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Acid-Mediated Oxychalcogenation of *o*-Vinylanilides with *N*-(Arylthio/arylseleno)succinimides

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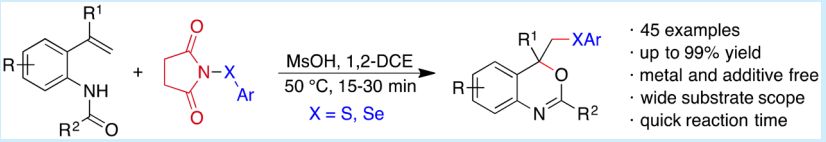
Supporting Information



ABSTRACT: An efficient acid-mediated oxythiolation of *o*-vinylanilides has been accomplished, employing *N*-(arylthio)-succinimide as an electrophilic arylthiolating reagent for the synthesis of various arylthio tethered benzoxazine derivatives in good to excellent yield. The important features of this method include wide functional group tolerance, quick reaction time, absence of metal or additive, and excellent substrates scope. The developed method was also successfully extended to the oxyselenation of *o*-vinylanilides in the absence of acid promoter.

Substituted 3,1-benzoxazines are widely present in various natural products and bioactive molecules and are also extensively used as building blocks in organic synthesis.[1] For example, etifoxine **1** and compound **2** containing a benzoxazine framework exhibit anticonvulsant and antifungicidal activities, respectively (Figure 1). In addition, arylthio moieties are also

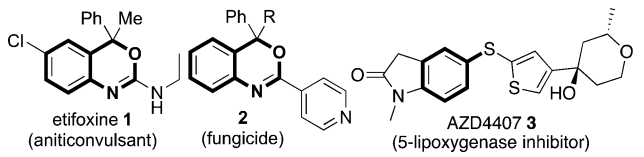
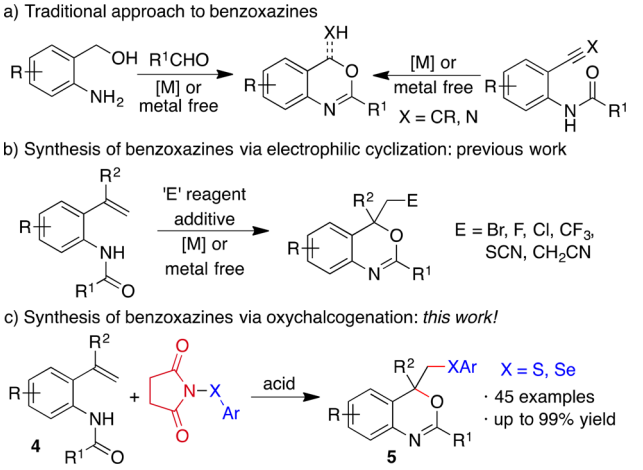


Figure 1. Bioactive molecule possessing benzoxazine and arylthio motifs.

present in various therapeutically important molecules, such as AZD4407 **3**.[2] Because of the importance of benzoxazine and arylthio moieties, development of an elegant strategy for their synthesis has been a long-standing interest in organic synthesis. Particularly, development of a new method for the construction of benzoxazine framework that incorporates arylthio motif would be highly desirable.

In the classical approach, synthesis of benzoxazines was achieved via the condensation of 2-aminobenzyl alcohols with carbonyl compounds[3] and the cyclization of *o*-alkynyl or cyanoanilides employing[4] or without[5] catalyst (Scheme 1a). However, these methods have found limited application in organic synthesis because of their harsh reaction conditions and narrow substrate scope. Recently, these traditional methods were replaced by the transition-metal-catalyzed or metal-free intramolecular cyclization of *o*-vinylanilides utilizing various electrophiles such as F,[6] Cl,[7] Br,[8] and CF_3[9] (Scheme 1b). Intramolecular oxidative cyclization of nucleophiles such as acetonitrile was also documented for the oxycyanomethylation of vinylanilides employing copper catalyst and a super-

Scheme 1. Approaches to the Synthesis of Benzoxazines



stoichiometric amount of oxidant.[10] However, construction of functionalized benzoxazine through oxychalcogenation of vinylanilides is rather limited. The only known report uses the metal free thiocyanooxygenation of alkene-tethered amide with potassium thiocyanate and $K_2S_2O_8$.[11]

Recently, we have demonstrated that *N*-(arylthio)-succinimide is an efficient electrophilic arylthio source in the direct palladium-catalyzed arylthiolation of arene for the synthesis of diaryl sulfides.[12] Inspired by the reactivity of *N*-(arylthio)succinimide and the high importance of benzoxazines and arylthio moieties, we herein disclose an efficient and general method for the synthesis of arylthio-/arylseleno-tethered benzoxazines involving acid-mediated oxychalcogenation of *o*-vinylanilides (Scheme 1c).

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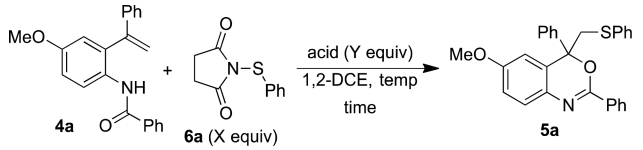
We began our investigation using *N*-(4-methoxy-2-(1-phenylvinyl)phenyl)benzamide **4a** as a model substrate. Reaction of **4a** (1 equiv) and 2 equiv of *N*-(phenylthio)-succinimide **6a** in the presence of 5 equiv of acetic acid as promoter in 1,2-DCE at 80 °C for 18 h led to the formation of expected oxythiolation product **5a** in only a detectable amount (Table 1, entry 1). After the formation of product was

Table 1. Acid-Mediated Oxythiolation of *o*-Vinylanilides: Optimization[a]



entry	*X*	acid (*Y*)	temp (°C)	time (h)	yield[b] (%)
1	2	AcOH (5)	80	18	3
2	2	AcOH (20)	80	18	18
3	2	AcOH (30)	80	18	18
4	2	TFA (20)	80	0.5	24
5	2	MsOH (20)	80	0.5	44
6	2	MsOH (10)	80	0.5	29
7	2	MsOH (10)	50	0.5	69
8	2	MsOH (10)	rt	0.5	61
9	2	MsOH (5)	50	0.5	77 (30)[c]
10	2.5	MsOH (5)	50	0.5	93

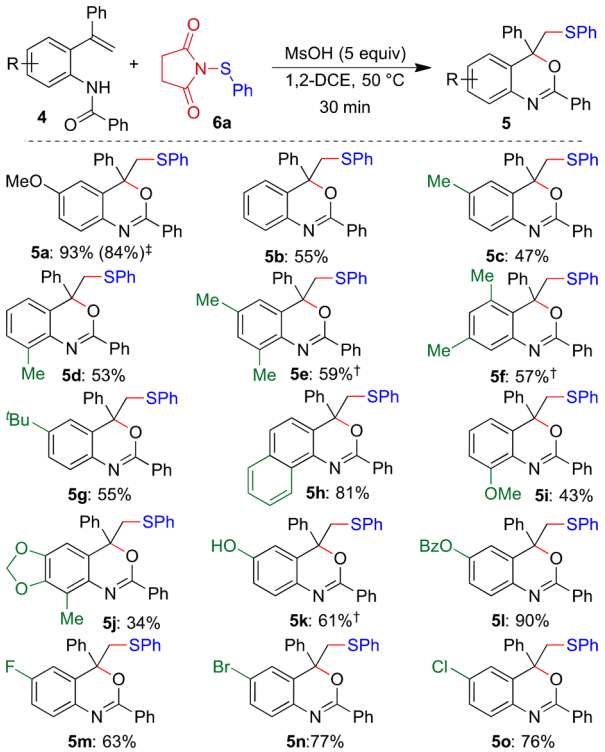
[a]Reaction conditions: **4a** (1 equiv), **6a** (*X* equiv), acid (*Y* equiv), 1,2-DCE (1 mL for 0.13 mmol), temp, time. [b]All are isolated yields. [c]With 1 equiv of MsOH for 2 h.

confirmed through ^{1}H, ^{13}C NMR and HRMS, the reaction conditions were optimized by studying various parameters. Increasing the amount of acetic acid to 20 equiv afforded the product **5a** in 18% yield. Further increasing the equivalents of acetic acid (30 equiv) did not show any improvement in the oxythiolation (Table 1, entires 2 and 3). Next, replacing the acetic acid with strong acids such as trifluoroacetic acid (TFA) and methanesulfonic acid (MsOH) in 1,2-DCE furnished the product **5a** in 24 and 44% yield, respectively (Table 1, entries 4 and 5). In both of these reactions, the reagent **6a** and *o*-vinylanilide **4a** were consumed in 30 min and converted to diphenyl disulfide and hydroalkoxylation product, respectively, along with the formation of product **5a**. This observation suggests that (1) the reagent **6a** is decomposing to diphenyl disulfide under strong acidic condition and at high temperature and (2) **4a** undergoes an acid promoted hydroalkoxylation possibly due to the unavailability of **6a**.

To control the decomposition of **6a** and hydroalkoxylation of **4a**, influence of the quantity of MsOH employed and temperature was investigated. As expected, reducing the equivalents of acid and temperature decreased the decomposition of **6a** and provided better oxythiolation products (Table 1, entries 6–9). Among them, use of 5 equiv of MsOH at 50 °C afforded the oxythiolation product **5a** in 77% yield (Table 1, entry 9). Subsequently, increasing the amount of **6a** to 2.5 equiv at 50 °C with 5 equiv of MsOH furnished the product **5a** in a best yield of 93% (Table 1, entry 10). Thus, these studies revealed that the best oxythiolation of **4** could be achieved by employing 2.5 equiv of **6a** and 5 equiv of MsOH in 1,2-DCE at 50 °C for 30 min.

After the optimal reaction conditions for the oxythiolation of *o*-vinylanilides were identified, scope and generality of the developed methodology was investigated. Initially, various substituted aniline derivatives were examined. Unsubstituted and alkyl-substituted (4-methyl, 6-methyl, 4,6-dimethyl, 3,5-dimethyl, and 4-*tert*-butyl) anilines gave the corresponding benzoxazines **5b–g** in good yields, irrespective of their position (Scheme 2). Sterically hindered 6-substituted and 1-naphthyl-

Scheme 2. MsOH-Mediated Oxythiolation of *o*-Vinylanilides 4: Scope of Anilines[a]



[a]All yields shown are isolated yields. †Yield based on ^{1}H NMR. ‡Yield of 1 mmol scale reaction.

amine-derived *o*-vinylanilides were well tolerated and furnished the oxythiolated product **5i** and **5h** in 43% and 81% yield, respectively. Acid-sensitive acetal containing electron-rich *o*-vinylanilide underwent smooth reaction to afford the product **5j** in moderate yield along with the hydroalkoxylation product, possibly due to the high electron-rich nature of the substrate. Similarly, reactive functional groups such as free hydroxy and benzyloxy have shown high compatibility under the optimized conditions and afforded the benzoxazines **5k** and **5l** in 61% and 90% yield, respectively. Formation of fluoro and readily functionalizable bromo- and chloro-substituted benzoxazines (**5m–o**) was also achieved from the corresponding anilides in good yield (Scheme 2).

Having demonstrated the generality of substitution on the aryl moiety of anilide, we next studied the scope of the substituted alkenes in acid-mediated oxythiolation. An inductively electron-donating alkyl-substituted aryl moiety on the alkene gave the cyclized products **5p–r** in moderate to good yields. Relatively electron-deficient 4-fluorophenyl-substituted alkene furnished the expected product **5s** in 75% yield (Scheme 3). However, mesomerically electron-donating methoxyphenyl containing alkene gave the product **5t** only in 17% yield, along with a major amount of hydroalkoxylation product. Thiophene-substituted alkene also underwent smooth

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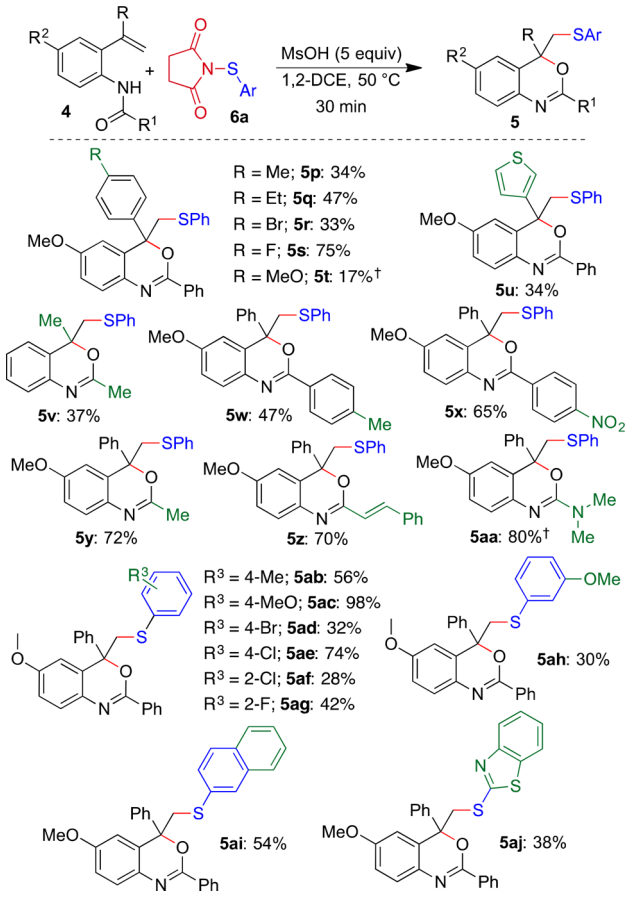
Scheme 3. MsOH-Mediated Oxythiolation of *o*-Vinylanilides 4: Scope of Alkenes, Anilides, and Aryl Thiols[a]



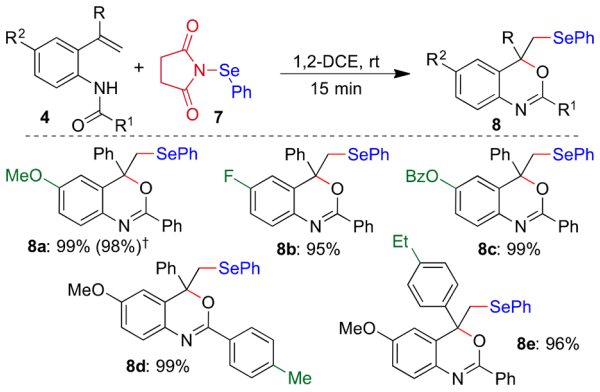
[a]All yields shown are isolated yields. [†]Yield based on ^{1}H NMR.

cyclization under the optimized conditions to afford the corresponding product **5u** in 34% yield. Replacing the aryl moiety with methyl substitution on the alkene also provided the product **5u** in 37% yield. These studies reveal that electron-donating groups either on the aniline or on the alkene system favor rapid hydroalkoxylation and lead to oxythiolation in relatively lower yield compared to electron-withdrawing substitutions.

Next, various substituted amides were studied under the optimal reaction conditions. *o*-Vinylanilides derived from *p*-toluic acid and *p*-nitrobenzoic acid on reaction with **6a** gave the expected cyclized product **5w** and **5x** in 47 and 65% yield. Instead of benzoic acid derivatives, amides of acetic acid and cinnamic acid also afforded the oxythiolation products **5y** and **5z** in up to 70% yield. Interestingly, employing the present strategy synthesis of bioactive etifoxine derivative **5aa** was achieved from urea derivative in 80% yield. Subsequently, the effect of various substituted arylthiols on the reagent **6** was investigated. 4-Methylphenylthio-substituted succinimide derivative furnished the product **5ab** in 56% yield (Scheme 3). Electron-donating methoxy-substituted phenylthio derivatives gave the products **5ac** and **5ah** in 98% and 30% yield. Similarly, halo substitution at the *para* position (**5ad** and **5ae**) was well tolerated under the optimized conditions. On the other hand, *ortho*-substituted *N*-(arylthio)succinimide derivatives afforded the products (**5af** and **5ag**) in moderate yield, possibly due the steric hindrance. Furthermore, reagent **6** derived from naphthyl-2-thiol and 2-mercaptobenzthiazole also gave products **5ai** and **5aj** in 54% and 38% yield, respectively.

After successful development of acid-mediated oxythiolation of *o*-vinylanilides, oxyselenation of **4** was examined (Scheme 4).

Scheme 4. Oxyselenation of *o*-Vinylanilides 4[a]

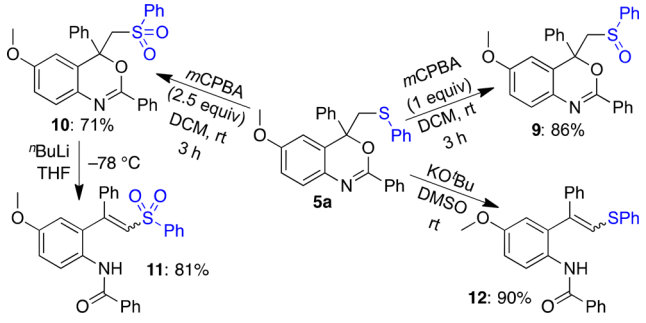


[a]All are isolated yields. [†]Five equiv of MsOH for <5 min.

Thus, reaction of *N*-(phenylseleno)succinimide **7**, the selenium analogue of **6**, with **4a** in the presence of 5 equiv of MsOH in 1,2-DCE at room temperature afforded the expected oxyselenated product **8a** in 98% yield in <5 min. Interestingly, a similar yield of **8a** was observed even in the absence of MsOH after 15 min, which revealed that the superior reactivity selenium reagent **7** over sulfur reagent **6**. Next, various substituted *o*-vinylanilides tested under the present oxyselenation conditions led to the formation of products **8b–e** in excellent yields.

Additionally, the utility of the synthesized benzoxazines containing an arylthio moiety was demonstrated through simple conversion to vital molecules. Thus, selective oxidation of sulfur with 1 equiv of *m*-CPBA furnished the sulfoxide **7** in 86% as mixture of diastereomer in a 4:3 ratio (Scheme 5). On

Scheme 5. Synthetic Utility



the other hand, oxidation with two 2equiv of *m*-CPBA gave the sulfone **8** in 71% yield. Treatment of sulfone with ^{n}BuLi at −78 °C afforded the ring opened vinyl sulfone **9** in 81% yield as single isomers. This is not surprising because the reaction of **5a** with KO^{t}Bu in DMSO at room temperature also gave the vinyl sulfide **10** in 90% yield as 2:1 mixture of isomers.

Preliminary NMR studies were performed to understand the interaction of reagent **6** with MsOH and the plausible pathway. Thus, an equimolar mixture of **6a** and MsOH was investigated under variable-temperature (VT) ^{1}H and ^{13}C NMR (see the Supporting Information). The ^{1}H NMR showed a significant

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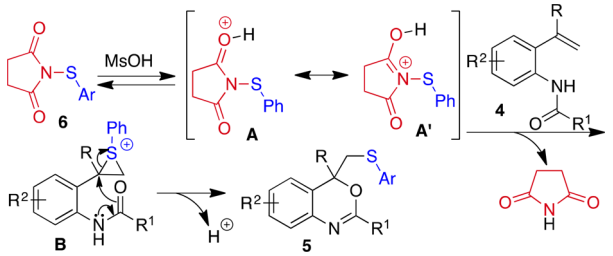
shift for methylenes of succinimide moiety on addition of MsOH in $CDCl_3$ at room temperature (2.80 ppm to 2.86 ppm). A similar shift was observed when the mixture was heated to 50 °C. Likewise, a large downfield shift of carbonyl carbon (176.5 ppm to 177.8 ppm) was seen in ^{13}C NMR at variable temperatures on addition of MsOH to **6a** in $CDCl_3$. These observations reveal that the carbonyl oxygen of succinimide moiety in **6a** is possibly protonated on the addition of MsOH, which makes the resultant species highly electron deficient. As a consequence, protonated succinimide moiety acts as the best leaving group, and the arylthio moiety is transferred to substrate **4** as an electrophile.

Based on the above observation, we postulate the mechanism shown in Scheme 6 for the oxythiolation of **4**. Activation of **6**

Scheme 6. Plausible Mechanism



with MsOH would provide the protonated species **A**, which possibly would exist in resonance with **A′**. Generation of three membered cyclic sulfonium ion **B** could be rationalized through the trapping of arylthio moiety of activated species **A** by the alkene of **4**. Intramolecular regioselective ring opening of sulfonium ion in **B** with amide oxygen followed by loss of proton would afford the arylthio-tethered benzoxazines **5**.

In conclusion, an efficient oxythiolation of *o*-vinylanilides has been successfully demonstrated employing *N*-(arylthio)-succinimides as electrophilic arylthio source and methanesulfonic acid as promoter. Excellent tolerance of various functional groups and synthesis of diverse arylthio tethered benzoxazines in good yield with quick reaction time are the merit of the present reaction. The developed method was also successfully extended to the oxyselenation of *o*-vinylanilides in the absence of acid promoter. Furthermore, preliminary variable-temperature NMR experiments were also studied to reveal the possible activation of the succinimide moiety with MsOH.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00065.

Experimental details, characterization data, and ^1H and ^{13}C NMR spectra of isolated compounds (PDF)

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Notes

The authors declare no competing financial interest.

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