ORGANIC
LETTERS

2008
Vol. 10, No. 14
3009−3011

Manganese-Catalyzed Construction of Tetrasubstituted Benzenes from 1,3-Dicarbonyl Compounds and Terminal Acetylenes

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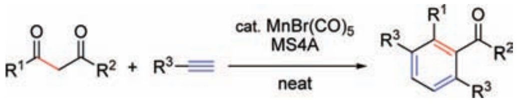
Received April 28, 2008

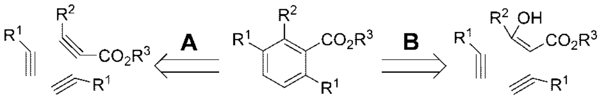
ABSTRACT



Treatment of β-keto esters with terminal acetylenes in the presence of a catalytic amount of a manganese complex, $MnBr(CO)_5$, and molecular sieves, gave multisubstituted aromatic compounds in good to excellent yields. This reaction employs [2 + 2 + 2] cycloaddition of β-keto esters and 2 equiv of terminal acetylenes with dehydration. In the case of a 1,3-diketone, the corresponding acetophenone derivative and its deacylated compound can be synthesized selectively.

Benzene rings are key structures in many organic molecules, such as functional materials and bioactive compounds. There have been many reports on the construction of aromatic rings; in particular, transition-metal-catalyzed reactions are powerful and efficient.[1,2] Among them, [2 + 2 + 2] cycloaddition of three acetylenes is one of the most well-known reactions;[3] however, the construction of the desired substituted benzene rings is difficult due to the low pair selectivity and regioselectivity (Scheme 1, **A**).[4] Here, we disclose a regioselective synthesis of terphenyls from two terminal acetylenes and one 1,3-dicarbonyl compound via dehydration (Scheme 1, **B**).

Scheme 1. Formation of Benzenes by [2 + 2 + 2] Cycloaddition



During an investigation on the catalytic activities of rhenium complexes,[5,6] we accidentally found that benzenes

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(1) (a) Asao, N.; Takahashi, K.; Lee, S.; Kasahara, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 12650–12651. (b) Shen, H.-C.; Pal, S.; Lian, S.-S.; Liu, R.-S. *J. Am. Chem. Soc.* **2003**, *125*, 15762–15763. (c) Shibata, T.; Fujimoto, T.; Yokota, K.; Takagi, K. *J. Am. Chem. Soc.* **2004**, *126*, 8382–8383. (d) Yoshida, K.; Imamoto, T. *J. Am. Chem. Soc.* **2005**, *127*, 10470–10471. (e) Yamamoto, Y. *Synth. Org. Chem. Jpn.* **2005**, *63*, 112–121. (f) Tanaka, K. *Synlett* **2007**, *1977*, 1993. (g) Austin, W. F.; Zhang, Y.; Danheiser, R. L. *Tetrahedron* **2008**, *64*, 915–925.

(2) Transition-metal-mediated reactions have also been reported. See: (a) Iwasawa, N.; Shido, M.; Maeyama, K.; Kusama, H. *J. Am. Chem. Soc.* **2000**, *122*, 10226–10227. (b) Ohe, K.; Miki, K.; Yokoi, T.; Nishino, F.; Uemura, S. *Organometallics* **2000**, *19*, 5525–5528. (c) Yawer, M. A.; Hussain, I.; Reim, S.; Ahmed, Z.; Ullah, E.; Iqbal, I.; Fischer, C.; Reinke, H.; Gorls, H.; Langer, P. *Tetrahedron* **2007**, *63*, 12562–12575.

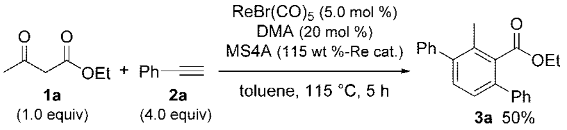
(3) (a) Grotjahn, D. B. In *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 12, pp 741−770. (b) Bonnemann, H.; Brijoux, W. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 1, pp 171−197.

(4) To overcome the difficulty, several methods have been developed. See: (a) Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539–556. (b) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901–2916. (c) Mori, N.; Ikeda, S.; Odashima, K. *Chem. Commun.* **2001**, 181–182.

(5) (a) Kuninobu, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2005**, *127*, 13498–13499. (b) Kuninobu, Y.; Inoue, Y.; Takai, K. *Chem. Lett.* **2006**, *35*, 1376–1377. (c) Kuninobu, Y.; Tokunaga, Y.; Takai, K. *Chem. Lett.* **2007**, *36*, 872–873. (d) Kuninobu, Y.; Ishii, E.; Takai, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 3296–3299. (e) Kuninobu, Y.; Yu, P.; Takai, K. *Chem. Lett.* **2007**, *36*, 1162–1163. (f) Yudha, S. S.; Kuninobu, Y.; Takai, K. *Org. Lett.* **2007**, *9*, 5609–5611.

10.1021/ol800969h CCC: $40.75

can be formed by reactions between β-keto esters and acetylenes.[7] Treatment of β-keto ester **1a** and phenylacetylene (**2a**) with a rhenium complex, $[ReBr(CO)_3(thf)]_2$ (2.5 mol%), at 50 °C for 24 h gave ethyl 2-acetyl-3-phenyl-3-butenoate, which is an insertion product of **2a** into an α-C-H of **1a**, in 93% yield.[8] When the reaction was conducted at 100 °C in the presence of molecular sieves 4A, ethyl (*E*)-3-phenyl-5-oxo-2-hexenoate and ethyl (*E*)-3-phenyl-5-oxo-3-hexenoate were produced in 48% and 24% yields, respectively.[9,10] However, when pyrrolidinone (20 mol %) was added before the mixture was heated at 115 °C in a sealed tube, a tetrasubstituted aromatic compound **3a** was produced in 44% yield.[10] The result encouraged us to carry out further investigations. By using a combination of $ReBr(CO)_5$ (5.0 mol %), *N*,*N*-dimethylacetoamide (DMA), and molecular sieves 4A as a catalyst, the yield of **3a** was improved to 50% (eq 1).[11]



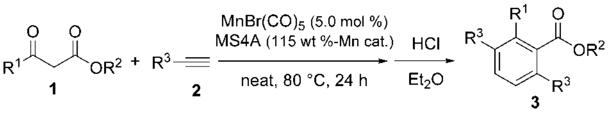
(1)

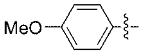
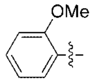
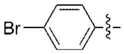
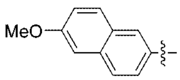
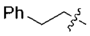
DMA = *N*,*N*-dimethylacetoamide

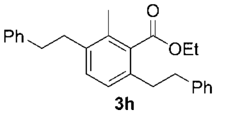
Following further investigations of catalysts, we found that a combination of $MnBr(CO)_5$[12] and molecular sieves 4A has a higher catalytic activity and wide applicability compared to the rhenium system. For example, treatment of ethyl 3-oxobutanoate (**1a**) with phenylacetylene (**2a**) in the presence of $MnBr(CO)_5$ (5 mol %) and molecular sieves 4A, without any solvents, gave ethyl benzoate (**3a**) in 85% yield (Table 1, entry 1).[13,14]

To investigate the scope and limitations of substrates, reactions between β-keto esters and acetylenes were carried out (Table 1, entries 2−8). Methyl 3-oxobutanoate (**1b**) and ethyl 3-oxo-3-phenylpropanoate (**1c**) also produced benzoates **3b** and **3c** in 65% and 88% yields, respectively (entries 2 and 3). However, by using β-keto esters with substituents at the active methylene moiety, the multisubstituted aromatic compounds were not formed, and carbon-chain extension reactions and formation reactions of 2-pyranones proceeded.[9] Aryl acetylenes bearing an electron-donating group at the *p*- and *o*-positions **2b** and **2c** afforded aromatic compounds **3d** and **3e** in 77% and 74% yields, respectively (entries 4 and 5).

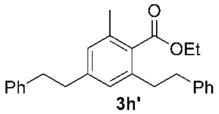
Table 1. Reactions between β-Keto Esters **1** and Acetylenes **2**[a]



entry	R^1	R^2		R^3			% yield[b]
1	Me	Et	**1a**	Ph	**2a**	**3a**	85
2	Me	Me	**1b**	**2a**		**3b**	65
3	Ph	Et	**1c**	**2a**		**3c**	88
4	**1c**				**2b**	**3d**	77
5	**1c**				**2c**	**3e**	74
6	**1c**				**2d**	**3f**	86
7	**1c**				**2e**	**3g**	71
8	**1c**				**2f**	**3h** + **3h′**	88 [2.7:1][c]



3h



3h'

[a] **1** (1.0 equiv), **2** (2.5 equiv). [b] Isolated yield. [c] The ratio between **3h** and **3h′**.

Benzoate **3f** was obtained in 86% yield using aryl acetylene **2d** with a bromo group at the *p*-position (entry 6). In this case, carbon−bromine bond remained intact during the reaction. 2-Ethynyl-6-methoxynaphthalene (**2e**) also provided tetrasubstituted benzene **3g** in 71% yield (entry 7). When 4-phenyl-1-butyne (**2f**) was used as an acetylene component, two regioisomeric benzenes **3h** and **3h′** were obtained in 88% yield in a ratio of 2.7:1 (entry 8). Internal acetylenes, however, did not react under the conditions.

Next, the effects of replacing β-keto esters with 1,3-diketones were investigated. Treatment of 2,4-pentanedione

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(6) (a) Kühn, F. E.; Scherbaum, A.; Herrmann, W. A. *J. Organomet. Chem.* **2004**, *689*, 4149–4164. (b) Luzung, M. R.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 15760–15761. (c) Nolin, K. A.; Ahn, R. W.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 12462–12463. (d) Kusama, H.; Yamabe, H.; Onizawa, Y.; Hoshino, T.; Iwasawa, N. *Angew. Chem., Int. Ed.* **2005**, *44*, 468–470. (e) Ouh, L. L.; Müller, T. E.; Yan, Y. K. *J. Organomet. Chem.* **2005**, *690*, 3774–3782.

(7) During the preparation of this manuscript, we learned that Prof. Eiichi Nakamura and Prof. Hayato Tsuji at the University of Tokyo also discovered a similar manganese-catalyzed reaction. We thank Profs. Nakamura and Tsuji for exchanging valuable information prior to publication: Tsuji, H.; Yamagata, K.; Fujimoto, T.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, in press

(8) For rhenium-catalyzed insertion of terminal acetylenes into a C−H bond of the active methylene moieties of 1,3-dicarbonyl compounds, see: (a) Kuninobu, Y.; Kawata, A.; Takai, K. *Org. Lett.* **2005**, *7*, 4823–4825.

(9) Insertion of acetylenes into a C−C bond of 1,3-dicarbonyl compounds occurs with a rhenium or manganese catalyst. See: Kuninobu, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2006**, *128*, 11368–11369.

(10) The reactivity is in sharp contrast to that of indium-catalyzed reaction between **1a** and **2a**, where only an alkenylated product at the α-position of the β-keto ester is formed quantitatively. (a) Nakamura, M.; Endo, K.; Nakamura, E. *J. Am. Chem. Soc.* **2003**, *125*, 13002–13003. (b) Endo, K.; Hatakeyama, T.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2007**, *129*, 5264–5271.

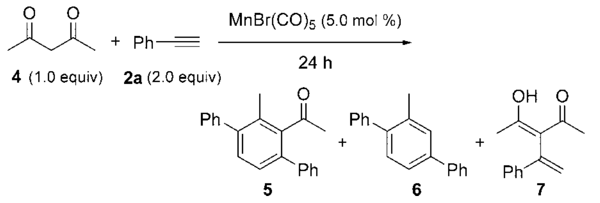
(11) Acetoamide, 20%; *N*-methylacetoamide, 22%; *N*-methylpyrrolidinone, 68%.

(12) For $MnBr(CO)_5$-catalyzed transformation, see: (a) Kuninobu, Y.; Nishina, Y.; Takeuchi, T.; Takai, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 6518–6520.

(13) There have been a few reports on the synthesis of aromatic compounds from 1,3-dicarbonyl compounds and acetylenes. However, in each case, terminal acetylenes having an ester moiety (or moieties) are necessary to promote the reaction. See: (a) Nair, V.; Vidya, N.; Biju, A. T.; Deepthi, A.; Abhilash, K. G.; Suresh, E. *Tetrahedron* **2006**, *62*, 10136–10140. (b) Zhou, Q.-F.; Yang, F.; Guo, O.-X.; Xue, S. *Synlett* **2007**, 2073–2076.

(14) When a gram scale reaction was carried out (**1a**: 1.04 g, 8.00 mmol), aromatic compound **3a** was obtained in 73% yield.

Table 2. Reactions between 1,3-Diketone **4** and Acetylene **2a**



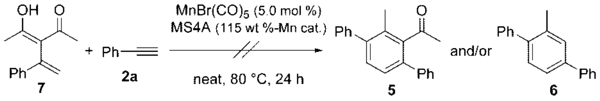
T (°C)	additive	solvent	% yield[a] 5	6	7
50	MS4A (115 wt % Mn)	toluene	69 (71)	5 (7)	7 (10)
80	none	toluene/H_2O (1:1)	20 (24)	66 (68)	– (trace)
80	$Sc(OTf)_3$ (5.0 mol %)	toluene/H_2O (1:1)	16 (20)	68 (70)	4 (6)

[a] Isolated yield. Yield determined by ^{1}H NMR is reported in parentheses.

(**4**) with phenylacetylene (**2a**) in the presence of a manganese complex, $MnBr(CO)_5$, as a catalyst at 80 °C for 24 h gave tetrasubstituted benzene **5** in 19% yield. Unexpectedly, the deacylated aromatic compound **6** was also obtained in 40% yield.[15,16] By using toluene as a solvent and molecular sieves as an additive, the ratio of **5** was increased, and **5**, **6**, and **7** were provided in 69%, 5%, and 7% yields, respectively (Table 2). Similar to the case of β-keto esters, 1,3-diketones with a substituent at the active methylene moiety did not afford tetrasubstituted aromatic compounds.

We next focused our attention on the synthesis of deacylated compound **6**. When a mixture of toluene and water (1:1) was used as a solvent, the ratio of **6** increased, and deacylated aromatic compound **6** and acetophenone derivative **5** were produced in 66% and 20% yields, respectively (Table 2). The ratio was slightly improved by addition of $Sc(OTf)_3$ as an additive.

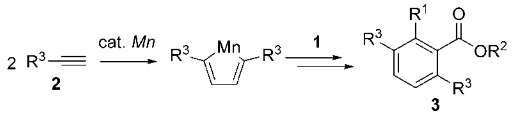
To elucidate the reaction mechanism, we carried out the following experiment. When the alkenylated product **7** was treated with phenylacetylene (**2a**), aromatic compounds **5** and **6** were not formed (eq 3). This result suggests that the formation reactions of aromatic compounds **5** and **6** do not proceed via **7** as an intermediate.



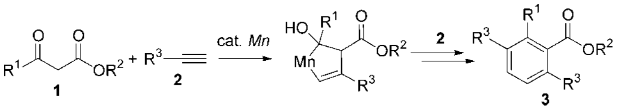
(3)

The para selectivity of two substituents derived from an acetylene suggests the formation of a manganacyclopentadiene intermediate, where both substituents are located at the 2- and 5-positions (Scheme 2). Another possibility is that the reaction proceeds via the formation of a metalacyclopentene intermediate by the reaction between a 1,3-dicarbonyl compound and an acetylene (Scheme 3). The intermediate is thought to be a manganese- and rhenium-catalyzed carbon-chain extension reaction.[8a] The mechanism for the formation of tetrasubstituted aromatic compounds, however, is still not clear.

Scheme 2. Formation of Tetrasubstituted Aromatic Compounds **3** via a Manganacyclopentadiene Intermediate



Scheme 3. Formation of Tetrasubstituted Aromatic Compounds **3** via a Manganacyclopentene Intermediate



In summary, we have succeeded in the regioselective synthesis of terphenyls by the [2 + 2 + 2] cycloaddition reactions of β-keto esters or 1,3-diketones with 2 equiv of terminal acetylenes in good to excellent yields. It is worth noting because pair-selective and regioselective preparation of only 2:1 adducts from two kinds of terminal acetylenes using [2 + 2 + 2] cycloadditions in one operation is rather difficult. Because of the versatility to introduce a substituent at the γ-position of β-keto esters, we hope that the transformations will become efficient methods to synthesize terphenyls.

Acknowledgment. Financial support from the Ministry of Education, Culture, Sports, Science, and Technology of Japan is gratefully acknowledged. We also appreciate the Sumitomo Foundation, Meiji Seika Co., and Okayama Foundation for Science and Technology for financial support. We thank Professor Isao Kadota (Department of Chemistry, Okayama University, Japan) for aquiring the HR-MS spectra.

Supporting Information Available: General experimental procedures, characterization data, and ^{1}H and^{13} C NMR spectra for aromatic compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) In this reaction, alkenylated product **7** was formed in 41% yield as a side product.

(16) For metal-catalyzed carbon–carbon single bond cleavage via retro-aldol reaction by the reactions of 1,3-dicarbonyl compounds with water, see: (a) Kawata, A.; Takata, K.; Kuninobu, Y.; Takai, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 7793–7795.