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Direct access to 1,4-benzothiazine 4,4-dioxides and 4-oxides *via* a domino reaction

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ABSTRACT

The domino reactions of 2-fluoro benzensulfonyl acetonitrile and α-chloro oximes in the presence of Cs_2CO_3 in aprotic high boiling point solvents have been achieved to provide isoxazole–fused 4*H*-1,4-benzothiazine-4,4-dioxides *via* an unprecedented transition metal-free one-pot addition/cyclization process. The tunable synthesis of either isoxozolo-1,4-benzothiazin-4-oxides or their precursor 5-aminoisoxazoles can be controlled depending on the solvent selection. The observed products were characterized by means of (IR, ^1H, ^{13}C NMR and HRMS) and physical methods.

1. Introduction

A domino reaction includes a consecutive series of organic reactions, which often proceed with highly reactive intermediates in a reaction vessel or in nature.[1,2] Single acyclic organic starting materials can be converted into multifunctional cyclic or heterocyclic organic molecules in this way.[3] It is well known that phenothiazine analogues of 1,4-benzothiazines have stimulated considerable interest in recent years due to their broad spectrum of pharmacological properties.[4] Their biological features have been well documented over the years.[5,6] Structure–activity analyses have revealed that the biological properties of 1,4-benzothiazines are strongly dependent on substitution, which makes them pharmacologically relevant and highly attractive.[7] In particular, antimalarial activity,[8] histamine H-receptor antagonist,[9] central nervous system depressants,[10] antifungal agents,[11] calcium ion channel antagonists,[12] potassium ion channel openers[13] and anticancer properties[14] make this class of compounds good candidates for biological studies.

In addition, isoxazole-fused heterocyclic systems have broad application in both synthetic organic chemistry and biological studies.[15–18] The synthesis of new heterocyclic systems, the development of facile procedures for the synthesis of these compounds and the improvement of available methods have been, and still remain, important areas of research in synthetic organic chemistry.

Several synthetic methods have been developed for the synthesis of 1,4-benzothiazines.[4] Reported procedures for the preparation of 1,4-benzothiazines include the reaction of 2-aminothiols with unsaturated C–C bonds,[19,20] ring expansions or ring cleavages of various heterocyclic systems[21–24] and metal catalyzed C–S bond formations[25–27] but, to the best of our knowledge, there is no literature concerning the synthesis of heterocycles, which contain isoxazolo-1,4-benzothiazines from simple starting materials *via* domino reactions. In addition, reports of isoxazole–fused heterocyclic systems are very limited in the literature.[28,29]

In continuation of our isoxazole chemistry,[30–34] herein, we have developed a robust, convenient and atom-economical method to obtain potentially bioactive isoxazolo-benzothiazines by reacting *ortho*-fluoro substituted phenylsulfonyl acetonitrile and α-chloro oximes. The reaction conditions produce an enamino moiety which is used as a reactive intermediate for obtaining the title compounds. There are examples of the enamino intramolecular nucleophilic substitution reaction with *ortho*-substituted halides to obtain 1,4-benzothiazine 4,4-dioxides. Lautens' group prepared enamines by the Rh-catalyzed addition of arylboronic acids to (*o*-

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fluorophenylsulfonyl)acetonitrile. The subsequent intramolecular nucleophilic substitution of those enamines gave *N*-unsubstituted 2-aryl-1,4-benzothiazine S,S-dioxides.[35] Another method, employing 2-aminopyrroles bearing a 2-chlorophenylsulfone group at the 3-position to obtain 1,4-benzothiazines *via* Pd-catalyzed intramolecular cyclization with carboxylic acid auxiliary, has also been reported.[36] However, the aforementioned studies required expensive metal catalysts to obtain either the starting materials or cyclization products. Recently, Gu et al. developed a method to obtain benzothiazines *via* the K_2S initiated sulfur insertion into enaminones without using a transition-metal catalyst.[37] In our work, a one-pot metal–free synthesis of isoxazolo-1,4-benzothiazine-4 oxides and 4,4-dioxides is reported for the first time. This method enables several advantages such as simple work-up procedure, high yields, broad applicability and practicability.

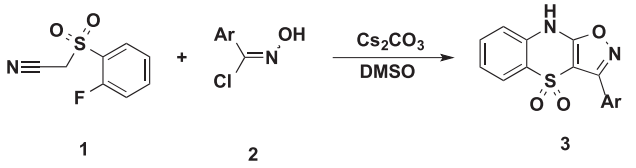
2-((2-Fluorophenyl)sulfonyl)acetonitrile **(1)** and 2-((2-fluorophenyl)sulfinyl)acetonitrile **(4)** were obtained from the oxidation of 2-((2-fluorophenyl)thio)acetonitrile with H_2O_2 (30%) and *m*-CPBA respectively. Then, 2-((2-fluorophenyl)sulfonyl) acetonitrile (**1**) reacted with α-chlorooximes to furnish isoxazolo [5,4-e][1,4]benzothiazine 4,4-dioxides **3a-k** and reaction conditions were optimized with conventional and microwave heating methods, see Table 1. Reactions with microwave heating had slightly higher yields and shorter reaction times than conventional heating. The reaction yields were similar for both electron– withdrawing and electron–releasing substituents of α-chlorooximes.

Having examined the scope of the sulfone functionality in the reaction, we next examined the synthesis of isoxazolo-1,4-benzothiazin-4-oxides. The reaction in a one-pot manner gave lower yields (for **6a-d**), but firstly isolation of 5-aminoisoxazole **5e-h** intermediate and then, its heating in high boiling point aprotic solvents (DMSO or DMF) in the presence of Cs_2CO_3 afforded the corresponding isoxazolo-1,4-benzothiazine 4-oxides **6a**–**h** with better yields, see Table 2.

The structures of all compounds were elucidated according to IR, ^1H and ^{13}C NMR spectroscopy and HRMS methods. The IR spectra of compounds **3a**–**k** showed NH stretching between 3244 cm^{-1} and 3214 cm^{-1}, SO_2 asymmetric stretching of compounds **3a**–**k** was seen at 1342-1261 cm^{-1} and symmetric stretching at 1173–1142 cm^{-1}. While NH_2 asymmetric and symmetric stretching frequencies for compounds **5e**–**h** appeared between 3383 and 3310 cm^{-1} and 3317–3171 cm^{-1}, NH stretching frequencies of compounds **6a**–**h** were observed between 3445 and 3433 cm^{-1}. The compounds **5e**–**h** and **6a**–**h** exhibited a SO stretching frequency at 1007–1069 cm^{-1} and 999–957 cm^{-1}, respectively. The ^1H NMR spectra of compounds **3a**–**k** and **6a**–**h** displayed a broad singlet for NH protons between 13.28–13.14 ppm and 13.21–12.97 ppm in DMSO respectively. When the ^1H NMR was run in DMSO, the amino protons resonated at 8.08–8.29 ppm due to interaction with water in DMSO, when same pattern of compound **5f** was run in $CDCl_3$, the amino group protons resonated at 5.57 ppm. The ^{13}C NMR spectra of compounds **3a**–**k** contained a signal in the range of 163.0–161.5, 158.7–147.9 and 95.1–91.3 ppm, which are in accordance with isoxazole carbons. There is no dramatic effect of the sulfoxide or sulfone groups on the carbon signals in isoxazole ring for the two series of compounds. In addition, the isoxazole ring showed similar signals for compounds **5e**–**h** for the C5 carbon at 171.0–169.1 ppm, for the C4 carbon at 161.2–159.3 ppm, for the C3 carbon at 91.9–90.6 ppm and for compounds **6a**–**h** for the C5 carbon at 161.8–160.7, for the C4 carbon at 160.2–157.6, for the C3 carbon at 95.0–93.0 ppm. Moreover, the proposed intermolecular nucleophilic substitution reaction can be easily understood by the disappearance of C–F couplings from starting materials (**5e**–**h**). When the ^{13}C NMR of compound **6a** was analyzed the restricted rotation for the 2,6-dichloro substituents results in each carbon atom on the ring having different resonances. HRMS results were in agreement with the expected molecular weights of all novel compounds.

Regarding the reaction mechanism, it would be reasonable to assume that two reaction mechanisms may occur until the formation of 5-aminoisoxazoles. First proposed mechanism may work through deprotonation of the carbon atom next to the nitrile occurs. This would then be followed by nucleophilic addition to the iminic carbon atom of α-hydroxymoyl chlorides. Finally, the

Table 1
Reactions of 2-((2-fluorophenyl)sulfonyl) acetonitrile **(1)** with α-chloro oximes **(2)**.

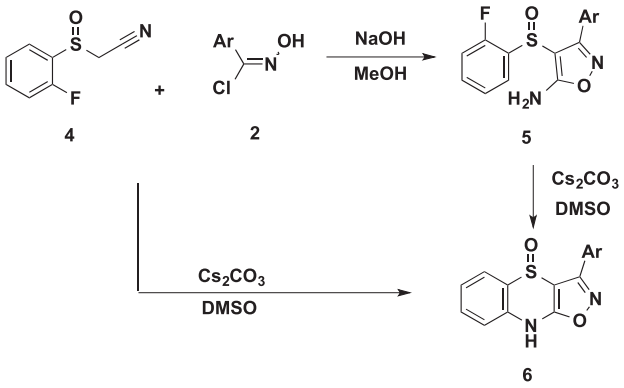


1 2 3

Entry	Compound	Ar	Yields[a] (%)	Yields[b] (%)
1	**3a**	2,6-di-ClC_6H_3	30	37
2	**3b**	2,4-di-ClC_6H_3	53	67
3	**3c**	4-F-C_6H_4	40	58
4	**3d**	4-Br-C_6H_4	54	58
5	**3e**	4-Cl-C_6H_4	59	67
6	**3f**	C_6H_5	46	51
7	**3g**	2-Cl-4,5-diMeO-C_6H_3	58	67
8	**3h**	2-O_2N-C_6H_4	50	69
9	**3i**	4-O_2N-C_6H_4	54	68
10	**3j**	5-Cl-2-thienyl	65	72
11	**3k**	5-Cl-2-furyl	52	64

[a] Yields obtained by conventional heating method.
[b] Yields obtained by microwave heating method.

Table 2
Synthesis of 1,4-benzothiazine-4-oxides.



4 2 5 6

Entry	Compound	Ar	Yield for **6** (%)	Yield for **5** (%)
1	**a**	2,6-di-ClC_6H_3	17[a]	
2	**b**	2,4-di-ClC_6H_3	19[a]	
3	**c**	4-F-C_6H_4	18[a]	
4	**d**	4-Br-C_6H_4	19[a]	
5	**e**	4-Cl-C_6H_4	16[a], 81[b]	37
6	**f**	C_6H_5	73[b]	38
7	**g**	2-Cl-4,5-diMeOC_6H_3	81[b]	50
8	**h**	2-$O_2NC_6H_4$	83[b]	46

[a] Yields obtained through one-pot single step reaction.
[b] Yields obtained through isolation of compounds **5 e**–**h** and then, reaction in the presence of Cs_2CO_3 in DMSO.