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Mechanistic study of 7-endo selective radical cyclization of the aryl radical

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ABSTRACT

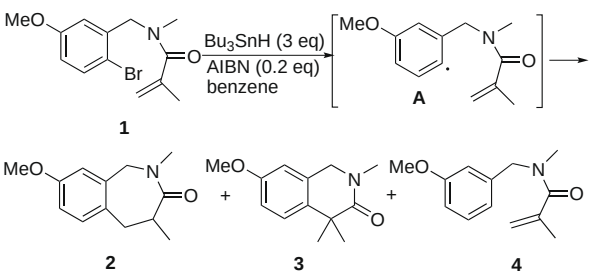
Mechanistic studies on the novel 7-endo selective radical cyclization were carried out. The reaction afforded three products, 7-endo product, 6-exo product, and reduced product. The distribution of these products was estimated by GC analyses. The 7-endo/6-exo selectivity was almost constant against variation in the concentration of Bu_3SnH, while the reduction/cyclization ratio was sensitive to the concentration of Bu_3SnH. The reduction/cyclization ratio was mainly affected by the rotational isomeric ratio of the cyclization precursor. Kinetic analyses indicated that the cyclization process should be irreversible, and the rate constant of 7-endo/6-exo radical cyclization was estimated to be about $3.3 \times 10^8\ s^{-1}$ at 80 °C.

Azepine derivatives are of interest in organic synthesis due to their unique biological activity.[1] Recently, we have found a useful preparation of 2-benzazepine derivatives[2] through 7-endo selective radical cyclization of aryl radical.[3] With our methodology, 2-benzazepine derivatives could be prepared in a few steps on the multigram scale. The regioselectivity of radical cyclization was controlled by the presence or absence of the α-substituent of an unsaturated amide unit.[4] We examined their biological activity and found that certain derivatives of 2-benzazepine promoted healing of skin wounds.[5] From the viewpoint of the reaction mechanism, there was a possibility of some rearrangement, such as the neophyl rearrangement between 6-exo and 7-endo radicals.[6] To investigate the unique selectivity of radical cyclization in detail, we performed careful analyses of the product distribution. In this Letter, we report kinetic analyses of the radical cyclization by comparison of yields of the products of aryl radical **A** at the initial stage of the reaction. The yields of the cyclized products were sensitive toward the concentration of tin hydride, while 6-exo/7-endo selectivity was almost constant as the concentration of Bu_3SnH varied.

We chose *N*-methyl-*N*-(2-bromo-5-methoxyphenylmethyl) methacrylamide **1** as the starting material. Treatment of **1** with Bu_3SnH in the presence of AIBN resulted in the smooth disappearance of **1**. GC analyses revealed that the reaction produced three compounds, 2-benzazepine **2**, isoquinolinone **3**, and reduced methacrylamide **4** (Scheme 1).

To estimate the product distribution by GC analyses, we prepared the products separately, as summarized in Scheme 2. Although compound **2** was prepared by the present synthesis, it was difficult to purify the compound due to contamination with side products **3** and **4**. Thus, we synthesized compound **2** through an alternative route, in which radical cyclization of *N*-Boc methacrylamide **5** was performed. Treatment of Boc-amide **5** with Bu_3SnH resulted in the selective formation of **6** in 29% yield. No 6-exo product was observed in the reaction. The *N*-Boc group was readily removed by acidic treatment to give **7** in 63% yield. The purification of **7** was achieved by recrystallization. Subsequent *N*-methylation of **7** occurred smoothly by treatment with KHMDS in the presence of 18-crown-6 to give **2** in 81% yield. Isoquinolinone, 6-exo adduct, **3** was prepared by 6-exo selective radical cyclization of acrylamide.[2] Exposure of precursor **9** to the standard radical cyclization conditions afforded 6-exo adduct **10** in 40% yield. No 7-endo adduct was formed through the reaction. α-Alkylation to lactam **10** performed under the basic conditions resulted in the smooth formation of 6-exo adduct **3** in 59% yield in crystal form. Compound **4** was prepared through the condensation reaction of *N*-methyl (3-methoxybenzyl)amine **11** and methacrylamide (Scheme 2).

With all of these compounds in hand, we investigated the reaction in detail. A mixture of **1** and Bu_3SnH (3 equiv) in the presence of AIBN (0.2 equiv) in benzene was heated to 78 °C. The reaction products were analyzed by GC, and the yields of each compound were estimated by the calibration curve method using anthracene



Scheme 1.

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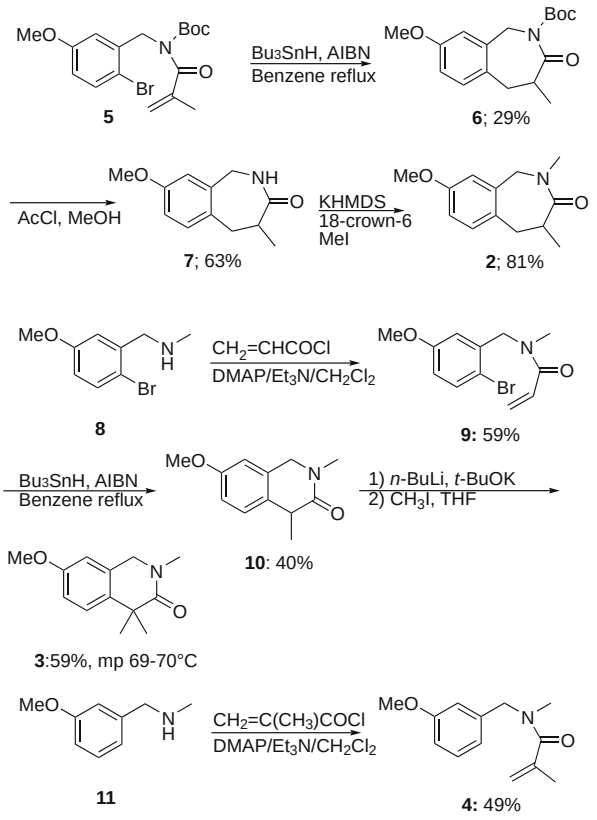


Scheme 2.

as an internal standard. For the reaction with a very low Bu_3SnH concentration, we performed the reaction by a syringe-pump technique. The yields were determined by GC after 2 h (entry 1). Figure 1 shows the time-course analysis of the reaction in 0.3 M of Bu_3SnH concentration. The results are summarized in Table 1.

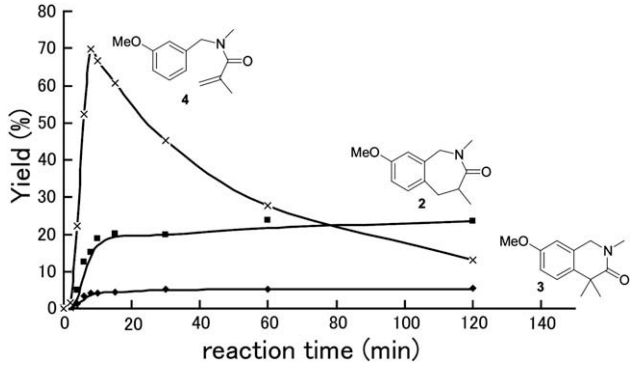


Figure 1. Plots of the changes of the yeilds of **2**, **3**, and **4**.

GC analyses clearly showed that the reaction produced only the three compounds, 7-endo adduct **2**, 6-exo adduct **3**, and reduced product **4**. No significant amounts of other products were observed. For each entry, the sum of the best yields for compounds **2**, **3**, and **4** exceeded 90%. Figure 1 indicates that the yields of **2** and **3** initially increased in proportion to the reaction time and became constant once they reached their maximum level. Hence, compounds **2** and **3** were stable and never isomerized under the present reaction conditions. On the other hand, the amounts of **4** decreased gradually with the reaction time after its peak yield (about 70%). This is probably owing to thermal radical polymerization of **4**, forming a white precipitate in the reaction pot after 2 h. The decay of **4** fits a reciprocal plot of the yield of **4**. This clearly suggests that compound **4** was consumed by the polymerization reaction of **4** that progressed through second-order kinetics.

We focused on the very initial product formation of the reaction. After a short induction period (2–6 min, depending on a batch), the amounts of **2**, **3**, and **4** increased in proportion to the reaction time. This is justified because the concentration of aryl radical intermediate **A** should be very low and almost constant during the reaction. We believe that these values are very useful for precisely determining the product yield of the reaction. We then calculated the slopes of the yields of each product by the least-squares method. Since the obtained slopes were regarded as the yield of the product at the time, the ratio of the slopes reflected the product ratios of the reaction. Thus, we derived the product ratios by using these values. The results are summarized in Table 1.

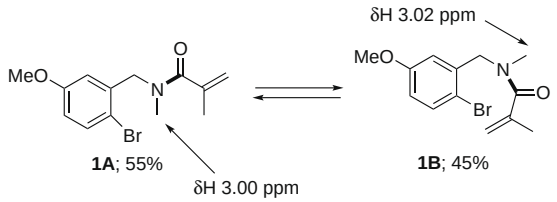
The 6-exo/7-endo product ratio, **3**/**2**, seemed almost the same regardless of variation in the Bu_3SnH concentration. Thus, the concentration of Bu_3SnH has very little influence on the regioselectivity of the cyclization.

Before starting detailed kinetic analyses, we examined the population of the rotational isomers of precursor **1**, because the C–N bond rotation of tertiary amide is regarded much slower than the hydrogen abstraction by alkyl radical from Bu_3SnH.[7] For example, the rate of amide rotation competes the rate of the hydrogen abstraction only if the reaction is carried out at very high temperature.[7g] In our case, the kinetic analyses were performed at 78 °C, which is a further lower temperature to open a pass of the amide rotation. Thus, the present radical reaction should be affected by the original conformation of the precursor. As the NMR spectra of compound **1** at room temperature showed broadened signals, compound **1** contained two rotational isomers that isomerized within a time scale comparable to the NMR observation. To check the ratio of the two isomers, low temperature NMR observation was carried out. The NMR signals at −30 °C were very sharp and the signals for the two isomers were clearly detected. The integration of the *N*-methyl group signals showed that the isomeric ratio was 55:45.

Table 1
Radical reaction of **1** and its product distribution

Entry	[Bu_3SnH] (mol/L)	**2**; yield[a] (%)	**3**; yield[a] (%)	**4**; yield[a] (%)	Total yield (%)	Kinetic product ratio of **2:3:4**[b]	**3**/**2**[b]
1	0.001[c]	37	6	53	96	38.5:6.3:55.1[d]	0.177[d]
2	0.05	29	7	56	92	31.2:7.2:61.7	0.229 ± 0.002
3	0.10	25	6	59	90	29.5:6.3:64.2	0.209 ± 0.002
4	0.15	25	6	67	98	24.1:5.9:70.0	0.227 ± 0.009
5	0.20	24	6	66	96	23.7:5.7:70.6	0.243 ± 0.022
6	0.25	26	6	68	100	20.6:5.5:73.9	0.270 ± 0.021
7	0.30	23	5	69	97	18.4:4.9:76.9	0.267 ± 0.005

[a] The maximum yield of the reaction.
[b] Calculated from the slope for each product formed (see in the text). Obtained values are averages of two or three independent experiments.
[c] Slow addition of Bu_3SnH was performed by a syringe-pump technique.
[d] Based on the yields of **2**, **3**, and **4**.



Scheme 3.

The singlet signal for the *N*-methyl group in the major isomer appears at 3.00 ppm, while the signal for the minor isomer was observed at 3.02 ppm. Comparing these results with the NMR spectra for *N*,*N*-dimethylacetamide,[8] the major isomer should be the rotational isomer **1A** that locates the expected radical center in a position distant from the acceptor double bond, and the minor isomer should be the rotational isomer **1B** that would place the aryl radical close to the double bond (Scheme 3).

We assumed that rotational isomer **1A** should not yield cyclized product **2** or **3** because the generated radical from **1A** is located too far from the terminal double bond to be attacked. As mentioned above, the present reaction temperature was much lower than the temperature the tertiary amide rotation would happen, the rotational isomeric ratio should affect directly to the distribution of the products. We assumed that 55% of the total product ratio of **4** should be converted from **1A**. Thus, compound **4** produced from rotamer **1B** should be estimated as the total yield of **4** minus 55%. Table 2 combines the product ratios from the kinetic operation. The reduction/cyclization ratio for rotamer **1B** is plotted in Figure 2.

In the plots, the reduction/cyclization ratio increased approximately linearly with the concentration of Bu_3SnH. The slope was calculated to be 3.0 M^{-1} by the least-squares method. This plot clearly indicates that the reduction/cyclization ratio for rotamer **1B** increased in proportion to the concentration of Bu_3SnH. The sum of the yields for the cyclized adducts **2** and **3** will be improved when cyclization is carried out with a very low Bu_3SnH concentration. Thus, the slow-addition technique for Bu_3SnH is reasonable for enhancing the yield of cyclized products, as the Bu_3SnH concentration is maintained at a very low level. The zero intercept of the line clearly suggests that the cyclization from intermediate radical **A2** should be irreversible.[9] This was also supported by the reaction of **12** with Bu_3SnH (Scheme 4).[10] Treatment of **12** with Bu_3SnH (0.05 M) at 80 °C resulted in the exclusive formation of **3** in 70% yield. No formation of **2** or **4** was detected by GC analyses throughout the reaction.

Combining these results, we assumed how the aryl radical intermediates **A1** and **A2** were consumed. Scheme 5 illustrates the supposed reaction mechanism of the present radical cyclization. Initially, treatment of **1A** and **1B** with a tin radical resulted in the abstraction of the bromine atom to generate radicals **A1** and **A2**, respectively. Radical **A1** cannot cyclize because the terminal carbon–carbon double bond is located very far from the radical center, while radical **A2** has two options for further reaction: to attack the terminal double bond intramolecularly to give radical **B** or **C** (cyclization), or to abstract hydrogen from Bu_3SnH intermolecularly to give **4** (reduction). The 7-endo/6-exo selectivity of the cyclization is almost constant in a variety of the concentration of Bu_3SnH. It should be noted that once radical **C** is generated, it never produces **A2** or **B** through the back reaction of the cyclization or the neophyl rearrangement, but abstracts hydrogen from Bu_3SnH to give **3** (Scheme 4). Therefore, the present radical cyclization from **A2** is irreversible. Consequently, 7-endo/6-exo selectivity is determined kinetically, and no rearrangement between **B** and **C** (neophyl rearrangement) occurs.

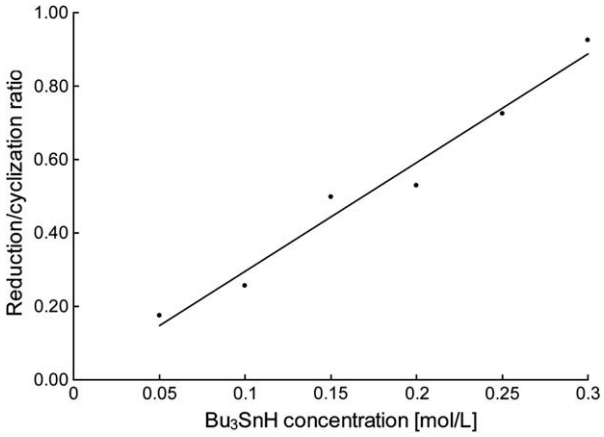
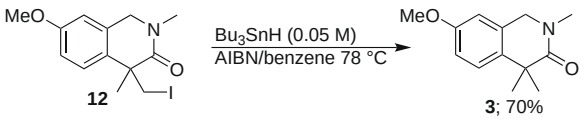


Figure 2. Plots of the product ratio and Bu_3SnH concentration.



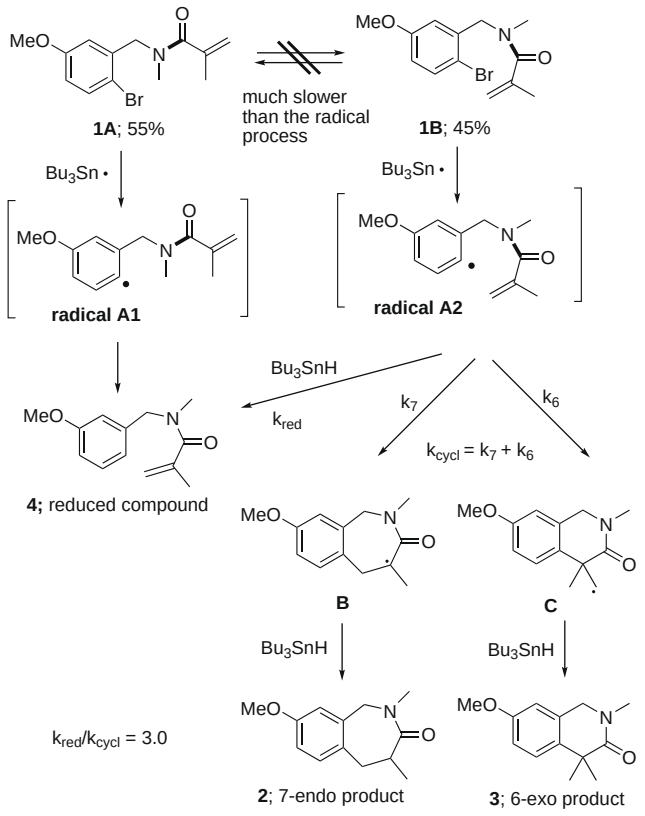
Scheme 4.

The graph shown in Figure 2 allows us to estimate the magnitude of the kinetic values for the cyclization process from **A2**. According to the equation suggested by Newcomb,[9] the slope in Figure 2 should indicate the value of k_{red}/k_{cycl}, where k_{red} is the rate constant of the reaction where the aryl radical abstracts hydrogen from Bu_3SnH, and k_{cycl} is the sum of the rates at which the aryl radical undergoes cyclization (Scheme 5). The rate constant at which phenyl radical abstracts hydrogen from Bu_3SnH is estimated to be 1.0×10^9 M^{-1} s^{-1} at 80 °C.[11] Although the present radical **A2** contains a methoxy group at the para position, and is not exactly the same radical as the phenyl radical, k_{cycl} could be estimated at around 3.3×10^8 s^{-1} at 80 °C if the **A2** radical has a kinetic value in a similar range. The present kinetic estimation of the 7-endo/

Table 2
Product distribution of the reaction

[Bu_3SnH] (mol/L)	Cyclized products[a]	Total **4**	**4** from **1A**	**4** from **1B**[b]	Reduction/cyclization[c]
0.05	38.3	61.7	55	6.68	0.17
0.1	35.8	64.2	55	9.18	0.26
0.15	30.0	70.0	55	15.0	0.50
0.2	29.4	70.6	55	15.6	0.53
0.25	26.1	73.9	55	18.9	0.72
0.3	23.4	76.6	55	21.6	0.93

[a] The sum of the product ratio of **2** and **3**.
[b] **4** from **1B** = total **4** minus 55 (=**4** from **1A**).
[c] The ratio of **4** from **1B** and cyclized products.



Scheme 5.

6-exo cyclization seems reasonable because other examples for kinetic studies for 7-endo cyclization at 80 °C also indicate the kinetic parameters in a similar range.[12]

In conclusion, we carefully examined the reaction profile of 7-endo selective radical cyclization using the precursor **1**. The cyclization gave three products, 7-endo adduct **2**, 6-exo adduct **3** and reduced product **4**. The reduction/cyclization ratio was affected by the rotamer population of precursor **1**. The major rotamer **1A** gave the reduced product **4** only. The cyclization selectivity of **1B** was enhanced when less concentration of Bu_3SnH was employed. The 7-endo/6-exo selectivity was almost constant against variations in the Bu_3SnH concentration. The kinetic analyses suggest that the radical cyclization from **A2** should be irreversible; the 7-endo/6-exo selectivity should be determined kinetically. Further studies on this reaction are in progress in our laboratory and will be published elsewhere.

Acknowledgment

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