Intramolecular Photochemical Cycloadditions of *N*-Alkenyloxycarbonylindoles and *N*-Alkenoylindoles

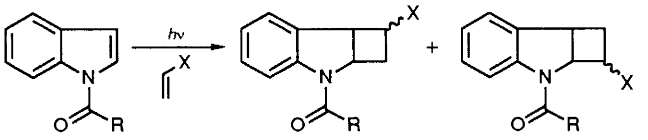
David L. Oldroyd and Alan C. Weedon*

The Photochemistry Unit, Department of Chemistry, University of Western Ontario, London, Ontario, N6A 5B7, Canada

Ultraviolet light irradiation of *N*-alkenoylindoles affords intramolecular [2 + 2] photocycloadducts with regiochemistry opposite to that obtained in the corresponding intermolecular reaction; in contrast, *N*-alkenyloxycarbonylindoles appear to be relatively photostable because they are frozen in an unreactive conformation for the duration of the excited state lifetime.

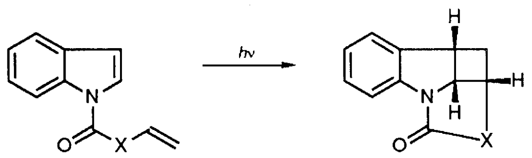
Ultraviolet light irradiation of *N*-acylindoles in the presence of mono-substituted alkenes leads to regioselective cyclobutane ring formation by addition of the alkene termini to the 2- and 3-positions of the five-membered ring of the heterocycle (Scheme 1).[1,2] We have examined the mechanism of this reaction[3] and have concluded that in the major pathway the 2-position of the *N*-acylindole triplet excited state becomes bonded to the less substituted end of the alkene; this yields a triplet 1,4-biradical which either closes to products or reverts to ground state starting materials. The proposed mechanism explains the preferential formation of the head-to-tail† cyclobutane adducts, **1**. The regioselectivity limits the synthetic utility of the reaction should the head-to-head regioisomers **2** be required. In principle, tethering the alkene to the acyl substituent of the *N*-substituted indole should direct the regiochemistry of the cycloaddition and yield the otherwise inaccessible head-to-head isomers.‡ To test this possibility the *N*-alkenyloxycarbonylindoles **3** ($n = 0, 1, 2$ or 3) were prepared and irradiated.§

The *N*-alkenyloxycarbonylindoles **3** were found to be relatively photostable and no evidence for the formation of intramolecular photocycloadducts such as **5** was observed. However, in the presence of alkenes (*e.g.* cyclopentene and octene), ultraviolet light irradiation led to the isolation of 1 : 1 *intermolecular* cycloaddition products, with an efficiency similar to that obtained with simpler *N*-acylindoles.[3] This suggests that the side chain alkene present in **3** does not interact with the indole excited state. Variable temperature ^{1}H NMR spectroscopy and molecular mechanics calculations indicate that in the ground state the *N*-alkenyloxycarbonylindoles **3** are preferentially oriented in a conformation in which the alkenyloxy function is *syn* with respect to the oxygen atom of the carbonyl group; in this conformation the side chain double bond is directed away from the 2,3-position of the indole ring, thus preventing the interaction necessary to afford the intramolecular cycloadducts. If conformational changes of the urethane function are slow during the excited state lifetime of **3** then this would explain the failure to yield intramolecular cycloadducts. Molecular mechanics calculations indicated that replacement of the urethane oxygen in **3** by a methylene group should remedy these conformational limitations. Accordingly, the *N*-alkenoylindoles **4** ($n = 1, 2$ or 3) were prepared and irradiated. In each case the major product was the intramolecular photocycloadduct **5**; the adducts were obtained with the isolated chemical yields and quantum yields shown in Table 1. The quantum yields indicate that the intramolecular cycloaddition reaction of **4** is most efficient when $n = 2$; in the presence of alkenes (*e.g.* 1–2 mol dm^{-3} cyclopentene) intermolecular cycloaddition was



1 major **2** minor

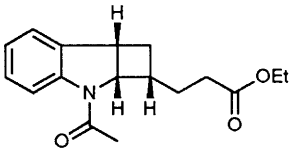
Scheme 1



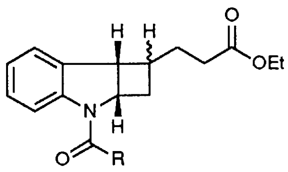
3; X = O(CH$_2$)$_n$
$n = 0, 1, 2$ or 3

4; X = (CH$_2$)$_n$
$n = 1, 2$ or 3

5; X = (CH$_2$)$_n$
$n = 1, 2$ or 3



6



7

Table 1 Yields for formation of intramolecular cycloadducts **5**

X	n	Chemical yield (%)	Quantum yield	$\Phi_{\text{inter}}/\Phi_{\text{intra}}$
CH$_2$	1	29	0.0078	1.6
CH$_2$	2	92	0.017	0.10
CH$_2$	3	25	0.0032	4.3
O	0, 1, 2 or 3	0	0	∞

---

† In this nomenclature, derived from that commonly used in enone [2 + 2] cycloaddition photochemistry, the 'head' of the indole molecule is the nitrogen atom.

‡ We are aware of only two published examples of intramolecular photocycloadditions of *N*-acylindoles (see ref. 4 and 5); one of these involves Paterno–Büchi reaction of an *N*-acylindole with a remote carbonyl group, while in the other addition occurs to an alkene tethered to the 3-position of an *N*-acylindole.

§ Compounds **3** ($n = 1, 2$ or 3) were prepared by reaction of the anhydride of indole *N*-carboxylic acid with the sodium salt of the appropriate alkenol. Compounds **4** ($n = 2$ or 3) were prepared by treatment of indole with hydroxide and the appropriate acid chloride under phase-transfer conditions; compound **3** ($n = 0$) was prepared in a similar manner using vinyl chloroformate while compound **4** ($n = 1$) was obtained by treatment of the sodium salt of indole with the anhydride of but-3-enoic acid. Irradiations were performed in benzene, both in the presence and absence of acetophenone sensitiser, using Pyrex and water filtered light from a medium pressure mercury lamp. Products were isolated by chromatography and their structures determined by ^{1}H NMR, ^{13}C NMR and mass spectroscopy.

competitive and the ratio of intermolecular *versus* intramolecular cycloaddition ($\Phi_{\text{inter}}/\Phi_{\text{intra}}$) correlated with the efficiency of intramolecular cycloaddition.

Our results extend the potential synthetic utility of the photocycloaddition of *N*-acylindoles with alkenes by demonstrating that the normally preferred regiochemistry of the reaction can be reversed, if desired, by attachment of the alkene to the indole nitrogen by an amide functionality, but not by a urethane functionality. The reversal of regiochemistry obtained in the intramolecular cycloaddition reaction was emphasized by conversion¶ of **5** (n = 2) into **6**; in contrast, irradiation of *N*-acetylindole with ethyl pent-4-enoate yielded stereoisomers of the head-to-tail intermolecular cycloadduct **7** exclusively.

Received, 20th July 1992; Com. 2/03868D

References

1 D. R. Julian and R. Foster, *J. Chem. Soc., Chem. Commun.*, 1973, 311.

2 M. Ikeda, K. Ohno, S. Mohri, M. Takahashi and Y. Tamura, *J. Chem. Soc., Perkin Trans.* 1, 1984, 405.

3 D. Andrew, D. J. Hastings, D. L. Oldroyd, A. Rudolph, A. C. Weedon, D. F. Wong and B. Zhang, *Pure Appl. Chem.*, 1992, **64**, 1327 and references cited therein.

4 M. Machida, H. Takechi and Y. Kanaoka, *Tetrahedron Lett.*, 1982, **23**, 4981.

5 J. D. Winkler, R. D. Scott and P. G. Williard, *J. Am. Chem. Soc.*, 1990, **112**, 8971.

¶ Compound **5** was converted into **6** by sequential treatment with ethanol–sulfuric acid and acetyl chloride.