Pergamon

Tetrahedron Letters 39 (1998) 7423–7426

TETRAHEDRON LETTERS

Photocycloaddition of N-4-Alkenyl Substituted Unsaturated Imides

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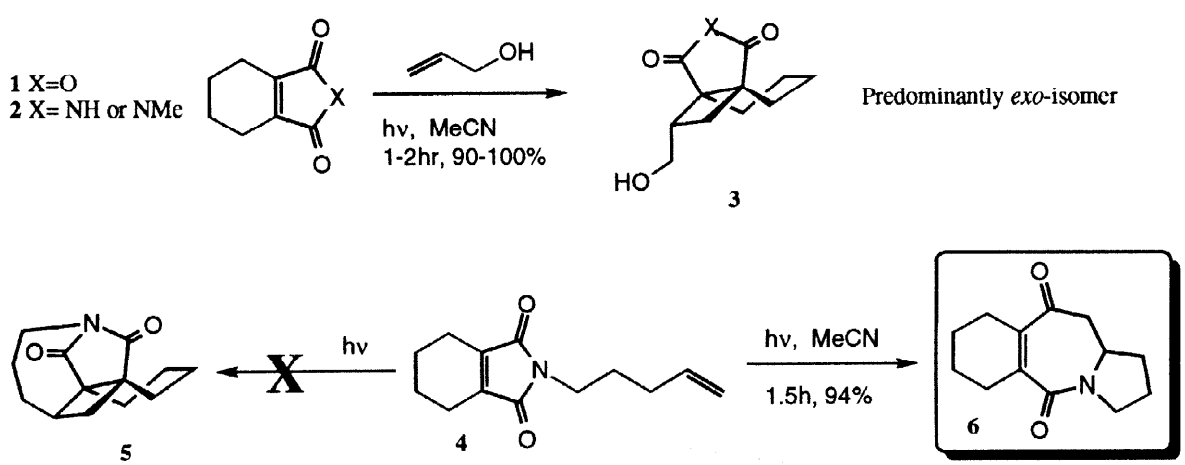
Received 24 June 1998; accepted 27 July 1998

Abstract: *UV irradiation of a number of N-alkenyl substituted maleimide and tetrahydrophthalimide derivatives leads to the formation of complex 1-azabicyclo[5.3.0]dec-3-enes in excellent yields.* © 1998 Elsevier Science Ltd. All rights reserved.

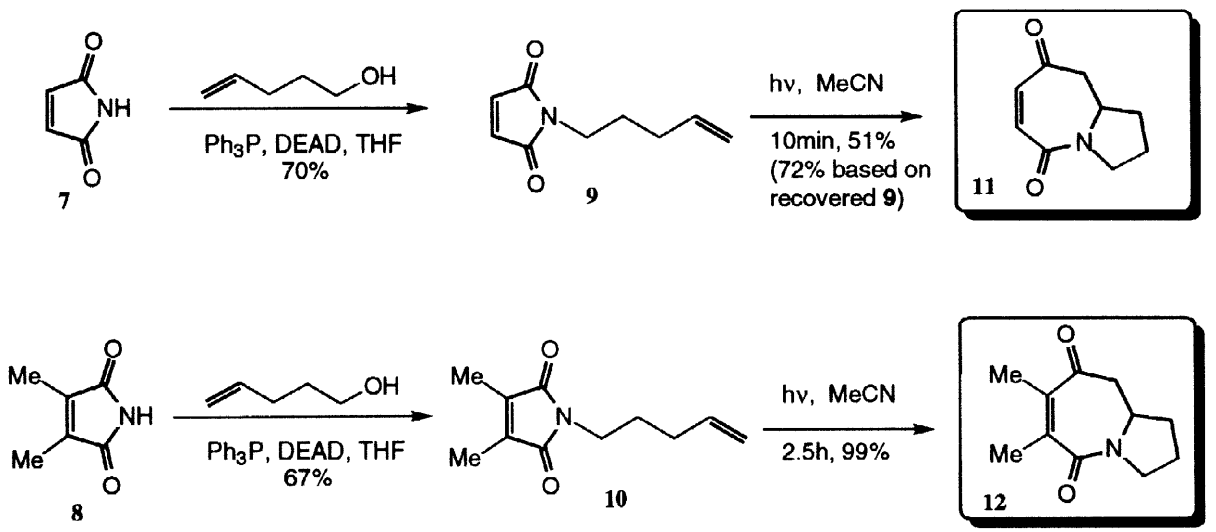
Over the past few years we have been studying the intermolecular [2+2] photocycloaddition reactions of tetrahydrophthalic anhydride **1** and the corresponding imide **2** with a variety of alkenol and alkynol derivatives. These [2+2] photocycloadditions proved to be remarkably efficient, with the cycloadducts **3** obtained in high yields with excellent stereoselectivity[1]. In Scheme 1 we intended to explore the intramolecular [2+2] photocycloaddition of the pentenyl substituted imide **4** to the cyclobutane **5**. We were somewhat surprised to observe the rapid and exclusive formation of the tricyclic azepine **6** in excellent yield. On close inspection of the photochemical literature it was found that Mazzocchi[2] had reported a related reaction with N-substituted phthalimides. An elegant series of papers followed in which Mazzocchi and co-workers[3] described the scope of the reaction with substituted phthalimides as well as proposing a plausible mechanism for this unusual type of cycloaddition. To our knowledge the conversion of **4→6** is the first example of this reaction with non-aryl imides and holds great promise as a powerful tool in the rapid construction of complex alkaloids. In this letter we describe our preliminary findings on the intramolecular photocycloaddition of a variety of unsaturated imides.



Scheme 1

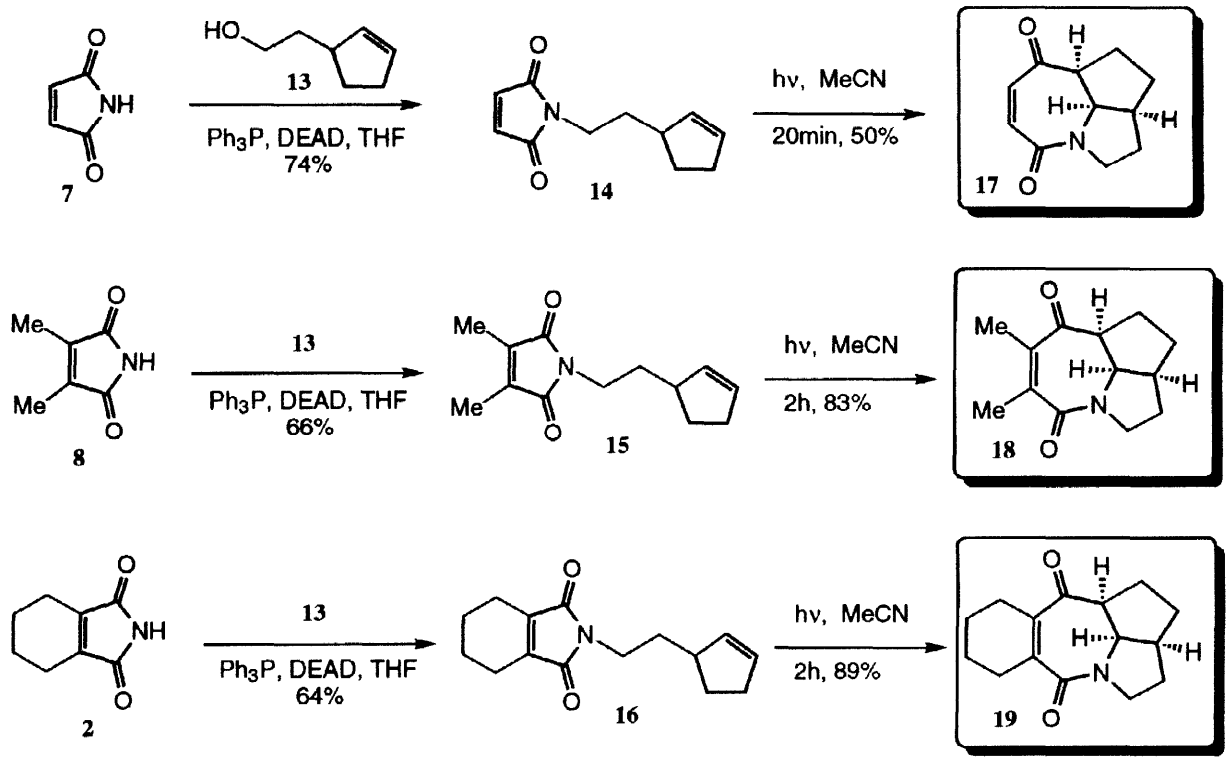
PII: S0040-4039(98)01613-X

The imide **4** was formed in 50% yield by alkylation of the sodium salt of the tetrahydrophthalimide **2** (X=NNa) with 5-bromopentene. Unfortunately attempts to alkylate maleimide **7** and dimethylmaleimide **8** with 5-bromopentene were unsuccessful as the maleimides appeared to polymerise on attempted deprotonation with sodium hydride. Fortunately, however, treatment of **7** and **8** with 4-penten-1-ol under standard Mitsunobu conditions gave the required substituted imides **9** and **10** in reasonably good yield. Irradiation of the parent imide **9** showed complete disappearance of the starting material after 2h, to give a product that appeared[4] to be the [2+2] dimer of the expected cycloadduct **11**. If **9** was irradiated for shorter periods of time it was possible to isolate the desired product **11** and unreacted starting material, in reasonably good yields, without loss to side reactions. Irradiation[5] of the dimethyl imide **10** gave an excellent yield of the desired cycloadduct **12** without any dimerisation of the product, even on prolonged irradiation (Scheme 2).



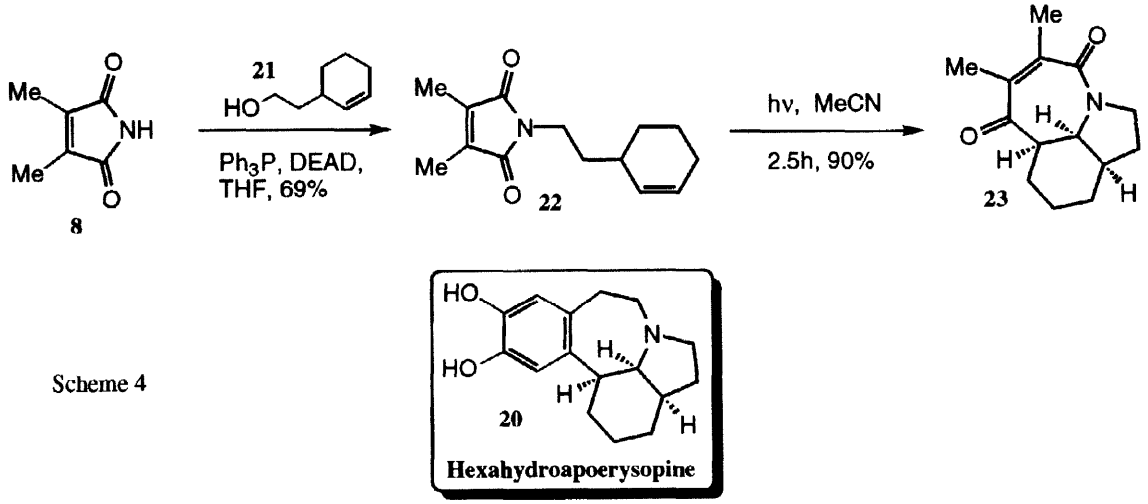
Scheme 2

We then turned our attention to the investigation of more complex alkene systems with a view to testing the limits of the photocycloaddition. We had at hand the cyclic alkenol **13**[6] which underwent successful Mitsunobu coupling with the imides **7**, **8** and **2** to yield the functionalised imides **14**, **15** and **16** respectively. Irradiation of **14** for 20min gave a 50% isolated yield of the tricyclic azepine **17** as a single diastereoisomer. Irradiation for >20min resulted in a dramatic reduction in the yield of **17** which again was presumably being consumed by dimerisation. Photocycloaddition of the dimethyl derivative **15** gave an excellent yield of the tricyclic azepine **18** without any dimerisation. This result proves that substitution of the imide alkene effectively shuts down any potential dimerisation of the photocycloadduct. Irradiation of the tetrahydrophthalimide derivative **16** gave rise to the exclusive formation of the tetracycle **19** in 89% yield (Scheme 3). The fact that a complex tetracyclic product such as **19** can be formed efficiently and stereoselectively in just two steps from readily available starting materials illustrates the great potential of this photocycloaddition. The stereochemistry observed in these cycloadditions was confirmed by nOe studies[7] and is consistent with the proposed mechanism[8] of this reaction.



Scheme 3

Finally, we turned our attention to the use of this reaction as a possible key step in the synthesis of the tetrahydroerythraline derivative hexahydroapoerysopine **20**[9]. Mitsunobu coupling of the cyclohexene alcohol **21**[10] with dimethylmaleimide gave the cycloaddition precursor **22** in reasonable yield. Irradiation of **22** then yielded the tricyclic azepine core **23** of hexahydroapoerysopine in excellent yield (Scheme 4). Future studies will investigate the development of methods to allow the introduction of the aryl ring in **20**.



Scheme 4

In summary, the photocycloaddition of 4-alkenyl substituted imide derivatives has proved to be a general process for the formation of fused azepine ring systems. The reaction works efficiently with both simple as well as more elaborate 4-alkenyl subunits and yields a number of ring systems in good yield, in only two steps, from simple starting materials. We believe that this will have wide application in the synthesis of azepine based alkaloids and will report progress in this area in due course.

Acknowledgements: We would like to thank the Engineering and Physical Sciences Research Council (EPSRC) for the provision of a research grant (GR/K15985) and Astra Charnwood for support of this work.

References and Notes

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4. Although MS and spectral data suggested the [2+2] dimer was formed, rigourous structural assignment was not possible due to the fact that the product was obtained as a complex mixture of stereoisomers.
5. In a 150ml pyrex immersion well photoreactor a solution of 1-(pent-4-enyl)-3,4-dimethylmaleimide **10** (0.201g, 1.04 mmol) in degassed acetonitrile (100 mL) was irradiated for 2.5 h using a 125W medium pressure Hg-lamp. The solvent was removed under reduced pressure and the resultant oil purified by silica gel column chromatography (eluent 30% EtOAc/ Petrol) to give 1-aza-2,5,-dioxo-3,4-dimethyl-bicyclo-[5.3.0]-dec-3-ene **12** as a white solid (0.199g, 99%). M.Pt. 81°C . IR υ_{max} 2955 (m), 2880 (m), 1670 (s), 1635 (s), 1605 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 4.23 (1H, m, NC*H*), 3.69-3.46 (2H, m, NC*HH*), 2.72 (1H, dd 18.8, 11.4 Hz, COC*H*H), 2.64 (1H, dd, 18.8, 3.7 Hz, COCH*H*), 2.18 (1H, m), 2.02 (3H, s, CH_3), 1.96-1.84 (2H, m), 1.89 (3H, s, CH_3), 1.70 (1H, m) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 202.5 (C), 166.8 (C), 139.3 (C), 138.3 (C), 52.3 (CH), 51.7 (CH_2), 45.9 (CH_2), 30.9 (CH_2), 22.9 (CH_2), 17.6 (CH_3), 15.9 (CH_3) ppm; $C_{11}H_{15}NO_2$ requires C 68.35, H 7.83, N 7.25 %; found C 68.23, H 7.65, N 6.95 %; LRMS (EI) 193 (100%, $[M]^+$), 178 (2.6%, $[M\text{-}Me]^+$), 138 (53%, $[M\text{-}CH_2CH_2CHCH_2]^+$), 124 (57%, $[M\text{-}(CH_2)_3CHCH_2]^+$) amu.
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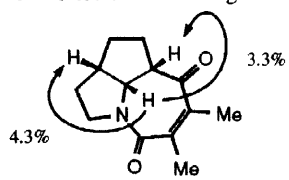
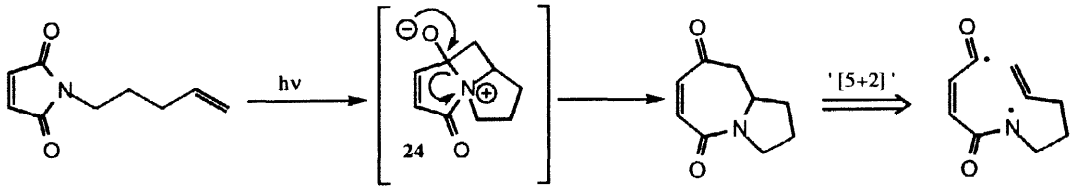
7. For example cycloadduct **18** exhibited the following nOe enhancements.



8. Although the mechanism is not known with certainty it can be postulated from the work of Mazzocchi (Ref. 3) that the reaction proceeds *via* direct [2+2] cycloaddition to the zwitterionic tricyclic species **24** followed by fragmentation to the product. The stereochemistry observed with the cyclic alkenes used in this study would support the Mazzocchi mechanism. These cycloadditions must be remarkably fast, given that we have found that the intermolecular [2+2] photocycloaddition of the maleimide alkene with other alkenes is a very facile and efficient process (Ref. 1). Although it is probably mechanistically incorrect we have found it useful, for retrosynthetic purposes, to consider this reaction as a diradical [5+2] cycloaddition as illustrated below.



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