The Reaction of Nitrones with Cyclopropanes: A Convenient Preparation of Tetrahydro-1,2-oxazines

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Abstract: Nitrones and dialkyl cyclopropane-1,1-dicarboxylates undergo smooth reaction in the presence of ytterbium(III) triflate to form tetrahydro-1,2-oxazines with a high degree of regio- and stereocontrol. A three-component protocol has also been developed wherein the nitrone is generated in situ from an aldehyde and a hydroxylamine. The reactions are often high yielding with broad substrate scope. The multicomponent nature of the reaction makes it amenable to the synthesis of compound libraries and also allows for highly convergent strategies to be developed in target-oriented synthesis.

Key words: cycloadditions, nitrones, tetrahydro-1,2-oxazines, cyclopropanes, hydroxylamines

The reactions of nitrones with cyclopropane-1,1-dicarboxylates by 1,3-dipolar cycloadditions are an important class of transformations for the construction of heterocyclic ring systems.1 The use of cyclopropanes as alternative dipolarophiles in classic cycloaddition chemistry provides access to one-carbon homologues of the analogous reactions with electron-deficient alkenes.2 One such example is the reaction of nitrones with cyclopropanes, which provides expedient access to tetrahydro-1,2-oxazines in a highly diastereoselective manner (where the substituents R1 and R3 bear a predominantly cis relationship to one another, Scheme 1).3 There are few methods for the direct construction of these heterocycles currently available.4 The value of nitro–cyclopropane cycloadditions in the synthesis of tetrahydro-1,2-oxazine containing natural products has recently been demonstrated through the total synthesis of (+)-nakadomarin A, a member of the manzamine family of marine alkaloids, serves as an excellent example of the use of tetrahydro-1,2-oxazines en route to complex pyrrolidine natural product scaffolds (Figure 1).5

Initial experiments aimed at the development of this reaction combined a variety of nitrones 2 (1.2 equiv) and cyclopropanes 1 (1.0 equiv) under ytterbium(III) triflate9 catalysis to produce tetrahydro-1,2-oxazines 3 in high yield with excellent regio- and stereochemical control (procedure 1, Scheme 2, Figure 2). Other Lewis acids screened (BF3·OEt2, Cu(OTf)2, TiCl4, AlCl3) offered no through intramolecular SN2 displacement of the activated alcohol.7 The total synthesis of (+)-nakadomarin A, a member of the manzamine family of marine alkaloids, serves as an excellent example of the use of tetrahydro-1,2-oxazines en route to complex pyrrolidine natural product scaffolds (Figure 1).5

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Figure 1 Natural products accessed using the reaction of nitrones with cyclopropane-1,1-dicarboxylates
improvement over ytterbium(III) triflate and often led to decomposition of either the cyclopropane or nitrone. While scandium(III) triflate can offer a slight rate enhancement compared to ytterbium(III) triflate in some cases,\textsuperscript{10} scandium(III) triflate is incompatible with more delicate substrates and is far more costly. Magnesium iodide was insufficiently soluble. 1,2-Dichloroethane served for oxazines prepared co-elute with the starting cyclopanes, these reactions were generally allowed to stir overnight to ensure complete conversion. Work up consisted of absorption of the reaction mixture onto silica gel (the three-component reactions were initially filtered) in preparation for flash column chromatography. Most reactions produced tetrahydrofuran. In order to eliminate the need to prepare and purify the starting nitrones, a three-component protocol was developed wherein the nitrones were generated in situ.\textsuperscript{6,13} (procedure 2, Scheme 1). A diverse library of tetrahydro-1,2-oxazines 3 (Figure 4) can be accessed in short order from a variety of hydroxylamines 4, aldehydes 5, and cyclopropanes 1 (Figure 3). It is necessary to pre-mix the aldehyde and hydroxylamine to ensure complete nitrone formation, in order to avoid undesired side reactions resulting from direct opening of the cyclopropane by the hydroxylamine. A typical procedure involves stirring the hydroxylamine (1.3 equiv), aldehyde (1.4 equiv), and 10 mol\% ytterbium(III) triflate in toluene (the solvent of choice for the three-component coupling method) over activated 4 Å molecular sieves (excess) for 30 minutes. The cyclopropane (1.0 equiv) is then added and the mixture is stirred at ambient temperature until it is deemed complete by thin-layer chromatography. Since many of the oxazines prepared co-elute with the starting cyclopropanes, these reactions were generally allowed to stir overnight to ensure complete conversion. Work up consisted of absorption of the reaction mixture onto silica gel (the three-component reactions were initially filtered) in preparation for flash column chromatography. Most reactions produced tetrahydro-1,2-oxazines as single diastereomers, however, small amounts of the 3,6-trans isomers (<10%) were observed for oxazines 3r, 3u, 3v, 3x, and 3y.

<table>
<thead>
<tr>
<th>Substrates</th>
<th>Cyclopropanes</th>
<th>Hydroxylamines</th>
<th>Aldehydes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a R¹ = H, R² = Et</td>
<td>1a</td>
<td>4a</td>
<td>5a</td>
</tr>
<tr>
<td>1b R¹ = Ph, R² = Me</td>
<td>1b</td>
<td>4b</td>
<td>5b</td>
</tr>
<tr>
<td>1c R¹ = styryl, R² = Me</td>
<td>1c</td>
<td>4c</td>
<td>5c</td>
</tr>
<tr>
<td>1d R¹ = vinyl, R² = Et</td>
<td>1d</td>
<td>4d</td>
<td>5d</td>
</tr>
</tbody>
</table>

Figure 2 Substrate scope (procedure 1)

Figure 3 Substrates for three-component coupling reactions
The substrate scope is broad with respect to all three components of the coupling reaction. Aryl-, vinyl-, heteroaromatic-, and alkyl-substituted, as well as unsubstituted cyclopropanes are well tolerated. Of these, cyclopropanes bearing substituents that are able to stabilize a developing positive charge (e.g., phenyl, styryl, etc.) appear to be the most reactive. Unsubstituted cyclopropanes required a higher catalyst loading [20 mol% Yb(OTf)_3] to achieve acceptable yields. All attempts to use cyclopropanes that do not contain geminal dicarbonyl substituents met with little success. Presumably, chelation of the lanthanide catalyst is required to activate the cyclopropane towards reaction with the nitrone. 1-Acetyl cyclopropanecarboxylates and 1-acetyl cyclopropanecarboxamides will react with nitrones to form tetrahydro-1,2-oxazines, however the yield, reaction rate, and degree of stereocontrol is greatly attenuated in comparison to cyclopropane-1,1-dicarboxylates.

Electron-rich and electron-poor benzaldehydes, heteroaromatic aldehydes, alkenals, and aliphatic aldehydes are all suitable substrates, with the latter two classes being the least reactive. The use of a linear aliphatic aldehyde (derived from pentane-1,5-diol) in this three-component coupling procedure was demonstrated in the total synthesis of (+)-phyllantidine, however, high temperatures and a higher catalyst loading were required [20 mol% Yb(OTf)_3, refluxing toluene]. Aromatic and aliphatic hydroxylamines were both acceptable substrates, however, higher yields and shorter reaction times are usually observed for the aromatic hydroxylamines.

When enantiomerically pure cyclopropanes are used in the cycloaddition, the reaction occurs with inversion of configuration (e.g., Scheme 3). In many cases, the reaction occurs without loss of enantiomeric excess. We have observed, however, that cyclopropanes bearing cation-stabilizing substituents, are susceptible to racemization under Lewis acid conditions. As such, care should be tak-
en to run these reactions at as low a temperature as possible.

In summary, a wide variety of tetrahydro-1,2-oxazines can be synthesized using the recently developed reaction of nitrones and cyclopropanes. Nitrones may either be isolated prior to reaction, or generated in situ from hydroxylamines and aldehydes. The broad substrate scope of the reaction allows for the preparation of diverse compound libraries and is attractive for applications in target-orientated synthesis.

Typical procedures for the reaction of nitrones with cyclopropanes follow. Detailed procedures for the preparation of all compounds in this article have been published; references for their preparation are noted. All reactions were performed under an argon atmosphere and toluene and CH2Cl2 were dried and deoxygenated by passing the N2 purged solvents through activated alumina columns prior to use, although it should be noted that reagent grade solvents can be used without an appreciable decrease in yield. Nitrones,14 hydroxylamines,15 and cyclopropanes16 were prepared according to literature procedures, or slight modifications thereof.

**Dimethyl (3R*,6R*,E)-3-Phenyl-6-styryl-2-(4-toly)-tetrahydro-2H-1,2-oxazine-4,4-dicarboxylate (3c); Typical Procedure 1**

Nitrone 2a (194 mg, 0.92 mmol) and cyclopropane 1c (200 mg, 0.768 mmol) were dissolved in CH2Cl2 (5 mL) and Yb(OTf)3·x H2O (24 mg, 0.0385 mmol, 5 mol%) was added. After stirring at r.t. for 5 h, the mixture was directly pre-absorbed on silica gel and purified (3c) (347 mg, 96%) as a colorless solid, colorless needles after recrystallization (slow diffusion of a CH2Cl2 soln into hexanes); mp 141–142 °C; Rf = 0.36 (20% EtOAc–hexanes).

**IR (thin film):** 3057, 3026, 2951, 2928, 1741, 1612, 1508, 1438, 1304, 1285, 1280, 1279, 1173, 1158, 77.1, 56.8, 39.0, 35.3, 35.6, 30.3.

**HRMS:** m/z [M]+ calcd for C22H23NO5: 381.1576; found: 381.1576.

**References**


