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Laboratoire de Chimie Organique Physique

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Unexpected $S(O)_2$–O Bond Scission upon Anionic Cycliarylation of Cyclic Sulfamidates. A New Route to *N*-Functionalized Benzosultams.

Magali Lorion, Vangelis Agouridas, Axel Couture,* Eric Deniau, Pierre Grandclaudon

Université Lille Nord de France, F-59000 Lille, France

USTL, Laboratoire de Chimie Organique Physique, EA CMF 4478, Bâtiment C3(2), F-59655 Villeneuve d'Ascq, France

CNRS, UMR 8181 'UCCS', F-59655 Villeneuve d'Ascq, France

Axel.Couture@univ-lille1.fr

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.

Keywords: carbanion, anionic cyclization, sulfamidates, benzosultams.

Introduction

Five-membered cyclic sulfamidates **1** (Figure 1), which are readily available in enantiomerically pure forms represent a versatile set of aminoalcohol derived electrophiles that undergo nucleophilic cleavage through a SN2 pathway [1].

The nucleophilic attack with a variety of (carbo) and (hetero)anionic species occurs selectively at the *O*-bearing carbon center [2] (Figure 2) and this regiospecific ring opening usually results in the formation of a *N*-sulfate which can be hydrolyzed to chiral amines equipped with heteroatomic functionalities [3].

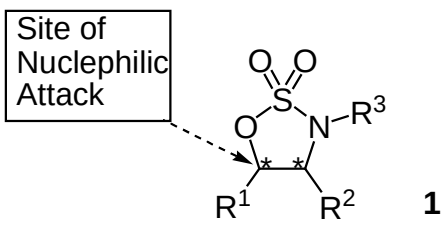


Figure 1.

It can also be involved in annulation processes to provide a flexible entry to enantiomerically pure heterocyclic scaffolds, including benzofused systems [4].

Bearing this facts in mind our interest was piqued by the outcome of a carbanionic process involving an aryl-based nucleophile, e.g. an aryllithiated species, carrying an adjacent benzylic sulfamidate moiety (Figure 2). We anticipated that *intra*molecular N–S(O)$_2$–O bridge scission (Figure 2, a) could be forced and favored over *inter*molecular nucleophilic displacement at the carbon center vicinal to the oxygen atom (Figure 2, b).

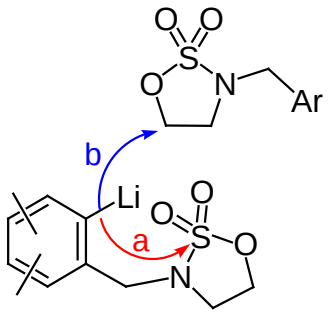


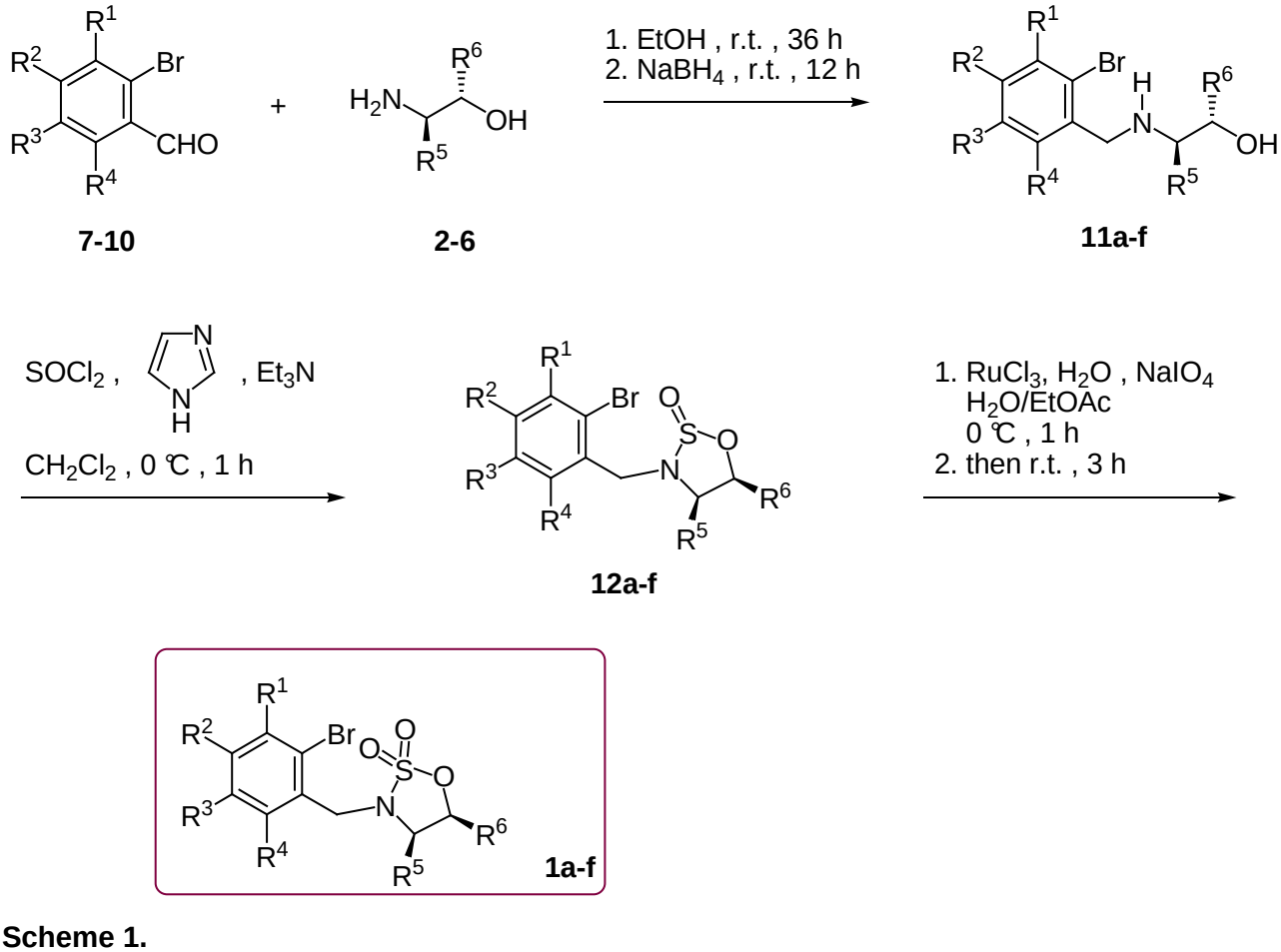
Figure 2.

We surmised that such a lithiated species could be easily generated through halogen-lithium interconversion applied to appropriate bromobenzylated precursors.

Results and Discussion

1. Synthesis of the parent bromobenzylsulfamidates 1a-f.

A representative set of (enantio)pure sulfamidates **1a-f** was readily assembled by preliminary reductive amination reaction between a variety of bromobenzaldehydes **7-10** and an array of enantiopure aminoalcohols **2-6** (Scheme 1). Subsequent treatment of the resulting bromobenzylated aminoalcohols **11a-f** with thiony chloride ($SOCl_2$) allowed for the elaboration of the five-membered cyclic sulfamidites **12a-f** (Table 1) and ultimate oxidation using catalytic $RuCl_3$ with $NaIO_4$ as reoxidant in biphasic madia delivered quit satisfactory yields of the constitutionally diverse models **1a-f**, candidates for the planned carbanionic cycliarylation process (Table 1).



Scheme 1.

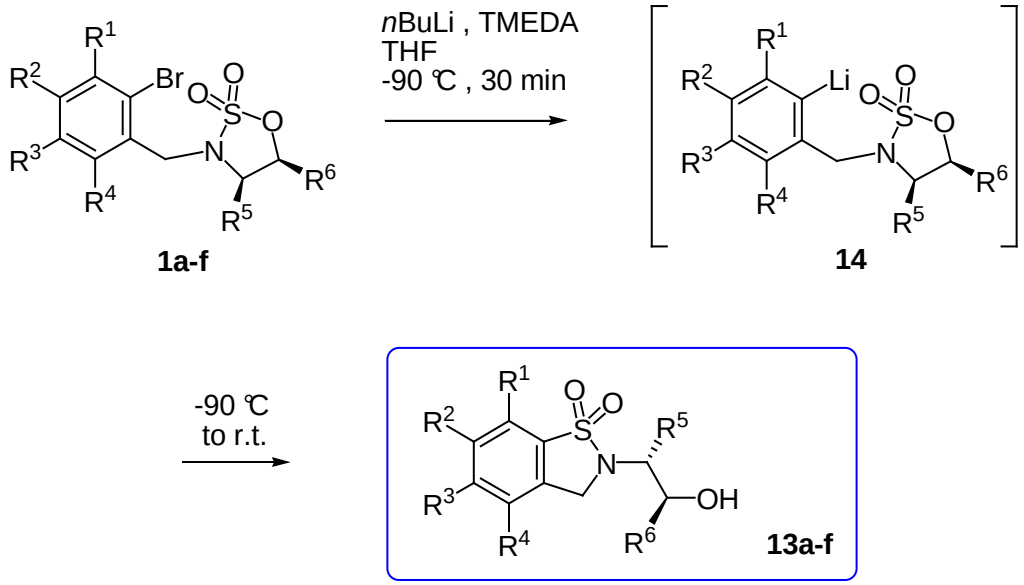
Table 1. Sulfamidites **12a-f** and Sulfamidates **1a-f** Synthesized.

	R^1	R^2	R^3	R^4	R^5	R^6	Starting Materials **7-10** + **2-6**		Amino-alcohol **11a-f** yield (%)	Sulfimidite **12a-f** yield (%)	Sulfamidate **1a-f** yield (%)
a	H	OMe	OMe	H	H	H	**7**	**2**	87	89	87
b	OMe	OMe	OMe	H	Ph	H	**8**	**3**	90	94	87
c	OMe	OMe	OMe	H	H	Me	**8**	**4**	91	93	90
d	H	H	OMe	OMe	H	Me	**9**	**4**	93	91	90
e	H	OCH_2O		H	*i*Pr	H	**10**	**5**	92	91	84
f	H	OCH_2O		H	Ph	Ph	**10**	**6**	47	92	87

Interestingly these operations spared the stereochemistry of the carbon centers embedded in the sulfamidate framwork.

2. The anionic cyclization process. A new route to poly, diversely and enantiopure N-functionalized benzosultams.

To ensure the optimal formation of the mandatory lithiated species, that is **14**, variation of the ethereal solvent (THF or Et_2O), base (*n*BuLi or *t*BuLi), temperature profile (-90℃, -78 ℃, 0 ℃, rt), course of the addition process (norm al or reverse) and inclusion of anion modifiers (TMEDA, crown-ether) were all screened in order to facilitate halogen/metal 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 ℃ fo r 30 min (normal addition) led to the complete consumption of the starting material.



Scheme 2.

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 2 where it can be seen that this simple procedure afford excellent yields of these new highly functionalized models.

Table 2. Benzosultams **13a-f** Synthesized.

	R^1	R^2	R^3	R^4	R^5	R^6	Benzosultam **13a-f** yield (%)
a	H	OMe	OMe	H	H	H	95
b	OMe	OMe	OMe	H	Ph	H	76
c	OMe	OMe	OMe	H	H	Me	82
d	H	H	OMe	OMe	H	Me	81
e	H	OCH_2O		H	*i*Pr	H	73
f	H	OCH_2O		H	Ph	Ph	90

From a mechanistic point of vue 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 with a simultaneous new ring forming reaction to generate the sultam unit.

Benzosultams have emerged as privileged structures in drug discovery [5] and have served as key functional groups in the development of non-steroidal anti-inflammatory agents and as agonists of $5HT_{1A}$ receptors [6]. They have been also reported to exhibit broad inhibitory properties against of a variety enzymes, including COX-2 [7], HIV integrase [8], lipoxygenase [9], Calpain I [10] and MMP-2 [11].

Interestingly the anionic cyclization process applied to **1a-f** provoke 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 multifarious 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 benzofused sultams [12].

This new methodology also represents an important advance that significantly underpins the utility of cyclic 1,2-sulfamidates as effective, synthetically useful electrophiles.

Conclusion

In summary we have demonstrated that aryllithiated species are effective nucleophiles towards 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, unusual 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.

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