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Ene reactions of pre-aromatic heterocycles – Oxazoles

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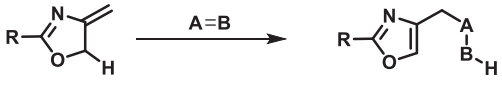
ABSTRACT

4-Methylidene substituted oxazolines are shown to be suitable substrates in thermal ene reactions with a variety of common enophiles. These pre-aromatic heterocycles provide access to a variety of adducts in modest to good yields. Interestingly, reaction with nitrosobenzene led to the formation of nitrones rather than the anticipated hydroxyl amine derivatives.

Oxazole derivatives have proven to be useful building blocks in pharmaceutical and agricultural settings [1] and many bioactive natural products contain 2,4-disubstituted analogues of these 5-membered heterocycles [1,2]. A large number of these heterocycles are found as biologically active secondary metabolites isolated from marine organisms [3]. Oxazoles, such as (-)-hennoxazole A (**1**, Fig. 1), display antiviral activity against herpes simplex virus type 1, as well as peripheral analgesic behavior [4]. Phorboxazoles A and B (**2a** and **2b**, Fig. 1) show antifungal activity against *Candida albicans* and *Saccharomyces carlsbergensis*. Phorboxazoles have also demonstrated exceptional inhibition of cell growth [5,6]. Often only very small quantities of these natural products can be isolated from the producing organism which makes the evaluation of the broader biological potential and structural elucidation of these metabolites fairly challenging [3,7]. Therefore, it is important to develop a viable synthetic route for the synthesis of these promising bioactive compounds and closely related analogs to evaluate their biological potential.



3 4

Traditional methods for the formation of substituted oxazole derivatives include oxidation of oxazolines, [8] functionalization of the parent oxazole ring [9], or a *de novo* construction of the oxazole ring [10]. An alternative approach is one in which a "pre-aromatic" heterocycle is constructed which is then subjected to an aromatizing bond forming process, for example using an ene reaction **3** → **4** (Scheme 1) [11–13]. Indeed, such a process might be broadly applicable in heterocycle synthesis as it provides a means to functionalize a core in a divergent manner [14]. The ene reaction has a rich history in organic synthesis but it has been less well explored in the context of heterocycle synthesis. In part, this can be attributed to a paucity of methods for the construction of appropriate precursors. Specifically, methylidine substituted heterocycles appear to offer an attractive approach for the construction of diverse heterocycles via an ene manifold because after the reaction an aromatic system would be formed.

Recently, the cyclization of acetylenic amides to construct the corresponding oxazole derivatives, e.g., **5** (Scheme 2) have attracted the attention of the synthetic community [15]. Interestingly, based on the reaction conditions these transformations can be stopped at the oxazoline stage [15] or taken through aromatization which consequently opens up the opportunity for the synthesis of 4/5 functionalized oxazoles [16]. Feng and coworkers utilized this opportunity and developed a Ni-catalyzed enantioselective hetero ene reaction for the synthesis of 2,5-disubstituted oxazole derivatives (**5** + **6** → **7**, Scheme 2a) [16]. Hashmi and coworkers have also reported a dual gold/copper-catalyzed asymmetric ene reactions with ethyl glyoxalate using propargylic amides-derived oxazolines (**5** + **8** → **9**, Scheme 2b) [17]. However, a recent literature report describing the construction of the isomeric dihydrooxazoles **13** from imidates **12** (Scheme 3) caught our attention as such substrates would afford isomeric 2,4-disubstituted oxazoles and thus provide complimentary access to these heterocycles [18].

Dihydrooxazoles were constructed following the method reported by Fennie and coworkers (Scheme 3). Specifically, imi-

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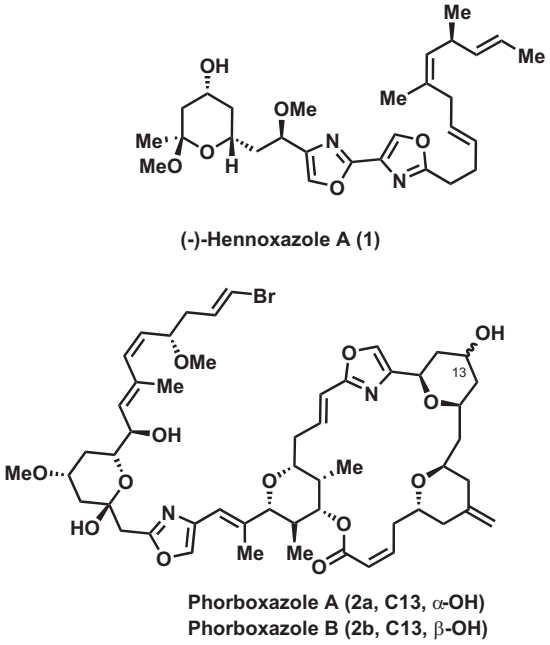
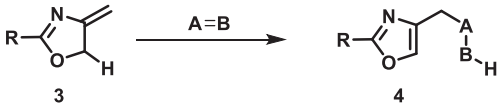
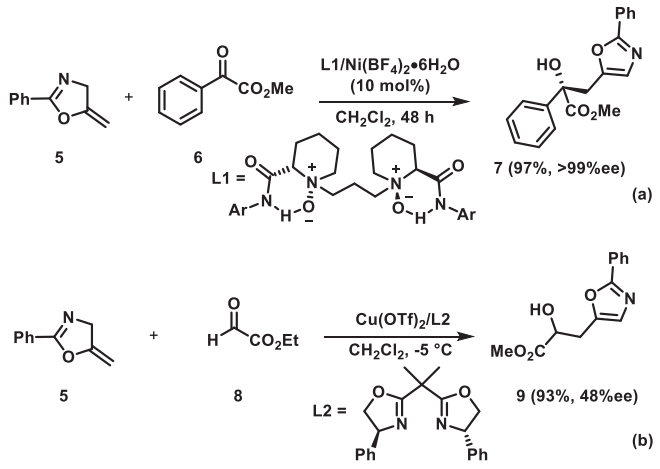


Fig. 1. Examples of bioactive 2, 4 disubstituted oxazoles.



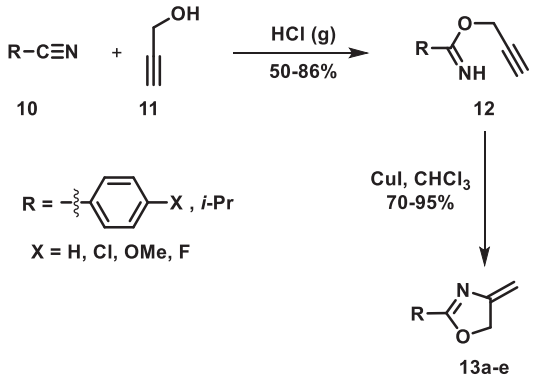
Scheme 1. General scheme for ene reaction on dihydrooxazoles.



Scheme 2. Previous ene reactions of 5-methylidene oxazolines.

dates were synthesized by reacting the appropriate nitrile and propargyl alcohol in presence of hydrochloric acid. These imidates were then treated with catalytic amount of CuI in chloroform to provide the desired dihydrooxazoles in good to moderate yields [18]. In their report, the Fennie group reported some chemistry of these oxazole derivatives including acid catalyzed aromatization, electrophilic bromination and a [3 + 2] cycloaddition reaction.

In preliminary experiments 2-phenyloxazoline **13a** was evaluated as the ene substrate and *N*-phenylmaleimide as enophile. The two substrates were dissolved in toluene and the progress of the reaction was monitored at various temperatures. No reaction was detected at rt and upon heating a complex reaction profile

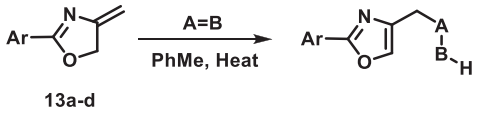


Scheme 3. General scheme for the synthesis of dihydrooxazoles.

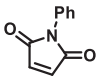
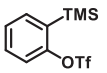
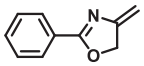
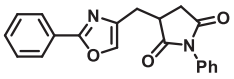
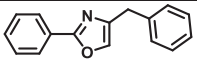
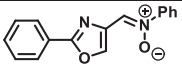
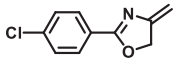
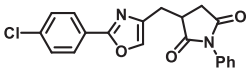
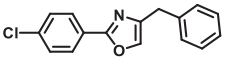
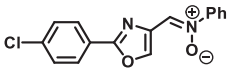
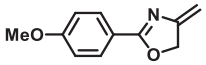
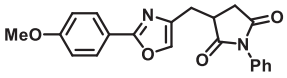
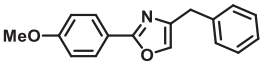
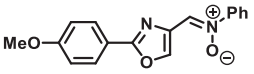
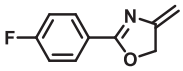
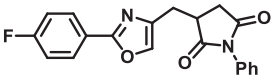
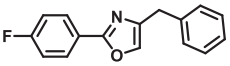
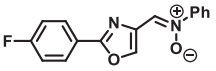
was observed by TLC analysis. We speculate that this occurred due to aromatization and/or oxidation of dihydrooxazoles prior to ene reaction [18,19]. This latter proposition can be supported in the results reported by Hashmi and coworkers on 5-methylene-dihydrooxazoles [20]. This group has shown that upon exposure to air, 5-methylene-dihydrooxazoles can be converted efficiently to the corresponding hydroperoxides. In fact, in this initial ene reaction, although no attempts were made to isolate the by-product, the ^{1}H NMR spectrum of the crude reaction mixture showed a proton signal at 9.1 ppm suggesting the likely formation of an aldehyde. To minimize the potential oxidative rearomatization, the reaction was performed under an inert atmosphere after degassing the solution with argon for 5 mins. As a result, the reaction profile was much cleaner, purification was easier, and the desired product **14a** was isolated with improved yield (Table 1). Other solvents were screened including DCM (52 °C, 26%), benzene (91 °C, 35%) and acetonitrile (91 °C, 50%). Reaction with the benzyne precursor (o-trimethylsilylphenyl triflate) in presence of 2.4 equiv of CsF with **13a** provided the corresponding adduct **15a** in modest yield (Table 1). Interestingly, attempts to engage nitrosobenzene in the addition reaction resulted in isolation of the nitrone **16a** rather than the expected hydroxylamine derivative. Presumably, the expected hydroxylamine is formed, but this then undergoes oxidation to the nitrone. Oxidation of hydroxylamines to the corresponding nitrones is well known [21,22] as is autoxidation in air [23]. It is also conceivable that nitrosobenzene serves as the oxidant (hydrogen acceptor) but we were unable to isolate any of the expected hydroxyl amine byproduct from a fairly complex reaction mixture to validate this hypothesis.

Although, Shi and coworkers showed little to no effect of EWGs/EDGs at the *C*2 position on the reaction yields for the oxidation of the double bond on the isomeric 5-methylene-dihydrooxazoles e.g. **5**, [19] it was suspected that the conjugated nature of the aryl moiety and the C=N bond in these isomeric substrates **13** may impact their propensity to rearomatize prior to ene reaction. Accordingly, we investigated the ene reactions of substituted aryl derivatives **13b-d** but actually found that their reactions largely mirrored those of the unsubstituted congener **13a** (see Table 1) with the exception of the *p*-methoxy substituted congener **13c**. The reaction of **13c** afforded consistently lower yields of the ene adduct with *N*-phenylmaleimide when conducted in toluene. In addition to aromatized starting material (*ca.* 25%), two additional products (impure) were isolated but were not identified. When this substrate was reacted with NPM in acetonitrile at 90 °C for 24 h afforded the adduct **14b** in an improved 38% yield. In the case of the *p*-chlorophenyl derivative **13b** an X-ray crystal structure of the adduct **14b** from *N*-phenylmaleimide was obtained which clearly confirmed both the connectivity and the orientation of the heteroatoms (Fig. 2).

Table 1
Ene products from 4-methylidene oxazolines and various enophiles.[a]



13a-d

Substrate	Product (%) 	Product (%)[c] 	Product (%) 
 **13a**	 **14a** (42, 50[b])	 **15a** (60)	 **16a** (29)
 **13b**	 **14b** (59)	 **15b** (39)	 **16b** (26)
 **13c**	 **14c** (21, 38[b])	 **15c** (40)d	 **16c** (35)
 **13d**	 **14d** (48)	 **15d** (37)	 **16d** (37)

[a] Unless otherwise noted, all reactions were carried out with **13a-d** (0.5 mmol), 2.4 equiv. of enophiles in toluene (1.5 mL) at 100 °C for 24 h and performed in duplicate. b. The reaction was conducted in acetonitrile at 90 °C for 24 h. c. 2.5 equiv of CsF. d. 2.0 equiv of TBAF.

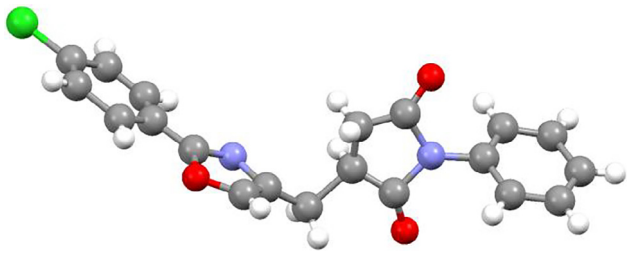
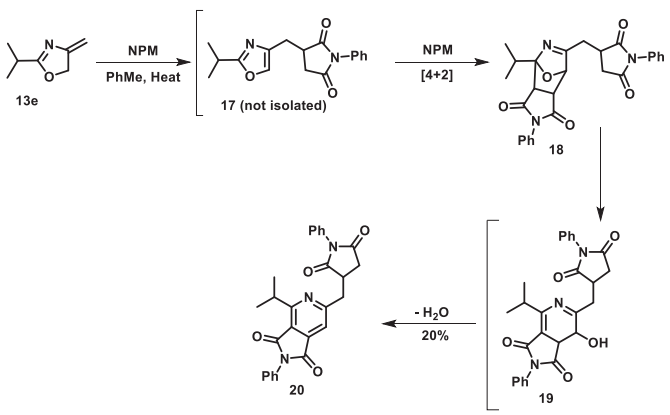
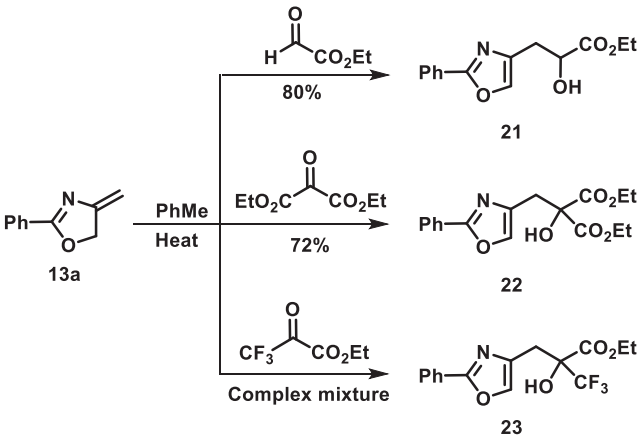


Fig. 2. An X-ray structure of ene adduct **14b** (CCDC 2053848).

One non-aryl substituted oxazoline **13e** was investigated in an ene reaction with *N*-phenylmaleimide (Scheme 4). The 2-isopropyl derivative delivered a new adduct **20** in modest yield that was clearly not an oxazole as the diagnostic aryl (of the oxazole ring) signal was absent in the ^{1}H NMR spectrum of this product. Based on analysis of the proton and carbon count of this product, it was clear that there was an additional unit of *N*-phenylmaleimide present. Oxazoles are well-known to behave as an electron deficient diene and react with the suitable (di)enophiles to form a cycloadduct *cf*. **18** (Scheme 4) [24]. Which upon ring-opening and dehydration produce substituted pyridines [25]. Upon closer analysis



Scheme 4. Tandem ene/Diels Alder reaction of oxazole 13e.



Scheme 5. Carbonyl ene reactions of oxazoline **13a**.

of the NMR data and mass spectrometric data, it was clear that the product formed **20** was the dehydration product of the initial cycloadduct **18** produced via Diels-Alder reaction. Although, efforts were not made to isolate this by-product with other ene substrates examined in Table 1, its formation cannot be ruled out which may account for the overall modest yields.

The carbonyl ene reaction was also evaluated using one substrate **13a** with three different enophiles and the corresponding alcohols were obtained in excellent yields in two cases (Scheme 5). Ethyl glyoxalate delivered the expected alcohol in excellent yield. Similarly, diethyl ketomalonate afforded the tertiary alcohol in good yield but the trifluoromethyl ketoester resulted in a complex reaction mixture. While there was some evidence that the addition had taken place, it was a minor product.

In summary, we have evaluated 4-methylidene oxazoline in ene reactions for the construction of 2,4-disubstitued oxazoles. Overall modest yields of adducts were obtained with a range of enophiles but this relative inefficiency is offset by the brevity of the three-step sequence from commercially available materials. Our lab is continuing to develop the ene reaction of other pre-aromatic heterocycles and these efforts will be reported in due course.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

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