Cycloaddition Reactions

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Synthesis of Nine-Membered Carbocycles by the [4+3+2] Cycloaddition Reaction of Ethyl Cyclopropylideneacetate and Dienynes**

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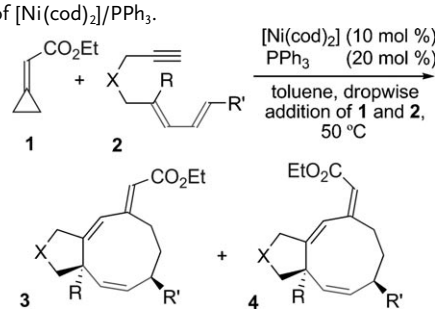
Medium-sized carbocycles are frequently incorporated in various natural products and the efficient construction of the carbocycle motif is an important issue.[1] Some transition-metal-catalyzed cycloaddition reactions provided unique and promising solutions for the preparation of the medium-sized rings.[2] For example, seven-membered carbocycles were prepared by the [5+2],[3] [4+3],[4] [3+2+2],[5] and other[6] cycloaddition reactions. Some reactions are also available for the synthesis of eight-[7] and ten-membered[8] carbocyclic compounds. On the other hand, the synthesis of nine-membered carbocyclic compounds by transition-metal-catalyzed cycloaddition reactions remains a very challenging issue.[9,10]

Recently, our research group has examined the cycloaddition reactions of ethyl cyclopropylideneacetate (**1**) in the presence of a nickel catalyst and disclosed the high and unique reactivity of **1**.[11] For example, the nickel(0)-catalyzed [3+2+2] cycloaddition between **1** and alkyne derivatives proceeded and cycloheptadiene compounds were isolated in good yields.[12] We also reported the [4+3] cycloaddition between **1** and conjugated diene derivatives.[4i] These results prompted us to examine the reactions of **1** with other unsaturated hydrocarbon compounds. Herein we report the unprecedented [4+3+2] cycloaddition of ethyl cyclopropylideneacetate (**1**) and dienynes.

The results of the [4+3+2] cycloaddition reactions are summarized in Table 1. The [4+3+2] cycloaddition between **1** and dienyne (**2a**) proceeded smoothly in the presence of $[Ni(cod)_2]$ (10 mol%) and PPh_3 (20 mol%). The dropwise addition of a solution of **1** (1.5 equiv) and **2a** in toluene to a solution of the nickel catalyst at room temperature was the best procedure, and the product **3a** was isolated in 82% yield (entry 1). A small amount of an isomer **4a** was also isolated (5% yield). Notably, the intramolecular [4+2] cycloaddition[13–15] between the alkyne and the diene moieties was not observed. The use of **1** as a substrate for this cycloaddition reaction is critical: if other alkylidenecyclopropanes such as unsubstituted methylenecyclopropane or benzylidenecyclopropane were used as the substrates, no cyclononadiene derivative was isolated.

The reactions of **1** with various dienyne derivatives were also examined. The reaction of a dienyne tethered with an *N*-tosyl group (**2b**) proceeded, though the yield of the corre-

Table 1: [4+3+2] Cycloaddition between **1** and dienynes **2** in the presence of $[Ni(cod)_2]/PPh_3$.



Entry	Dienyne	X	R	R′	Cond.[a]	*t* [h]	Yield of **3**+**4** [%][b]
1	**2a**	$(EtO_2C)_2C$	H	H	A[c]	14	87 (82,5)
2	**2b**	TsN	H	H	B	17	32[d]
3	**2c**	O	H	H	A[c]	14	76 (67,9)
4	**2d**		H	H	B	22	74 (48,26)
5	**2e**	$(EtO_2C)_2C$	Me	H	B	8	57
6	**2f**	TsN	Me	H	B	8	65
7	**2g**	O	Me	H	A	3	47
8	**2h**	TsN	H	Me	B	12	38
9	**2i**	O	H	Me	B	6	35

[a] Conditions A: a solution of **1** (1.5 equiv) and **2** (1.0 equiv) was added slowly over 10 h. The final concentration of **1** was 0.1 M. Conditions B: a solution of **1** (1.0 equiv) and **2** (1.2 equiv) was added slowly over 5 h. The final concentration of **1** was 1.0 M. [b] The yields of isolated **3** and **4** are shown in parentheses when compound **4** was isolated. The formation of **4** was not observed in the other reactions. [c] The reaction was carried out at room temperature. [d] A small amount of an intramolecular cycloadduct of **2** was isolated. cod = 1,5-cyclooctadiene, Ts = 4-toluenesulfonyl.

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sponding cyclononadiene decreased (entry 2). The reaction of **1** with an oxygen-tethered dienyne (**2c**) also proceeded and gave the corresponding cycloadduct (entry 3). The reaction of a spirodienyne **2d** gave a mixture of isomeric cyclononadienes in 74% combined yield (entry 4). We introduced a methyl group to the diene moiety of the dienyne and studied the [4+3+2] cycloaddition (entries 5–9). When dienyne **2e** was employed as the substrate, the cocyclization proceeded and a single isomer (**3e**) with a quaternary carbon center was isolated (entry 5). The reaction of **2f** as well as **2g** proceeded and the products were isolated in moderate yields (entries 6–7). The cocyclization reaction also proceeded in lower yields when the methyl group was introduced to the terminal carbon of the diene moiety (entries 8–9). In these reactions, the formation of one stereoisomer (a compound with the *cis* configuration of the methyl group and the annulated five-membered ring) was observed.[16,17] The structure of **3i** was confirmed by an X-ray crystallographic analysis (Figure 1).[18,19]

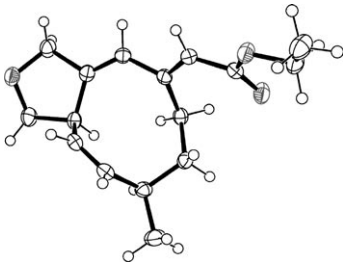
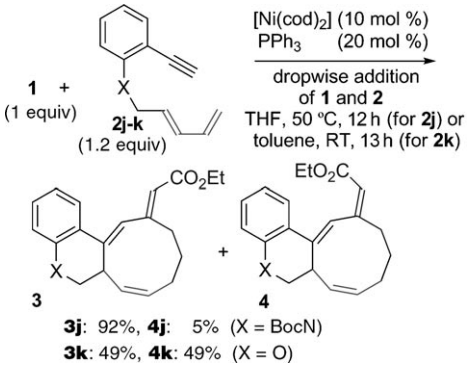


Figure 1. X-ray crystal structure of **3i**.

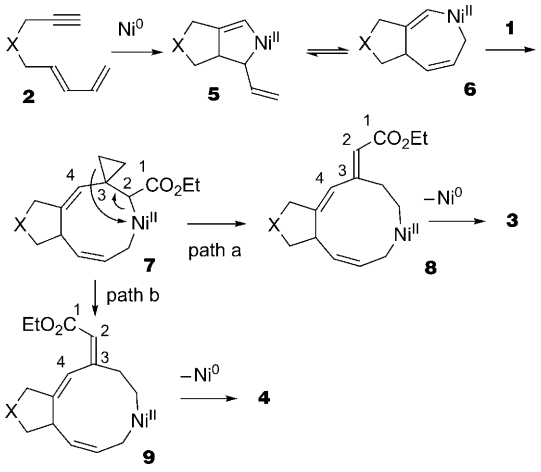
This reaction was applied to the synthesis of tricyclic compounds (Scheme 1). Thus, the reaction of **1** with **2j**, the alkyne moiety and the diene moiety of which are tethered with an aniline derivative, proceeded efficiently at 50°C and the *E* isomer (**3j**) was isolated in 92% yield, together with a small amount of the *Z* isomer (5%; **4j**). A phenol derivative **2k** was also treated with **1** and the *E* and *Z* isomers were isolated in 98% combined yield. In this reaction, however, no *E*/*Z* selectivity was observed.



Scheme 1. Synthesis of tricyclic compounds. THF = tetrahydrofuran. Boc = *tert*-butoxycarbonyl.

We confirmed that the mixture of *E* and *Z* isomers was not formed by the isomerization of the initially formed *E* or *Z* isomer in the reaction mixture. Thus, when compound **3j** or **4j** was treated with $[Ni(cod)_2]/PPh_3$ in THF at 50°C, no isomerizaiton was observed and the starting material was recovered.

A working hypothesis of this reaction is shown in Scheme 2. We assume that the reaction would proceed through the formation of a nickelacycle **6**[20,21] by the reaction



Scheme 2. Proposed mechanism of the [4+3+2] cycloaddition.

of **2** with the Ni^0 species. The insertion of **1** to **6** occurred regioselectively: the reactive vinyl nickel moiety would undergo Michael-type addition to **1**, and **7** would be formed as an intermediate. The ester group bound to **1** would play a crucial role for this process. Finally, the cyclopropylmethylbutenyl rearrangement[22] and the reductive elimination of the Ni^0 species from **8** would proceed to give **3** (**4**) as the final product. The stereochemistry of the exomethylene group of the product would be determined when the rearrangement of **7** to **8** takes place. In most examples, the predominant formation of **3** was observed. This could be explained by considering the conformation of **7**. Thus, the dihedral angle between the two C–C bonds (C1–C2 and C3–C4 in Scheme 2) would be important. When the angle is large, the selective formation of **8** would be observed (path a). On the other hand, the formation of **9** would proceed when the dihedral angle is small (path b). The dihedral angle would be large and the *s*-trans conformer is predominant in most reactions because of the cyclic structure of **7**, and compound **3** would be isolated as the major product. In the reactions of some dienynes, however, a significant amount of the *s*-cis conformer would be present and compound **4** would be isolated. We assume that the linkers and substituents introduced to the dienyne would affect the conformation of **7**, thus leading to the observed stereochemistry.[23,24]

In summary, we have developed a new [4+3+2] cycloaddition of ethyl cyclopropylideneacetate with dienynes in the presence of a Ni^0 catalyst. The reaction provided a new route for the synthesis of nine-membered carbocyclic rings.

Detailed studies related to the scope and mechanism of this reaction is in progress.

Experimental Section

General procedure for the synthesis of **3**: A solution of **1** (1.5 mmol) and **2** (1 mmol) in dry toluene (5 mL) at 50 °C under Ar was added dropwise over 10 h to a dark red mixture of $[Ni(cod)_2]$ (27.5 mg, 0.1 mmol) and PPh_3 (52.5 mg, 0.2 mmol) in dry toluene (5 mL). The progress of the reaction was monitored by TLC and GC-MS, and the reaction mixture was stirred until the starting material **2** disappeared. The mixture was passed through a short silica gel column (eluent: diethyl ether). Evaporation of the solvent gave an oil, which was further purified by column chromatography on silica gel and gave **3** (and **4**).

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[15] Wender et al. reported that $[Ni(cod)_2]/PPh_3$ is a poor catalyst for the [4+2] cycloaddition reactions of dienynes and used tri-*o*-biphenyl phosphite as the ligand (Ref. [14a]). We assume that the bulky phosphite ligand accelerated the reductive elimination of the Ni species from the nickelacycloheptadiene intermediate. On the other hand, the reductive elimination is slow in the presence of PPh_3, and the insertion of **1** to the nickelacycloheptadiene would occur.

[16] The attempted reactions of dienynes with internal alkyne moiety did not proceed.

[17] The details of the observed regioselectivity will be studied in due course.

[18] X-ray data were collected on a CCD detector. The crystal structure was solved by direct methods SHELXS-97 and refined by full-matrix least-squares SHELXL-97 (Ref. [17]). All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included as their calculated positions. Crystal data for **3i**: $C_{16}H_{22}O_3$; $M_r = 262.34\ g\,mol^{-1}$, colorless prism measuring $0.4 \times 0.4 \times 0.35$ mm, triclinic, $P\bar{1}$, $a = 10.481(2)$, $b = 10.876(2)$, $c = 13.831(2)$ Å, $\alpha = 103.367(2)$, $\beta = 110.059(2)$, $\gamma = 90.337(2)°$, $V = 1434.6(4)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.215\ g\,cm^{-3}$, $2\theta_{max} = 56.56°$, $T = 150$ K, 8014 reflections measured, 6094 unique ($R_{int} = 0.0157$), $\mu = 0.082\ mm^{-1}$. The final R_1 and wR_2 was 0.0584 and 0.1323 (all data). The residual electron densities (peak and hole) were 0.284 and $-0.197\ e\,Å^{-3}$. Two independent molecules are included in an asymmetric unit of the crystal. CCDC 741408 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[21] Alternatively, a nickelacycle might be formed by the reaction of the alkyne or diene moiety of the dienyne with **1**. We assume that the formation of **6** is more likely since this is a partially intramolecular reaction and the formation of [4+2] cycloadduct under closely related reaction conditions could be reasonably explained.

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[24] For example, the conformation of the nickelacycle formed by the reaction of **2j** would be different from the nickelacycle prepared from **2k** owing to the presence of the bulky Boc group, and it would affect the outcome of the reaction. The electronic effect of the substituents might also influence the outcome of the reaction.

