CL-170937 Received: October 5, 2017 | Accepted: November 13, 2017 | Web Released: January 11, 2018

Efficient Approach to Medium-sized Cyclic Molecules Containing (*E*)-Alkene via *Z* to *E* Photochemical Isomerization in the Presence of $AgNO_3$-impregnated Silica Gel

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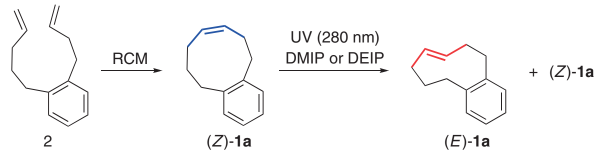
Efficient synthesis of medium-sized cyclic molecules containing an (*E*)-alkene was performed via the highly (*E*)-selective photochemical isomerization of the (*Z*)-isomer, facilitated by $AgNO_3$-impregnated silica gel.

Keywords: Photochemical isomerization | Medium-sized cyclic molecules | $AgNO_3$-impregnated silica gel

Medium-sized cyclic molecules containing an alkene group often form the key skeleton of a variety of natural products. Among them, (*E*)-alkene-containing derivatives have aroused particular interest in structural organic chemistry because of their unique stereochemical properties and reactivity.[1] Therefore, a variety of approaches for the synthesis of (*E*)-cycloalkenes and their derivatives [(*E*)-cyclic molecules] have been attempted.[2] However, the lower thermodynamic stability of the (*E*)-cyclic molecules relative to that of the (*Z*)-isomer causes difficulty in the (*E*)-selective synthesis by common approaches. For example, one of the most efficient methods for constructing medium-sized cyclic skeletons, ring-closing-olefin-metathesis (RCM), generally affords the (*Z*)-cyclic molecules as the predominant product.[3,4] To address the issue of obtaining the (*E*)-cyclic molecules, photochemical isomerization of (*Z*)-isomer to the (*E*)-isomer is a prospectively efficient solution.[5] Indeed, we previously synthesized planar-chiral medium-sized cyclic molecules with the (*E*)-alkene moiety, e.g., (*E*)-4-[7]orthocyclophene [(*E*)-**1a**], where the acyclic diene **2** was subjected to RCM to yield (*Z*)-**1a**, followed by *Z* to *E* photochemical isomerization by irradiation with UV light (280 nm) in the presence of dimethyl isophthalate (DMIP) or diethyl isophthalate (DEIP) as the photosensitizer.[5c,6,7] As expected, the reaction afforded (*E*)-**1a** in 22% yield, albeit the (*E*)-selectivity was not high [(*E*)-**1a**/(*Z*)-**1a** = 22:78] [see a) in Scheme 1].

More recently, we found that the addition of 10 wt% of $AgNO_3$-impregnated silica gel (10 wt% Ag-silica gel)[8,9] dramatically improved the (*E*)-selectivity of the reaction to (*E*)-**1a**/(*Z*)-**1a** = 89:11 [isolated yield of (*E*)-**1a**: 76%] [see b) in Scheme 1]. This enhancement would be attributed to selective adsorption of the (*E*)-isomer by the Ag-silica gel, where the (*E*)-isomer was efficiently removed from the solution during the photochemical isomerization process, as shown in Figure 1.[10]



a) without Ag silica gel: (*E*)-**1a**/(*Z*)-**1a** = 22:78 (quant)[a]
b) with 10 wt% Ag silica gel: (*E*)-**1a**/(*Z*)-**1a** = 89:11 (88%)[a]

[a] Combined yields of (*E*)-**1a** and (*Z*)-**1a**. Determined by GC analysis.

Scheme 1. Synthesis of (*E*)-**1a** from **2**.

To clarify the generality of the developed method, we examined its application to other (*E*)-cyclic molecules. Herein, we provide the details of our attempts.

At the outset, we examined the *Z* to *E* isomerization of cyclooctene (**3**), a representative medium-sized alkene.[2b] The reaction was performed in a three-necked round-bottomed Pyrex flask equipped with a cylindrical Teflon-coated magnetic stir bar. A side neck was capped with a rubber septum, the center neck was fitted with a Teflon connecter holding a quartz photoinlet adapter, and the other neck was fitted with a three-direction cock connected to an argon balloon (Figure 2). The flask was charged

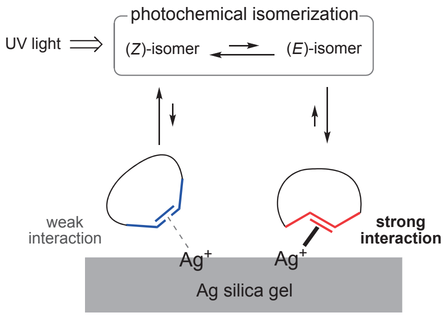


Figure 1. Concept of photochemical isomerization in the presence of Ag-silica gel.

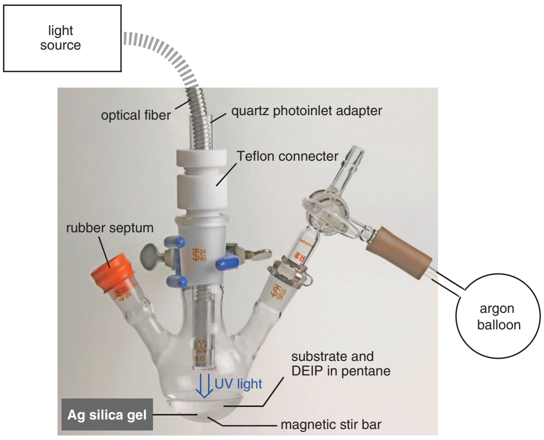
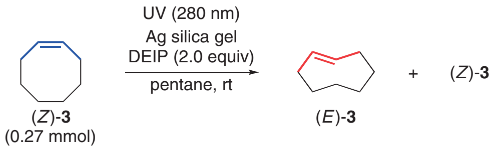


Figure 2. Reaction apparatus for photochemical isomerization in the presence of Ag silica gel.

Table 1. Photochemical isomerization of (*Z*)-**3**



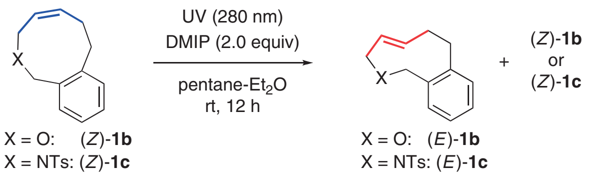
Entry	Ag silica gel		Time /h	(*E*)-**3**/(*Z*)-**3**	Yield /%[a]
	$AgNO_3$-content /wt%	Amount /mg			
1	—	none	42	23:77	87
2	5	400	42	75:25	81
3	10	400	42	93:7	81
4	20	400	42	77:23	73
5	10	500	42	97:3	88
6	10	500	24	67:33	72

[a]Combined yields of (*E*)-**3** and (*Z*)-**3**. Determined by GC analysis.

with Ag-silica gel and a solution of (*Z*)-**3** and DEIP (2.0 equiv) in pentane.[11] UV light (280 nm) generated by an Asahi Spectra MAX-301 was introduced into the flask through the optical fiber inserted into the photoinlet adapter. The reaction mixture was gently stirred at ambient temperature. After adequate photoirradiation, aminopropylated silica gel and Et_2O were added to the reaction mixture for the liberation of **3** from the Ag-silica gel, and the resulting reaction mixture was washed with Et_2O to afford the crude product.

The reactions successfully provided (*E*)-**3** as the predominant product (Entries 2–6, in Table 1);[12] this is in sharp contrast with the reaction without the Ag-silica gel, which provided (*Z*)-**3** predominantly [(*E*)-**3**/(*Z*)-**3** = 23:77] (Entry 1). To optimize the reaction conditions, we explored the influence of the $AgNO_3$ content and the amount of Ag-silica gel. The reactions were performed with 0.27 mmol of (*Z*)-**3** in the presence of 400 or 500 mg of Ag-silica gel with UV irradiation for 42 h. The reaction with 10 wt% Ag-silica gel (Entry 3) showed higher (*E*)-selectivity than those with 5 or 20 wt% Ag-silica gel (Entries 2 and 4). The highest yield of (*E*)-**3** was achieved with the use of 500 mg of 10 wt% Ag-silica gel (Entry 5). In this case, it was confirmed that (*E*)-**3** was efficiently adsorbed from the reaction solution by the Ag-silica gel, based on GC analysis.[13] On the other hand, a shorter irradiation duration (24 h) provided low (*E*)-selectivity of the product (Entry 6).

The developed protocol is applicable to the synthesis of nine-membered heterocycles containing an (*E*)-alkene, such as planar chiral (*E*)-[7]orthocyclophene **1b** and **1c**.[14] As shown in Scheme 2, the photochemical isomerization in the presence of DMIP without the Ag-silica gel provided (*E*)-**1b** and (*E*)-**1c** as the minor isomer [(*E*)-**1b**/(*Z*)-**1b** = 31:69, (*E*)-**1c**/(*Z*)-**1c** = 26:74]. In sharp contrast, the corresponding reactions with 10 wt% Ag-silica gel provided (*E*)-**1b** and (*E*)-**1c**, predominantly [(*E*)-**1b**/(*Z*)-**1b** = 74:26, (*E*)-**1c**/(*Z*)-**1c** = 64:36] in good yields.[15]

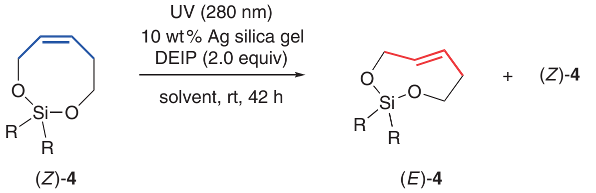


a) without Ag silica gel: (*E*)-**1b**/(*Z*)-**1b** = 31:69 (79%)[a]
(*E*)-**1c**/(*Z*)-**1c** = 26:74 (81%)[a]

b) with 10 wt% Ag silica gel: (*E*)-**1b**/(*Z*)-**1b** = 74:26 (88%)[a]
(*E*)-**1c**/(*Z*)-**1c** = 64:36 (67%)[a]

[a] Combined yield of (*E*)-**1** and (*Z*)-**1**. Determined by ^1H NMR analysis.

Scheme 2. Photochemical isomerization of orthocyclophenes (*Z*)-**1b** and (*Z*)-**1c**.



(*Z*)-**4a** (R = *t*Bu)
solvent: pentane

(*E*)-**4a**/(*Z*)-**4a** = 89:11 (61%)[a]

(*Z*)-**4b** (R = Ph)
solvent: pentane-Et_2O

(*E*)-**4b**/(*Z*)-**4b** = >98:<2 (48%)[a]

[a] Combined isolated yield of (*E*)-**4** and (*Z*)-**4**.

Scheme 3. (*E*)-Selective photochemical isomerization of dialkoxysilane (*Z*)-**4**.

Furthermore, highly strained eight-membered dialkoxysilane (*E*)-**4**[16] with very stable planar chirality was synthesized with excellent (*E*)-selectivity using the developed protocol (Scheme 3). The reaction of (*Z*)-**4a** (R = *t*Bu) provided **4a** in 61% yield with high (*E*)-selectivity [(*E*)-**4a**/(*Z*)-**4a** = 89:11].[15] Moreover, the reaction of (*Z*)-**4b** (R = Ph) provided **4b** with almost perfect (*E*)-selectivity [(*E*)-**4b**/(*Z*)-**4b** in >98:<2] in 48% isolated yield. The study of the significant substituent effect of the R group on the (*E*)-selectivity of the photochemical isomerization is in progress.

In summary, a concise method for the synthesis of medium-sized cyclic molecules containing an (*E*)-alkene group was developed. The key feature of the synthesis is the *Z* to *E* photochemical isomerization in the presence of the Ag-silica gel. The sequential approach with the RCM to provide medium-sized (*Z*)-cyclic molecules and the *Z* to *E* photochemical isomerization may be efficient for a variety of (*E*)-cyclic molecules. Further synthetic applications of this approach are being explored.

This research was supported by JSPS KAKENHI Grants JP16H04113 and JP16H01158 in Middle Molecular Strategy, and the Cooperative Research Program "NJRC Mater. & Dev.". We thank T. Nishi (IMCE in Kyushu Univ.) for assistance with the HRMS measurements.

Supporting Information is available at http://dx.doi.org/10.1246/cl.170937.

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