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

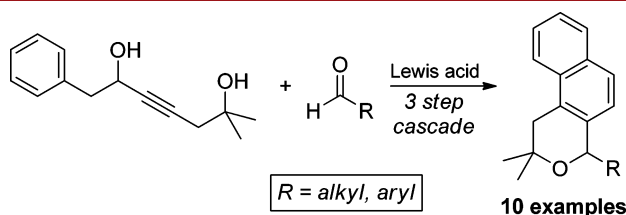
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## ABSTRACT



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-1*H*-benzo[*f*]isochromene compounds. Aliphatic aldehydes as well as electron-deficient and -rich aromatic aldehydes can be used.

In efforts to increase atom economy,<sup>1</sup> reduce harmful environmental effects, and increase the overall efficiency of experimental sequences, one-pot multicomponent reactions<sup>2</sup> and cascade<sup>3</sup> or domino reactions<sup>4</sup> have become much more common in organic synthesis.<sup>5,6</sup> We have recently described a three-component addition–cyclization protocol<sup>7</sup> as well as a mechanistic investigation of a Bi(III)-initiated

silyl-Prins cyclization toward dihydropyrans.<sup>8</sup> Herein, we report a cascade sequence involving an alkynyl-Prins cyclization, Friedel–Crafts arylation, and dehydration/aromatization to afford unique tricyclic benzo[*f*]isochromene derivatives<sup>9</sup> in which only H<sub>2</sub>O is generated as a byproduct from the two reaction components. A minimum of 72% average yields are observed for each of the reactions involved in the cascade.

The Prins cyclization<sup>10,11</sup> and related reactions<sup>12,13</sup> are versatile methods for the synthesis of dihydropyran and tetrahydropyran rings as well as numerous derivatives. Recently, a tandem intermolecular Prins/Friedel–Crafts reaction was reported to furnish 4-aryldihydropyrans from homopropargylic alcohols and 4-aryltetrahydropyrans from homoallylic alcohols (Scheme 1) when the aromatic compound was used as solvent.<sup>14</sup> An intramolecular

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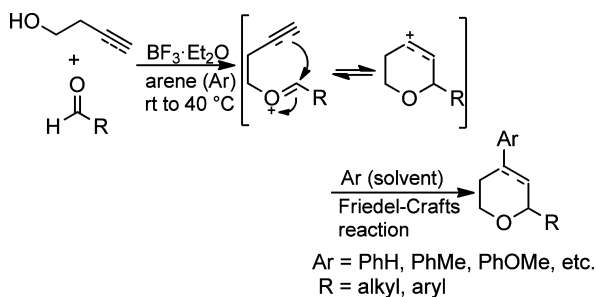
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### Scheme 1. Intermolecular Friedel–Crafts



variation of this reaction with homoallylic alcohols provided a number of tricyclic compounds via an intermediate secondary alkyl carbocation.<sup>15</sup> 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.<sup>16</sup> In contrast to these results, the reaction we describe occurs via a putative, high-energy alkenyl cation and includes a subsequent dehydrative aromatization to afford 2,4-dihydro-1*H*-benzo[*f*]isochromenes, which also represent a novel class of heterotricycles.

Based on our previous work, we envisioned that a tricyclic 2,4,5,6-tetrahydro-1*H*-benzo[*f*]isochromen-5-ol product

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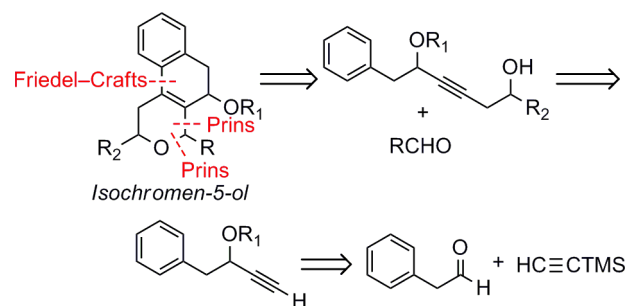
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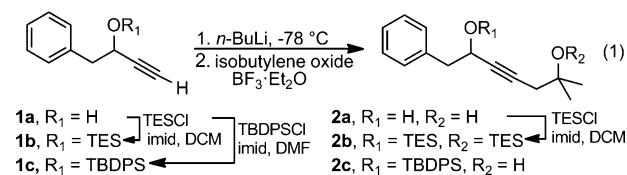
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might be accessible utilizing a cascade sequence involving an alkynyl-Prins reaction<sup>17,18</sup> and Friedel–Crafts cyclization<sup>19</sup> from an unsymmetrical alkynediol and an aldehyde (R–CHO) under Lewis acid mediated conditions (Scheme 2).

### Scheme 2. Retrosynthetic Analysis



The requisite unprotected alkynediol **2a** was synthesized from the known propargylic alcohol **1a**<sup>20</sup> by conversion to the dianion with *n*-BuLi followed by addition to isobutylene oxide in the presence of BF<sub>3</sub>·OEt<sub>2</sub> (eq 1).<sup>21</sup>



Several different Lewis acid conditions were examined with alkynediol **2a** and propionaldehyde or isobutyraldehyde as electrophiles (Table 1). When using propionaldehyde (entry 1) relatively low yields were obtained with 1.1 equiv of BF<sub>3</sub>·OEt<sub>2</sub> (average of 72% per reaction). Reactions with the silylated derivative **2b** (eq 1) and stoichiometric Bi(OTf)<sub>3</sub> 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 isobutyraldehyde were more efficient (entries 3–6), although stoichiometric amounts of BiBr<sub>3</sub> and Bi(OTf)<sub>3</sub> provided **3b** in lower yields (entries 4 and 5). Halving the concentration of the reaction had no effect on the isolated yield (entry 6).

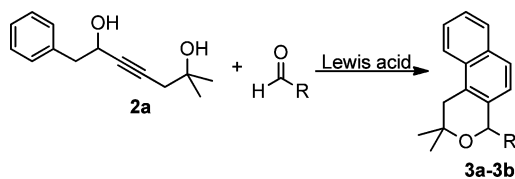
As a result of our success with catalytic quantities of Bi(III) compounds in the synthesis of dihydropyrans, catalytic quantities (10–20%) of BiBr<sub>3</sub> and Bi(OTf)<sub>3</sub> were screened as potential initiators,<sup>7,8</sup> but starting materials

(18) The descriptor “Prins cyclization” has been used inconsistently in the literature. However, many authors now interpret the typical Prins cyclization to involve formation of two bonds in the tetrahydropyran product, and we are using this definition. See ref 10b for a discussion of the Prins cyclization.

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**Table 1.** Brief Survey of Lewis Acid Activators

entry	aldehyde	product	Lewis acid	yield (%) <sup>a,b</sup>
1			BF <sub>3</sub> ·OEt <sub>2</sub>	38
2			Bi(OTf) <sub>3</sub>	19 <sup>c</sup>
3			BF <sub>3</sub> ·OEt <sub>2</sub>	47
4			Bi(OTf) <sub>3</sub>	42
5			BiBr <sub>3</sub>	36
6			BF <sub>3</sub> ·OEt <sub>2</sub>	47 <sup>d</sup>

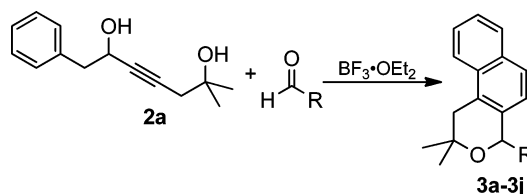
<sup>a</sup> Reactions were run under argon at ~0.25 M in **2a** using 1.2 equiv of aldehyde and 1.1 equiv of corresponding Lewis acid. <sup>b</sup> Isolated yields of compounds after silica gel chromatography. <sup>c</sup> The *bis*-TES protected analog **2b** was used. <sup>d</sup> Reaction conducted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

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 TiCl<sub>4</sub> and SnCl<sub>4</sub> 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 BF<sub>3</sub>·OEt<sub>2</sub> 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 BF<sub>3</sub>·OEt<sub>2</sub> at rt in CH<sub>2</sub>Cl<sub>2</sub> (Table 2). Compounds **3a–3j** were all isolated as extremely viscous oils after column chromatography and were characterized by IR, <sup>1</sup>H, <sup>13</sup>C APT, and <sup>13</sup>C DEPT NMR spectroscopy as well as combustion or mass spectral analysis.

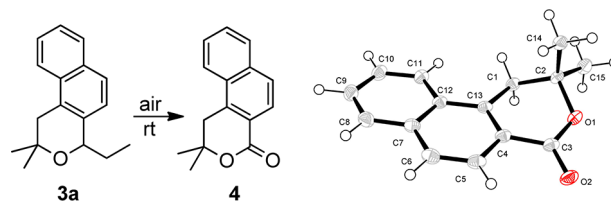
Alkyl-substituted products, **3a–3e**, were generally less stable than the corresponding aryl-substituted analogs, **3f–3j**, and decomposed at rt when exposed to air. As reported by Guiso et al., analogs with only one aromatic ring (isochromans) are easily oxidized to lactones.<sup>22</sup> Based on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

Reactions using benzaldehyde and substituted benzaldehydes afforded benzo[*f*]isochromenes (**3f–3j**) containing

**Table 2.** One-Pot Cascade Synthesis of Benzo[*f*]isochromenes

entry	product	aldehyde (R)	yield (%) <sup>a</sup>
1	<b>3a</b>	Et–	38
2	<b>3b</b>	<i>i</i> -Pr–	47
3	<b>3c</b>	<i>sec</i> -Bu–	52
4	<b>3d</b>	pentan-3-yl–	44
5	<b>3e</b>	PhCH <sub>2</sub> CH <sub>2</sub> –	43
6	<b>3f</b>	Ph–	58
7	<b>3g</b>	<i>p</i> -Br-Ph–	58
8	<b>3h</b>	<i>p</i> -CF <sub>3</sub> -Ph–	43
9	<b>3i</b>	<i>p</i> -NO <sub>2</sub> -Ph–	46
10	<b>3j</b>	<i>p</i> -MeO-Ph–	58

<sup>a</sup> Isolated yields of compounds after silica gel column chromatography.

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

both electron-withdrawing and -donating substituents. These aryl-substituted benzo[*f*]isochromenes 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.

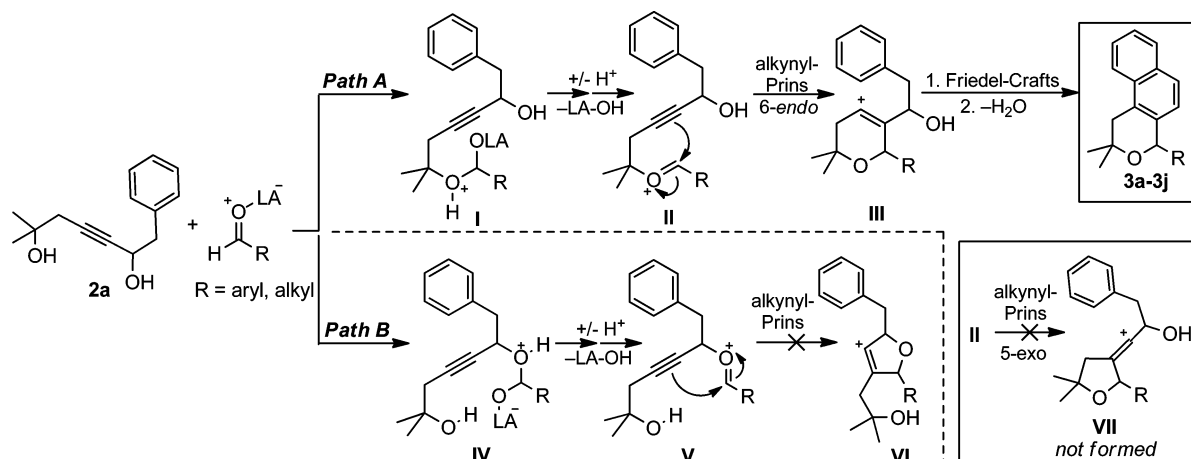
We believe that the reaction progresses through a sequence of steps outlined in Scheme 4. Either of the two hydroxyls in **2a** could attack the putative Lewis acid activated aldehyde generating intermediate **I** or **IV** via *Path A* or *B*, respectively (Scheme 4). Subsequent formation of oxocarbenium ion **II** or **V** then allows for progression of the cascade. Intramolecular 6-*endo* attack of the alkyne via *Path A* would generate **III**, the alkenyl cation of a dihydropyran, 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.<sup>24</sup> In accord with this difference in

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**Scheme 4.** Mechanistic Rationale for Product Formation



energies, solvolyses of cyclopentenyl nonaflates occur by S–O bond cleavage rather than alkenyl cation formation.<sup>25</sup> 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<sup>26</sup> occurs to generate the observed benzo[*f*]isochromenes **3a–3j**. In the case of protected alkyne diol **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<sup>27</sup> as well as Cho and co-workers<sup>28</sup> 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-1*H*-benzo[*f*]isochromenes **3a–3j** are novel tricyclic compounds that are obtained in four chemical steps from commercially available trimethylsilyl-acetylene. 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 <sup>1</sup>H and <sup>13</sup>C APT, and <sup>13</sup>C 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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