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Green Organocatalytic Synthesis of Isoxazolines via a One-Pot Oxidation of Allyloximes

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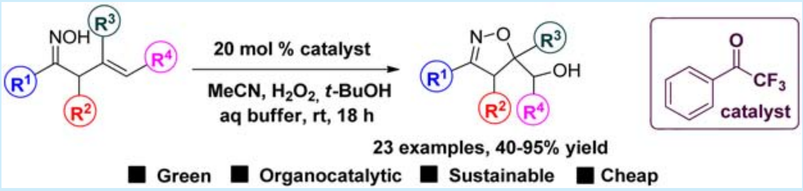
S Supporting Information



ABSTRACT: A green, sustainable, organocatalytic, and efficient synthesis of isoxazolines from allyloximes was developed. A 2,2,2-trifluoroacetophenone-catalyzed oxidation of allyloximes, utilizing H_2O_2 as the green oxidant, was taken advantage of in order to introduce a cheap and environmentally friendly protocol for the synthesis of substituted isoxazolines. A variety of substitution patterns, both aromatic and aliphatic moieties, are well tolerated, leading to isoxazolines in moderate to excellent yields.

Isoxazolines and the corresponding unsaturated analogues, isoxazoles, constitute very useful and versatile scaffolds in modern organic chemistry that can be found in a plethora of complex natural products and in numerous molecules of biological importance. Compounds bearing the isoxazoline moiety have been described to exhibit impressive anti-inflammatory,[1] antifungal,[2] antimicrobial,[3] and antibacterial[4] activity (Figure 1). For example, the top left isoxazoline compound in Figure 1 exhibits a medicinal profile very similar to that of the marketed drug Zyvox.[4] From a variety of simple molecules having the isoxazoline scaffold as the key structural backbone, ISO-1 was identified as a remarkable MIF antagonist exhibiting remarkable antidiabetic activity.[5] Along the same lines, another simple isoxazoline derivative has been recently identified as a very highly potent DNA methyltransferase 1 inhibitor (Figure 1).[6] In addition, the corresponding unsaturated analogue, the isoxazole moiety, constitutes an important pharmacophore in medicinal chemistry, since it is extensively found in many marketed drugs, such as valdecoxib and parecoxib, which are used as nonsteroidal anti-inflammatory drugs treating osteoarthritis, rheumatoid arthritis, and menstrual symptoms,[7] or cloxacillin and related compounds (oxacillin and flucloxacillin), which are widely used clinically against infections caused by penicillin-resistant *Staphylococcus aureus* (Figure 1).[8]

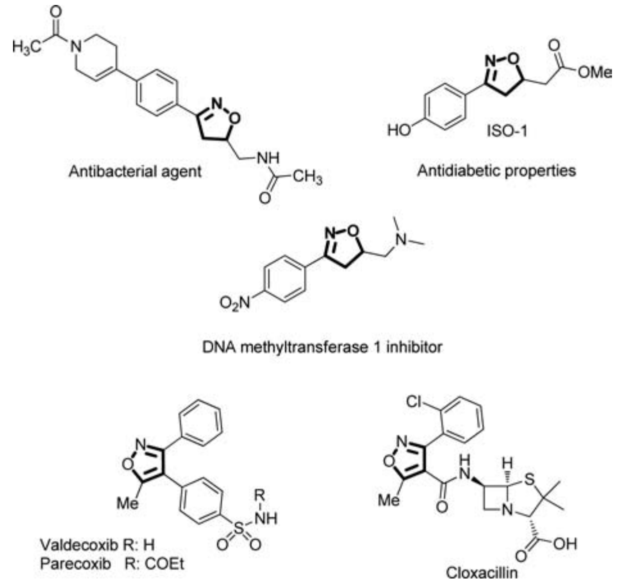


Figure 1. Representative bioactive molecules containing the isoxazoline or the isoxazole group.

Putting aside their pharmacophore nature, isoxazolines are also useful in organic synthesis as precursors for the production of β-hydroxy ketones[9] and 1,3-diols,[10] which are present in numerous natural products.

As a consequence of their synthetic utility, a plethora of synthetic approaches have been devised for the synthesis of isoxazolines (Scheme 1). The most common synthetic approach to isoxazolines constitutes cycloaddition reactions,[11] with the 1,3-dipolar cycloaddition of nitrile oxides with alkenes having the lion's share.[11a−e] Alternatively, one can envisage the cyclization of allyl oximes to lead to substituted isoxazolines (Scheme 1). In this context, oxidative cyclization of allyloximes has been achieved by employing a variety of metal catalysts

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Scheme 1. Synthetic Approaches for the Synthesis of Isoxazolines

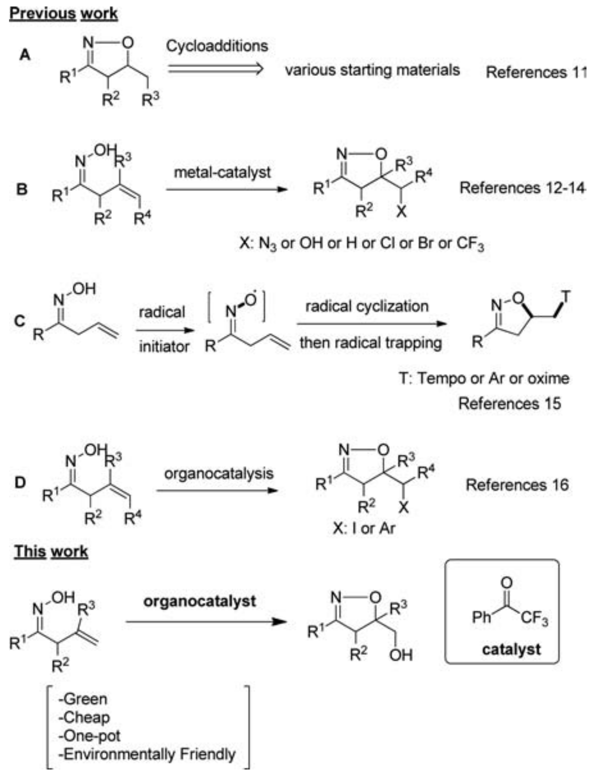
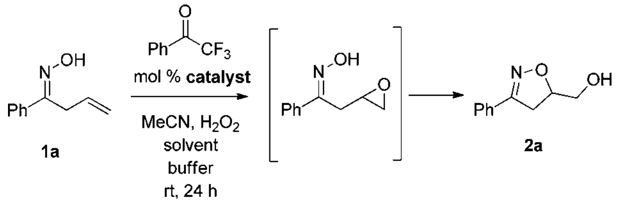


Table 1. Optimization of the Reaction Conditions for the Synthesis of Isoxazolines from Allyloximes[a]



entry	catalyst (mol %)	MeCN/H_2O_2 (equiv)	solvent	yield[b] (%)
1	10	12	*t*-BuOH	28
2	0	12	*t*-BuOH	5
3	20	16	*t*-BuOH	76
4	20	16	MeCN	74
5	20	16	EtOAc	75
6	20	16	MeOH	12
7	20	16	THF	38
8	20	16	$CHCl_3$	40
9[c]	**20**	**16**	***t*-BuOH**	**78**
10[d]	20	16	*t*-BuOH	73

[a] All reactions were carried out with **1a** (0.30 mmol), 2,2,2-trifluoro-1-phenylethanone, solvent (0.6 mL), aqueous buffer solution (0.6 mL, 0.6 M K_2CO_3–4 × 10^{-4} M EDTA disodium salt), acetonitrile, and 30% aqueous H_2O_2. The reaction mixture was allowed to stir for 18 h. [b] Isolated yield. [c] *t*-BuOH (0.3 mL), aq buffer (0.3 mL). [d] *t*-BuOH (1.2 mL), aq buffer (1.2 mL).

such as palladium,[5,12] copper,[13] or cobalt[14] (Scheme 1, B). Despite the widespread popularity of these reactions, the toxicity of metals and high levels of inorganic waste make their application harmful for the environment. A few metal-free methods for the synthesis of isoxazolines have been reported using either stoichiometric radical pathways (TEMPO-mediated, hypervalent iodine-, or TBN-mediated processes)[9b,15] or organocatalysts (thioureas or TBAI) (Scheme 1, path D).[16] However, as strange as it may seem, to our knowledge there is no report (stoichiometric or catalytic) in the literature for the in situ epoxidation of allyloximes followed by C–O cyclization to the desired isoxazoline via the intramolecular ring opening of the epoxide (Scheme 1, bottom).

We have been actively involved in the field of organocatalysis and very recently reported a cheap, green, and environmentally friendly protocol for various oxidations employing H_2O_2 as the green oxidant, whose only byproduct is water with 2,2,2-trifluoroacetophenone as the organocatalyst.[17] We envisaged we could extend this organocatalytic oxidative protocol via the introduction of an one-pot procedure for the isolation of isoxazolines. We postulated that once the intermediate epoxide is formed, an intramolecular ring opening reaction of the in situ prepared epoxide would afford the desired cyclized compound bearing a hydroxy moiety. Although the hydroxy group can be easily transformed to a variety of functional groups, there are only sparse reports for the synthesis of isoxazolines bearing this group.[11f,12a,14]

Our study began by employing the optimum reaction conditions for the epoxidation of terminal alkenes (Table 1, entry 1).[17c] Starting from allyloxime **1a**, the direct synthesis of isoxazolines is demonstrated. Initially, the epoxide is formed as the intermediate, and once the optimal pH is utilized (pH = 11), the hydroxy group of the oxime ring opens the epoxide, forming isoxazoline **2a**, albeit in low yield. However, no additional heating or additives are required for this one-pot transformation to occur. If the catalyst is omitted, traces of the product are observed (Table 1, entry 2). By increasing the catalyst loading to 20 mol % and the equivalents of the oxidant, the product could be isolated in high yield (Table 1, entry 3). Further optimization regarding the organic solvent did not lead to higher yield (Table 1, entries 4–8). Subtle changes in the reaction concentration led to the highest yield of the isoxazoline **2a** (Table 1, entries 9 and 10).

Having in hand the optimum reaction conditions, we focused on exploring the substrate scope of this new green and sustainable protocol (Scheme 2). Initially, a number of substituted aromatic allyloximes (**1a–i**) were utilized (Scheme 2). In all cases, the products were isolated in high to excellent yields. Various substitution patterns with different electron-rich and electron-poor substituents were well tolerated. In addition, starting from isoxazoline **2i** and following literature procedures,[6] the DNA methyltransferase 1 inhibitor of Figure 1 was synthesized following a two-step reaction sequence. Next, a series of bulky α-substituted aliphatic allyloximes were prepared and tested, affording the desired isoxazolines **2j–m** in moderate to high yields. When the aromatic moiety was replaced by an aliphatic chain, the yield remained at high levels (Scheme 2, compounds **2n–q**). It must be mentioned that additional functional groups as protected alcohols and aromatics can be well tolerated. In an effort to push the limits of the methodology and test more hindered classes of substrates, a number of alkenes were tested. Disubstituted alkene **1r** afforded the corresponding isoxazoline in excellent yield, affording a tetrasubstituted carbon in the final product. Finally, trisubstituted isoxazolines, like **2s**, can be prepared by this methodology in excellent yield; however, a mixture of diastereomers is observed. Furthermore, 1,2-disubstituted or

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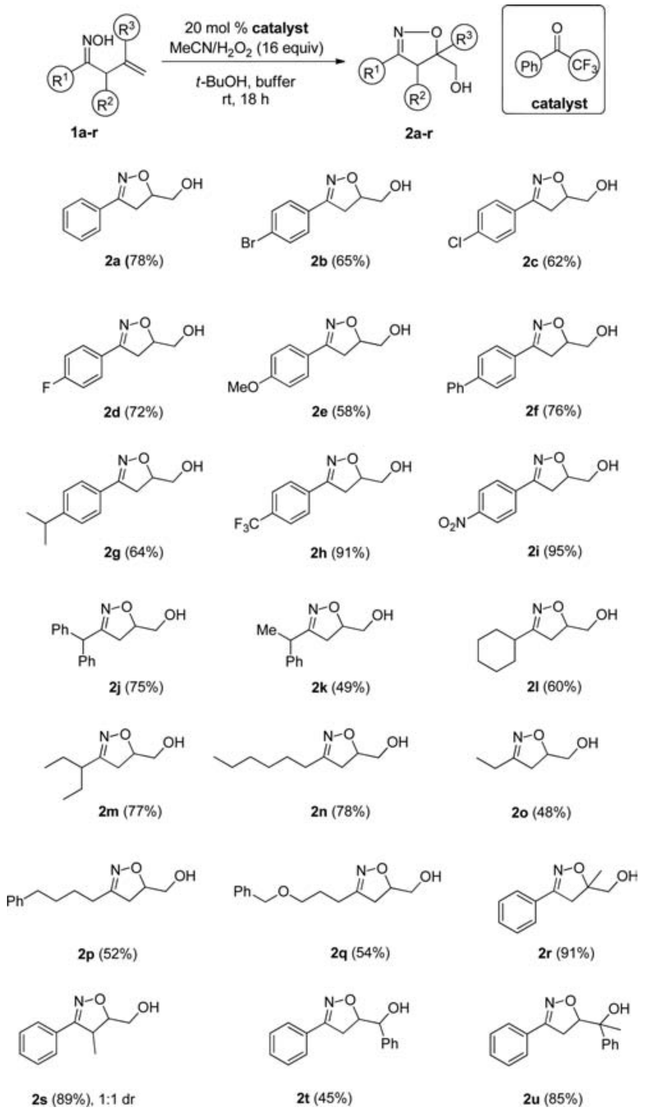
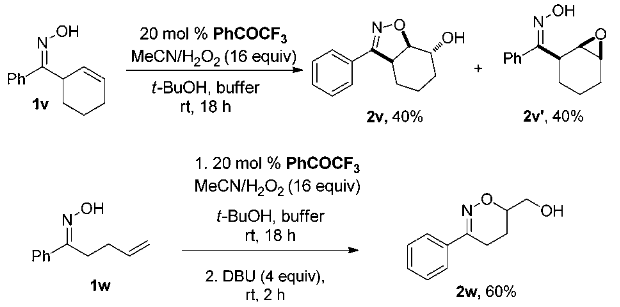
Scheme 2. Substrate Scope of the One-Pot Organocatalytic Oxidation of Allyloximes to Isoxazolines



trisubstituted substrates were tested, affording the desired products in good to excellent yields (**2t,u**).

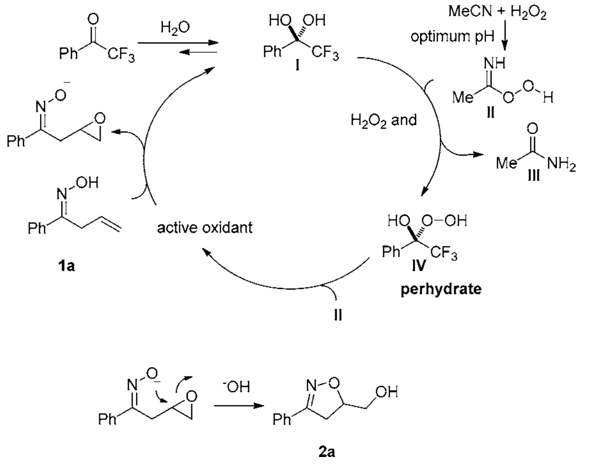
In an attempt to further expand the possibilities of this protocol, additional substrates were prepared and tested with interesting results (Scheme 3). Starting from allyloxime **1v**, and after the epoxidation reaction, a preferred cyclization took place to afford the cyclized isoxazoline **2v** in 40% yield, along with 40% of the *all-cis* epoxide. This can be easily explained by the propensity of the *trans*-diastereomer (where epoxide and oxime moieties are away) to cyclize, while the *cis*-diastereomer (where epoxide and oxime moieties are in the same side, all *cis*) is unable to perform such a transformation. In addition, in some cases where the alkene moiety is placed one carbon atom further away from the oxime, like in oxime **1w**, the literature reports a failure for the reaction to take place.[14] In our case, when oxime **1w** was subjected to the reaction conditions, the epoxidation occurred. In order to ensure cyclization, DBU was added in situ to afford the six-membered product **2w** (which is a dihydro-1,2-oxazine) in a satisfactory yield.

Scheme 3. Additional Substrate Scope of the One-Pot Organocatalytic Oxidation of Allyloximes to Isoxazolines



In order to summarize the events that take place in this protocol, a proposed reaction mechanism is shown in Scheme 4. Initially, the catalyst in the presence of the aqueous buffer affords diol **I**. Then, at the appropriate pH, MeCN reacts with H_2O_2 to afford **II**, which in conjunction with H_2O_2 oxidizes **I** to perhydrate **IV**.[17] Another molecule of **II** reacts with **IV** and affords the active oxidant of the protocol,[18] which epoxides allyloxime **1a**. Then the deprotonated epoxyoxime (aqueous buffer pH 11, pK_a of oximes ~11.3 in H_2O) ring opens the epoxide with simultaneous cyclization to isoxazoline **2a**.

Scheme 4. Proposed Reaction Mechanism



In conclusion, a green, sustainable, and organocatalytic protocol for the synthesis of isoxazolines from allyloximes was developed. This synthetic approach utilizes a cheap and commercially available metal-free organic molecule (2,2,2-trifluoroacetophenone) as the catalyst and H_2O_2 as the green oxidant and reports for the first time the one-pot epoxidation of allyloximes followed by an in situ ring opening/cyclization process leading to isoxazolines in good to excellent yields. The substrate scope of the reaction is very general, since a variety of aromatic and aliphatic substituted allyloximes bearing additional functional groups can be well tolerated. Further substitution of the allyl moiety can lead to polysubstituted isoxazolines, even bearing tetrasubstituted carbon atoms. In addition, a preferred cyclization approach was revealed for the synthesis of bicyclic isoxazolines. Finally, allyloximes can be replaced by homoallylic oximes leading to six-membered 1,2-oxazine derivatives. This unprecedented, for this kind of transformation process was made possible by simple addition of DBU followed by stirring at room temperature. This novel approach of combining our organocatalytic oxidation protocol in one-pot transformations leading to products of high molecular complexity is currently being pursued in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03380.

Experimental procedure, full optimization data, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(18) The structure of the active oxidant of the oxidation protocol is still unknown, while the possibility of a dioxirane intermediate cannot be ruled out.