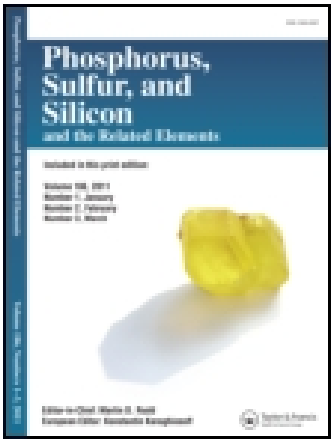

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Sulfenic Acids from L-Cysteine Involved in the Synthesis of Alliin Analogues

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Sulfenic Acids from L-Cysteine Involved in the Synthesis of Alliin Analogues

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L-cysteine is a stimulating starting product for the generation of transient sulfenic acids that add to suitable acceptors, allowing formation of sulfoxides showing a biologically active residue. For instance, N-(tert-*butoxycarbonyl)-L-cysteine methyl ester furnished in few steps (*R*)-2-*tert*-butoxycarbonylamino-2-methoxycarbonyl-ethanesulfenic acid, which was readily converted into (*R,S_S*)-(2-*tert*-butoxycarbonylamino-2-methoxycarbonyl-ethylsulfinyl)ethene, the methyl ester of Boc-protected* nor-*alliin.*

Keywords Alliin analogues; L-cysteine derivatives; stereoselection; sulfenic acids; sulfoxides

INTRODUCTION

The importance of sulfenic acids RSOH as transient intermediates in biological processes is widely recognised.[1] Sulfenic acids are also very useful as intermediates in the synthesis of a large number of sulfoxides. In fact the addition of RSOH to alkenes or alkynes allows an easy and stereocontrolled introduction of a sulfinyl group into a suitably unsaturated substrate.[2]

In continuing our previous studies on the addition of enantiopure sulfenic acids to appropriate unsaturated molecules,[2] we envisioned

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that L-cysteine derivatives could represent convenient chiral starting products for the generation of the desired sulfenic acids. L-cysteine is easily accessible in various protected forms and possesses functional groups that can be ulteriorly transformed. Using this kind of starting products, we have performed the synthesis of a number of enantiopure molecules, analogues to alliin and isoalliin, containing both the sulfinyl and amino acidic moieties.

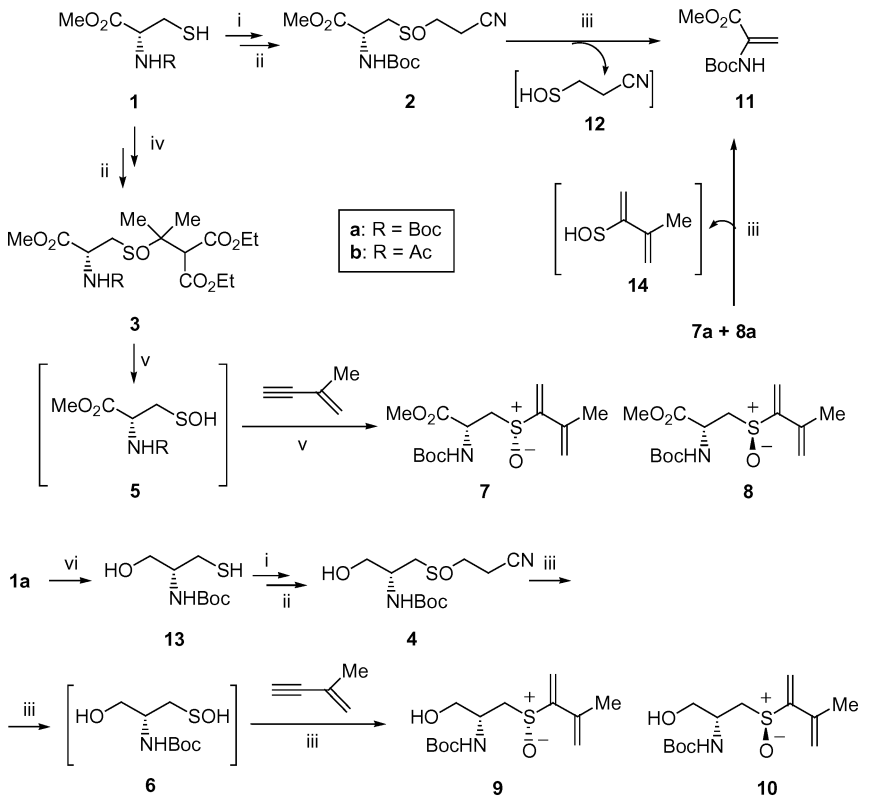
RESULTS AND DISCUSSION

Commercial *N*-(*tert*-butoxycarbonyl)-L-cysteine methyl ester (**1a**) and *N*-acetyl-L-cysteine methyl ester (**1b**) were adopted as starting materials for preparing sulfoxides **2–4** bearing alkyl residues with β-hydrogens to the sulfinyl group and electron-withdrawing substituents in suitable position to help the thermal *syn*-elimination of sulfenic acid (Scheme 1). Acetyl and *tert*-butoxycarbonyl are among the most popular protecting groups of the amine function in amino acid compounds. Therefore we found the comparison of synthetic results in the steps required for the preparation of sulfoxides **3a** and **3b** meaningful.

In the first instance, we chose 2-methyl-1-buten-3-yne as trapping agent of sulfenic acids **5** and **6** because the completely chemo- and regioselective addition of **5** and **6** onto the triple bond of the enyne leads to enantiopure 2-sulfinylbuta-1,3-dienes, epimeric at the sulfur atom (**7** and **8** from **3**, and **9** and **10** from **4**). On the basis of our previous studies[2] sulfinyl dienes **7–10** are expected to be effective partners in asymmetric Diels–Alder cycloadditions.

The structural features of **1a** attracted our attention from the beginning because its conversion in sulfoxides **2** and **3a** occurs with maintenance, in the cysteine residue, of a β-proton to SO group whose mobility is guaranteed by the presence of both the ester and amine functions on the same carbon atom. These characteristics posed a problem of chemoselectivity in the elimination of sulfenic acid. Indeed, when we warmed sulfoxides **2**, in refluxing toluene and in the presence of 2-methyl-1-buten-3-yne, we obtained amino ester **11**,[3] as an unique, isolated product of the *syn*-elimination of sulfenic acid **12**.

LAH reduction of the ester moiety of the cysteine derivative **1a** to the hydroxymethyl function in **13** led to a significant modification of the initial structural features of **1a**, because the acidic character of the geminal hydrogen to NHBoc decreased in the cysteine-like residue, and a hydroxy function was introduced in the chiral auxiliary. It has been well demonstrated that the involvement of the sulfur-linked oxygen atom in intramolecular hydrogen bonding can prevent self-condensation of the sulfenic acid, enhance the stereoselectivity of the sulfenic acid

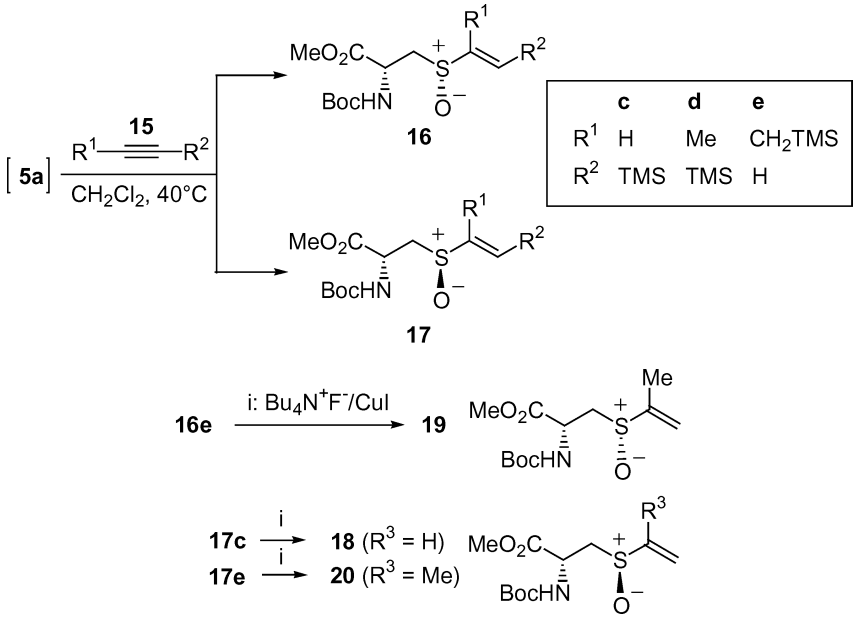


i) CH_2=CHCN, $Me_3(PhCH_2)N^+OH^-$; ii) *m*-CPBA; iii) PhMe, 110°C;
iv) Me_2C=$C(CO_2Et)_2$, $Me_3(PhCH_2)N^+OH^-$; v) CH_2Cl_2, 40°C; vi) LAH, -15°C

SCHEME 1

addition in some cases, and facilitate the chromatographic separation of the obtained diastereoisomeric sulfoxides.[2a] Sulfoxides **4** underwent thermolysis in the presence of 2-methyl-1-buten-3-yne in refluxing toluene for 2.5 h and the addition of sulfenic acid **6** to the triple bond of the enyne led to a mixture of sulfinyl dienes **9** and **10** in 70% total yield. The considerable difference in chromatographic mobility between the two epimeric dienes **9** and **10** confirmed the presence of an important intramolecular hydrogen bonding between the sulfoxide oxygen and the hydroxy group. Therefore, the absolute configuration at sulfur atom in dienes **9** and **10** was assigned on the basis of intramolecular hydrogen bonding, related conformational preferences, and chromatographic mobility, as previously stated.[4]

The introduction of a highly and suitably substituted alkyl group such as the 1,1-diethoxycarbonyl-2-methylprop-2-yl residue[5] into the cysteine derivatives **1** enabled, finally, the generation of sulfenic acids **5** that retain amine and carboxy function, typical of the cysteine. Two epimers at the sulfur atom were obtained in a 1:1 ratio for sulfoxides **3a** and 1:2 for sulfoxides **3b**. This low stereoselectivity was the only significant difference induced by the protective group Ac instead of Boc. Thermolysis of sulfoxides **3** in refluxing dichloromethane generated the transient species **5**, which added to the triple bond of 2-methyl-1-buten-3-yne, giving sulfinyl dienes **7** and **8** in very good yields, isolated in enantiomerically pure form by column chromatography. Compounds **7** and **8** still possess a "masked" sulfenic acid function, which was expected to be producible from the cysteine moieties by their heating at moderate temperature. Thermolysis of the mixture of sulfinyl dienes **7a** and **8a** in refluxing toluene led indeed to amino ester **11**. The isolation of **11** represents indirect evidence of the elimination, from **7a** + **8a**, of sulfenic acid **14**, which self-condensates to volatile thiosulfinates whose structural features are greatly related to the alkenyl thiosulfinates, produced in *Allium* species by enzymic reaction when they are cut or ruptured, and characterizing the aroma profile of these vegetables.[1]



SCHEME 2

Sulfenic acid **5a**, generated *in situ* from sulfoxides **3a**, was also added to the functionalized triple bond of commercially available alkynes **15c–e** (Scheme 2). The reactions were performed in dichloromethane and led to sulfoxides **16c–e** and **17c–e** in good yields. All the additions occurred with complete regioselectivity, and the mixtures of sulfoxides were separated by column chromatography, furnishing vinylsulfinyl L-cysteine derivatives **16** and **17** in enantiomerically pure form. Protodesilylation of compounds **17c**, **16e**, and **17e** with tetrabutylammonium fluoride and CuI[6] led to the formation of **18**, **19**, and **20**, respectively, and represented the last step of an easy route of access to some enantiopure alliin analogues.

We assigned the absolute configuration of sulfur atom in sulfoxides **7**, **8**, **16**, and **17** (Schemes 1 and 2), moving from the X-ray analysis of (R, E, S_S)-trimethyl-[2-(2-*tert*-butoxycarbonylamino-2-methoxycarbonyl-ethylsulfinyl)vinyl]silane (**17c**).[7]

CONCLUSIONS

L-cysteine represents a versatile source of sulfenic acids that can easily furnish several enantiopure sulfoxides. Both compounds **3a** and **3b** can act as convenient starting products for introducing L-cysteine *S*-oxide moiety into a suitable acceptor, *via* sulfenic acids **5**. Application of this strategy to the synthesis of alliin analogues **18–20** in enantiomerically pure form illustrates the versatility of this procedure. Moreover, the elimination of sulfenic acid **14** from the mixture **7a** + **8a** suggests that complex sulfoxides, such as **7** and **8**, obtained by addition of sulfenic acids **5** to unsaturated acceptors, can be stereoselectively derivatized and warmed again to eliminate enamine **11** and simultaneously generate a new sulfenic acid moiety, useful in subsequent stereoselective transformations toward still more complex and enantiopure sulfoxides. This last application can be regarded as a further stimulating development of this chemistry.

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