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Efficient Catalytic Insertion of Acetylenes into a Carbon−Carbon Single Bond of Nonstrained Cyclic Compounds under Mild Conditions

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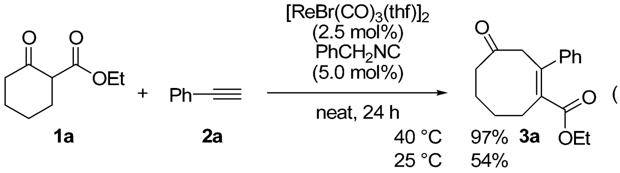
Chemical transformations starting from the dissociation of carbon−carbon bonds are important and highly efficient methods to synthesize useful organic compounds because the transformations can change the skeletons of organic compounds directly. However, it is generally difficult to carry out the transformations under mild reaction conditions because carbon−carbon bonds are very strong and are usually covered with carbon−hydrogen or other bonds. Thus, such transformations have been limited mostly to stoichiometric reactions[1] or to catalytic reactions using highly strained substrates,[1] such as three-membered rings,[2] four-membered rings,[3] norbornenes,[4] and norbornadienes.[5] In catalytic reactions, the release of strain energy is the driving force to promote the reactions. Although there have been a few reports on chemical transformations starting from the dissociation of nonstrained carbon−carbon bonds,[6] these transformations suffer from harsh reaction conditions, a long reaction time, and the requirement of chelation.[7] They also suffer from low yields or the formation of decarboxylation products.[8] We report herein that a rhenium catalyst promotes the insertion of terminal acetylenes into a carbon−carbon single bond next to a carbonyl group of nonstrained cyclic compounds under mild conditions.

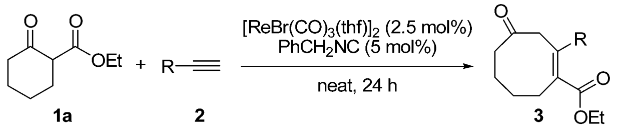
The reaction of cyclohexanone-2-carboxylic acid ethyl ester **1a** (1.0 equiv) with phenylacetylene **2a** (1.2 equiv) in the presence of catalytic amounts of a rhenium complex, $[ReBr(CO)_3(thf)]_2$[9] (2.5 mol %), and benzyl isocyanide (5.0 mol %)[10] at 40 °C for 24 h under solvent-free conditions gave an eight-membered ring product **3a** quantitatively (eq 1).[11−14] Although the yield was low (**2a**: 1.0 equiv, 54%), this reaction proceeded even at room temperature (eq 1).

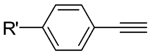
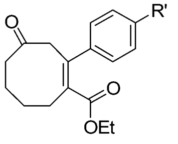
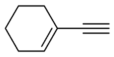
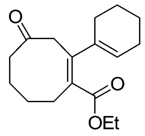


(1)

In general, an effective synthesis of medium-size cyclic compounds is rather difficult because of unfavorable entropic and enthalpic factors.[15] From this view point, the yield and reaction conditions deserve special mention (Table 1, entry 1). The formation reaction of **3a** proceeded in toluene at 50 °C by using $ReBr(CO)_5$ or $MnBr(CO)_5$ as a catalyst (5.0 mol %), although the yields of **3a** were low (45 and 59%).[16] When the amount of benzyl isocyanide was increased from 5 to 10 mol % in the reaction shown in eq 1, the reaction did not proceed. This is probably because the coordination of the two isocyanides to the rhenium center decreased the catalytic activity.

Table 1. Reactions of 1,3-Keto Ester with Several Acetylenes[a]



entry	acetylene	temp / °C	product	% yield[b]
1	 R' = H	40		97 (98)
2	MeO	40		95 (>99)
3	Me	40		92 (97)
4[c]	CF_3	50		86 (88)
5[d]	Br	40		92 (96)
6		40		99 (>99)

[a] **1a**, 0.50 mmol; **2**, 0.60 mmol (1.2 equiv). [b] Isolated yield. The yield determined by ^1H NMR is reported in parentheses. [c] Acetylene (2.0 equiv), $[ReBr(CO)_3(thf)]_2$ (5.0 mol %), benzyl isocyanide (10 mol %). [d] Acetylene (1.5 equiv).

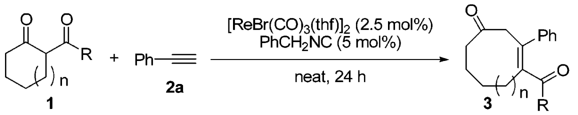
Treatment of **1a** with arylacetylenes bearing substituents, such as electron-donating methoxy and methyl groups and electron-withdrawing trifluoromethyl and bromo groups, at the *para*-position, afforded the corresponding eight-membered cyclic compounds in 86−97% yields (Table 1, entries 2−5). In the latter case, carbon−bromine bond remained intact during the reaction (Table 1, entry 5). The ring-expansion reaction of **1a** with an enyne, 1-ethynylcyclohexene, gave the corresponding eight-membered cyclic compound quantitatively (Table 1, entry 6).[17]

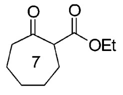
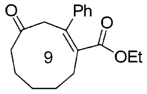
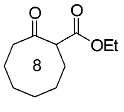
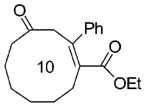
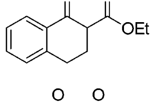
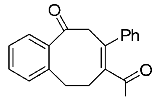
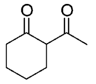
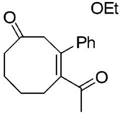
Next, we investigated several cyclic dicarbonyl compounds (Table 2). A nine-membered cyclic ester was produced at 40 °C from a seven-membered β-keto ester in excellent yield (Table 2, entry 1). Although the reaction conditions were not applied to the formation of a ten-membered ring from an eight-membered β-keto ester, heating the reaction mixture of a cyclooctanone-2-carboxylic acid ethyl ester and **2a** at 90 °C provided a ten-membered cyclic ester in 50% yield. The yield of the ten-membered cyclic compound was increased to 78% in the absence of benzyl isocyanide (Table 2, entry 2).[18] The reaction of a tetralone-2-carboxylic acid ethyl ester with **2a** in dichloromethane gave a cyclic compound connected with an aromatic ring in good yield (Table 2, entry 3). The corresponding eight-membered cyclic compound was formed in 61% yield at 100 °C by the reaction of β-diketone with **2a** (Table 2, entry 4).[19]

Although an alkenyl derivative,[11] which is formed by the insertion of phenylacetylene **2a** into a C−H bond of the cyclohexanone-2-carboxylic acid ethyl ester **1a**, was exposed to similar reaction conditions, the ring-expansion reaction did not proceed and the starting material was recovered completely. This result indicates that the ring expansion does not occur via alkenyl derivatives. The proposed reaction mechanism is as follows (Scheme 1): (1) the

10.1021/ja064022i CCC: $33.50

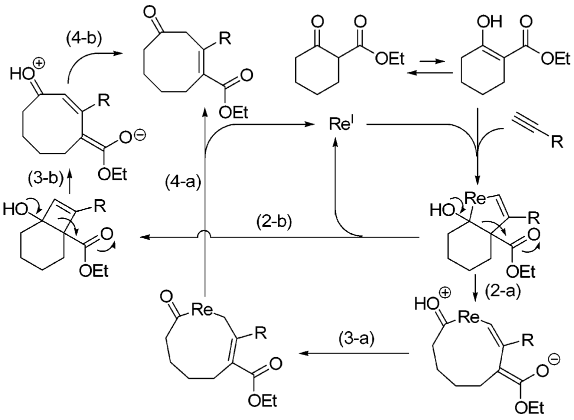
Table 2. Reactions of 1,3-Dicarbonyl Compounds with Phenylacetylene[a]



entry	1,3-dicarbonyl compound	temp / °C	product	% yield[b]
1		40		87 (92)
2[c]		50		78 (80)
3[d]		40		78 (81)
4[e]		100		61 (63)

[a] **1**, 0.50 mmol; **2a**, 0.60 mmol (1.2 equiv). [b] Isolated yield. The yield determined by ^{1}H NMR is reported in parentheses. [c] Benzyl isocyanide was not added. [d] Dichloromethane (1.0 mL) was used as a solvent. [e] Acetylene (2.0 equiv) and 1,2-dichloroethane (1.0 mL) were used as a solvent.

Scheme 1. Proposed Mechanism of the Ring Expansion Reactions



formation of a rhenacyclopentene intermediate by the reaction of a rhenium catalyst, β-keto ester, and terminal acetylene. After the formation of the rhenacyclopentene intermediate, there are two possible pathways; the difference is the timing of reductive elimination. Path A: (2-a) Ring opening by a retro-aldol reaction; (3-a) isomerization; (4-a) reductive elimination. Path B: (2-b) Reductive elimination; (3-b) ring opening by a retro-aldol reaction; (4-b) isomerization.

Thermally prohibited [$2\pi + 2\pi$] cycloaddition reactions of olefins with acetylenes occur in the presence of a ruthenium catalyst.[20] From this point of view, the reaction reported here can be seen as a rhenium-catalyzed version of the de Mayo reaction.[21] The rhenium-catalyzed reaction reported here proceeded under mild conditions without light, and in addition, the second ring-opening step occurred sequentially in one pot without any additives.

We have succeeded in the rhenium-catalyzed ring-expansion reaction of strained and nonstrained cyclic compounds starting from carbon−carbon bond fission and the construction of medium-size rings under mild conditions. We hope that this method will become a useful way to construct compounds having medium-size cyclic compounds.

Acknowledgment. Financial support was provided by a Grant-in-Aid for Scientific Research on Priority Areas (No. 18037049, "Advanced Molecular Transformations of Carbon Resources") from the Ministry of Education, Culture, Sports, Science, and Technology of Japan, and for Young Scientists (B) (No. 18750088) from the Japan Society for the Promotion of Science.

Supporting Information Available: General experimental procedure, characterization data for cyclic compounds, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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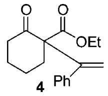
(9) We reported on efficient chemical transformations via C−H bond activation with a rhenium catalyst, [ReBr(CO)$_3$(thf)]$_2$. See: (a) Kuninobu, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2005**, *127*, 13498. (b) Kuninobu, Y.; Tokunaga, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2006**, *128*, 202. (c) Kuninobu, Y.; Nishina, Y.; Shouho, M.; Takai, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2766.

(10) The promotion effect of isocyanide has also been reported by Suginome and Ito. See: Suginome, M.; Ito, Y. *Top. Organomet. Chem.* **1999**, *3*, 131.

(11) This result differs from the result that **4** was obtained by the rhenium-catalyzed reaction of a β-keto ester with phenylacetylene in the absence of *tert*-butylisocyanide. See: Kuninobu, Y.; Kawata, A.; Takai, K. *Org. Lett.* **2005**, *7*, 4823.



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(12) Investigation of isocyanides (phenylacetylene: 1.0 equiv, 40 °C, 24 h): *tert*-butyl isocyanide, 88%; cyclohexyl isocyanide, 84%; benzyl isocyanide, 80%; 1,1,3,3-tetramethylbutyl isocyanide, 50%.

(13) Investigation of solvents ([ReBr(CO)$_3$(thf)]$_2$, 1.5 mol %; benzyl isocyanide, 3.0 mol %); neat, 89%; dichloromethane, 85%; tetrachloroethane, 52%; toluene, 24%; hexane, 13%; THF, 1%; DMF, 0%; methanol, 0%.

(14) The structure of **3a** was determined by X-ray single-crystal structure analysis after converting **3a** to the thioacetal **4a**. See the Supporting Information.

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(16) The eight-membered ring product **3a** was not obtained by using RuH$_2$(CO)(PPh$_3$)$_3$, Ru$_3$(CO)$_{12}$, RhCl(PPh$_3$)$_3$, PtCl$_2$, AuCl$_3$, and GaCl$_3$.

(17) The reaction with 1-octyne, ethynyltrimethylsilane, 1-benzyloxy-2-propyne, and 1-phenyl-1-propyne did not proceed; the starting materials were recovered quantitatively.

(18) The seven-membered cyclic compound was not obtained from a cyclopentanone-2-carboxylic acid ethyl ester, and an alkenyl derivative, which was generated by the insertion of **2a** into a C−H bond of the β-keto ester, was formed.[11]

(19) 1,3-Cyclohexanedione did not provide the corresponding eight-membered ring product at 50 °C for 24 h in dichloroethane or in the absence of the solvent.

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JA064022I