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Ruthenium-Catalyzed Diyne Hydrative Cyclization: Synthesis of Substituted 1,3-Diene Synthons

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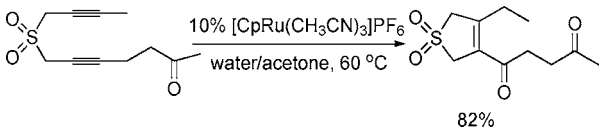
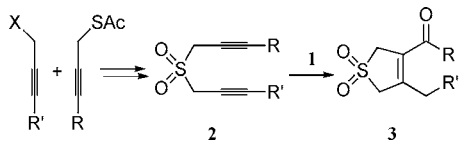
ABSTRACT



A novel and versatile strategy for the synthesis of highly functionalized substituted 3-sulfolenes based on $[CpRu(CH_3CN)_3]PF_6$-catalyzed hydrative cyclization has been developed. A marked ketone directing effect in ruthenium-catalyzed cyclization was observed for the first time. This provides complementary chemoselectivity for the synthesis of 3-sulfolenes and other cyclic enones. The utility of this method has been demonstrated by SO_2 extrusion of 3-sulfolenes to afford 1,3-dienes and the subsequent inter- and intramolecular Diels–Alder reaction.

The ruthenium-catalyzed hydrative cyclization of diynes holds promise as a versatile ring-forming process.[1] Among heterocycles, 3-sulfolenes have a special significance as conjugated diene synthons, since they generate 1,3-dienes readily by thermal desulfonylation and have been employed for Diels−Alder reactions in a number of complex syntheses.[2,3] Several methods for the synthesis of substituted 3-sulfolenes have been described in the literature. One approach involves the construction of the corresponding cyclic sulfides from functionalized precursors that usually require multistep manipulations, followed by oxidation of the sulfide to sulfone.[4] One of the most common approaches involves the addition of SO_2 to functionalized dienes,[5] a method demanding availability of the type of functionality that is being made but useful to convert simple 1,3-dienes to more substituted ones. Most recently, substituted 3-sulfolenes have been prepared by ring-closing metathesis.[6] Our group has established that the hydrative diyne cyclization catalyzed by $[CpRu(CH_3CN)_3]PF_6$ (**1**) is an excellent method to prepare cyclic systems,[1] although its chemoselectivity with respect to potential leaving groups such as sulfonyl in the propargylic position remains to be tested. Further, the synthetic flexibility for preparation of substrates arising from the acetylenic functionality facilitates their synthesis. In this communication, we describe a novel and versatile strategy for the synthesis of highly functionalized substituted 3-sulfolenes based on the catalyzed hydrative cyclization of dipropargylic sulfones (eq 1). During these studies, a marked ketone directing effect in ruthenium-catalyzed cyclizations was observed for the first time.



(1)

Diethyl dipropargylic sulfone **2a** (R = R′ = Et), which was efficiently prepared from 1-bromo-2-butyne in two steps,[7] was used as a model substrate. Optimization studies showed that the presence of an appropriate amount of water

(1) (a) Trost, B. M.; Rudd, M. T. *J. Am Chem. Soc.* **2002**, *124*, 4178. (b) Trost, B. M.; Rudd, M. T. *J. Am Chem. Soc.* **2003**, *125*, 11516.
(2) (a) Leonard, J.; Hague, A. B.; Knight, J. A. *Organosulfur Chem.* **1998**, *2*, 227. (b) Luh, T. Y.; Wong, K. T. *Synthesis* **1993**, *4*, 349. (c) Chou, S. P.; Tsai, C. *J. Org. Chem.* **1988**, *53*, 5305.
(3) (a) Shing, T. K.; Tang, Y. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1625. (b) Leonard. J.; Hague, A. B.; Jones, M. F. *Tetrahedron Lett.* **1997**, *38*, 3071.
(4) Nakayama, J.; Machida, H.; Saito, R. *Chem. Lett.* **1985**, 1173.
(5) Roversi, E.; Monnat, F.; Vogel, P.; Schenk, K.; Roversi, P. *Helv. Chim. Acta* **2002**, *85*, 733 and references therein.
(6) Yao, Q. *Org. Lett.* **2002**, *4*, 427.
(7) Cao, X.; Yang, Y.; Wang, X. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2485.

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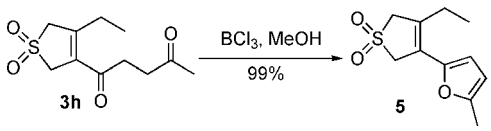
(~11 equiv, 2 vol %) was important to secure high yields of 3-sulfolene **3a** (Table 1).

Table 1. Optimization of Hydrative Cyclization

entry	substrate	H_2O (equiv)	yield (**3a**)[a,b]
1	**2a**	55	80%
2	**2a**	11	97%
3	**2a**	5	90%
4	**2a**	2	91%

[a] All reactions at 0.1 M in acetone at 60 °C with 10% **1** for 6 h. [b] Isolated yields after chromatography.

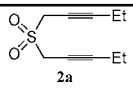
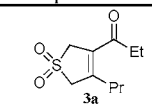
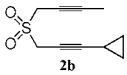
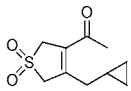
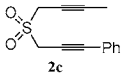
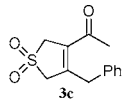
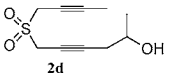
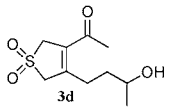
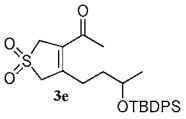
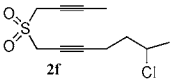
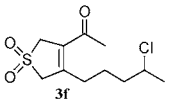
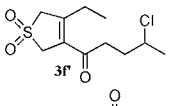
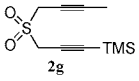
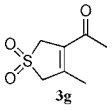
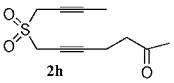
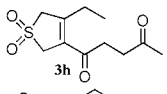
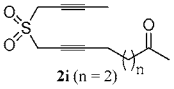
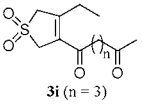
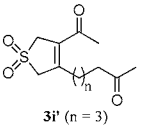
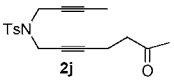
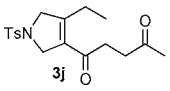
Table 2 illustrates the scope of the method. The substrates are easily accessible from a propargylic thioacetate and a propargylic halide.[7] Unsymmetrical dipropargylic sulfone substrates displayed very good chemoselectivity, and the addition of water usually takes place at the more sterically accessible side (entry 2−7).[1] A variety of functional groups can be tolerated in this transformation, including a free hydroxyl (entry 4), a silyl ether (entry 5), and a chloride (entry 6). The desilylation product **3g** was obtained when an alkynylsilane was used as the starting diyne (entry 7). Most interestingly, a carbonyl group was found to direct the addition of water to the more sterically hindered side to form 3-sulfolene **3h** in excellent yield and with excellent chemoselectivity (entry 8). Carbonyl-group-directed product **3i** was still predominant when the carbonyl group was in the δ-position with respect to the alkyne function (entry 9). The carbonyl group directing effect was also observed when the tether was changed from sulfone to nitrogen (entry 10). A synthetic application of this ketone-directed addition is demonstrated by the formation of furan **5** from diketone **3h** (eq 2).[8]



(2)

A plausible mechanistic rationalization for the ketone directing effect is depicted in Scheme 1. The carbonyl oxygen coordinates with ruthenium in the ruthenacycle (**A**/**B**).[9] This facilitates the hydration of the ketone to generate intermediate **C**, and subsequent rearrangements (**C** → **D** → **E**) give the observed carbonyl directing product. This mechanism explains the results of entries 8 and 9 in Table 2. In entry 8, the six-membered ruthenacycle in intermediate **B** gives a completely carbonyl-directed diketone (**3h**). In entry 9, there is a seven-membered ruthenacycle in intermediate **B**. This

Table 2. Representative Examples of Hydrative Cyclization

entry	substrate	conditions[a]	product	yield[b]
1	 **2a**	10% **1** 6 h	 **3a**	97%
2	 **2b**	10% **1** 22 h	 **3b**	76%
3	 **2c**	10% **1** 20 h	 **3c**	81%
4	 **2d**	10% **1** 15 h[c]	 **3d**	55%
5	 **2e**	10% **1** 24 h	 **3e**	84%
6	 **2f**	10% **1** 4.5 h	 **3f**	76%
			 **3f'**	11%
7	 **2g**	10% **1** 20 h	 **3g**	75%
8	 **2h**	10% **1** 18 h	 **3h**	82%
9	 **2i** (n = 2)	10% **1** 6 h	 **3i** (n = 3)	63%
			 **3i'** (n = 3)	18%
10	 **2j**	10% **1** 2 h	 **3j**	72%

[a] Reactions were carried out at 0.1 M (in substrate) in 2 vol % water/acetone at 60 °C. [b] Isolated yields after chromatography. [c] Performed with 5 vol % water/acetone.

allows water to add to the less hindered side to form **3i′** as the minor product.

To demonstrate the synthetic utility of substituted 3-sulfolenes, compound **3a** was transformed into 1,3-diene **6** in

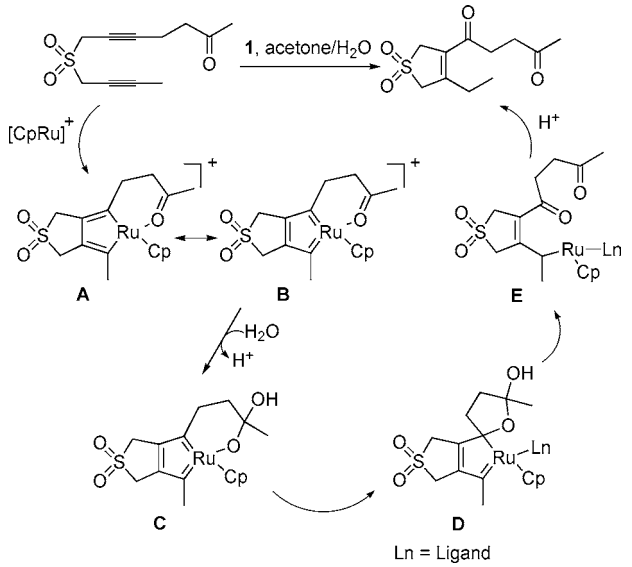
(8) Khan, M.; Hashmi, M.; Ahmad, F.; Osman, S. M. *J. Chem. Soc., Chem. Commun.* **1983**, 1057.

(9) (a) Becker, E.; Mereiter, K.; Puchberger, M.; Schmid, R.; Kirchner, K. *Organometallics* **2003**, *22*, 2124−2133. (b) Becker, E.; Ruba, E.; Mereiter, K.; Schmid, R.; Kirchner, K. *Organometallics* **2001**, *20*, 3851−3853. (c) Le Paih, J.; Monnier, F.; Derien, S.; Dixneuf, P. H.; Clot, E.; Eisenstein, O. *J. Am. Chem. Soc.* **2003**, *125*, 11964−11975. (d) Le Paih, J.; Derien, S.; Dixneuf, P. H. *Chem. Commun.* **1999**, 1437−1438.

(10) Smith Synthesizer from Personal Chemistry was used for the microwave studies.

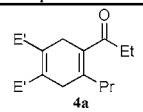
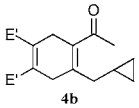
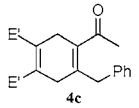
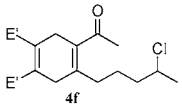
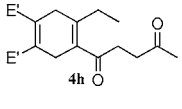
(11) SO_2 extrusion was carried out at 160 °C microwave for our convenience. This reaction could be carried out in refluxing toluene or at even lower (ambient) temperature: (a) Winkler, J. D.; Quinn, K. J.; MacKinnon, C. H.; Hiscock, S. D.; McLaughlin, E. C. *Org. Lett.* **2003**, *5*, 1805. (b) Yang, T.-K.; Chu, H.-Y.; Lee, D.-S.; Jiang, Y.-Z.; Chou, T.-S. *Tetrahedron Lett.* **1996**, *37*, 4537.

Scheme 1. A Mechanistic Rationale for the Carbonyl-Directed Hydrative Cyclization



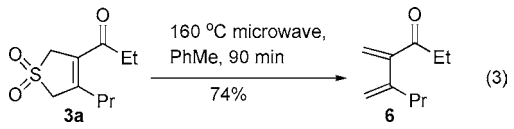
good yield under thermal conditions at 160 °C in a microwave (eq 3).[10,11] Such substituted 3-sulfolenes can be directly used in intermolecular Diels−Alder reactions. The Diels−Alder adducts were isolated in high yields by heating a mixture of the sulfolenes with DMAD at 160 °C in a microwave apparatus (Table 3).

Table 3. Selected Examples of Diels−Alder Reactions Using Substituted 3-Sulfolenes as 1,3-Diene

entry	substrate	conditions[a]	product	yield[b]
1	**3a**	1.5 equiv DMAD,[c] 2 h	 **4a**	79%
2	**3b**	3 equiv DMAD, 2 h	 **4b**	81%
3	**3c**	2 equiv DMAD, 2 h	 **4c**	82%
4	**3f**	2.9 equiv DMAD, 2 h	 **4f**	83%
5	**3h**	1 equiv DMAD, 45 min	 **4h**	70%

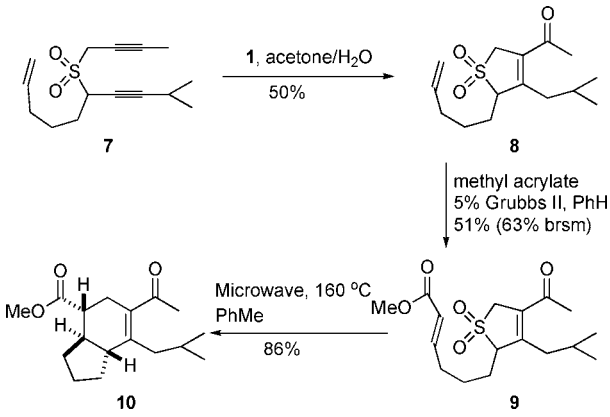
[a] Reactions were carried out at 0.5 M (in substrate) in PhMe at 160 °C microwave, E′ = CO_2Me. [b] Isolated yields after chromatography. [c] DMAD = dimethyl acetylenedicarboxylate.

The utility of this method was further showcased in the preparation of bicyclic enone **10** (Scheme 2). Under our



standard ruthenium-catalyzed cyclization conditions, 3-sulfolene **8** was formed in 50% yield from dipropargylic sulfone **7**. Treatment of **8** with methyl acrylate in the presence of Grubbs II catalyst afforded enoate **9**.[12] Exposure of **9** to microwaves at 160 °C in PhMe gave bicyclic enone **10** in good yield (86%) as a single diastereomer.[13]

Scheme 2. Formation of Bicyclic Enone **10** by an Intramolecular Diels−Alder Reaction



In conclusion, a general and efficient synthesis of substituted 3-sulfolenes has been developed. Their synthetic utility has been demonstrated by SO_2 extrusion to afford 1,3-dienes, which can be trapped by either inter- or intramolecular Diels−Alder reactions. A marked ketone directing effect in ruthenium-catalyzed cyclizations was observed for the first time. This phenomenon provides complementary chemoselectivity for the synthesis of substituted 3-sulfolenes and other cyclic enones by this method.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences, for their generous support of our programs. Mass spectra were provided by the Mass Spectrometry Regional Center of the University of California−San Francisco, supported by the NIH Division of Research Resources.

Supporting Information Available: Experimental procedures for the preparation of new compounds as well as characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0502937

(12) (a) Smith, C. M. O'Doherty, G. A. *Org. Lett.* **2003**, *5*, 1959. (b) Choi, T. L.; Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1277. (c) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783.

(13) The trans−trans relationship assignment of compound **10** was based on two-dimensional ROESY NMR.