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Jill B. Williamson  
*College of William and Mary*

Emily R. Smith  
*College of William and Mary*

Jonathan R. Scheerer  
*College of William and Mary, [jrscheerer@wm.edu](mailto:jrscheerer@wm.edu)*

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## A Merged Aldol Condensation, Alkene Isomerization, Cycloaddition/Cycloreversion Sequence Employing Oxazinone Intermediates for the Synthesis of Substituted Pyridines

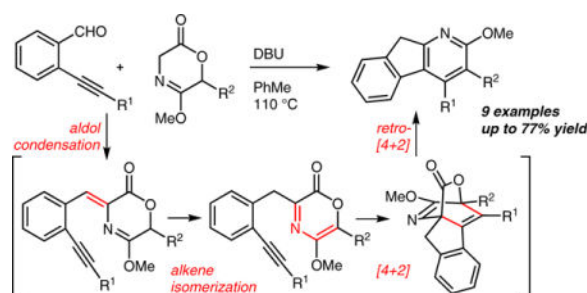
Jill B. Williamson<sup>1</sup>, Emily R. Smith, and Jonathan R. Scheerer

Department of Chemistry, The College of William & Mary, P.O. Box 8795, Williamsburg, VA 23187, USA

### Abstract

A domino reaction sequence has been evaluated that begins with union of novel dihydrooxazinone precursors with 2-alkynyl-substituted benzaldehyde components through aldol condensation. Ensuing operations, including alkene isomerization, Diels–Alder, and retrograde Diels–Alder with loss of CO<sub>2</sub> occurs in the same reaction vessel to provide polysubstituted tricyclic pyridine products.

### Graphical abstract



### Keywords

cycloaddition; cycloreversion; pyridine synthesis; domino reactions; Diels; Alder; oxazinone

The value of domino reactions, which consist of two or more chemical events that occur in a single flask, has been most clearly elucidated by Tietze,<sup>2</sup> and is also apparent to the practicing chemist: fewer time-consuming purification processes and mitigation of solvent waste is advantageous as compared to stepwise synthesis and is more aligned with the principles of the ideal synthesis.<sup>3</sup>

Correspondence to: Jonathan R. Scheerer.

<sup>1</sup>Present address: J. B. Williamson Department of Chemistry, The University of North Carolina, Chapel Hill, NC 27599, USA.

### Supporting Information

Supporting information for this article is available online at <http://dx.doi.org/10.1055/s-0036-1588729>.

Previous efforts from our lab have employed a domino reaction process involving an aldol condensation of diketopiperazine precursors, alkene isomerization to an intermediate pyrazinone, and cycloaddition to construct the [2.2.2]diazabicyclic functionality (Scheme 1, eq. 1).<sup>4</sup> If the cycloaddition event intercepts an alkyne dienophile, the resulting diazabicycloalkene adduct (e.g., **2**) can undergo further reaction: cycloreversion and extrusion of one bridging lactam function (as an isocyanate or cyanogen derivative) to afford 2-pyridone or pyridine structures.<sup>5</sup> We determined that intermediate [2.2.2]diazabicyclic structures resembling **2** could be reliably converted into the derived pyridone **4** through a three-step process that involved activation of one lactam bridge as the derived acetylated intermediate **3** prior to thermal extrusion (microwave, 300 W, 1 h, max. temp ca. 200 °C). While the three-step process for conversion of [2.2.2]diazabicycloalkene adducts such as **2** into pyridone products resembling **4** was general, we desired a more expedient overall sequence. We anticipated that an analogous domino reaction process initiated with a dihydrooxazinone precursor **5** might also undergo aldol condensation and isomerization and intercept oxazinone **7** (Scheme 1, eq. 2). Following cycloaddition of **7**, the resulting intermediate cycloadduct **8**, which bears a lactone-bridging function, would extrude CO<sub>2</sub> possibly at the temperatures necessary for the preceding cycloaddition and thereby deliver the tricyclic pyridine product **9**. In this way, we anticipated that the cycloaddition and cycloreversion steps could be merged into a single operation. Although not widely explored, oxazinone cycloaddition/cycloreversion reactions are known from the work Hoornaert,<sup>6</sup> however, our desire to incorporate these pericyclic processes into more elaborate domino reaction pathways was not established. We reasoned that successful execution of the desired plan would advance new chemistry and provide complementary methods for the rapid assembly of polycyclic substituted pyridines, a widespread and privileged scaffold that is shared among many molecules that find application in medicine, agriculture, and material science.<sup>7</sup> Given the many valuable properties of pyridines, continued efforts directed toward the construction of pyridines are warranted and remain an active research area.<sup>8</sup> Metal-free domino reaction processes, such as the one described in this letter, offer the potential for direct synthesis of substituted pyridines with minimal environmental impact.<sup>9</sup>

In order to begin our study of the domino reaction sequence, we first needed to prepare the requisite dihydrooxazinone precursors (e.g., **5**), which were apparently unknown. We determined that the glycine-glycolate derived dihydrooxazinone precursor **5a** could be prepared in three steps starting from chloroacetic acid (Scheme 2).<sup>10</sup> The lactim ether functionality in **5a** was established by Staudinger reduction of the derived azide and cyclization of the intermediate aza-Wittig intermediate on the pendant methyl ester at 90 °C. The desired product **5a** was separated from the stoichiometric phosphine oxide byproduct most conveniently by distillation using a Kugelrohr apparatus.

Although dihydrooxazinone **5a** was somewhat prone to degradation (by putative polymerization to insoluble products with unresolved spectroscopic characteristics), material purified by Kugelrohr distillation was stable in the freezer on the duration of weeks. The C-5 methyl- and phenyl substituted dihydrooxazinones **5b** and **5c** were prepared using a modified sequence starting from lactate and mandelate precursors (Scheme 2). The synthesis of C-5 phenyl-dihydrooxazinone **5c** required more elevated temperatures (110 °C) and

longer duration (24 h) in order to promote complete cyclization of the aza-Wittig intermediate on the methyl ester and deliver the lactim *O*-methyl ether functionality. The more robust stability of **5b** and **5c** was a favorable attribute that enabled purification on silica gel and improved the efficiency of the reaction sequence (31 and 48% yield over three steps).

With three dihydrooxazinone precursors (**5a–c**) in hand, we selected the most simple 2-alkynyl benzaldehyde derivative **10** with which to initiate our studies of the domino reaction sequence (Scheme 3). When **10** and **5a** were heated in toluene at 110 °C with DBU (1.5 equiv) we observed a small amount of the desired tricyclic 2-methoxypyridine product **13a** (ca. 10–20%). Slow addition of the aldehyde via syringe pump improved the yield of product **13a** to 77%.<sup>11</sup> No intermediate products resulting from aldol addition, condensation, isomerization, or cycloaddition were evident, and the unpurified reaction mixture appeared to contain only **13a** and unreacted aldehyde component (in some cases). It was remarkable to us that DBU is sufficiently basic to promote enolization and aldol condensation of dihydrooxazinone substrates, which contrasts with our previous work using diketopiperazine starting materials (e.g., **1**), which required a stronger base (NaOMe or LiHMDS) to promote enolization and aldol addition (see Scheme 1, eq. 1).<sup>3,4</sup>

Two additional benzaldehyde derivatives **11** and **12** (extending either *n*-butyl or phenyl residues from the alkyne terminus) were prepared in order to explore this domino sequence in more detail. Using the unsubstituted dihydrooxazinone precursor **5a** with either **11** or **12**, the resulting 2-methoxypyridine products **13b** and **13c** were obtained, however, the isolated yield for these products was low (10% and 13%). Attempts to improve the reaction yield efficiency by varying temperature, stoichiometry, or base were met without success.

Reactions performed with the methyl-substituted dihydrooxazinone precursor **5b** gave more consistent results with each of the three benzaldehyde reaction components (**10–12**), and the desired products **14a**, **14b**, and **14c** were obtained in 58, 54, and 61% yield. Use of 5-phenyl dihydrooxazinone **5c** was also successful in the reaction sequence with the alkynyl benzaldehyde derivatives **10–12** and afforded the respective tricyclic products **15a**, **15b**, and **15c** in 32%, 22%, and 50% yield. Overall, reactions with the 5-alkyl dihydrooxazinones **5b** or **5c** did not benefit from slow addition of aldehyde; as such these reactions did not require the syringe pump and were thus more convenient to execute. In all reactions performed, the unpurified reaction products were uncomplicated and contained desired products and unreacted starting materials and only trace impurities. Accordingly, we attribute the modest yields in several cases to poor mass recovery, a feature consistent with the observed propensity of the dihydrooxazinone precursors to degrade and polymerize.

The reaction sequence described in this letter demonstrates the proof of principle of a domino reaction sequence that features several base-promoted and pericyclic bond-forming and bond-cleaving processes. The sequence is initiated by condensation of novel dihydrooxazinone starting materials with aromatic aldehyde precursors. The ensuing alkene isomerization to the intermediate oxazinone precedes merged cycloaddition and cycloreversion sequence (evolving CO<sub>2</sub>) to give 2-methoxypyridine products. The overall

multicomponent domino reaction process is promoted with mild organic base (DBU) and occurs at conveniently accessible temperatures (110 °C).

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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- See Supporting Information for procedures that accompany Scheme 2 and the spectra and corresponding characterization data for all new compounds (including **5a–c**, **13b,c**, **14a–c**, **15a–c**).
- Representative Procedure for the Domino Reaction Leading to Tricyclic Pyridine Product 13a** Dihydrooxazinone **5a** (50 mg, 0.38 mmol) was dissolved in toluene (3.0 mL, 0.12 M) and DBU (85  $\mu$ L, 0.57 mmol, 1.5 equiv) was added. The reaction vessel was heated in an oil bath to a gentle reflux (110 °C) and 2-alkynyl benzaldehyde **10** (74 mg, 1.5 equiv) in toluene (1.0 mL) was introduced slowly to the reaction over 2 h (using a syringe pump). After stirring for 18 h at 110 °C, the reaction was cooled to r.t., transferred to a separatory funnel, and partitioned between sat. aq NH<sub>4</sub>Cl (10 mL) and EtOAc (10 mL). The organic layer was removed, and the aqueous portion was extracted with EtOAc (3  $\times$  10 mL). The combined organic layers were washed with brine (10 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered through Celite, and concentrated in vacuo. The resulting residue (82 mg) was purified by flash column chromatography on silica gel (gradient elution: 20%  $\rightarrow$  80% of

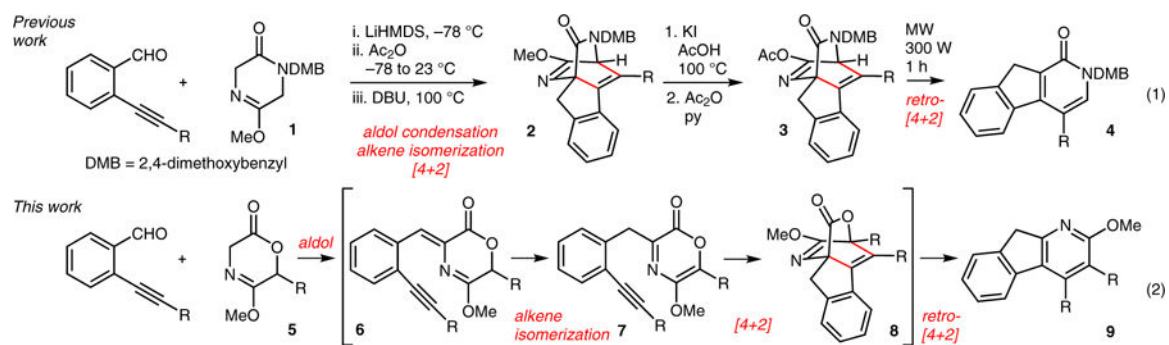
CHCl<sub>3</sub> in hexane) to afford compound **13a** (57 mg, 77% yield) as a light yellow oil;  $R_f$  = 0.20 (50% CHCl<sub>3</sub>-Hex). IR (film): 1586, 1463, 1307, 1029, 772 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.88 (d,  $J$  = 8.6 Hz, 1 H), 7.62 (d,  $J$  = 7.8 Hz, 1 H), 7.52 (d,  $J$  = 7.4 Hz, 1 H), 7.34 (t,  $J$  = 7.4 Hz, 1 H), 7.26 (t,  $J$  = 7.4 Hz, 1 H), 4.00 (s, 3 H), 3.87 (s, 2 H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 163.9, 162.5, 140.4, 139.8, 130.0, 128.4, 126.9, 126.0, 125.0, 119.2, 108.7, 53.7, 38.6. HRMS:  $m/z$  calcd for C<sub>13</sub>H<sub>9</sub>NONa [M + Na]<sup>+</sup>: 198.0913; found: 198.0913.

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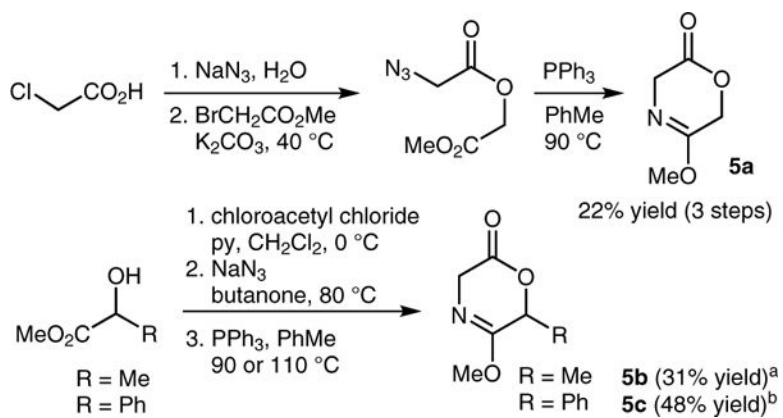
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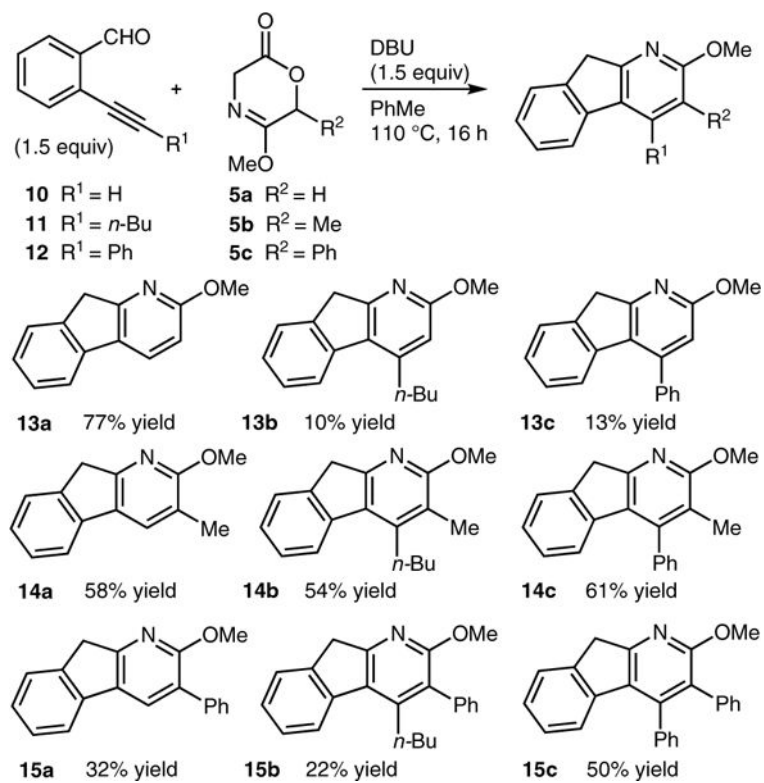
**Scheme 1.**

Comparison of domino reactions using diketopiperazine or oxazinone precursor in the synthesis of pyridone and pyridine products

**Scheme 2.**

Synthesis of dihydrooxazinone precursors. <sup>a</sup>Step 3: 90 °C. <sup>b</sup>Step 3: 110 °C.



**Scheme 3.**

Domino reaction sequence leading to tricyclic pyridine products