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Chemoselectivity Control in the Reactions of 1,2-Cyclic Sulfamidates with Amines

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Abstract: Although 1,2-cyclic sulfamidates derived from α-methylisoserine undergo nucleophilic displacement at the quaternary center, to the best of our knowledge their behavior with amines as nucleophiles has never been explored. We have found that a broad range of amines can be used, demonstrating the scope of the reaction, and that excellent control of the chemoselectivity can be achieved. Application of this methodology for the synthesis of a chiral α,β-diamino acid and an important piperazinone heterocycle is also presented. Additionally, we have found that DMF and DMSO behave not only as polar aprotic solvents but also as O-nucleophilic reagents, allowing the incorporation of an oxygen atom at a quaternary center of the electrophile, with inversion of configuration.

Keywords: amines · amino acids · chemoselectivity · nucleophilic substitution · ring-opening reactions

Introduction

The amino group is an integral feature of compounds important to life, such as α-amino acids. Amines of great relevance (histamine, dopamine, tyramine, and so on) are formed by decarboxylation of amino acids.[1] In the pharmaceutical industry, such amine moieties are present in a large number of drugs and have a wide variety of functions. In many cases, only specific chiral forms show the desired biological activity.[2] Due to the abundance of amino groups in natural compounds such as peptides, alkaloids, nucleosides, and so on, and their importance in relation to the properties and biological functions of these molecules, a large number of synthetic methodologies for the formation of C–N bonds have been developed.[3] In this context, the use of amines as nucleophiles (Hofmann alkylation, for instance) is very limited because the degree of alkylation is difficult to control and so, in general, amines are prepared by alternative methods. There are, however, some exceptions and some examples in which amines serve as nucleophiles in substitution reactions have been described. Among them, ring-opening reactions of epoxides[4] and aziridines[5] have great significance because the products obtained, 1,2-amino alcohols[6] and 1,2-diamines,[7] are of interest in medicinal chemistry and the pharmaceutical industry. Nevertheless, the use of amines as nucleophiles in ring-opening reactions of 1,2-cyclic sulfamidates, which represent alternative heterocyclic synthetic intermediates to epoxides and aziridines,[8] has received less attention. To the best of our knowledge, very few examples have been reported,[8a,9] and in most cases the amine attacks at a secondary carbon, because when more hindered sulfamidates have been employed the substitution reaction has been difficult to accomplish.[9c]

In this field, we have reported the use of 1,2-cyclic sulfamidates derived from α-methylisoserine as outstanding chiral building blocks to obtain a variety of important compounds,[10] especially α,α-disubstituted β-amino acids, named as $\beta^{2,2}$-amino acids. The key step involves nucleophilic attack on the tertiary carbon with inversion of configuration. We examined the use of several sulfur, oxygen, and nitrogen nucleophiles, obtaining excellent results. As nitrogen nucleophiles, we used azide and aromatic nitrogen-heterocycles, such as imidazole, pyrazole, pyridine, and their derivatives. However, as far as we are aware, the particular case of treating this substrate with amines has never been explored. Moreover, it is important to note that these cyclic sulfamidate-based building blocks have several reaction sites and that amines can act both as nucleophiles and as bases.

Results and Discussion

To study the issue of regioselective ring opening, we have explored the reactivity of α-methylisoserine-derived sulfamidates with amines. We started our study with propylamine as a representative primary amine because it is readily available and liquid at room temperature. Following a protocol similar to that described for other reactions of sulfamidates with various nucleophiles,[9a] we carried out the reaction of sulfamidate (*R*)-**1** with propylamine (4.0 equiv) in the presence of Cs_2CO_3 in THF as solvent at room temperature (Table 1, entry 1). After 8 h of reaction, we obtained a 42% yield of compound (*R*)-**2** derived from N-deprotection of

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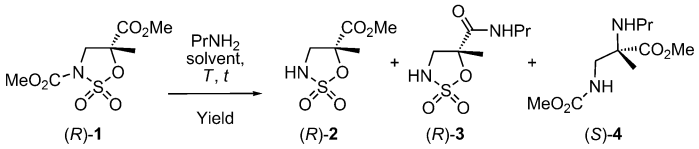
Table 1. Reactivity of cyclic sulfamidate (*R*)-**1** with propylamine.



Entry	$PrNH_2$ [equiv]	Base	Solvent	*T* [°C]	*t* [h]	(*R*)-**2** [%][a]	(*R*)-**3** [%][a]	(*S*)-**4** [%][a]
1	4.0	Cs_2CO_3	THF	RT	8	42	–	–
2	4.0	–	CH_3CN	reflux	1	60	–	–
3	1.0	BuLi	THF	RT	48	81	–	–
4	neat	–	$PrNH_2$	RT	7	–	94	–
5	neat	–	$PrNH_2$	48	0.5	–	93	–
6	4.0	–	THF	RT	48	–	92	–
7	2.0	–	THF	reflux	5	52	–	23
8	1.0	–	THF	reflux	6	45	–	14
9	2.0	–	DMF	reflux	0.5	35	–	49

[a] Yield after column chromatography.

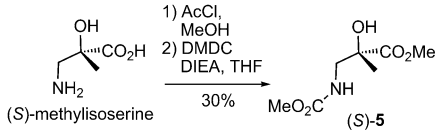
the sulfamidate (cleavage of methyl carbamate). We were able to improve the yield of this reaction to 60% by using acetonitrile (CH_3CN) as solvent and increasing the temperature without addition of a supplementary base (Table 1, entry 2). We even achieved an 81% yield by using only 1.0 equivalent of propylamine in THF in conjunction with 1.2 equivalents of BuLi at −78°C and allowing the reaction to proceed at room temperature for 48 h (Table 1, entry 3).

When propylamine was used as the solvent and the reaction was allowed to proceed for 7 h at room temperature, the only product obtained, in an excellent yield of 94%, was the sulfamidate (*R*)-**3**. Hence, not only N-deprotection occurred, but also a concomitant amidation reaction that involved conversion of the methyl ester into propylcarboxamide (Table 1, entry 4). A similar yield of (*R*)-**3** (93%) was obtained when this reaction was carried out for 30 min at 48°C (Table 1, entry 5). Finally, the best conditions for obtaining compound (*R*)-**3** (92% yield) were identified as the use of only 4.0 equivalents of propylamine in THF as solvent, with a reaction time of 48 h at room temperature (Table 1, entry 6). An increase in temperature, even with control of the number of equivalents of amine, led to cleavage of the carbamate to generate compound (*R*)-**2**, along with a small quantity of compound (*S*)-**4** arising from ring opening of the cyclic sulfamidate by propylamine (Table 1, entries 7 and 8).

The use of *N*,*N*-dimethylformamide (DMF) as an aprotic and polar solvent favored this third type of reaction between sulfamidate (*R*)-**1** and propylamine. By using only 2.0 equivalents of propylamine in DMF at reflux for 30 min, compound (*S*)-**4** was obtained in 49% yield, accompanied by a 35% yield of compound (*R*)-**2** (Table 1, entry 6). Compound (*S*)-**4** arose from nucleophilic ring opening of the cyclic sulfamidate with inversion of configuration. In general, reactions of this type require a second step for hydrolysis of the sulfamic moiety. In the present case, however, this step was not necessary, which may be considered as an advantage.

Therefore, we have verified that the chemoselectivity in the reaction of propylamine with cyclic sulfamidate (*R*)-**1** is mainly controlled by the choice of solvent. Acetonitrile favors N-deprotection of the sulfamidate, in THF there is not only N-deprotection, but also conversion of the methyl ester to propylcarboxamide, whereas in DMF there is nucleophilic attack at the quaternary center of the sulfamidate with inversion of configuration, circumventing the need for a second step for hydrolysis of the sulfamic moiety. In all cases, no elimination products were detected.[11]

Several attempts were made to increase the yield of compound (*S*)-**4** by using DMF as solvent, but we observed the formation of a new product, the tertiary alcohol (*S*)-**5**, along with compounds (*S*)-**4** and (*R*)-**2**. To confirm the structure of this compound, we prepared it from (*S*)-methylisoserine, which was obtained according to a previously published methodology.[10f] (*S*)-Methylisoserine was first transformed to the corresponding methyl ester derivative by treatment with acetyl chloride in methanol, and then the amino group was protected as a methyl carbamate by reaction with dimethyl dicarbonate (DMDC) in the presence of diisopropylethylamine (DIEA) with THF as solvent (Scheme 1. The



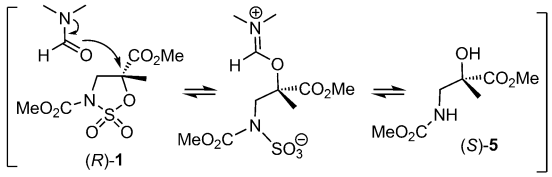
Scheme 1. Synthesis of (*S*)-**5** from (*S*)-methylisoserine.

optical rotation measured for alcohol (*S*)-**5** derived from sulfamidate (*R*)-**1** was identical to that measured for the (*S*)-**5** derived from methylisoserine, confirming the absolute configuration at the quaternary stereocenter (Scheme 1).

DMF is an excellent polar solvent and has also been used as an effective ligand in metallic compounds. Moreover, DMF can react as either an electrophilic or a nucleophilic agent, as has recently been reviewed.[12] In fact, DMF has been described as a precursor of different units (e.g., an oxygen atom, or carbonyl, dimethylamino, dimethylaminocarbonyl, or methyl groups). To the best of our knowledge, only a few reports have been published concerning the use of DMF as an O-nucleophile and source of an oxygen atom.[13]

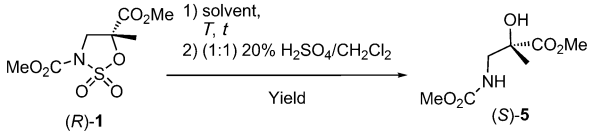
In view of the above, we propose DMF as the source of the hydroxyl oxygen atom in the formation of compound (*S*)-**5**. A possible mechanism that would account for the formation of (*S*)-**5** involves nucleophilic attack of the oxygen of DMF followed by aminolysis by propylamine to cleave the sulfamic moiety (Scheme 2 and the Supporting Information).

To confirm this proposal, we carried out the reaction of sulfamidate (*R*)-**1** with DMF at room temperature and at 70°C in the absence of propylamine, obtaining in both cases compound (*S*)-**5** in yields of 36 and 96%, respectively (Table 2, entries 1 and 2). To demonstrate that residual



Scheme 2. Mechanism of the generation of (*S*)-**5** from DMF.

Table 2. Reactivity of cyclic sulfamidate (*R*)-**1** with polar solvents.

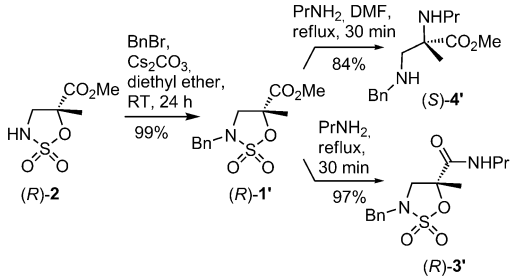


Entry	Solvent	*T* [°C]	*t* [h]	(*S*)-**5** [%][a]
1	DMF[b]	RT	48	36
2	DMF[b]	70	6	96
3	anhyd. DMF[c]	70	6	97
4	DMF/H_2O[d]	70	6	95
5	DMSO	RT	30	98
6	CH_3CN	RT	48	–

[a] Yield after column chromatography. [b] The reaction was carried out in air. [c] The reaction was carried out under an inert atmosphere with anhydrous DMF (< 0.005 % water, Aldrich 227056-100 mL). [d] The reaction was carried out in air with using 100 equivalents of H_2O.

water does not participate as a nucleophile in the ring-opening reaction, we carried out the reaction under the same conditions as those in Table 2 entry 2 but by using anhydrous DMF and an inert atmosphere. The results (yield and optical rotation) matched those obtained previously (Table 2, entry 3). Moreover, no effects were observed when the reaction was carried out by using a mixture of DMF/water (Table 2, entry 4). When we carried out the same reaction for 30 h at room temperature in DMSO as an alternative polar aprotic solvent, compound (*S*)-**5** was obtained in excellent yield (Table 2, entry 5). In all cases, an additional hydrolysis step was needed to cleave the sulfamate group. For this, as in other nucleophilic ring-opening reactions of sulfamidates, an equimolecular mixture of 20 % aqueous H_2SO_4 and dichloromethane was used. When we attempted the same reaction with acetonitrile as solvent and without propylamine, the starting material (*R*)-**1** was recovered (Table 2, entry 6). This chemistry is important because, to the best of our knowledge, this is the first report of DMF and DMSO serving as O-nucleophiles, leading, in a clean and straightforward way, to the incorporation of an oxygen atom at a quaternary carbon of an electrophile system with inversion of configuration. This fact could also be the most logical justification for the observed decrease in yield in this type of reaction when DMF was used as solvent.[9b]

Considering that it was not possible to use polar solvents of this type to carry out the ring-opening reaction of sulfamidate (*R*)-**1** with propylamine in good yield, we decided to transform the carbamate to a benzylamine group in the sulfamidate structure. To this end, sulfamidate (*R*)-**2** was transformed into the benzyl derivative (*R*)-**1′** (99 % yield; Scheme 3) by treatment with benzyl bromide in diethyl



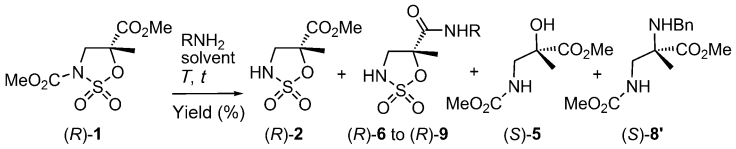
Scheme 3. Synthesis of (*R*)-**3′** and quaternary chiral 1,2-diamine (*S*)-**4′** (Bn = benzyl).

ether at room temperature for 24 h by using Cs_2CO_3 as a base. When benzyl derivative (*R*)-**1′** was treated with propylamine in DMF at reflux for 30 min, the corresponding ring-opened product (*S*)-**4′**, a chiral quaternary 1,2-diamine, was obtained in 84 % yield. Interestingly, when compound (*R*)-**1′** was treated with propylamine in the absence of DMF, only ester–amide exchange was observed, furnishing compound (*R*)-**3′** in excellent yield (Scheme 3).

The reactions of cyclic sulfamidate (*R*)-**1** were extended to other amines besides propylamine in order to achieve both N-deprotection of the sulfamidate and conversion of the methyl ester group to different amides. We carried out the reactions of (*R*)-**1** with methylamine, allylamine, benzylamine, and isopropylamine under the optimal conditions established as described above, that is, by using 4.0 equivalents of the amine in THF as solvent or by using only the corresponding amine neat (as the solvent), always at room temperature. In all cases, we obtained excellent yields of the corresponding amide derivatives (*R*)-**6**, (*R*)-**7**, (*R*)-**8**, and (*R*)-**9**, respectively. These results are gathered in Table 3. The structures of these new carboxamides were confirmed by X-ray analyses of single crystals obtained by slow evaporation of the solvent (Figure 1). Because of the importance of sulfamidates of this type as interesting chiral building blocks, this methodology could be considered as an excellent means of obtaining carboxamides from a methyl ester group, especially in cases in which other reactive sites are present in the molecule.

In addition, we explored the scope of ring-opening reactions of sulfamidate (*R*)-**1** with primary alkylamines. To this end, we carried out reactions of cyclic sulfamidate (*R*)-**1** with methylamine, allylamine, and benzylamine under the optimal conditions established for propylamine, which involved the use of DMF at reflux. With methylamine and allylamine, the starting material (*R*)-**1** was consumed, generating, in both cases, an almost equimolecular mixture of two products: (*R*)-**2** as a result of carbamate deprotection, and the tertiary alcohol (*S*)-**5**, arising from the behavior of DMF as an O-nucleophile (Table 3, entries 6 and 7). The use of

Table 3. Reactivity of cyclic sulfamidate (*R*)-**1** with amines.



Entry	Amine [equiv]	R	Solvent	*T*	*t* [h]	Products ([%])[a]
1	methylamine (4.0)	Me	THF	RT	24	(*R*)-**6** (94)
2	allylamine (neat)	Allyl	allylamine	RT	4	(*R*)-**7** (96)
3	benzylamine (4.0)	Bn	THF	RT	18	(*R*)-**8** (82)
4	isopropylamine (neat)	*i*Pr	isopropylamine	RT	6	(*R*)-**9** (97)
5	isopropylamine (4.0)	*i*Pr	THF	RT	72	(*R*)-**9** (77)
6	methylamine (2.0)	Me	DMF	reflux	0.5	(*R*)-**2** (47) (*S*)-**5** (51)
7	allylamine (2.0)	Allyl	DMF	reflux	0.5	(*R*)-**2** (41) (*S*)-**5** (48)
8	benzylamine (2.0)	Bn	DMF	reflux	0.5	(*R*)-**2** (23) (*S*)-**5** (31) (*S*)-**8′** (37)

[a] Yield after column chromatography.

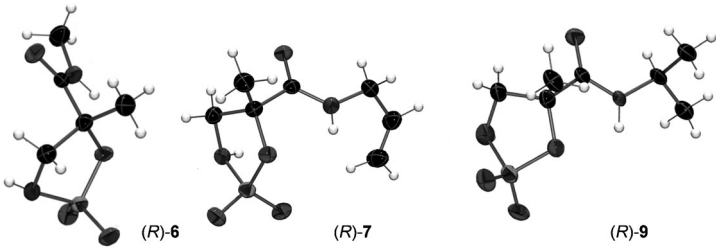


Figure 1. ORTEP structures of cyclic sulfamidates (*R*)-**6**, (*R*)-**7**, and (*R*)-**9**. Ellipsoids are drawn at the 50% probability level.

benzylamine afforded a mixture of three products, (*R*)-**2** in 23% yield, (*S*)-**5** in 31% yield, and the new ring-opened product (*S*)-**8′** in 37% yield (Table 3, entry 8).

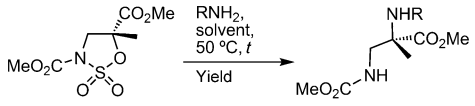
Primary arylamines are another important class of amines that we tested in the reaction with sulfamidate (*R*)-**1**. The use of aniline as both solvent and nucleophile gave, after only 15 min at 50 °C, a good yield of compound (*S*)-**10**, derived from nucleophilic ring opening of the cyclic sulfamidate (Table 4, entry 1). We were also able to isolate from this reaction a white solid that corresponded to the subproduct of aminolysis of the sulfamic moiety, which was analyzed by HRMS (see the Supporting Information). In order to reduce the number of equivalents of aniline, we carried out the reaction by using DMF as solvent. The use of 2.0 equivalents of aniline in DMF at 50 °C gave, after 18 h of reaction, compound (*S*)-**10** in 90% yield (Table 4, entry 2). When the same reaction was carried out with only 1.0 equivalent of aniline, compound (*S*)-**10** was again obtained, but in only 45% yield along with a 32% yield of tertiary alcohol (*S*)-**5** (Table 4, entry 3). At least one equivalent of aniline was needed to open the cyclic sulfamidate and a further equivalent for aminolysis of the sulfamic moiety. To extend this reactivity to other primary arylamines, we selected the optimal conditions and examined the reactions with *para*-bromoaniline and *para*-(methylthio)aniline, obtaining excellent yields of compounds (*S*)-**11** and (*S*)-**12**, respectively (Table 4, entries 4 and 5).

To study the steric and electronic effects of the substituents on the aniline derivatives, we initially tested the electron-withdrawing substituent -CO_2Me at the *para*- and *meta*-positions of aniline, by using DMF as solvent at 50 °C. In both cases, the starting material was not consumed and we only observed small quantities of the ring-opened product (*S*)-**5**, arising from the action of DMF as an O-nucleophile. We then proceeded to explore the presence of the electron-withdrawing substituent -OMe at the *para*-, *ortho*-, and *meta*-positions of aniline, under the same conditions. Fortunately, the reaction worked very well in the case of *para*-anisidine, furnishing compound (*S*)-**12a** in good yield (Table 4, entry 6). In the other two cases, decreased yields of the ring-opened products (*S*)-**12b** and (*S*)-**12c** were observed, particularly when *ortho*-anisidine was used as the nucleophile (Table 4, entries 7 and 8). Moreover, in these two cases, the formation of compound (*S*)-**5** was again observed.

The next step was to explore the reactivity of sulfamidate (*R*)-**1** with secondary and tertiary alkylamines. In the case of diethylamine, which also served as the solvent, N-deprotection was observed at room temperature, furnishing compound (*R*)-**2** in 60% yield after 24 h (Scheme 4). When triethylamine was used under the same conditions, no reaction occurred, but when the temperature was increased to 89 °C (reflux) for 2 h, compound (*R*)-**2** was obtained in an almost equimolecular ratio with a known compound (**13**) arising from a β-elimination reaction[10a] (Scheme 4).

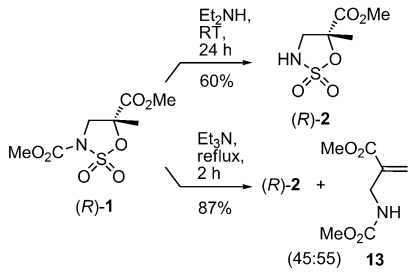
To conclude this study of reactivity, we examined the reaction of sulfamidate (*R*)-**1** with a representative of the most important class of com-

Table 4. Reactivity of cyclic sulfamidate (*R*)-**1** with primary arylamines.



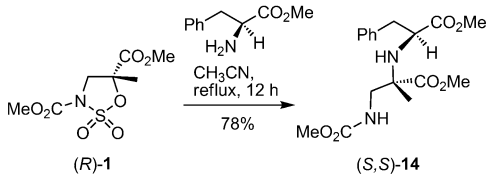
Entry	Arylamine [equiv]	R	Solvent	*t* [h]	Products [%][a]
1	aniline (neat)	Ph	aniline	0.25	(*S*)-**10** (89)
2	aniline (2.0)	Ph	DMF	18	(*S*)-**10** (90)
3	aniline (1.0)	Ph	DMF	24	(*S*)-**10** (45)[b]
4	*para*-bromoaniline (2.0)	*p*-BrC_6H_4-	DMF	18	(*S*)-**11** (83)
5	*para*-(methylthio)aniline (2.0)	*p*-$MeSC_6H_4$	DMF	18	(*S*)-**12** (72)
6	*para*-anisidine (2.0)	*p*-$MeOC_6H_4$	DMF	18	(*S*)-**12a** (85)
7	*meta*-anisidine (2.0)	*m*-$MeOC_6H_4$	DMF	18	(*S*)-**12b** (57)[b]
8	*ortho*-anisidine (2.0)	*o*-$MeOC_6H_4$	DMF	18	(*S*)-**12c** (16)[b]

[a] Yield after column chromatography. [b] Ring-opened products (*S*)-**10**, (*S*)-**12b**, and (*S*)-**12c** were obtained along with 32, 15, and 21% yields of (*S*)-**5**, respectively.



Scheme 4. Reactions of sulfamidate (*R*)-**1** with secondary and tertiary amines.

pounds that bear an amino group, namely α-amino acid derivatives. Specifically, we examined the reaction with phenylalanine methyl ester[14] under different conditions (solvent, temperature, and number of equivalents). The best yield (78%) of the ring-opened product (*S*,*S*)-**14** was obtained after heating at reflux for 12 h with 3.0 equivalents of the α-amino ester in acetonitrile (Scheme 5). It is noteworthy that



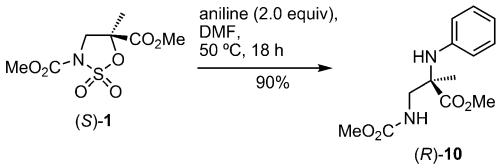
Scheme 5. Reaction of sulfamidate (*R*)-**1** with phenylalanine methyl ester.

in this case the use of DMF as a polar solvent was not necessary. As in the reactions with arylamines, we were able to isolate a new white solid compound, which was characterized by HRMS as a phenylalanine sulfamate derivative, formed by aminolysis of the sulfamic moiety.

In conclusion, sulfamidate (*R*)-**1** reacts differently with different types of amines. Arylamines and α-amino acid derivatives, and even propylamine under certain conditions, give a ring-opening reaction with inversion of configuration at the tertiary carbon (quaternary stereocenter), and a second step for hydrolysis of the sulfamic moiety is not required. In general, primary alkylamines give rise to two concomitant reactions: N-deprotection and ester–amide conversion. Secondary alkylamines give only N-deprotection of the cyclic sulfamidate. The use of tertiary alkylamines produces a mixture of N-deprotection and β-elimination products. In an attempt to rationalize the experimental observations, we compared the reactivities of the amines with their basicities.[15] Thus, less basic amines (arylamines and amino esters have pK_{aH} values of 3.89 to 7.11) behave as excellent nucleophiles in the ring-opening reaction of the cyclic sulfamidate, whereas more basic amines (alkylamines have pK_{aH} values of 9.33 to 10.84) are disfavored for this reaction, promoting instead N-deprotection or even the concomitant conversion of ester to amide, depending on steric hindrance.

One of the most attractive features of this class of 1,2-cyclic sulfamidates is their use as a synthetic tool allowing easy access to new acyclic chiral quaternary $\beta^{2,2}$-amino acids.[10] In the present study, the products obtained bear an additional amino substituent at the α-position, and so they can be regarded not only as important $\beta^{2,2}$-amino acids,[16] but also as α,β-diamino acids. α,β-Diamino acids and their derivatives have attracted a great deal of attention due to their ubiquitous nature as key structural fragments of biologically active compounds. An excellent review has recently been published,[17] dealing with their biological significance, therapeutic uses, and synthetic approaches for obtaining them. Their syntheses can be divided into two principal groups, those involving C–C bond formation and those involving C–N bond formation. The methodology proposed herein, based on the ring-opening of cyclic sulfamidates with amines, belongs to the second group.

On the other hand, *N*-aryl α-amino acids have been synthesized by various methodologies, such as nucleophilic ring opening of aziridines,[18] N-arylation by using palladium or copper catalysts,[19] and Michael additions of aniline derivatives to acrylates.[20] In view of the fact that both *N*-aryl α-amino acids and α,β-diamino acids have attracted considerable attention, we selected the reaction of sulfamidate (*R*)-**1** with aniline in order to synthesize a new amino acid with an arylated α-amino group. Initially, we carried out the same reaction but starting from the enantiomer of sulfamidate (*R*)-**1**, compound (*S*)-**1** (Scheme 6), and obtained a similar

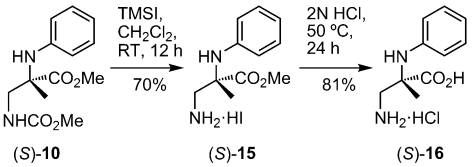


Scheme 6. Reaction of sulfamidate (*S*)-**1** with aniline.

result to that in Table 4, entry 2. The next step was to determine the enantiomeric excess of the ring-opened products (*S*)-**10** and (*R*)-**10** by chiral HPLC (see the Supporting Information). From these data, we concluded that the enantiomeric excess of the starting sulfamidate (which we previously established as 93% *ee*)[10b] was maintained in the ring-opening reactions, and that there was no racemization.

Selective deprotection of the carbamate group in the ring-opened product (*S*)-**10** by using iodotrimethylsilane (TMSI)[21] under an inert atmosphere gave diamino ester (*S*)-**15** (Scheme 7).. Subsequent acid hydrolysis of (*S*)-**15** with aqueous 2 N HCl at 50 °C for 24 h gave the α,β-diamino acid (*S*)-**16** as a hydrochloride derivative (Scheme 7).

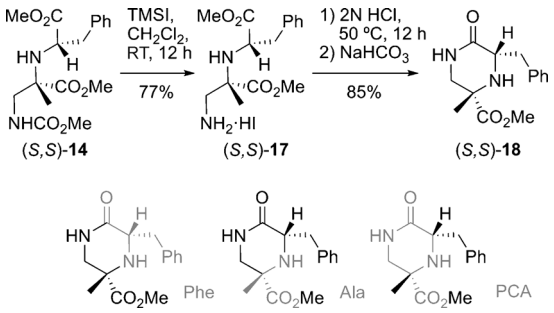
In looking for synthetic applications of the ring-opening reaction of sulfamidate (*R*)-**1** with α-amino esters, we focused our attention on the piperazinone substructure because it is a constituent of various natural products extracted from marine sponges, such as the phakellins group, (−)-agelastine A, and pseudoteonamides A_1 and A_2.[22]



Scheme 7. Synthesis of $\beta^{2,2}$-amino acid (*S*)-**16**.

Moreover, the piperazinone ring is also found in compounds of great interest to the pharmaceutical industry; for instance, in the family of renieramycins,[23] which show antitumor activity, and in some antihelmintic derivatives (marcfortine B and praziquantel).[24] The piperazinone substructure has also been incorporated into new peptidomimetics, with a view to generating structural modifications in the backbone due to the limited conformational flexibility of this cycle. In fact, the amino acid 5-oxopiperazine-2-carboxylic acid (abbreviated as PCA) is able to induce different turns when it is incorporated into tetrapeptides.[25] In general, the piperazinone substructure is obtained by cyclization reactions generating the C–N bond,[26] although other syntheses involving tandem reactions have been reported.[27] To synthesize *N*,*N*-disubstituted piperazinones, Gallagher and co-workers used a strategy that involved nucleophilic ring-opening reactions of cyclic sulfamidates with *N*-tosyl-α-amino esters in the presence of a base (NaH or Cs_2CO_3), followed by lactamization in an acid medium.[28] It is important to note that although this is the most closely related example of sulfamidate ring-opening to the work reported herein, there are two important differences. First, in the published report, the nucleophilic agent was not the amino group but the tosylamide derivative (TsN^-), a much more efficient nucleophile, which attacked an achiral secondary carbon atom. Second, in our case, the attack of the amino group occurs on a hindered system, a chiral quaternary center (tertiary carbon atom), with inversion of configuration.

Taking into account the importance of the piperazinone heterocycle, we synthesized compound (*S*,*S*)-**18**, a chiral 3,5,5-trisubstituted piperazinone derivative by starting from (*S*,*S*)-**14**, which was obtained by nucleophilic ring-opening of sulfamidate (*R*)-**1** with phenylalanine methyl ester (Scheme 8). The methylcarbamate group of compound (*S*,*S*)-**14** was transformed into an amino group by treatment with TMSI[21] to afford compound (*S*,*S*)-**17** as a hydroiodide derivative. The subsequent lactamization, accomplished by the action of aqueous 2 N HCl solution at 50 °C for 12 h, followed by neutralization with saturated aqueous $NaHCO_3$, afforded the required piperazinone derivative (*S*,*S*)-**18** in good yield (Scheme 8). This piperazinone can be regarded as a "chimera" of the α-amino acids phenylalanine and alanine. In particular, the phenylalanine substructure shows a huge conformational restriction, with *phi* and *psi* dihedral angles typical of folded conformations. In contrast, the alanine substructure shows only a restriction in the *phi* dihedral angle. Moreover, it is important to note that compound (*S*,*S*)-**18** incorporates the substructure of the above-cited PCA amino acid (Scheme 8).



Scheme 8. Synthesis of a chiral 3,5,5-trisubstituted piperazinone.

Compound (*S*,*S*)-**18** was also used to corroborate the configuration at the stereocenter created in the nucleophilic attack. Thus, in 2D NOESY experiments, observation of a clear NOE signal between H_α of the phenylalanine substructure and the methyl group attached to the quaternary stereocenter allowed us to conclude that the quaternary center had an (*S*)-configuration, indicating that the nucleophilic attack of this amine had proceeded with total inversion of configuration (Figure 2).

Conclusion

The reactivity of different amines with the 1,2-cyclic sulfamidate (*R*)-**1** derived from α-methylisoserine, which has previously provided a flexible and generally efficient entry to a range of $\beta^{2,2}$-amino acids, has been studied. Although this type of cyclic electrophile incorporates several reactive sites, we have found conditions that allowed us to control the chemoselectivity of the reaction. The reactivity of propylamine is controlled by the solvent: acetonitrile favors N-deprotection of the sulfamidate, in THF there is also N-deprotection, but this is accompanied by conversion of the methyl ester into a carboxamide, and DMF favors nucleophilic attack of propylamine (also observed with benzylamine) at the quaternary center of the sulfamidate with inversion of configuration, avoiding the use of a second step for sulfamic moiety hydrolysis. The chemoselectivity of the reaction is also controlled by the type of amine used. The use of arylamines and α-amino acid derivatives also led to ring opening of the sulfamidate with inversion of configuration, whereas, in general, primary alkylamines led to two concomitant reactions, N-deprotection and ester–amide conversion. Secondary alkylamines led to exclusive N-deprotection of the cyclic sulfamidate in a clean and simple manner. Additionally, we have found that DMF and DMSO behave not only as polar solvents, but also as nucleophilic reagents, allowing the incorporation of an oxygen atom in the electrophile.

As a synthetic application of this reactivity study, and taking into account the biological significance of α,β-diamino acids, we have developed the synthesis of a new type of chiral α,β-diamino acid with an arylated α-amino group. Since this sulfamidate readily undergoes a nucleophilic dis-

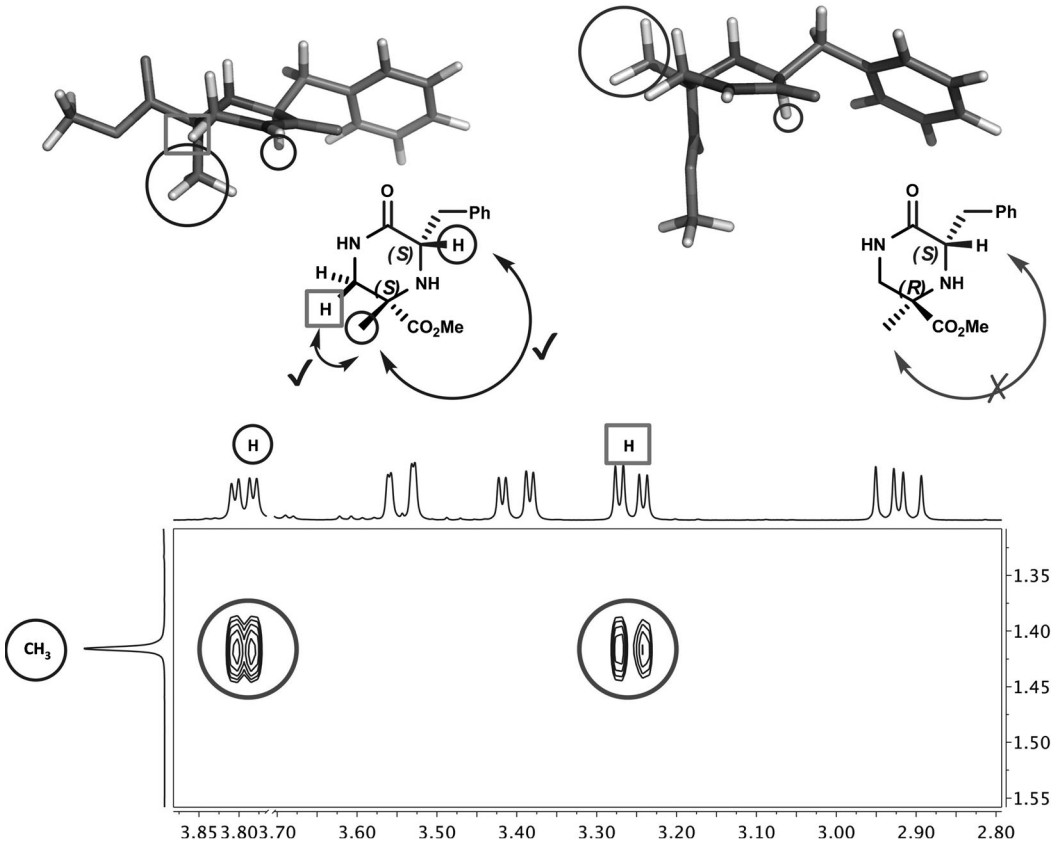


Figure 2. NOE NMR study of compound (*S*,*S*)-**18**.

placement by α-amino esters, application of this chemistry provided an example of an important class of chiral *N*-heterocycles based on the piperazinone ring, which can be regarded as a restricted scaffold that is suitably predisposed for use in peptide chemistry.

Experimental Section

General procedures: Solvents were purified according to standard procedures. Column chromatography was performed by using silica gel 60 (230–400 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer by using $CDCl_3$, CD_3OD, or D_2O as solvents (chemical shifts are reported in ppm on the δ scale, coupling constants in Hz). All resolved signals in the ^{1}H NMR spectra were assigned on the basis of coupling constants and ge-COSY and ge-HSQC experiments performed on the 400 MHz spectrometer. The results of these experiments were processed with MestReC and MestreNova software (Mestrelab Research, Spain). Melting points were determined on a Büchi melting-point apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer polarimeter from solutions in 1.0 dm cells of capacity 1.0 or 0.3 mL. Electrospray mass spectra were recorded on a micrOTOF-Q Bruker spectrometer; accurate mass measurements were achieved by using sodium formate as an external reference. Full experimental details and physical data for all new compounds are provided in the Supporting Information.

NMR experiments: NMR experiments were performed on a Bruker Avance 400 spectrometer at 298 K. Magnitude-mode ge-2D COSY spectra were acquired with gradients by using the cosygpqf pulse program with a pulse width of 90°. Phase-sensitive ge-2D HSQC spectra were acquired by using *z*-filter and selection before *t*1 removing the decoupling during acquisition by use of the invigpndph pulse program with CNST2 (JHC) = 145. Phase-sensitive ge-2D NOESY experiments were performed. NOE intensities were normalized with respect to the diagonal peak at zero mixing time.

X-ray diffraction analysis:[29] A summary of crystal data for (*R*)-**6**, (*R*)-**7**, and (*R*)-**9** is presented in the Supporting Information. The SHELXL97 program[30] was used for the refinement of crystal structures and hydrogen atoms were fitted at theoretical positions.

(*R*)-5-Methyl-2,2-dioxo-2λ⁶-[1,2,3]-oxathiazolidine-5-carboxylic acid methyl ester ((*R*)-2): Propylamine (73 mg, 1.24 mmol) was added to a solution of sulfamidate (*R*)-**1** (87 mg, 0.31 mmol) in acetonitrile (10 mL) and the mixture was stirred at reflux for 1 h. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with hexanes/ethyl acetate (7:3), to give compound (*R*)-**2** (36 mg, 60%) as a colorless oil. The physical properties of the product were found to be identical to those reported previously.[8f] Elemental analysis calcd (%) for $C_5H_9NO_5S$: C 30.77, H 4.65, N 7.18, S 16.43; found: C 30.89, H 4.63, N 7.16, S 16.45; $[\alpha]_D^{20}$ (c = 1.30 in $CHCl_3$): −24.4; MS (ESI+): m/z: 196.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.75 (s, 3H; CH_3), 3.44–3.58 (m, 1H; CH_2N), 3.87 (s, 3H; CO_2CH_3), 3.94–4.09 (m, 1H; CH_2N), 4.91 ppm (br s, 1H; NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.5 (CH_3), 52.1 (CH_2N), 53.7 (CO_2CH_3), 88.0 (CCH_3), 169.8 ppm (CO_2).

General procedure for the synthesis of carboxamides from sulfamidate (*R*)-1: Sulfamidate (*R*)-**1** and the requisite amine were dissolved in THF (or the amine was used as the solvent). The reaction mixture was stirred at room temperature for the time indicated in Table 3. After evaporation of the solvent, the residue was purified by column chromatography on silica gel eluting with hexanes/ethyl acetate (3:7).

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