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Rhenium-Catalyzed Insertion of Terminal Acetylenes into a C–H Bond of Active Methylene Compounds

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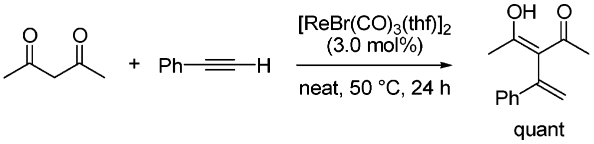
ABSTRACT



A rhenium complex, $[ReBr(CO)_3(thf)]_2$, catalyzed the intermolecular reactions of 1,3-dicarbonyl compounds with terminal acetylenes and gave the corresponding alkenyl derivatives in excellent yields. These reactions could apply to an intramolecular version and gave the corresponding cyclic compounds quantitatively.

Carbon−carbon bond formation reactions via enolate anions or enols are fundamental transformations.[1] There have been many reports on the transition metal-mediated reactions of enolate anions or enols with olefins or acetylenes.[2] Because the formation of enolate anions or enols and/or their reactions with acetylenes usually requires harsh conditions,[3] reactions that do not require this step have been desired. Recently, metal-catalyzed addition reactions of active methylene compounds with terminal acetylenes under mild conditions without the preparation step of enolate or enol have been reported. For example, gold[4] and nickel/ytterbium catalysts[5] have been used for intramolecular cyclization of δ- and ϵ-acetylenic 1,3-dicarbonyl compounds, respectively. In contrast, to our knowledge there have only been a few reports on an intermolecular version of the reaction in which the indium-catalyzed transformation could be carried out with or without the addition of bases.[6]

In the process of our investigation on the catalytic activities of rhenium complexes,[7,8] we found rhenium-catalyzed in-

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[3] Strong acid: (a) Boaventura, M. A.; Drouin, J.; Conia, J. M. *Synthesis* **1983**, 801. UV irradiation: (b) Cruciani, P.; Aubert, C.; Malacria, M. *Tetrahedron Lett.* **1994**, *35*, 6677. (c) Cruciani, P.; Stammler, R.; Aubert, C.; Malacria, M. *J. Org. Chem.* **1996**, *61*, 2699. (d) Renaud, J.-L.; Petit, M.; Aubert, C.; Malacria, M. *Synlett* **1997**, 931. (e) Renaud, J.-L.; Aubert, C.; Malacria, M. *Tetrahedron* **1999**, *55*, 5113.

[4] (a) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526. (b) Staben, S. T.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 5350.

[5] Gao, Q.; Zheng, B.-F.; Li, J.-H.; Yang, D. *Org. Lett.* **2005**, *7*, 2185.

[6] (a) Nakamura, M.; Endo, K.; Nakamura, E. *J. Am. Chem. Soc.* **2003**, *125*, 13002. (b) Nakamura, M.; Endo, K.; Nakamura, E. *Org. Lett.* **2005**, *7*, 3279.

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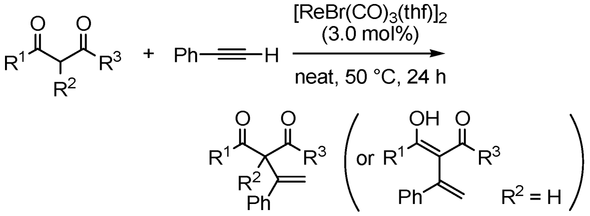
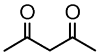
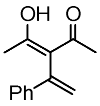
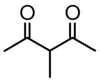
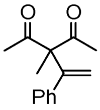
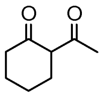
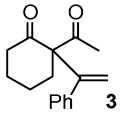
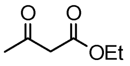
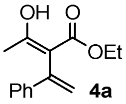
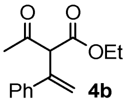
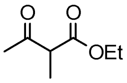
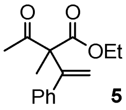
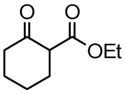
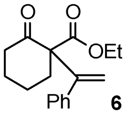
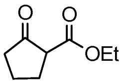
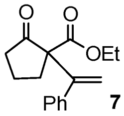
10.1021/ol0515208 CCC: $30.25

termolecular and intramolecular reactions of active methylene compounds with terminal acetylenes under mild reaction conditions.

Treatment of a mixture of pentane-2,4-dione (1.0 equiv) and phenylacetylene (1.0 equiv) in the presence of a rhenium catalyst, $[ReBr(CO)_3(thf)]_2$, at 50 °C for 24 h under solvent-free conditions gave **1** quantitatively and regioselectively (Table 1, entry 1). The product **1** results from the insertion of the terminal acetylene into the C−H bond of the active methylene compound. In this reaction, a regioisomeric product generated by C−C bond formation at the terminal carbon atom of the acetylene was not observed. Under higher temperature conditions (90 °C and reflux), the yield of **1** decreased owing to the polymerization of acetylene. When 3-methylpentane-2,4-dione was used as the active methylene compound, the yield was low (Table 1, entry 2). However, the reaction proceeded in excellent yield in the case of 2-acetylcyclohexanone (Table 1, entry 3). A β-keto ester, ethyl 3-oxobutanoate, also reacted with phenylacetylene to give the corresponding alkenyl derivative in excellent yield (Table 1, entry 4).[9] The reaction of ethyl 2-methyl-3-oxobutanoate and phenylacetylene gave an alkenyl derivative **5** in 70% yield (Table 1, entry 5). In this case, addition of dysprosium triflate, $Dy(OTf)_3$, as a co-catalyst improved the yield markedly (Table 1, entry 6).[10] Both ethyl 2-oxocyclohexanecarboxylate and 2-oxocyclopentanecarboxylate could be used as active methylene compounds, and the corresponding products **6** and **7** were obtained in quantitative yields (Table 1, entries 7 and 8).[11]

Table 1. Reaction of 1,3-Diketone or β-Keto Ester with Phenylacetylene

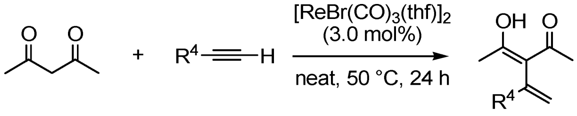


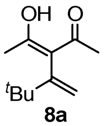
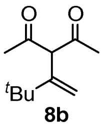
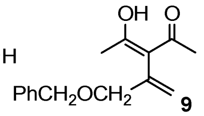
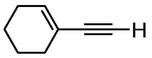
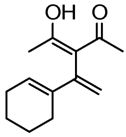
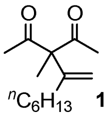
entry	substrate	product	yield[a] (%)
1[b]		 **1**	94% (>99%)
2[c]		 **2**	59% (62%)
3[d]		 **3**	92% (98%)
4[e]		 	93% (98%)[f]
5[g]		 **5**	67% (70%)
6[h]			95% (>99%)
7[d]		 **6**	95% (>99%)
8[i]		 **7**	94% (98%)

[a] Isolated yield. ^{1}H NMR yield is given in parentheses. [b] Acetylene (1.0 equiv). [c] Acetylene (2.0 equiv), 40 °C, 48 h. [d] Acetylene (1.5 equiv), 40 °C. [e] Acetylene (2.0 equiv), toluene was used as a solvent. [f] The ratio of enol/1,3-diketone was 95:5. [g] Acetylene (1.5 equiv). [h] $Dy(OTf)_3$ (5.0 mol %) was used as a co-catalyst, acetylene (1.5 equiv). [i] Acetylene (1.1 equiv), 40 °C.

Next, we examined reactions between several acetylenes and pentane-2,4-dione (Table 2). As described above, the reaction of phenylacetylene and pentane-2,4-dione gave the corresponding alkenyl compound **1** in quantitative yield

Table 2. Reaction of Pentane-2,4-dione with Several Acetylenes



entry	acetylene	product	yield[a] (%)
1[b]	$^{t}Bu-\equiv-H$	 **8a**  **8b**	88% (94%)[c]
2[d]	$PhCH_2OCH_2-\equiv-H$	 **9**	86% (>99%)
3[e]		 **10**	94% (98%)
4[f]	$^{n}C_6H_{13}-\equiv-H$	 **11**	95% (>99%)

[a] Isolated yield. ^{1}H NMR yield is given in parentheses. [b] Acetylene (3.0 equiv), 60 °C. [c] The ratio of enol/1,3-diketone was 1:1. [d] Acetylene (2.0 equiv), 40 °C. [e] Acetylene (1.1 equiv). [f] 3-Methylpentane-2,4-dione was used as a dicarbonyl substrate, acetylene (1.1 equiv).

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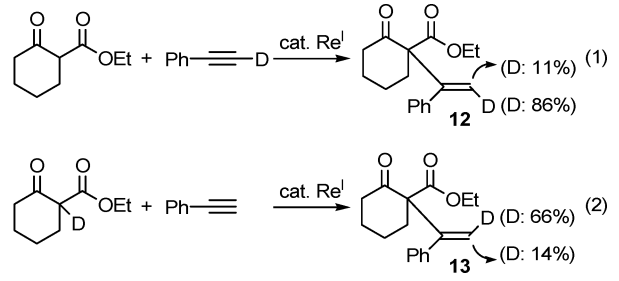
[8] For rhenium-catalyzed reactions from other groups, see: (a) Nishiyama, Y.; Kakushou, F.; Sonoda, N. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2779. (b) Hua, R.; Tian, X. *J. Org. Chem.* **2004**, *69*, 5782. (c) Jiang, J.-L.; Gao, F.; Hua, R.; Qiu, X. *J. Org. Chem.* **2005**, *70*, 381. (d) Liu, Y.; Hua, R.; Sun, H.-B.; Qiu, X. *Organometallics* **2005**, *24*, 2819. (e) Nishiyama, Y.; Kakushou, F.; Sonoda, N. *Tetrahedron Lett.* **2005**, *46*, 787.

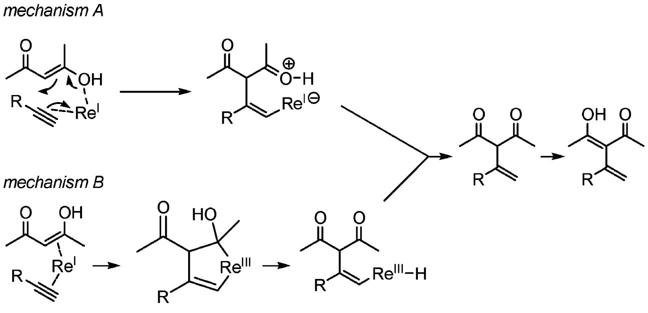
(Table 1, entry 1). By using *tert*-butylacetylene as a bulky acetylene, the desired product was formed in 94% yield (Table 2, entry 1). However, the reaction did not proceed with trimethylsilylacetylene or an internal acetylene (1-phenyl-1-propyne). An ether group connected to the terminal acetylene did not disturb the reaction, and the corresponding compound **9** was obtained quantitatively (Table 2, entry 2). The reaction of 1-ethynylcyclohex-1-ene with pentane-2,4-dione also proceeded in excellent yield (Table 2, entry 3). Also, the reaction of 1-hexyne with 3-methylpentane-2,4-dione instead of pentane-2,4-dione gave the corresponding alkenyl derivative **11** in quantitative yield (Table 2, entry 4).

To elucidate the mechanism of these reactions, we carried out deuterium labeling experiments (eqs 1 and 2). The reaction of ethyl 2-oxocyclohexanecarboxylate and deuterated phenylacetylene afforded an alkenyl derivative **12** selectively, in which the deuterium locates anti to the β-keto ester moiety (eq 1). On the other hand, by the reaction of deuterated ethyl 2-oxocyclohexanecarboxylate with phenylacetylene, **13** was obtained selectively, with deuterium syn to the β-keto ester group (eq 2).

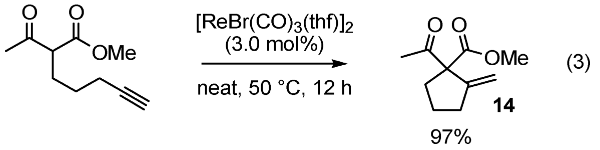


These deuterium labeling results support the proposed mechanisms of the addition reactions of active methylene compounds with terminal acetylenes as shown in Scheme 1. The rhenium catalyst coordinates to a terminal acetylene and an enol, derived from a 1,3-dicarbonyl compound.[5,8b] Nucleophilic addition of the enol to the rhenium-coordinated acetylene gives an alkenylrhenium(I) intermediate (mechanism A). After protonation, the rhenium catalyst is regenerated and a 2-alkenyl-substituted 1,3-dicarbonyl compound is formed. The other possibility is as follows: Cyclization of the enol−rhenium(I)−acetylene species give a rhenacyclopentene intermediate. Then, β-hydride elimination followed by reductive elimination affords a 2-alkenyl-substituted 1,3-dicarbonyl compound (mechanism B). When the 1,3-dicarbonyl compound does not have a substituent at the 2-position, the corresponding enol is obtained as a product after the isomerization of the olefin moiety.

Scheme 1. Proposed Mechanism of the Catalytic Alkenylation



The reaction can be applied in an intramolecular version, which is the same transformation as the Conia-ene reaction (eq 3).[12] By heating a β-keto ester bearing a terminal acetylene moiety at 50 °C for 12 h, the Conia-ene reaction occurred and the corresponding methylenecyclopentane **14** was obtained in excellent yield.



In summary, we succeeded in the rhenium complex, $[ReBr(CO)_3(thf)]_2$, catalyzed intermolecular nucleophilic addition of an active methylene compound with a terminal acetylene under mild reaction conditions. This reaction could be applied to the intramolecular version (Conia-ene reaction), and the corresponding cyclic compound could be obtained. These reactions are the first examples of rhenium-catalyzed additions of active methylene compounds with terminal acetylenes, and are useful for the synthesis of 2-alkyl-substituted 2-ethenyl-1,3-dicarbonyl compounds under mild conditions. We are now investigating C−C bond formation reactions based on the activation of acetylenes with rhenium catalysts.

Acknowledgment. Financial support by a Grant-in-Aid for Scientific Research on Priority Areas (No. 14078219, “Reaction Control of Dynamic Complexes”) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan.

Supporting Information Available: General experimental procedure and characterization data for alkenyl derivatives. This material is available free of charge via the Internet at http://pubs.acs.org.

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[9] Investigation of solvents: toluene; 22%, THF.; 1%, CH_2ClCH_2Cl; 45%.

[10] $Dy(OTf)_3$ did not show the promotion activity in the reaction of 1,3-diketone and phenylacetylene (Table 1, entry 2).

[11] The reaction did not proceed by using dimethyl malonate, 1-phenyl-2-(phenylsulfonyl)ethanone, ethyl 2-cyanoacetate, 3-pentanone and propiophenone.

[12] For a review, see: Conia, J. M.; Le Perchec, P. *Synthesis* **1975**, 1.