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Cyclic Sulfamidates as Vehicles for the Synthesis of Substituted Lactams

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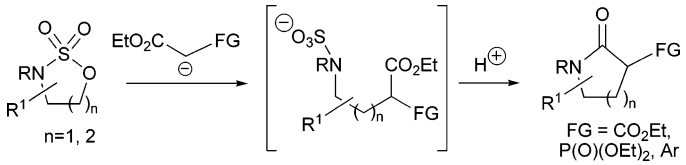
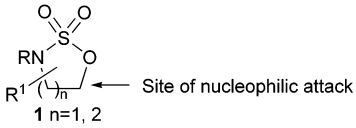
ABSTRACT



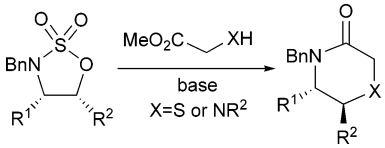
A structurally diverse series of mono- and disubstituted 1,2- and 1,3-cyclic sulfamidates react with stabilized enolates, including malonate and phosphonoacetate variants, to provide, after lactamization, substituted and α-functionalized pyrrolidinone and piperidinone derivatives.

Cyclic sulfamidates **1** represent a readily accessible and versatile set of amino alcohol-derived electrophiles that undergo facile and regiospecific nucleophilic substitution at the O-bearing carbon center.[1]



This reactivity profile makes 1,2- and 1,3-cyclic sulfamidates equivalent to activated aziridines and azetidines respectively, and the reaction of cyclic sulfamidates with simple nucleophiles, e.g., CN^-, F^-, N_3^-, has been reported.[2] In earlier work we demonstrated that enantiomerically pure 1,2-cyclic sulfamidates react efficiently with α-amino and α-thiol esters to provide substituted piperazinones and thiomorpholinones in a highly stereocontrolled manner (Scheme 1).[3]

Scheme 1. Piperazinones and Thiomorpholinones from 1,2-Cyclic Sulfamidates



This sequence involves nucleophilic ring opening (via N or S) and a subsequent lactamization step to create the heterocyclic framework. However, the reactivity of cyclic sulfamidates toward synthetically more versatile carbon-based nucleophiles such as enolates have been less widely exploited.[4] In this paper we describe the reactivity of a series of readily available and structurally representative cyclic sulfamidates toward functionalized enolates that leads, via initial nucleophilic ring opening and subsequent lactamiza-

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(1) For a recent and very comprehensive review, see: Meléndez, R. E.; Lubell, W. D. *Tetrahedron* **2003**, *59*, 2581−2616.

(2) Details of nucleophilic displacements up until 2003 are available in ref 1. For very recent work leading to $\beta^{2,2}$-amino acids via 1,2-cyclic sulfamidates, see: Avenoza, A.; Busto, J. H.; Corzana, F.; Jiménez-Osés, G.; Peregrina, J. M. *Chem. Commun.* **2004**, 980−981.

(3) Williams, A. J.; Chakthong, S.; Gray, D.; Lawrence, R. M.; Gallagher, T. *Org. Lett.* **2003**, *5*, 811−814.

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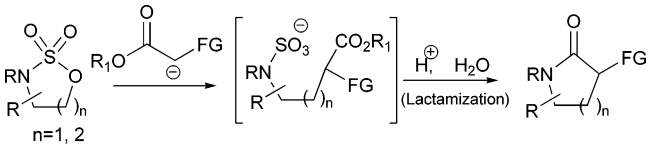
tion, to substituted and functionally useful pyrrolidinones and piperidinones (Scheme 2).

Scheme 2. Pyrrolidinones and Piperidinones via 1,2- or 1,3-Cyclic Sulfamidates and Enolates



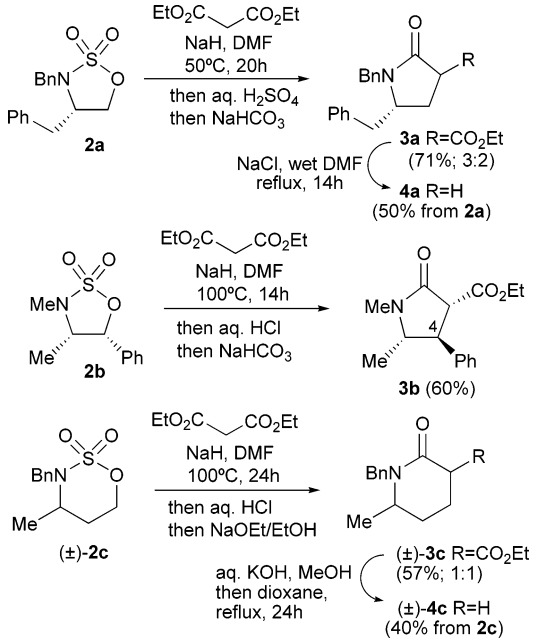
We have focused on α-functionalized enolates primarily for the advantages associated with the use of stabilized enolates as nucleophiles and also for the additional synthetic flexibility that these reactants provide within the heterocyclic product.

The enantiomerically pure phenylalaninol-derived cyclic sulfamidate **2a**[5] reacts readily with the enolate of diethyl malonate and, following treatment with acid (to cleave the initially formed *N*-sulfate) and neutralization, lactam **3a** (as a 3:2 mixture of C(3) diastereomers) was isolated in 71% yield (Scheme 3). This intermediate underwent ester cleavage and decarboxylation to give pyrrolidinone **4a** in 50% overall yield from **2a**. Under similar conditions, cyclic sulfamidate **2b** derived from ephedrine gave the trisubstituted pyrrolidinone **3b** as a single diastereomer in 60% yield, with clean inversion of stereochemistry at C(4) being observed.[6] The racemic 1,3-sulfamidate **2c** afforded piperidinone **3c** (57%, as a 1:1 mixture of diastereomers), which gave **4c** (71%) following decarboxylation. The only issue in this last case was the need for a separate lactamization step, which was carried out under basic conditions; while 5-ring lactamization (leading to **3a** and **3b**) occurred spontaneously, the corresponding cyclization to form the six-membered ring of **3c** was more sluggish.

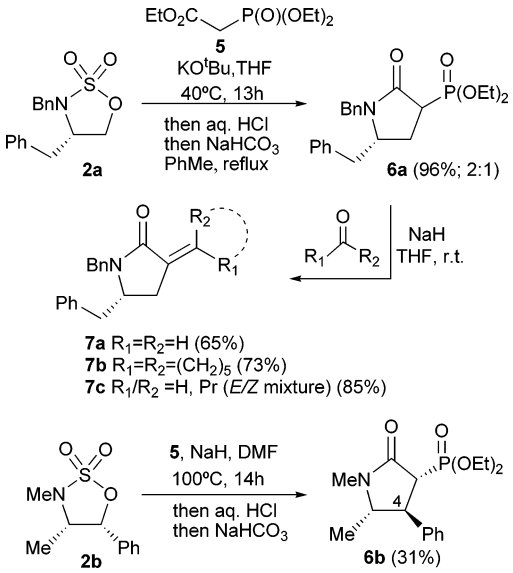
The reactivity of a series of cyclic sulfamidates toward a phosphorus-stabilized enolate has also been studied (Scheme 4). These reactions proceed in a manner similar to those outlined in Scheme 3, but certain modifications were necessary. Using **2a** as a model substrate, reaction with triethyl phosphonoacetate **5** under basic conditions, followed by acidic hydrolysis and thermally induced lactamization (PhMe, reflux), gave phosphonate **6a** in 96% yield.[7] The use of this intermediate in the Wadsworth−Emmons olefination process was also validated using paraformaldehyde, cyclohexanone, and butanal to give the exoalkylidene derivatives **7a**−**c**, respectively.[8]

Similarly, the 4,5-disubstituted cyclic sulfamidate **2b** was converted to trisubstituted lactam-based phosphonate **6b** in

Scheme 3. Malonate as an Effective Carbon Nucleophile



Scheme 4. Phosphonate-Stabilized Enolates and Wadsworth−Emmons Olefinations



(4) (a) Baldwin, J. E.; Spivey, A. C.; Schofield, C. J. *Tetrahedron: Asymmetry* **1990**, *1*, 881−884. (b) Boulton, L. T.; Stock, H. T.; Raphy, J.; Horwell, D. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1421−1429. (c) Wei, L.; Lubell, W. D. *Org. Lett.* **2000**, *2*, 2595−2598. (d) Wei, L.; Lubell, W. D. *Can. J. Chem.* **2001**, *79*, 94−104. Cyclic sulfamidates react with certain carbon-based nucleophiles (cuprates, RLi, $^{-}$CN) (see ref 1), but specific examples involving enolates have also been described. Lubell[4c,d] has shown that a 1,2-cyclic sulfamidate derived from serine reacts with enolates both directly and via an elimination−addition sequence, which results in significant loss of enantiomeric integrity. However, in a related but sterically more demanding sulfamidate, Boulton[4b] showed that enolates and silyl enol ethers failed to react. A 1,3-cyclic sulfamidate derived from homoserine underwent nucleophilic ring opening with a stabilized enolate.[1]

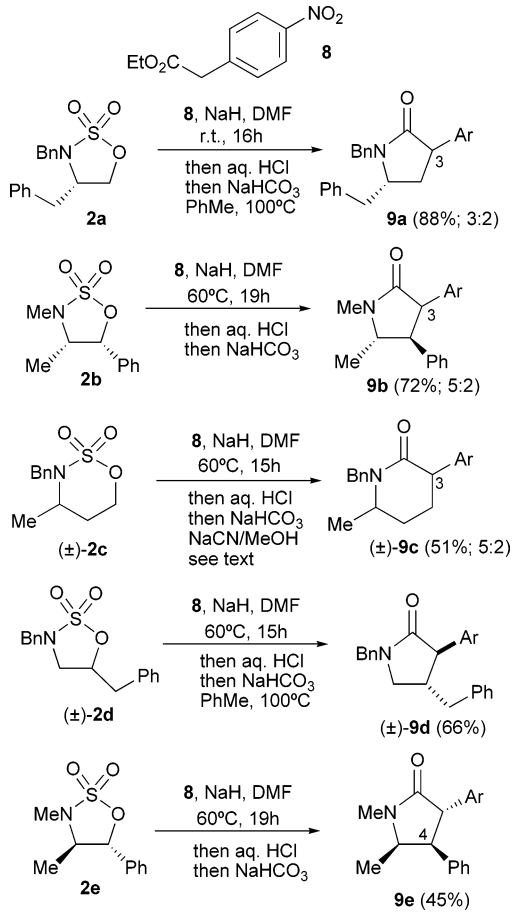
(5) (a) Wehn, P. M.; Lee, J. H.; Du Bois, J. *Org. Lett.* **2003**, *5*, 4823−4826. (b) Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935−6936. (c) Posakony, J. J.; Grierson, J. R.; Tewson, T. J. *J. Org. Chem.* **2002**, *67*, 5164−5169. 1,2-Cyclic sulfamidates were prepared as described earlier from the corresponding 2-amino alcohols.[3] 1,3-Cyclic sulfamidate **2c** was prepared using the method of Du Bois. Subsequent N-benzylation was carried out under Tewson's phase transfer conditions. See Supporting Information. A more conventional approach to **2c** from the corresponding amino alcohol was examined, but oxidation of the intermediate 1,3-cyclic sulfamidite was inefficient. Substrates **2a**, **2b**, and **2e** were prepared using enantiomerically pure starting materials and **2c** and **2d** were racemic.

(6) The structure of **3b** was determined by X-ray crystallographic analysis. Details are available in Supporting Information.

31% overall yield. Lactamization in this latter case occurred spontaneously upon neutralization, and again complete inversion of stereochemistry at C(4) was observed. On the other hand, although **2c** did react with the enolate of **5**, this step and in particular the subsequent lactamization were not efficient reactions.

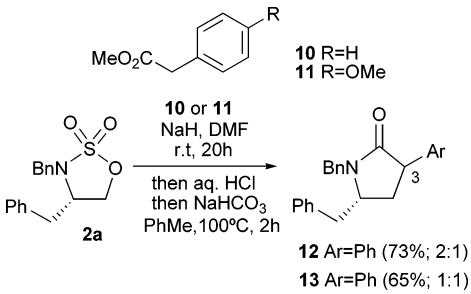
Diethyl malonate and triethyl phosphonoacetate both provide stabilized enolates that impart additional synthetic flexibility to the lactam products. We were also interested in examining less classically stabilized and more basic enolates in order to define the scope of this methodology more effectively. (The malonate and phosphonate-derived products, e.g., **3a**−**c** and **6a**/**b**, are stereochemically labile at C(3), but less acidic centers offer a possibility of kinetic control of stereochemistry at this site.)[9] Enolates derived from α-aryl acetates were particularly attractive, as they offered access to α-arylated pyrrolidinones (Schemes 5 and 6). The

Scheme 5. Aryl-Substituted Enolates as Nucleophiles: Synthesis of α-Arylated Lactams (Ar = 4-$NO_2C_6H_4$)



enolate derived from ethyl 4-nitrophenylacetate **8** was studied most widely and provided a range of substitution patterns that were determined by the cyclic sulfamidate used. These reactions paralleled those described earlier: initial nucleophilic displacement, *N*-sulfate cleavage using acid, neutralization, and lactamization. The lactamization step occurred either spontaneously (upon neutralization with $NaHCO_3$) or

Scheme 6. Aryl-Substituted Enolates as Nucleophiles: Synthesis of α-Arylated Lactams



was induced thermally (PhMe, reflux). In the case of piperidinone **9c**, lactamization was evaluated under a series of different conditions with the use of NaCN (10 mol %) as a nucleophilic catalyst being most efficient.[10,11] Several other stereochemical points require clarification. The relative configuration of racemic **9d** was established by X-ray crystallographic analysis (details are available in Supporting Information), and the S_N2 nature of the initial displacement was clearly demonstrated using the pseudoephedrine-derived cyclic sulfamidate **2e**. This provided **9e** (as a single diastereomer), a stereoisomer of the two products **9b** derived from the analogous reaction of the ephedrine derivative **2b**. It is also important to note that the α-arylated lactams **9a**−**c** were isolated as 1.5−2.5:1 mixtures of diastereomers at C(3).

The nitrophenyl derivative **8** provides a relatively stabilized enolate, but other, more conventional aryl acetates **10** (Ar = Ph) and **11** (Ar = 4-$MeOC_6H_4$) are also effective (Scheme 6).[12] Using **2a** as a representative cyclic sulfamidate, enolates derived from both **10** and **11** provided the α-arylated analogues **12** and **13** in 73 and 65% yields, respectively, and as mixtures of diastereomers at C(3).

In summary, we have demonstrated that a series of structurally representative 1,2- and 1,3-cyclic sulfamidates, react well with a variety of both stabilized and more conventional enolates, leading to heterocyclic products that

(7) α-Phosphonolactams analogous to **6a** have been prepared previously in a number of different ways and utilized in olefination processes. For recent representative examples, see: Gois, P. M. P.; Afonso, C. A. M. *Eur. J. Org. Chem.* **2003**, 3798−3810. Gois, P. M. P.; Afonso, C. A. M. *Tetrahedron Lett.* **2003**, *44*, 6571−6573. Du, Y. M.; Wiemer, D. F. *J. Org. Chem.* **2002**, *67*, 5709−5717.

(8) α-Phosphonolactam **6a** was a mixture of diastereomers at C(3), which had no impact on the subsequent Wadsworth−Emmons reaction. In the case of **6b**, a single isomer was isolated and assigned by analogy to **3b**.[6]

(9) In the case of **9b**, a 5:2 ratio of C(3) diastereomers was observed, while single (presumably thermodynamically more stable) diastereomers were seen for the corresponding malonate and phosphonate adducts **3b** and **6b**, respectively.

(10) Mori, K.; Tominaga, M.; Takigawa, T.; Matsui, M. *Synthesis* **1973**, 790−791. Högberg, T.; Ström, P.; Ebner, M.; Rämsby, S. *J. Org. Chem.* **1987**, *52*, 2033−2036. For an earlier application of cyanide-mediated lactamization, see ref 3.

(11) Our observations are that the initial nucleophilic displacement reaction involving **2c** occurs efficiently, but the subsequent lactamization leading to a six-membered ring is more demanding. In addition to NaCN/MeOH, lactamization to give **9c** was also achieved using either *p*-xylene at reflux (37%) or EtONa/EtOH at reflux (23%).

(12) A trend is apparent here. Sulfamidate **2a** gives lowered yields of 3,5-disubstituted lactams as the enolate becomes more basic: **9a** (88%); **12** (73%); **13** (65%). It is also pertinent to mention that attempts to use simple alkyl enolates, e.g., sodium ethyl propanoate, have failed.

can be further utilized in other ways. It is also important to recognize α-amino acids and 2-amino alcohols are precursors to 1,2-cyclic sulfamidates (e.g., **2a** and **2b**), which in turn provides access to the corresponding enantiomerically pure nitrogen heterocycles. Other recent work has also defined new routes to 1,2-, 1,3-, and 1,4-cyclic sulfamidates, which serves to extend further the potential of these units as substrates for heterocyclic synthesis.[13]

(13) Nicolaou, K. C.; Snyder, S. A.; Nalbandian, A. Z.; Longbottom, D. A. *J. Am. Chem. Soc.* **2004**, *126*, 6234−6235. Liang, J. L.; Yuan, S. X.; Huang, J. S.; Che, C. M. *J. Org. Chem.* **2004**, *69*, 3610−3619. Fruit, C.; Müller, P. *Tetrahedron: Asymmetry* **2004**, *15*, 1019−1026. Liang, J. L.; Yuan, S. X.; Huang, J. S.; Yu, W. Y.; Che, C. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3465−3468. Duran, F.; Leman, L.; Ghini, A.; Burton, G.; Dauban, P.; Dodd, R. H. *Org. Lett.* **2002**, *4*, 2481−2483. Nicolaou, K. C.; Huang, X. H.; Snyder, S. A.; Rao, P. B.; Bella, M.; Reddy, M. V. *Angew. Chem., Int. Ed.* **2002**, *41*, 834−838. Yu, X. Q.; Huang, J. S.; Zhou, X. G.; Che, C. M. *Org. Lett.* **2000**, *2*, 2233−2236.

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Supporting Information Available: Experimental and characterization data, including copies of ^{1}H and ^{13}C NMR for all new compounds, and crystallographic details for **3b** and **9d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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