ORGANIC LETTERS

1999
Vol. 1, No. 6
873−875

Enantioselective Preparation of 4-Substituted Cyclohexenes by Radical Fragmentation of Sulfoxides†

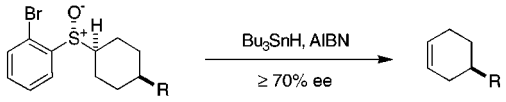
Christoph Imboden, Félix Villar, and Philippe Renaud*

Université de Fribourg, Institut de Chimie Organique, Pérolles, CH-1700 Fribourg, Switzerland

philippe.renaud@unifr.ch

Received July 23, 1999

ABSTRACT

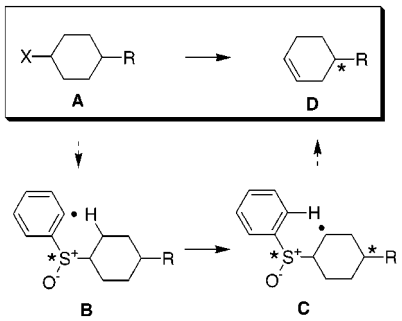


Radical fragmentation of *o*-bromophenyl sulfoxides is reported. Starting from enantiomerically pure material, 4-substituted cyclohexene derivatives have been prepared with enantiomeric excesses between 70% and 86%. The key step of the process is a diastereoselective abstraction of a hydrogen atom by the initial aryl radical. The highest enantiomeric exesses have been obtained in the presence of aluminum Lewis acids.

Recently, radical reactions have been applied to the preparation of enantiomerically enriched material.[1] All of the reported reactions were based on diastereoselective (chiral auxiliary control) or enantioselective (catalyst or reagent control) formation of carbon−carbon and carbon−hydrogen bonds.[2] No process involving bond breaking has been reported. In this Letter, we report the first example of this type: a radical fragmentation reaction of sulfoxides leading to highly enantiomerically enriched material has been designed. The key step of the process is a diastereoselective hydrogen atom abstraction.

The thermal syn elimination of sulfoxides is a well-known reaction occurring at temperatures higher than 200 °C when nonstabilized alkenes are formed.[3] This reaction has been applied in a pioneer work of Goldberg for the preparation of 4-substituted cyclohexene.[4] We were very interested in finding a mild alternative to this process. Our intention was to develop an enantioselective elimination procedure of H−X from 4-alkylcyclohexyl halides via a radical process. The strategy is depicted in Scheme 1 and is based on the conversion of the halide **A** into a sulfoxide followed by generation of an *o*-aryl radical **B** which undergoes 1,5-hydrogen atom translocation. The 2-sulfinylated radical **C** fragments extremely rapidly to the desired alkene **D**.[5] The fragmentation of a 2-phenylsulfinylated radical of type **C** is a fast and well documented process whose rate is approximately 10 times faster than the radical elimination of a bromine atom and only two times slower than the elimination of an iodine atom.[6−8] The stereoselectivity control of the

Scheme 1



† Part of the Ph.D. Dissertation of Christoph Imboden, Université de Fribourg, Switzerland (Diss. Nr. 1241).

(1) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1996.

(2) Chatgilialoglu, C.; Renaud, P. In *General Aspects of Free Radical Chemistry*; Alfassi, Z. B., Ed.; Wiley: Chichester, U.K., 1999; pp 501−538.

(3) Cram, D. J.; Kingsbury, C. A. *J. Am. Chem. Soc.* **1960**, *82*, 1810−1819.

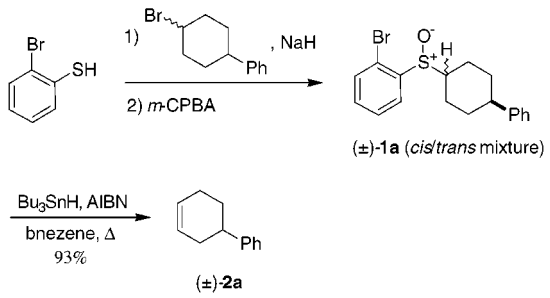
(4) Goldberg, S. I.; Sahli, M. S. *Tetrahedron Lett.* **1965**, 4441−4444. Goldberg, S. I.; Sahli, M. S. *J. Org. Chem.* **1967**, *32*, 2059−2062.

10.1021/ol990859p CCC: $18.00
Published on Web 08/24/1999

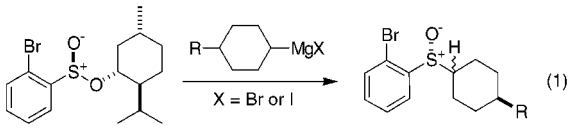
whole process should take place in the hydrogen atom abstraction step.[9]

To test the feasibility of the translocation−elimination cascade, the *o*-bromosulfoxide **1a** was prepared in racemic form from 2-bromothiophenol by alkylation with the corresponding bromide followed by oxidation with *m*-CPBA (Scheme 2). The cis/trans mixture of isomers of **1a** was treated with tin hydride AIBN in refluxing benzene to give 4-phenylcyclohexene **2a** in excellent yield.

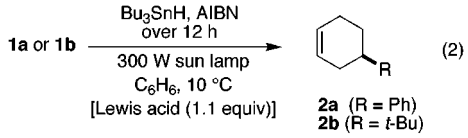
Scheme 2



The enantiomerically pure sulfoxides **1a** and **1b** were prepared from the diastereomerically pure menthyl (*S*)-2-bromophenylsulfinate **3** (eq 1).[10] The cis and trans isomers were separated by flash chromatograhy. To isolate satisfactory quantities of the minor cis isomer, epimerization of the α-center was achieved by deprotonation of *trans*-**1a** with LDA followed by protonation with 2,6-di-*tert*-butyl-4-methylphenol. This procedure afforded **1a** as a cis/trans 2:1 mixture of diastereomers. After flash chromatography, diastereomerically pure *cis*-**1a** (52%) and *trans*-**1a** (25%) were isolated. A nonoptimized isomerization procedure was used with *trans*-**1b** using water instead of 2,6-di-*tert*-butyl-4-methylphenol for the protonation step. It afforded **1b** as a cis/trans 1:1 mixture in 80% yield. Separation of the diastereomers was also possible by flash chromatography. The optical purity (>99% ee) of the four sulfoxides *trans*-**1a**, *cis*-**1a**, *trans*-**1b**, and *cis*-**1b** was determined by HPLC on a chiral column (Daicel, Chiralcel OB-H).



The cis and trans isomers of **1a** and **1b** were submitted separately to classical radical tin hydride reduction conditions according to eq 2 (slow addition of Bu_3SnH over 12 h, AIBN, 300 W sun lamp, 10 °C); results are shown in Table 1, entries 1−4.



The expected 4-substituted cyclohexenes **2a** and **2b** were isolated in 65−75% yields. Starting from the trans isomer, the cyclohexenes **2a** and **2b** were nearly racemic. However, *cis*-**1a** and *cis*-**1b** gave **2a** and **2b** with ee's of 70% and 80%, respectively. The absolute configuration the major isomer of **2b** was deduced from the comparison of the optical rotatory power with the one reported in the literature for (*R*)-**2b**.[11] The absolute configuration of **2a** was assigned by analogy to the case to **2b**. A model for the transition state of the reaction with *cis*-**1b** supported by ab initio calculations (UHF 6-31G*) is reported in Figure 1. The cyclohexane ring lies in a chair conformation, and the sulfinyl group occupies an axial position. The distance between the C_{ar}(•) and the abstracted hydrogen atom was set at 1.4 Å. The preferred transition state **E** ($\Delta\Delta H_f = 0$ kcal/mol) minimizes the steric interactions between the oxygen atom of the sulfoxide and the cyclohexyl group. The minor transition state **F** ($\Delta\Delta H_f = +2.0$ kcal/mol) is destabilized by interaction of the oxygen atom with the cyclohexyl ring.

Table 1. Radical Mediated Fragmentation of Sulfoxides **1a** and **1b** According to eq 2

	sulfoxide	Lewis acid	product	yield [%]	ee [%]
1	*trans*-**1a**	none	**2a**	75	0
2	*cis*-**1a**	none	**2a**	65	70 (*R*)
3	*trans*-**1b**	none	**2b**	70	0
4	*cis*-**1b**	none	**2b**	70	80 (*R*)
5	*cis*-**1a**	MAD[a]	**2a**	60	76 (*R*)
6	*cis*-**1a**	MADPP[b]	**2a**	65	84 (*R*)
7	*cis*-**1a**	MADP[c]	**2a**	57	86 (*R*)

[a] MAD = methylaluminum di(2,6-di-*tert*-butyl-4-methylphenoxide). [b] MADPP = methylaluminum di(2,6-diphenylphenoxide). [c] MADP = methylaluminum diphenoxide.

(5) For a related hydrogen abstraction/fragmentation process involving sulfones, see: Brown, C. D. S.; Dishington, A. P.; Shiskin, O.; Simpkins, N. S. *Synlett* **1995**, 943−914. Vandort, P. C.; Fuchs, P. L. *J. Org. Chem.* **1997**, *62*, 7142−7147.

(6) For mechanistical and kinetic studies, see: Wagner, P. J.; Sedon, J. H.; Lindstrom, M.-J. *J. Am. Chem. Soc.* **1978**, *100*, 2579−2580. Synthetic applications: Shevlin, P. B.; Boothe, T. J.; Greene, J. L.; Willcott, M. R.; Inners, R. R.; Cornelis, A. *J. Am. Chem. Soc.* **1978**, *100*, 3874−3879. Russel, G. A.; Tashtoush, H.; Ngoviwatchai, M. *J. Am. Chem. Soc.* **1984**, *106*, 4622−4623.

(7) For an early synthetic application of the radical fragmention of β-sulfinylated radicals, see: Miyamato, N.; Furuoka, D.; Utimoto, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 503−504. For a recent application to the preparation of allenes, see: Delouvrié, B.; Lacôte, E.; Fensterbank, L.; Malacria, M. *Tetrahedron Lett.* **1999**, *40*, 3565−3568.

(8) For an application in asymmetric synthesis, see: (a) Malacria, M.; Lacôte, E.; Delouvrié, B.; Fensterbank, L. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2116−2118. For a related example based on sulfimide, see: (b) Clark, A. J.; Rooke, S.; Sparey, T. J.; Taylor, P. C. *Tetrahedron Lett.* **1996**, *37*, 909−912.

(9) The diastereoselectivity of hydrogen transfer has not been investigated in a systematic fashion. For an isolated example of diastereoselective hydrogen transfer, see: Bogen, S.; Malacria, M. *J. Am. Chem. Soc.* **1996**, *118*, 3992−3993.

(10) Imboden, C.; Renaud, P. *Tetrahedron: Asymmetry* **1999**, *10*, 1051−1060.

(11) Sodozai, S. K.; Lepoivre, J. A.; Dommisse, R. A.; Alderweireldt, F. C. *Bull. Soc. Chim. Belg.* **1980**, *89*, 637−642.

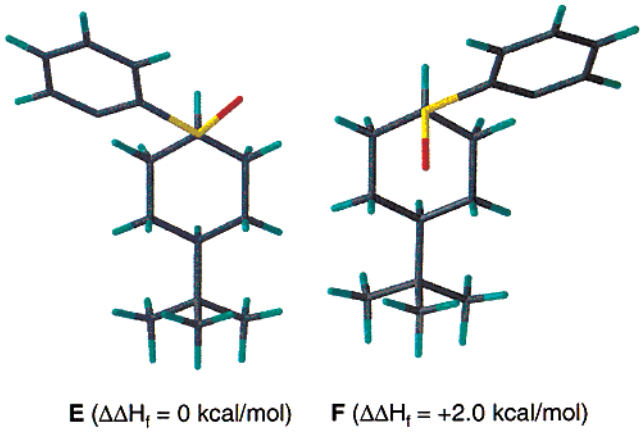
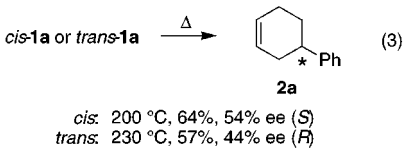


Figure 1. Calculated transitions states (ab initio UHF 6-31g*) **E** and **F** leading to (*R*)-**2b** (major) and (*R*)-**2b** (minor), respectively.

According to the models **E** and **F**, complexation of the oxygen atom of the sulfinyl group by a Lewis acid should destabilize **F** relative to **G** due to an increase of steric interactions between the complexed oxygen atom and the cyclohexyl ring.[12] This hypothesis was confirmed by our experiments with methylaluminum di(aryloxide) derivatives (Table 1, entries 5−7). In the presence of methylaluminum di(2,6-di-*tert*-butyl-4-methylphenoxide) (= MAD),[13] the selectivity went slightly up (entry 5, 76% ee) relative to the reaction in the absence of Lewis acid (entry 2, 70% ee). Better results were obtained with less bulky Lewis acid such as methylaluminum di(2,6-diphenylphenoxide) and methylaluminum diphenoxide (entries 6 and 7, 84% and 86% ee) indicating that presumably only partial complexation was taking place with the sterically highly hindered MAD.

For comparison purposes, the thermal elimination of the sulfoxide *cis*-**1a** and *trans*-**1a** was examined (eq 3). The cis isomer fragmented at 200 °C and gave (*S*)-**2a** in 64% yield and moderate enantioselectivity (54% ee). The trans isomer gave (*R*)-**2a** in 57% yield and 44% ee.



(3)

In conclusion, we have presented here a new way for the elimination of sulfoxides under extremely mild conditions. This reaction is expected to find applications for regio-, diastereo-, and enantioselective preparation of alkenes. For instance, we have shown that by using enantiomerically pure 4-substituted cyclohexyl sulfoxides, it is possible to prepare enantiomerically enriched 4-substituted cyclohexenes. Further applications to other classes of chiral alkenes such as tropidine alkaloids are currently being investigated in our laboratory.

Acknowledgment. This work was funded by the Fonds National Suisse de la Recherche Scientifique and by the Office Fédéral pour l'Education et la Science (project COST-D2). We thank Professor Max Malacria for helpful discussions.

Supporting Information Available: Experimental details for all procedures including full characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL990859P

(12) For a recent review on the use of Lewis acids in radical reaction, see: Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2562−2579. For the use of Lewis acids in radical reactions involving sulfoxides, see ref 8a and Waldner, A.; De Mesmaeker, A.; Hoffmann, P.; Mindt, T.; Winkler, T. *Synlett* **1991**, 101−104. Renaud, P.; Ribezzo, M. *J. Am. Chem. Soc.* **1991**, *113*, 7803. Curran, D. P.; Kuo, L. H. *J. Org. Chem.* **1994**, *59*, 3259−3261. Renaud, P.; Bourquard, T.; Gerster, M.; Moufid, N. *Angew Chem., Int. Ed. Engl.* **1994**, *33*, 1601−1603. Renaud, P.; Moufid, N.; Kuo, L. H.; Curran, D. P. *J. Org. Chem.* **1994**, *59*, 3547−3552. Renaud, P.; Bourquard, T.; Gerster, M.; Moufid, N. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1601−1603. Renaud, P.; Bourquard, T.; Carrupt, P.-A.; Gerster, M. *Helv. Chim. Acta* **1998**, *81*, 1048−1063. Toru, T.; Watanabe, Y.; Tsusaka, M.; Ueno, Y. *J. Am. Chem. Soc.* **1993**, *115*, 10464−10465. Toru, T.; Watanabe, Y.; Mase, N.; Tsusaka, M.; Hayakawa, T.; Ueno, Y. *Pure Appl. Chem.* **1996**, *68*, 711−714. Mase, N.; Watanabe, Y.; Ueno, Y.; Toru, T. *J. Org. Chem.* **1997**, *62*, 7794−7800.

(13) Maruoka, K.; Itoh, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 4573−4576. Saito, S.; Yamamoto, H. *Chem. Commun.* **1997**, 1585−1592.