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Selective Formation of Six-Membered Cyclic Sulfones and Sulfonates by C–H Insertion

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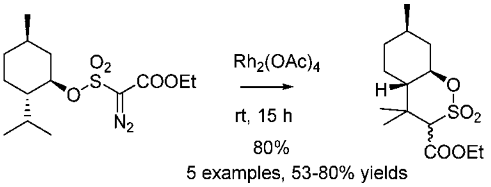
ABSTRACT



Carbethoxy diazosulfones and sulfonates, easily available from corresponding sulfones and sulfonates, undergo C–H insertion with preferential formation of six membered cyclic sulfones and sulfonates.

C−H insertion has emerged as a powerful and valuable synthetic method thanks to the pioneering works of Davies,[1] Doyle,[2] Du Bois,[3] Taber,[4] and others. A number of effective total syntheses have been performed with the use of C−H insertion as a key step.[5]

While it is possible to perform intermolecular C−H insertion effectively in some cases,[6] typically the intramolecular reaction is used to achieve the desired regioselectivity; in this case, formation of five-membered rings is greatly favored.[1b,3a,7] Four- and six-membered rings preferentially form only on select substrates.[8] Recently, however, Du Bois[4] demonstrated that this preference could be overturned in case of intramolecular nitrene C−H insertion in favor of 6-membered rings by the use of oxosulfamides.[4] Apparently, the difference in bond lengths and bond angles around the sulfur is responsible for the change of preference.

It appears that a logical extension of this approach would be an attempt at a carbene C−H insertion on a similar substrate to form a six-membered cyclic sulfone or sulfonate. This has not been done to our knowledge.

Several examples of C−H insertion leading to the construction of cyclic sulfones have been reported.[9] Formation of five-membered rings has been observed. However, the reported substrates disfavor or completely disallow formation of six-membered rings.

Consequently, we decided to undertake a study to investigate the feasibility of the preferential formation of six-

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[1] (a) Davies, H. M. L.; Hodges, L. M.; Matasi, J. J.; Hansen, T.; Stafford, D. G. *Tetrahedron Lett.* **1998**, *39*, 4417. (b) Davies, H. M. L.; Hansen, T. *J. Am. Chem. Soc.* **1997**, *119*, 9075. (c) Davies, H. M. L.; Hansen, T.; Hopper, D. W.; Panaro, S. A. *J. Am. Chem. Soc.* **1999**, *121*, 6509. (d) Davies, H. M. L.; Antoulinakis, E. G.; Hansen, T. *Org. Lett.* **1999**, *1*, 383. (e) Davies, H. M. L.; Antoulinakis, E. G. *Org. Lett.* **2000**, *2*, 4153.

[2] (a) Doyle, M. P.; Dyatkin, A. B.; Roos, G. H. P.; Canas, F.; Pierson, D. A.; Basten, A. V.; Mueller, P.; Polleux, P. *J. Am. Chem. Soc.* **1994**, *116*, 4507. (b) Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958.

[3] Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935.

[4] (a) Taber, D. F.; Petty, E. H. *J. Org. Chem.* **1982**, *47*, 4808. Taber, D. F.; Ruckle, R. E., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 7686. (b) Taber, D. F.; Sahli, A.; Yu, H.; Meagley, R. P. *J. Org. Chem.* **1995**, *60*, 6571. (c) Taber, D. F.; Malcolm, S. C. *J. Org. Chem.* **1998**, *63*, 3717.

[5] A review: Taber, D. F.; Stiriba, S.-E. *Organic Synthesis Highlights IV*; Wiley: Weinheim, Germany, 2000; pp 130−135.

[6] For instance: (a) See ref 3b. (b) Mueller, P.; Tohill, S. *Tetrahedron* **2000**, *56*, 1725. (c) Davies, H. M. L.; Ren, P.; Jin, Q. *Org. Lett.* **2001**, *3*, 3587.

[7] Lee, E.; Jung, K. W.; Kim, Y. S. *Tetrahedron Lett.* **1990**, *31*, 1023.

[8] For instance: (a) Cane, D. E.; Thomas, P. J. *J. Am. Chem. Soc.* **1984**, *106*, 5295. (b) Doyle, M. P.; Pieters, R. J.; Taunton, J.; Pho, H. Q.; Padwa, A.; Hertzog, D. L.; Precedo, L. *J. Org. Chem.* **1991**, *56*, 820.

[9] (a) Hrytsak, M.; Etkin, N.; Durst, T. *Tetrahedron Lett.* **1986**, *27*, 5679. (b) Babu, S. D.; Hrytsak, M. D.; Durst, T. *Can. J. Chem.* **1989**, *67*, 1071.

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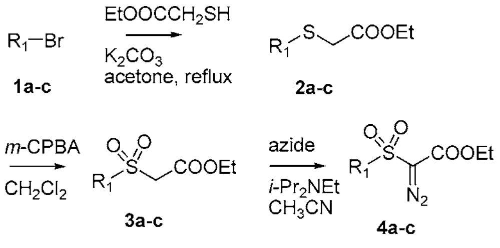
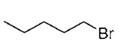
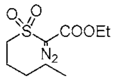
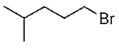
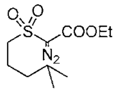
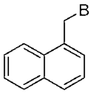
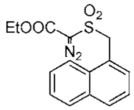
membered cyclic sulfones and sulfonates by intramolecular carbene C−H insertion. In this paper, we report the initial results of this study.

The required substrates (diazosulfones **4a**,**b**,**c** and diazosulfonates **7a**,**b**,**d)** were prepared according to two general methods.

Table 1. Preparation of Diazosulfone Substrates



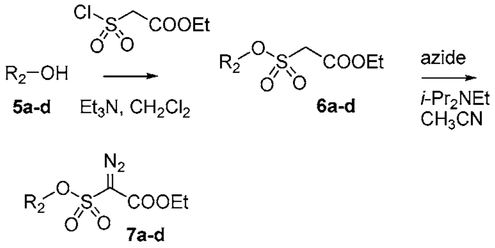
R₁Br	product	yields, % a	b	c
 **1a**	 **4a**	90	95	60
 **1b**	 **4b**	85	90	65
 **1c**	 **4c**	88	85	65

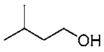
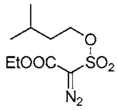
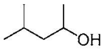
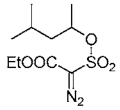
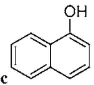
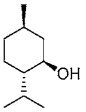
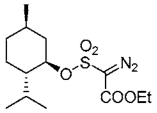
[a] Yield in the preparation of RSCH$_2$COOEt (**1a−c** → **2a−c**). [b] Yield in the preparation of RSO$_2$CH$_2$COOEt (**2a−c** → **3a−c**). [c] Yield in the preparation of the diazo compound (**3a−c** → **4a−c**).

For preparation of diazosulfones (Table 1) the appropriate alkyl bromide was subjected to nucleophilic substitution by ethyl mercaptoacetate in presence of potassium carbonate and catalytic amounts of sodium iodide in refluxing acetone. The resulting sulfide was oxidized to sulfone by excess of *m*-CPBA in methylene chloride. The obtained sulfone was subjected to diazo-transfer conditions (azide, triethylamine, acetonitrile). Initially used *p*-acetamidobenzenesulfonyl azide (ABSA) produced poor yields of diazo compounds, presumably due to side reactions similar to those observed in the preparation of α-nitrodiazocompounds.[10] Replacement of ABSA with *p*-nitrosulfonyl azide (NosN$_3$) improved the yields. Use of diisopropylethylamine (Hunig's base) in place of triethylamine was introduced for sulfonate substrates to suppress side reactions, but later was extended to sulfones as well.

The carbethoxydiazosulfonates were prepared according to the two-step sequence (Table 2).

Table 2. Preparation of Diazosulfonate Substrates



R₂OH	product	yields, % a	b
 **5a**	 **7a**	80	65
 **5b**	 **7b**	85	70
 **5c**	-	30	0
 **5d**	 **7d**	85	75

[a] Yield in the preparation of the sulfonate (**5a−d** → **6a−d**) [b] Yield in the preparation of the diazo compound (**6a−d** → **7a−d)**

The corresponding alcohols were treated with ethyl chlorosulfonylacetate (prepared as described from ethyl mercaptoacetate[11]) in presence of triethylamine. This procedure worked well for primary and secondary alcohols, but gave an unexpectedly low yield (30%) for naphthol (**5c**). The resulting sulfonates were subjected to the modified diazo-transfer conditions (*p*-nitrosulfonyl azide, di-*iso*-propylethylamine, acetonitrile). Similarly, use of *p*-nitrobezenesulfonyl azide proved superior. The yields were additionally increased by the use of diisopropylethylamine in place of triethylamine. Unexpectedly, complete decomposition was observed with naphthylsulfonate (**6c**) instead of formation of the diazo compound.

The obtained diazo compounds were subjected to C−H insertion conditions (rhodium(II) acetate, methylene chloride, slow addition at rt over 5 h, then 10 h at rt). Typically, complex mixtures of decomposition products formed. However, to our satisfaction, the desired cyclization products could be isolated from these mixtures. In case of the very first tested substrate (**4a**), the expected six-membered cyclization product (**8)** was isolated in 55% yield (Table 3).

The results of the cyclizations are summarized in Table 3. The possibility of insertion into a tertiary C−H was

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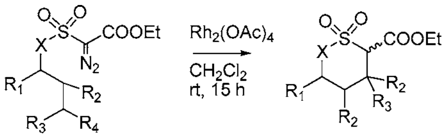
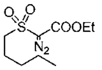
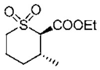
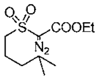
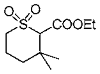
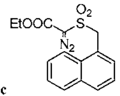
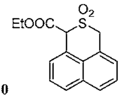
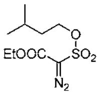
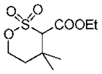
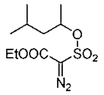
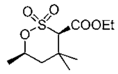
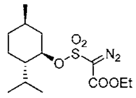
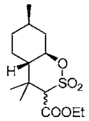
(10) (a) Charette, A. B.; Wurz, R. P.; Ollevier, T. *J. Org. Chem.* **2000**, *65*, 9252. (b) Wurz, R. P.; Lin, W.; Charette, A. B. *Tetrahedron Lett.* **2003**, *44*, 8845.

(11) Szymonifka, M. J.; Heck, J. V. *Tetrahedron Lett.* **1989**, *30*, 2869.

Table 3. C−H Insertion of the Sulfonate and Sulfone Substrates



substrate	product	yield, %
4a 	**8** 	55[a]
4b 	**9** 	56
4c 	**10** 	0
7a 	**11** 	53
7b 	**12** 	55[a]
7d 	**13a,b** 	80[b]

[a] Isolated as a single isomer. [b] Diastereomeric ratio varied from experiment to experiment, ranging from complete (the other diastereomer not detected by NMR) to 2:1 in favor of the same diastereomer.

demonstrated by substrates **4b**. Disappointingly, an attempt at insertion into aromatic position was unsuccessful. No cyclization products were isolated when substrate **4c** was subjected to reaction conditions. The possibility of formation of cyclic sulfonates in this transformation was confirmed by substrate **7a**. Sulfonates derived from secondary alcohols can also be effectively used, as demonstrated by substrates **7b** and **7d**. The cyclization product of **7b**, sulfonate **12**, was isolated as a single diastereomer in 55% yield. The cyclization of menthol sulfonate **7d** provided a potentially useful synthetic intermediate **13** in 80% yield. The diastereomeric ratio (**13a** to **13b**, Figure 1) in this reaction erratically changed from experiment to experiment, ranging from complete selectivity in favor of **13a** to 2:1 in favor of the same diastereomer (while the high yield apparently attributed to the decreased flexibility of the structure, was consistent). This behavior can be attributed to the changing nature of rhodium(II) acetate catalyst during the reaction, as noted by Du Bois in nitrene C−H insertions.[12] This could also provide a clue for the future optimization studies.

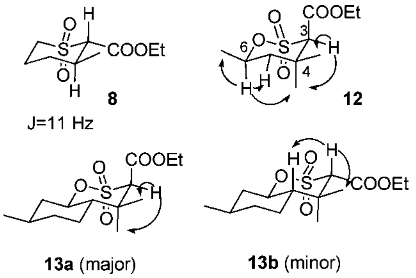


Figure 1. Spectroscopic evidence for stereochemistry of products.

The relative stereochemistry of the products was determined using standard NMR techniques (Figure 1). The larger coupling constant (11 Hz) between the two protons in **8a** suggested their diaxial arrangement, supporting the expected *trans*-arrangement of the methyl and carbethoxy groups. For compound **12**, presence of the NOE enhancements between the hydrogen at C3 and both of the methyl groups at C4, indicated the axial position of carbethoxy group. At the same time, NOE correlations between the hydrogen at C6 and one of the methyl groups at C4 indicated the equatorial position of the methyl at C6. Thus, overall *cis* relative arrangement between the methyl and carbethoxy groups is observed.

Similar correlations between the hydrogen at C3 and both methyl groups at C4 were observed in **13a** (the major diastereomer). Meanwhile, **13b** revealed NOE correlations between the hydrogen at C3 and only one of the methyl groups at C4, as well as with the hydrogen at C5, indicating the opposite stereochemistry. That additionally confirmed the assignment for **13a**.

Thus, we demonstrated the preferential formation of six-membered cyclic sulfones and sulfonates by C−H insertion. Further studies are being carried out, and the results will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data for new compounds, copies of ^{1}H NMR,^{13}C NMR, and NOE difference spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL062592H

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[12] Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378.