doi:10.1246/cl.2010.894
Published on the web July 14, 2010

Editor's Choice

Rhenium-catalyzed Regioselective Synthesis of Phenol Derivatives from 1,3-Diesters and Terminal Alkynes

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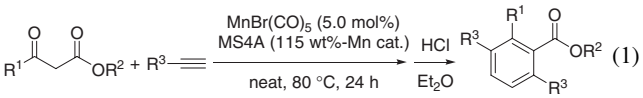
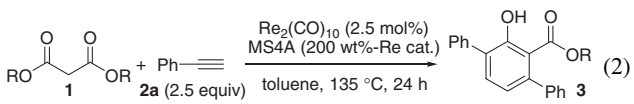
Treatment of malonates without a substituent at the active methylene moiety with terminal alkynes gave salicylates regioselectively. In contrast, when malonates bearing a substituent at the active methylene moiety were used, cyclic β-keto esters were generated regioselectively. Treatment of the formed cyclic β-keto esters with $In(OTf)_3$ gave phenol derivatives via decarboxylation.

[2 + 2 + 2] Cycloaddition is an efficient and powerful method to synthesize multisubstituted aromatic compounds. For example, cyclotrimerization of alkynes is well known.[1] However, it is usually difficult to introduce substituents regioselectively when unsymmetrical alkynes are used. In particular, reactions between two or three kinds of alkynes usually produce complex mixtures because it is difficult to control pair- and regioselectivity. Very recently, our group[2] and Tsuji, Nakamura, and co-workers[3] independently reported the manganese-catalyzed regioselective synthesis of benzoates from β-keto esters and two equivalents of terminal alkynes (eq 1). In these reactions, the two substituents, which are introduced from terminal alkynes, are located at the *para*-position. During our investigation of the reactions between other active methylene compounds and alkynes, we found that phenol derivatives were formed by the reactions between malonates and alkynes in the presence of a rhenium catalyst.



(1)

Treatment of dimethyl malonate (**1a**) with phenylacetylene (**2a**) in the presence of a rhenium complex, $Re_2(CO)_{10}$, as a catalyst in toluene at 135 °C for 24 h, gave methyl salicylate **3a** in 46% yield (61% yield based on conversion) and **1a** was recovered in 24% yield (eq 2).[4] In this reaction, [2 + 2 + 2] cycloaddition of 1 equivalent of **1a** and 2 equivalents of **2a** proceeded regioselectively and two phenyl groups of **3a** orient at *para*-positions relative to each other. In this reaction, cyclotrimerization of **2a** and insertion of **2a** into a carbon–carbon single bond of **1a**[5] did not occur. The following yields were calculated based on the conversion yields. Using diethyl malonate (**1b**) or dibutyl malonate (**1c**), the corresponding salicylates **3b** and **3c** were formed in 95% and 85% yields, respectively. However, diphenyl malonate did not produce the corresponding salicylate.

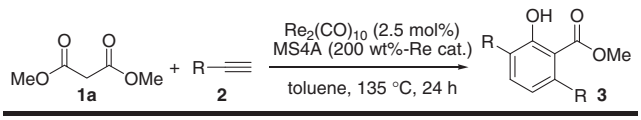


(2)

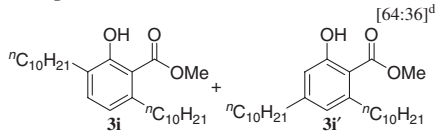
R		Conversion/%[a]		Yield/%[b]	R		Conversion/%[a]		Yield/%[b]
Me	**1a**	76	**3a**	46 (61)	^{n}Bu	**1c**	33	**3c**	28 (85)
Et	**1b**	57	**3b**	54 (95)					

[a]Determined by ^{1}H NMR. [b]Isolated yield. Isolated yield based on conversion is reported in parentheses.

Table 1. Reactions between dimethyl malonate (**1a**) and several alkynes **2**[a]



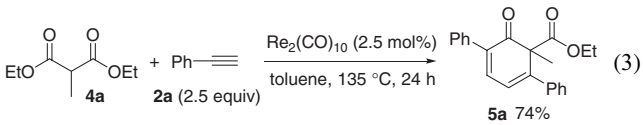
Entry	R		Conversion/%[b]	Yield/%[c]
1	4-$MeOC_6H_4$	**2b**	70	**3d** 47 (67)
2	4-MeC_6H_4	**2c**	60	**3e** 40 (67)
3	4-$CF_3C_6H_4$	**2d**	56	**3f** 44 (79)
4	4-BrC_6H_4	**2e**	36	**3g** 30 (83)
5	2-MeC_6H_4	**2f**	67	**3h** 36 (54)
6	$^n C_{10}H_{21}$	**2g**	86	**3i** + **3i′** 48 (56) [64:36][d]



[a]**2** (2.5 equiv). [b]Determined by ^{1}H NMR. [c]Isolated yield. Isolated yield based on conversion is reported in parentheses. [d]The ratios between **3i** and **3i′** are reported in square blacket.

Next, several alkynes were investigated (Table 1). Alkynes with an electron-donating or -withdrawing group, **2b**–**2d**, afforded the corresponding salicylates **3d**–**3f** in 67%–79% yields (Entries 1–3). The corresponding salicylate bearing a bromine atom, **3g**, was obtained in 83% yield without losing the bromine atom (Entry 4). This enables the construction of further derivatives through cross-coupling reactions. The yield was not decreased when arylacetylene having a methyl group at the *ortho*-position, **2f**, was used (Entry 5). In the case of an aliphatic alkyne, **2g**, a mixture of two regioisomers was generated (Entry 6). The reaction did not proceed with diphenylacetylene.

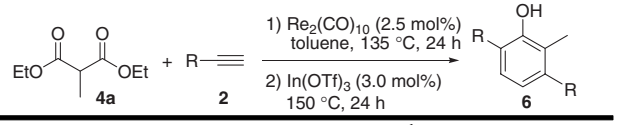
In the case of malonates with a substituent at the active methylene moiety, the product changed markedly from the products obtained from malonates without a substituent at the active methylene moiety. Treatment of diethyl 2-methylmalonate (**4a**) with phenylacetylene (**2a**) in the presence of a catalytic amount of a rhenium complex, $Re_2(CO)_{10}$, in toluene at 135 °C for 24 h, gave cyclic β-keto ester **5a** in 74% yield (81% conversion) (eq 3).[6–8] In this reaction, [2 + 2 + 2] cycloaddition between 1 equivalent of **4a** and 2 equivalents of **2a** proceeded regioselectively, and the two phenyl groups were introduced at the 2- and 5-positions of **5a**.



(3)

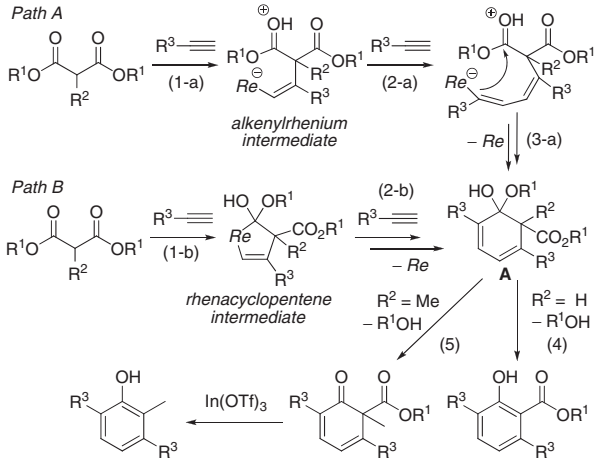
After the reaction as shown in eq 3, Lewis acid, such as indium triflate $In(OTf)_3$, was added without isolation of the cyclic β-keto ester **5a**.[9] As a result, the ethoxycarbonyl group was

Table 2. Reactions between diethyl 2-methylmalonate (**4a**) and several alkynes **2**[a]



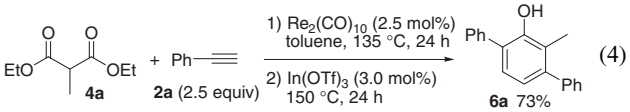
Entry	R		Conversion/%[b]		Yield/%[c]
1	4-MeOC$_6$H$_4$	**2b**	68	**6b**	47 (69)
2	4-MeC$_6$H$_4$	**2c**	82	**6c**	54 (66)
3	4-CF$_3$C$_6$H$_4$	**2d**	86	**6d**	47 (55)
4	4-BrC$_6$H$_4$	**2e**	58	**6e**	12 (21)

[a]**2** (2.5 equiv). [b]Determined by ^{1}H NMR. [c]Isolated yield. Isolated yield based on conversion is reported in parentheses.



Scheme 1. Proposed mechanism for the formation of phenol derivatives **3** and **6**.

eliminated from **5a**, and phenol derivative **6a** was obtained in 73% yield (79% conversion) (eq 4).[10,11]



(4)

Next, several terminal alkynes were investigated (Table 2). Terminal alkynes with an electron-donating group, **2b** and **2c**, provided phenol derivatives **6b** and **6c** in 69% and 66% yields, respectively (Entries 1 and 2), whereas the yield of phenol derivative was slightly decreased when terminal alkyne bearing an electron-withdrawing group, **2d**, was employed (Entry 3). The corresponding phenol derivative **6e** was generated in low yield using 4-bromophenylacetylene (**2e**) (Entry 4). The corresponding phenol derivatives were not formed using *o*-tolylacetylene (**2f**) and diphenylacetylene, and 1-dodecyne (**2g**) gave a complex mixture.

When salicylates **3** and phenol derivatives **6** are formed, intermediate **A** is a key intermediate. There are two possible pathways to produce intermediate **A** (Scheme 1). In path A, the sequence is as follows: (1-a) formation of an alkenylrhenium intermediate by nucleophilic addition of a 1,3-diester to an alkyne, which is activated by a rhenium catalyst; (2-a) insertion of second alkyne into the rhenium–carbon bond of the formed alkenylrhenium intermediate; (3-a) intramolecular nucleophilic addition to give cyclic intermediate **A**.[12] Another possible route for the formation of cyclic intermediate **A** is path B: (1-b) formation of a rhenacyclopentene intermediate by oxidative cycloaddition between a 1,3-diester, an alkyne, and a rhenium catalyst; (2-b) insertion of second alkyne into the rhenium–carbon bond of the formed rhenacyclopentene intermediate. After the formation of cyclic intermediate **A**, (4) a salicylate is produced by the elimination of an alcohol when $R^2 = H$. In the case of $R^2 = Me$, (5) a cyclic β-keto ester is generated via the elimination of an alcohol.

In summary, we have succeeded in the regioselective synthesis of salicylates from 1,3-diesters without a substituent at the active methylene moiety and terminal alkynes using a rhenium catalyst, $Re_2(CO)_{10}$. On the other hand, using 1,3-diesters bearing a substituent at the active methylene moiety, phenol derivatives were obtained. In these reactions, two substituents from terminal alkynes are introduced at the *para*-positions.[13] We hope that these reactions will become a useful method to regioselectively synthesize phenol derivatives.

References and Notes

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

2 Y. Kuninobu, M. Nishi, S. Yudha S., K. Takai, *Org. Lett.* **2008**, *10*, 3009.

3 H. Tsuji, K.-i. Yamagata, T. Fujimoto, E. Nakamura, *J. Am. Chem. Soc.* **2008**, *130*, 7792.

4 Investigation of several catalysts: $ReBr(CO)_5$, 4%. No reaction: $[ReBr(CO)_3(thf)]_2$, $Mn_2(CO)_{10}$, $MnBr(CO)_5$, $Cr(CO)_6$, $Mo(CO)_6$, $Fe_2(CO)_9$, $Fe_3(CO)_{12}$, $Ru_3(CO)_{12}$, $Ir_4(CO)_{12}$, $Rh_4(CO)_{12}$, $Co_2(CO)_8$.

5 a) Y. Kuninobu, A. Kawata, K. Takai, *J. Am. Chem. Soc.* **2006**, *128*, 11368. b) Y. Kuninobu, A. Kawata, M. Nishi, H. Takata, K. Takai, *Chem. Commun.* **2008**, 6360.

6 When the reaction was carried out at 180 °C, only **3a** was formed in 63% yield.

7 Investigation of several catalysts: $ReBr(CO)_5$, 17%; $[ReBr(CO)_3(thf)]_2$, 22%. No reaction: $Mn_2(CO)_{10}$, $MnBr(CO)_5$, $Cr(CO)_6$, $Mo(CO)_6$, $W(CO)_6$, $Fe_2(CO)_9$, $Fe_3(CO)_{12}$, $Ru_3(CO)_{12}$, $Ir_4(CO)_{12}$, $Rh_4(CO)_{12}$, $Co_2(CO)_8$.

8 Investigation of several solvents: neat **3a** 32%, **4a** 8%; CH_2ClCH_2Cl **3a** 39%, **4a** 10%; THF **3a** 19%, **4a** trace; CH_3CN **3a** 0%, **4a** 0%; *N*,*N*-dimethylformamide (DMF) **3a** 0%, **4a** 0%.

9 Investigation of several catalysts: $Fe(OTf)_3$, **6a** 66%; $In(OTf)_3$, **6a** 78%; $Cu(OTf)_2$, **6a** 71%; AgOTf, **6a** 58%.

10 Phenol derivative **6a** was obtained in 92% yield by the treatment with 3.0 mol % of $In(OTf)_3$ after the isolation of the cyclic β-keto ester **5a**.

11 When β-keto ester **5a** was treated at 150 °C for 24 h with powdered NaOH instead of $In(OTf)_3$, decarboxylation of the β-keto ester proceeded to give **6a** in 41% yield (cf. $In(OTf)_3$, 58%). In contrast, the decarboxylation did not occur with NaI.

12 Very recently, Nakamura's group reported theoretical calculations on the regioselective formation of benzoates from β-keto esters and two equivalents of terminal alkynes. The results suggest that the reactions proceed via a similar route as shown in Scheme 1, Path A. See: N. Yoshikai, S. Zhang, K.-i. Yamagata, H. Tsuji, E. Nakamura, *J. Am. Chem. Soc.* **2009**, *131*, 4099.

13 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

