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Robert J. Hinkle
William & Mary, rjhink@wm.edu

Shane E. Lewis
William & Mary

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Atom Economical, One-Pot, Three-Reaction Cascade to Novel Tricyclic 2,4-Dihydro-1H-benzo[f]isochromenes

Robert J. Hinkle* and Shane E. Lewis

Department of Chemistry, The College of William & Mary, P.O. Box 8795, Williamsburg, Virginia 23187-8795, United States

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ABSTRACT

Reaction of 6-methyl-1-phenylhept-3-yne-2,6-diol with various aldehydes under Lewis acid conditions provides an atom economical, two-component cascade reaction sequence to novel 2,4-dihydro-1H-benzo[f]isochromene compounds. Aliphatic aldehydes as well as electron-deficient and -rich aromatic aldehydes can be used.

In efforts to increase atom economy,1 reduce harmful environmental effects, and increase the overall efficiency of experimental sequences, one-pot multicomponent reactions2 and cascade3 or domino reactions4 have become much more common in organic synthesis.5,6 We have recently described a three-component addition–cyclization protocol7 as well as a mechanistic investigation of a Bi(III)-initiated component cascade reaction sequence to novel 2,4-dihydro-1H-benzo[f]isochromene compounds. Aliphatic aldehydes as well as electron-deficient and -rich aromatic aldehydes can be used.

Reaction of 6-methyl-1-phenylhept-3-yne-2,6-diol with various aldehydes under Lewis acid conditions provides an atom economical, two-component cascade reaction sequence to novel 2,4-dihydro-1H-benzo[f]isochromene compounds. Aliphatic aldehydes as well as electron-deficient and -rich aromatic aldehydes can be used.


9 Fused pyrans have been investigated as antioxidants and for antiplatelet and antiproliferative properties: (a) Reddy, K. R.; Longato, G. B.; de Carvalho, J. E.; Ruiz, A. L.; Silva, L. F., Jr. Molecules 2012, 17, 9621–9630.


variation of this reaction with homoallylic alcohols provided a number of tricyclic compounds via an intermediate secondary alkyl carbocation. While a number of fused polycyclic pyran derivatives exist in the literature, this represented a novel approach to their construction, as many other examples use substrates with a preformed ring system. In contrast to these results, the reaction we describe occurs via a putative, high-energy alkyl cation and includes a subsequent dehydrative aromatization to afford 2,4-dihydro-1H-benzo[7j]isochromenes, which also represent a novel class of heterocycles.

Based on our previous work, we envisioned that a tricyclic 2,4,5,6-tetrahydro-1H-benzo[f]isochromen-5-ol product might be accessible utilizing a cascade sequence involving an alkynyl-Prins reaction and Friedel–Crafts cyclization from an unsymmetrical alkenediol and an aldehyde (R—CHO) under Lewis acid mediated conditions (Scheme 2).

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**Scheme 1. Intermolecular Friedel–Crafts**

![Diagram](image1)

**Scheme 2. Retrosynthetic Analysis**

![Diagram](image2)

The requisite unprotected alkenediol 2a was synthesized from the known propargylic alcohol 1a by conversion to the diazonium with n-BuLi followed by addition to isobutylene oxide in the presence of BF₃·OEt₂ (eq 1).

Several different Lewis acid conditions were examined with alkenediol 2a and propionaldehyde or isobutynaldehyde as electrophiles (Table 1). When using propionaldehyde (entry 1) relatively low yields were obtained with 1.1 equiv of BF₃·EtO (average of 72% per reaction). Reactions with the silylated derivative 2b (eq 1) and stoichiometric Bi(OTf)₃ made isolation of 3a more difficult (entry 2). We also attempted cyclizations with the mono-TBDPS protected analog 2c, but recovered starting materials. Reactions using isobutynaldehyde were more efficient (entries 3–6), although stoichiometric amounts of BiBr₃ and Bi(OTf)₃ provided 3b in lower yields (entries 4 and 5).

Halving the concentration of the reaction had no effect on the isolated yield (entry 6).

As a result of our success with catalytic quantities of Bi(III) compounds in the synthesis of dihydropyran, catalytic quantities (10–20%) of BiBr₃ and Bi(OTf)₃ were screened as potential initiators, but starting materials were more difficult.
were largely recovered. Although the reaction did proceed with stoichiometric amounts of both reagents (entries 2, 4, and 5), the high molecular weight and associated cost limited the appeal of each. Other, less expensive Lewis acids such as TiCl4 and SnCl4 were examined in catalytic and stoichiometric quantities, but each was more hazardous to dispense and led to more complex mixtures as well as decomposition of starting materials. Overall, a 10 mol % excess of BF3·OEt2 over diol 2a provided the least complex reaction mixtures (entries 1 and 3).

Alkynediol 2a was then reacted with various other aldehydes in the presence of 1.1 equiv of BF3·OEt2 at rt in CH2Cl2 (Table 2). Compounds 3a–C03j were all isolated as extremely viscous oils after column chromatography and were characterized by IR, 1H, 13C, APT, and 13C DEPT NMR spectroscopy as well as combustion or mass spectral analysis.

Alkyl-substituted products, 3a–3e, were generally less stable than the corresponding aryl-substituted analogs, 3f–3j, and decomposed at rt when exposed to air. As reported by Guiso et al., analogs with only one aromatic ring (isochromans) are easily oxidized to lactones.22 Based on X-ray crystallographic analysis of a sample left at rt in air, the alkyl 2,4-dihydro-1H- benzof/fisochromenes 3a–3f herein appear to be prone to oxidation via a similar pathway (Scheme 3).23

Reactions using benzaldehyde and substituted benzaldehydes afforded benzof/fisochromenes (3f–3j) containing both electron-withdrawing and -donating substituents. These aryl-substituted benzof/fisochromenes were significantly more stable than the corresponding alkyl-substituted products 3a–3e. This trend was also verified by GC MS analysis in which the molecular ions of the aryl-substituted substrates 3f–3j were much more evident relative to fragments.

We believe that the reaction progresses through a sequence of steps outlined in Scheme 4. Either of the two hydroxyls in 2a could attack the putative Lewis acid activated aldehyde generating intermediate I or IV via Path A or B, respectively (Scheme 4). Subsequent formation of oxocarbenium ion II or V then allows for progression of the cascade. Intramolecular 6-end0 attack of the alkyne via Path A would generate III, the alkenyl cation of a dihydrofuran, whereas intramolecular attack of the alkyne via Path B would generate VI, the vinyl cation of a dihydrofuran. Classic studies conducted by Mayr et al. established that cyclic, five-membered alkenyl cations are approximately 10 kcal/mol higher in energy than cyclic, six-membered analogs, which are in turn similar to open-chain alkenyl cations.24 In accord with this difference in

Table 1. Brief Survey of Lewis Acid Activators

<table>
<thead>
<tr>
<th>entry</th>
<th>aldehyde</th>
<th>product</th>
<th>Lewis acid</th>
<th>yield (%)ab</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>2a</td>
<td>BF3·OEt2</td>
<td>38</td>
</tr>
<tr>
<td>2</td>
<td>i-Pr</td>
<td>2a</td>
<td>BF3·OEt2</td>
<td>19°</td>
</tr>
<tr>
<td>3</td>
<td>sec-Bu</td>
<td>3a</td>
<td>BF3·OEt2</td>
<td>47</td>
</tr>
<tr>
<td>4</td>
<td>p-Br-Ph</td>
<td>3g</td>
<td>BF3·OEt2</td>
<td>47°</td>
</tr>
<tr>
<td>5</td>
<td>p-CF3-Ph</td>
<td>3h</td>
<td>BF3·OEt2</td>
<td>58</td>
</tr>
<tr>
<td>6</td>
<td>p-NO2-Ph</td>
<td>3i</td>
<td>BF3·OEt2</td>
<td>58</td>
</tr>
</tbody>
</table>

a Reactions were run under argon at ∼0.25 M in 2a using 1.2 equiv of aldehyde and 1.1 equiv of corresponding Lewis acid. b Isolated yields of compounds after silica gel column chromatography. c The bis-TES protected analog 2b was used. d Reaction conducted at ∼0.125 M.

Table 2. One-Pot Cascade Synthesis of Benzo/fisochromenes

<table>
<thead>
<tr>
<th>entry</th>
<th>product</th>
<th>aldehyde (R)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>Et–</td>
<td>38</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>i-Pr–</td>
<td>47</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>sec-Bu–</td>
<td>52</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>pentan-3-yl–</td>
<td>44</td>
</tr>
<tr>
<td>5</td>
<td>3e</td>
<td>PhCH2CH2–</td>
<td>43</td>
</tr>
<tr>
<td>6</td>
<td>3f</td>
<td>Ph–</td>
<td>58</td>
</tr>
<tr>
<td>7</td>
<td>3g</td>
<td>p-Br–Ph–</td>
<td>58</td>
</tr>
<tr>
<td>8</td>
<td>3h</td>
<td>p-CF3-Ph–</td>
<td>43</td>
</tr>
<tr>
<td>9</td>
<td>3i</td>
<td>p-NO2–Ph–</td>
<td>46</td>
</tr>
<tr>
<td>10</td>
<td>3j</td>
<td>p-MeO–Ph–</td>
<td>58</td>
</tr>
</tbody>
</table>

* Isolated yields of compounds after silica gel column chromatography.

Scheme 3. Air Oxidation of 3a and ORTEP of Lactone 4

(23) See the Supporting Information for details of the X-ray analysis.
energies, solvolyses of cyclopentenyl nonaflates occur by S–O bond cleavage rather than alkenyl cation formation. As predicted by these energetic differences, we do not observe products from cyclization by the higher energy manifold (Path B); however, some complex polymerization products are generated, and we cannot completely discount this intermediate in the formation of those materials. In Path A, a subsequent intramolecular Friedel–Crafts reaction would occur at the ortho-position of the pendant aromatic ring. After rearomatization of the original phenyl moiety, the central ring is formed and acid-catalyzed dehydration/aromatization occurs to generate the observed benzof[f]isochromenes 3a–3j. In the case of protected alkynediol 2c (vide supra), the large TBDPS group likely prevented cyclization due to severe steric interactions, and the initial intermolecular addition to I is reversible (Scheme 4, Path A).

It is somewhat surprising that tetrahydrofuran products are not observed. Rychnovsky and co-workers as well as Cho and co-workers reported that internal alkynes afford 5-exo products rather than the 6-endo adducts we observe. However, a 5-exo reaction of intermediate II would produce VII (Scheme 4, lower right), which would contain an alkenyl cation that would be destabilized by the adjacent hydroxyl group. Therefore, the products formed proceed through Path A.

In summary, 2,4-dihydro-1H-benzof[f]isochromenes 3a–3j are novel tricyclic compounds that are obtained in four chemical steps from commercially available trimethylsilylacetylene. The only ring present in the initial compound is the phenyl moiety shown in compounds 1a–1c and 2a–2c. Conversion of 2a to the tricyclic products is achieved by an atom economical cascade involving an alkynyl-Prins cyclization, Friedel–Crafts arylation, and dehydrative aromatization. Although overall yields appear modest, three separate reactions are part of the cascade, and the average yields for each of these reactions involved in the cascade are a minimum of 72%. Further studies involving a wider variety of substrates and further optimization are underway and will be reported in due course.

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**Supporting Information Available.** X-ray crystallographic tables of lactone 4 and characterization data, including 1H and 13C APT, and 13C DEPT NMR spectra for 2a–2c and 3a–3j. GC MS traces also included for 3a–3j. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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