From Transient Sulfenic Acids towards Peculiar Sulfurated Molecules

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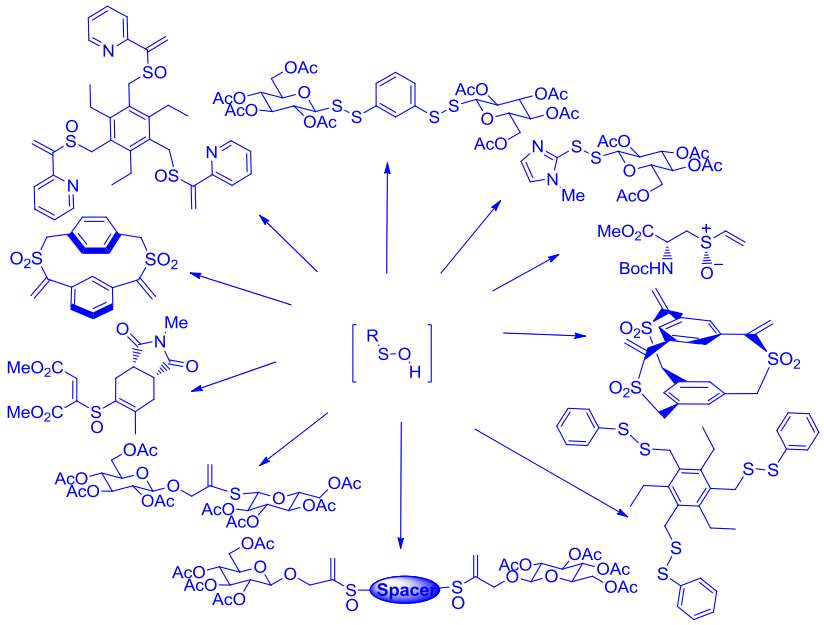
Abstract

Sulfenic acids (R-SOH) frequently act as reactive intermediates in biological and synthetic chemistry. Among the numerous examples that Nature offers to our knowledge, cysteine-derived sulfenic acids are recognized as key intermediates in signal transduction, transcriptional regulation events, and oxidative stress response. They also play catalytic and structural roles in enzymes. Furthermore, the sulfenic function is involved in the biosynthesis of thiosulfinates that give the characteristic odor and flavor to the Allium species and in the lachrymatory process of cut onion. On the other hand, the electronic nature of their S--O bond and its involvement in various, often stereospecific, reactions have prompted many applications of sulfenic acids in organic synthesis, such as their use as key intermediates in the preparation of peculiar sulfurated molecules. This paper aims at summarizing recent contributions on the generation and use of transient sulfenic acids in the stereocontrolled synthesis of sulfoxides and disulfides. These substrates offer a wide range of synthetic opportunities such as the synthesis of sulfinyl dienes to be involved in stereoselective DA reactions, the preparation of libraries of bioactive sulfurated molecules, the synthesis of unsymmetrical disulfides and tripodal sulfoxides and disulfides.

GRAPHICAL ABSTRACT



Keywords

Sulfenic acids, Vinyl sulfoxides, Unsymmetrical disulfides, Thiacyclophanes, Thiaglycoconjugates

INTRODUCTION

Sulfenic acids are usually very reactive intermediates. In a proteic environment, they can be considered as the oxidation products of Cysteine thiols. With the oxidation number of zero in sulfenic acids, sulfur shows its unique ability to function as both a nucleophile and electrophile. This dual nature is illustrated by the formation of thiosulfinates, where the reaction is favored by inter-molecular hydrogen bonding. Sulfenic acids have an acidic pK ranging from 5 to 12 in dependence of their structure.[1] In general, it is difficult to have an exact measure of their acidity since their anhydrides, the thiosulfinates, are more stable than their precursors, the sulfenic acids.

This sulfurated species play relevant roles in a variety of chemical and biochemical reactions. Significant cellular processes such as signal transduction, oxidative stress response transcriptional regulation involve the sulfenic function embedded in several protein skeletons. The sulfenic function is also involved in the biosynthesis of thiosulfinates that give the characteristic odor and flavor to the *Allium* species and in the lachrymation process when a onion is cut.[2] A vast majority of literature on sulfenic acids is concerned with their biological role and most of the publications have been devoted to the synthesis of chemical probes for the detection of the transient cysteine sulfenic acids (CysSOH) in proteins.[3]

Stable sulfenic acids, that resemble some of the protein sulfenic residues have been synthesized and accurately studied, allowing significant improvements in the studies on the biological role of CysSOH.[4] There is a number of papers on the use in cross-coupling reactions of sulfenate anions,[5] which can be in turn generated from sulfenic acids.[6]

The key step in the generation of transient sulfenic acids is the thermolysis of sulfinyl precursors that must possess an acidic H atom in the beta carbon. To enhance the mobility of the

H and, hence, to lower the thermolysis temperature electron-withdrawing groups linked to the beta C atom are needed and/or sterically demanding groups on the alfa C atom.[7] The sulfinyl precursors of sulfenic acids are prepared in two steps starting from thiols that are reacted with electron-deficient alkenes to obtain the corresponding sulfides that are oxidized, in a controlled manner, to sulfoxides. These sulfoxides usually are prepared and immediately used for the generation.[8]

RESULTS AND DISCUSSION

The Alkyne/sulfenic acid reaction proceeds with a concerted mechanism. It is a regioselective reaction: the sulfur adds to the most electrophilic C atom of a substituted triple bond. It is a stereospecific, *syn*-addition that affords vinylsulfoxides with a known stereochemistry at the double bond. A new stereogenic centre at the sulfoxide sulfur is formed. If no chiral elements are present in the starting products, a racemic mixture is obtained. With chiral groups attached to the sulfenic function, the addition affords epimeric mixtures of sulfoxides. These epimeric mixtures are generally separable by column chromatography and enantiopure vinyl sulfoxides can be obtained by this way.

Inspired by the *Allium* chemistry, we decided to use L-Cysteine as starting thiol for the generation of the enantiomerically pure L-Cysteine sulfenic acid **1** (**Scheme 1**) that we involved in the synthesis of enantiomerically pure *nor*-allin **2** or in the synthesis of diastereomeric sulfinyl dienes **3** which were separated and the major diastereisomer **3a** was involved in a Diels-Alder cycloadditon with N-methyl-maleimide (NMM).[9] We then used the Cysteine sulfoxide residue, possessing a further mobile H, of the major cycloadduct **4** in the generation of a new sulfenic

function, which we reacted again with the triple bond of the 1,4-dimethyl ester of 2-butynedioic acid **5**. Although we lose the Cysteine residue, this could represent a way to construct sulfoxides with not accessible functionalities.

We also decided to generate anomeric sulfenic acids from sugar units. 1-Thio-alfa-D-glucopyranose and its anomer were used in the synthesis of sulfinyl precursors **6** and **7** (**Scheme 2**) that were thermolyzed at different temperatures to generate the anomeric glucosylsulfenic acids **8** and **9**.[10] We prepared thioglucoconjugates by reacting the glucosulfenic acid **9** with a glucosyl unsaturated acceptor. Reflux in DCM (40°C), no acid or basic conditions, led to compounds **10** with unaltered configuration at the anomeric carbon atom.

Condensation with thiols to give disulfides is also a typical reaction of sulfenic acids and we have used it to developed a methodology which allows the synthesis of unsymmetrical disulfides in good yields and just three steps of procedure (**Scheme 3**).[11] By this methodology we prepared a collection of dithioglycoconjugates, with the disulfide bond linking two sugar units with different spacers, some of which showed apoptotic properties towards cancer cells. dithiogalactoconjugate **11** gave the best results.[12]

We prepared thiacyclophanes (thiaCPs) from bis-sulfinyl precursors **12** and **13**, as shown in **Scheme 4**, by adopting diluted conditions for the generation of the transient species in DCM at reflux and in the presence of an equivalent molar quantity of diethynylbenzenes. The stereochemical outcome of these reactions was quite unexpected since, in both cases, when *p*-diethynylbenzene was used as trapper of the sulfenic functions a complete stereoselectivity was observed towards the *meso* compound, whereas with *m*-diethynylbenzene a 1:1 diastereoisomeric mixture of the *meso* and the racemate was obtained.[13] Recently, we have described an approach

to new dithiaCP *S,S*-dioxides showing both planar and central chirality.[14] We have chosen a different precursor to generate the sulfenic functions and the thermolysis was conducted at 83°C.

We isolated intermediates such as **14** and **15** (**Figure 1**), still possessing a sulfinyl function on one of the two arms.

Therefore, we had to observe that the formation of thiaCPs is a stepwise process, in these conditions. The cyclization reaction proceeds in four distinct steps: i) formation of a first sulfenic acid function, ii) addition to the triple bond, to give a vinyl sulfoxide-containing intermediate, iii) generation of the second sulfenic acid function, iv) cyclization *via* intramolecular addition to the second triple bond of the diethynylbenzene to generate the second vinyl sulfoxide bridging unit. These open intermediates **14** and **15** gave us the possibility to study the stereochemical results obtained in the synthesis of these macrocycles. Computational calculations suggest that the exclusive formation of the *meso* thiaCPs in the reaction with *p*-diethynylbenzene takes place under kinetic control.[15]

The synthesis of thiaCPs with a "cylindrical" structure appeared also interesting because of their cage-like form. *Syn*-addition of the trisulfinyl precursor **16** to the triple bonds of an equimolecular quantity of 1,3,5-triethynylbenzene led to the formation of the thiaCPs **17** as diastereomeric mixture in about 1:1 ratio, respectively, of the cage possessing a C_3 axis of symmetry, and the cage with not C_3 symmetry (**Scheme 5**).[13] They were not completely separable by column chromatography and for this reason were converted into the sulfonyl derivative **18** by oxidation with *m*-CPBA.

A synthetic procedure, to prepare sulfurated tripodal molecules from 1,3,5-triethylbenzene, was also performed and is shown in **Scheme 6**. The best conditions for the generation of the sulfenic functions and their *syn*-addition onto the 2-ethynylpyridine[16] or their condensation to different thiols,[17] such as benzenethiol, have been found in dioxane at its refluxing temperature of 101°C. The tripodal compound **18** was a mixture of C_3 and not C_3 diastereisomers which were easily separated by column chromatography. The C_3 symmetric tripodal diastereoisomer of **1**, with the two coordinating nitrogen and sulfur atoms in the correct relative position, was reacted with square planar platinum(II) complexes, in toluene at rt, allowing the formation of a new class of tripodal bidentate ligands.[16]

CONCLUSIONS

In conclusion, we have described the synthesis of peculiar sulfurated molecules via sulfenic acid generation and reaction with suitably substituted triple bonds or thiols. The choose of the proper sulfenyl precursor is of dramatic importance for the outcome of the overall process and the obtainment of the desired final products. The use of such molecules can space in many chemical fields. Sulfinyl and disulfide derivatives containing the natural occurring residues of cysteine, galactose, glucose have shown biological potentiality. Tripodal trivinylsulfoxides have opened the way for their application in coordination chemistry. In thiacyclophanes the presence of elements of chirality appears as a promising feature in their use as organocatalysts and tripodal disulfides offer the opportunity to develop new functionalized nanoparticles.

REFERENCES

1. McGrath, A.J.; Garrett, G.E.; Valgimigli, L.; Pratt D.A. *J. Am. Chem. Soc.* **2010**, *132*, 16759–1676.
2. Block, E. *Garlic and Other Alliums: The Lore and the Science*, Block E. ed.; Royal Society of Chemistry: Cambridge, 2009 (hardback), 2010 (softback) ; 454 pp.
3. Gupta, V.; Carroll, K.S. *Biochimica et Biophysica Acta* **2014**, *1840*, 847–875.
4. Goto, K.; Holler, M.; Okazaki, R. *J. Am. Chem. Soc.* **1997**, *119*, 1460–1461.
5. Maitro, G.; Vogel, S.; Prestat , G.; Madec , D.; Poli G. *Org. Lett.* **2006**, *8*, 5951-5954; Maitro, G.; Vogel, S.; Sadaoui , M.; Prestat , G.; Madec , D.; Poli G. *Org. Lett.* **2007**, *9*, 5493,-5496; Izquierdo, F.; Chartoire, A.; Nolan S.P. *ACS Catal.* **2013**, *3*, 2190-2193; Jia, T.; Bellomo, A.; Montel, S.; Zhang, M.; EL Baina, K.; Zheng, B.; Walsh, P.J. *Angew. Chem. Int. Ed.* **2014**, *53*, 260-264
6. Gelat, F.; Lohier, J.-F.; Gaumont, A.-C.; Perrio S. *Adv. Synth. Catal.* **2015**, *357*, 2011 –2016.
7. Adams, H.; Anderson, J.C.; Bell, R.; Jones, D.N.; Peel, M.R.; Tomkinson, N.C.O. *J. Chem. Soc., Perkin Trans. I* **1998**, 3967-3974; Aversa, M.C.; Barattucci, A.; Bonaccorsi, P.; Giannetto, P.; Policicchio, M. *J. Org. Chem.*, **2001**, *66*, 4845-4851; Aversa, M.C.; Barattucci, A.; Bonaccorsi, P.; Giannetto, P. *ARKIVOC* **2002**, *xi*, 79-98; Aversa, M.C.; Barattucci, A.; Bilardo, M. C.; Bonaccorsi, P.; Giannetto, P. *Synthesis*, **2003**, 2241-2248; Aversa, M.C.; Barattucci, A.; Bonaccorsi, P.; Contini, A. *J. Phys. Org. Chem.* **2009**, *22*, 1048–1057.

8. Aversa, M.C.; Barattucci, A.; Bonaccorsi, P.; Rollin, P.; Tatibouët, A. *ARKIVOC* **2009**, *viii*, 187-198; Menichetti, S.; Aversa M.C.; Bonaccorsi, P.; Lamanna, G.; Moraru, A. *J. Sulfur Chem.* **2006**, *27*, 393-400.
9. Aversa, M.C.; Barattucci, A.; Bonaccorsi, P.; Giannetto, P. *J. Org. Chem.* **2005**, *70*, 1986-1992.
10. Aucagne, V.; Bonaccorsi, P.; Giannetto, P.; Rollin, P.; Tatibouët, A. *J. Org. Chem.* **2002**, *67*, 6925-6930; Aversa, M.C.; Barattucci, A.; Bilardo M.C.; Bonaccorsi, P.; Giannetto, P.; Rollin, P.; Tatibouët, A. *J. Org. Chem.* **2005**, *70*, 7389-7396.
11. Aversa, M.C.; Barattucci, A.; Bonaccorsi, P. *Eur. J. Org. Chem.* **2009**, 6355-6359.
12. Aversa, M.C.; Barattucci, A.; Bonaccorsi, P.; Marino-Merlo, F.; Mastino, A.; Sciortino, M.T. *Bioorg. Med. Chem.*, **2009**, *17*, 1456-1463; Bonaccorsi, P.; Marino-Merlo, F.; Barattucci, A.; Battaglia, G.; Papaianni, E.; Papalia, T.; Aversa, M.C.; Mastino, A. *Bioorg. Med.Chem.* **2012,** *20*, 3186-3195.
13. Aversa, M.C.; Barattucci, A.; Bonaccorsi, P.; Faggi C.; Papalia T. *J. Org. Chem.* **2007**, *72*, 4486–4496.
14. Barattucci, A.; Di Gioia, M.L.; Leggio, A.; Minuti, L.; Papalia, T.; Siciliano, C.; Temperini, A.; Bonaccorsi P. *Eur. J. Org. Chem.* **2014**, 2099-2104.
15. Barattucci, A.; Bonaccorsi , P.; Papalia, T.; Manganaro, N.; Gattuso G. *Tetrahedron Letters* **2014**, *55*, 5096–5100.
16. Barattucci, A.; Plutino, M.R.; Faggi C.; Bonaccorsi, P.; Monsù Scolaro L.; Aversa, M.C. *Eur. J. Inorg. Chem.* **2013**, 3412–3420.
17. Aversa, M.C.; Barattucci, A.; Bonaccorsi, P. *SynLett* **2011**, 254-258.

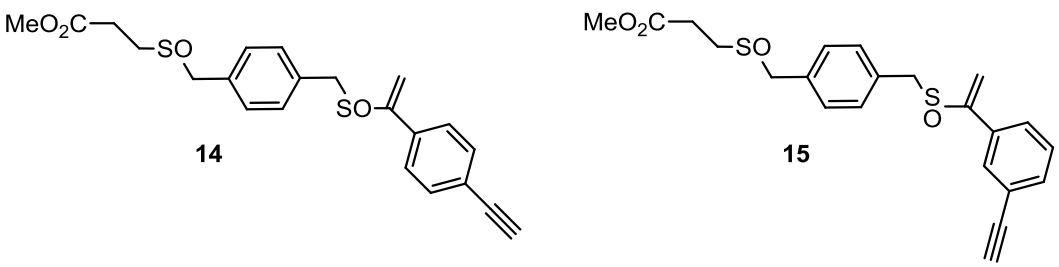
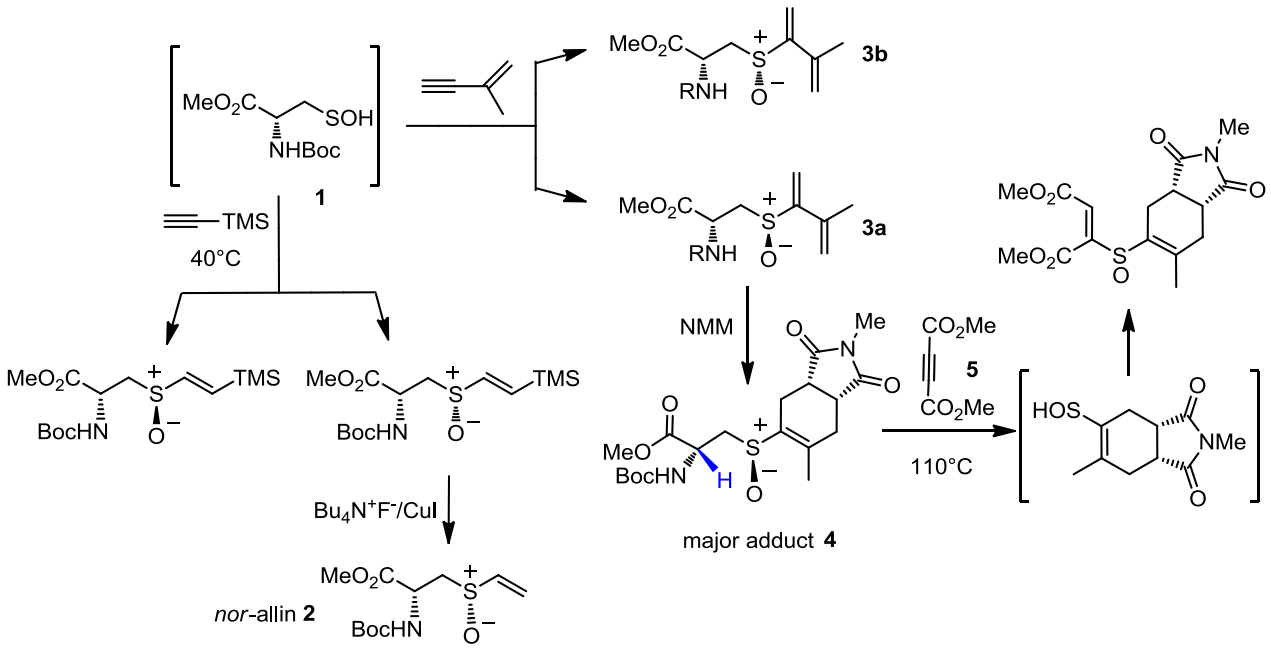
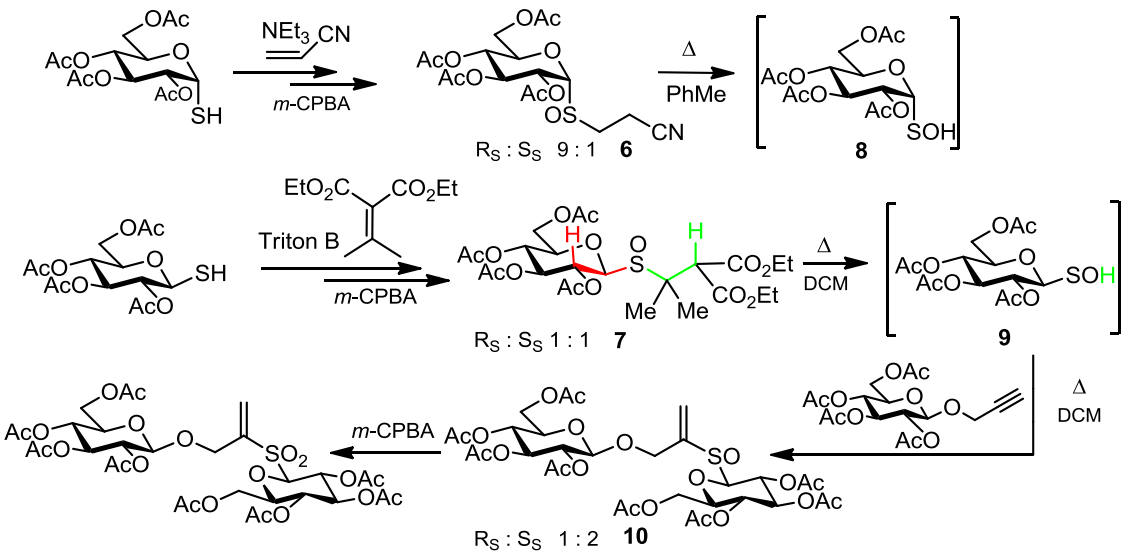


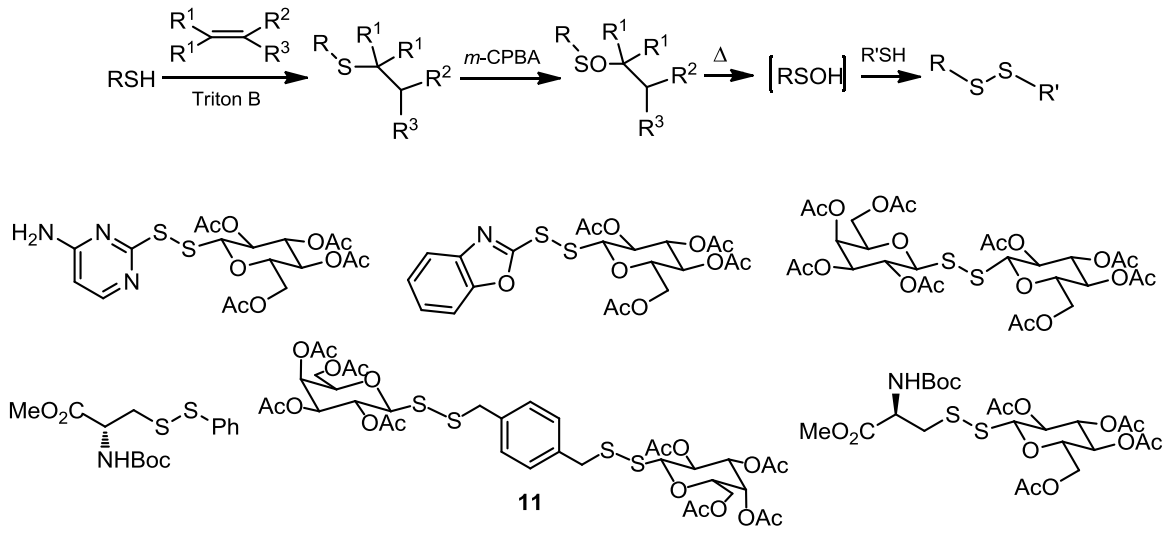
Figure 1 Intermediates in the synthesis of thiaCPs



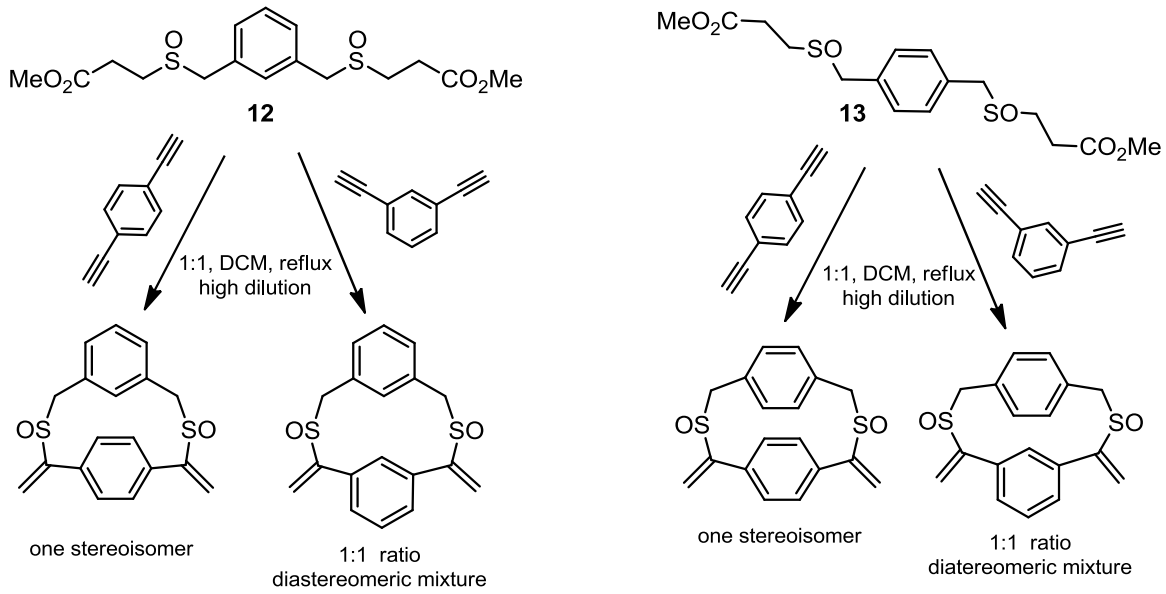
Scheme 1 Reactivity of L-Cysteine sulfenic acid **1** with suitably substituted triple bonds



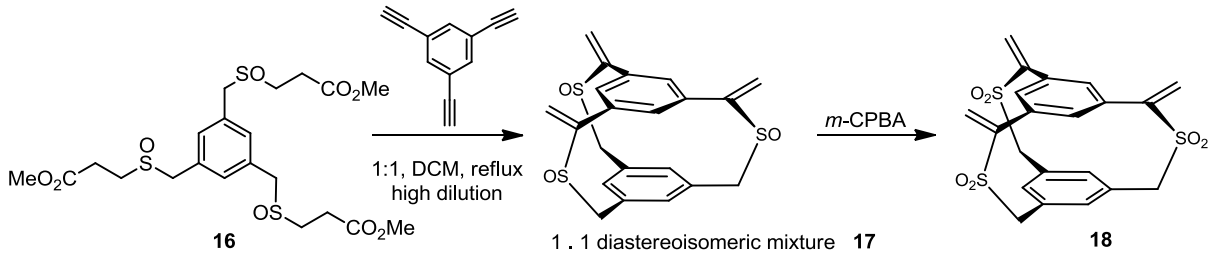
Scheme 2 From 1-thioglucopyranoses to diglucoconjugates via sulfenic acids



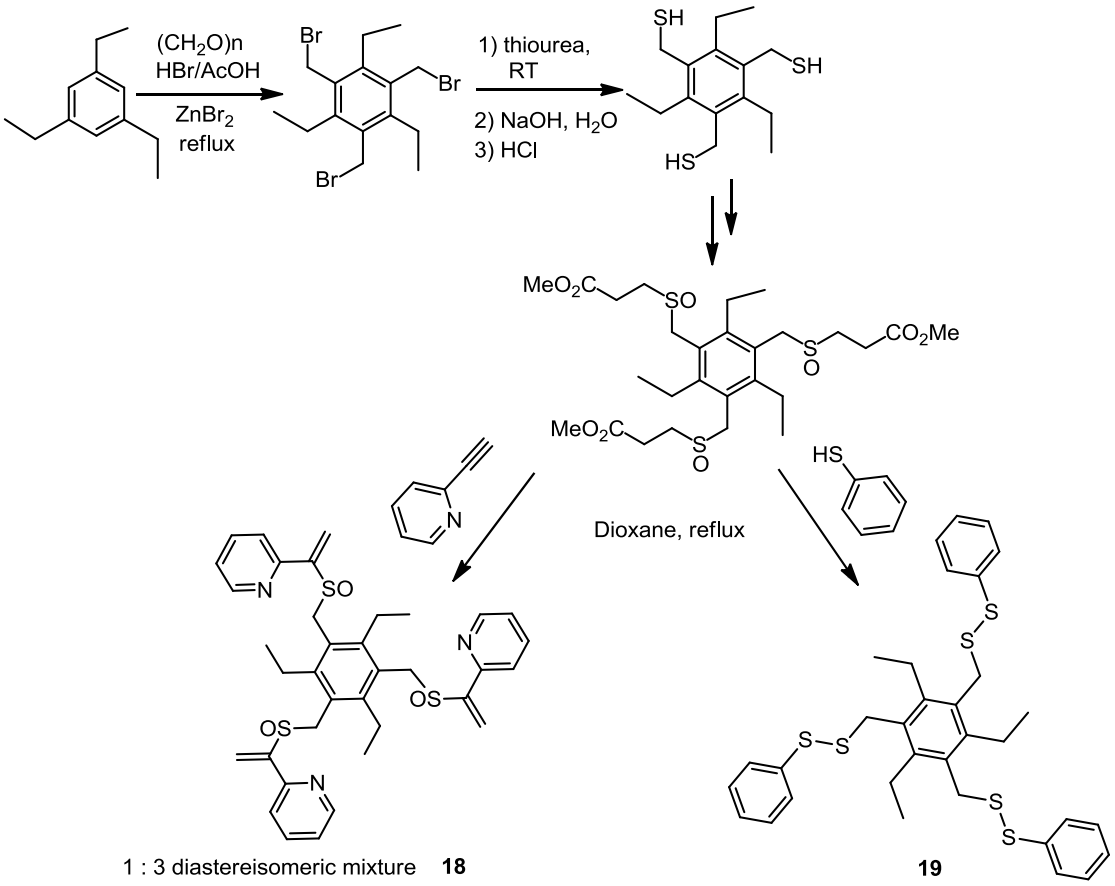
Scheme 3 Procedure for the synthesis of unsymmetrical disulfides via sulfenic acids



Scheme 4 Synthesis of thiacyclophanes via sulfenic acids



Scheme 5 Synthesis of cylindral thiacyclophanes via sulfenic acids



Scheme 6 Synthesis of tripodal sulfurated molecules via sulfenic acid