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S_N2 Reaction of Sulfur Nucleophiles with Hindered Sulfamidates: Enantioselective Synthesis of α-Methylisocysteine

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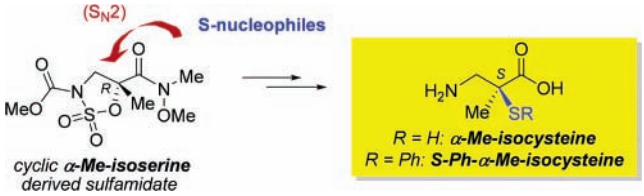

The work described here demonstrates that the five-membered cyclic α-methylisoserine-derived sulfamidate, (*R*)-**1**, behaves as an excellent chiral building block for the ring-opening reaction by S_N2 attack with sulfur nucleophiles at the quaternary carbon. As a synthetic application of this methodology, and to show that this sulfamidate is a valuable starting material, the synthesis of two new α-methylisocysteine derivatives has been carried out to cover the lack of α- and *β*-methylated amino acids that incorporate the cysteine or isocysteine skeleton. These compounds are two new α,α-disubstituted *β*-amino acids ($\beta^{2,2}$-amino acids), and the synthetic routes involve nucleophilic ring opening followed by acid hydrolysis.

The important roles that cyclic sulfamidates have played in organic synthesis, as well as the recent developments in their chemistry, have made the synthesis and reactivity of these systems the subject of a recent review.[1] Moreover, this subject has already been analyzed in the context of a review of their analogues: cyclic sulfate derivatives.[2] In particular, the five-membered cyclic sulfamidates have been the most widely described sulfamidate systems. These compounds have been extensively used as reactive intermediates in organic synthesis because most intermolecular ring-opening reactions of cyclic sulfamidates with nucleophiles proceed by the S_N2 pathway with total inversion at the stereogenic center.[1] Furthermore, the most direct method to obtain five-membered cyclic sulfamidates has been the use of the *β*-amino alcohol and sulfuryl chloride,[1] a protocol that involves the catalytic asymmetric dihydroxylation reaction,[3] followed by treatment of the corresponding 1,2-diol with a Burgess-type reagent.[4] This approach has contributed to the expansion of the chemistry of these compounds.[5]

On the other hand, since Seebach and co-workers discovered that short chains of *β*-amino acids generally form more stable secondary structures than their natural counterparts, *β* peptides have been the subject of extensive investigation. In addition to the numerous secondary structures that have been identified, *β* peptides have also displayed interesting biological properties. These features have made the field of *β*-amino acids a matter of constant interest.[6] Particularly attractive are the *β*- or α-substituted *β*-amino acids (β^3- or β^2-amino acids), because these substituents favor folded conformations in *β* peptides.[6c,7] For this reason, several approaches have been described to prepare these amino acids, although very few routes have been reported for chiral α,α-disubstituted *β*-amino acids ($\beta^{2,2}$-amino acids).[8] Accordingly, the development of practical methods for the synthesis of *β*-amino acids bearing a chiral quaternary center in the α position would be especially important.[9]

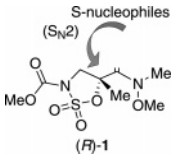

FIGURE 1. S_N2 reaction on cyclic sulfamidate (*R*)-**1**.

Bearing these facts in mind, we focused our attention on the five-membered cyclic α-methylisoserine-derived sulfamidate (*R*)-**1** (Figure 1) as an excellent chiral building block for the synthesis of α-methylated *β*-amino acids by nucleophilic ring-opening reactions. In this sense, we recently communicated a synthetic approach to a varied collection of *β*-amino acids, namely, $\beta^{2,2}$-amino acids and unsaturated *β*-amino acids, by opening the mentioned sulfamidate with C, N, and O nucleophiles.[10]

Although the synthesis and reactivity of several sulfamidates have been described in detail, in all cases, these compounds were monosubstituted or α,*β*-disubstituted.[1,2,11] In contrast, little is known about hindered sulfamidates.[12] On this basis, and

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considering that several synthetic reviews of quaternary carbon centers in a stereoselective fashion have been carried out in recent years,[13] we decided to undertake an in-depth study into the behavior of the five-membered cyclic sulfamidate (*R*)-**1**. In this compound, the quaternary carbon center is activated for nucleophilic displacement, and the reactivity with several sulfur nucleophiles (S nucleophiles) in the S_N2 reaction was explored (Figure 1).

Significant β-amino acids such as α-methylisocysteine and S-phenyl-α-methylisocysteine were selected to prove the applicability of the methodology presented here, that is, the S_N2 reaction of cyclic sulfamidate (*R*)-**1**, followed by acid hydrolysis, for the synthesis of $\beta^{2,2}$-amino acids as a result of the significance that some amino acid analogues have attained in recent years. For example, a large number of studies have focused on S-phenyl-L-cysteine as a biological marker of human exposure to benzene.[14] Moreover, amino acids bearing a thiol group appear to be particularly valuable for the generation of disulfide bridges and, therefore, are capable of generating restrictions in the peptide backbone.[15] β-Methylcysteine has been used to synthesize glutathione (GSH) analogues, which have been designed as potential glyoxalase I inhibitors.[16] Several syntheses of α-methylcysteine[17] have been reported, and once again, GSH analogues incorporating both enantiomers of this amino acid have recently been synthesized.[18] Moreover, the total synthesis of halipeptin A, a potent anti-inflammatory cyclic depsipeptide that incorporates an α-methylcysteine derivative unit, was recently achieved by Ma and co-workers.[19]

As far as isocysteine and its derivatives are concerned, various syntheses have been reported in the literature,[20] and the replacement of cysteine with this compound in a specific peptidic sequence generates potent peptide inhibitors of stromelysin.[21] Moreover, suitably protected isocysteine-based building blocks have been used to provide convenient access to isocysteinyl peptides.[22] β-Methylisocysteine derivatives have been synthesized in enantiomerically pure forms by the ring opening of (2*S*,3*S*)-3-methyl-2-aziridinecarboxylic acid.[23] Bearing in mind the crucial role played by the 3-hydroxyl function of β-phenylisoserine in taxol, the synthesis of analogues containing the α-thiol function has also been developed.[24]

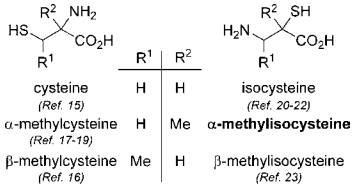

FIGURE 2. Mercapto amino acids and their α- and β-methylated derivatives.

In summary, with regard to the α-amino acid cysteine and the β-amino acid isocysteine, as well as their α- and β-methylated series (Figure 2), all compounds or derivatives of them have been previously synthesized in enantiomerically pure forms, except for α-methylisocysteine. In an effort to cover this gap, we report here the enantioselective synthesis of this new $\beta^{2,2}$-amino acid isocysteine derivative. To the best of our knowledge, only two racemic syntheses of a $\beta^{2,2}$-amino acid incorporating the isocysteine skeleton have been reported in the literature and these concerned α-methyl-β-phenylisocysteine[25] and *N*-tosyl-α-methylisocysteine derivatives.[26]

As mentioned above,[10] a very short methodology to obtain enantiomerically pure (*R*)-**1** was used, and this involved using the recent method reported by Nicolaou and co-workers[5] to synthesize regio- and stereoselective sulfamidates from chiral 1,2-diols using Burgess' reagent. The nucleophilic ring opening of sulfamidate (*R*)-**1** was examined using several S nucleophiles (Table 1). In our procedure, sulfamidate (*R*)-**1** (1.00 equiv) and the S nucleophile (1.05 or 1.10 equiv, dependent on the method) were heated in DMF at 50 °C for 1 h, and the sulfamic acid intermediate was hydrolyzed in an acid medium. The use of the corresponding method in each case was dependent on the S nucleophile and on the lability of the functional groups. Indeed, with sulfur anion derivatives as S nucleophiles, methods A1 or A2 (absence of base) were selected, while with thiols as S nucleophiles, DBU was added as a base to deprotonate the SH group (methods B1 or B2). On the other hand, methods A1 or B1 (20% H_2SO_4) were used to hydrolyze the sulfamic acid intermediate when functional groups that are resistant to acid hydrolysis are present in the molecule. By contrast, when the molecule incorporates functional groups that are sensitive to acid media, methods A2 or B2 (1 M NaH_2PO_4) were preferred (Table 1).

All of the S nucleophiles used were commercially available. In a previous study[10] we observed that the S_N2 reaction progresses satisfactorily when a simple S nucleophile (sodium methanethiolate) was used to give compound (*S*)-**16** in 93% yield. To explore the scope of the hindered sulfamidate (*R*)-**1** in the ring-opening with different S nucleophiles, we initially

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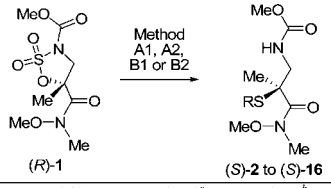
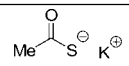
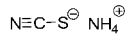
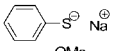
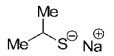
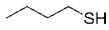
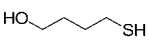
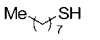
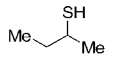
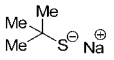
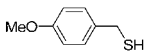
TABLE 1. S_N2 Reaction of Cyclic Sulfamidate (*R*)-1 with Different S Nucleophiles



S-Nucleophile	Method[a]	Product[b]	Yield[c] (%)
	A1	(*S*)-**2**	97
	A2	(*S*)-**3**	84
	A1	(*S*)-**4**	98
	B1	(*S*)-**5**	97
	B1	(*S*)-**6**	94
	A1	(*S*)-**7**	96
	B1	(*S*)-**8**	98
	B1	(*S*)-**9**	94
	B1	(*S*)-**10**	95
	B1	**11a,b**[d]	94
	A1	(*S*)-**12**	91
	B2	(*S*)-**13**	86
	B1	(*S*)-**14**	94
	B1	(*S*)-**15**	99
	---	(*S*)-**16**[e]	93

[a] Method A1: (i) S nucleophile (1.05 equiv), DMF, 50 °C, 1 h; (ii) 20% H_2SO_4 (aq)/CH_2Cl_2 (1:1), rt, 8 h. Method A2: (i) S nucleophile (1.05 equiv), DMF, 50 °C, 1 h; (ii) 1 M NaH_2PO_4 (aq)/CH_2Cl_2 (1:1), 2 h. Method B1: (i) S nucleophile (1.10 equiv), DBU (1.05 equiv), DMF, 50 °C, 1 h; (ii) 20% H_2SO_4 (aq)/CH_2Cl_2 (1:1), rt, 8 h. Method B2: (i) S nucleophile (1.10 equiv), DBU (1.05 equiv), DMF, 50 °C, 1 h; (ii) 1 M NaH_2PO_4 (aq)/CH_2Cl_2 (1:1), rt, 2 h. [b] We have unambiguously determined the absolute configuration of compounds **2**, **4**, **12**, **13**, and **15** by derivatization and X-ray analysis. However, because we have not found scientific evidence of absolute configurations in the case of other products, we have assumed that they are the same as those cited above for their parent compounds. [c] Measured after column chromatography. [d] The mixture of compounds **11a** and **11b** corresponds to the diastereomers (*S*,*S*)-**11** and (*R*,*S*)-**11**, which could not be separated by column chromatography. [e] Reference 10.

attempted the S_N2 reaction with primary alkanethiols in which the chain size increased gradually: 1-butanethiol, 4-sulfanyl-1-butanol, 1-octanethiol, and 4-(methoxyphenyl)methanethiol to give compounds (*S*)-**8**, (*S*)-**9**, (*S*)-**10**, and (*S*)-**15**, respectively, in excellent yields (94 to 99%).

Moreover, we did not encounter any problems regarding other functional groups present in the S nucleophiles, such as alcohols [see compound (*S*)-**9**]. Similarly, when secondary alkanethiols were used as nucleophiles (sodium 2-propanethiolate, 2-butanethiol, and cyclohexanethiol), the S_N2 reaction on the quaternary center of the sulfamidate gave excellent yields (94 to 96%) of the following products: (*S*)-**7**, **11a,b**, and (*S*)-**14**, respectively.

Surprisingly, in the same opening reactions with highly hindered reagents, for example, tertiary alkanethiols, sodium 2-methyl-2-propanethiolate, and triphenylmethanethiol, sulfamidate (*R*)-**1** and the S nucleophiles gave compounds (*S*)-**12** (91%) and (*S*)-**13** (86%), respectively, in very good yields. To the best of our knowledge, these reactions constitute the first examples of S_N2 reactions on quaternary carbons with highly hindered S nucleophiles.[27] The investigation of aromatic thiols as S nucleophiles was explored using sodium thiophenolate and two other ortho-substituted aromatic thiols, one of which has a donor substituent (2-methoxybenzenethiol) and the other an electron-withdrawing group [2-(trifluoromethyl)benzenethiol]. The opening products (*S*)-**4**, (*S*)-**5**, and (*S*)-**6**, respectively, were again obtained with excellent yields (94 to 98%). Finally, other types of S nucleophiles were tested (potassium thioacetate and ammonium thiocyanate), and these gave compounds (*S*)-**2** and (*S*)-**3**, respectively, in good yields (97 and 84%). It is important to highlight that, in all of the cases explored for the reaction of sulfamidate (*R*)-**1** with S nucleophiles, elimination products were not detected.

The stereochemical assignment of the opening products was supported by X-ray analysis of the corresponding monocrystals of compound (*S*)-**2** (Table 1), which were obtained by the slow evaporation of an ethyl ether/hexane solution.

The enantiomeric purity of the starting material, (*R*)-**1**, was determined by ^{1}H NMR spectroscopy using a europium(III) chelate as a chiral shift reagent (93% ee). Different chemical shifts for the methyl carbamate protons were observed when a 0.12 molar ratio of Eu(hfc)$_3$/substrate (hfc = 3-(heptafluoropropyl-hydroxymethylene)-D-camphorate) and a concentration of 0.1 mmol/mL substrate in deuterated chloroform at 22 °C were used. Indeed, we prepared a mixture [56.5% (*R*)-**1** + 43.5% (*S*)-**1**] without Eu(hfc)$_3$, and this showed a singlet centered at 3.42 ppm, corresponding to the methyl carbamate, while the same mixture with Eu(hfc)$_3$ showed two singlets, one centered at 3.93 ppm (*S*-isomer) and the other at 3.96 ppm (*R*-isomer) as a result of splitting by the action of Eu(hfc)$_3$. In a similar way, to determine the enantiomeric purity of the opening products, compound (*S*)-**4** was selected as a reference compound, showing a 93% ee. This compound shows a splitting of the NH proton at 6.05 and 6.35 ppm when a 0.15 molar ratio of Eu(hfc)$_3$/substrate and a concentration of 0.1 mmol/mL substrate in deuterated chloroform at 22 °C were used. In the selected case, the enantiomeric purity of the corresponding product was, therefore, similar to that described for starting material (*R*)-**1**. We were unable to determine the enantiomeric ratio of the opening products using GC-MS with α-, β-, or γ-DEX chiral capillary columns because the separation of the two enantiomers could not be achieved after testing several sets of conditions on different products.

To confirm that the nucleophilic displacement on the quaternary carbon of sulfamidate (*R*)-**1** corresponds to a second-order process, we developed a kinetic study for the ring-opening reaction of sulfamidate (*R*)-**1** with potassium thioacetate as the nucleophile. The rate of this opening reaction was determined by ^{1}H NMR analysis, with the reaction carried out in an NMR tube at room temperature in DMF-d_7. The initial concentrations of the reagents (*R*)-**1** and potassium thioacetate were 0.101 M. The ^{1}H NMR experiments were monitored every minute over 30 min, at which time the conversion level was 81% (Figure 3).

(27) We have carried out kinetic studies using different concentrations of Ph_3CS^- as a nucleophile, showing that this reaction follows a second-order process (see Supporting Information).

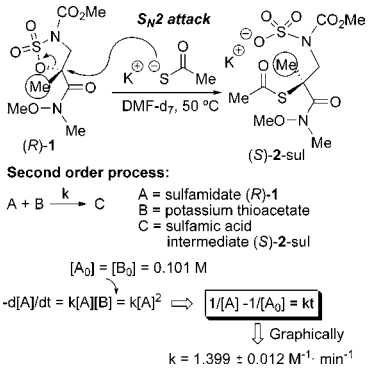
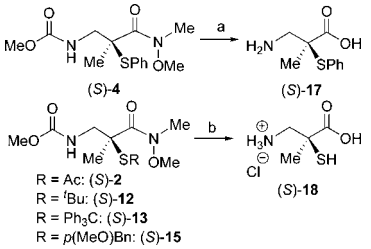


FIGURE 3. Kinetic study of the opening reaction of sulfamidate (*R*)-**1** with potassium thioacetate.

SCHEME 1[a]



[a] (a): (i) 6 M HCl, reflux, 12 h; (ii) propylene oxide/EtOH (3:1), 70 °C, 2 h, 89%. (b): 12 M HCl, reflux, 12 h, 63% (from **2**), 71% (from **12**), 88% (from **13**), 91% (from **15**).

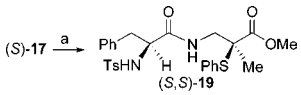
We analyzed the experiments by monitoring the disappearance of the signal at 1.89 ppm, corresponding to the quaternary methyl of (*R*)-**1**, and the appearance of the signal at 1.69 ppm, corresponding to the quaternary methyl of the sulfamic acid intermediate (*S*)-**2**-sul (denoted with circles in Figure 3). The second-order kinetics were determined from the observed linearity in the representation of $1/[A] - 1/[A_0]$ versus the reaction time in minutes.[28] As a result, the slope of this plot gives a second-order rate constant (k) value of 1.399 M^{-1} min^{-1} (Figure 3).

Furthermore, we demonstrated the synthetic utility of sulfamidate (*R*)-**1** as an excellent chiral building block by carrying out the synthesis of two new $\beta^{2,2}$-amino acids, α-methylisocysteine derivatives (*S*)-**17** and (*S*)-**18**, by means of an acid hydrolysis of opening products (*S*)-**4**, (*S*)-**2**, (*S*)-**12**, (*S*)-**13**, and (*S*)-**15** (Scheme 1). In particular, and as a suggestion of the referees, in the last case we have enlarged the reaction scale by five times; therefore, we carried out the S_N2 reaction of 5.45 mmol of sulfamidate (*R*)-**1** with 4-(methoxyphenyl)methanethiol to generate the opening product (*S*)-**15**, which was hydrolyzed to α-methylisocysteine hydrochloride (*S*)-**18** with an excellent yield of 91%.

Additionally, the absolute configuration of α-methylisocysteine derivative (*S*)-**17** was unambiguously determined by the transformation of the methyl ester derivative of this $\beta^{2,2}$-amino acid, obtained by esterification with acetyl chloride in MeOH, into the dipeptide **19**, a chiral derivative with two stereogenic centers, whose absolute configuration was found to be (*S,S*) by X-ray analysis (Scheme 2).

(28) Attempts to represent the data points according to a first-order process ($\ln[A_0] - \ln[A]$ vs t) gave a poor adjustment (see Supporting Information). Moreover, we observed that the change of the nucleophile concentration influences the reaction rate.

SCHEME 2. Determination of the Absolute Configuration of (*S*)-17[a]



[a] (a): (i) AcCl, MeOH, reflux, 10 h; (ii) *N*-(tosyl)phenylalaninyl chloride, DIEA, CH_2Cl_2, 25 °C, 14 h, 88%.

In conclusion, we present a simple methodology to obtain two new classes of enantipure $\beta^{2,2}$-amino acids with a methyl-containing quaternary carbon center: α-methylisocysteine and its S-phenyl derivative. The route starts with the ring opening of a cyclic α-methylisoserine-derived sulfamidate, which behaves as an excellent chiral building block for the S_N2 reaction with sulfur nucleophiles.

Experimental Section

Experimental Procedure for the S_N2 Reaction of (*R*)-1 with 4-(Methoxyphenyl)methanethiol. The sulfamidate (*R*)-**1** (1.54 g, 5.45 mmol), DBU (0.88 mL, 5.72 mmol), and 4-(methoxyphenyl)-methanethiol (0.93 mL, 5.98 mmol) were heated in DMF (20 mL) at 50 °C for 1 h, until the consumption of the sulfamidate was observed by TLC and/or GC-MS. The solution was then cooled, the solvent removed, and the residue dissolved into a mixture of aqueous 10% H_2SO_4/CH_2Cl_2 (1:1), which was stirred for 8 h at room temperature. The aqueous layer was successively extracted with EtAcO (2 × 20 mL), dried over Na_2SO_4, and concentrated, and the crude product was chromatographed on silica gel (hexane/EtAcO, 7:3) to give 1.97 g of (*S*)-**15** as a colorless oil. Yield: 99%. $[\alpha]^{25}_D$ −14.3° (*c* 1.84, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.58 (s, 3H), 3.22 (s, 3H), 3.53−3.82 (m, 13H), 5.38 (br t, 1H), 6.81 (d, 2H, J = 8.5 Hz), 7.18 (d, 2H, J = 8.5 Hz). ^{13}C NMR ($CDCl_3$, 300 MHz): δ 20.1, 33.2, 33.8, 48.7, 51.8, 52.2, 55.0, 60.5, 113.7, 128.8, 129.9, 157.2, 158.5, 172.2. ESI$^+$ (*m/z*): 357.4. Anal. Calcd. for $C_{16}H_{24}N_2O_5S$: C, 53.91; H, 6.79; N, 7.86; S, 9.00. Found: C, 53.87; H, 6.77; N, 7.83; S, 8.94.

Experimental Procedure for the Synthesis of (*S*)-α-Methylisocysteine Hydrochloride (*S*)-18. Compound (*S*)-**15** (1.97 g, 5.50 mmol) was suspended in an aqueous solution of 12 M HCl (10 mL), and the mixture was heated under reflux for 12 h. The solvent was removed, and the residue was dissolved in H_2O. After washing this solution with EtAcO, it was basified by the dropwise addition of 10% NaOH. Toluene was then added, and the mixture was concentrated. This operation was repeated several times until the disappearance of methoxymethylamine was observed (followed by ^{1}H NMR). An aqueous solution of 6 M HCl was then added to the mixture, the resulting solution was completely evaporated, and ethanol was added. This solution was filtered and evaporated to give 851 mg (4.99 mmol) of (*S*)-α-methylisocysteine as a hydrochloride derivative (*S*)-**18** (white solid). Yield: 91%. $[\alpha]^{25}_D$ −10.4° (*c* 1.00, H_2O). ^{1}H NMR (D_2O, 300 MHz): δ 1.60 (s, 3H), 3.30 (d, 1H, J = 13.6 Hz), 3.45 (d, 1H, J = 13.6 Hz). ^{13}C NMR (D_2O, 300 MHz): δ 24.2, 46.7, 47.9, 176.0. ESI$^+$ (*m/z*): 172.6. Anal. Calcd. for $C_4H_{10}ClNO_2S$: C, 27.99; H, 5.87; N, 8.16; S, 18.68. Found: C, 28.06; H, 5.89; N, 8.19; S, 18.75.

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Supporting Information Available: Experimental details, spectroscopic characterization, as well as crystal structure data. This material is available free of charge via the Internet at http://pubs.acs.org.

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