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An Efficient and Straightforward Access to Sulfur Substituted [2.2]Paracyclophanes: Application to Stereoselective Sulfenate Salt Alkylation

Jean-François Lohier,[†] Florian Foucoin,[†] Paul-Alain Jaffrès,[‡] José I. Garcia,[§] Jana Sopková–de Oliveira Santos,[||] Stéphane Perrio,*[,†] and Patrick Metzner[†]

Laboratoire de Chimie Moléculaire et Thio-organique, ENSICAEN, Université de Caen Basse-Normandie, CNRS, 6 Boulevard du Maréchal Juin, 14050 Caen, France, Laboratoire de Chimie Electrochimie Moléculaire Chimie Analytique, Université de Bretagne Occidentale, CNRS, 6 Avenue Le Gorgeu, 29238 Brest, France, Departamento de Química Orgánica, Instituto de Ciencia de Materiales de Aragon, Universidad de Zaragoza−CSIC, 50009 Zaragoza, Spain, and Centre d'Etudes et de Recherche sur le Médicament de Normandie, Université de Caen Basse-Normandie, 5 Rue Vaubénard, 14032 Caen, France

stephane.perrio@ensicaen.fr

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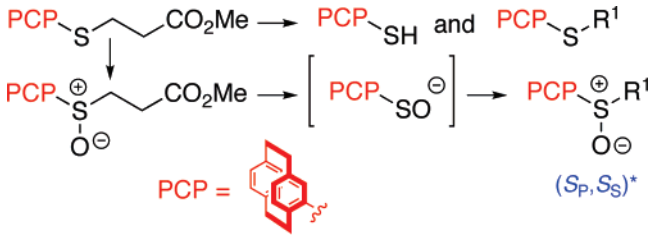
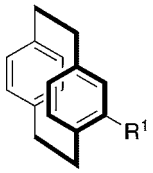
ABSTRACT



A straightforward and high-yielding access to various [2.2]paracyclophanes possessing a sulfur-based functional group is reported, the key step being a S_EAr reaction mediated by a sulfonium salt. The versatility of the methodology was exemplified by an original application in sulfenate salt chemistry, from which a remarkable chirality transfer was observed.

[2.2]Paracyclophane **1** is the parent molecule for a fascinating family of compounds consisting of two benzene rings held face-to-face by two ethano bridges at the para positions (Figure 1). The strong electronic interaction between the arene fragments combined with rigidly defined geometric relationships between substituents gives rise to the unique properties of these molecules, with successful application in various areas, including polymers, materials, and planar chiral catalysts.[1] Considering the great potential of these systems, it is however surprising that research in this field is still in its infancy when compared to the analogous ferrocenyl or η^6-arene transition metal complexes. The most



1 R^1 = H
2 R^1 = SH
3 R^1 = SAlkyl
4 R^1 = $SCH_2CH_2CO_2Me$
5 R^1 = $S(O)CH_2CH_2CO_2Me$
6 R^1 = $S(O)CH_2CH_2SiMe_3$

Figure 1. [2.2]Paracyclophane and sulfur derivatives.

[†] Laboratoire de Chimie Moléculaire et Thio-organique.
[‡] Laboratoire de Chimie Electrochimie Moléculaire Chimie Analytique.
[§] Instituto de Ciencia de Materiales de Aragon.
[||] Centre d'Etudes et de Recherche sur le Médicament de Normandie.

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significant reason appears to be the lack of attractive strategies for the preparation of functionalized structures, associated also to a limited number of commercially available starting materials.

In this regard, very few derivatives incorporating a sulfur function, even in racemic form, have been described so far.[2−6] As a prominent example, (±)-[2.2]paracyclophane-4-thiol **2** was mentioned[2] for the first time in 2001, the few syntheses of which still suffering from multistep derivatization reactions and low overall yields.[7] To overcome these severe shortcomings, we were interested in developing a precursor that could facilitate the synthesis of a variety of sulfur-containing [2.2]-paracyclophanes, including previously cited thiol **2** but also related sulfides[8] **3**. β-Sulfanyl ester **4** was postulated as a suitable candidate for the following criteria. In principle, it should be prepared from simple paracyclophane **1** using an elegant but surprisingly overlooked S_EAr reaction mediated by a sulfonium salt.[9,10] Conversion into **2** and **3** should then be directly secured according to a retro-Michael pathway.[9]

Having a current interest into sulfenate salts[11] (sulfur nucleophiles with general structure R^1SO^-), oxidation of **4** into the analogous sulfinyl compound **5** could also permit a straightforward extension toward this unusual chemistry.[12] As sulfenates are normally converted into sulfoxides upon quenching with soft electrophiles[13] (*S*-alkylation), the investigation we suggest using paracyclophane-based species could provide a diastereoselective version of this reaction. Compared to the successful but scarce precedents, an obvious originality concerns the unprecedented use of planar chirality as element of stereocontrol.[14] Full accounts on this work are provided in this manuscript.

Symmetrical sulfoxide **7**[15] was activated by triflic anhydride to give a highly electrophilic intermediate, which was further reacted with unsubstituted [2.2]paracyclophane **1** to produce the corresponding sulfonium trifluoromethanesulfonate **8** (Figure 2). Subsequent treatment with Et_3N induced a single β-elimination-based dealkylation and delivered the pivotal intermediate **4** in 75% yield. Conversion of **4** into the targeted compounds **2**−**5** was then cleanly achieved as detailed below. Reaction with *t*-BuOK with subsequent acidification afforded thiol **2** in 89% yield, thereby providing by far the most elegant access[2] to this compound. Use of alkyl halides as alternative electrophilic partners furnished also, in a single procedural step, the analogous sulfides **3** (85−93% yield). Finally, oxidation of **4** with H_2O_2[16] gave the sulfenate precursor **5** in 96% yield as an inseparable 3:2 diastereoisomeric mixture. Attractive features of the syntheses include introduction of the sulfur moiety on the paracyclophane core in an extremely simple way with stable and readily available reagents, convenient protocols appropriate for scalability, and straightforward purifications.

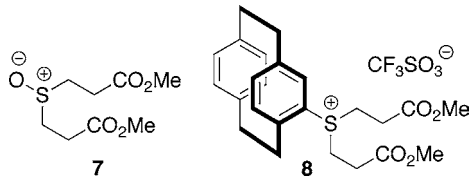

Figure 2. Intermediates in the synthesis of **4**.

(±)-[2.2]Paracyclophane-4-sulfenic acid salt was generated in THF by deprotonation of **5** with *t*-BuOK at low temperature (−78 °C), followed by a spontaneous retro-Michael reaction. After in situ quenching with alkyl halides, we were delighted to uniformly isolate in excellent yields the anticipated sulfoxides as single diastereoisomers **9a**−**c** (Table 1, entries 1−3).[17] The (S_P,S_S)* configuration was unambigu-

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(3) Sulfides: (a) Menichetti, S.; Faggi, C.; Lamanna, G.; Marrocchi, A.; Minuti, L.; Taticchi, A. *Tetrahedron* **2006**, *62*, 5626−5631. (b) Pelter, A.; Mootoo, B.; Maxwell, A.; Reid, A. *Tetrahedron Lett.* **2001**, *42*, 8391−8394. (c) Marchand, A.; Maxwell, A.; Mootoo, B.; Pelter, A.; Reid, A. *Tetrahedron* **2000**, *56*, 7331−7338. (d) Hou, X.-L.; Wu, X.-W.; Dai, L.-X.; Cao, B.-X.; Sun, J. *J. Chem. Soc., Chem. Commun.* **2000**, 1195−1196.

(4) Sulfoxides: (a) Hitchcock, P. B.; Rowlands, G. J.; Seacome, R. J. *Org. Biomol. Chem.* **2005**, *3*, 3873−3876. (b) Hitchcock, P. B.; Rowlands, G. J.; Parmar, R. *J. Chem. Soc., Chem. Commun.* **2005**, 4219−4221. (c) Reich, H. J.; Yelm, K. E. *J. Org. Chem.* **1991**, *56*, 5672−5679.

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(6) Sulfonic acid: (a) van Lindert, H. C. A.; Koeberg−Telder, A.; Cerfontain, H. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 379−388. (b) van Lindert, H. C. A.; van Doorn, J. A.; Bakker, B. H.; Cerfontain, H. *Recl. Trav. Chim. Pays-Bas* **1996**, *115*, 167−178.

(7) The sulfur atom was introduced via a Newman−Kwart reaction, treatment of lithiated species with elemental sulfur or a Pd-catalysis with triisopropylsilanethiol. See ref 2.

(8) To the best of our knowledge, only the *t*-butylsulfanyl derivative of **3** (alkyl = *t*-Bu) has been described so far. See ref 4a.

(9) (a) Becht, J.-M.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* **2003**, *68*, 5758−5761. (b) Becht, J.-M.; Wagner, A.; Mioskowski, C. *Tetrahedron Lett.* **2004**, *45*, 7031−7033.

(10) It was previously shown that the aromatic sulfonation of **1** with sulfur trioxide, in the presence of 1,4-dioxane, proceeds cleanly to afford [2.2]paracyclophane-4-sulfonic acid. See ref 6.

(11) (a) Sandrinelli, F.; Perrio, S.; Beslin, P. *J. Org. Chem.* **1997**, *62*, 8626−8627. (b) Sandrinelli, F.; Perrio, S.; Averbuch-Pouchot, M.-T. *Org. Lett.* **2002**, *4*, 3619−3622. (c) Sandrinelli, F.; Fontaine, G.; Perrio, S.; Beslin, P. *J. Org. Chem.* **2004**, *69*, 6916−6919. (d) Sandrinelli, F.; Boudou, C.; Caupène, C.; Averbuch-Pouchot, M.-T.; Perrio, S.; Metzner, P. *Synlett* **2006**, 3289−3293. (e) Boudou, C.; Bergès, M.; Sagnes, C.; Sopková−de Oliveira Santos, J.; Perrio, S.; Metzner, P. *J. Org. Chem.* **2007**, *72*, 5403−5406.

(12) (a) Caupène, C.; Boudou, C.; Perrio, S.; Metzner, P. *J. Org. Chem.* **2005**, *70*, 2812−2815. (b) Maitro, G.; Prestat, G.; Madec, D.; Poli, G. *J. Org. Chem.* **2006**, *71*, 7449−7454. (c) Maitro, G.; Vogel, S.; Prestat, G.; Madec, D.; Poli, G. *Org. Lett.* **2006**, *8*, 5951−5954. (d) Colobert, F.; Ballesteros−Garrido, R.; Leroux, F. R.; Ballesteros, R.; Abarca, B. *Tetrahedron Lett.* **2007**, *48*, 6896−6899. (e) Maitro, G.; Vogel, S.; Sadaoui, M.; Prestat, G.; Madec, D.; Poli, G. *Org. Lett.* **2007**, *9*, 5493−5496.

(13) For a review: O'Donnell, J. S.; Schwan, A. L. *J. Sulfur Chem.* **2004**, *25*, 183−211.

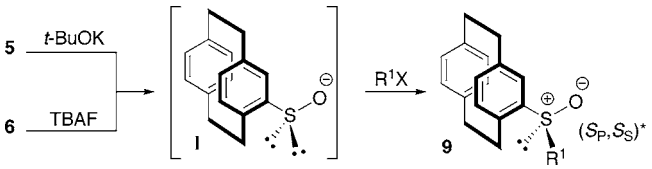
(14) Excellent diastereocontrols were already reported using isoborneol, cysteine and (α)-phenylethylamine derivatives. See ref 13.

(15) This compound was prepared in a 93% overall yield by Michael addition of 3-sulfanylpropanoic acid methyl ester on methyl acrylate, followed by oxidation with $NaIO_4$. See Supporting Information.

(16) An H_2O_2/2,2,2-trifluoroethanol combination was used: Bégué, J.-P.; Bonnet-Delpon, D.; Crousse, B. *Synlett* **2004**, 18−29.

(17) Previously reported [2.2]paracyclophan-4-yl sulfoxides were synthetized using oxidation or Andersen approaches. See ref 4.

Table 1. Sulfoxides by Sulfenate Alkylation



entry	precursor	R^1X	conditions[a]	product[b]	yield[c]
1	**5**	BnBr	*t*-BuOK, −78 °C	**9a**	82
2	**5**	MeI	*t*-BuOK, −78 °C	**9b**	88
3	**5**	EtI	*t*-BuOK, −78 °C	**9c**	90
4	**5**	BnBr	*t*-BuOK, −40 °C	**9a**	80
5	**5**	BnBr	*t*-BuOK, −0 °C	**9a**	77
6	**6**	BnBr	TBAF, 60 °C	**9a**	72

[a] Commercial 1M *t*-BuOK or TBAF solutions (1.1 equiv) in THF and R^1X (1.1−2.1 equiv). [b] No sulfenic ester, which might arise through a competing *O*-alkylation of the ambident sulfenate was detected. [c] Isolated yield.

ously assigned by X-ray crystallography.[18] A perfect diastereoselectivity was observed likely when the reaction was carried at higher temperatures (entries 4 and 5). Having very recently identified sulfoxides displaying the 2-(trimethylsilyl)ethyl moiety as an alternative source of sulfenates according to a fluoride-triggered fragmentation, we also tested this methodology.[19] Treatment of silyl sulfoxide **6**[20] with TBAF in the presence of benzyl bromide led efficiently to diastereoisomer **9a** as the sole reaction product (entry 6).

The remarkably high diastereoselectivity observed can be accounted for by the preferred conformation of the intermediate sulfenate **I**, with the S−O bond lying in the plane of the aromatic ring and oriented toward the ortho arene hydrogen (Scheme of Table 1). If this conformational preference is maintained in the alkylation transition state, the nucleophilic attack proceeds from the more readily available sulfur lone pair, away from the paracyclophane lower deck. This induction model is fully supported by the results of a molecular modeling study as summarized in Figure 3 (see also Supporting Information for additional comments).[21]

This approach involving sulfenates was then compared with the alternative and traditional strategy toward sulfoxides, based on the oxidation of the corresponding thioethers. As shown in Table 2, the degree of stereocontrol highly depends on the reaction conditions. Oxidation of benzyl compound **5a** with H_2O_2 or *m*-CPBA led to poor diastereoselectivities (entries 1 and 2), whereas improvement was observed (30:70 ratio) with the Davis *N*-sulfonyloxaziridine **11a**[22] (entry

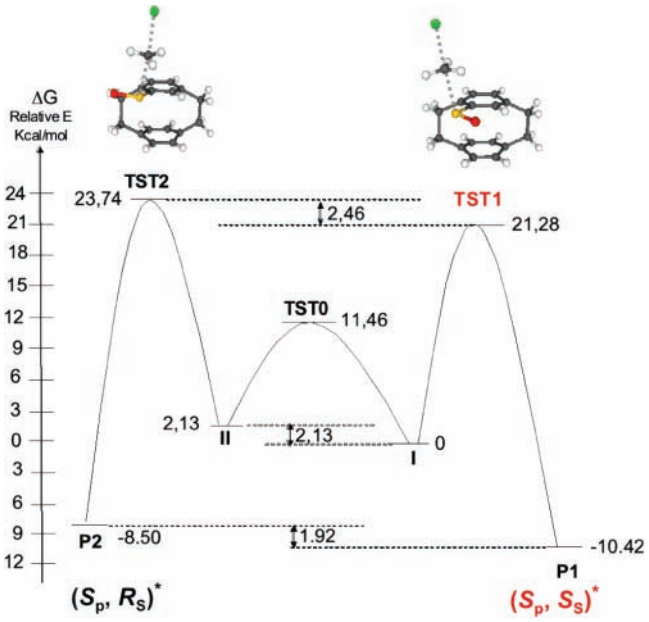
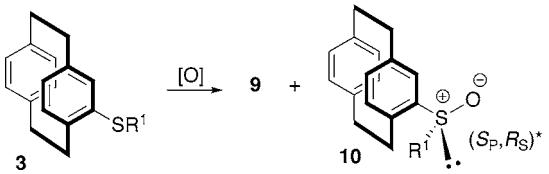


Figure 3. Calculated (HF/6-31+G*) sulfenate alkylation pathway.

3). Optimal results with diastereoisomeric compositions[23] up to 9:91 were reached using the reagent **11b**[11d] derived from pinacolone (entries 4−6). The major product **10** being (S_P,R_S)* configured, the stereochemical outcome is complementary to that available with the sulfenate process.

Table 2. Sulfoxides by Thioether Oxidation



entry	sulfide	R^1	oxidant	ratio **9:10**	yield[a]
1	**3a**	Bn	H_2O_2	42:58	92
2	**3a**	Bn	*m*-CPBA	60:40	77
3	**3a**	Bn	**11a**[b]	30:70	68
4	**3a**	Bn	**11b**[c]	16:84	70
6	**3b**	Me	**11b**[c]	9:91	90
5	**3c**	Et	**11b**[c]	19:81	82

[a] Isolated yield. [b] (±)-*trans*-3-Phenyl-2-(phenylsulfonyl)loxaziridine. [c] (±)-*trans*-3-(*t*-Butyl)-3-methyl-2-(phenylsulfonyl)oxaziridine.

An interesting stereochemical point also to mention is that oxidation of the *t*-butyl sulfide of **3** (R^1 = *t*-Bu) with both

(18) Crystal structures of **9** showed that the S−O bond is almost in the same plane than the arene, the oxygen atom oriented towards the ortho proton (torsional angle values between S−O and C4−C5 ranging from −8.84 to 1.8°). See Supporting Information.

(19) Foucoin, F.; Caupène, C.; Lohier, J.-F.; Sopková −de Oliveira Santos, J.; Perrio, S.; Metzner, P. *Synthesis* **2007**, 1315−1324.

(20) Sulfoxide **6** was prepared in an 78% overall yield by a regioselective radical addition of thiol **2** on vinyltrimethylsilane in the presence of a catalytic amount of AIBN (1%), followed by oxidation. See Supporting Information.

(21) Previously reported conformational studies involving calculations concern exclusively ethenesulfenate species. See ref 13.

(22) (a) Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703−5742. (b) Vishwakarma, L. C.; Stringer, O. D.; Davis, F. A. *Org. Synth.* **1988**, *66*, 203−210. (c) Davis, F. A.; Chattopadhyay, S.; Towson, J. C.; Lal, S.; Reddy, T. *J. Org. Chem.* **1988**, *53*, 2087−2089.

(23) A remarkable difference in chemical shift, resulting of the strong anisotropy of the sulfinyl group, is observed for the signal of one diastereotopic H2. It occurs in the range of 2.6−2.9 ppm in **9** but is substantially deshielded at δ = 4.1−4.2 ppm in **10**. See also ref 4a.

m-CPBA or $NaIO_4$ was previously shown by Rowlands to furnish exclusively diastereoisomer **9**.[4a] A probable interpretation for the reversal in diastereoselectivity is illustrated in Figure 4.[24] When R^1 = methyl, ethyl, or benzyl, we

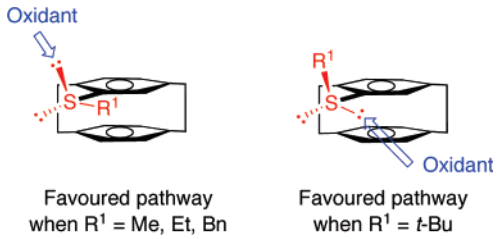


Figure 4. Preferred conformations for thioether oxidation.

assume that thioether **3** adopts a conformation with the alkylsulfanyl group lying in the arene plane opposite to the bridge. One of the sulfur lone pairs is hence exposed on the exo face of the paracyclophane and reacts selectively with the oxidant to afford diastereoisomer **10**. Switching to a bulkier substituent such as R^1 = *t*-Bu, increasing eclipsing interactions restrict the sulfanyl substituent to the conformation illustrated, in which neither of the sulfur lone pairs is on the exo face. Consequently, the oxidant is forced to approach the endo face past the bridge to afford diastereoisomer **9**.

In conclusion, we report in this paper an elegant access to a range of paracyclophanyl thiol, sulfides, and sulfoxides. The latter were also efficiently prepared as single diastereoisomers from the related sulfenate salt. Even if all compounds were produced in racemic forms, the presented methodology already affords an appreciable synthetic progress in the area. Access to enantiopure substrates is currently investigated in our laboratory and will be reported in due course.

Acknowledgment. We acknowledge financial support from the "Ministère de la Recherche", CNRS (Centre National de la Recherche Scientifique), the "Région Basse-Normandie", and the European Union (FEDER funding). We also thank Stéphan Pellinghelli (ENSICAEN), Cédric Boudou (CNRS), and Anaïs Prunier (University of Caen Basse Normandie) for the synthesis of starting materials.

Supporting Information Available: General methods of the experimental section, full spectroscopic data, X-ray structure of **9**, and sulfenate conformation study. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) Similar precedents have already been reported with tricarbonyl(η^6-arene)chromium(0) complexes: (a) Pérez-Encabo, A.; Perrio, S.; Slawin, A. M. Z.; Thomas, S. E.; Wierzchleyski, A. T.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1993**, 1059−1062. (b) Pérez-Encabo, A.; Perrio, S.; Slawin, A. M. Z.; Thomas, S. E.; Wierzchleyski, A. T.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 629−642.