



Reactivity of cyclic sulfamidates towards lithium acetylides: synthesis of alkynylated amines

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ABSTRACT

A synthetically useful level of reactivity of cyclic sulfamidates toward acetylides is described. Ring-opening reactions of a structurally diverse set of 1,2- and 1,3-cyclic sulfamidates with a range of lithium acetylides from aliphatic, cyclic, aromatic, heteroaromatic, and functionalized alkynes proceed smoothly in a regioselective manner to give the corresponding *N*-sulfate intermediates. Hydrolysis of these intermediates under acidic conditions furnishes the alkynylated amines in yields ranging from 29% to 98%. The scope of the acetylenic substitution reaction with the structural variations in both the cyclic sulfamidates and alkynes is briefly examined.

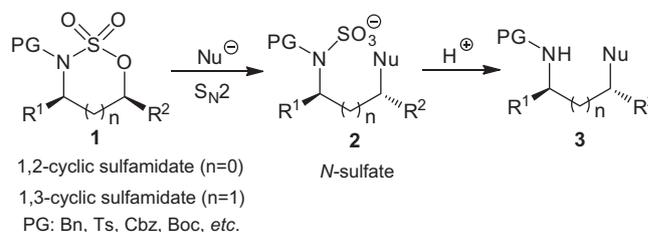
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Cyclic sulfamidates **1** represent a versatile class of readily accessible, often enantiomerically pure, aminoalcohol-derived electrophiles.¹ Increasing synthetic use of these heterocyclic compounds across a wide range of areas of synthesis over the last decade is based upon the fact that the formation of sulfamidates activates simultaneously the hydroxy group toward nucleophilic displacement while providing partially concurrent protection to the amino group. Nucleophilic attack occurs regioselectively at the oxygen-bearing carbon center in a stereospecific fashion (S_N2) to form *N*-sulfate intermediate **2** which can be hydrolyzed under mild acidic conditions to give the substitution product **3** (Scheme 1).

The reactivity profile of 1,2- and 1,3-cyclic sulfamidates toward nucleophilic cleavage corresponds to that associated with activated aziridines and azetidines, respectively, but sulfamidate chemistry offers several additional advantages.² The regioselectivity of nucleophilic attack on the activated aziridines and azetidines is not a straightforward issue, particularly in the absence of any steric and/or electronic directing effect. However, with the use of cyclic sulfamidates, the regioselectivity is largely defined by the higher reactivity exhibited by the C–O bond which enables a nucleophilic attack to take place in a regioselective manner, and the attack at the C–N bond is not generally observed. In contrast to their azacycle counterparts that strictly require a highly activating protecting group such as *N*-tosyl for efficient displacement, cyclic sulfamidates allow flexibility with respect to the protecting group on the nitrogen. A range of protecting groups including Ts, Bn, Cbz,

and Boc can be used with very little effect on the ability of the sulfamidates to undergo nucleophilic cleavage.^{3,4} Moving from three- to four-membered ring systems, azetidines may lack the required reactivity to be used as electrophiles.⁵ In the case of cyclic sulfamidates, on going from five- to six-membered ring systems, an acceptable level of activation is achievable as the reactivity of 1,2-cyclic sulfamidates is not largely derived from the ring strain. Recent studies describing successful fluoro⁶ and stereoselective³ alkylations with cyclic sulfamidates, otherwise not possible with azacycles, clearly emphasise the usefulness of sulfamidates.

There are many reports on the ring-opening of cyclic sulfamidates with nitrogen,⁷ oxygen,⁸ sulfur,⁹ phosphorus,¹⁰ and halogen¹¹ nucleophiles in the literature.¹² Of particular value is cleavage with carbon-based nucleophiles generating a new carbon–carbon bond that could enable the synthesis of functionalized amines. In this respect, the reactivity of cyclic sulfamidates toward synthetically more versatile carbon-based nucleophiles has been less widely exploited. Leading studies, especially by Gallagher and co-workers¹³



Scheme 1. Nucleophilic substitution of cyclic sulfamidates.

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and others¹⁴ have demonstrated that cyclic sulfamidates possess a high level of reactivity toward stabilized-carbon nucleophiles. The reactivity of 1,2- and 1,3-cyclic sulfamidates toward, for example, stabilized-enolates could be readily manipulated in a number of ways for asymmetric syntheses of substituted pyrrolidine and piperidine ring systems, respectively.¹³ To the best of our knowledge, there has been no report concerning the reactivity of the sulfamidates with acetylides.¹⁵ As a closely related class of electrophiles, cyclic sulfates are known to undergo efficient nucleophilic cleavage with acetylides to afford alkynylated alcohols.¹⁶ Thus a similar reactivity profile is anticipated with cyclic sulfamidates, and it is the purpose of this communication to report the reactivity of cyclic sulfamidates toward acetylides. The acetylenic displacement of cyclic sulfamidates is envisaged to serve as an effective alternative route for the synthesis of alkynylated amines.¹⁷

Initially, in trial experiments, enantiomerically pure phenylalaninol 1,2-cyclic sulfamidate **6** was prepared using the literature protocol.^{12c} Phenylacetylene (**4a**) was lithiated with *n*-butyllithium in THF at $-10\text{ }^{\circ}\text{C}$ for 1 h.¹⁸ The resulting solution of phenylacetylide **5** then reacted with **6** for 24 h to form *N*-sulfate intermediate **7**. Acidic hydrolysis of this intermediate was performed with 5 M HCl solution for 2 h.^{12c} Neutralization of the reaction mixture with aqueous saturated NaHCO_3 solution followed by chromatographic purification afforded (*S*)-*N*-benzyl-1,5-diphenyl-pent-4-yn-2-amine (**8a**) in essentially quantitative yield (Scheme 2). A slight excess (1.5 equiv) of the nucleophilic component **5** was required for the complete consumption of **6**.

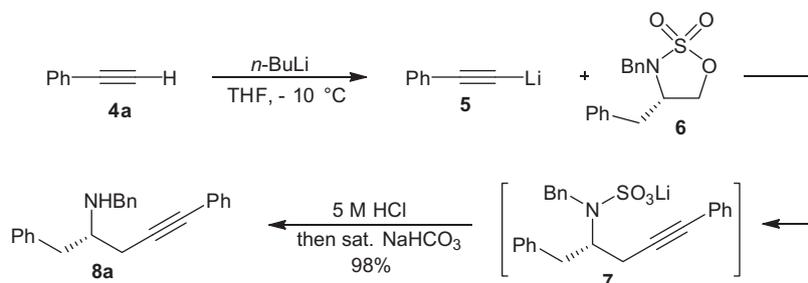
Gratified by this result, we decided to perform investigations on two separate sets in order to define briefly the scope of the acetylenic substitution reaction of 1,2-sulfamidates. For the first set, **6** was chosen as the model 1,2-cyclic sulfamidate and the structure of the alkyne component was varied. In the second set, phenylacetylene (**4a**) was the model terminal alkyne, and the 1,2-cyclic sulfamidate structure was altered. Besides, we encountered aggregation problems with some acetylide species, which was overcome by the addition of HMPA as a polar solvent.⁶ Inclusion of 10% HMPA by volume in the reaction mixtures was found to enhance significantly both the reaction rates and yields. For example, the ring-opening reaction of **6** with **5** was complete in less than 1 h. Therefore, the substitution reactions were investigated without (Procedure A) and with HMPA (Procedure B). As 1.5 equiv of nucleophilic component was not sufficient to achieve complete consumption of the sulfamidate, in particular for some of those reactions studied without HMPA, 2 equiv of the acetylides was generally used.

Nucleophilic cleavages of phenylalaninol 1,2-cyclic sulfamidate **6** with a diverse set of lithium acetylides are shown in Table 1. The acetylenic substitution appears to be a general reaction with regard to the structural effect of the nucleophilic component. A range of functionalities including ether, acetal, orthoester, tertiary amine, heteroaromatic on the acetylide were tolerated.¹⁹ Using procedure A, hydrocarbon-based lithium acetylides from aromatic

4a, conjugated **4b**, aliphatic **4c–d**, and cyclic **4e** alkynes all reacted efficiently with **6** to deliver the corresponding β -alkynylated amines **8a–e** in excellent yields after the standard acidic-basic work-up. Reactions of acetylides with acetal **4f** and orthoester **4g** functionalities also took place smoothly to form the intermediate *N*-sulfates. During the standard acidic hydrolysis of these intermediates the orthoester group was hydrolyzed concurrently to obtain an ethyl ester while the acetal group was sufficiently stable to obtain the β -alkynylated chiral amine **8f** in 85% yield. A similar ring-opening reaction with phenylpropargyl ether **4j**, which is prone to rearrangements,²⁰ gave a complex mixture rendering the corresponding alkynylated amine inaccessible. Following procedure A, benzyl ether-containing alkyne **4i** gave alkynylated amine **8i** in a modest yield (remaining mass balance was unreacted **6**). Changing the reaction conditions to procedure B increased drastically the reaction yield to 96%. Without HMPA acetylides from **4h**, **4k**, and **4l** showed sluggish reactivity in the alkylation reactions. On successful alkylation of the hydrocarbon-based alkynes, the reaction mixtures were clear pale yellow solutions. On the contrary, the acetylide solutions of **4h,k,l** appeared rather cloudy which could be caused by aggregation problems. Thus, the addition of HMPA was necessary to effect the successful alkynylation in these cases. In this way, β -alkynylated amines **8h** and **k** were obtained in high yields. Alkylation of the acetylene **4l** containing a pyridine moiety proved to be more problematic. Reaction of **4l** with **6** using HMPA produced an intractable mixture. The reaction temperature had to be lowered to $-78\text{ }^{\circ}\text{C}$ to achieve a reasonable yield of product **8l** (entry 12).

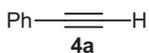
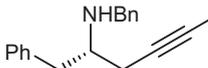
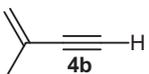
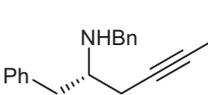
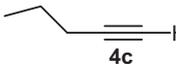
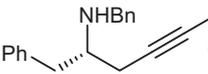
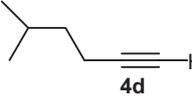
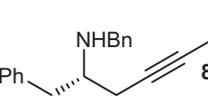
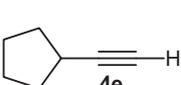
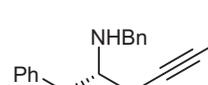
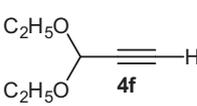
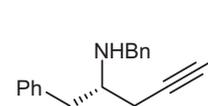
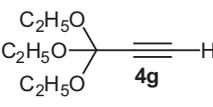
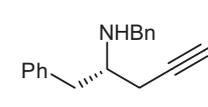
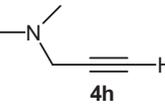
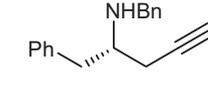
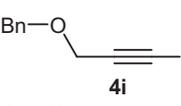
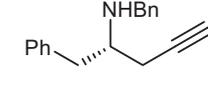
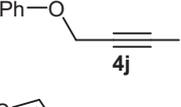
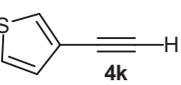
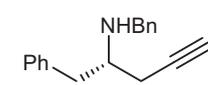
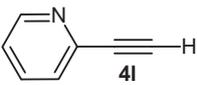
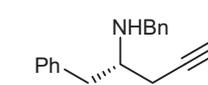
A representative set of 1,2-cyclic sulfamidates was synthesized for examination of the structural effect of the sulfamidate on the alkylation.²¹ We preferred to use the benzyl group for *N*-protection considering the ease of its installation and subsequent removal by hydrogenation as well as its stability under the basic conditions employed. Enantiomerically pure primary carbon-centered sulfamidates **9a–d** were prepared from *L*-alanine, valine, norvaline, and proline using literature protocols.^{9a,12c,12g} Among secondary carbon-centered 1,2-cyclic sulfamidates, ephedrine-derived **9e** and lactate-derived **9f** were optically pure, **9g** was prepared in a racemic form for convenience.^{12c} The synthesis of **9f** from (*S*)-ethyl lactate was achieved via amidation with benzylamine,²² reduction with LAH,²³ and a two-step sulfamidate formation reaction sequence.

With the exception of proline-derived **9d**, primary carbon-centered 1,2-cyclic sulfamidates **9a–c** were found to be particularly effective in the alkylation reaction with phenylacetylide **5** delivering the expected β -alkynylated amines **10a–c** in excellent yields (Table 2). The reactivity difference between **9b** and **9c** can be attributed to the steric effect of the isopropyl group as the reaction of **9b** proceeded relatively slowly without HMPA. Reaction of bicyclic **9d**, according to procedure A or B, occurred readily to form an intermediate (all of **9d** was consumed in both cases by TLC), but we were unable to hydrolyze this intermediate using the standard



Scheme 2. Reaction of phenylalaninol 1,2-cyclic sulfamidate **6** with phenylacetylide **5**.

Table 1
Reactions of phenylalaninol sulfamidate **6** with various terminal alkynes at $-10\text{ }^{\circ}\text{C}$

Entry	Terminal alkyne 4	Product 8	Procedure	Yield (%) ^a
1			A	98
2			A	95
3			A	91
4			A	90
5			A	95
6			A	85
7			A	89
8			A B	– 95
9			A B	60 96
10		complex mixture	A B	– –
11			A B	19 92
12			A B	– 71 ^b

Procedure **A**: reactions run in THF without the addition of HMPA.

Procedure **B**: reactions run in THF with the addition of 10% HMPA by volume.

^a Yield of isolated product after chromatographic purification.

^b Reaction run at $-78\text{ }^{\circ}\text{C}$.

conditions. Attempted hydrolysis of the intermediate under various acidic conditions (concd. HCl, 20% and 50% H_2SO_4) failed to produce any success; heating usually resulted in degradation of the intermediate.^{14c} Sterically demanding ephedrine-derived sulfamidate **9e** was completely unreactive with acetylide **5** without HMPA. When HMPA was present, the same reaction run at either $-10\text{ }^{\circ}\text{C}$ or $-78\text{ }^{\circ}\text{C}$ gave a complex mixture. Secondary carbon-centered lactic acid derived **9f**, of sterically less demanding nature, underwent uneventful alkylation with **5** in a stereospecific manner to furnish the amine **10f** in 85% yield with an inversion of stereochemistry. The lability of the sulfamidate **9g** toward elimination has been already reported.^{12c} Thus, the use of **9g** is

considered to be a test of the given nucleophilic component for the elimination pathway. Using procedure **A**, the alkylation reaction of **9g** with **5** led to the formation of the desired substitution product **10g** along with *N*-benzyl cinnamylamine **11** in 29% and 67% yields, respectively. Performing the reaction in a more polar solvent system afforded **11** as the sole reaction product in 85% yield. Increasing the polarity of the solvent system seemed to favor the elimination pathway. Lowering the reaction temperature was not effective in altering at the substitution–elimination product distribution in favor of **10g**. This attempt only slowed the reaction rate without any desirable effect on the formation of **10g**.

Table 2
Reactions of **5** with various 1,2-cyclic sulfamidates **9a–g** at $-10\text{ }^{\circ}\text{C}$

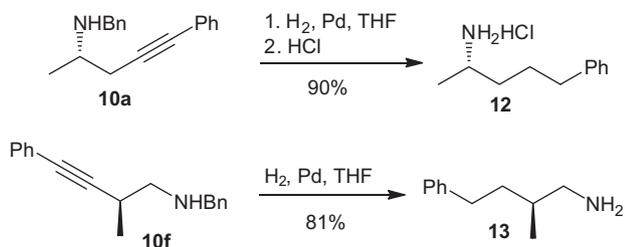
Entry	1,2-Cyclic sulfamidate	Product 10	Procedure	Yield (%) ^a
1			A	95
2			A B	60 88
3			A	95
4		see text	A B	– –
5		complex mixture	A B	– –
6			A B	63 85
7			A B	29 –
			A B	67 85

Procedure **A**: reactions run in THF without the addition of HMPA.

Procedure **B**: reactions run in THF with the addition of 10% HMPA by volume.

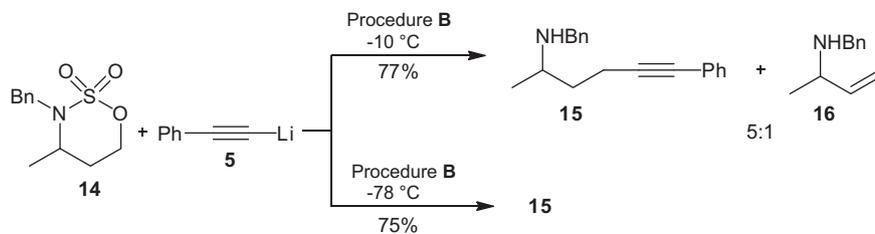
^a Yield of isolated product after chromatographic purification.

^b Reaction performed at $-78\text{ }^{\circ}\text{C}$ (see text).



Scheme 3. Conversion of alkyne products into saturated amine derivatives.

The critical issues of the alkylation reactions described in this study that require clarification are the stereochemical integrity of the stereogenic centers of the sulfamidates and the S_N2 nature of the displacement with **9f**. For this purpose, amine **10a** was converted into (*S*)-5-phenyl-2-pentylamine hydrochloride (**12**) ($[\alpha]_D^{30} -5.5$ (c 1, EtOH), for *R* **12**, $[\alpha]_D^{20} +3.0$ (c 0.63, EtOH), 92% e.e.²⁴) by atmospheric hydrogenation over palladium²⁵ (Pd/C and Pd(OH)₂/C) to effect both saturation and debenylation (Scheme 3). Similarly, lactate derived-amine **10f** was also converted into known (*S*)-2-methyl-4-phenylbutylamine (**13**). The specific rotation ($[\alpha]_D^{30} -16.2$ (c 1, CHCl₃)) of **13** was in close agreement with



Scheme 4. Reaction of 1,3-cyclic sulfamidate **14** with phenylacetylide **5**.

the literature value ($[\alpha]_{\text{D}}^{20} -15.9$ (c 1.11, CHCl_3)).²⁶ Derivatization of saturated amines **12** and **13** with (+)-MTPA²⁷ to give the corresponding Mosher amides showed that there was a single diastereoisomer present in each case by analysis of ^1H NMR spectra. This result rules out any racemization of the stereogenic centers occurring during the alkylation reactions. Observation of the diastereomerically pure Mosher amide derivative of **13** indicates clean inversion of the stereochemistry during the alkylation of **9f** with **5**, which is frequently observed in the literature.¹³

We were also interested in the reactivity of 1,3-cyclic sulfamidates in the alkylation reaction. Methyl substituted **14** as the only studied 1,3-cyclic sulfamidate exhibited considerably lower reactivity toward **5** compared with alanine-derived **9a** (Scheme 4). Using procedure A, sulfamidate **14** failed to react with **5** even over a longer reaction time (48 h). The use of HMPA nevertheless brought about an acceptable degree of reactivity, and the corresponding reaction of **14** with **5** afforded the desired γ -alkynylated amine **15** along with a by-product. Separation of **15** from the by-product was not possible by column chromatography. Conversion of these compounds into the amide or carbamate derivatives did not facilitate chromatographic separation. The structure of the by-product was tentatively proposed to be *N*-benzyl-3-buten-2-amine (**16**)²⁸ by analysis of the ^1H NMR spectrum of the purified mixture that could result from the competing elimination pathway. The ratio of **15**/**16** was estimated as 5:1 by ^1H NMR spectroscopy and the products were obtained in 77% overall yield. Fortunately, lowering the reaction temperature to $-78\text{ }^{\circ}\text{C}$ reduced the amount of **15** to 2–3%.²⁹

In summary, a useful level of reactivity of the cyclic sulfamidates toward a range of acetylides has been reported. The ready availability of cyclic sulfamidates and alkynes coupled with the reactivity profile provides a practical and efficient entry for the syntheses of γ - and β -alkynylated amines. Given the array of versatile functionalities present and the widespread use of amines in diverse areas of organic synthesis, the alkynylated amines are valuable compounds for downstream manipulations. Further exploitation of functionalized alkynylated amines is currently underway and will be reported elsewhere.

Acknowledgments

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Supplementary data

Supplementary data associated with this Letter can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.171.

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