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Rhenium-Catalyzed Formation of Bicyclo[3.3.1]nonene Frameworks by a Reaction of Cyclic β-Keto Esters with Terminal Alkynes

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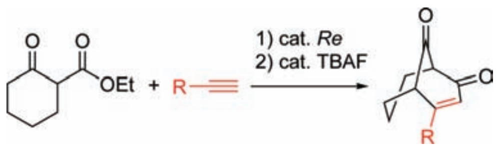
ABSTRACT



Treatment of cyclic β-keto esters with terminal alkynes in the presence of a catalytic amount of a rhenium complex, $[ReBr(CO)_3(thf)]_2$, gave bicyclo[3.3.1]nonene derivatives. The reaction conditions and yields of the bicyclo[3.3.1]nonenes were improved by the sequential use of tetrabutylammonium fluoride (TBAF) after the rhenium-catalyzed reactions.

Many bioactive compounds contain bicyclic skeletons. For example, hyperforin,[1] garsubellin A,[2] and papuaforin A[3] are well-known natural products containing bicyclo[3.3.1]nonene frameworks. Therefore, several studies on the construction of bicyclo[3.3.1]nonene frameworks, such as hyperforin,[4] garsubellin A,[5] papuaforin A,[6] and their derivatives have been carried out.[7] As an alternative synthetic route to bicyclo[3.3.1]nonene derivatives, we investigated the synthesis of bicyclo[3.3.1]nonene skeletons from six-membered cyclic β-keto esters and terminal alkynes via the formation of eight-membered unsaturated cyclic δ-keto esters (Figure 1).[8] We report herein the synthesis of bicyclo[3.3.1]nonene derivatives by rhenium-catalyzed insertion of alkynes into a carbon−carbon single bond of cyclic β-keto esters and successive intramolecular cyclization via the elimination of ethanol.

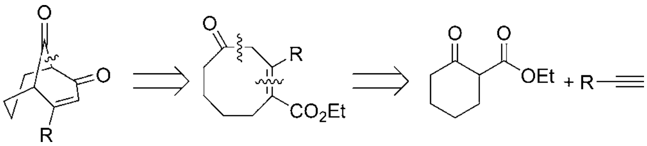


Figure 1. Proposed strategy for the retrosynthesis of bicyclo[3.3.1]nonenes.

Treatment of cyclic β-keto ester **1a** with phenylacetylene (**2a**) in the presence of a rhenium complex, $[ReBr(CO)_3$-

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(1) (a) Gurevich, A. I.; Dobrynin, V. N.; Kolosov, M. N.; Popravko, S. A.; Ryabova, I. D.; Chennov, B. K.; Derbentseva, N. A.; Aizenman, B. E.; Garagulya, A. D. *Antibiotiki* **1971**, *6*, 510–513. (b) Bystrov, N. S.; Chernov, B. K.; Dobrynin, V. N.; Kolosov, M. N. *Tetrahedron Lett.* **1975**, *16*, 2791–2794.

(2) Fukuyama, Y.; Kuwayama, A.; Minami, H. *Chem. Pharm. Bull.* **1997**, *45*, 947.

(3) Winkelmann, K.; Heilmann, J.; Zerbe, O.; Rali, T.; Sticher, O. *J. Nat. Prod.* **2001**, *64*, 701–706.

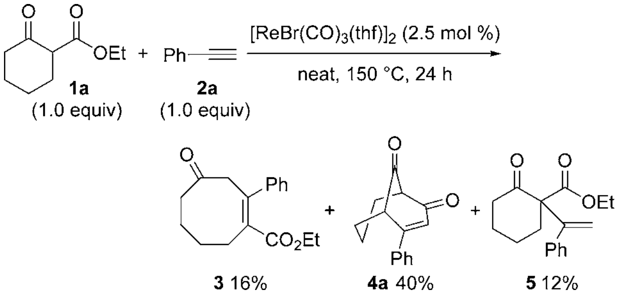
(4) Nicolaou, K. C.; Carenzi, G. E. A.; Jeso, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 3895–3899.

(5) (a) Spessard, S. J.; Stoltz, B. M. *Org. Lett.* **2002**, *4*, 1943–1946. (b) Usuda, H.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 3621–3624. (c) Takagi, R.; Nerio, T.; Miwa, Y.; Matsumura, S.; Ohkata, K. *Tetrahedron Lett.* **2004**, *45*, 7401–7405. (d) Kuramochi, A.; Usuda, H.; Yamatsugu, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 14200–14201.

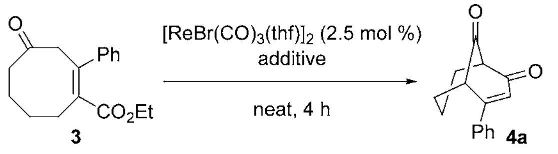
(6) Kraus, G. A.; Jeon, I. *Tetrahedron Lett.* **2008**, *49*, 286–288.

10.1021/ol900772h CCC: $40.75

(thf)]$_2$, as a catalyst at 150 °C for 24 h gave the ring expanded product **3**, bicyclo[3.3.1]nonene derivative **4a**, and alkenylated product **5** in 16, 40, and 12% yields, respectively (eq 1).[9,10] In this reaction, we considered that the bicyclic compound **4a** may be formed by intramolecular cyclization of the eight-membered cyclic compound **3** via the elimination of ethanol. To elucidate the hypothesis, **3** was treated with [ReBr(CO)$_3$(thf)]$_2$ in toluene at 150 °C for 4 h (eq 2). As a result, **4a** was afforded in 56% yield. This result showed that bicyclic compound **4a** was produced from the eight-membered product **3**. However, **4a** was not formed at 40 °C. Interestingly, by adding a catalytic amount of tetrabutylammonium fluoride (TBAF) and molecular sieves 4A (MS4A), the reaction was promoted dramatically; that is, the reaction temperature could be decreased to 40 °C and **4a** was produced in 95% yield (eq 2).[11−15]



(1)



(2)

additive		yield / %[a]
—	150 °C	56
—	40 °C	0
TBAF (20 mol %) + MS4A (100 wt %-Re cat.)	40 °C	95

[a] ^{1}H NMR yield.

The structure of bicyclic compound **4** was determined by X-ray single crystal structure analysis (Figure 2). A single crystal could be obtained using bicyclic compound **4e** (Table 2, entry 5). The result shows that bicyclic compound **4e** has a bicyclo[3.3.1]nonene framework. In addition, the two carbonyl and naphthyl groups are located at C1, C3, and C5 positions, respectively. The bond length between C4 and C5 is 1.350(3) Å, which is suitable for a double bond and shorter than other carbon−carbon bonds of the bicyclo[3.3.1]nonene framework (1.469(3) Å-1.569(4) Å).

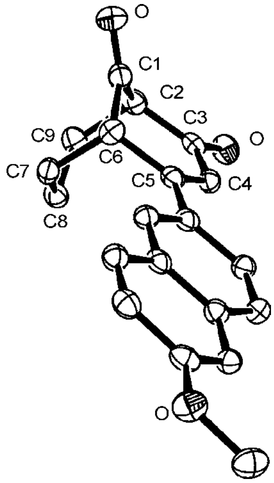
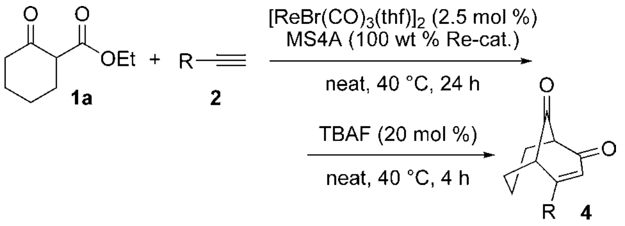
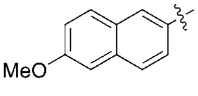
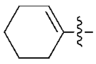


Figure 2. X-ray crystal structure of bicycle[3.3.1]nonene derivative **4e**. Hydrogen atoms are omitted for clarity.

When the reaction was carried out as a one-pot reaction using MS4A in the first step and TBAF in the second step, the yield of bicyclo[3.3.1]nonene derivative **4a** was improved (Table 1, entry 1). Treatment of cyclic β-keto ester **1a** with phenylacetylene (**2a**) in the presence of a catalytic amount of a rhenium complex, [ReBr(CO)$_3$(thf)]$_2$, and MS4A at 40

Table 1. Reactions between Cyclic β-Keto Ester **1a** and Alkynes **2**[a]



entry	alkyne (R)		yield / %[b]	
1	Ph	**2a**	**4a**	90
2	*p*-MeOC$_6$H$_4$	**2b**	**4b**	92
3[c]	*p*-CF$_3$C$_6$H$_4$	**2c**	**4c**	68
4[d]	*p*-BrC$_6$H$_4$	**2d**	**4d**	92
5[e]	 MeO	**2e**	**4e**	93
6		**2f**	**4f**	66
7[f]	^{n}C$_{10}$H$_{21}$	**2g**	**4g**	79

[a] **1a** (1.0 equiv), **2** (1.0 equiv). [b] Isolated yield. [c] Step 2: 6 h. [d] Step 1: toluene, 80 °C. Step 2: 80 °C, 2 h. [e] Step 1: 100 °C. Step 2: 80 °C, 2 h. [f] Step 1: 80 °C. Step 2: 80 °C, 2 h.

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(7) For the reviews of the synthesis of bicyclo[3.3.1]nonanes, see: (a) Peters, J. A. *Synthesis* **1979**, 321–336. (b) Butkus, E. *Synlett* **2001**, 1827–1835.

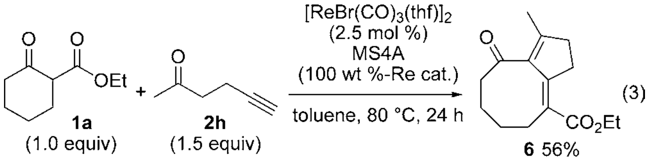
(8) We already reported on rhenium-catalyzed ring expansion reaction by the insertion of alkynes into a carbon-carbon single bond of cyclic β-keto esters. See: Kuninobu, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2006**, *128*, 11368–11369.

(9) The formation reaction of **4a** did not proceed using ReBr(CO)$_5$, RuH$_2$(CO)(PPh$_3$)$_3$, Ru$_3$(CO)$_{12}$, AuCl$_3$, PtCl$_2$, and GaCl$_3$.

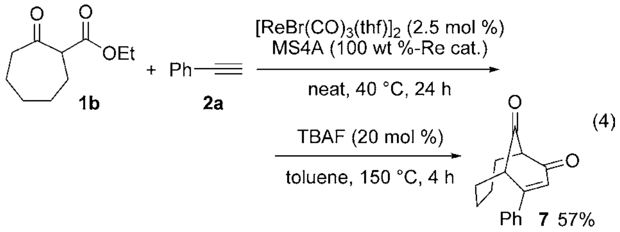
(10) This reactivity is in sharp contrast to the result that phenylacetylene (**2a**) inserts into a C−H bond of β-keto ester **1a** and yielded alkenylated product **5** quantitatively. See: Kuninobu, Y.; Kawata, A.; Takai, K. *Org. Lett.* **2005**, *7*, 4823–4825.

°C for 24 h followed by the treatment of a catalytic amount of TBAF at 40 °C for 4 h gave bicyclic compound **4a** in 90% yield (Table 1, entry 1).[16] Next, we investigated the scope and limitations of alkynes. *p*-Methoxyphenylacetylene (**2b**) also afforded bicyclo[3.3.1]nonene derivative **4b** in 92% yield (Table 1, entry 2). However, by using an alkyne bearing an electron-withdrawing group, **2c**, the yield of bicyclic compound **4c** was moderate (Table 1, entry 3). An aryl-substituted alkyne bearing a bromine also produced bicyclo[3.3.1]nonene derivative **4d** in 92% yield without losing the bromine (Table 1, entry 4). Naphthyl acetylene **2e** also provided bicyclic compound **4e** in 93% yield (Table 1, entry 5). In this reaction, alkenyl- and alkyl-substituted alkynes **2f** and **2g** could also be employed as substrates, and the corresponding bicyclo[3.3.1]nonene derivatives **4f** and **4g** were produced in 66% and 79% yields, respectively (Table 1, entries 6 and 7). However, in the case of trimethylsilylacetylene and diphenylacetylene, the reaction did not proceed.

When an alkyne having a carbonyl group, **2h**, was used, a different reaction proceeded (eq 3). By the reaction of cyclic *β*-keto ester **1a** with alkyne **2h** in the presence of a catalytic amount of a rhenium complex, $[ReBr(CO)_3(thf)]_2$, and MS4A in toluene at 80 °C for 24 h, bicyclic compound **6** was generated in 56% yield (eq 3). This reaction is likely to proceed via the insertion of the acetylene moiety of **2h** into a carbon−carbon single bond of cyclic *β*-keto ester **1a** followed by intramolecular cyclization via the elimination of water.

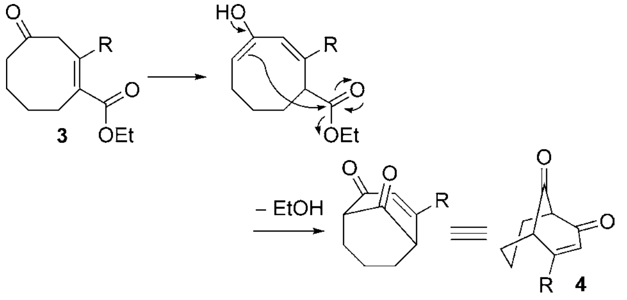


Next, we investigated using several cyclic *β*-keto esters. Seven-membered cyclic *β*-keto ester **1b** also provided the corresponding bicyclic product **7** in 57% yield (eq 4). However, cyclopentanone-2-carboxylic acid ethyl ester, cyclooctanone-2-carboxylic acid ethyl ester, and 1,3-cyclohexanedione did not react under the conditions.[17]



A proposed reaction mechanism for the formation of bicyclo[3.3.1]nonene derivatives from the corresponding eight-membered cyclic compounds **3**[8] is as follows; (1) isomerization of an olefin moiety and keto to enol form; and (2) intramolecular Claisen-type reaction via the elimination of ethanol.

Scheme 1. Proposed Mechanism for the Formation of Bicyclo[3.3.1]nonene Derivatives **4**



In summary, we have succeeded in the synthesis of bicyclo[3.3.1]nonene derivatives in good to excellent yields from cyclic *β*-keto esters and terminal alkynes. During the formation of the bicyclo[3.3.1]nonene framework from an eight-membered cyclic compound, TBAF plays a key role to promote the reaction efficiently under mild conditions. Since this reaction can be carried out as a one-pot reaction, and the starting materials, cyclic *β*-keto esters and terminal alkynes are easily available from chemical suppliers or by preparation, the reaction will become a useful and efficient method to synthesize bicyclo[3.3.1]nonene derivatives.

Acknowledgment. Financial support from the Ministry of Education, Culture, Sports, Science, and Technology of Japan is gratefully acknowledged.

Supporting Information Available: General experimental procedure, characterization data for bicyclo[3.3.1]nonenes **4**, **6**, and **7**, and data for X-ray crystal structure analysis of **4e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) The role of TBAF is not clear. However, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (20 mol %) also promoted the reaction and the corresponding bicyclic compound **4a** was formed in 16% yield. 1,4-Diazabicyclo[2.2.2]octane (DABCO) gave bicyclic compound **4a** in a trace amount. This result indicates that TBAF works as a base. There have been several reports on the use of TBAF as a base. See: (a) Gao, S.; Tseng, C.; Tsai, C. H.; Yao, C.-F. *Tetrahedron* **2008**, *64*, 1955. (b) Okutani, M.; Mori, Y. *J. Org. Chem.* **2009**, *74*, 442–444.

(12) Several bases, such as NaOH, $NaHCO_3$, Na_2CO_3, NEt_3, and pyridine, did not provide **4a** at 80 °C.

(13) Other ammonium halides, $^nBu_4NCl$, $^nBu_4NBr$, and $^nBu_4NI$, did not give **4a** at 80 °C.

(14) $^nBu_4NOH$ produced **4a** in 56% yield.

(15) Several metal fluoride, such as KF, KF+18-crown-6, and CsF did not promote the reaction at 80 °C.

(16) By using a manganese complex, $MnBr(CO)_5$ (5.0 mol %), as a catalyst, **4a** was formed in 57% yield (step 1: 80 °C, 24 h; step 2: 40 °C, 4 h).

(17) Cyclododecanone-2-carboxylic acid ethyl ester afforded a 2-pyranone derivative in 76% yield. For the synthesis of 2-pyranones from *β*-keto esters and alkynes, see: Kuninobu, Y.; Kawata, A.; Nishi, M.; Takata, H.; Takai, K. *Chem. Commun.* **2008**, 6360–6362.