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Regiospecific Bi-Catalysed Domino C-N/C-S Bonds Formation: Synthesis of 1,4-Thiazines/1,4-Thiomorpholines

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Abstract. A domino Bi-catalysed C-N/C-S bond formation of *N*-sulfonylaziridines is developed with 1,4-dithiane-2,5-diol to give 3,4-dihydro-1,4-thiazines at room temperature. The use of $Bi(OTf)_3$ as a catalyst, atom economy and regioselectivity are the important practical features.

Keywords: 1,4-thiazine; 1,4-thiomorpholine; domino; Bi-catalysis; regioselectivity

N,S-Heterocycles are privileged structural scaffolds due to their interesting medicinal and agrochemical properties.[1] Among them, the structural frameworks bearing 3,4-dihydro-1,4-thiazine motifs are attractive, because of their important antibacterial,[2] antibiotic,[3] 5-lipoxygenase inhibitor[4] properties, and the use in flavor (Figure 1).[5] In addition, the compounds having 1,4-thiomorpholine structural units show anti-inflammatory,[6] antimycobacterial,[7] hypolipidemic[8] and DPP-IV inhibitor properties.[9] Development of effective synthetic routes for their construction is thus important in synthetic chemistry.[10-11] Recently, Wan and co-workers demonstrated a Cu-catalysed coupling of enaminones with β-aminoethanethiol to produce 1,4-thiazines (Scheme 1a),[10k] while Cossy and co-workers reported a Fe-catalysed cyclization of sulfonamides to give 1,4-thiomorpholines (Scheme 1b).[11] Aziridines are versatile building blocks and several excellent examples are available for the selective nucleophilic ring opening.[12,13] Similarly, 1,4-dithiane-2,5-diol is a versatile synthon for the synthesis of S-containing heterocycle motifs.[14] Herein we report a Bi-catalysed[15] domino[16] C-N/C-S bonds formation of *N*-sulfonylaziridines with 1,4-dithiane-2,5-diol to provide 3,4-dihydro-1,4-thiazines at room temperature (Scheme 1c). At 0 °C produces 1,4-thiomorpolin-3-ol, which leads to dehydration to yield 3,4-dihydro-1,4-thiazines that can be oxidized to 1,4-thiazine-1,1-dioxides.

First, we commenced the optimization using 2-(*p*-toluyl)aziridine **1j** as a model substrate with 1,4-dithiane-2,5-diol **2** in the presence of different Lewis acids (Table 1). Gratifyingly, the reaction occurred to give 2-phenyl-4-tosyl-3,4-dihydro-2*H*-1,4-thiazine **3j** in 68% yield when **1j** and **2** were stirred employing 10 mol% $Bi(OTf)_3$ in CH_2Cl_2 at room temperature (entry 1). In a set of Lewis acids screened, $Bi(OTf)_3$, $Sc(OTf)_3$, $Yb(OTf)_3$, $Cu(OTf)_2$, $Zn(OTf)_2$ and AgOTf, the former furnished the best result (entries 1-6). CH_2Cl_2 was found to be the solvent of choice, whereas toluene, $(CH_2Cl)_2$ and THF produced **3j** in <62% yield (entries 7-9). At 0 °C, 1,4-thiomorpholin-3-ol **4a** was formed in 45% yield (entry 10), which led to dehydration to give **3j** at room temperature. Control experiment confirmed that **3j** was not formed in the absence of the Lewis acid.

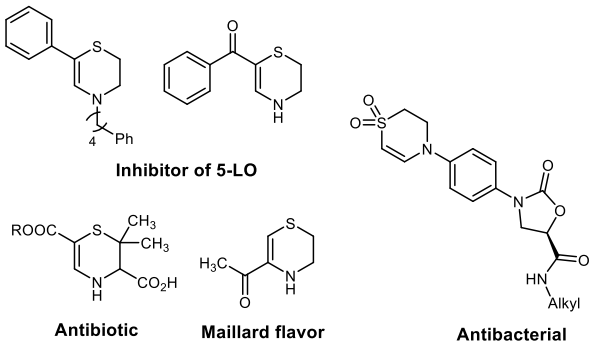
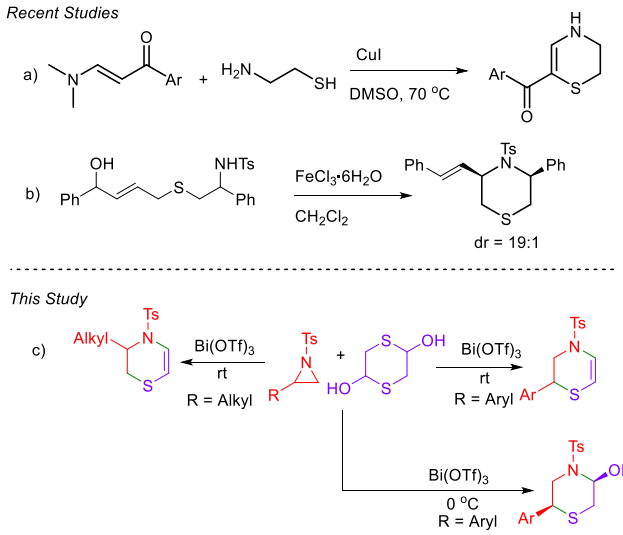


Figure 1. Examples of biologically important 3,4-dihydro-1,4-thiazine derivatives.

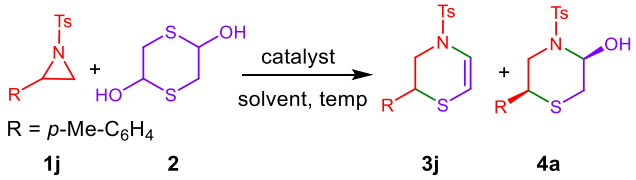
Having optimized the reaction, the substrate scope was studied (Scheme 2). 2-Phenylaziridine **1a** reacted to give 3,4-dihydro-1,4-thiazine **3a** in 62% yield. The reaction of aziridines bearing at the 2-position of the aryl ring with chloro **1b** and fluoro **1c** groups gave **3b** and **3c** in 54 and 56% yield, respectively. Aziridines containing substitution at the 3-position of the aryl ring with bromo **1d**, methyl **1e** and nitro **1f** functional groups provided **3d-f** in 64-68% yields. The reaction of aziridines having substitution at the 4-position with bromo **1g**, chloro **1h**, fluoro **1i**, chloromethyl **1k** and acetate **1l** groups afforded thiazines **3g-l** in 56-64% yields. Similar result observed with aziridine **1m**

having 2,4,6-trimethyl group, producing **3m** in 57% yield. In addition, 2-naphthylaziridine can be reacted to give **3n** in 55% yield.



Scheme 1. Recent approaches for the syntheses of 3,4-dihydro-1,4-thiazines and 1,4-thiomorpholines.

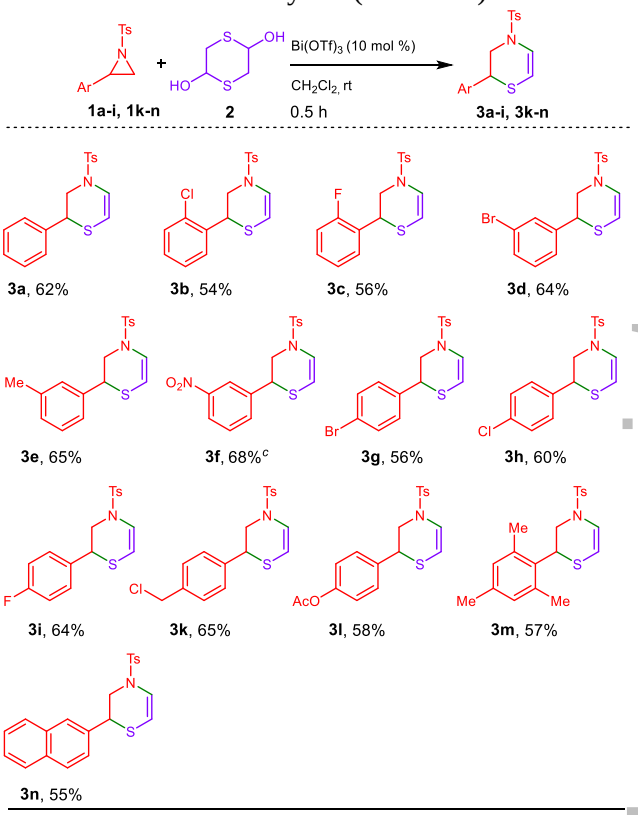
Table 1. Optimization of the reaction conditions[a,b]



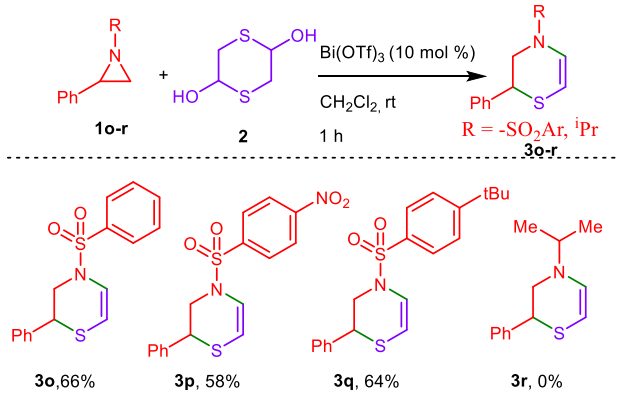
Entry	Catalyst	Solvent	Time	Yield (%)[b]	
				3j	**4a**
1	$Bi(OTf)_3$	CH_2Cl_2	0.5	68	n.d
2	$Sc(OTf)_3$	CH_2Cl_2	3	30	n.d
3	$Yb(OTf)_3$	CH_2Cl_2	3	n.d	n.d
4	$Cu(OTf)_2$	CH_2Cl_2	3	60	n.d
5	$Zn(OTf)_2$	CH_2Cl_2	3	10	trace
6	AgOTf	CH_2Cl_2	3	n.d	n.d
7	$Bi(OTf)_3$	$PhCH_3$	3	20	n.d
8	$Bi(OTf)_3$	$(CH_2Cl)_2$	0.5	62	n.d
9	$Bi(OTf)_3$	THF	3	32	n.d
10[c]	$Bi(OTf)_3$	CH_2Cl_2	3	trace	45

[a] Aziridine **1j** (0.5 mmol), 1,4-dithiane-2,5-diol **2** (0.3 mmol), catalyst (10 mol %), solvent (1 mL). [b]Isolated yield. [c] Reaction temperature 0 °C. n.d = Not detected.

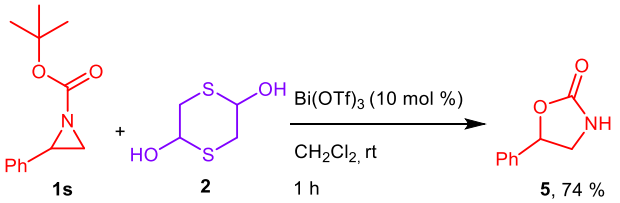
The utility of the protocol was extended to the coupling of aziridines with different *N*-substituents (Scheme 3). 1-(Phenylsulfonyl)aziridine **1o** underwent reaction to furnish **3o** in 66% yield. Similar result observed with **1p** having 1-(4-nitrophenyl)sulfonyl group, affording **3p** in 58% yield, whereas **1q** with 1-(4-*tert*-butylphenyl)sulfonyl substituent afforded **3q** in 64% yield. In contrast, 1-alkylaziridine **1r** was an unsuccessful substrate and the starting material was recovered intact. The reaction was further studied for the coupling of *N*-acetyl and *N*-Boc aziridines. The reaction of *N*-acetyl aziridine produced an inseparable complex mixture, while *N*-Boc aziridine **1s** underwent reaction to give oxazolidinone **4** in 74% yield (Scheme 4).[17]



Scheme 2. Reaction of different 2-arylaziridines with **2.** [a,b] [a] Aziridine **1a-l**, **1k-n** (0.5 mmol), **2** (0.3 mmol), $Bi(OTf)_3$ (10 mol %), CH_2Cl_2 (1 mL), rt. [b]Isolated yield. [c] Reaction time 1 h.

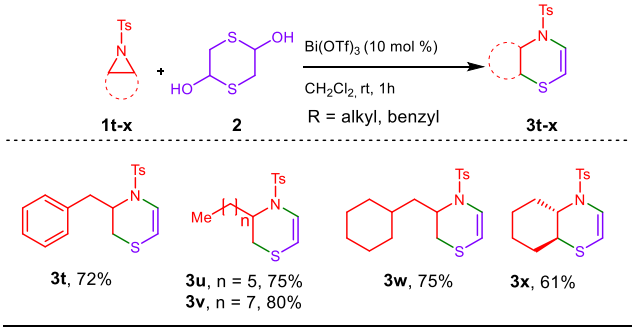


Scheme 3. Reaction of different *N*-sulfonyl aziridines with **2.** [a,b] [a] Aziridine **1o-r** (0.5 mmol), **2** (0.3 mmol), $Bi(OTf)_3$ (10 mol %), CH_2Cl_2 (1 mL), rt. [b]Isolated yield.

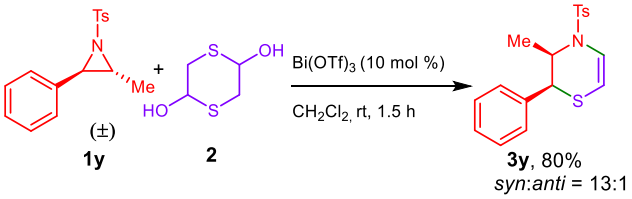


Scheme 4. Reaction of aziridine **1s** with **2.**

Next, we explored the scope of the reaction with 2-alkylaziridines (Scheme 5). 2-Benzylaziridine **1t** underwent reaction to give **3t** in 72% yield. The reaction of **1u-v** bearing 2-hexyl and 2-heptyl groups afforded **3u** and **3v** in 75 and 80% yields, respectively. Similar result observed with 2-(cycloxhexylmethyl)-aziridine **1w** giving **3w** in 75% yield. Further, *meso*-cyclohexylaziridine **1x** reacted to afford **3x** in 61% yield.

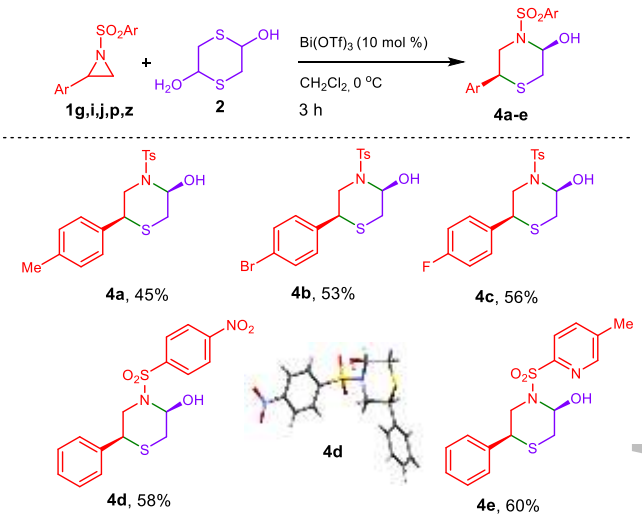


Scheme 5. Reaction of different 2-alkyl-*N*-tosylaziridines with **2**.[a,b] [a] Aziridine **1t-x** (0.5 mmol), **2** (0.3 mmol), $Bi(OTf)_3$ (10 mol %), CH_2Cl_2 (1 mL), rt. [b]Isolated yield.

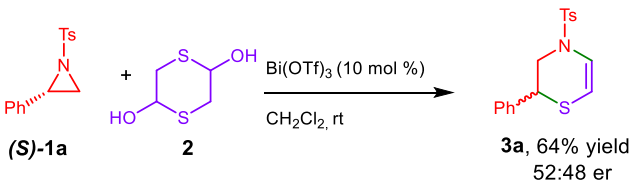


Scheme 6. Reaction of aziridine **1y** with **2.**

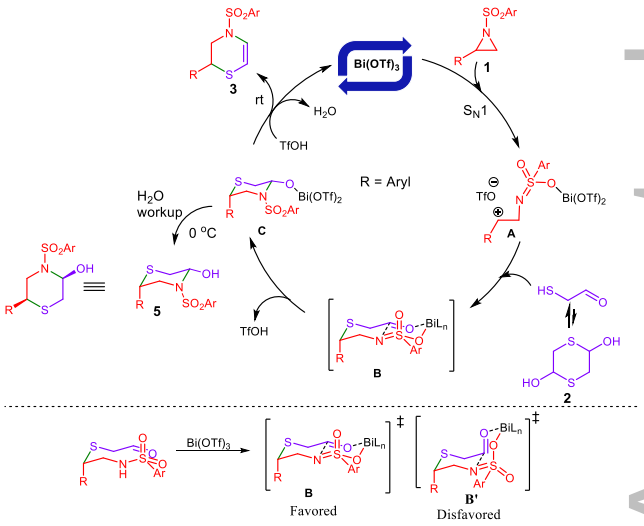
Finally, the reaction of 2-methyl-3-phenylaziridine **1y** was studied (Scheme 6). The reaction occurred to produce **3y** in 80% yield as a 13:1 (*syn*:*anti*) mixture of diastereomers. *Syn* isomer was crystallized in ethyl acetate and hexane mixture whose structure was determined using a single crystal X-ray analysis (see SI). The reaction is temperature dependant. At 0 °C, the reaction can be stopped to give 1,4-thiomorpholin-3-ol (Scheme 7). For examples, the reaction of 2-(4-bromophenyl)aziridine gave **4b** in 53% yield. Similar result observed with 2-(4-flurophenyl)aziridine to give thiomorpholin-3-ol **4c** in 56% yield. In addition, 2-phenylaziridine bearing arylsulfonyl with electron withdrawing 4-nitro group underwent reaction to give **4d** in 58% yield, whereas **1e** containing *N*-(4-methylpyridinyl)-2-sulfonyl group furnished **4e** in 60% yield. Recrystallization of **4d** in $CDCl_3$ afforded single crystals whose structure was determined using X-ray analysis (See SI). The reaction conditions was further investigated for the coupling of aziridine **1a** with 2,5-dimethyl-1,4-dithiane-2,5-diol in place of 1,4-dithiane-2,5-diol. However, the substrate was failed to react and no annulation product was observed.



Scheme 7. Reaction of aziridines with **2** at 0 °C. [a,b] [a] Aziridine (0.5 mmol), **2** (0.3 mmol), $Bi(OTf)_3$ (10 mol %), CH_2Cl_2 (1 mL), rt. [b]Isolated yield.



Scheme 8. Reaction of chiral aziridine (*S*)-**1a** with **2.**

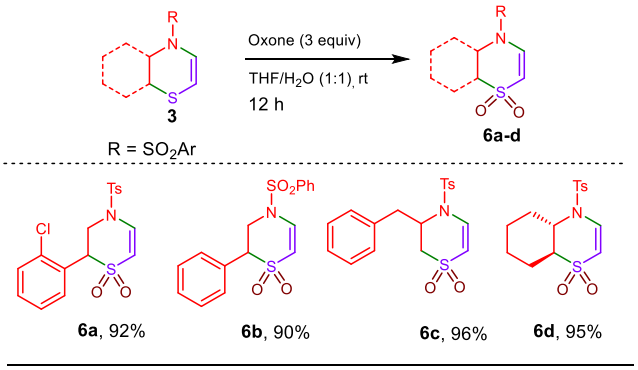


Scheme 9. Proposed catalytic cycle.

To get into the reaction pathway, the reaction of enantiopure aziridine *(S)*-**1a** (99% ee) was studied (Scheme 8). The annulation occurred to furnish **3a** in 64% yield with 52:48 er, which suggests that the reaction involves a S_N1 pathway. Thus, chelation of $Bi(OTf)_3$ with 2-arylaziridine can lead to ring opening to give the benzyl carbocation **A**, which can react with **2** to yield **B**. Intramolecular cyclization of

B can furnish **C** that can provide 1,4-thiomorpholin-3-ol by aqueous workup (0 °C). Alternatively, **C** can undergo dehydration at room temperature to furnish 3,4-dihydro-1,4-thiazines **3** to complete the catalytic cycle. The formation of a single diastereomer of **4** suggests that a chair like transition state **B** is favoured, in which, the carbonyl and sulfonyl groups are *trans* to each other due to steric and electronic repulsion (pl see the crystal structure of **4d**), whereas the transition state **B'** is disfavoured due to unfavourable interaction between the -C=O and -SO_2 groups (Scheme 9). These results suggest that the ring opening takes place in 2-arylaziridines at the benzylic carbon due to an electronic effect, while steric effect favours in 2-alkylaziridines to occur the ring opening at the less hindered CH_2 carbon.[18]

The product can be oxidized using oxone in THF-water (Scheme 10).[11] For examples, the oxidation of **3b**, **3o**, **3t** and **3x** was performed as the representative examples. The reaction took place to produce **6a-d** in quantitative yields.



Scheme 10. Synthesis of 1,4-thiazine 1,1-dioxides. [a,b] **3** (0.2 mmol), oxone (0.6 mmol), THF/H_2O (1:1) (1 mL), rt. [b] Isolated yield.

In summary, we have developed the ring expansion of *N*-sulfonylaziridines with 1,4-dithiane-2,5-diol using a Bi-catalysis to give 3,4-dihydro-1,4-thiazines and 1,4-thiomorpholines. The products can be readily oxidized to 1,1-dioxides in quantitative yields. The regioselectivity and mild reaction condition are the important practical features.

Experimental Section

General Procedure for the Synthesis of 3,4-Dihydro-1,4-Thiazines.
Aziridine (0.5 mmol), 1,4-dithiane-2,5-diol (0.3 mmol) and $Bi(OTf)_3$ (10 mol%) were stirred in CH_2Cl_2 (1 mL) at room temperature. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as an eluent. After completion, the solvent was evaporated and the residue was purified on a silica gel column chromatography using ethyl acetate and hexane (1:9) as eluent.

General Procedure for the Synthesis of Thiomorpholin-3-ol.
Aziridine (0.5 mmol), 1,4-dithiane-2,5-diol (0.3 mmol) and $Bi(OTf)_3$ (10 mol%) were stirred in CH_2Cl_2 (1 mL) at 0 °C. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as an eluent. After completion, the reaction mixture was quenched with water and the aqueous layer was extracted using CH_2Cl_2 (3 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue, which was purified on a silica gel column chromatography using ethyl acetate and hexane (4:6) as an eluent.

General Procedure for the Synthesis of 3,4-Dihydro-1,4-Thiazine-1,1-dioxide.
1,4-Thiazines (0.2 mmol) and oxone (0.6 mmol) were stirred in THF and H_2O (1:1, 1 mL) at room temperature. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as an eluent. After completion, the solvent was evaporated and aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue, which was purified on a silica gel column chromatography using ethyl acetate and hexane as eluent.

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