Catalyst-Free Regioselective (3+2)-Cycloadditions of \( \alpha, \beta \)-unsaturated \( N \)-arylnitrones with Alkenes to Access Functionalized Isoxazolidines: A DFT Study

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Abstract: The catalyst-free regioselective [3+2]-cycloaddition of \( \alpha, \beta \)-unsaturated \( N \)-arylnitrones with alkenes are developed. The series of synthetically important functionalized isoxazolidines are prepared in good to excellent yields by step economic pathway under ligand and transition metal-free condition. The regioselective cycloaddition pathway supported by control experiment and computational study.

Introduction

The \( N \)-substituted \( \alpha, \beta \)-unsaturated nitrones are powerful synthons because the double bond in nitrones can be introduced into the target molecules through various transformations. Nevertheless, control cycloaddition reactions of \( \alpha, \beta \)-unsaturated systems is a challenge as multiple reaction sites are available. Particularly, for cycloaddition reactions of \( \alpha, \beta \)-unsaturated nitrones, the challenge is not only to control which olefin reacts in the cycloaddition, but also to control the regioselectivity. Moreover, 1,3-dipolar cycloaddition reactions of nitrones with olefins is a very useful methodology for the formation of isoxazolidines. These heterocycles are present in different bioactive compounds and have been applied as precursors for the asymmetric synthesis of natural products and pharmaceutically important molecules (Fig. 1). In addition, a number of molecules containing isoxazolidine ring have attracted much attention as nucleoside analogues. Nevertheless, isoxazolidines are also vital and versatile intermediates due to the ease of reductive N-O bond cleavage, which can be converted into a \( \alpha \)-amino acids, \( \beta \)-chiral and 1,3-amino alcohol, very often applied in organic chemistry.

![Fig. 1 Natural products containing isoxazolidines unit.](image)

Therefore, it is not surprising that great effort has been devoted to the development of novel, efficient and practical methods for the construction of isoxazolidines including cycloadditions, annulation, cascade reaction, and others (Scheme 1a). For instance, Jorgensen and co-workers reported the first cascade 1,3-dipolar cycloaddition on the remote olefin with good to excellent regio- and stereo-selectivity by iminium-ion activation process with a secondary amine catalyst. (Scheme 1b). Typically, these strategies require the utilization of either transition-metal catalysts or organocatalyst which still suffer from high cost and complicated purifying procedures. During the preparation of this manuscript, Yang et al. reported, catalyst-free cycloaddition of oxa(aza)bicyclic alkenes with nitrones as the 1,3-dipolar cycloaddition under mild conditions, which can afford the new products of fused bicyclic tetrahydroisoxazoles (Scheme 1c). The reactions occur diastereoselectively, with a notable exo- and anti-preference and thus, observed diastereoselectivity trends as predicted by DFT calculations. Despite the success of these important and valuable strategies for isoxazoline synthesis, more efficient, convenient, regioselective and preactivation-free cycloaddition strategy integrating the use \( \alpha, \beta \)-unsaturated \( N \)-aryl nitrone under metal-free condition are still highly appealing. Therefore, while pursuing our interest in the reactivity of nitrones as precursors for the synthesis of functionalized molecules, we are interested to test the reactivity of \( \alpha, \beta \)-unsaturated \( N \)-aryl nitrones with alkenes. In this context, the construction of isoxazolidines including cycloadditions is discussed.

Scheme 1: Strategies for synthesis of functionalized isoxazolidines

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hersewith, we report step and atom-economic pathway for regioslective [3+2]-cycloadditions of α, β-unsaturated N-aryl nitrones with alkenes to form a highly functionalized isoxazolidine under catalyst and ligand-free condition (Scheme 1d). Importantly, the theoretical studies is demonstrated in this work.

Results and Discussion

We commenced our studies by examining the reaction parameters in reaction of (Z)-N-((E)-3-phenylallylidene) aniline oxide 1a (0.5 mmol) and ethyl vinyl ether 2a (5.0 equiv) in THF (3.0 mL) solvent at 25 °C (Table 1). The newly formed products were isolated by column chromatography and analyzed by \(^1\)H and \(^13\)C NMR spectroscopy which indicates regioslective formation of isoxazolidines 3a (31%) via [3+2]-cycloaddition reaction while, formation of 4 (47%) may occur presumably due to nitrolysis of product by trace amount of water present in THF\(^{22}\) (entry 1). Further, significant improvement in the reaction efficiency is noticed while using dry THF with 4 Å molecular sieves and product 3a was furnished in 48% yield (entry 2). In addition, the reaction efficiency was further stimulated by heating the reaction mixture to 60 °C and product 3a was obtained in 78% yield (entry 3). Gratifyingly, further improvement in the yield is observed using excess (10.0 equiv.) Ethyl vinyl ether (entry 4). The significant loss in yield is observed with less equiv. of ethyl vinyl ether (See supporting information for details).

With an optimized condition in hand, the scope of reaction is investigated using differently substituted C-alkyl nitrones (1c – 1j) with ethyl vinyl ether 2a (Scheme 2). Initially, C-alkyl substituted nitrones (1c–1i) prepared from electronically diverse cinamaldehyde reacts smoothly with ethyl vinyl ether furnishing desired [3+2]-cycloadducts 3c–3i in 63–86% yield. Interestingly, C-alkyl substituted nitrode prepared form 2-naphthyl substituted cinamaldehyde provides desired product 3j in moderate yield.

In continuation, the scope of reaction is subsequently tested with N-aryl substituted nitrones (1k-1r, Scheme 3). Initially, electron donating substituents such as 4-methyl, 3-methyl group on N-aryl ring of nitrode are treated with ethyl vinyl ether which works smoothly and provides desired cycloadducts 3k and 3l in 71 and 73% yield, respectively. While, electron withdrawing substituents such as 3-chloro, 4-chloro, 4-fluoro, 4-bromo and 4-iodo furnishes cycloadducts 3m-3q in 72–83% yield.

In Table 1, Optimization of reaction condition is shown.

<table>
<thead>
<tr>
<th>S. N</th>
<th>OR (X equiv)</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OEt (5)</td>
<td>THF</td>
<td>25/18</td>
<td>3a (31%)/4 (47)</td>
</tr>
<tr>
<td>2</td>
<td>OEt (5)</td>
<td>THF</td>
<td>25/24</td>
<td>3a (48)/4 (15)</td>
</tr>
<tr>
<td>3</td>
<td>OEt (5)</td>
<td>THF</td>
<td>60/12</td>
<td>3a (78)/4 (5)</td>
</tr>
<tr>
<td>4</td>
<td>OEt (10), THF</td>
<td>60/6</td>
<td>3a (87)/4 (trace)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Ph (10), THF</td>
<td>60/8</td>
<td>3b (65)/4 (15)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>OEt (10), Toluene</td>
<td>60/12</td>
<td>3a (71)/4 (trace)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>OEt (10), CH-CN</td>
<td>60/18</td>
<td>3a (58)/4 (10)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>OEt (10), 1,4-dioxane</td>
<td>60/12</td>
<td>3a (63)/4 (trace)</td>
<td></td>
</tr>
</tbody>
</table>

\(^{1}\)Reaction condition: 1a (0.5 mmol), 2a (3-10 equiv), 4 Å MS, solvent (3.0 mL) at 25–60 °C in 8-24 h. \(^{2}\)Yields are reported after purification from silica gel column chromatography (average of two run).

This indicates that, ethyl vinyl ether may undergo polymerization at higher temperature. Interestingly, subjecting styrene as an alkene precursor instead of ethyl vinyl ether works smoothly furnishing desired cycloadduct 3b in 65 % yield (entry 5). Further, change in solvent to toluene, acetonitrile and 1,4-dioxane furnishes the moderate yield (entries 6-8), while other solvents such as dichloromethane, ethanol, chloroform furnishes poor yield (See the supporting information for more details).

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Further, N-(4-phenyl)nitrone also tolerates by furnishing desired product 3r in 65% yield. Interestingly, structure of compound 3n is unambiguously confirmed by X-ray crystallographic analysis indicating the trans geometry of tethered alkene substituent.

Density functional theory (DFT) calculations were performed to shed light on the mechanism of catalyst-free [3+2] cycloaddition reaction. We performed calculations at the M06-2X/6-311+G(d,p) level of theory in THF as solvent with Gaussian 09 set of programs (for computational details see supporting information). In order to rationalize the regioselectivity of the reaction, firstly we optimize the diene and dienophile and the electronic effects taken under consideration. The frontier molecular orbitals (FMO) and their energies are shown in Figure 2. The energy difference between HOMO of the nitrones (-6.94 eV) and LUMO of dienophile (-0.48 eV) are smaller, as compared to the HOMO of dienophile (-7.78 eV) and LUMO of nitrones (-1.65 eV). Based on FMO it is evident that this reaction is HOMO controlled nitrones.

In order to determine the selectivity of the reaction, on the basis of control experiments, we believe that this reaction occurs through one-step [3+2] cycloaddition mechanism. In this context, we considered all the commutative pathways, the most likely pathway is illustrated in Figure 3(a). In such a process, 1n and alkene gives adduct complex which is 8.5 kcal/mol higher in energy. Subsequently, [3+2]-cycloaddition of 1n and C=C of an alkene to form 3n, traversing the transition state 1n-TS with an overall barrier of 29.90 kcal/mol. The barrier calculated for this step is consistent with the reaction condition. Interestingly the formation of the product is exergonic from the starting material by 16.57 kcal/mol. Figure 3(b) highlights the structural differences in the five transition states, in which for [3+2]-cycloadduction are 1n-TS, 1n-TS_1, 1n-TS_2, 1n-TS_3 and for the [5+2]-cycloaddition is 1n-TS_4 reported. Importantly, the crystal structure of compound 3n is demonstrated.

Our protocol can be scaled up in gram scale without affecting the chemical yield (eq. 1). Given the unique features of the metal free [3+2]-cycloaddition reaction, we became intrigued in unravelling its mode of action. To this end, we performed competition experiments using nitrones (1a and 1a') with ethyl vinyl ether 2a under standard condition. The reaction is stopped in 2h and crude reaction mass is analyzed by 1H NMR indicating that, the rate of formation of 3a:3a' is in comparable ratio (eq. 2). See SI for crude 1H NMR and computational study. This proves that, reaction is highly regioselective irrespective of type of nitrene used for cycloaddition (eq. 2). Further, we have also performed one-pot synthesis of isoxazolidines directly from cinamaldehyde and nitrobenzene (eq. 3). The in-situ formed nitrene intermediate is obtained simply by filtration and utilized without further purification for the reaction with ethyl vinyl ether forming a desired product in 49% yield (eq. 3). See SI for more details.

In conclusion, the transition metal-free and step economic synthesis of isoxazolidines is successfully developed using α, β-unsaturated nitrone and ethyl vinyl ether. The various electronically biased C-alkyl and N-aryl substituted nitrones are tolerated for the synthesis of polyfunctionalized isoxazolidines in good to excellent yields. The DFT calculation and the control experiments supports the regioselective [3+2]-cycloaddition pathway and products formation is confirmed by X-ray analysis. The feasibility of reaction condition is studied by performing one-pot reaction and gram scale synthesis.
The further complication of newly synthesized isoxazolidines leading to the biologically active and pharmacologically relevant drug like molecules is currently ongoing in our laboratory.

Experimental Details.

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Keywords: regioselective • isoxazolidines • DFT study • nitrone cycloaddition • metal and ligand free

References:


Table of Content

Text for Table of Contents: The metal-free synthesis of isoxazolidines is successfully developed using α, β-unsaturated nitrore and ethyl vinyl ether. The wide substrate scope was studied and feasibility of reaction was studied by performing one-pot reaction and gram scale synthesis. The DFT calculation and the control experiments supports the regioselective [3+2]-cycloaddition pathway and products formation is confirmed by X-ray analysis.