relation to acyclic analogs.[17] Since conjugation can occur through a sulfonyl group,[18] conjugated anion **6a** is anticipated to possess some aromatic stabilization (Figure 2).[17a,18a]

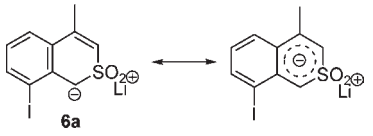


Figure 2. Carbanions at the 2-position of 1*H*-2-benzothiopyran-*S*,*S*-dioxides (e.g., **6a**) possess some aromatic stabilization.

It follows that the transition state for cyclization also benefits from an amount of conjugation through the sulfone. If that is the case the cyclization may be a 6-electron electrocyclic ring closure. Moreover, since α-sulfonyl carbanions often hold the lithium counterion on one or both sulfonyl oxygens,[19,20] the cyclization which delivers α-sulfonyl anion **5a** from α-sulfonyl anion **4a** can proceed with minimal repositioning of the lithium counterion.

Compounds with the 1*H*-2-benzothiopyran-*S*,*S*-dioxide (or isothiochromene 2,2-dioxide) core have been evaluated as coumarin isosteres for the inhibition of gyrase B[21] and are known to provide protection against cardiac arrhythmia.[22] Furthermore, this ring system can act as a source of carbocycles after extrusion of SO_2.[23] The 7*H*-thieno[2,3-*c*]thiopyran-*S*,*S*-dioxide fused heterocyclic system (**2p,x−z**) is not known. The ring skeleton is known for the sulfane oxidation state, and its formation requires functional groups capable of promoting condensation based ring closures.[24] The chemistry presented herein offers a general and high-yielding means of forming the 7*H*-thieno[2,3-*c*]thiopyran heterocyclic skeleton, in its sulfone state, without the need for additional functionality.

To summarize, a new intramolecular cyclization affording 1*H*-2-benzothiopyran-*S*,*S*-dioxides and 7*H*-thieno[2,3-c]thiopyran-*S*,*S*-dioxides is outlined. In the cyclization, an α-sulfonyl benzyl anion temporarily disrupts aromaticity to effect a conjugate addition on a triple bond on the opposite side of the sulfone. The benzyl anion can be formed through direct deprotonation; alternatively there are a variety of instances when the cyclization is initiated through deprotonation γ to the sulfone on the triple bond side of the molecule. The stable anion after cyclization (e.g., **6a**) and the functionalized aromatic provide opportunity for adaptation of the cyclized products. Future work will also include the assessment of other functional groups including enolates, which are expected to hold the counterion static on the oxygen and selected phosphorus groups.[18b]

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Supporting Information Available. Experimental procedures, characterization data, and copies of NMR's of sulfones; selected ReactIR data. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) Lambert, C.; Schleyer, P. v. R.; Wuerthwein, E. U. *J. Org. Chem.* **1993**, *58*, 6377.

(16) Monitoring the disappearance of the 1908 cm^{-1} peak by ReactIR at −45 °C reveals the fate of **3a** is not first-order decay.

(17) (a) Pagani, G.; Bradamante, P. S.; Maiorana, S.; Mangia, A. *J. Chem. Soc. B* **1971**, 74. (b) Pagani, G.; Bradamante, P. S.; Mangia, A. *J. Chem. Soc. B* **1971**, 545.

(18) (a) Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1991**, *56*, 4218. (b) Fraenkel, G.; Kolp, C. J.; Chow, A. *J. Am. Chem. Soc.* **1992**, *114*, 4307.

(19) Gais, H.-J. In *Organosulfur Chemistry in Asymmetric Synthesis*; Toru, T., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2008; Chapter 12.

(20) The anionic species may also be dimeric in solution, especially under high concentration.

(21) Peixoto, C.; Laurin, P.; Klich, M.; Dupuis-Hamelin, C.; Mauvais, P.; Lassaigne, P.; Bonnefoy, A.; Musicki, B. *Tetrahedron Lett.* **2000**, *41*, 1741.

(22) Kleemann, H.-W.; Below, P. WO 066620A1, 2003.

(23) (a) Hall, C. R.; Smith, D. J. H. *Tetrahedron Lett.* **1974**, 3633. (b) Finlay, J. D.; Hall, C. R.; Smith, D. J. H. *Tetrahedron Lett.* **1977**, 1149.

(24) (a) Saito, T.; Shizuta, T.; Kikuchi, H.; Nakagawa, J.; Hirotsu, K.; Ohmura, H.; Motoki, S. *Synthesis* **1994**, 727. (b) Mandal, S. S.; Chakraborty, J.; De, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2639.