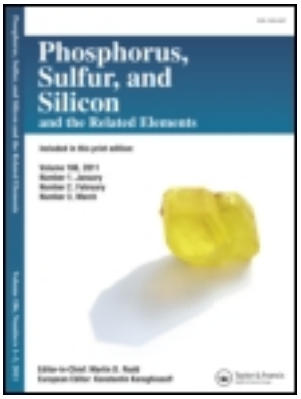

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Unsymmetrical Target Disulfides from Transient Sulfenic Acids

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UNSYMMETRICAL TARGET DISULFIDES FROM TRANSIENT SULFENIC ACIDS

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Abstract *In accordance with our research interests devoted to the development of synthetic procedures involving sulfenic acids as intermediates, their condensation with various thiols has been exploited as an easy and versatile methodology to obtain unsymmetrical disulfides. Even if this reaction is well known, to the best of our knowledge it has never been used before as a methodology to synthesize unsymmetrical disulfides. The mild generation of mono-, di-, and tri-sulfenic acids from different sulfoxide precursors, depending on the required reaction conditions, allows the presence of even base/acid-sensitive and thermolabile functional groups and the synthesis, in excellent yields, of various kinds of unsymmetrical disulfides, some of which carry typical moieties of natural substances.*

Keywords Condensation; disulfides; sulfenic acids; thiols

INTRODUCTION

It is generally assumed that the biological function of the cysteine thiol moiety depends, to a large extent, on the oxidation of the SH group to the cystine disulfide bridge, through the generation of the cysteine sulfenic acid.[1] A sulfenic acid intermediate is also formed in the enzymatic reactions involving the methionine sulfoxide reductases, repair enzymes that reduce methionine sulfoxide oxidized by reactive oxygen or nitrogen species.[2] The biological role that sulfenic acids play appears significant not only in oxidative stress response but in several other cellular processes.

Indeed, sulfenic acids cannot be considered casual intermediates in synthetic processes and their transient nature has been used with cleverness in the synthesis of sulfur-containing molecules[3] or in the removal of a sulfinyl moiety to obtain compounds not easily accessible by different procedures.[4] Sulfenic acid additions/eliminations are stereospecific, and highly stereoselective processes are sometimes observed in the formation of a sulfur stereogenic center of the sulfoxide moiety generated from the sulfenic one; both these

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characteristics allow the stereo-controlled formation of molecules with definite structural features.

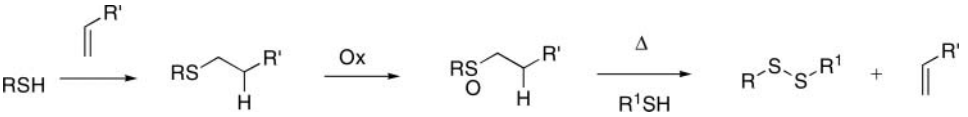
The β-elimination of sulfenic acids from suitable sulfoxides can be regarded as one of the best ways for their generation and involvement in intra- or intermolecular *syn*-addition to unsaturated compounds or in coupling reactions with other sulfurated molecules, as well as one of the best ways for the extrusion of a sulfinyl moiety. Several applications of both of these synthetic aspects of the sulfenic acid chemistry have been reported in the recent literature.[5]

As part of a research program centered on the development of synthetic procedures involving sulfenic acids as intermediates,[6] we forecast that the condensation reaction of in situ generated sulfenic acids with thiols could represent an efficient procedure to obtain unsymmetrical disulfides. Although this reaction has been previously reported for trapping transient sulfenic acids and recognizing their involvement in some organic processes,[7] it has never been regarded as a general methodology for the synthesis of disulfides. In this article we describe the controlled generation of the sulfenyl moiety from suitable precursors and the development of the sulfenic acid/thiol condensation for the construction of the disulfide bridge between two different structural skeletons.

In particular, we are now developing libraries of molecules containing at least two small sugar units, linked by spacers of different lengths and flexibility, as pro-apoptotic inducers, taking into account the pivotal role of apoptosis regulation in both the controlled expansion and removal of immune cells and cancer progression and therapy.[8] Because the control of molecular architecture and sugar residue distance can play a significant role in the enhancement of cytotoxic activity, the introduction into the molecular skeleton of the disulfide bond, present in many biological systems and hydrolysis resistant, can provide a basis for the development of a new series of biologically active glycoconjugates.

RESULTS AND DISCUSSION

Our synthetic strategy for the formation of the disulfide bridge has already been described.[9] The desired products can be obtained by a three-step procedure, starting from a thiol to prepare the suitable sulfoxide precursor of the corresponding sulfenic acid in two steps and concluding the process with the condensation of the in situ generated sulfenic acid with a thiol—different from the one acting as a starting product toward the sulfenic acid—to obtain unsymmetrical disulfides (Scheme 1).

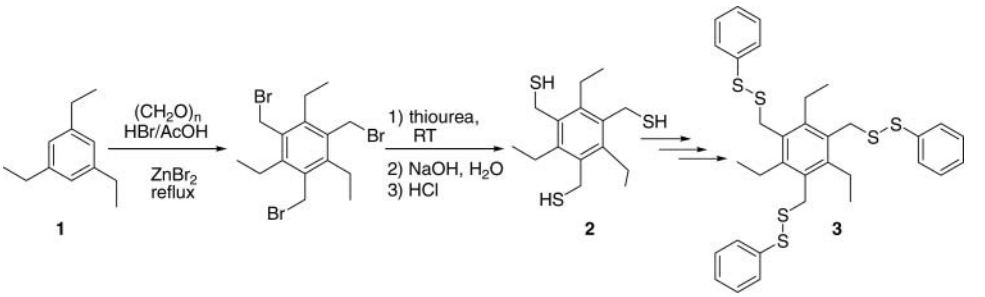


Scheme 1

The generation of the sulfenic acid is achieved by β-*syn*-elimination, through the thermolysis of a sulfoxide bearing at least a mobile hydrogen in β-position to the sulfinyl group.[6]

The methodology offers the possibility of reacting even structurally complex thiols, such as **2**, giving access to unconventional disulfides such as compound **3**, showing a tripodal skeleton (Scheme 2). The tripodal disulfide **3** has been prepared starting from 1,3,5-triethylbenzene (**1**) to obtain thiol **2**, following literature procedures.[10] Thiol **2** underwent

the three steps procedure mentioned above, and compound **3** was obtained in 55% total yield.[11]

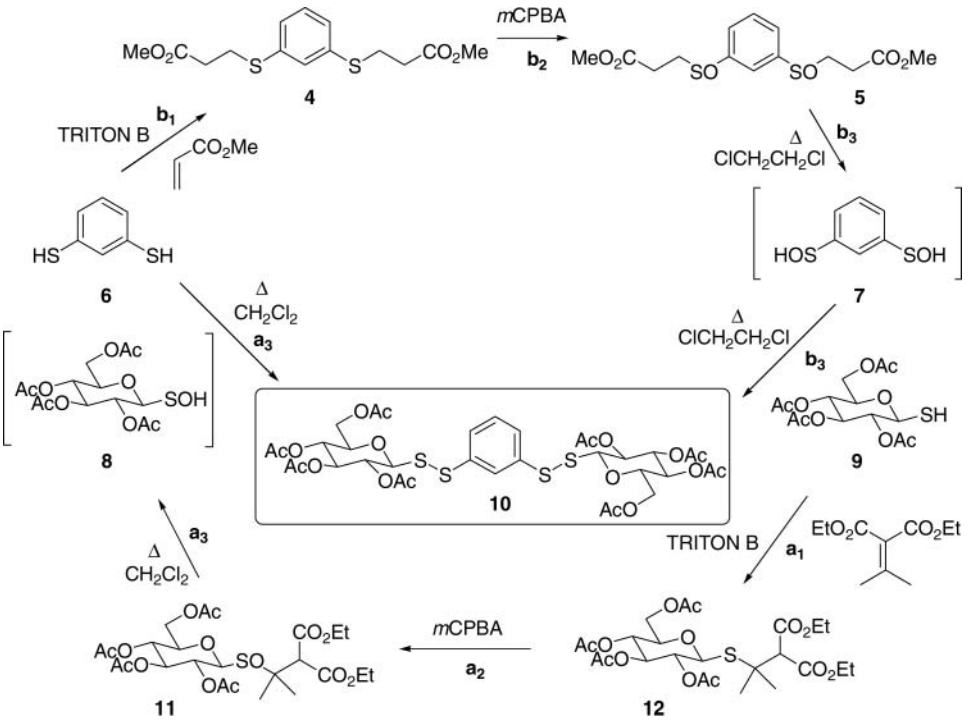


Scheme 2

Compound **3** has been synthesized as a model for the development of a small library of tripodal molecules. The use of the 1,3,5-trisubstituted-2,4,6-triethylbenzene scaffold in supramolecular chemistry has emerged rapidly. Several receptor molecules for cationic and anionic guests have been designed by placing various conformationally controlled binding groups around the benzene platform. The presence of the disulfide bonds lends characteristics of flexibility and the possibility of reversible formation and cleavage of the S-S bond to these molecules, promoting their use not only in molecular recognition[12] but also in material science.[13]

Thiols are used either as starting compounds to synthesize sulfenic acid precursors or as sulfenic acid acceptors, which allows a wide modulation of the procedure, as exemplified in Scheme 3. Starting from thiol **6** we have synthesized disulfide **10**[9] running through two different routes (**a** and **b**), and the results obtained deserve some comments. Sulfoxides **5**[11] and **11** are suitable precursors of transient sulfenic acids **7** and **8**, respectively. They show a different alkane sulfinyl moiety involved in the β-*syn*-elimination: the mobile hydrogen in the β-position to the sulfinyl group in sulfoxide **11** allows the generation of sulfenic acid **8** at 40°C (refluxing CH_2Cl_2), because of the two electron-withdrawing ester functions attached to the same carbon atom and the two methyl groups in the α-position to the sulfur atom. Sulfoxide **11** was prepared starting from thiol **9**, through a controlled oxidation of sulfide **12**,[6g] and must be handled with caution because it easily undergoes spontaneous β-*syn*-elimination, leading to undesirable mixtures of self-condensation products of glucosulfenic acid **8**. Therefore, freshly prepared sulfoxide **11** was thermolyzed in refluxing CH_2Cl_2 in the presence of the bis-thiol **6** (**11/6** molar ratio 5:1) to give compound **10** in 50% yield.

The quite low yield of compound **10**, obtained following this approach ($\mathbf{a_1}$ to $\mathbf{a_3}$),[9] was overcome using the bis-sulfenic acid **7** as intermediate. Compound **6** was considered as a suitable starting product for the synthesis of sulfoxide **5** ($\mathbf{b_1}$ to $\mathbf{b_2}$), precursor of the bis-sulfenic acid **7** to be generated in situ in the presence of thiol **9** ($\mathbf{b_3}$). In our experience, the presence of a methoxycarbonylethyl residue involved in the β-*syn*-elimination allows the thermolysis of sulfoxide **5** to occur at 83°C (refluxing $ClCH_2CH_2Cl$). The expertise gained in the choice and preparation of sulfenic acid precursors[6] directed us toward the use of sulfoxide **5**, which, contrary to sulfoxide **11**, can be kept on the bench without any trace of decomposition and easily purified by column chromatography, thus raising its reactivity as generator of the corresponding sulfenic acid **7** (Scheme 3). The thermolysis of sulfoxide **5** in the presence of thiol **9** led to the obtainment of compound **10** in 85% yield, a result



Scheme 3

comparable with others achieved using this methodology for the formation of the disulfide link.[9] The bio-potentialities of bis-disulfide **10** and its deprotected analogue are under study.

CONCLUSIONS

In conclusion, we have described an easy synthetic approach to unsymmetrical disulfides. It is a general procedure that allows the preparation of even structurally complex disulfides, in mild conditions and good yields. The generation of mono-, di-, or tri-sulfenic acids, from suitable sulfinyl precursors, in the presence of various kinds of thiols, as applied for the synthesis of compounds **3** and **10**, illustrates the versatility of our procedure.

REFERENCES

1. Hozoji, M.; Kimura, Y.; Kioka, N.; Ueda, K. *J. Biol. Chem.* **2009,** *284*, 11293–11300.
2. Moskovitz, J.; Poston, J. M.; Berlett, B. S.; Nosworthy, N. J.; Szczepanowski, R.; Stadtman, E. R. *J. Biol. Chem.* **2000,** *275*, 14167–14172.
3. Grainger, R. S.; Tisselli, P.; Steed, J. W. *Org. Biomol. Chem.* **2004,** *2*, 151–153.
4. (a) Carreño, M. C. *Chem. Rev.* **1995,** *95*, 1717–1760; (b) Kesters, E.; Swier, S.; van Assche, G.; Lutsen, L.; Vanderzande, D.; van Mele, B. *Macromolecules* **2006,** *39*, 3194–3201.
5. Aversa, M. C.; Barattucci, A.; Bonaccorsi, P.; Giannetto P. *Curr. Org. Chem.* **2007,** *11*, 1034–1052.
6. (a) Aversa, M. C.; Barattucci, A.; Bonaccorsi, P.; Giannetto, P.; Jones, D. N. *J. Org. Chem.* **1997,** *62*, 4376–4384; (b) Aversa, M. C.; Barattucci, A.; Bonaccorsi, P.; Giannetto, P.; Nicolò, F. *J. Org. Chem.* **1999,** *64*, 2114–2118; (c) Aversa, M. C.; Barattucci, A.; Bonaccorsi, P.; Giannetto, P.;

Policicchio, M. *J. Org. Chem.* **2001,** *66*, 4845–4851; (d) Aucagne, V.; Aversa, M. C.; Barattucci, A.; Bonaccorsi, P.; Giannetto, P.; Rollin, P.; Tatibouët, A. *J. Org. Chem.* **2002,** *67*, 6925–6930; (e) Aversa, M. C.; Barattucci, A.; Bilardo, M. C.; Bonaccorsi, P.; Giannetto, P. *Synthesis* **2003,** *14*, 2241–2248; (f) Aversa, M. C.; Barattucci, A.; Bonaccorsi, P.; Giannetto, P. *J. Org. Chem.* **2005,** *70*, 1986–1992; (g) Aversa, M. C.; Barattucci, A.; Bilardo, M. C.; Bonaccorsi, P.; Giannetto, P.; Rollin, P.; Tatibouët, A. *J. Org. Chem.* **2005,** *70*, 7389–7396; (h) Aversa, M. C.; Barattucci, A.; Bonaccorsi, P.; Faggi, C.; Papalia, T. *J. Org. Chem.* **2007,** *72*, 4486–4496.

7. Davis, F. A.; Billmers, R. L. *J. Am. Chem. Soc.* **1981,** *103*, 7016–7018.
8. Aversa, M. C.; Barattucci, A.; Bonaccorsi, P.; Marino-Merlo, F.; Mastino, A.; Sciortino, M. T. *Bioorg. Med. Chem.* **2009,** *17*, 1456–1463.
9. Aversa, M. C.; Barattucci, A.; Bonaccorsi, P. *Eur. J. Org. Chem. 2009*, 6355–6359.
10. (a) Houk, J.; Whitesides, G. M. *J. Am. Chem. Soc.* **1987,** *109*, 6825–6836 (b) Vacca, A.; Nativi, C.; Cacciarini, M.; Pergoli, R.; Roelens, S. *J. Am. Chem. Soc.* **2004,** *126*, 16456–16465.
11. Compounds **3** (mp 54–57°C), **4** (oil), and **5** (oil), not yet reported in the literature, have shown all spectral data consistent with assigned structures.
12. Hennrich, G.; Anslyn, E. V. *Chem. Eur. J.* **2002,** *8*, 2219–2224.
13. Crivillers, N.; Mas-Torrent, M.; Vidal-Gancedo, J.; Veciana, J.; Rovira, C. *J. Am. Chem. Soc.* **2008,** *130*, 5499–5506.