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Rhenium-Catalyzed Synthesis of Multisubstituted Aromatic Compounds via C−C Single-Bond Cleavage

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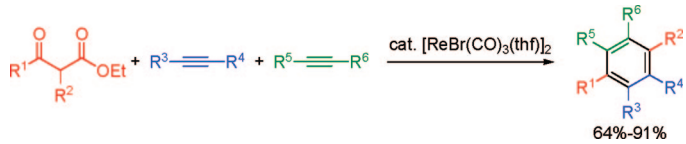
ABSTRACT



A reaction between a β-keto ester and an acetylene in the presence of a rhenium complex, $[ReBr(CO)_3(thf)]_2$, as a catalyst, provided a 2-pyranone derivative in excellent yield via retro-aldol reaction (C−C single bond cleavage). By adding an acetylene-bearing ester group(s) after the formation of 2-pyranones, an aromatization reaction proceeded and multisubstituted aromatic compounds were obtained in good to excellent yields.

Aromatic skeletons are important as the fundamental structures of natural products, functional materials, and starting substrates of organic molecules. Thus, the development of an efficient method for the synthesis of aromatic compounds, in particular multisubstituted ones, is useful. Several methods for the synthesis of multisubstituted aromatic compounds have previously been reported.[1] As a new strategy for the synthesis of multisubstituted aromatic compounds, we disclose here the retro-synthesis of a multisubstituted aromatic compound from a β-keto ester and two kinds of acetylenes via carbon−carbon bond cleavage of the β-keto ester (Figure 1).

As a preliminary investigation, a reaction of β-keto ester **1a** with diphenylacetylene (**2a**) was carried out in the presence of a rhenium complex, $[ReBr(CO)_3(thf)]_2$, in a sealed tube at 180 °C for 24 h. We unexpectedly obtained 2-pyranone **3a** in a quantitative yield (eq 1).[2–4] The compound is formally generated via cleavage between α- and β-carbons of **1a**, insertion of the acetylene,[5] followed by cyclization. This result encouraged us to use the 2-pyranone as a component of a multisubstituted aromatic compound by the reaction with a second acetylene.[6]

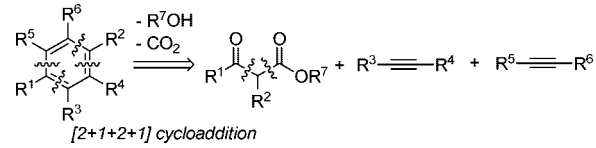
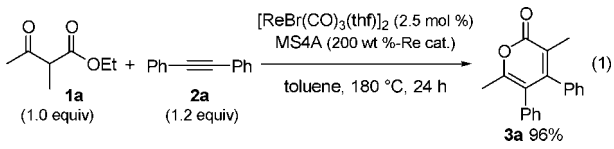


Figure 1. Synthetic strategy for the multisubstituted aromatic compounds.



(1) Trimerization of acetylenes: (a) Vollhardt, K. P. C *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539. Dehydrative trimerization of ketones: (b) Elmorsy, S. S.; Pelter, A.; Smith, K *Tetrahedron Lett.* **1991**, *32*, 4175. [3 + 3] Cycloaddition: (c) Katritzky, A. R.; Li, J.; Xie, L *Tetrahedron* **1999**, *55*, 8263. Diels−Alder reaction: (d) Danishefsky, S.; Yan, C.-F.; Singh, R. K.; Gammill, R. B.; McCurry, P. M., Jr.; Fritsch, N.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 7001. (e) Olsen, R. K.; Feng, X.; Campbell, M.; Shao, R.; Math, S. K. *J. Org. Chem.* **1995**, *60*, 6025. (f) Sestelo, J. P.; Real, M. d. M.; Mouriño, A.; Sarandeses, L. A. *Tetrahedron Lett.* **1999**, *40*, 985. Bergman cyclization: (g) Jones, R. R.; Bergmann, R. G *J. Am. Chem. Soc.* **1972**, *94*, 660. Benzannulation of vinylketenes with acetylenes: (h) Danheiser, R. L.; Gee, S. K *J. Org. Chem.* **1984**, *49*, 1672. [4 + 2] Cycloaddition of carbonyl compounds: (i) Boger, D. L.; Mullican, M. D. *J. Org. Chem.* **1980**, *45*, 5002. Ring-closing metathesis: (j) Yoshida, K.; Imamoto, T *J. Am. Chem. Soc.* **2005**, *127*, 10470.

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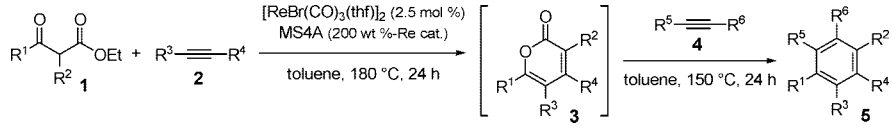
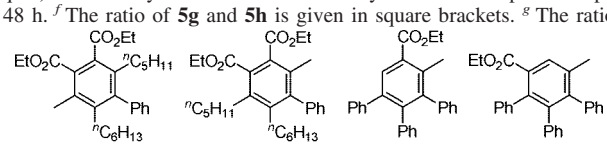
Table 1. Synthesis of Aromatic Compounds from β-Keto Esters and Two Acetylenes[a]



entry	R^1	R^2	R^3	R^4	R^5	R^6	yield[b]/%
1	Me	Me **1a**	Ph	Ph **2a**	CO_2Et	CO_2Et **4a**	**5a**, 83 (88)
2	Ph	Me **1b**	**2a**		**4a**		**5b**, 64 (67)
3	Me	H **1c**	**2a**		**4a**		**5c**, 84 (89)
4	**1a**		Me	Ph **2b**	**4a**		**5d**, 91 (92)
5	**1a**		H	Ph **2c**[c]	**4a**[d]		**5e**, 87 (93)
6	**1a**		H	$^nC_{10}H_{21}$ **2d**[e]	**4a**[d]		**5f**, 72 (77)
7	Me	$^nC_5H_{11}$ **1d**	$^nC_6H_{13}$	Ph **2e**	**4a**		**5g** + **5h**, 85 (89) [**5g**:**5h** = 96:4][f]
8	$^nC_5H_{11}$	Me **1e**	**2e**		**4a**		**5g** + **5h**, 83 (89) [**5g**:**5h** = 6:94][f]
9	**1a**		**2a**		CO_2Et	H **4b**	**5i**, 86 (89)
10	**1b**		**2a**		**4b**		**5j** + **5k**, 77 (81) [**5j**:**5k** = 39:61][g]

[a] **1** (1.0 equiv); **2** (1.2 equiv); **4** (2.0 equiv). [b] Isolated yield. Yield determined by ^{1}H NMR is reported in parentheses. [c] 80 °C, 8 h; 180 °C, 16 h. [d] **4a** (1.0 equiv, 8 h) was added three times. [e] 48 h. [f] The ratio of **5g** and **5h** is given in square brackets. [g] The ratio of **5j** and **5k** is given in square brackets.



Treatment of **1a** with **2a** in the presence of a catalytic amount of $[ReBr(CO)_3(thf)]_2$ and molecular sieves at 180 °C for 24 h, followed by the addition of acetylene dicarboxylic acid ethyl ester (**4a**) and heating at 150 °C for 24 h, gave hexasubstituted benzene derivative **5a** in 83% yield (Table 1, entry 1).[7,8] Stepwise syntheses of hexasubstituted benzenes were examined (Table 1). β-Keto esters bearing a phenyl group at the R^1 position, **1b**, and without any substituents at the R^2 position, **1c**, also afforded the corresponding aromatic compounds **5b** and **5c** in 64% and 84% yields, respectively (Table 1, entries 2 and 3). 1-Phenyl-1-propyne (**2b**) inserted into a carbon−carbon single bond of the β-keto ester regioselectively and provided the hexasubstituted aromatic compound **5d** in 91% yield (Table 1, entry 4). Next, terminal acetylenes were investigated. It was found that insertion of terminal acetylenes into a carbon−carbon bond of β-keto esters occurred regioselectively, and pentasubstituted benzene derivatives **5e** and **5f** were obtained as single products (Table 1, entries 5 and 6).[9] Because the introduction of the substituents into β-keto esters (R^1 and R^2 positions) and acetylenes (R^3 and R^4 positions) is easy, multisubstituted aromatic compounds can be synthesized regioselectively. For example, treatment of ethyl 2-acetylheptanoate (**1d**) with 1-phenyl-1-octyne (**2e**) followed by the reaction with **4a** produced hexasubstituted aromatic compounds **5g** and **5h** (96:4) in 85% yield (Table 1, entry 7). Also, a reaction between ethyl 2-methyl-3-oxooctanoate (**1e**), **2e**, and **4a** gave **5g** and **5h** (6:94) in 83% yield (Table 1, entry 8).

By the reaction of β-keto ester **1a** with diphenylacetylene (**2a**) at 180 °C for 24 h, followed by the addition of ethyl propiolate (**4b**) and heating at 150 °C for 24 h, multisubstituted benzene **5i** was produced regioselectively in 86% yield (Table 1, entry 9). However, as with the acetylene component **4**, diphenylacetylene and 6-dodecyne did not produce the corresponding multisubstituted aromatic compounds. By using dissymmetric acetylene **4b**, the reaction proceeded with moderate regioselectivity, and the mixture of pentasubstituted aromatic compounds, **5j** and **5k** (39:61), was provided in 77% yield (Table 1, entry 10).

(2) 2-Pyranones are useful as building blocks in organic synthesis and partial structures of bioactive compounds. See: (a) Ichihara, A.; Murakami, K.; Sakamura, S *Tetrahedron* **1987**, *43*, 5245. (b) Shi, X.; Leal, W. S.; Schrader, E.; Meinwald, J. *Tetrahedron Lett.* **1995**, *36*, 71. (c) Kamano, Y.; Nogawa, T.; Yamashita, A.; Hayashi, M.; Inoue, M.; Drasar, P.; Pettit, G. R. *J. Nat. Prod.* **2002**, *65*, 1001.

(3) For some representative examples of 2-pyranone synthesis, see: (a) Cho, S. H.; Liebeskind, L. S. *J. Org. Chem.* **1987**, *52*, 2631. (b) Tsuda, T.; Morikawa, S.; Sumiya, R.; Saegusa, T. *J. Org. Chem.* **1988**, *53*, 3140. (c) Larock, R. C.; Han, X.; Doty, M. J. *Tetrahedron Lett.* **1998**, *39*, 5713. (d) Fukuyama, T.; Higashibeppu, Y.; Yamaura, R.; Ryu, I. *Org. Lett.* **2007**, *9*, 587.

(4) In our previous report (ref [5]), an isocyanide ligand is efficient for the expansion of ring skeletons. However, the addition of isocyanide was not effective for this reaction.

(5) For a ring-expansion reaction via insertion of an acetylene into a carbon−carbon single bond of β-keto esters, see: (a) Kuninobu, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2006**, *128*, 11368.

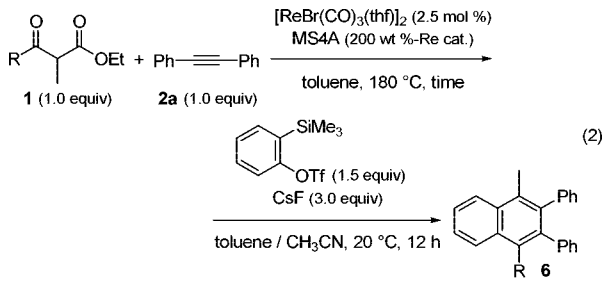
(6) For the formation of aromatic compounds from 2-pyranones and acetylenes, see: (a) Tam, T. F.; Coles, P. *Synthesis* **1988**, 383. (b) Afarinkia, K.; Vinader, V.; Nelson, T. D.; Posner, G. H. *Tetrahedron* **1992**, *48*, 9111.

(7) The addition of molecular sieves is important to promote the reaction efficiently. In the absence of molecular sieves, aromatic compound **5a** was obtained in only 49% yield.

(8) Aromatic compound **5a** was not formed because polymerization of acetylene **4a** occurred when **4a** was added at the beginning.

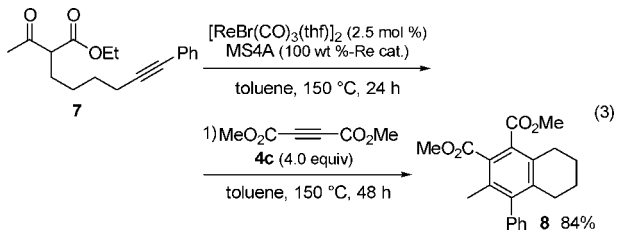
(9) When propargyl alcohol, ether, and amine were employed as terminal acetylene **2** in the equation of Table 1, neither multisubstituted aromatic compound **5** nor 2-pyranone **3** was produced. Instead, an enamine of the keto moiety of β-keto ester **1** was generated in the case of propargylamine. Both reactions using propargyl alcohol and ether gave complex mixtures.

As the second acetylene component, benzyne generated in situ from 2-trimethylsilylphenyl triflate and cesium fluoride could be employed; naphthalene derivatives **6a** and **6b** were obtained in 92% and 96% yields, respectively (eq 2).



R	time	yield / %
Me **1a**	24 h	**6a** 92%
Ph **1b**	48 h	**6b** 96%

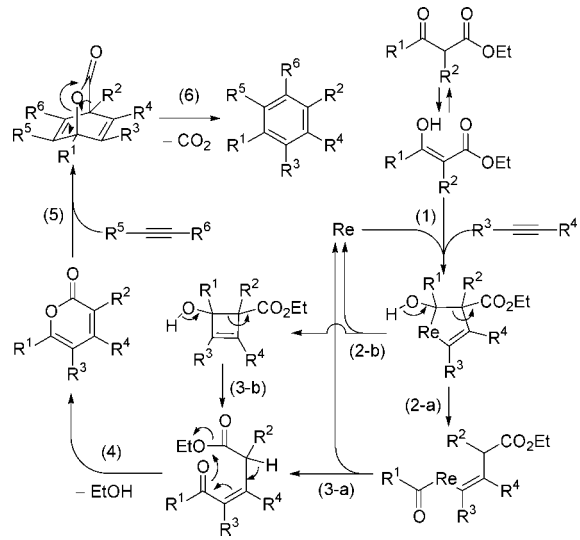
The first step of this substituted benzene synthesis could be applied to an intramolecular reaction (eq 3). By heating β-keto ester **7** in toluene at 150 °C for 24 h in the presence of a catalytic amount of the rhenium complex and a stoichiometric amount of molecular sieves, followed by the addition of an acetylene **4c** and heating at 150 °C for 24 h, tetrahydronaphthalene derivative **8** was obtained in 84% yield (eq 3).



The proposed reaction mechanism is as follows (Scheme 1): (1) A rhenacyclopentene intermediate is formed by the reaction between a rhenium catalyst, β-keto ester, and acetylene. In this step, the β-keto ester and acetylene orient regioselectively. After the formation of the rhenacyclopentene intermediate, δ-keto ester is generated via (2-a and 3-a) carbon−carbon bond cleavage via retro-aldol reaction,[10,11] followed by reductive elimination or (2-b and 3-b), a pathway that has a different timing for the reductive elimination.[8,9] (4) Isomerization of the olefinic moiety of the δ-keto ester and cyclization leads to 2-pyranone.[12] (5) Diels−Alder reaction occurs between 2-pyranone and the second acetylene. (6) Decarboxylation occurs.[5]

In the case of synthesizing multisubstituted aromatic compounds, it is important to introduce the desired substituents regioselectively. From this viewpoint, the method is advantageous because substituents can easily be introduced into acetylenes and the α- and γ-positions of β-keto esters, and the reaction proceeds regioselectively. We hope that this reaction will give useful insights into synthetic organic chemistry based on carbon−carbon bond cleavage under transition metal catalysis.

Scheme 1. Proposed Mechanism for the Formation of Multisubstituted Aromatic Compounds



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

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(10) There have been some examples on chemical transformations via carbon−carbon bond cleavage. See: (a) Murakami, M.; Ito, Y.; Murai, S. *Top. Organomet. Chem.* **1999**, *3*, 97. (b) Jun, C.-H. *Chem. Soc. Rev.* **2004**, *33*, 610.

(11) (a) Kochetkov, N. K.; Kudryashov, L. J.; Gottich, B. P. *Tetrahedron* **1961**, *12*, 63. (b) Crombie, L.; James, A. W. G. *Chem. Commun.* **1966**, 357.

(12) (a) Fried, J.; Elderfield, R. C. *J. Org. Chem.* **1941**, *6*, 566. (b) Wiley, R. H.; Jarboe, C. H.; Hayes, F. N. *J. Am. Chem. Soc.* **1957**, *79*, 2602.