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Cyclic Sulfamidates as Vehicles for the Synthesis of Poly- and Diversely Substituted Benzosultams via Unusual $S(O)_2-O$ Bond Cleavage

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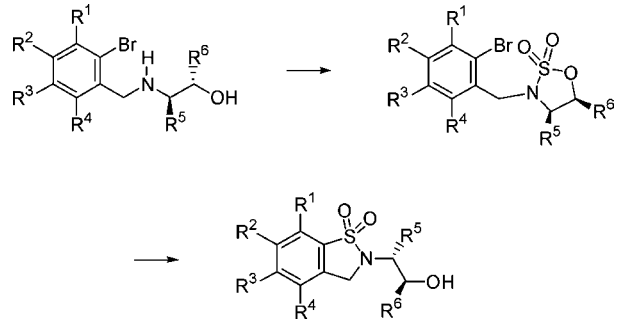
ABSTRACT



1,2-Cyclic sulfamidates undergo novel, efficient, and regiospecific intramolecular nucleophilic cleavage with aryllithiated species to provide an entry to poly-, diversely, and enantiopure N-substituted benzosultams.

Five-membered cyclic sulfamidates play an important role in organic synthesis, and their reactivity and synthetic importance have been widely harnessed and profusely described in the literature.[1] These heterocyclic compounds, which are readily available in enantiomerically pure form, represent a readily accessible and versatile set of β-amino alcohol derived electrophiles that undergo facile nucleophilic cleavage.[1a] The nucleophilic attack which proceeds by a S_N2 pathway occurs selectively at the *O*-bearing carbon center (Figure 1) in a highly stereospecific manner, and this nucleophilic displacement with carbon (cyanide and organometallic reagents), [18 and 19]F^-, nitrogen (e.g., azide, thiocyanate, amines and pyrazole), oxygen (e.g., MeO^-, AcO^- and ArO^-), and RS^- nucleophiles has been widely explored.[1,2] The regiospecific ring-opening then results in the formation of a *N*-sulfate which can be readily hydrolyzed under mildly acid conditions to final chiral amines equipped with heteroatomic functional groups.[1] Alternatively, the ring-opening operation can be accompanied with a number of annulation processes to provide a flexible entry to a range of substituted and enantiomerically pure heterocyclic scaffolds,[1d,e,3] including benzo-fused systems.[4]

The key feature of these reactions is then the high reactivity exhibited by the C−O bond toward nucleophiles and the activation of the carbon center for exclusive intermolecular nucleophilic displacement. Bearing these facts in mind, we were then intrigued by the chemical outcome of a carbanionic process involving an aryl-based nucleophile, e.g., an aryllithiated species, carrying an adjacent benzylic sulfamidate moiety. In this regard, we surmised that intramo-

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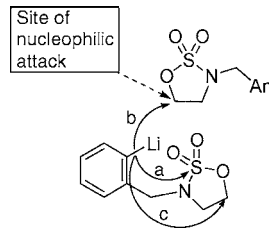

Figure 1. Sites for inter- and/or intranucleophilic attacks.

lecular N−S(O_2)−O bridge scission (Figure 1a) could be forced and strongly favored over well-established intermolecular nucleophilic displacement at the carbon center neighboring the oxygen atom (Figure 1b), the latter process being highly unlikely in the intramolecular version (Figure 1c). This unexpected and unusual ring-opening/ring-closing reaction sequence would notably enrich the repertoire of the Parham-type anionic cyclization process[5] and would also provide the basis of a flexible entry to a range of new heterocyclic scaffolds.

We then embarked on the synthesis of a structurally representative set of cyclic sulfamidates **1a**−**f**. These compounds were readily and efficiently synthesized from the corresponding β-amino alcohols **2**−**6** using a modification of literature conditions[6] (Scheme 1). In the first instance, a reductive amination process involving a variety of 2-bromobenzaldehyde derivatives **7**−**10** and an array of (enantio)pure amino alcohols **2**−**6** delivered a high yield of the bromobenzylated amino alcohols **11a**−**f**. Subsequent treatment with thionyl chloride proceeded smoothly to afford the cyclic sulfamidites **12a**−**f** in very satisfactory yield. In most cases, these preliminary annulated compounds were obtained as diastereoisomeric mixtures, but stereochemical considerations at this stage were not crucial since conversion into the achiral dioxides **1** was envisaged in the sequel. The literature protocols for the oxidation into the desired sulfamidates using catalytic $RuCl_3$ with $NaIO_4$ as reoxidant clearly indicate that the chemoselectivity of the oxidation step can be tailored via judicious choice of the reaction solvent.[3d] We observed that efficiency of this process was slightly better in biphasic media (H_2O-ethyl acetate; e.g., 87% for **1a**)[3a,7] than in the more commonly used H_2O−MeCN solvent system (e.g., 78% for **1a**) presumably due to competing oxidation of the polyalkoxylated bromobenzyl substituent, a precedented phenomenom.[3d] These operation are known to spare the stereochemistry at the carbon centers embedded in the sulfamidate framework and allowed for the assembly of the constitutionally diverse models **1a**−**f**, candidates for the planned Parham-type cyclization process.

The protocol developed by Parham which cursorily hinges upon aromatic lithiation and subsequent capture with an internal electrophile occupies a place of choice in the arsenal of synthetic tactics for the elaboration of carbo- and heterocyclic systems,[5] but applications of this concept to build up five-membered heterocyclic systems are rather scarce.[8] To ensure the optimal formation of the mandatory lithiated species, variation of the ethereal solvent (THF or Et_2O), base (*n*-BuLi or *t*-BuLi), temperature profile (−90, −78, 0 °C, rt), course of the addition process (normal or reverse), and inclusion of anion modifiers (TMEDA, crown-ether) were all screened in order to facilitate halogen/metal

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Scheme 1. Synthesis and Nucleophilic Opening of Sulfamidates **1a−f**

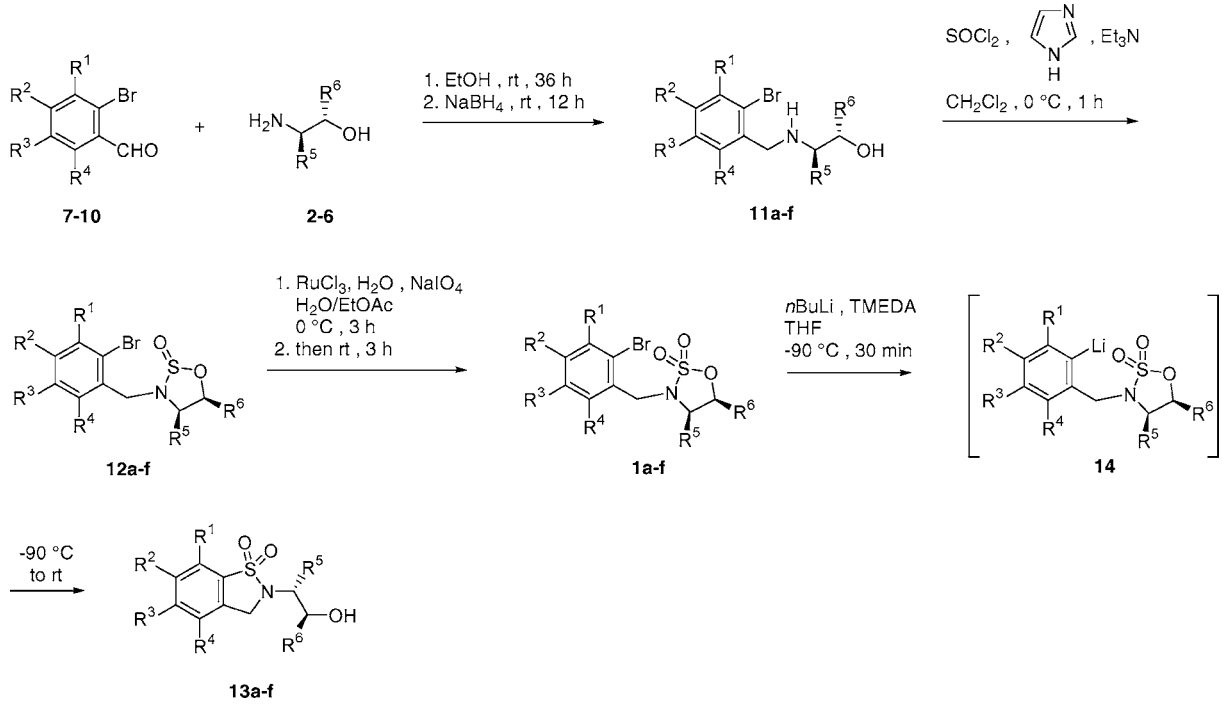

Table 1. Sulfamidates **1a−f** and Benzosultams **13a−f** Synthesized

							starting materials		yield (%)			
									amino alcohol	sulfimidite	sulfamidate	benzosultam
	R^1	R^2	R^3	R^4	R^5	R^6	**7−10**	**2−6**	**11a−f**	**12a−f**	**1a−f**	**13a−f**
a	H	OMe	OMe	H	H	H	**7**	**2**	87	89	87	95
b	OMe	OMe	OMe	H	Ph	H	**8**	**3**	90	94	87	76
c	OMe	OMe	OMe	H	H	Me	**8**	**4**	91	93	90	82
d	H	H	OMe	OMe	H	Me	**9**	**4**	93	91	90	81
e	H	OCH_2O		H	*i*-Pr	H	**10**	**5**	92	91	84	73
f	H	OCH_2O		H	Ph	Ph	**10**	**6**	47	92	87	90

conversion while sparing the sulfamidate moiety. After considerable experimentation, we found that adding *n*-BuLi (1.1 equiv) to a degassed solution of **1a−f** (1 equiv) and TMEDA (1.1 equiv) in THF at −90 °C for 30 min (normal addition) led to the complete consumption of the starting material. The intramolecular ring closure was highly efficient as demonstrated by isolation solely of the hydroxyalkyl chain tethered benzosultams **13a−f**. A representative series of annulated compounds which have been prepared by this method are presented in Table 1, where it can be seen that this simple procedure afford excellent yields of these new highly functionalized models. One can reasonably assume that the nucleophilic attack by the preliminary formed aryllithiated species **14** triggers scission of the N−S−O bridge, and ring opening is accompanied by a simultaneous new ring-forming reaction to generate the sultam unit.

Benzosultams, which can be regarded as conformationally constrained cyclic counterpart of sulfonamides, have emerged as privileged structures in drug discovery[9] and have served as key functional groups in the development of nonsteroidal anti-inflammatory agents and as agonists of $5HT_{1A}$ receptors.[10] They have been also reported to exhibit broad inhibitory properties against of a variety enzymes, including COX-2,[11] HIV integrase,[12] lipoxygenase,[13] calpain I,[14] and MMP-2.[15] Beyond their significance in the treatment of diseases, the sultam compounds are an important class of

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chiral auxiliaries which have been successfully applied to a number of asymmetric reactions[16] and of chemical reagents employed with considerable success in contemporary organic reactions. Interestingly, the anionic cyclization process applied to **1a**−**f** provokes the concomitant creation of a tailor-made hydroxyalkyl appendage, possibly equipped with stereocontrolled carbon centers, which may serve as a handle for further synthetic manipulations, in particular, installation of tethered functionalities liable to act on the biological profile of targeted models. The method is tolerant to a wide variety of structurally different sulfamidates and provide a flexible entry to a collection of poly and diversely alkoxylated models, one of the most challenging tasks in the elaboration of these benzo-fused sultams.[17]

In summary, we have demonstrated that aryllithiated species are effective nucleophiles toward a set of structurally representative cyclic 1,2-sulfamidates and undergo regioselective intramolecular $S(O)_2$−O bond cleavage to provide the basis of a new and efficient entry to substituted benzosultams. These readily available building blocks provide the functionalized title compounds with the capacity to incorporate additional substituents/functionalities at a later stage. High yields, one-pot ring-opening/ring-closing reaction, procedural simplicity, and easy isolation of the products are the key feature of this new methodology. This methodology represents an important advance that significantly underpins the utility of cyclic 1,2-sulfamidates as effective, synthetically useful electrophiles.

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Supporting Information Available: Experimental procedures, spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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