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Oxime-Mediated Facile Access to 5-Methylisoxazoles and Applications in the Synthesis of Valdecoxib and Oxacillin

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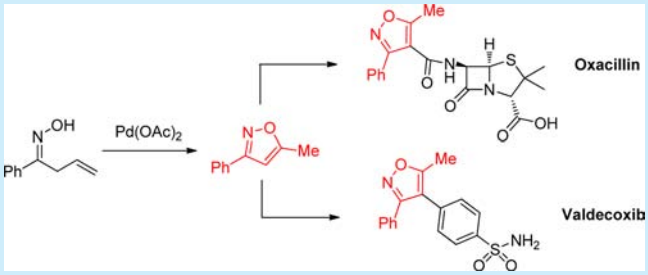
S *Supporting Information*

ABSTRACT: A palladium-catalyzed efficient synthesis of 5-methylisoxazoles via oxime-mediated functionalization of unactivated olefins is described. The reaction affords a variety of 5-methylisoxazoles in moderate to good yields. To further demonstrate the utility of the method, the rapid synthesis of valdecoxib and oxacillin is reported.



Isoxazole motifs are extensively found in natural products, such as muscimol and ibotenic acid.[1] They also constitute the basis for a number of molecules with biological activities. As a specifically outstanding subunit of isoxazole, 5-methylisoxazole exists in many marketed drugs. As depicted in Figure 1, valdecoxib and its prodrug parecoxib are nonsteroidal anti-inflammatory drugs for the treatment of osteoarthritis, rheumatoid arthritis, and menstrual symptoms;[2] oxacillin, cloxacillin, flucloxacillin, and dicloxacillin are a group of β-lactamase-resistant antibiotics which are widely used clinically to treat the infections caused by penicillin-resistant *Staphylococcus aureus*.[3] Consequently, the divergent synthesis of isoxazoles is of great importance and interest to organic and medicinal chemists.[4] For the sake of the studies in medicinal chemistry, we need to establish an efficient route to access a variety of functionalized 5-methylisoxazoles.

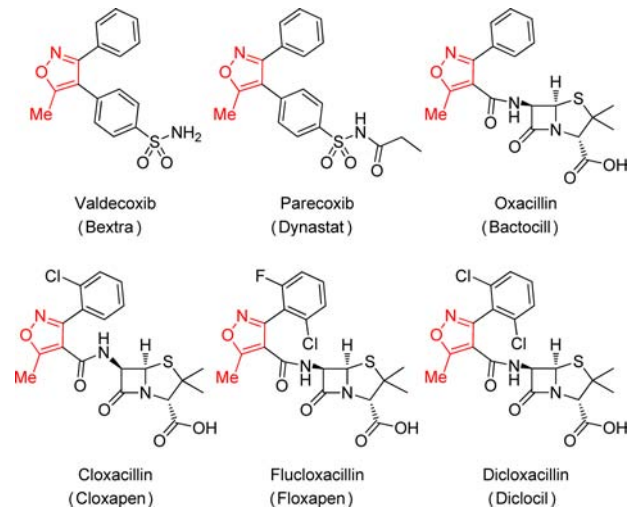


Figure 1. Marketed drugs based on 5-methylisoxazole.

We have a long-term interest in the directed functionalization of unactivated olefins, which provides a potent tool for the construction of heterocycles.[5] We recently reported the palladium-catalyzed synthesis of tetrahydrofurans via hydroxyl-directed oxyarylation of olefins.[5a] Alcohol therein served as both the heteroatom source and the directing group for gaining precise regioselectivity. We consider if a similar strategy of combining palladium catalysis and a directing group can be applied to the synthesis of isoxazoles.

Oxime is a versatile building block in organic synthesis.[6] Owing to its excellent coordinating ability and the unique feature of the C═N−O moiety, oxime is realized to be an apt directing group for our hypothesis. Recently, Chen and co-workers reported the palladium-catalyzed carboetherification of β,γ-unsaturated oximes to generate isoxazolines;[7] Loh and co-workers developed the palladium-catalyzed oxime-assisted intramolecular dioxygenation of alkenes.[8] Mechanistically, in both reports the carbopalladium intermediate generated by oxypalladation uniformly undergoes reductive elimination to give isoxazoline derivatives (Scheme 1, path A). However, an alternate pathway is possible: the intermediate undergoes β-

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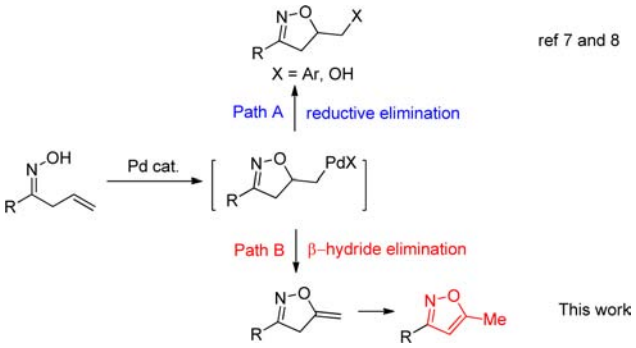
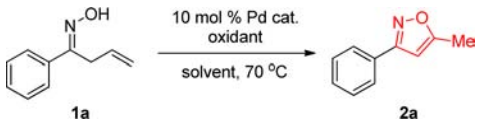
Scheme 1. Mechanistic Consideration



hydride elimination, leading to 5-methylisoxazoles after subsequent isomerization (Scheme 1, path B). Herein, we report a palladium-catalyzed oxime-directed efficient synthesis of 5-methylisoxazoles. The utility of the method is demonstrated in the synthesis of valdecoxib and oxacillin.

At the outset, the reaction parameters were surveyed (Table 1). Organic solvents were first assessed, showing that

Table 1. Reaction Parameters Survey[a]



entry	Pd cat.	oxidant	solvent	time (h)[b]	yield (%)[c]
1	$Pd(OAc)_2$	Ag_2CO_3	toluene	2.5	38
2	$Pd(OAc)_2$	Ag_2CO_3	DCE	8	82
3	$Pd(OAc)_2$	Ag_2CO_3	THF	18	30
4	$Pd(OAc)_2$	Ag_2CO_3	DMF	1.5	34
5	$Pd(OAc)_2$	Ag_2CO_3	DMSO	1	50
6	$Pd(OAc)_2$	Ag_2CO_3	PhF	4	47
7	$Pd(OAc)_2$	Ag_2CO_3	PhCl	3	82
8	$Pd(TFA)_2$	Ag_2CO_3	PhCl	5	33
9	$PdCl_2$	Ag_2CO_3	PhCl	4	61
10	$Pd(OAc)_2$	AgOAc	PhCl	4	79
11	$Pd(OAc)_2$	$CuCl_2$	PhCl	12	54
12	$Pd(OAc)_2$	BQ	PhCl	12	30
13	$Pd(OAc)_2$	air	PhCl	12	38
14[d]	$Pd(OAc)_2$	Ag_2CO_3	PhCl	8	37
15[e]	$Pd(OAc)_2$	Ag_2CO_3	PhCl	16	68

[a] **1a** (0.15 mmol), oxidant (Ag_2CO_3 0.22 mmol; AgOAc 0.45 mmol; $CuCl_2$ 0.45 mmol; BQ 0.22 mmol; air balloon) in 5 mL of solvent. [b] Based on entire conversion. [c] Isolated yield. [d] 5 mol % Pd catalyst. [e] 50 °C.

chlorobenzene was the best one in terms of chemical yield and reaction rate (entries 1–7). Palladium acetate displayed better catalytic ability than the trifluoroacetate and chloride salts (entries 8–9). Silver carbonate was more efficient for the redox cycle compared to other oxidants (entries 10–13). Reducing either the amount of the catalyst or the reaction temperature resulted in lower yields (entries 14–15).

With the optimized reaction conditions in hand, we applied it to a wide range of β,γ-unsaturated oximes. The process readily provided 5-methylisoxazoles regardless of the electronic properties of the substituents on arenes (Figure 2). Substrates with both electron-rich (**2b–f**) and -deficient (**2g–l**) substituents gave the corresponding products in moderate to

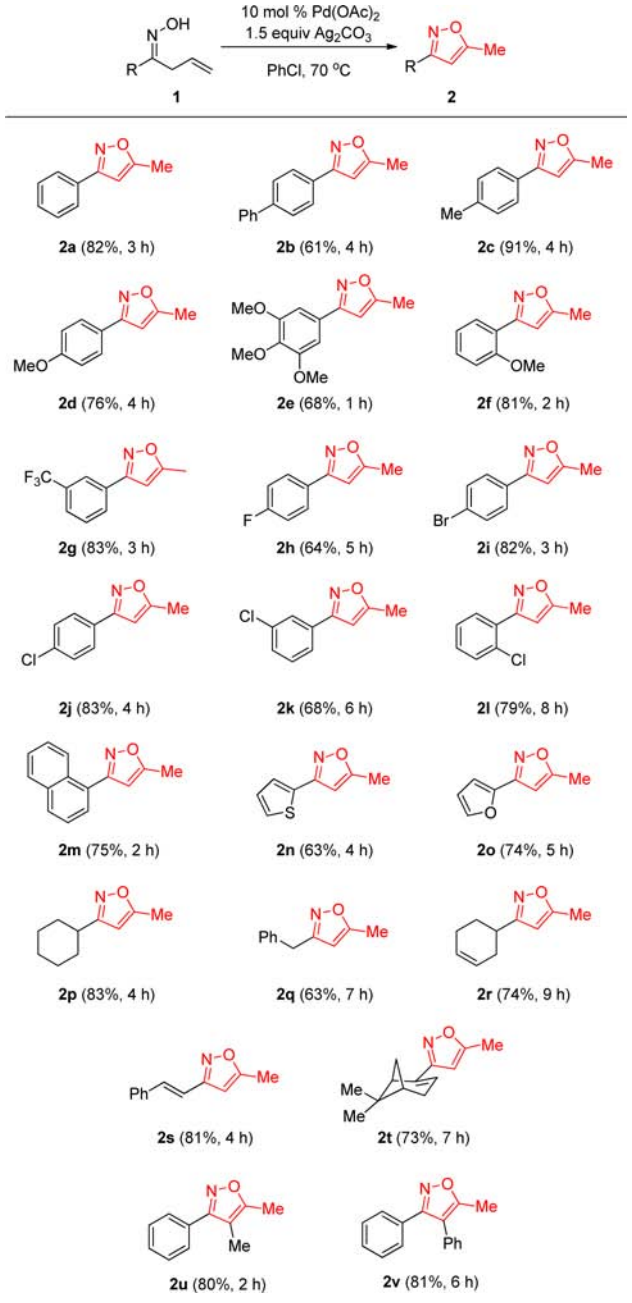


Figure 2. Scope of 5-methylisoxazoles.

good yields; the former generally resulted in completion in a shorter time. The steric hindrance seemed to have little impact on the reactions. The example of bromide (**2i**) was noteworthy, since the surviving bromo atom reserved the options for further cross-coupling. Polyaryl (**2m**) and heteroaryl (**2n–o**) oximes were compatible with the reaction conditions; the latter furnished diheteroarenes in useful yields. Not only aryl but also alkyl substrates were apt (**2p–2t**). In the examples of **2r** and **2s**, the other olefinic unit did not impede the Wacker-type oxypalladation of the allyl group. Substrate **2t** derived from the natural product Myrtenal also gave a satisfactory yield. The chemical yield was not compromised when alkyl/aryl substitution occurred on the allyl group, giving fully functionalized 5-methylisoxazoles **2u**/**2v**. However, using crotyl oxime instead of allyl oxime, which was supposed to give 5-ethylisoxazole, only furnished trace amounts of the expected

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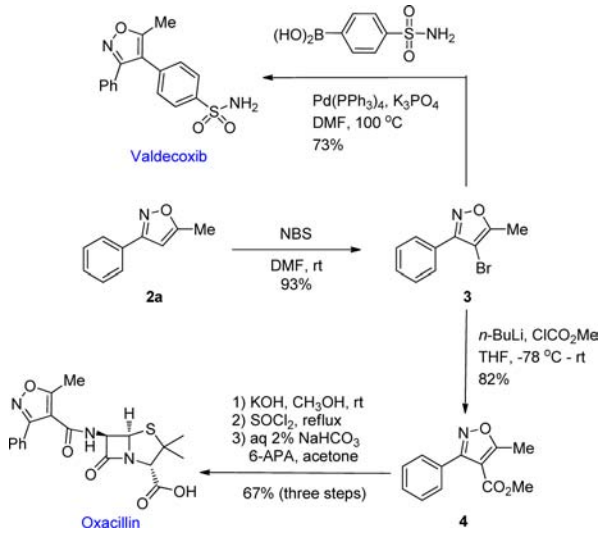
product.[9] It was reasoned that upon β-H elimination the external rather than internal olefin was generated that impeded the subsequent isomerization.

To demonstrate the utility of this method, we applied it in the synthesis of valdecoxib and oxacillin (Scheme 2). First,

Scheme 2. Synthesis of Valdecoxib and Oxacillin



bromination of isoxazole **2a** using NBS gave rise to **3**, which was the common precursor for both valdecoxib and oxacillin. Suzuki coupling of **3** with 4-sulfamoylbenzeneboronic acid readily furnished valdecoxib in 73% yield. On the other hand, methoxycarbonylation of **3** led to ester-substituted isoxazole **4** in good yield. After demethylation and the subsequent treatment with thionyl chloride, **4** was coupled with 6-aminopenicillanic acid (6-APA) to give oxacillin in an overall 67% yield for three steps. Significantly, both valdecoxib and oxacillin were synthesized in a few steps starting from 5-methylisoxazole. It can be anticipated that a series of valdecoxib and oxacillin analogues can be readily accessed after gaining various 5-methylisoxazoles from the current method.

In conclusion, we have developed a palladium-catalyzed synthesis of 5-methylisoxazoles via oxime-directed functionalization of unactivated olefins. The reaction affords a variety of 5-methylisoxazoles in moderate to good yields. The value of the method has been clearly demonstrated in the rapid synthesis of valdecoxib and oxacillin. The oxime-directed functionalization of olefins paved the way for a straightforward approach to the construction of vicinal N,O-containing heterocycles.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, characterizations, and copies of ^{1}H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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