Stereoselective Construction of Cycloheptene-fused Indoline Frameworks through Photosensitised Formal [5+2] Cycloaddition

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Key words

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Abstracts

Irradiation of 1-acylindole derivatives that possess a vinylcyclopropane moiety at the end of the acyl side chain by a high-pressure mercury lamp through Pyrex glass under sensitization of an aromatic ketone gave the corresponding cyclised products stereoselectively in high yields. The distribution of the products was highly dependent on the substituents on the cyclopropane ring. In the case of a simple cyclopropane, the product was a mixture of ring-expanded cycloheptene-fused indoline and all-cis-fused cyclopropylcyclobutane-fused indoline through [2+2] cycloaddition, while cycloheptene-fused indolines were predominantly produced via formal [5+2] cyclisation in the case of substituted cyclopropanes. In particular , the product selectivity was substantially high in the case of silylcyclopropane.

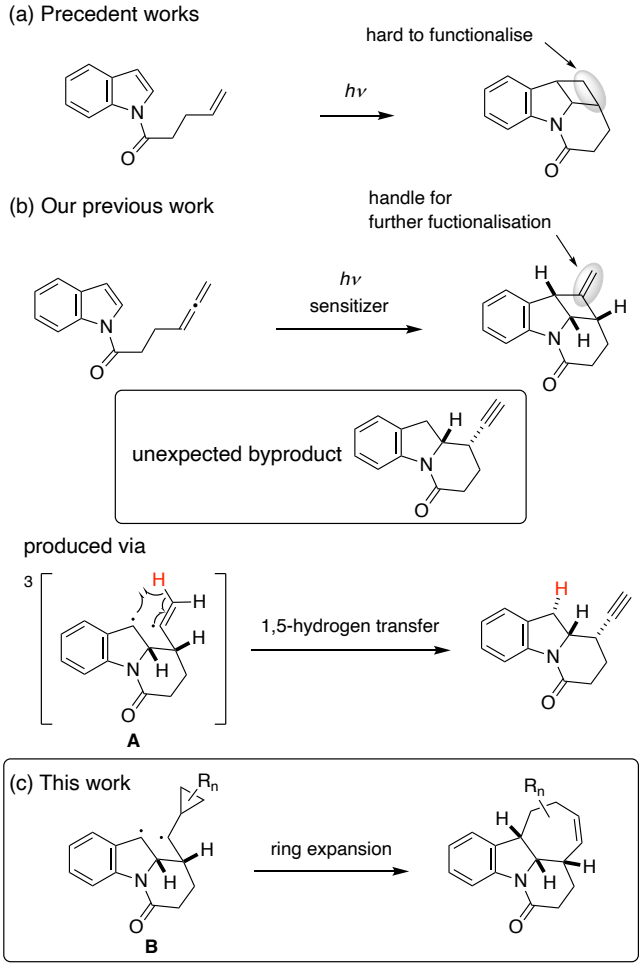
Introduction

Indoline-fused cyclic compounds form an important class of bioactive natural products, and they are also typical structural motifs in several useful organic compounds exemplified by pharmaceuticals.[1] Novel fused cyclic indoline frameworks frequently attract interest in bioactive screening for new pharmaceutical candidates.[2] To satisfy the demands for such frameworks, new methods of synthesizing diverse indoline derivatives are in demand. Up to now, a number of synthetic methods have been reported for indoline-fused cyclic compounds, whereas those that contain a cycloheptane ring are much less explored.[3,4]

Photocycloaddition is an attractive method for the construction of cyclic frameworks, because a complex ring system that is hardly achievable via thermochemical reaction can be obtained from a relatively simple molecule in short steps. The [2+2] photocycloaddition using 1-acylindoles as

components is a common transformation and has been extensively examined as a route to the cyclobutane-fused compounds.[5–7] 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 polycyclic indoline frameworks. In fact, intramolecular [2+2] photocycloadditions by UV irradiation have been investigated by tethering the alkene to the acyl substituent of the indoles.[8,9] More recently, the reaction under visible light irradiation was extensively studied by using an Ir complex photocatalyst.[10,11] These strategies gave the [2+2] adducts in a regio- and stereoselective manner, while the resulting cyclobutane ring often did not have any functional groups that were useful for further molecular transformation (Scheme 1, a). In the course of our investigation on the photochemistry of 5-membered heteroaromatic compounds,[12] we recently found 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 – which provide a clue for further transformation – through [2+2] cycloaddition, (Scheme 1, b).[13] We were intrigued by the unexpected, simultaneous formation of terminal alkyne in this reaction. The mechanism of the formation of this alkyne was investigated by a deuterium-labelled experiment and turned out to involve intramolecular 1,5-hydrogen atom transfer of the triplet biradical intermediate **A**.[13c] This result also shows that the intermediate **A** has a sufficiently long lifetime to allow the hydrogen transposition. The rate constant of the 1,5-hydrogen shift is estimated to be approximately 10^6–10^7 s^{-1} in the literature.[14–16]

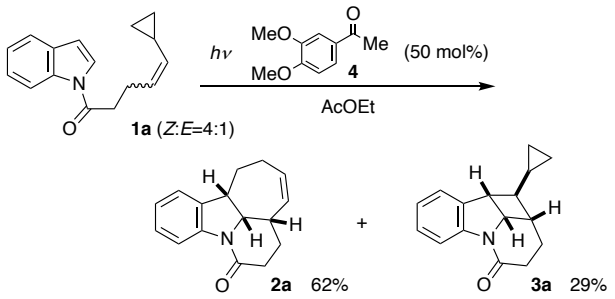
Prompted by these experimental results, we envisaged that replacement of the allene terminal with a vinylcyclopropane moiety would lead to formation of cycloheptene ring via cyclopropane ring-opening, which is sufficiently faster (10^8–10^9 s^{-1})[17] than the 1,5-shift and could occur in the lifetime of the triplet intermediate **B** (Scheme 1, c). Quite recently, You and collaborators have reported a similar transformation by visible-light-induced dearomative cyclisation of indoles with vinylcyclopropanes.[18] Their elegant method provides a rare example of indole dearomative functionalization by using visible-light-induced reactivity; however, in many cases the reaction requires 2-aryl- or 2-alkoxycarbonylindoles that have $\Delta G(T_1\text{-}S_0)$ values appropriate for the visible-light-excited energy transfer system. They focused their investigation mainly on 1,1-bis(alkoxycarbonyl)cyclopropane, and the substituent effect on the cyclopropane was not sufficiently elucidated. We report herein our independent findings on the relationship between the product distribution and the substitution of the cyclopropane ring in the photocycloaddition of vinylcyclopropane-tethered indole derivatives.



Scheme 1. Photochemical dearomative cycloaddition of 1-acylindoles to give polycyclic indolines.

Results and Discussion

Our investigation commenced with photocycloaddition of the simplest vinylcyclopropane derivative **1a**. Referring to our previous results,[13c] a solution of 1-acylindole **1a** (*Z*:*E*=4:1) and 3',4'-dimethoxyacetophenone (**4**, sensitizer, 50 mol%) in ethyl acetate (degassed by freeze–thaw cycles before use) was irradiated by a high-pressure mercury lamp through Pyrex glass (Scheme 2). To our delight, the expected cycloheptene-fused tetracyclic indoline **2a** was obtained in 62% yield accompanied with product **3a**, which was formed by ring-closure before cyclopropane ring-opening. The relative configuration of **2a** and **3a** was determined by conventional NOE experiments. We detected small amounts (less than 1-2%) of by-products that were possibly stereoisomers of the main products, but they were not fully characterised due to their scarce amounts. Irradiation of isolated **3a** under the same reaction conditions for 4 h did not give **2a** at all, resulting in recovery of **3a** (94%). This result clearly ruled out the possibility that ring-expanded product **2a** was formed via [2+2] product **3a**. Though solvents suitable for the dearomative cycloaddition have already been found in our previous study,[13c] several reactions in representative solvents were attempted in the expectation of improving the **2a**/**3a** ratio (Table 1).



Scheme 2. Photochemical formal [5+2] cycloaddition of 1-acylindole **1a**.

Table 1 Solvent effect on the reaction.

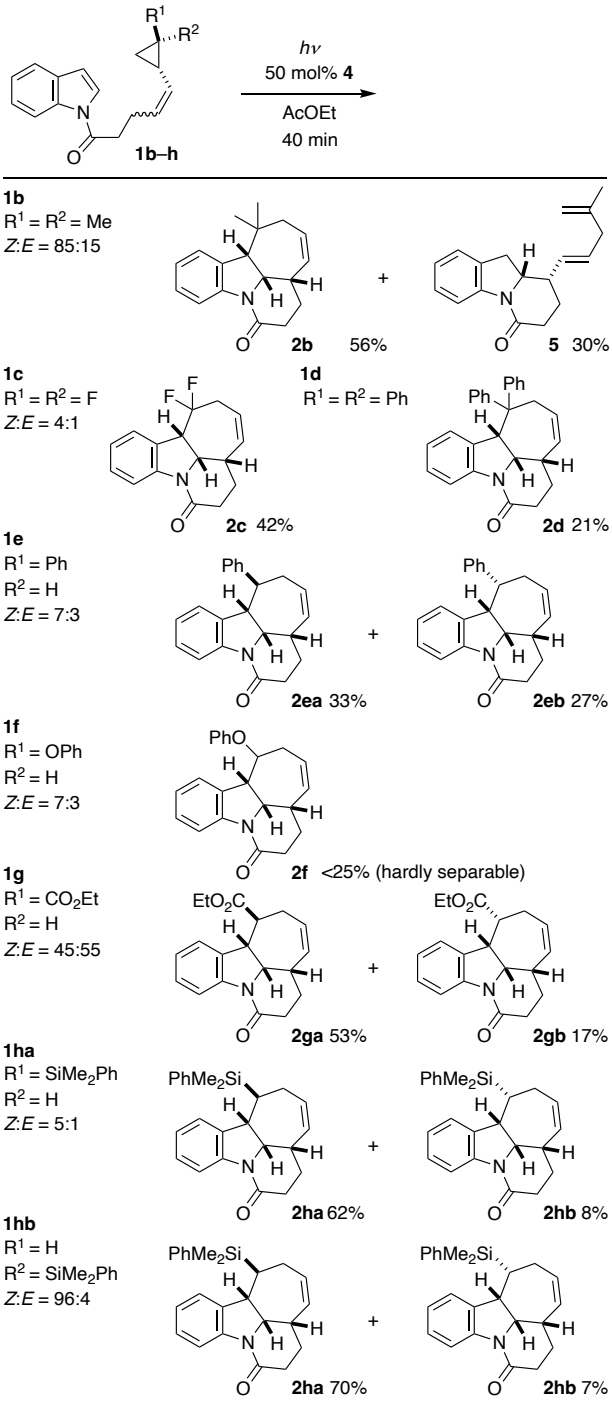
Entry	Solvent	**2a** (%)[c]	**3a** (%)[c]
1[a]	AcOEt	62	29
2[b]	MTBE	57	34
3[b]	Benzene	61	34
4[b]	CH_3CN	56	30
5[b]	CH_3OH	55	26

[a] The reaction was performed using **1a** on a 0.2 mmol scale in a Pyrex reaction vessel for photochemical reaction by internal irradiation for 40 min with a high-pressure Hg lamp at a concentration of 10 mM. [b] The reaction was performed using **1a** on a 0.1 mmol scale in a Pyrex test tube by external irradiation for 1 h. [c] Isolated yields.

Disappointingly, the yields of **2a** and **3a** were almost the same in the attempted reactions, implying that the product distribution was determined mainly by the intrinsic property of the substrates and would be difficult to improve by tuning the reaction conditions.

Then we turned our attention to promoting the cyclopropane ring-opening by stabilising the ring-opened radical (Scheme 3). The reactions shown in Scheme 3 were carried out in a photochemical reaction vessel for internal irradiation. The reactions were discontinued as soon as possible after consumption of the starting materials (40 min in many cases). The substituents at the cyclopropane ring of the side chain had significant influence on the reaction as expected. The reactions of **1b** (gem-dimethyl) gave a yield of the [5+2]-type products comparable to that of **1a**. The [2+2] product was not obtained in this case. Instead, a skipped diene **5**, which was likely formed via 1,8-hydrogen transposition similar to that of Scheme **1b**, was obtained in 30% yield. We surmised that ring opening of the *gem*-dimethylcyclopropane is too fast (about 10^2 times faster than that without methyl groups)[17a] to allow the formation of the cyclobutane ring as in **3a**, giving the hydrogen-transferred product **5**. This result also suggested that alkyl substitution at the cyclopropane is not suitable for promoting the 7-membered ring formation because it causes this type of hydrogen translocation. Irradiation to **1c** (gem-difluoro) gave the fluorine-containing [5+2]-type product **2c** in moderate yield, which is interesting from the viewpoint of medicinal chemistry.[19] The [2+2] product was not detected in this case. With the intention of increasing the cyclopropane ring-opened radical, gem-diphenyl derivative **1d** was irradiated. Contrary to our expectation, the desired product **2d** was produced only in 21% yield with the formation of uncharacterisable polymeric by-products, which were likely caused by retarded radical termination due to the too high radical stability. When monophenyl

substrate **1e** was irradiated in the same manner, moderate yields of the [5+2] adducts were obtained with almost 1:1 diastereoselectivity. The reaction also proceeded in the case of **1f**, which had a phenoxy group at the cyclopropane, but in this case the products seemed unstable and the reaction mixture was relatively complex. The [5+2] product with unsatisfactory purity was isolated in less than 25% yield. Though a diastereomer was obtained predominantly, configuration at the phenoxy position was not determined due to overlapping of the important signals. Introduction of an electron-withdrawing ester moiety (**1g**) improved the yield of the [5+2] product with a diastereomeric ratio of about 3:1. Compounds **1e**, **1f**, **1g** were prepared as single diastereomers with respect to the cyclopropane moiety as shown in Scheme 3. We succeeded in obtaining a single crystal of **2ga** suitable for X-ray crystallographic analysis to confirm its structure unambiguously as shown in Fig. 1 (CIF in the Supporting Information). Expecting that the use of a more sterically demanding substituent would improve the diastereoselectivity, we chose a silyl group that is known to stabilize radicals at its alpha position.[20] Employing a silyl group has the additional advantage that this group has no potential to cause hydrogen transposition as was observed in the case of **1b**. To allow for the further functional group manipulation of the products, we selected the dimethylphenylsilyl group. Irradiation of **1ha** afforded the [5+2] cycloaddition product in 70% yield and improved the diastereomeric ratio to 8:1 as expected. A diastereomeric substrate **1hb** gave somewhat better yield of the products and diastereoselectivity (10:1). The stereoselectivity was easily understood as the bulky dimethylphenylsilyl group favouring the convex position. Since **1ha** and **1hb**, which have different configurations both at the cyclopropane and at the alkene moiety, gave quite similar results, stereochemistry at the side chain seemed to be less important for the reaction. It should be noted that the product **2ha** could be transformed to a cycloheptanol derivative **6** with complete retention of the configuration at the carbon where the silyl group was located via Fleming-Tamao oxidation (Scheme 4).[21,22]



Scheme 3. Effect of the substituents at the cyclopropane on the reaction. The reaction was performed using **1** on a 0.2 mmol scale in a Pyrex reaction vessel for photochemical reaction by internal irradiation with a high-pressure Hg lamp at a concentration of 10 mM. Isolated yields.

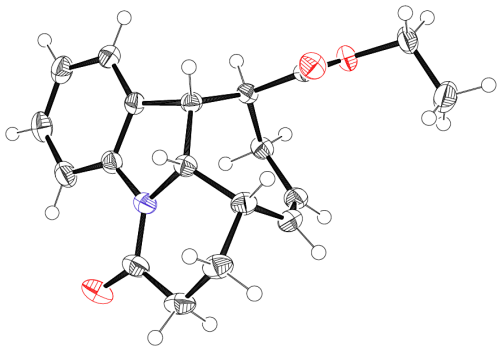
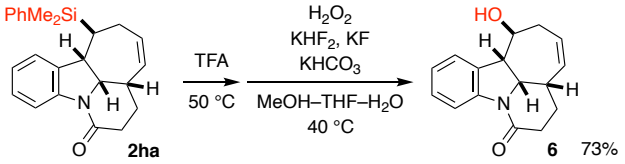


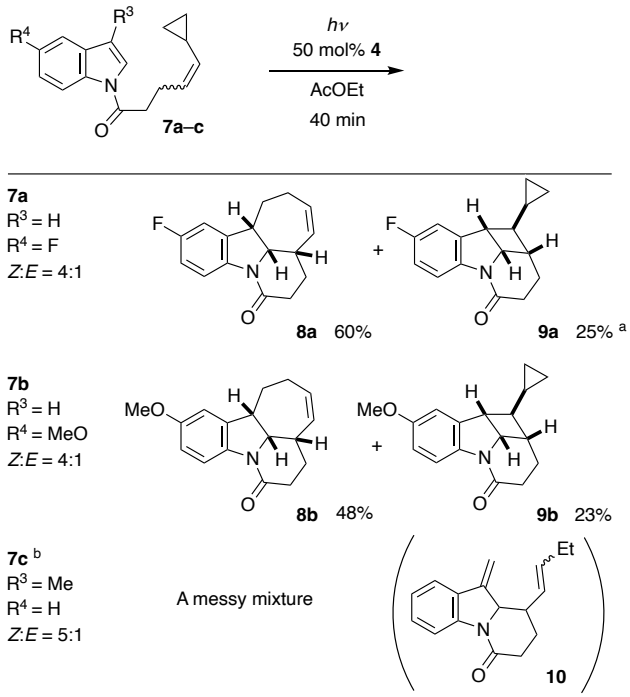
Figure 1. ORTEP drawing of **2ga**.



Scheme 4. Conversion of the silylated product to an alcohol with retention of the configuration.

This silylcyclopropane ring expansion/stereospecific oxidation sequence provides a useful method for stereoselective preparation of functionalised polycyclic indoline derivatives.

Next, we examined the reaction using several substrates substituted at the indole core (Scheme 5). The reaction of **7a**, in which the aromatic ring was substituted by an electron-withdrawing group, gave almost the same result as that of **1a**, giving moderate yields of the cyclized products **8a** and **9a**, respectively. On the other hand, in the case of **7b**, in which the aromatic ring was substituted by an electron-donating group, the yields of the cyclized products were somewhat decreased likely due to slight increase of yellow-coloured uncharacterisable by-products. When substrate **7c** substituted with a methyl group at 3-position was employed, the reaction gave a messy mixture, in which we could not find any ^{1}H NMR signals specific to [5+2] product. The starting material was not consumed completely despite prolonged irradiation. A considerable amount of compound that seemed to be **10**, which was likely produced through hydrogen transposition from the methyl group to the ring-opened radical, was obtained as a mixture with **4** and other compounds after separation by silica gel preparative TLC. Unfortunately, full characterization of **10** was not achievable due to difficulty in purification and its instability.



Scheme 5. Effect of the substituents at the indole core on the reaction. The reaction was performed using **1** on a 0.2 mmol scale in a Pyrex reaction vessel for photochemical reaction by internal irradiation with a high-pressure Hg lamp at a concentration of 10 mM. Isolated yields. [a] A small amount of inseparable **4** was contained. [b] The reaction mixture was irradiated for 60 min because the starting material persisted.

Conclusion

We have developed a method for constructing tetracyclic indoline frameworks that contain a cycloheptene ring by photochemical formal [5+2] cycloaddition of 1-(cyclopropylalkenyl)indoles using a combination of photochemical cycloaddition and cyclopropane ring-opening. 3',4'-Dimethoxylacetophenone acts as an effective photosensitizer in this reaction. The reaction has a broad substrate scope, affording a range of functionalised cycloheptene-fused indolines. Especially in the case of substrates with silylcyclopropane, the reaction proceeds in a highly stereoselective manner to give the silyl-substituted product in good yields. The silylated compound **2ha** can be readily transformed to alcohol **6** with retention of the configuration by using Fleming-Tamao oxidation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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