ORGANIC
LETTERS

2006
Vol. 8, No. 18
4031−4033

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

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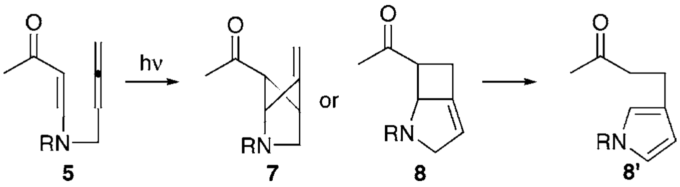
Received June 13, 2006

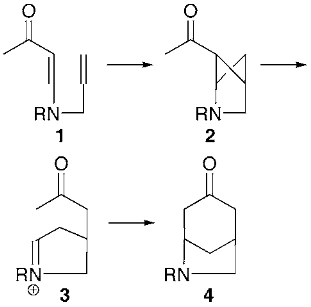
ABSTRACT



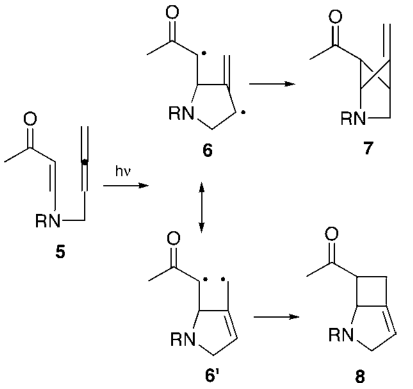
Irradiation of vinylogous amide or imide 5 (R = H, alkyl, or Ac) leads to the selective formation of either crossed photoadduct 7 (R = Ac) or parallel photoadduct 8 (R = H or alkyl) as a function of the nature of the group R. The latter result leads to a novel approach to the synthesis of pyrroles, that 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**.[1] 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



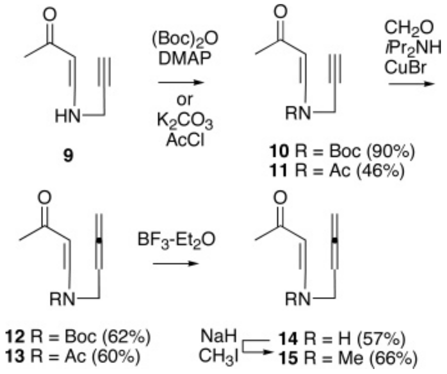
Scheme 2. Intramolcular Photocycloaddition of Vinylogous Amides with Allenes



[†] Recipient of the Eli Lilly Predoctoral Fellowship, 2002−2003.

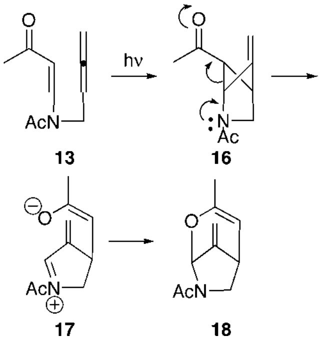
10.1021/ol061453x CCC: $33.50

Scheme 3. Preparation of Photosubstrates



preparation of the photosubstrates is outlined in Scheme 3. Condensation of 3-butyn-2-one with propargylamine and protection of the resulting vinylogous amide **9** with (Boc)$_2$O 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 Crabbe[2] 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**.

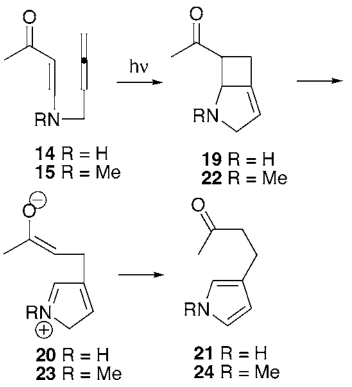
Scheme 4. Photocycloaddition of Vinylogous Imides



Irradiation of **13** (1.0 mM, CH$_3$CN, 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.

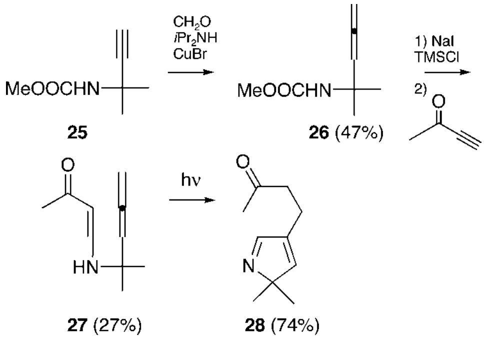
In contrast, irradiation of either **14** or **15** (1.0 mM, CH$_3$CN, Pyrex) led to the formation of pyrroles **21** and **24** via cyclobutane photoadducts **19** and **22** (Scheme 5). These results establish the critical role of the nitrogen R group on the regiochemical outcome of the photocycloaddition. 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.

Scheme 5. Synthesis of Pyrroles via Intramolecular Photocycloaddition of Vinylogous Amides



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**[4] via the Crabbe methodology, led to the formation of the 2H-pyrrole product **28** in 74% yield.

Scheme 6. Synthesis and Photoreaction of Dimethylated Photosubstrate **27**



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(1) Kwak, Y.-S.; Winkler, J. D. *J. Am. Chem. Soc.* **2001**, *123*, 7429–7430.

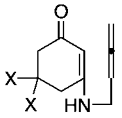
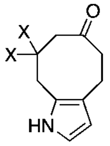
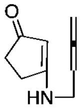
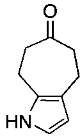
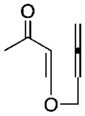
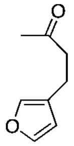
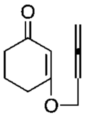
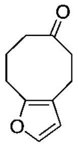
(2) Searles, S.; Li, Y.; Nassim, B.; Lopes, M.-T. R.; Tran, P. T.; Crabbe *J. Chem. Soc., Perkin Trans. 1* **1984**, 747–751.

(3) Becker, D.; Harel, Z.; Nagler, M.; Gillon, A. *J. Org. Chem.* **1982**, *47*, 3297–3306.

(4) Vereshchagin, L. I.; Kirillova, L. P.; Luzgina, G. M.; Gareev, G. A. *Russ. J. Org. Chem.* **1984**, *20*, 29–33.

We next examined the scope and limitations of this reaction, the results of which are summarized in Table 1.

Table 1. Synthesis of Pyrroles and Furans via Intramolecular Photocycloaddition

entry	photosubstrate	product	yield
1 2	 **29** X = H **31** X = Me	 **30** X = H **32** X = Me	87% 77%
3	 **33**	 **34**	31%
4	 **35**	 **36**	0%
5	 **37**	 **38**	43%

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.

Acknowledgment. We warmly thank Ms. Esther Lee (University of Pennsylvania) for her invaluable assistance in the preparation of this manuscript. We are grateful to the NIH, GlaxoSmithKline, Wyeth-Ayerst, Merck, Amgen, Boehringer Ingelheim, and Novartis for their generous support of this work.

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.

OL061453X

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[5] Kimura, M.; Tanaka, S.; Tamaru, Y. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1689−1706.

[6] Turro, N. J. *Modern Molecular Photochemistry*; Benjamin Cummings Publishing Co.: Menlo Park, CA, 1978.

[7] For a review, see: Crimmins, M. *Chem. Rev.* **1988**, 1453−1473.