The Diels—Alder Cyclization of Ketenimines

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Received March 22, 2012

ABSTRACT

A Diels—Alder reaction between cyclopentadiene and a variety of ketenimines is reported. A copper(I)-bis(phosphine) complex catalyzes the cycloaddition across the C—N bond of the ketenimine in a [4 + 2] reaction to give an enamine intermediate that is hydrolyzed upon purification to generate aminoketones.

The Diels—Alder reaction of ketenes and dienes has achieved a mythical status in organic chemistry due to its problematic nature and the unusual mechanistic pathways it follows. For example, ketenes are known to react by parallel [4 + 2] and/or subsequent [2 + 2] manifolds, often in complex ways (Scheme 1).1 In contrast, keteniminium salts are known to add dienes across their C==C bonds in a [4 + 2] manner.2 However, the corresponding Diels—Alder reaction involving ketenimines is scarcely known3,4 in the literature; the basic documentation of such a reaction would provide an important mechanistic counterpoint to the seminal ketene cycloaddition reaction. In this communication, we present a Lewis acid catalyzed Diels—Alder reaction between dienes with ketenimines and elucidate the similarities and differences of this unique reaction to the corresponding process involving ketenes. What is more, this reaction represents a different approach to the catalytic synthesis of enamine intermediates,5 whose importance to synthetic chemistry grows with each passing year.6 In contrast to other catalytic enamine syntheses, the amino group is retained in the product, affording potential appeal


10.1021/ol300742t © 2012 American Chemical Society  
Published on Web 04/05/2012
for the synthesis of amine building blocks and pharmaco-
logically relevant targets.  

Scheme 1. Diels–Alder Cyclization Pathways

At the beginning of our study, the first question we
addressed was in the nature of the products that would
form during the reaction of a ketenimine and a diene
(Scheme 1). For example, would the reaction follow the
ketene precedent and afford the corresponding mixture
of enamine or cyclobutanimine products from [4 + 2] and
[2 + 2] reactions? Would the iminium salt precedents be
followed instead to yield [4 + 2] adducts across the C=C
bond? Would the ketenimine operate as an imine and
undergo a [4 + 2] Povarov if provided with an N-substituted
aromatic ring? Or would it follow its own unique variation?

In analogy with the reaction of cyclopentadiene (CpH)
and disubstituted ketenes, at first we attempted a reaction of
CpH with 1,3,3-trisubstituted ketenimines. Under all condi-
tions, we observed at most trace amounts of cycloadducts.
Next we examined potentially more reactive (but much harder
to handle) 1,3-disubstituted ketenimines. For example, we first
investigated the reaction of 1,3-diphenylketenimine
with CpH. We found that the thermal pathway proceeds in
a sealed tube at elevated temperatures (180 °C)
to afford a modest amount of cycloadduct (20%). At
that time, we turned instead to screening potential Lewis
catalysts for the reaction. We first tried Lewis acids
that were previously shown to catalyze the cyclization of
dienes with imines, such as Sc(OTf)3, AgOTf, and BF4-etherate; all of these candidates gave (at most)
trace amounts of product, with the notable exception of
(Ph3P)2CuClO4 (MeCN)2, which resulted in 3a (60% yield) after aqueous workup (Scheme 2). The other possible
products listed in Scheme 1 were ruled out based on NMR
data, and only 3a was isolated from each reaction.

Scheme 2. Diels–Alder Cyclization of 1,3-Diphenylketenimine

Rather than an imine or enamine, spectroscopic evi-
dence surprisingly revealed 3a to be an amino ketone
possessing a five-membered ring core. This product would
be most likely derived from the hydrolysis of strained
enamine 2a upon workup conditions after the Diels–Alder
cyclization had occurred. To examine this possibility, we
performed an in situ NMR experiment in order to observe
the enamine directly. A standard catalyzed reaction was
conducted in CDCl3 and monitored by 1H and 13C NMR.


120 (a) Bhargava, G.; Mohan, C.; Mahajan, M. P. Tetrahe-
dron 2008, 64, 3017–3024. (b) Bhargava, G.; Kumar, V.; Mahajan, M. P. Tetra-
8451. (g) Kobayashi, S.; Kusakabe, K.; Komiyama, S.; Ishitani, H.

The ketenimines proved to be fairly unstable and are best prepared immediately before use. 14 Electron withdrawing substituents on the N-aromatic ring give products in good yield (entries 2, 5, 6, and 7, Table 1), although when the electron withdrawing character is too potent (i.e., –NO2 groups) the ketenimine becomes quite unstable and condenses with itself. Some electron donating groups can be used with success (entry 3). Interestingly, electron donating groups such as 4-methoxy substituents give products in trace amounts regardless of placement on either ring. This result suggests that a “push-pull” mechanism is unlikely.

Table 1. Cyclization Product Table

<table>
<thead>
<tr>
<th>entry</th>
<th>product</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>60</td>
</tr>
<tr>
<td>2</td>
<td>b</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>c</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>d</td>
<td>62</td>
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<td>6</td>
<td>f</td>
<td>38</td>
</tr>
<tr>
<td>7</td>
<td>g</td>
<td>73</td>
</tr>
</tbody>
</table>

*Reaction conditions: PPh3 (0.1 mmol), CuClO4 (0.05 mmol), 1 mL of CH2Cl2, rt, 1 h; then 0 °C, 5 mL of CH2Cl2, ketenimine (0.5 mmol), 0.2 mL of cyclopentadiene (3.24 mmol), rt, overnight. * All yields are isolated yields.

However, placement of one m-methoxy substituent on each ring gave the best yield. It may be the case that increasing the electronegative character of the ketenimine would result in higher yields for cycloaddition products were it not for the basic instability of the ketenimines themselves.

Additionally, if the reaction progresses as envisaged, we should observe a negligible secondary kinetic isotope effect 15 upon cycloaddition of 1D with enamine formation. In fact, that is exactly what we see when we submit the label isomer 1D to the reaction and monitor it by 1H NMR. In conclusion, we have developed a copper(I) catalyzed Diels–Alder reaction between ketenimines and dienes that proceeds at room temperature. We have observed an enamine intermediate by spectroscopic means that is best explained by a [4 + 2] cycloaddition between the diene and the C≡N bond of the ketenimine. Hydrolysis of the enamine upon workup yields products in good yield. Future work will concern an expansion of scope and a detailed mechanistic study.

Acknowledgment. J.E. thanks JHU for a Gary H. Posner Graduate Fellowship.

Supporting Information Available. Experimental procedures, spectroscopic characterization of new compounds, and DFT calculations. This material is available free of charge via the Internet at http://pubs.acs.org.