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COMMUNICATIONS

Published on Web 02/28/2007

# Intermolecular Ene Reactions Utilizing Oxazolones and Enol Ethers

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Ene reactions represent an atom efficient and powerful reaction for the formation of carbon−carbon bonds.[1] One example of such a reaction is the Conia-ene reaction, which is a popular alternative to enolate alkylations.[2] Traditionally, the Conia-ene reaction is thought of as an intramolecular ene reaction of unsaturated ketones and aldehydes, in which the carbonyl serves as the ene component via its enol tautomer (Scheme 1).[2] The reaction is generally conducted at very high temperatures to overcome the large activation energy barrier of the reaction.[3] Metal-catalyzed versions of the reaction allow for lower temperatures, although enolate generation,[4] strong acid,[5] or photochemical activation[6] are usually required. Recent reports have demonstrated that using catalysts such as gold[7] and nickel[8] can effectively promote Conia-ene cyclizations under much milder conditions. More recently the first enantioselective Conia-ene cyclization reaction was reported using a Pd(II)/Yb(III) dual catalyst system.[9]

An intermolecular version of this type of ene reaction would greatly enhance the utility of ene reactions as an enolate alkylation alternative. We report herein a new intermolecular ene reaction using oxazolones (also referred to as azlactones) under very mild conditions without the use of any catalyst. We hypothesized that oxazolones would be ideal substrates for the development of an intermolecular ene reaction of this nature on the basis of the ease of formation of the aromatic enol tautomer (Scheme 1).[10] In addition, the use of oxazolones provides a highly efficient and rapid route to the preparation of biologically important quaternary amino acids.[11] The overall transformation closely resembles that of the Conia-ene reaction, although this intermolecular reaction utilizes enol ethers as the enophile rather than alkenes and alkynes normally associated with Conia-ene reactions.

Our initial studies focused on the use of ester substituted oxazolones because of their predominant enol character.[10] To our delight, reaction of the methyl ester substituted oxazolone with *tert*-butyl vinyl ether in $CH_2Cl_2$ provided the ene-product in near quantitative yields within 20 min (Table 1, entry 1). No degradation of the enol ether was observed providing plausible evidence of a concerted reaction. The choice of solvent did not affect the reaction rate or yield significantly as seen by the fact that $CH_2Cl_2$, THF, and toluene all provided similar results at room temperature. Following the alkylation, the reaction mixture was treated with methanol to provide the more stable quaternary substituted amino ester derivative.

The methyl ester substituted oxazolone was subsequently evaluated for its reactivity with a range of substituted enol ethers. Unsubstituted enol ethers provided the alkylated oxazolones within minutes in near quantitative yields (Table 1, entries 1 and 2). Interestingly, the alkylated oxazolone product obtained using the 1-alkyl substituted enol ether 2-methoxy propene appeared to be fairly unstable and reverted back to the starting materials over time (Table 1, entry 3). Both 2,3-dihydrofuran and 3,4-dihydro-(2*H*)-pyran also provided the desired products in good yields, albeit with longer reaction times (Table 1, entries 4 and 5, 2 and 22 h, respectively). A decrease in yield was noted for the higher substituted enol ethers (Table 1, entries 6 and 7), which were refluxed in $CH_2Cl_2$ for 24 h. The nature of the protection group of the enol ether appeared to be critical to the success of the reaction. Replacement of the alkyl or benzyl moiety with an electron withdrawing group, such as an acetate, completely abrogated the

***Scheme 1.*** Intramolecular Conia-ene Reaction versus Intermolecular Ene Reaction utilizing Oxazolones

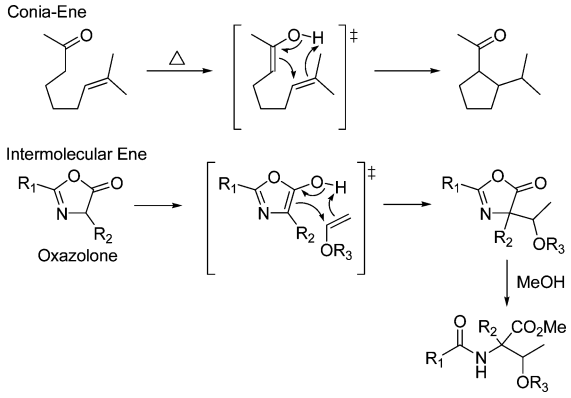
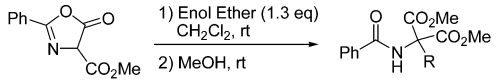



***Table 1.*** Ene Reaction with Various Enol Ethers




| entry | Enol Ether | R | % yield |
|---|---|---|---|
| 1 |  |  | 99 |
| 2 |  |  | 98 |
| 3 |  |  | >95[a] |
| 4 |  |  | 99 |
| 5 |  |  | 99 |
| 6 |  |  | 68[b] |
| 7 |  |  | 81[b] |
| 8 |  |  | 0[c] |

[a] Yield based on the crude oxazolone intermediate. [b] Reaction refluxed for 24 h and 3.0 equiv of the enol ether used. [c] Reaction resulted in recovery of starting materials.



**10.1021/ja0627904 CCC: $37.00** 

***Scheme 2.*** Proposed Reaction Pathways

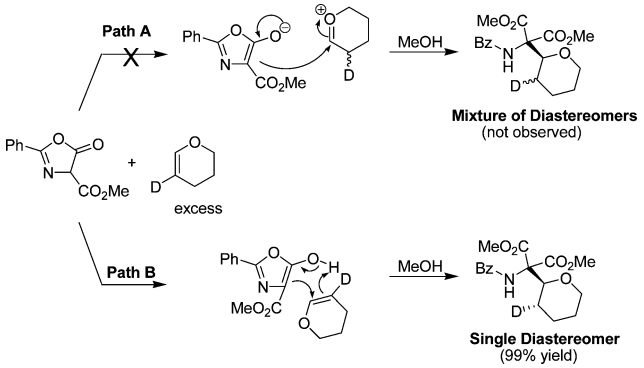
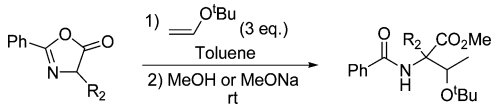



***Table 2.*** Substituted Oxazolones




| entry | $R_2$ | temp (°C) | time | % yield |
|---|---|---|---|---|
| 9 | $CO_2Me$ | room temp | 20 min | 99 |
| 10 | $COCH_3$ | room temp | 24 h | 98[a] |
| 11 | Ph | 110 | 8 h | 95 |
| 12 | 1-naphthyl | 110 | 26 h | 99[a] |
| 13 | Me | 110 | 24 h | 0[b] |

[a] Yield based on the crude oxazolone intermediate. [b] Reaction resulted in recovery of starting materials.

reaction resulting in isolation of only starting materials after several hours (Table 1, entry 8). This may be in part due to the need to stabilize positive charge accumulation on the carbon adjacent to the oxygen atom.

Insight into the mechanistic nature of the reaction was obtained when the ester substituted oxazolone was reacted with 5-deutero-3,4-dihydro-2*H*-pyran (Scheme 2). Protonation of the enol ether by the acidic oxazolone[12] followed by condensation on to the resulting oxonium ion (path A) would result in a mixture of diastereomers, whereas a more concerted reaction (path B) would be stereospecific and result in the formation of one single diastereomer. Treatment of the oxazolone with a large excess of deuterium labeled enol ether provided the product in near quantitative yields as a single diastereomer after methanol workup as determined by NOE. The stereospecific nature of this reaction argues against the possibility that mere protonation of the enol ether induces an aldol-type reaction and supports a more concerted mechanism.

In order to further expand the scope of this reaction, the nature of the substituent at the $R_2$ position of the oxazolone was explored (Table 2). Various oxazolones were reacted with *tert*-butyl vinyl ether and evaluated for ene-product formation. The data supports the hypothesis that increased enol character of the oxazolone is helpful for the induction of this ene-reaction. Substituents that stabilize the aromatic enol tautomer of the oxazolone appear to promote the reaction much more readily than those that do not. For example, acylated oxazolones (Table 2, entries 9 and 10) reacted readily to provide the ene-products in excellent yields at room temperature. Aryl substituted oxazolones also provided ene-products in excellent yields (Table 2, entries 11 and 12), albeit at higher temperatures (reflux in toluene). On the other hand, oxazolones containing alkyl substituents did not produce any desired product and resulted in the isolation of starting materials under the current reaction conditions (Table 2, entry 13).

In summary, we report a new intermolecular ene reaction using oxazolones and enol ethers. These reactions occur under very mild reaction conditions and in most cases result in near quantitative yields. The overall transformation of the reaction complements the intramolecular Conia-ene cyclization and makes ene reactions a useful alternative to enolate alkylation chemistry. Further studies are currently under investigation to determine the reaction scope and synthetic utility.

**Acknowledgment.** The authors gratefully acknowledge the financial support provided by the American Cancer Society (Grant RSG CDD-106972) and Michigan State University.

**Supporting Information Available:** Full experimental protocols; IR, $^1$H NMR, $^{13}$C NMR, and HRMS data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA0627904