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Synthesis of Spiroisoxazolines via an Oximation/Dearomatization Cascade under Air

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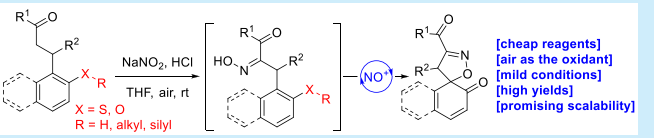
ABSTRACT: A catalytic, transition-metal-free synthesis of spiroisoxazolines is outlined. This protocol provides, for the first time, a direct access to spiroisoxazolines from aryl (thio)ethers or (thio)phenols in one synthetic step via an oximation/dearomatization cascade. In this reaction, sodium nitrite plays dual roles: as a hydroxylamine source and also a precatalyst to promote the aerobic dearomatization. This methodology features unprecedented substrate scope, high yields, promising scalability, sustainable oxidant, and mild conditions.



Spiroisoxazoline motifs are widely found in a variety of natural products[1] and biologically active molecules.[2] Figure 1 illustrates a selection of these molecules with broad

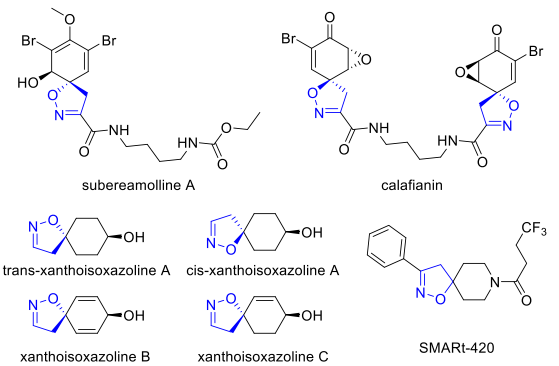
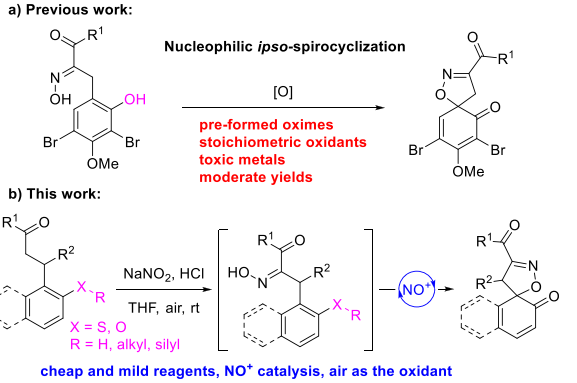


Figure 1. Spiroisoxazoline in natural products and drug candidates.

spectrum of biological activities. A wide range of bioactive bromotyrosine-derived spiroisoxazoline derivatives have been first isolated from marine sponges. For instance, subereamolline A[3] exhibits highly antimigratory activity against metastatic human breast cancer cells, and calafianin[4] displays significant antimicrobial activity. Aside from marine spiroisoxazolines, four spiroisoxazoline analogues—*trans*-xanthoisoxazoline A, *cis*-xanthoisoxazoline A, and xanthoisoxazolines B and C—have been recently isolated from the terrestrial plant *Xanthoceras sorbifolia*.[5] Furthermore, synthetic spirocyclic isoxazoline derivatives are also promising drug candidates.[2] For example, SMARt-420[2b] has been found to revert antibiotic resistance in *Mycobacterium tuberculosis*.

Not surprisingly, considerable synthetic efforts have been dedicated to the search for approaches to assemble these privileged motifs.[6] Such specific motifs are typically built via 1,3-dipolar cycloaddition reactions.[6b,h] However, this strategy often requires multistep to prepare exocyclic methylene dipolarophiles, especially for accessing spiro-cyclohexadienyl isoxazoline core in bromotyrosine alkaloids. Alternatively, oxidative cyclization of phenolic oxime esters provides a complementary approach to spiroisoxazoline motifs using stoichiometric oxidants, such as $PhI(OAc)_2$,[6c,p] $PhI(OCOCF_3)_2$,[6q,r] Br_2,[6u] NBS,[6e,l] $Mn(acac)_3$,[6v] and $Tl(OCOCF_3)_3$,[6s,t] etc. (see Scheme 1a). Nonetheless, these reactions still suffer from at least one of the following limitations: the use of corrosive or stoichiometric highly oxidative reagents, toxic metals, low selectivity, moderate yields, and limited examples. Furthermore, a general catalytic

Scheme 1. Dearomative Spiroisoxazoline Synthesis



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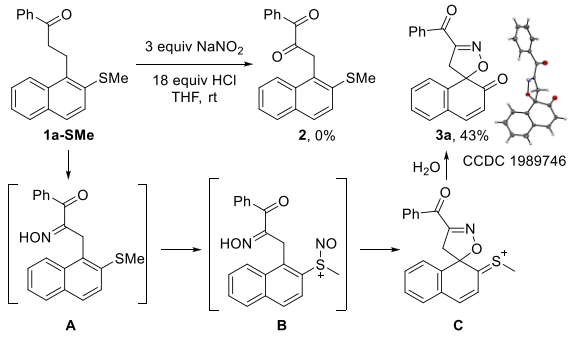
oxidative oxo-spirocyclization of aryl ethers with good functional compatibility is highly desirable.

Herein, we report a one-pot, efficient synthesis of spiroisoxazolines via oximation/dearomatization cascade reactions under air at room temperature (Scheme 1b). This cascade provided a novel tool to access spiroisoxazoline scaffolds through easily accessible dihydrochalcone derivatives without the requirement for protection/deprotection. Note that the dearomatization step features a catalytic oxidative dearomatization of aryl (thio)ethers and thiophenols using air as the terminal oxidant with water as the byproduct, as compared with conventional hypervalent iodine-mediated dearomatization of phenols.[7] This cascade protocol can be performed at room temperature, with broad substrate scope, high yields, and promising scalability.

Initially, ketone sulfide **1a-SMe**,[8] was intended to be converted to 1,2-diketone **2** (Scheme 2). In a preliminary

Scheme 2. Initial Discovery

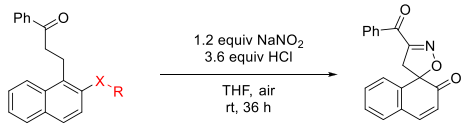


experiment, we assumed that a treatment of naphthyl methyl thioether **1a-SMe** with $NaNO_2$ (3 equiv) and HCl (18 equiv) would deliver diketone **2** as the expected product.[9] To our surprise, spiroisoxazoline **3a** was isolated in 43% yield, which was further confirmed by single-crystal X-ray diffraction (XRD) (CCDC No. 1989746). It is reasonable to hypothesize that oxime **A** could be formed by the reaction of **1a-SMe** with sodium nitrite and aqueous HCl.[10] Subsequent complexation of S with NO^+ would provide the activated sulfide **B**.[11] Finally, an oxo-cyclization reaction and hydrolysis would afford spiroisoxazoline **3a**.

Inspired by this unexpected result that provides a novel and concise access to spiroisoxazolines, we decided to explore this transformation further. First, naphthyl methyl ether **1a** was also found to be compatible in this spirocyclization, giving the same product **3a**. We then optimized the reaction conditions using naphthyl ether **1a** as the model substrate (see Tables S1−S5 in the Supporting Information). A variety of reaction conditions, including different amounts of $NaNO_2$, acids, solvents, and concentrations, were examined. Ultimately, the desired dearomatization product **3a** was obtained in almost-quantitative yield, in the presence of 1.2 equiv of $NaNO_2$ only at room temperature under air (Scheme 3).

With the optimized cascade conditions in hand, we set about examining the generality of this metal-free oximation/dearomatization cascade. As shown in Scheme 3, both naphthyl methyl thioether **1a-SMe** and naphthyl methyl ether **1a** exhibited excellent reactivity under the standard conditions. The cascade process also extended to free (thio)arenols **1a-SH** and **1a-OH**, which provided **3a** in yields

Scheme 3. Scope of (Thiol)Ether Derivatives[a]



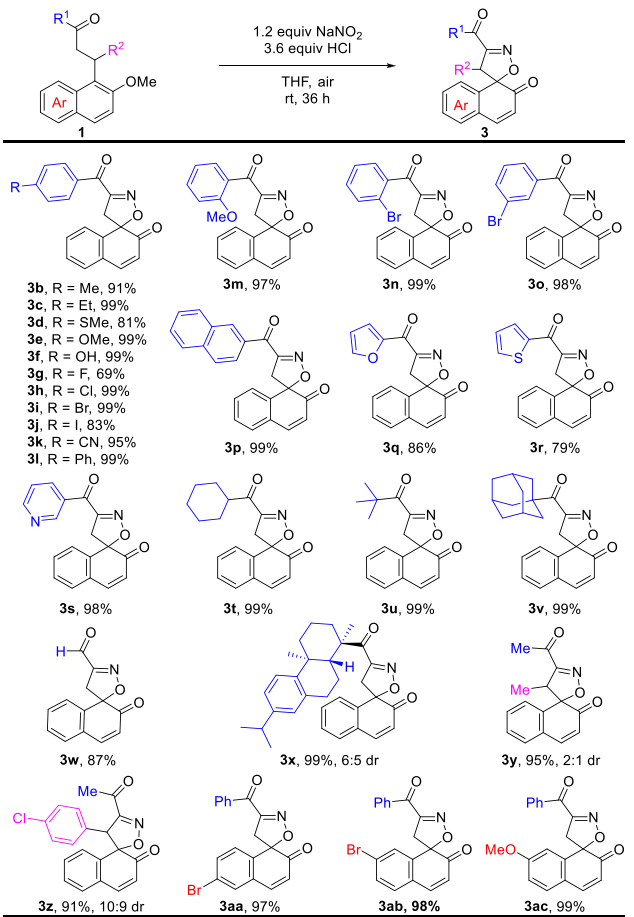
1a-SMe, X = S, R = Me	**3a**, 94%
1a, X = O, R = Me	**3a**, 99%
1a-SH, X = S, R = H	**3a**, 81%
1a-OH, X = O, R = H	**3a**, 84%
1a-O*n*Pr, X = O, R = *n*Pr	**3a**, 99%
1a-O*i*Pr, X = O, R = *i*Pr	**3a**, 83%
1a-OBn, X = O, R = Bn	**3a**, 99%
1a-OTMS, X = O, R = TMS	**3a**, 83%
1a-OTIPS, X = O, R = TIPS	**3a**, 85%

[a]Reactions were performed on a 0.2 mmol scale, and all yields represent isolated yields.

of 81% and 84%, respectively. Notably, the cascade reaction can be performed with high efficiency from other alkyl protected arenols (O-*n*Pr **1a-O*n*Pr**, O-*i*Pr **1a-O*i*Pr**, and O-Bn **1a-OBn**). With O-silyl protected arenols (**1a-TMS** and **1a-TIPS**), the reactions proceeded smoothly to provide the corresponding product **3a** in high yields.

We next explored the scope with respect to *ortho*-methoxynaphthalenes. The variation of substituents R^1 in methoxynaphthalene (Scheme 4) was first examined. Substrates with *para*-substituted arenes, including electron-donating and

Scheme 4. Scope of *ortho*-Methoxynaphthalenes[a]



[a]Reactions were performed on a 0.2 mmol scale, and all yields represent isolated yields.

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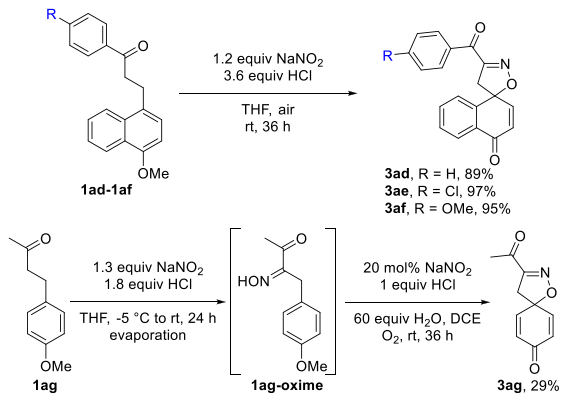
electron-withdrawing groups, underwent the desired oximation/dearomatization with high efficiency to give the corresponding spiroisoxazolines **3b**−**3l** in 69%−99% yield. *ortho*- and *meta*-Substituents had marginal effect on the reaction efficiency, giving **3m**−**3o** in excellent yields. Naphthyl-substituted substrate also engaged in this reaction to deliver product **3p** in excellent yield. Pleasingly, heteroaryl substituents, such as furyl, thiophenyl, and pyridyl, were also tolerable, affording **3q**−**3s** in yields of 79%−98%. Substrates bearing bulky alkyl groups, including cyclohexyl, *tert*-butyl, and adamantanyl, readily participated in this reaction, giving **3t**−**3v** in excellent yields. It is noteworthy that aldehyde group was also found to be compatible with the present conditions (**3w**, 87% yield). Furthermore, dehydroabietic acid-derived ketone substrate exhibited excellent reactivity, leading to the desired product **3x** in 99% yield. Variation of R^2 was also plausible, where alkyl and aryl substituents were readily integrated into the products (**3y** and **3z**) at the 4-position of the isoxazoline ring. With additional substituents on the naphthyl ring of *ortho*-methoxynaphthalenes, the reactions proceeded smoothly to afford **3aa**−**3ac** in excellent yields.

Further substrate scope evaluation revealed that the cascade protocol can be extended to *para*-methoxyarenes (Scheme 5).

Scheme 5. Scope of *para*-Methoxyarenes[a]

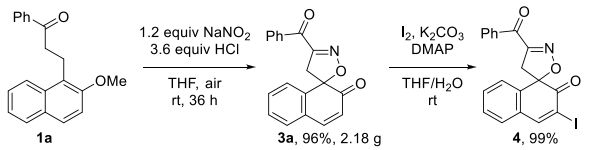


[a]Reactions were performed on a 0.2 mmol scale, and all yields represent isolated yields.

Ketones tethered to 1-methoxynaphthalenes via their 4-position were efficient substrates, to provide **3ad**−**3af** in yields of 89%−97%. Of particular note, this oximation/dearomatization cascade is also amenable to 4-(4-methoxyphenyl)butan-2-one **1ag**. After the oximation of **1ag**, the resulting **1ag-oxime** underwent catalytic dearomatization using 20 mol % of $NaNO_2$, and 1 equiv of HCl in dichloroethane (DCE) under 1 atm O_2, delivering the desired spiroisoxazoline **3ag** in 29% overall yield.

The synthetic utility of this protocol was further demonstrated (see Scheme 6). This one-pot cascade reaction

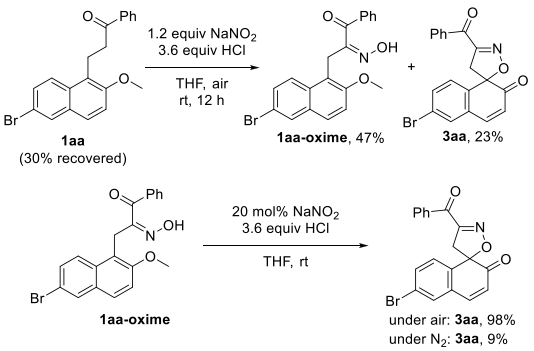
Scheme 6. Gram-Scale Reaction and Derivatization



is robust and scalable. On a gram scale, spiroisoxazoline **3a** was obtained in 96% yield from substrate **1a** in an open-flask operation. Selective iodination of **3a** delivered **4** in excellent yield, and the vinyl iodide could be potentially further elaborated.

To gain some insight into the reaction mechanism, several control experiments were performed, as shown in Scheme 7.

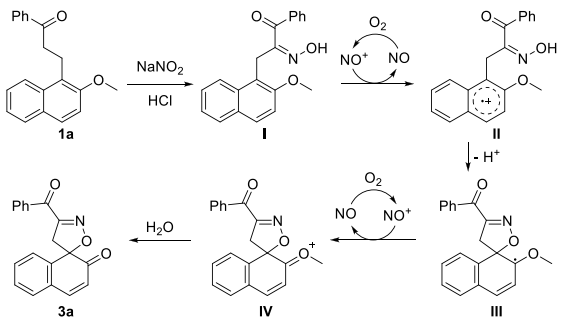
Scheme 7. Control Experiments



Intermediate **1aa-oxime** could be isolated in 47% yield, along with 23% of spiroisoxazoline **3aa** and 30% of starting material **1aa**, when the reaction was quenched after 12 h. With **1aa-oxime** as the substrate in the presence of a catalytic amount of $NaNO_2$ and 3.6 equiv of HCl under air, the reaction afforded the desired product **3aa** in excellent yield, which indicated that oxime **1aa-oxime** might be the reaction intermediate for the cascade approach. Furthermore, when the reaction of **1aa-oxime** was conducted under a nitrogen atmosphere, the desired product **3aa** was obtained in only 9%, which suggesting that the dearomatization is a catalytic, aerobic oxidative process.

Based on the above investigations and previous reports,[11,12] a plausible mechanism for the cascade was postulated as outlined in Scheme 8. Initially, oxime **I** is produced by

Scheme 8. Proposed Mechanism



nitrosation of the methylene adjacent to the carbonyl group in **1a** by NO^+, generated from $NaNO_2$ and HCl, and subsequent isomerization. The methoxynaphthalene in **I** is then oxidized by NO^+ via single-electron-transfer (SET), affording radical cation **II** and nitrogen monoxide (NO). Meanwhile, NO^+ is regenerated by the oxidation of NO by O_2 in the presence of HCl.[13] Further spirocyclization[14] and deprotonation lead to radical **III**, which is oxidized by NO^+ to furnish oxocarbenium cation **IV**. Finally, the desired product **3a** is formed upon hydrolysis with water. In this cascade, $NaNO_2$ acts as a

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bifunctional agent, a hydroxylamine source for the oximation and a precatalyst for the dearomative cylization.

In summary, we have developed a facile synthesis of spiroisoxazolines, wherein various aryl (thio)ethers or (thio)-phenols can be well-accommodated to construct the spirocyclic scaffolds through an oximation/dearomatization cascade. Notably, this cascade approach enables the direct synthesis of spiroisoxazolines from aryl (thio)ethers in one synthetic step; neither prior formation of oxime nor deprotection of aryl (thio)ethers is required. Our preliminary mechanistic experiments suggest that the oxime is involved as the reaction intermediate and the following dearomatization reaction is catalyzed by nitrosonium ion, using air as the terminal oxidant at room temperature. Sodium nitrite functions as both a hydroxylamine source and a precatalyst in this cascade. Further utilization of this protocol to the synthesis of spiroisoxazoline containing natural products and analogues can be anticipated.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01429.

Experimental procedures and characterization data (PDF)

Accession Codes

CCDC 1989746 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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