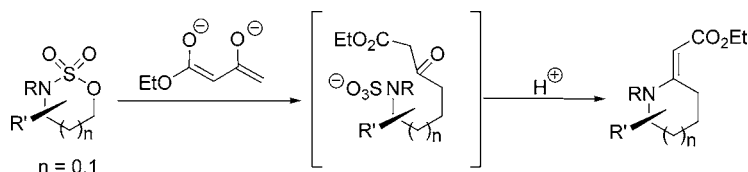


Cyclic Sulfamidates as Precursors to
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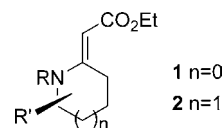
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ABSTRACT



The reaction of the dienolate of ethyl acetoacetate (and related dienolates) with a range of 1,2- and 1,3-cyclic sulfamidates provides an entry to substituted and enantiopure alkylidenated pyrrolidines and piperidines. These heterocycles function as convenient precursors to heterocyclic β -amino acid derivatives.

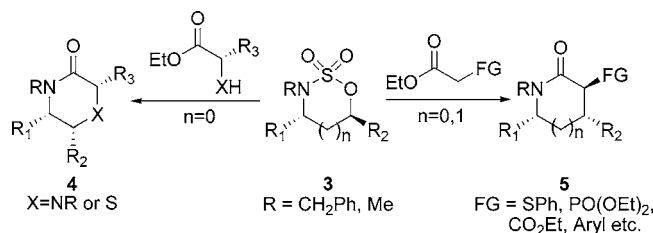
Alkylidene variants of pyrrolidines and piperidines (**1** and **2**) represent a versatile family of *N*-heterocycles which have found numerous applications in a variety of synthetic settings.¹ The most common route to members of this class of compound involves alkylidenation of a lactam precursor by activation of the otherwise unreactive carbonyl unit. In this regard, the classical Eschenmoser sulfide contraction of thiolactams has found widespread application² as has lactam activation via the corresponding iminoether.^{3,4} While efficient, these approaches necessarily rely on first obtaining a suitably substituted (and enantiopure) lactam precursor.



We are interested in heterocyclic alkylidenes **1** and **2** as suitable intermediates for the synthesis of substituted (and enantioenriched) homoproline and homopiecolinic acid derivatives, respectively. Accordingly, we sought a direct but flexible entry which would provide access to range of substitution patterns, and in this paper, we disclose our studies in this area. We have explored the reactivity of 1,2- and 1,3-cyclic sulfamidates **3** with both heteroatom and carbon-based nucleophiles to provide a variety of *N*-heterocyclic scaffolds, including **4** and **5** (Scheme 1).^{5,6}

[†] University of Bristol.[‡] GlaxoSmithKline.(1) For a review on the synthesis and reactivity of alkylidene pyrrolidines, see: Elliott, M. C.; Wood, J. L.; Wordingham, S. V. *Trends Heterocycl. Chem.* **2005**, *10*, 73–95.(2) (a) Fischli, A.; Eschenmoser, A. *Angew. Chem., Int. Ed.* **1967**, *6*, 866–868. (b) Yamada, Y.; Miljkovic, D.; Wehrli, P.; Golding, B.; Löliger, P.; Keese, R.; Müller, K.; Eschenmoser, A. *Angew. Chem., Int. Ed.* **1969**, *8*, 343–348. (c) Roth, M.; Dubs, P.; Götschi, E.; Eschenmoser, A. *Helv. Chim. Acta*, **1971**, *54*, 710–734. For other selected examples of this method, see: (d) Gossauer, A.; Hinze, R.-P.; Zilch, H. *Angew. Chem., Int. Ed.* **1977**, *16*, 418–418. (e) Shiosaki, K.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 1229–1239. (f) Honda, T.; Kimura, M. *Org. Lett.* **2000**, *2*, 3925–3927.(3) For selected examples of lactam alkylidenation via the intermediacy of imino ethers, see: (a) Célérier, J.-P.; Deloisy, E.; Lhomme, G.; Maitte, P. *J. Org. Chem.* **1979**, *44*, 3089–3089. (b) Coppola, G. M.; Damon, R. E. *A. J. Heterocyclic Chem.* **1990**, *27*, 815–817. (c) Millet, R.; Domarkas, J.; Rombaux, P.; Rigo, B.; Houssin, R.; Hénichart, J.-P. *Tetrahedron Lett.* **2002**, *43*, 5087–5088.(4) For other selected approaches to alkylidene pyrrolidines, see: (a) Breuer, E.; Zbaida, S. *J. Org. Chem.* **1977**, *42*, 1904–1910. (b) Hannick, S. M.; Kishi, Y. *J. Org. Chem.* **1983**, *48*, 3833–3835. (c) Lambert, P. H.; Vaultier, M.; Carrié, R. *J. Org. Chem.* **1985**, *50*, 5352–5356. (d) Shaw, K. J.; Luly, J. R.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 4515–4523. (e) Michael, J. P.; Hosken, G. D.; Howard, A. S. *Tetrahedron* **1988**, *44*, 3025–3036. (f) Jacobi, P. A.; Brielmann, H. L.; Hauck, S. I. *J. Org. Chem.* **1996**, *61*, 5013–5023. (g) Jacobi, P. A.; Buddhu, S. C.; Fry, D.; Rajeswari, S. *J. Org. Chem.* **1997**, *62*, 2894–2906. (h) Langer, P.; Freifeld, I. *Chem. Commun.* **2002**, 2668–2669. (i) Elliott, M. C.; Wordingham, S. V. *Synthesis* **2006**, 1162–1170.(5) For a review on the synthesis and reactivity of cyclic sulfamidates, see: Meléndez, R. E.; Lubell, W. D. *Tetrahedron* **2003**, *59*, 2581–2616.

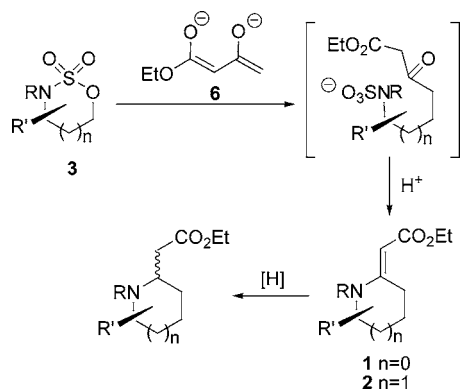
Scheme 1. Cyclic Sulfamides as Precursors to *N*-Heterocycles



Nucleophilic attack occurs exclusively at the C–O bond in a highly stereospecific ($\text{S}_{\text{N}}2$) manner to afford an *N*-sulfate intermediate which, after acid-promoted hydrolysis and lactamization, delivers the target heterocycles.

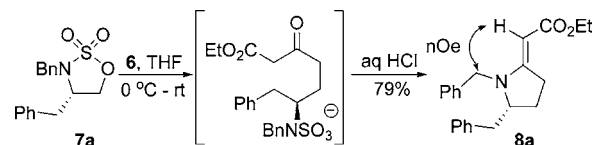
We reasoned that an enolate-based strategy relying on the reaction of 1,2- and 1,3-cyclic sulfamides with the dianion **6** of ethyl acetoacetate (and related nucleophiles) would also provide a general entry to alkylidenepyrrolidines and -piperidines. Acid-promoted hydrolysis of the resulting *N*-sulfate intermediate and cyclization would afford heterocycles **1** and **2** which can be converted to the requisite amino acid derivatives under reductive conditions (Scheme 2).

Scheme 2



Using a structurally representative set of cyclic sulfamides **7a–f** we have been able to generate a range of substituted and enantiopure adducts **8a–f** in good to moderate yield (Scheme 3 and Table 1).⁷ Formation of dianion **6** was achieved by successive treatment of ethyl acetoacetate

Scheme 3. Synthesis of Alkylidenepyrrolidine **8a**^a



^a For other examples, see Table 1.

with NaH (1 equiv) and then *n*-BuLi (1 equiv) at 0 °C prior to addition of the cyclic sulfamidate.

The *N*-benzylated phenylalanine-derived cyclic sulfamidate **7a**, which serves to illustrate the process involved, reacted efficiently at room temperature to afford adduct **8a** in 79% yield after *N*-sulfate hydrolysis and cyclization; the latter occurred spontaneously under the acidic conditions employed. The stereochemistry of **8a** was determined by a

Table 1. Alkylidene Pyrrolidines and Piperidines via the Dienolate of **6** and Cyclic Sulfamides **7a–f**

	sulfamidate	dienolate precursor	heterocycle (yield)
1			
2			
3			
4			
5			
6			

^a In these cases, racemic cyclic sulfamidate was employed.

(6) (a) Williams, A. J.; Chakthong, S.; Gray, D.; Lawrence, R. M.; Gallagher, T. *Org. Lett.* **2003**, 5, 811–814. (b) Bower, J. F.; Švenda, J.; Williams, A. J.; Charmant, J. P. H.; Lawrence, R. M.; Szeto, P.; Gallagher, T. *Org. Lett.* **2004**, 6, 4727–4730. (c) Bower, J. F.; Szeto, P.; Gallagher, T. *Chem. Commun.* **2005**, 5793–5795. (d) Bower, J. F.; Chakthong, S.; Švenda, J.; Williams, A. J.; Lawrence, R. M.; Szeto, P.; Gallagher, T. *Org. Biomol. Chem.* **2006**, 4, 1868–1877. (e) Bower, J. F.; Szeto, P.; Gallagher, T. *Org. Biomol. Chem.* **2007**, 5, 143–150. (f) Bower, J. F.; Riis-Johannessen, T.; Szeto, P.; Whitehead, A. J.; Gallagher, T. *Chem. Commun.* **2007**, 728–730. (g) Bower, J. F.; Williams, A. J.; Woodward, H.; Szeto, P.; Lawrence, R. M.; Gallagher, T. *Org. Biomol. Chem.* **2007**, 5, 2636–2644. (h) Bower, J. F.; Szeto, P.; Gallagher, T. *Org. Lett.* **2007**, 9, 3283–3286.

diagnostic NOE enhancement observed between the *N*-benzylmethylene moiety and the alkene proton; similar NOE correlations provided the basis of the assignments shown in Table 1 for the other substrates studied. Carbamate-protected cyclic sulfamidates are also suitable for this chemistry, and Boc-protected derivative **7b** was equally effective, affording **8b** in 76% yield.⁸ It is relevant to note that the Boc group survives the acidic conditions required for hydrolysis of the *N*-sulfate intermediate.

The scope and present limitations of this heteroannulation process are illustrated in Table 1. Other sterically more demanding and less reactive substrates (Table 1, entries 3–6) did require elevated temperatures to deliver the target adducts **8c–f** albeit in more modest yields. In these cases, prolonged heating at 50 °C was preferable (24–72 h) as use of higher temperatures led to degradation of the enolate component. In some cases, e.g., entry 6, it was still difficult to achieve complete consumption of the starting cyclic sulfamidate but heterocycle **8f** was nevertheless isolated in a synthetically useful 45% yield.

The S_N2 nature of the nucleophilic displacement step is clearly demonstrated by directly comparing entries 3 vs 4, each of which was stereospecific. One limitation of this dienolate-based methodology involves base-sensitive substrates, such as **7e**. In this case, and in addition to **8e** (19%), a substantial amount (30%) of *N*-benzylcinnamylamine (the product of elimination of **7e**) was also isolated.⁹

Using cyclic sulfamidate **7a**, we have explored the scope of the nucleophilic component (Table 2). For example, substitution at both C(2) and C(4) of the nucleophile (as in **9a** and **9b**) is tolerated and the respective products **10a** and **10b** were obtained in good yield. In the case of **10a**, little stereochemical control was observed at the newly installed C(3) stereocenter, and the product was isolated as a 3:2 mixture of diastereomers. Additional rings are also tolerated within the nucleophile as demonstrated by entry 3. In this case, product **10c** was isolated in high diastereoselectivity, although traces (<10%) of the minor diastereomer were evident. While the structure of **10b** was assigned by NOE experiments (see the Supporting Information), this was not possible with **10c** as no suitable signals were available, and a tentative assignment (on steric grounds and by analogy to **8a**) is shown in Table 2. More hindered nucleophiles are, however, not suitable partners for less reactive cyclic sulfamidates and reaction of the ephedrine derivative **7c** with the dianion derived from **9a** resulted in only trace amounts of the desired adduct.

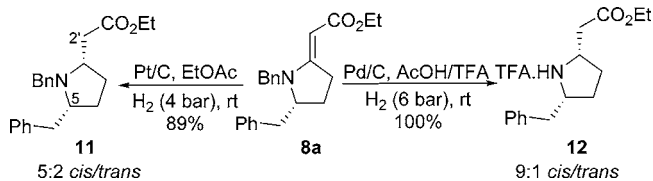
Validation of these alkylidene substrates as precursors of β -amino acids has been carried out on **8a** using Rapoport's

Table 2. Reactivity of Cyclic Sulfamidate **7a** toward Substituted Dienolates Derived from **9a–c**

	sulfamidate	dienolate precursor	heterocycle (yield)
1			 10a (68%) dr=3/2
2			 10b (58%)
3			 10c (46%; <i>E/Z</i> = >9/1) (+ 10% 7a)

conditions [5% Pt/C (30 wt %), EtOAc, H₂ (4 bar)] (Scheme 4).¹⁰ Alkylidene reduction occurred without *N*-debenzylation

Scheme 4. Reductive Manipulation of Pyrrolidine **8a**



to afford **11** in excellent yield (89%) but modest diastereoselectivity (5:2 *cis/trans* by ¹H NMR analysis of the crude product). The stereochemical outcome of this reaction was assigned on the basis of NOE experiments, which were consistent with literature precedent: irradiation of H(5) in *trans*-**11** showed an enhancement of one of the H(2') methylene protons. On this basis, the minor isomer of **11** was assigned as *trans* and the major component as the *cis* diastereomer. Under more forcing conditions [H₂ (6 bar), AcOH, TFA, 10% Pd/C (55 wt %)], hydrogenation of both the alkene and *N*-benzyl groups occurred to give β -amino ester **12** in essentially quantitative yield and with an increased (9:1) level of *cis/trans* selectivity.¹¹

In summary, we have shown that a structurally representative range of 1,2- and 1,3-cyclic sulfamidates undergo nucleophilic cleavage with the dianion of ethyl acetoacetate

(7) For details of the preparation of cyclic sulfamidates **7a–f**, see our earlier work.^{6a,b} Cyclic sulfamidates **7a–d** were prepared from the corresponding enantiopure 1,2-amino alcohols, whereas substrates **7e** and **7f** were most conveniently obtained in racemic form. We have already demonstrated an ability to exploit enantiomerically pure 3-substituted 1,3-cyclic sulfamidates (cf. **7f**) in related chemistry.^{6f}

(8) In this case, analysis of the crude reaction product by ¹H NMR indicated the presence of some uncyclized material (in addition to **8b**); complete cyclization then occurred during chromatographic purification. Analogous observations have been reported by Elliott on related systems.⁴ⁱ

(9) We have previously shown that this substrate has a propensity to β -elimination under basic conditions.^{6d}

(10) Hernández, A.; Marcos, M.; Rapoport, H. *J. Org. Chem.* **1995**, *60*, 2683–2691.

to afford, after *N*-sulfate hydrolysis and cyclization, a range of substituted and enantiopure alkylidene pyrrolidines and piperidines. The scope of this chemistry has been probed in terms of both the nucleophilic and electrophilic components, and the conversion of a representative alkylidene pyrrolidine to a C(5)-substituted homoproline derivative (**11/12**) has been demonstrated. The direct nature of this methodology, which complements existing approaches, provides an attractive

(11) Reduction of *exo*-alkylidene variants of pyrrolidines and piperidines to provide β -amino acids has been extensively reported; see: Hashimoto, N.; Funatomi, T.; Misaki, T.; Tanabe, Y. *Tetrahedron* **2006**, *62*, 2214–2223 and references therein. For an example related to **8a** involving a substituted heterocyclic variant, see: Calvet-Vitale, S.; Vanucci-Bacqué, C.; Fargeau-Bellassoued, M. C.; Lhommet, G. *Tetrahedron* **2005**, *61*, 7774–7782.

entry to alkylidenated lactams, enhanced by the availability of substituted and enantiopure 1,2- and 1,3-cyclic sulfamides.

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Supporting Information Available: Full experimental details, compound characterization data, and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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