

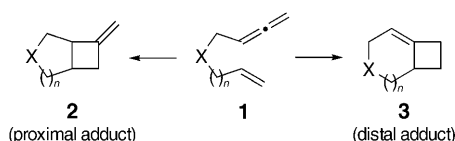
Synthetic Methods

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Thermal Intramolecular [2+2] Cycloaddition of Allenes and Allenynes: Diastereoselective Access to Bicyclic Nitrogen Heterocycles**

Hiroaki Ohno,* Tsuyoshi Mizutani, Yoichi Kadoh, Kumiko Miyamura, and Tetsuaki Tanaka*

Cycloaddition reactions that occur without the use of reagents or catalysts and without creating any waste have attracted much attention in recent years as an ideal process in terms of atom economy.^[1] Considerable research efforts have been particularly focused on the development of cycloaddition of allenes,^[2] on account of the current interest in the reactions of allenes with an additional multiple bond, including transition-metal-catalyzed carbocyclizations.^[3,4] The [2+2] cycloaddition reactions^[5] between allenes and alkenes are extremely useful for the synthesis of methylenecyclobutane derivatives.^[6] Especially, intramolecular cycloaddition constitutes a versatile method for the stereoselective synthesis of a variety of bicyclic compounds having a strained bicyclo[*n*.2.0] framework (Scheme 1).^[7] In most reported intramolecular [2+2]



Scheme 1. Intramolecular [2+2] cycloaddition of allenes.

cycloaddition reactions of simple unactivated allenes, the proximal 2 π component of the allene moiety participates in the cycloaddition to form bicyclic products **2**.^[2] Only limited examples of the intramolecular [2+2] reaction of the distal allenic double bond to give **3** have been reported to date, which used a special class of allenes such as allene carbox-

ylates,^[8] allenyl sulfones,^[9] difluoroallenes,^[10] β -lactam-tethered allenes,^[11] or diyne-diallenes.^[12]

In the course of our efforts toward the development of a new methodology for the synthesis of heterocyclic compounds by the transition-metal-catalyzed cyclization of allenes,^[4,13] we found that the thermal cycloaddition of simple allenes with an additional multiple bond proceeds by simply heating the allenes or allenynes in the absence of any catalyst. Herein, we present an intramolecular [2+2] cycloaddition of unactivated allenes to form distal adducts of type **3**, which constitute an important class of compounds in synthetic^[14] and natural product chemistry.^[15]

Various allenes **4–10** (Table 1) were prepared according to the reported procedure^[4d] and their thermal cycloaddition reaction was investigated. First, the [2+2] cycloaddition of

Table 1: Thermal [2+2] cycloaddition of allenes.^[a]

Entry	Substrate	<i>t</i> [h]	Product	Yield [%] ^[b]
1		65 ^[c]		89
2		3		96
3		3		71
4		1		93
5		2		73
6		24 ^[d]		82
7		19 ^[d]		68
8		30		69

[a] Unless otherwise stated, reactions were carried out in DMF at 150°C. [b] Yields of isolated products. [c] Reaction was carried out in dioxane under reflux conditions. [d] Reaction was carried out in DMF under reflux conditions. Mts = 2,4,6-trimethylphenylsulfonyl.

allene **4** was examined under various reaction conditions. Among the solvents employed, dioxane and dimethylformamide (DMF) were the solvents of choice leading to 3-azabicyclo[4.2.0]oct-5-ene derivative **11** in 89 and 96% yields, respectively, as the sole isolable isomer (Table 1, entries 1 and 2). The structure and configuration of **11** were confirmed by

[*] Dr. H. Ohno
Graduate School of Pharmaceutical Sciences
Kyoto University
Sakyo-ku, Kyoto 606-8501 (Japan)
Fax: (+81) 7-5753-4570
E-mail: hohno@pharm.kyoto-u.ac.jp

T. Mizutani, Y. Kadoh, K. Miyamura, Prof. Dr. T. Tanaka
Graduate School of Pharmaceutical Sciences
Osaka University
1-6 Yamadaoka, Suita, Osaka 565-0871 (Japan)
Fax: (+81) 6-6879-8214
E-mail: t-tanaka@phs.osaka-u.ac.jp

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heteronuclear multiple quantum correlation (HMQC) and NOESY analysis of the corresponding hydrogenated derivatives. The reaction in dioxane under reflux was rather slow (Table 1, entry 1), and therefore the cycloaddition of the other allenenes **5–10** was conducted in DMF. All the allenenes were successfully converted into the corresponding bicyclic products in good to excellent yields, with complete regioselectivity. The reaction of the allenene **5** bearing an electron-donating aryl group gave **12** in relatively low yield (71 %, Table 1, entry 3), whereas the allenene **6** with an electron-withdrawing group afforded **13** in 93 % yield within a shorter reaction time (1 h, Table 1, entry 4). Allene **7** with an α,β -unsaturated ester group showed sufficient reactivity to give the cycloadduct **14** in 73 % yield. Allenene **8** with a geminal dimethyl group on the olefinic carbon atom (Table 1, entry 6), α -unsubstituted allene derived substrate **9** (Table 1, entry 7), and dimethyl malonate derived allenene **10** (Table 1, entry 8) gave the distal cycloadducts **15–17** in 68–82 % yields, although prolonged reaction times were required.

Next, the thermal cycloaddition of allenyne **18–23** (Table 2) was investigated, which were easily prepared by the N-arylpropargylation of known amino allenes. In contrast to the cycloaddition of allenenes **4** (Table 1, entries 1 and 2), the reaction of the allenyne **18** was complete within 2 h in dioxane under reflux conditions to give 3-azabicyclo-[4.2.0]octa-1(8),5-diene derivative **24** in 92 % yield (Table 2, entry 1). In the reaction of N-tosylated allenyne derivatives **19–21**, the effect of the electron-donating and -withdrawing

aryl group on the reactivity was not dramatic (Table 2, entries 2–4). More important is the α substituent of the allene: the reaction of the allenyne **22** bearing a smaller substituent at the α position was complete in 8 h, whereas the cycloaddition of α -unsubstituted allene derivative **23** required a prolonged reaction time (117 h) to give **29** in 94% yield.

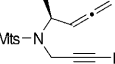
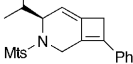
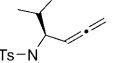
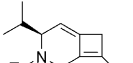
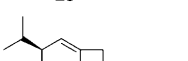
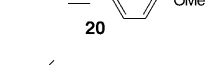
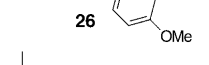
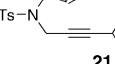
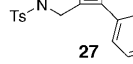
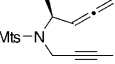
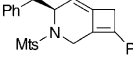
The related [2+2] thermal reactions of allenes are thought to proceed by a two-step mechanism, that is, via a diradical intermediate.^[2,9b,c,16] In the present [2+2] cyclization of simple allenenes and allenynes, the substituent on the double or triple bond, which effectively stabilizes the radical intermediate, is essential for successful conversion: the corresponding allenenes or allenynes without the radical-stabilizing group were completely inert to the thermal [2+2] cycloaddition. This experimental result supports the diradical mechanism; however, further study is necessary to elucidate the reaction mechanism.

In conclusion, a stereoselective route to bicyclo[4.2.0]octane derivatives has been developed by using thermal [2+2] cycloaddition of allenes with an additional multiple bond. This study first demonstrated that unactivated allenes and allenynes can regioselectively undergo intramolecular [2+2] cycloaddition of the distal double bond of the allene moiety. This simple and environmentally benign process would extend the potential application of fused bicyclic cyclobutane derivatives in synthetic and medicinal chemistry.

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Table 2: Thermal [2+2] cycloaddition of allenynes.^[a]

Entry	Substrate	<i>t</i> [h]	Product	Yield [%] ^[b]
1	 18	2	 24	92
2	 19	3	 25	70
3	 20	2	 26	61
4	 21	2	 27	67
5	 22	8	 28	91
6	 23	117	 29	94

[a] All reactions were carried out in dioxane under reflux conditions. [b] Yields of isolated products. Mts = 2,4,6-trimethylphenylsulfonyl; Ts = *p*-toluenesulfonyl.

Keywords: allenes · bicyclic compounds · cycloaddition · nitrogen heterocycles · regioselectivity

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