Tetrahedron Letters 52 (2011) 6336–6341

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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

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ARTICLE INFO

Article history:
Received 28 June 2011
Revised 12 August 2011
Accepted 30 August 2011
Available online 5 September 2011

Keywords:
Cyclic sulfamidates
Nucleophilic substitution
Lithium acetylides
Alkynylated amines

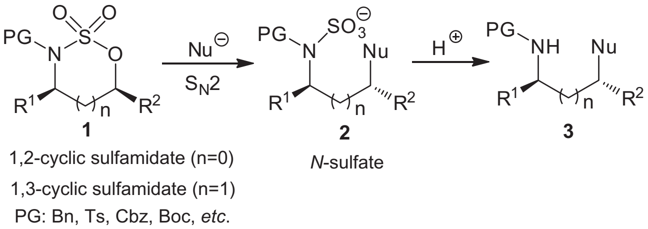
ABSTRACT

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.

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 fluoro[6] and stereoselective[3] 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 halogen[11] 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-workers[13]



Scheme 1. Nucleophilic substitution of cyclic sulfamidates.

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doi:10.1016/j.tetlet.2011.08.171

and others[14] 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]

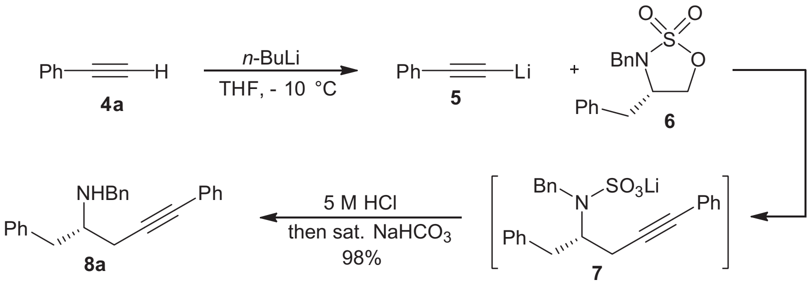
Initially, in trial experiments, enantiomerically pure phenylalaninol 1,2-cyclic sulfamidate **6** was prepared using the literature protocol.[12c] Phenylacetylene (**4a**) was lithiated with *n*-butyllithium in THF at −10 °C for 1 h.[18] The resulting solution of phenylacetylide **5** then reacted with **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 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 rearrangments,[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 °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**, occured 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**.