Zinc Chloride Catalyzed Ring Opening of *N*-Arylsulfonyl Aziridines by Thioamides: A New Approach to the Synthesis of Amidines

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Abstract: The first zinc chloride catalyzed ring opening of *N*-arylsulfonyl aziridines by thioamides is described. Various thioamides were reacted with *N*-arylsulfonyl aziridines in the presence of a catalytic amount of dry zinc chloride to provide the corresponding *N*-arylsulfonyl amidine derivatives with good to excellent yields.

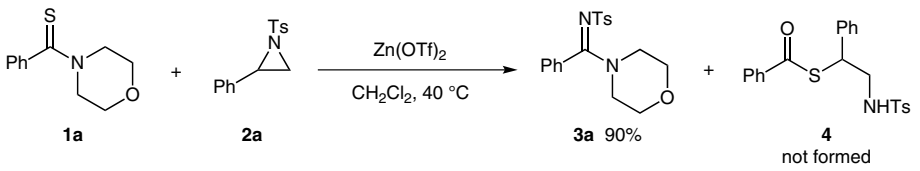
Key words: amides, Lewis acids, nitrogen, homogeneous catalysis, sulfur

Amidine derivatives are the key structural framework of many natural products and pharmaceuticals[1] and have substantial biological activities.[2] Various methods have been developed for the preparation of amidines. Recently, a new route for the synthesis of amidines via NaI-catalyzed direct condensation of sulfonamide and formamide derivatives has been reported.[3] Numerous three-component copper-catalyzed reactions have also been reported for the construction of *N*-sulfonyl formamidines.[4–6] Moreover, tandem dehydrogenation of aliphatic tertiary amines and reaction with sulfonyl azides present other innovative alternatives for the preparation of *N*-sulfonylamidine derivatives.[7] Another method to synthesize *N*-sulfonylamidines benefits from the reaction of enamines with *p*-toluenesulfonyl azide.[8] However, although, these protocols have synthetic application and diverse substrate scope, they suffer from the use of harsh conditions, intrinsically explosive and/or expensive starting materials, and corrosive and/or specialized reagents.

Aziridines exhibit high order of reactivity towards nucleophilic attack due to their ring strain. Therefore they have been received much attention in organic synthesis as a good nitrogen source for the preparation of amino-functionalized compounds in recent years.[9] Concerning the reactivity, the most general transformations of these three-membered ring systems are the ring-opening reactions initiated by either electrophilic or nucleophilic reagents.[10] Although ring-opening reactions of aziridines with various nucleophiles such as thiols, amines, alcohols, and silylated nucleophiles have been developed,[11] there are few reactions involving other sources of nucleophilic sulfur in ring-opening reactions of aziridines. Aziridines have been shown to react with dithiocarbamates to give the corresponding β-sulfonamido dithiocarbamates[12] and they also react with carbon disulfide to give the corresponding thiazolidin-2-thiones in the presence of several Lewis acids.[13] Recently, a ring-opening reaction between aziridine derivatives and thioaroylates generated in situ from the reaction of acyloxyphosphonium and tetrathiomolybdate salts has been reported.[14] In light of these developments, we were led to study the reaction of thioamides as other sources of nucleophilic sulfur with aziridines.

The sulfur atom of a tertiary thioamide has a high order of nucleophilicity and readily reacts with electrophiles.[15] Earlier, we reported on the synthesis of thioesters starting from thioamides as a source of nucleophilic sulfur and reacting with protonated alcohols[16] and α-haloketones[17] as different electrophiles. In continuation of our studies on the reaction of thioamides with diverse electrophiles, we herein describe a simple and fundamentally different approach to *N*-arylsulfonyl formamidine derivatives based on the direct reaction of *N*-arylsulfonyl aziridines and morpholino(aryl) methanethiones catalyzed by zinc chloride.

At the outset of our study, we examined the reaction of morpholino(phenyl)methanethione (**1a**) as a test substrate with 2-phenyl-1-tosylaziridine (**2a**) in the presence of dry $Zn(OTf)_2$ as a Lewis acid catalyst. Although, we expected that thioester **4** would be the product of the reaction, we were very surprised by the fact that, the reaction product was not thioester **4** but instead, amidine compound **3a** was obtained as the sole product and in excellent yield (90%, Scheme 1). Intrigued by this finding and in order to explore the scope of the reaction, we decided to examine other nitrogen sources bearing a sulfonyl functionality.



1a **2a** **3a** 90% **4** not formed

Scheme 1

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First, TsN_3 as a source of nitrene having a sulfonyl moiety was chosen and reacted with thioamide **1a**. As expected, the reaction progressed smoothly but the corresponding amidine **3a** was produced in a lower yield (62%, Table 1). Other nitrene sources were also tested in the reaction with thioamide **1a** under similar conditions. While TsN·NaCl (chloramine-T) furnished the amidine **3a** in a rather moderate yiled (45%), PhI=NTs produced the desired compound in very low yield (10%). However, no product yield was observed in the case of using $TsN=PPh_3$ as an unusual nitrene source.

Table 1 Comparison of the Synthesis of Compound **3a** through the Reaction of Thioamide **1a** with Different Nitrogen Sources[a]

Entry	Nitrogen source	Catalyst	Temp (°C)	Time (h)	Yield (%)[b]
1	TsN_3	–	40	24	62
2	$TsN=PPh_3$	–	40	48	0
3	PhI=NTs	–	40	78	10
4	*N*-tosyl-2-phenylaziridine	$Zn(OTf)_2$	40	2	90
5	TsN·NaCl	–	40	2	45

[a] Reaction conditions: **1a** (1.0 mmol), nitrogen source precursor (1.2 mmol), and catalyst (2 mol%) in CH_2Cl_2 (3 mL).
[b] Isolated yield.

As indicated in Table 1, only 2-phenyl-1-tosylaziridine (**2a**) operated as a successful nitrogen transfer agent to the thioamide substrate **1a** leading to the corresponding *N*-sulfonyl amidine **3a**. It is worth noting that all of the above-mentioned sources of nitrene result in dark-colored complex mixtures which are hard to separate. This could be the reason for their notably lower product yields. It should be mentioned that some degree of conversion of the thioamide **1a** into its analogous amide was also observed. These results imply that the reaction of thioamide substrate **1a** with 2-phenyl-1-tosylaziridine (**2a**) most likely proceeds by a quite different mechanism.

In further trials, the role of the catalyst in the reaction was also probed. Our preliminary findings indicated that various types of Lewis acids can be applied in the course of reaction, but only those which are based on the zinc salts gave the better results (Table 2).

In this manner, the reaction of the test thioamide **1a** with 2-phenyl-1-tosylaziridine (**2a**) in the presence of dry $Zn(OTf)_2$ in CH_2Cl_2 under reflux conditions was investigated. This was very successful and produced the desired amidine product **3a** in 90% yield (Table 2, entry 6). To avoid the use of moderately expensive $Zn(OTf)_2$ we next decided to utilize dry $ZnCl_2$ as a cheap and readily available catalyst and obtained a similar yield (Table 2, entry 7). Fortunately, the reaction of all of the thioamide substrates **1a**–**m** with the arylsulfonyl aziridines **2a**,**b** occurred smoothly in the presence of dry $ZnCl_2$ at 40 °C without the formation of any colored or tarry materials in moderate to excellent yields (67–91%).

Table 2 Optimization of the Reaction Conditions for Compound **3a**[a]

Entry	Catalyst	Solvent	Temp (°C)	Time (h)	**3a** (%)[b]
1	–	CH_2Cl_2	40	24	0
2	–	–	130	2	14
3	$FeCl_3$	CH_2Cl_2	40	2	56
4	$InCl_3$	CH_2Cl_2	40	24	0
5	$BF_3·OEt_2$[c]	THF	70	24	11
6	$Zn(OTf)_2$	CH_2Cl_2	40	2	90
7	$ZnCl_2$	CH_2Cl_2	40	2	91
8	$ZnCl_2$[d]	CH_2Cl_2	40	2	83
9	$ZnCl_2$[e]	CH_2Cl_2	40	2 (72)	41 (61)
10	$ZnCl_2$	CH_2Cl_2	r.t.	2	67
11	$ZnCl_2$	THF	40	2	78
12	$ZnCl_2$	MeCN	40	2	80
13	TsOH	CH_2Cl_2	40	24	<5
14	TsOH[f]	–	130	2	29

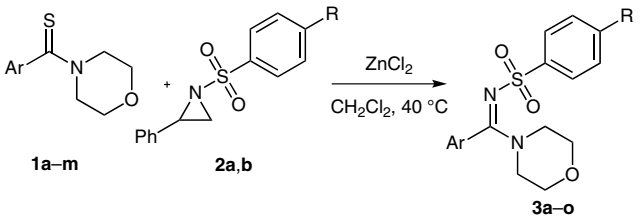
[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.2 mmol), and catalyst (2 mol%) in solvent (3 mL) for 2 h.
[b] Isolated yield.
[c] The reaction was carried out under a nitrogen atmosphere.
[d] Conditions: 1 mol% catalyst was used.
[e] Conditions: 0.5 mol% catalyst were used.
[f] Considerable amounts of tarry materials were observed.

It was found that, in addition to $ZnCl_2$, dry $FeCl_3$ worked in this reaction and afforded the desired amidine **3a** in moderate yield (Table 2, entry 3). However, using this catalyst, great difficulty was observed in the separation of the product. No product was observed when using PTSA as a Brønsted acid at 40 °C even after prolonged reaction time, but small amount of the product alongside of the large amounts of tarry material were obtained at higher temperature (Table 2, entries 13 and 14). As we expected the reaction did not proceed in the absence of catalyst at low temperature (40 °C) but very small amounts of the amidine product **3a** were obtained under solvent-free conditions at elevated temperature (Table 2, entry 2). The reaction was also tested in a variety of solvents using $ZnCl_2$ as catalyst at 40 °C. Our investigation revealed that the best solvent for the reaction was CH_2Cl_2. The effect of different catalyst loadings was also examined, and it was found that 2 mol% of $ZnCl_2$ (relative to the aziridine **2a**) was the best quantity to complete the reaction. At a lower catalyst loading the reaction took longer time and was not complete even after stirring for several days (Table 2, entry 9).

After optimizing the conditions, we next examined the generality of the method by using the reaction of a variety

of thioamides **1a**–**m** and two different arylsulfonyl aziridines **2a**,**b**, and the results are summarized in Table 3.[21] It was found that the electronic nature of the aryl substituent on the arylsulfonyl aziridines **2** and the thiomide substrates **1** can impact on the efficiency of the reaction. A notable decrease in yields (Table 3, entries **3j**–**o**) was observed when an electron-withdrawing group was attached to the aryl substituent of the arylsulfonyl aziridine or thioamide. On the other hand, the efficiency of the reaction was also affected by steric factors and bulky substituents on the aryl groups caused the product yield to decline slightly (Table 3, entries **3d**–**g**).

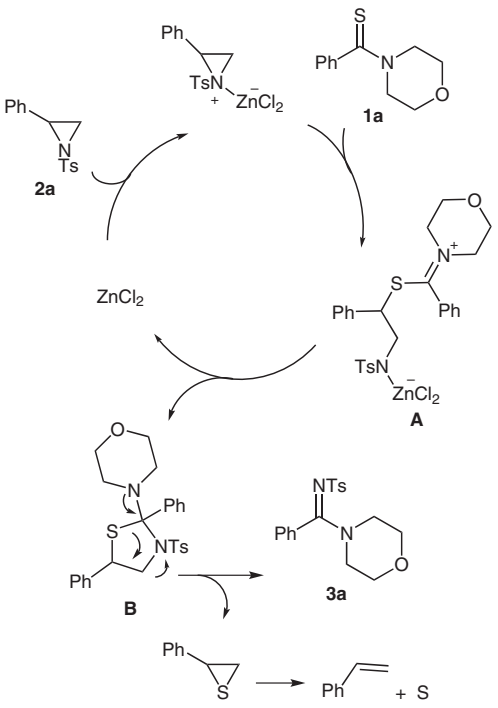
Table 3 $ZnCl_2$-Catalyzed Conversion of Thioamides to Amidine Derivatives[a]



Entry	R	Ar	Product **3**	Yield (%)[b]
1	Me	Ph	**3a**	91
2	Me	4-MeC_6H_4	**3b**	90
3	Me	4-$Me_2NC_6H_4$	**3c**	84
4	Me	4-*i*-PrC_6H_4	**3d**	79
5	Me	2-naphthyl	**3e**	85
6	Me	2-quinolyl	**3f**	81
7	Me	4-biphenyl	**3g**	78
8	Me	4-HOC_6H_4	**3h**	88
9	Me	3,4-$(MeO)_2C_6H_3$	**3i**	87
10	Me	4-ClC_6H_4	**3j**	76
11	Me	4-BrC_6H_4	**3k**	72
12	Me	3-BrC_6H_4	**3l**	70
13	Me	4-$O_2NC_6H_4$	**3m**	69
14	NO_2	4-*i*-PrC_6H_4	**3n**	73
15	NO_2	2-naphthyl	**3o**	67

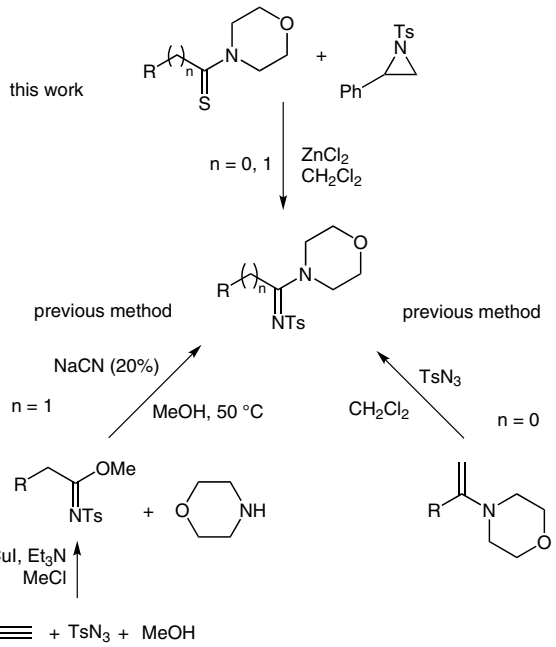
[a] Reaction conditions: **1a**–**m** (1.0 mmol), **2a**,**b** (1.2 mmol), and catalyst (2 mol%) in CH_2Cl_2 (3 mL) for 2 h.
[b] Isolated yields.

A probable mechanism for the formation of amidine **3a** is depicted in Scheme 2. 2-Phenyl-1-tosylaziridine (**2a**) is first activated by the $ZnCl_2$ catalyst. Then thioamide **1a** undergoes an S-alkylation through nucleophilic attack on the activated aziridine to form intermediate **A**. This intermediate then cyclizes to form thiazolidine intermediate **B** and transforms to the final amidine product **3a** with the elimination of an unstable 2-phenylthiirane molecule. It is proposed that the thiirane molecule spontaneously decomposes to the corresponding styrene and elemental sulfur under the reaction conditions.

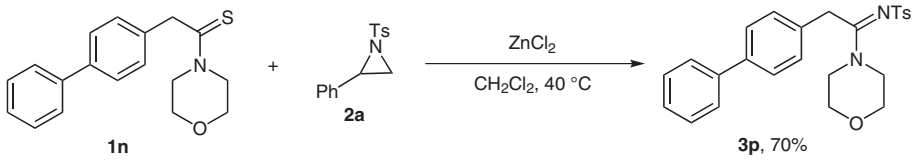


Scheme 2

The immediacy and the simplicity of this methodology are demonstrated in Scheme 3 by comparison with two of the previous methods. In one of the typical previous procedures, *N*-sulfonylimidate, formed by three-component re-



Scheme 3



Scheme 4

action of a terminal alkyne, an arylsulfonyl azide, and an alcohol is treated with different amines in the presence of catalytic amounts of NaCN to produce the corresponding *N*-arylsulfonyl amidines in two steps.[4b] Another approach profits from the reaction of enamines and sulfonyl azides to attain the desired product.[18] Both of these methods are very effective and useful, but use potentially explosive arylsulfony azide or toxic NaCN catalyst and require multiple steps; these are drawbacks compared to our protocol.

To demonstrate the versatility of the presented method, the reaction was further extended to a different thioamide having a methylene moiety (Scheme 4). Hence, thioamide **1n** as an example was chosen and reacted with 2-phenyl-1-tosylaziridine (**2a**) at the same reaction conditions. As expected the bulky thioamide reacted efficiently and provided **3p** in a good yield of 70% (Scheme 4).

Fortunately, all of starting thioamides used in the presented method could be readily accessible by the Willgeroadt–Kindler reaction of their corresponding aldehyde or acetophenone derivatives.[19] The aziridine derivatives were also simply prepared by the known methods.[20]

In conclusion, we have developed a simple procedure for the imidation of thioamides catalyzed by simple zinc salts leading to the corresponding *N*-arylsulfonyl amidines by utilizing *N*-arylsulfonyl aziridines as the nitrogen source. The method is applicable to a broad range of thioamides and is performed under mild conditions, without need for an expensive catalyst and gives good yields of product. Furthermore the thioamides and nitrogen precursors are readily prepared.

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Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

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(21) Complete experimental procedures and relevant ^{1}H NMR and ^{13}C NMR spectra and elemental microanalysis for new compounds are available in the Supporting Information.

Typical Procedure for the Synthesis of *N*-Arylsulfonyl Amidine 3a

A suspension of anhydrous $ZnCl_2$ (3.2 mg, 2 mol%) in anhydrous CH_2Cl_2 (2.0 mL) was refluxed for 5 min, a solution of 2-phenyl-1-tosylaziridine (**2a**, 328 mg, 1.2 mmol) in anhydrous CH_2Cl_2 (1.0 mL) was added slowly, and the mixture was stirred at 40 °C for a further 5 min. Morpholino(phenyl) methanethione (**1a**, 207 mg, 1 mmol) was then added, and the mixture was stirred at the same temperature for 2 h. The reaction mixture was then triturated with H_2O (5 mL) to remove $ZnCl_2$ and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. Finally, the residue was subjected to column chromatography on silica gel eluting with PE–EtOAc (1:1) to furnish amidine **3a** as a white solid (314 mg, 91%).

