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Stereoselective preparation of methylenecyclobutane-fused angular tetracyclic spiroindolines via photosensitized intramolecular [2+2] cycloaddition with allene

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ABSTRACT

Irradiation of 3-(hexa-4,5-dienyl)indole derivatives in the presence of 3′,4′-dimethoxyacetophenone by a high-pressure mercury lamp through Pyrex glass gave the corresponding [2+2] cycloaddition products stereoselectively in high yields. The major product was a methylenecyclobutane-fused angular tetracyclic spiroindoline derivative produced by the [2+2] cycloaddition through a parallel orientation. The minor product was a hexahydromethanocarbazole derivative through a crossed orientation. Electron-withdrawing substituents, such as acyl or alkoxycarbonyl, on the indole nitrogen were suitable for this reaction.

Indoline-fused polycyclic compounds are frequently seen in bioactive natural products, and they have also attracted much attention as typical structural motifs in several useful pharmaceuticals [1–3]. Novel fused cyclic indoline frameworks are of interest in bioactive screening for new pharmaceutical candidates [4–7]. To date, a number of synthetic methods have been reported for this important class of compounds, whereas potential methods for synthesizing cyclobutane-fused indolines have been much less explored [8–17].

The [2+2] photocycloaddition between 1-acylindoles and substituted ethenes is known to proceed under the sensitization of acetophenone with Pyrex-filtered irradiation (>300 nm) to yield cyclobutane-fused indolines [18]. These reactions can also be performed with 1-aroylindoles in the absence of the sensitizer [18]. From a synthetic point of view, an intramolecular dearomatizing [2+2] cycloaddition of indole derivatives seems to be the most straightforward method to construct the cyclobutane-fused indolines [19]. In fact, intramolecular [2+2] photocycloadditions have been investigated by tethering the alkene to the acylsubstituent of the indoles [20]. This strategy gave the [2+2] adducts regio- and stereoselectively, while the resulting cyclobutane ring often did not have any functional groups useful for further molecular transformation (Scheme 1, top) [21,22]. More recently, You and collaborators reported an intramolecular dearomatization of indole derivatives based on visible-light-promoted [2+2] cycloaddition via an energy transfer mechamism [23]. This elegant method provides a rare example of indole functionalization by exploiting visible-light-induced reactivity; however, the reaction requires 2-arylindoles in many cases that have $\Delta G(T_1 - S_0)$ values appropriate for the visible-light-excited energy transfer system.

In the course of our investigation on the photochemistry of 5-membered heteroaromatic compounds [24], we recently disclosed that irradiation of 1-(hexa-4,5-dienoyl)indole derivatives in the presence of an aromatic ketone, particularly 3′,4′-dimethoxyacetophenone, by a high-pressure mercury lamp through Pyrex glass gave all-*cis*-fused methylenecyclobutane-containing compounds through [2+2] cycloaddition [25]. To the best of our knowledge, photochemical [2+2] cycloaddition between indole and allene has not been reported previously [26]. Prompted by this result, we envisaged that installation of the allene moiety on the C3 side chain of indoles instead of the side chain on the indole nitrogen would lead to various angular tetracyclic spiroindolines accompanied by inversion of the regioselectivity with respect to the allene moiety (Scheme 1, bottom). We report herein the novel photocyclization of 3-(hexa-4,5-dienyl)indole derivatives sensitized by 3′,4′-dimethoxyacetophenone, which yields methylenecyclobutane-fused angular tetracyclic indoline derivatives in a highly stereoselective manner.

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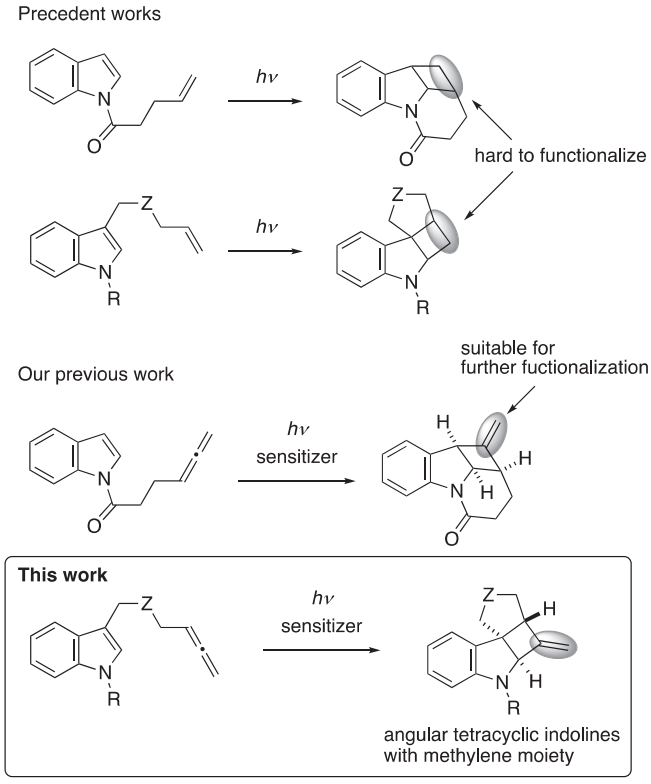


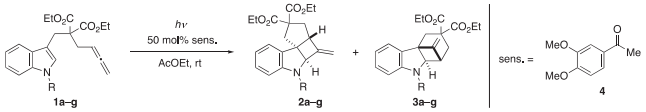
Scheme 1. Photochemical [2+2] cycloaddition of indoles.

Our investigation began with elucidating the effect of the nitrogen protecting group on the reaction. We chose a series of indole derivatives **1** linked with an allene moiety at the C3 position through diethylmalonate due to their ease of preparation. Referring to our previous result [25], we carried out reactions of **1a**–**g** sensitized by 3′,4′-dimethoxyacetophenone (**4**, 50 mol%) in ethyl acetate under irradiation by a high-pressure mercury lamp through Pyrex glass (Table 1). Gratifyingly, our initial attempt to irradiate the *N*-acetyl derivative **1a** gave the expected [2+2] cycloaddition product **2a** (through parallel orientation) in 71% yield accompanied by a small amount of hydrocarbazole-type product **3a** (through crossed orientation) (entry 1). It should be noted that each isomer was obtained as a diastereomerically pure form. The relative configurations of **2a** and **3a** were determined by NOE experiment. Next, the acetyl group was replaced with a propanoyl group with the expectation that the chromatographic separation of the regioisomers would be easier. Since the insufficient recovery of the sensitizer **4** (44%) and formation of unidentified messy products in entry 1 implied an undesirable side reaction that proceeded after the desired reaction was complete, we shortened the irradiation time in the subsequent experiments.

Thus, the reaction with **2b** in the same manner gave the corresponding addition products in improved yields (entry 2). The sensitizer **4** was recovered quantitatively in this case. A substrate protected with Boc group **1c** afforded the product in nearly quantitative yield (entry 3). Unfortunately, separation of the products **2c** and **3c** was not achievable, and these compounds gave a broadened ^{1}H NMR spectrum likely due to slow movement around the Boc moiety. Since these properties of **2c** and **3c** made studying the product difficult, we replaced the Boc group with a methoxycarbonyl group (Moc) and attempted the reaction. Irradiation of **1d** under the same conditions afforded a nice result, comparable to that by irradiation of **1c** (entry 4). In this case, separation of the regioisomer **2d** and **3d** was possible by repeated preparative thin layer chromatography. The reaction was significantly retarded in the absence of the sensitizer **4** (entry 5). The reaction with the sulfonamide derivative **1e** resulted in complete decomposition, giving no characterizable product (entry 6). The reaction with non-protected indole **1f** and Me-protected **1g** was quite sluggish and caused gradual decomposition of the starting material and the sensitizer (entries 7 and 8). We checked the stability of the major product **2d** by irradiating isolated **2d** under the same irradiation conditions, and observed very little decomposition of **2d** was observed (Scheme 2). Based on these results, we selected the Moc group as the protecting group of choice in this reaction.

With a suitable protecting group in hand, we next explored the reaction using a variety of indole derivatives (Table 2). Some of the reactions shown in Table 2 were carried out in a photochemical reaction vessel for internal irradiation. The reactions were

Table 1
Screen of the nitrogen protecting group.[a]



Entry	Substrate	R	Time (min)	Yield (%)[b]		Recovery (%)[b]	
				2	**3**	**1**	**4**
1	**1a**	Ac	60	71	9	0	44
2	**1b**	COEt	45	76	19	0	100
3	**1c**	Boc	45	>99 (86:14)[c]		0	98
4	**1d**	Moc[d]	45	84	12	0	96
5[e]	**1d**	Moc[d]	45	9 (83:17)		87	–
6	**1e**	Ts	60	Decomposition		[f]	[g]
7	**1f**	H	45	Trace		75	41
8	**1g**	Me	45	30	[h]	34	46

[a] All reactions were carried out using 0.10 mmol of **1a**–**g** in a Pyrex test tube by external irradiation with a high-pressure mercury lamp at a concentration of 10 mM.
[b] Isolated yield or recovery.
[c] Chromatographic separation of **2c** and **3c** was quite difficult.
[d] Moc = methoxycarbonyl.
[e] The reaction was carried out in the absence of the sensitizer. The products were not separated.
[f] Not quantified, but only a small amount was recovered.
[g] Not quantified, but almost all the sensitizer remained.
[h] Not clearly detected in ^{1}H NMR analysis.

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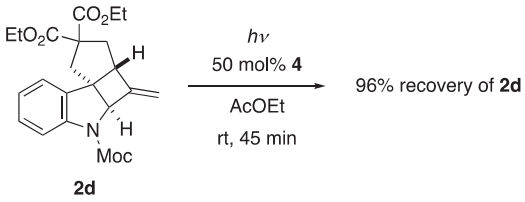


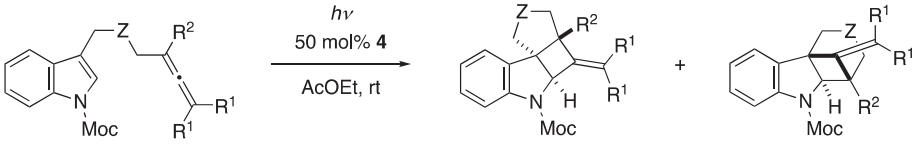
2d

Scheme 2. Irradiation to isolated **2d**.

discontinued as soon as possible after consumption of the starting materials. The reaction with **1d** under internal irradiation at a concentration 5-times higher than that of the initial study proceeded as well (entries 1 and 2). A 1 mmol scale reaction for **1d** was performed without problem to afford the products in good yields (entry 3). The amount of the sensitizer **4** could be reduced to 20 mol% with a slight sacrifice of the yield (entry 4). The sensitizer **4** was recovered almost quantitatively in each case. The reaction also worked well when the allene moiety was substituted by a methyl group. Irradiation of a substrate with two terminal methyl groups **5a** gave the [2+2] adducts in a relatively large population of the cross-type product **7a** (entry 5). When indole **5b**, which had a methyl group at the internal allenyl carbon, was irradiated under the typical conditions, the cycloaddition products **6b** and **7b** were obtained in comparable yields (entry 6). It is worth mentioning that a sterically congested framework that contains contiguous quaternary sp^3 carbons can be constructed by this reaction. We were able to employ linker moieties other than a diethyl malonate moiety. Thus, compounds linked with Boc-protected nitrogen or oxygen (**5c**, **5d**) gave the corresponding products in moderate to high yields (entries 7 and 8). In the case of substrates with a heteroatom linker, parallel-type adducts (**6c**, **6d**) were produced in a population larger than that of **1d**. This is likely because the more strained transition state leading to the cross-type adduct is made unfavorable by having a C—N or C—O bond shorter than the C—C bond.

In order to show the versatility of this method for the construction of a fused indoline framework, we attempted a reaction with a substrate that had a carbon linker other than the malonate moiety. Irradiation to a secondary alcohol substrate **8a** under the typical conditions afforded four addition products in 96% total yield: **9a** (46%), **10a** (26%), **11a** (15%), and **12a** (9%) (Scheme 3). The parallel (**9a**+**10a**)/cross (**11a**+**12a**) ratio was somewhat smaller than that of the reaction with **1d**. The diastereomeric selectivity with respect to the stereochemical relationship between the hydroxy group and the cyclobutane moiety was around 2:1. When TBS ether **8b** was irradiated in the same manner, the corresponding products were obtained in almost the same population as in the case of **8a**. Unexpectedly, the steric hindrance around the hydroxy moiety scarcely affected the product distribution.

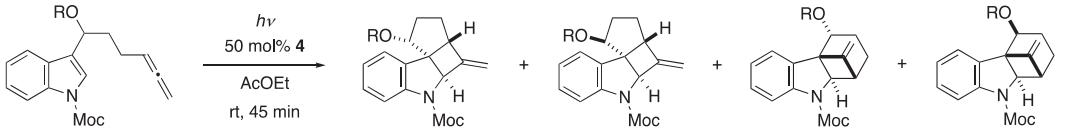
Table 2
Substrate screen.



1d, **5a–d** **2d**, **6a–d** parallel **3d**, **7a–d** cross

Entry	Substrate	Z	Conditions[a]	Concentration (mM)	R^1	R^2	Parallel (%)[b]	Cross (%)[b]
1	**1d**	$C(CO_2Et)_2$	A	10	H	H	**2d**, 84	**3d**, 12
2	**1d**	$C(CO_2Et)_2$	A	50	H	H	**2d**, 85	**3d**, 12
3	**1d**	$C(CO_2Et)_2$	B[c]	50	H	H	**2d** and **3d**, 98 (85:15)[d]	
4	**1d**	$C(CO_2Et)_2$	A[e]	10	H	H	**2d** and **3d**, 94 (85:15)[d]	
5	**5a**	$C(CO_2Et)_2$	B	10	Me	H	**6a**, 63	**7a**, 32
6	**5b**	$C(CO_2Et)_2$	A	10	H	Me	**6b**, 73	**7b**, 13
7	**5c**	NBoc	B	10	H	H	**6c** and **7c**, 95 (93:7)[d]	
8	**5d**	O	A	10	H	H	**6d**, 97	**7d**, <2%[f]

[a] A: The reaction was carried out using 0.10 mmol of the substrate in a Pyrex test tube by external irradiation with a high-pressure mercury lamp for 45 min. B: The reaction was carried out using 0.10 mmol of the substrate in a Pyrex reaction vessel for photochemical reaction by internal irradiation with a high-pressure mercury lamp for 30 min.
[b] Isolated yield.
[c] The reaction was carried out using 1.0 mmol of **1d**.
[d] Separation of the regioisomeric products was not carried out.
[e] The reaction was carried out using 20 mol% of **4**.
[f] Detected by ^{1}H NMR analysis, but not fully characterized.



8a (R = H) **9a** 46% **10a** 26% **11a** 15% **12a** 9%
8b (R = TBS) **9b** 45% **10b** 22% **11b** 16% **12b** 8%

Scheme 3. Irradiation to secondary alcohol derivatives **8a** and **8b**.

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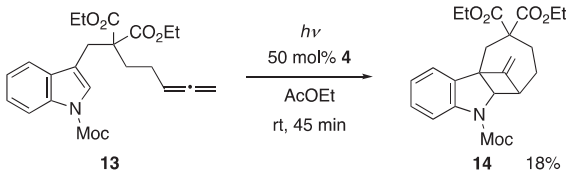

Scheme 4. Photochemical [2+2] cycloaddition of **13**.

To obtain information on the significance of the linker length, we carried out a reaction with allenyl indole **13**, which has a linker moiety longer than **1d** by a methylene (Scheme 4). The reaction was sluggish and gave a hardly separable mixture of many products. The predominant product was a cross-type adduct **14** (18% isolated yield), and the **13** was recovered in 40% yield. The formation of a parallel-type product was not ruled out due to the complexity of the mixture, but such a product would have been produced in only a small amount, if any.

Though the mechanism underlying this reaction was not clarified at this stage, we presumed that the reaction followed a pathway similar to that discussed in the literature on photosensitized [2+2] cycloaddition between indoles and alkenes, which includes triplet sensitization of the substrates (**1**, **5**, **8**, and **13**) by **4** followed by ring formation via a biradical intermediate [25,27].

In conclusion, we have developed a method for the construction of fused tetracyclic indoline frameworks through the [2+2] photochemical cycloaddition reaction of 3-(hexa-4,5-dienyl)indole derivatives under effective sensitization with 3′,4′-dimethoxylacetophenone. The reaction with appropriate substrates proceeds cleanly in less than an hour to afford methylenecyclobutane-fused indolines that are suitable for further functional group manipulation around the four-membered ring. The perfect diastereoselection in the methylenecyclobutane formation is noteworthy.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151229.

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