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Photoinduced Intramolecular Addition of 3-Acyl-2-haloindoles to Alkenes

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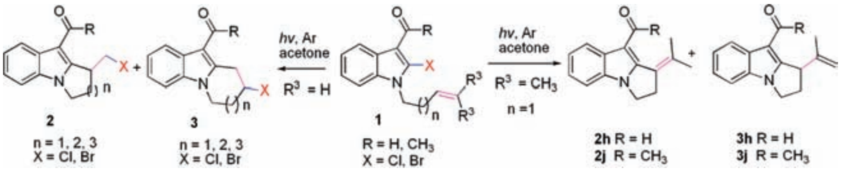
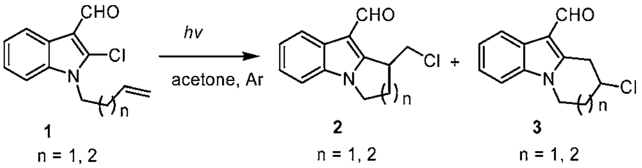
ABSTRACT



1,2-Fused indoles and pyrroles were prepared via an efficient intramolecular photoaddition reaction of 1-(ω-alkenyl)-2-haloindole-3-carbaldehydes and 1-(ω-alkenyl)-2-chloropyrrole-3-carbaldehydes. The presence of an acyl group was necessary for the photocyclization reactions. The halogen-atom-retained exo- and endo-cyclization products were generally produced with results similar to those of an atom-transfer cyclization reaction. In contrast, unsaturated cyclization products were obtained in the photoreaction of substrates having methyl groups on the vinyl group.

The photochemistry of α,β-unsaturated carbonyl compounds has long been the subject of extensive investigation for both mechanistic revelation and synthetic application.[1] Among them, the light-induced [2 + 2] reaction of an excited-state α,β-unsaturated ketone to a ground-state alkene is a highly useful reaction in organic synthesis since two new carbon−carbon bonds are formed and a maximum of four new stereogenic centers are introduced into the molecule in the process.[2] The de Mayo reaction has provided an efficient approach to the synthesis of bicyclic ring systems by the photocycloaddition/retro-aldol fragmentation reactions of β-diketones with alkenes.[3] Winkler and his collaborators have established the utility of the intramolecular photocycloaddition/retro-Mannich fragmentation of β-acylamino enones with alkenes in the synthesis of azabicyclic ring systems.[4] We have long been interested in the inter- and intramolecular photoreactions of β-acyl-substituted heterocycles with alkenes in order to develop a new method for the synthesis of polycyclic heterocycles.[5] Recently, we found that irradiation of 2-chloro-1-(ω-alkenyl)indole-3-carbaldehyde (**1**) could afford high yields of cyclization products **2** and **3** with retained chlorine atoms (Scheme 1), but no reaction could be detected after a long irradiation of the reactant without a chlorine atom, 1-(but-3-enyl)indole-3-carbaldehyde, in acetone, although it was reported that [2 + 2] products could be obtained in the photoreaction of 1-benzoylindole-3-carbaldehyde with vinyl acetate[6a] and in the intramolecular

Scheme 1. Photoinduced Intramolecular Addition Reactions



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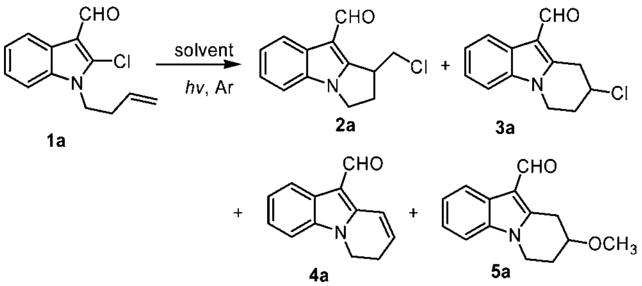
photoreaction of 1-alkenoylindoles.[6b] Therefore, the presence of a chlorine atom on the α-position of the indole ring is important for both driving the photoreaction of **1a** and presenting new cyclization products which are different from that obtained in the intermolecular photoreaction of 1-benzoylindole-3-carbaldehyde with vinyl acetate.[6a]

Several methods have been reported for the synthesis of 1,2-fused indoles. For example, SmI$_2$-promoted reductive cyclization of indole dialdehydes,[7a] Fenton agent-mediated oxidative cyclization of 1-(ω-iodoalkyl)indole,[7b] R$_2$BH-mediated reductive cyclization of 1-(ω-alkenyl)indoles,[7c] sodium benzenesulfinate−copper acetate catalyzed radical cyclization of 1-(ω-allylsulfonylalkyl)indole,[7d] and Bu$_3$SnH−AIBN-mediated radical cyclization of 1-(ω-iodoalkyl)-indoles.[7e] However, these reactions required the use of metallic catalysts, especially the tributyltin hydride, and the yields were not satisfactory and always accompanied by noncyclization reactions. Therefore, a more effective and metal-free process is desirable.

We first investigated the effect of solvent on the photoreaction of 1-(but-3-enyl)-2-chloroindole-3-carbaldehyde (**1a**) (Table 1). It was found that **1a** could be reacted in all selected solvents to afford two cyclization products. The conversions of **1a** and the yields and ratio of the products depended on solvents. In methylene dichloride and acetone, two chlorine-retained products **2a** and **3a** were obtained in excellent overall yields; in acetonitrile or ethyl acetate, an unsaturated compound **4a** was formed in addition to **2a**; in methanol, a new product **5a** was produced, which was obviously derived from the coupling of carbocation with methanol, and only minor chlorine-retained product **2a** was separated. The results indicated that secondary carbocation was formed in more polar solvents probably from electron transfer between the secondary radical and chlorine atom. In comparison, the reaction was more efficient in acetone than in other solvents as shown in Table 1. Therefore, acetone was selected as the solvent in all other photoreactions of 1-(ω-alkenyl)-2-haloindoles **1a−o** (Table 2). All products were fully identified by ^{1}H, ^{13}C NMR and MS, and the structures of **2b**, **3b** were further confirmed by X-ray crystallography (Figure 1). Compound **2b** (CCDC 695497) forms a monoclinic unit cell that belongs to the $P2(1)/c$ space group with the unit cell parameters $a = 9.601(4)$ Å, $b = 10.575(5)$ Å, $c = 12.022(5)$ Å, $\beta = 92.744(7)°$, $V = 1219.3(10)$ Å^3. Compound **3b** (CCDC 695496) forms a monoclinic unit cell that belongs to the $P2(1)/c$ space group with the unit cell parameters $a = 9.2370(7)$ Å, $b = 15.9270(12)$ Å, $c = 7.9660(6)$ Å, $\beta = 93.3640(10)°$, $V = 1169.92(15)$ Å^3.

Table 1. Photoreaction of **1a** in Different Solvents[a]



entry	solvent	time (h)	convn[b] (%)	yield[c] (%) 5-exo	yield[c] (%) 6-endo	yield[c] (%) 6-endo
1	CH$_2$Cl$_2$	4	81	**2a** 48	**3a** 39	
2	Me$_2$CO	4	99	**2a** 53	**3a** 43	
3	AcOEt	8	78	**2a** 72		**4a** 14
4	MeCN	8	76	**2a** 38		**4a** 48
5	MeOH	8	81	**2a** 6		**5a** 88

[a] 0.3 mmol of **1a** was dissolved in different solvents (20 mL). The solution was irradiated at $\lambda \geq 300$ nm with a high-pressure mercury lamp (500 W) under argon atmosphere at ambient temperature. [b] Conversion was calculated on the basis of **1a**. [c] Yield of isolated product based on consumed **1a**.

It is noticeable from Table 2 that the photoreactions of 1-(ω-alkenyl)-2-halo-3-acylindoles (**1a**,**b**,**d−l**) exclusively led to the cyclization products when these substrates were irradiated in the deaerated acetone solution at ambient temperature except **1c**. Two halogen-retained products were generally produced in each photoreaction, which was much like the result of an atom-transfer cyclization reaction.[8] The advantages of this reaction over Bu$_3$SnH-mediated cyclization of 1-(ω-alkenyl)-2-haloindoles[7e] are not only the high yields but also the halogen-atom retention in the products which allows for further functionalization. However, it was found that 1-(but-3-enyl)-2-chloro-3-methylindole (**1n**) and ethyl 1-(but-3-enyl)-2-chloroindole-3-carboxylate (**1o**), both of which had no acyl groups on indoles, could not afford the cyclization products under similar conditions. It could be deduced that the formyl and acetyl groups were necessary for the photocyclization reaction of 1-(ω-alkenyl)-2-haloindoles. Since both a halogen is needed on the α-position and an acyl group on the β-position of the indole ring, it could be proposed that the reaction mechanism of 3-acyl-2-haloindoles with alkenes was much like that of the [2 + 2] photoreaction of α,β-unsaturated enones with alkenes.[2c,4b] The Michael-like coupling of the β-carbon of the diradical in excited 3-acylindoles with double bonds of alkenes gave new diradicals (Scheme 2). Subsequently, the halogen atom transfer occurred from the diradical before the coupling of diradical to form cyclobutane. Comparatively, it is difficult for 3-methylindole and ethyl indole-3-carboxylate to become

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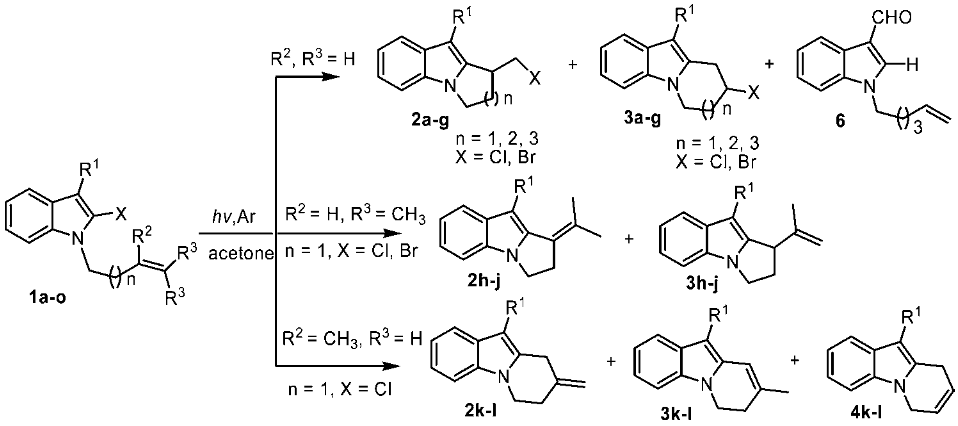
Table 2. Photoreaction of *N*-(*ω*-Alkenyl)-2-halo-3-acylindoles[a]



entry	substrate	R1	R2	R3	X	*n*	time (h)	convn[b] (%)	yield[c] (%)					
1	**1a**	CHO	H	H	Cl	1	4	99	**2a**	53	**3a**	43		
2	**1b**	CHO	H	H	Cl	2	6	98	**2b**	58	**3b**	36		
3	**1c**	CHO	H	H	Cl	3	6	87	**2c**	32	**2c**	27	**6**	20
4	**1d**	$COCH_3$	H	H	Cl	1	6	96	**2d**	56	**3d**	39		
5	**1e**	$COCH_3$	H	H	Cl	2	5	95	**2e**	80	**3e**	16		
6	**1f**	CHO	H	H	Br	1	6	89	**2f**	51	**3f**	40		
7	**1g**	CHO	H	H	Br	2	6	92	**2g**	71	**3g**	21		
8	**1h**	CHO	H	CH_3	Cl	1	6	97	**2h**	54	**3h**	37		
9	**1i**	CHO	H	CH_3	Br	1	6	85	**2h**	58	**3h**	33		
10	**1j**	$COCH_3$	H	CH_3	Cl	1	6	92	**2j**	34	**3j**	61		
11	**1k**	CHO	CH_3	H	Cl	1	6	95	**2k**	33	**3k**	24	**4k**	31
12	**1l**	$COCH_3$	CH_3	H	Cl	1	6	90	**2l**	37	**3l**	32	**4l**	23
13	**1m**	CHO	H	H	Cl	0	9	0						
14	**1n**	CH_3	H	H	Cl	1	9	0						
15	**1o**	CO_2Et	H	H	Cl	1	9	0						

[a] 0.3 mmol of **1a**−**o** was dissolved in acetone (20 mL). The solution was irradiated at $\lambda \geq 300$ nm with a high-pressure mercury lamp (500 W) under argon atmosphere at ambient temperature. [b] Conversion was calculated on the basis of substrate. [c] Yield of isolated product based on consumed substrate.

diradicals. Thus, no reaction took place in the irradiation of the two substances under the same conditions.

The length of the chain between the indolyl and vinyl groups and the substitutents on the vinyl group had great effects on the photoaddition reactions of **1a**−**c**,**m** as shown in Table 2. No cyclization product was detected in the photoreaction of 1-allyl-2-chloroindole-3-carbaldehyde (**1m**). When the chain length was extended in **1a**−**c**, the chlorine-atom-retained exo- and endo-cyclization products were obtained in high yields. However, a noncyclization reduction product **6** was produced when the chain length further extended in **1c** in addition to the normal cyclization products. Although the photoreaction of **1a**−**g** afforded mainly the halogen-atom-retained cyclization products, the photoreaction of **1h**−**l** gave only unsaturated cyclization products which were derived from deprotonation of carbocation intermediates. It could be proposed that the methyl groups linked to a double bond directed the coupling of *β*-carbon of the diradical in excited 3-acylindole only with a small hindered carbon of a double bond, leading to more stable tertiary radicals; the subsequent dehalogenation and electron transfer between the tertiary radicals and halogen atoms occurred to give the tertiary carbocations (Scheme 2). Therefore, only unsaturated cyclization products were produced from **1h**−**l**.

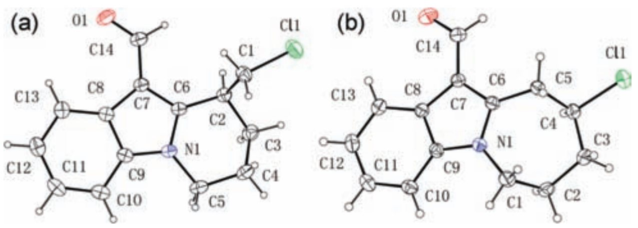
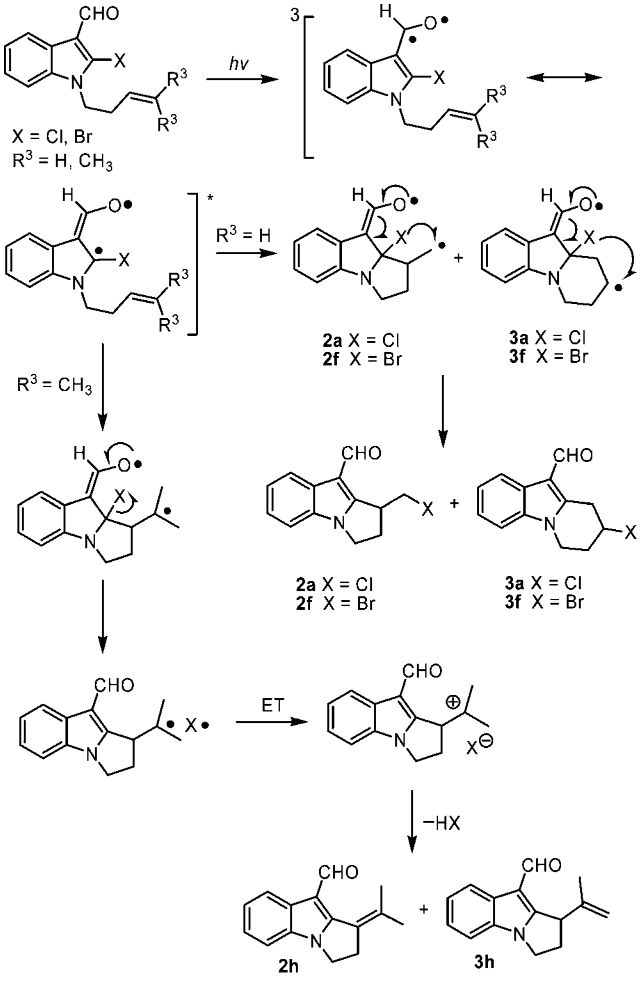


Figure 1. (a) X-ray crystal structure of **2b**. (b) X-ray crystal structure of **3b**.

In order to expand the scope of this photoinduced addition reaction, we further investigated the photoreactions of *N*-(*ω*-alkenyl)-2-chloropyrrole-3-carbaldehydes in acetone. As shown in Table 3, the results of photoreactions were very similar to those of *N*-(*ω*-alkenyl)-2-haloindole-3-carbaldehydes. The photoinduced intramolecular addition reactions afforded chlorine-retained exo- and endo-cyclization products

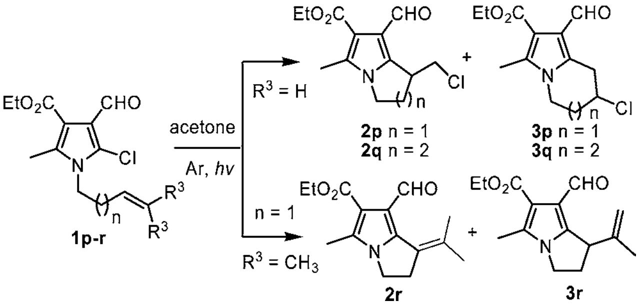
Scheme 2. Plausible Photoreaction Mechanism of 1-(Alkenyl)-2-haloindole-3-carbaldehydes in Acetone



from **1p−q** and two unsaturated cyclization products from **1r** in high yields.

In conclusion, we have developed an efficient method for the annulation of indolecarbaldehydes and pyrrolecarbaldehydes by the photoinduced intramolecular additions of *N*-alkenyl-2-haloindole-3-carbaldehydes and *N*-alkenyl-2-chloropyrrole-3-carbaldehydes in acetone. The photoreactions afforded the halogen-atom-retained exo- and endo-cyclization products in excellent yields, which were much like the results of an atom-transfer cyclization reaction. In contrast, the photoreactions of substrates having methyl groups on a vinyl group gave only unsaturated cyclization products. Further investigations into the detailed mechanism is currently underway in our laboratory.

Table 3. Photoreaction of *N*-(ω-Alkenyl)-2-chloropyrrole-3-carbaldehydes[a]



entry	substrate	time (h)	convn[b] (%)	yield[c] (%)			
1	**1p**	4	98	**2p**	63	**3p**	32
2	**1q**	4	98	**2q**	81	**3q**	16
3	**1r**	4	96	**2r**	6	**3r**	83

[a] 0.3 mmol of **1p−r** was dissolved in acetone (20 mL). The solution was irradiated at $\lambda \geq 300$ nm with a high-pressure mercury lamp (500 W) under argon atmosphere at ambient temperature. [b] Conversion was calculated on the basis of substrate. [c] Yield of isolated product based on consumed substrate.

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Supporting Information Available: Experimental procedures, solubility data, spectroscopic data, ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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