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ROM–RCM of azabicycloheptene derivatives—Study of products distribution by the substituent on alkyne

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Abstract

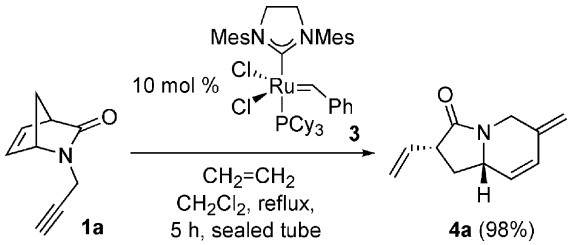
ROM–RCM (ring-opening metathesis and ring-closing metathesis) of azabicyclo[2.2.1]heptene-ynes using the second-generation Grubbs catalyst was investigated. When an azabicycloheptene derivative was exposed to a catalytic amount of a ruthenium carbene complex, pyrrolizidine and indolizidine derivatives were obtained in good yields. The distribution of these products depends on the substituents on the alkyne.

Keywords: Enyne metathesis; Ring-opening metathesis and ring-closing metathesis; Pyrrolizidine; Indolizidine; Ethylene

In the last decade, olefin metathesis has played an important role as a powerful tool for carbon–carbon double bond forming reactions in synthetic organic chemistry [1]. Enyne metathesis, which takes place between a double bond and a triple bond, is a synthetically useful transformation with a large number of recent applications [2]. ROM–RCM is also an attractive reaction because cycloalkenes are rearranged to provide an alternative functionalized cyclic compound [3]. Recently, we have developed ROM–RCM of cycloalkene-ynes under an ethylene atmosphere providing a new cyclic compound containing a triene moiety, or a bicyclic compound having a diene moiety [4]. This method is applied to the synthesis of isoquinoline derivatives from cyclobutene derivatives having an alkyne moiety in a tether by a one-step reaction [5].

In this communication, we report azabicyclo[2.2.1]heptene-ynes **1** using ROM–RCM. Our plan is shown in Scheme 1. The ruthenium methylidene carbene complex should react with an alkene moiety of azabicycloheptene derivative **1** to afford ruthenium carbene complex **I**, which reacts with an alkyne moiety of **I** to give ruthenacyclobutene intermediate **II**. Ring-opening of **II** gives ruthenium carbene complex **III**. If the reaction is carried out under an ethylene atmosphere, the generated ruthenium carbene of **III** should react with ethylene to provide bicyclic compound **2**.

During the course of our investigation of this project, Arjona et al. reported the same ROM–RCM of an azabicycloheptene derivative **1a** (Eq. (1)) [6]. They obtained indolizidine derivative **4a** from **1a** in nearly quantitative yield when a CH_2Cl_2 solution of **1a** and **3** was heated in a sealed tube. We have obtained compound **4a** along with a fair amount of pyrrolizidine derivative when the reaction was carried out in toluene upon heating. The result is interesting because the possibility existed for the formation of either pyrrolizidine or indolizidine derivatives. Thus, we decided to continue further investigation of this reaction, especially, product distribution by the substituent on the alkyne.



(1)

When a CH_2Cl_2 solution of **1a** was stirred in the presence of first- or second-generation ruthenium carbene complex under an ethylene atmosphere at room temperature, none of the product was obtained. Thus, a CH_2Cl_2 solution of **1a** and **3** was refluxed for 5 h, but indolizidine derivative **4a** was not obtained although the round bottom flask equipped with ethylene balloon was used [7]. Next, the solvent was changed for higher reaction temperature. When a toluene solution of **1a** was stirred with 10 mol% of

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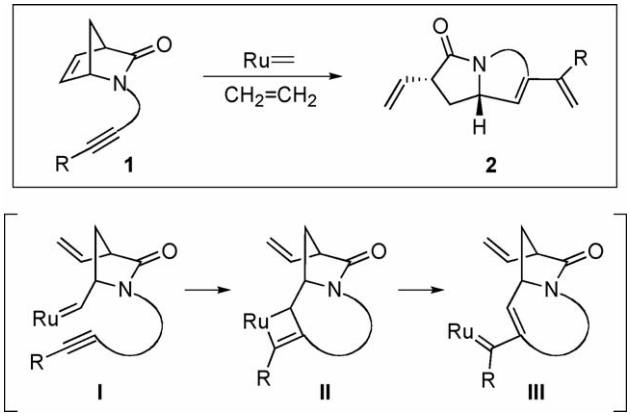
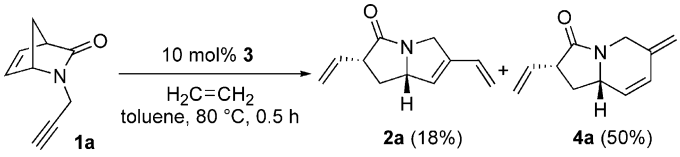


Scheme 1. Plan for one-step synthesis of bicyclic heterocycles.

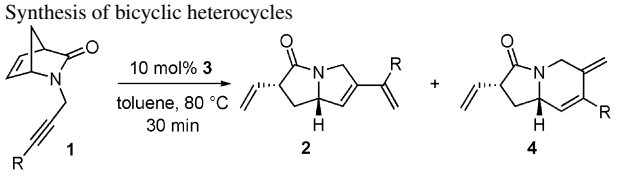
the second-generation ruthenium carbene complex **3** under an ethylene atmosphere at 80 °C for 0.5 h, indolizidine derivative **4a** was obtained in 50% yield along with pyrrolizidine derivative **2a** in 18% yield (Eq. (2)).



(2)

Subsequently, we examined the substituent effect on the alkyne. When the reaction of **1b** (R = Me) was carried out under our optimized conditions (in toluene at 80 °C), pyrrolizidine derivative **2b** was obtained in 30% yield along with indolizidine derivative **4b** in 40% yield (Table 1, entry 1). It was interesting that ethylene is required for this reaction because compound **1b** did not provide the desired products under argon atmosphere although starting material **1b** was consumed (entry 2) [8]. A change of the product distribution was observed when compound **1c** having the phenyl group on the alkyne was used for this reaction, and pyrrolizidine derivative **2c** was obtained as a major product (entry 3). To examine the electronic effect of the

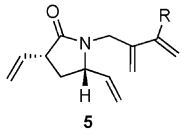
Table 1
Synthesis of bicyclic heterocycles



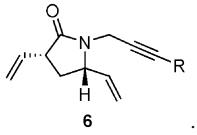
Entry	R	Atmosphere	**2** (%)	**4** (%)
1	Me (**1b**)	CH_2=CH_2	30	40
2	Me (**1b**)	Ar	0	0
3	Ph (**1c**)	CH_2=CH_2	56	15
4[a]	C_6H_4-*p*-OMe (**1d**)	CH_2=CH_2	40	21
5	C_6H_4-*p*-CO_2Et (**1e**)	CH_2=CH_2	34	18
6	TMS (**1f**)	CH_2=CH_2	51	23
7[b]	TIPS (**1g**)	CH_2=CH_2	31	–

TIPS = Si(^{i}Pr)$_3$.

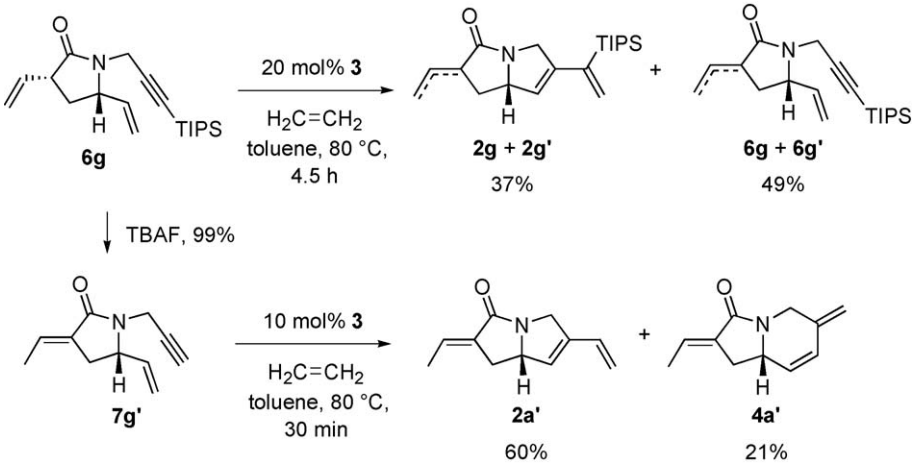
[a] **5d** was obtained in 12% yield



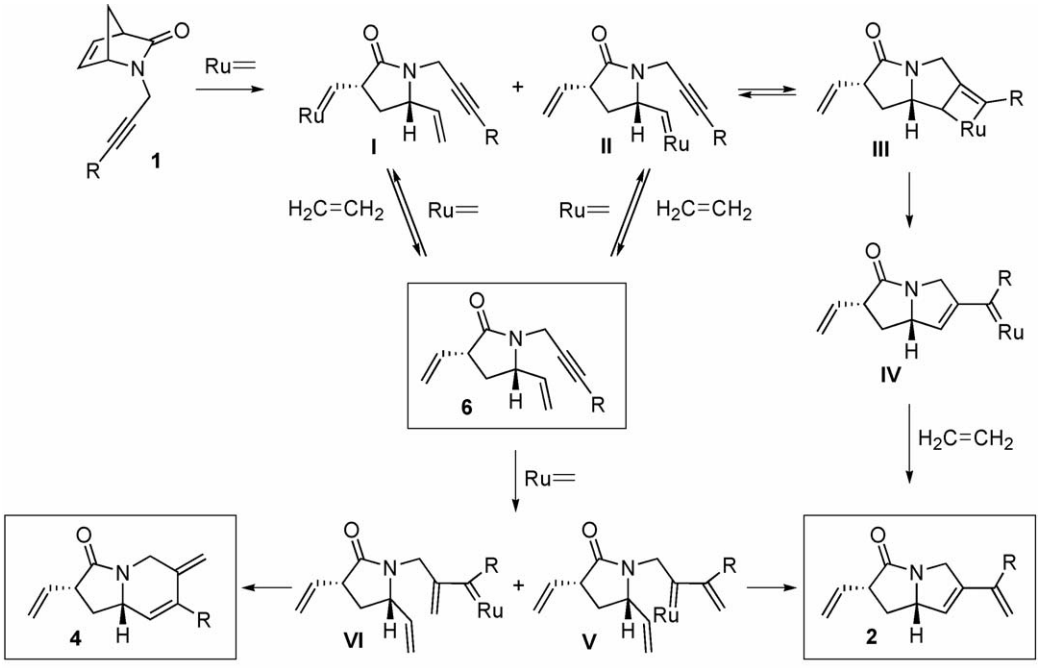
[b] **6g** was obtained in 36% yield



substituent on the alkyne, compound **1d** or **1e** was subjected to the reaction. But the similar result with that of **1c** was obtained, and in each case, pyrrolizidine derivative, **2d** or **2e**, was obtained as the major product (entry 3). In the case of **1d**, tetraene **5d** was obtained in 12% yield (entry 4). When **5d** was re-exposed to Grubbs catalyst **3** under the same reaction conditions, RCM did not proceed and **5d** was recovered in 82% yield. It means that **2d** and **4d** were not formed from **5d**. A TMS group was also effective for the formation of pyrrolizidine derivative **2f** (entry 6). To explore the steric effect on the alkyne, the bulky TIPS group was introduced on the terminal alkyne. Interestingly, **1g** gave only the pyrrolizidine derivative in 31% yield along with ring-opening product **6g** in 36% yield.



Scheme 2. Effect of alkyne TIPS-substitution on ROM–RCM product distribution.

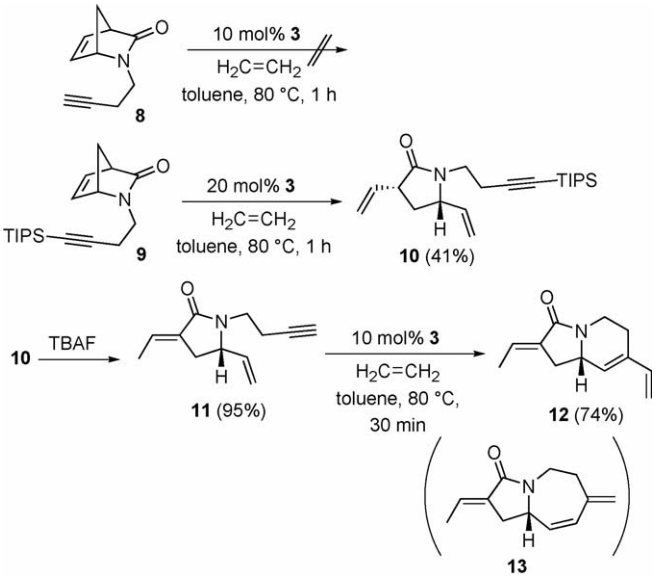


Scheme 3. Possible reaction course for formation of pyrrolizidine and indolizidine derivatives.

When a toluene solution of **6g** was treated with 20 mol% of **3** at 80 °C for 4.5 h under ethylene, a mixture of **2g** and **2g′** (an olefin of **2g′** conjugated with the carbonyl group) was obtained in 37% yield, and the starting material **6g** and **6g′** (olefin isomer of **6g**) was recovered in 49% yield (Scheme 2). In this case, indolizidine derivative **4g** was also not observed. Furthermore, the TIPS group of **6g** was removed by treatment with TBAF and the resultant **7g′** was treated in a similar manner. As a result, pyrrolizidine derivative **2a′** and indolizidine derivative **4a′** were obtained in 60% and 21% yields, respectively. It is noteworthy that pyrrolizidine derivative **2a′** was formed as a major product in this case although the reaction of **1a** gave indolizidine derivative **4a** as the major product.

The possible reaction course is shown in Scheme 3 on the basis of the preceding results. The cycloaddition and subsequent cycloreversion of the ruthenium methylidene complex to the double bond of cycloalkene **1** provide **I** and **II**, which would be converted to **6** under an ethylene atmosphere. If the ruthenium carbene of **II** reacts with the alkyne part intramolecularly, **IV** would be formed via ruthenacyclobutene **III**, and **IV** reacts with ethylene to afford pyrrolizidine derivative **2**. The ruthenium carbene of **I** would not react with the alkyne moiety due to the resultant ring strain. On the other hand, if the ruthenium methylidene complex reacts with the alkyne moiety in **6**, complexes **V** and **VI** would be formed, giving pyrrolizidine derivative **2** and indolizidine derivative **4** by intramolecular reaction. Ethylene is required for the formation of **2** and **4** from ruthenium carbene complexes **I**, **II** and **IV**. If this reaction proceeds through this reaction mechanism, an indolizidine derivative would be formed from complex **VI**. Thus, the bulky substituents on the alkyne would disturb the formation of **V** and **VI** from **6**, and the formation of pyrrolizidine derivative **2** by intramolecular metathesis of **II** would be taken precedence over that of indolizidine derivative **4** [9].

When a toluene solution of **8** having one-carbon elongated side chain and 10 mol% of **3** was warmed at 80 °C for 1 h, the metathesis products were not obtained although the spot of the starting material **8** disappeared on TLC. However, when compound **9**, which possessed a TIPS group on the terminal alkyne, was subjected to the same reaction conditions, ROM–RCM with ethylene proceeded to give **10** in 41% yield. The removal of the TIPS group of **10** gave **11**, which was subjected to the metathesis conditions to afford only indolizidine derivative **12** in 74%



Scheme 4. Synthesis of indolizidine derivative **12**.

yield, and bicyclic compound **13**, containing a 7-membered ring was not formed (Scheme 4).

ROM–RCM of azabicyclo[2.2.1]heptene-ynes was examined, and pyrrolizidine and indolizidine derivatives were obtained in only one step. In this reaction, the ratio of the pyrrolizidine and the indolizidine derivatives was affected by the substituent on the alkyne. When azabicyclo[2.2.1]heptene-ynes, bearing large substituents on the alkyne were treated with ruthenium catalyst **3**, a pyrrolizidine derivative was obtained as the major product. Further studies of this reaction are in progress in our laboratory.

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[7] The use of the sealed tube was not tried.
[8] ROMP (ring-opening metathesis polymerisation) of cycloalkene would proceed under argon atmosphere.
[9] In the cases of enynes, **1a** and **7g**, having terminal alkyne, the initial reaction may occur between methylidene ruthenium carbene complex and an alkyne part.