Intramolecular Photoaddition of Vinylogous Amides with Allenes: A Novel Approach to the Synthesis of Pyrroles

Jeffrey D. Winkler* and Justin R. Ragains†

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104
winkler@sas.upenn.edu

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ABSTRACT

Irradiation of vinylogous amide or imide 5 (R = H, alkyl, or Ac) leads to the selective formation of either crossed photoadduct 7 (R = Ac) or parallel photoadduct 8 (R = H or alkyl) as a function of the nature of the group R. The latter result leads to a novel approach to the synthesis of pyrroles, that is, 8′.

We have reported that the [2+2] photocycloaddition reaction of 1 leads to an efficient synthesis of azabicyclo[3.2.1]octane 4, as outlined in Scheme 1. Retro-Mannich fragmentation of the crossed photoadduct 2 gives ketoiminium 3 that, upon Mannich cyclization, affords 4.† We describe herein the intramolecular photocycloaddition of vinylogous amides and imides with allenes, that is, 5, in which the presence or absence of an electron-withdrawing R group on nitrogen directs the regiochemical outcome of the ring closure of triplet 6/6′, leading to the selective formation of products derived from either 7 or 8, respectively (Scheme 2). The

Scheme 1. Synthesis of Azabicyclooctanones via Crossed Intramolecular Vinylogous Amide Photocycloaddition

Scheme 2. Intramolecular Photocycloaddition of Vinylogous Amides with Allenes
preparation of the photosubstrates is outlined in Scheme 3. Condensation of 3-butyne-2-one with propargylamine and protection of the resulting vinylogous amide 9 with (Boc)₂O or acetyl chloride generated 10 (R = Boc) and 11 (R = Ac), respectively. Homologation of 10 and 11 to the corresponding allenes was achieved using the method of Crabbe² to afford photosubstrates 12 (R = Boc) and 13 (R = Ac). Secondary vinylogous amide photosubstrate 14 could be prepared via Boc deprotection of 12. N-Methylation of 14 afforded tertiary vinylogous amide photosubstrate 15.

Irradiation of 13 (1.0 mM, CH₃CN, Pyrex) led to the formation of bridged bicyclic 18 in 52% yield (Scheme 4).

The formation of 18 can be explained via crossed photocycloaddition of 13 to generate intermediate 16, which undergoes retro-Mannich fragmentation to afford zwitterionic intermediate 17, cyclization of which provides the observed product 18. The N-Boc photosubstrate 12 underwent the same transformation, although the N-Boc product corresponding to 18 proved unstable to purification.

In contrast, irradiation of either 14 or 15 (1.0 mM, CH₃CN, Pyrex) led to the formation of pyrroles 21 and 24 via cyclobutane photoadducts 19 and 22 (Scheme 5). These results establish the critical role of the nitrogen R group on the regiochemical outcome of the photocycloaddition. When R = Boc or Ac, we observe products, that is, 18, derived exclusively from the crossed photoproducts corresponding to 16. However, when R = H or Me, that is, 14 or 15, only products derived from parallel cycloaddition to the terminal olefin of the allene, via 19 or 22, respectively, are observed. This is the first example of which we are aware of the parallel intramolecular photocycloaddition to the terminal olefin of an allene,³ which leads, among other things, to a direct process for the synthesis of 3-substituted pyrroles.

We next examined the effect of a geminal dimethyl group as shown in 27 (Scheme 6) on the pyrrole-forming reaction. We reasoned that the presence of the geminal dimethyl group in zwitterionic intermediate corresponding to 20/23 would preclude pyrrole formation and result in the isolation of a 2H-pyrrole. In the event, irradiation of 27, which was readily prepared from carbamate 25 via the Crabbe methodology, led to the formation of the 2H-pyrrole product 28 in 74% yield.

We next examined the scope and limitations of this reaction, the results of which are summarized in Table 1. While irradiation of cyclohexane-1,3-dione-derived vinylogous amides 29 and 31 gave pyrrole products 30 and 32 in excellent yield, we were surprised to find that irradiation of the corresponding cyclopentenone 33 proceeded in only 31% yield to give 34. The basis for this difference in efficiency with five- and six-membered ring chromophores is not clear.

We next attempted to extend this methodology to the irradiation of vinylogous esters, which should lead by analogy to the synthesis of furan products. Irradiation of 35, which was prepared by reaction of 3-butyn-2-one with allenylmethanol,\(^5\) led to none of the furan product 36. Only a mixture of cis- and trans-35 was observed, presumably a consequence of rotational deactivation of the acyclic chromophore. Constraining the vinylogous ester into a six-membered ring, as shown in 37 (prepared via Mitsunobu reaction of allenylmethanol with cyclohexan-1,3-dione), led to the formation of the desired furan product 38, albeit in modest yield.

The striking difference in reactivity between acyclic vinylogous amides (and imides) and esters is a particularly noteworthy feature of this study. While the photochemical literature is replete with examples of the failure of acyclic chromophores to undergo intramolecular photocycloaddition,\(^6,7\) we have shown that vinylogous amides are the exception, a result that can be attributed to stabilization of the vinylogous amide triplet by the nitrogen atom, an effect that is clearly not as significant with oxygen. This rotational deactivation is precluded with the cyclic vinylogous ester 37, which affords furan product, albeit in modest yield.

This novel approach to the synthesis of substituted pyrrole products from readily available cyclic and acyclic precursors underscores the utility of this photochemically mediated process in organic synthesis. Further studies of the application of this methodology are currently underway in our laboratory, and our results will be reported in due course.

Table 1. Synthesis of Pyrroles and Furans via Intramolecular Photocycloaddition

<table>
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<th>entry</th>
<th>photosubstrate</th>
<th>product</th>
<th>yield</th>
</tr>
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<td><img src="attachment.png" alt="Diagram" /></td>
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</tr>
<tr>
<td>2</td>
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<td><img src="attachment.png" alt="Diagram" /></td>
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<tr>
<td>4</td>
<td><img src="attachment.png" alt="Diagram" /></td>
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<tr>
<td>5</td>
<td><img src="attachment.png" alt="Diagram" /></td>
<td><img src="attachment.png" alt="Diagram" /></td>
<td>43%</td>
</tr>
</tbody>
</table>

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Supporting Information Available: Experimental procedures and \(^1\)H NMR, \(^13\)C NMR, and FTIR are available for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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