Manganese-catalyzed Synthesis of Hydantoin Derivatives from Terminal Alkynes and Isocyanates

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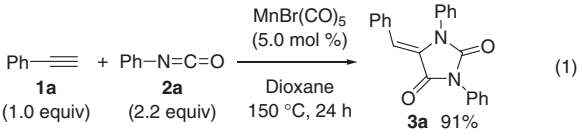
Hydantoin derivatives were obtained by the reactions of terminal alkynes with isocyanates in the presence of a catalytic amount of a manganese complex, $MnBr(CO)_5$. This reaction also proceeded using a rhenium complex, $Re_2(CO)_{10}$, or an iron complex, $Fe(CO)_5$, as a catalyst.

Hydantoin derivatives have been used in a wide number of applications, such as bioactive compounds[1] and amino acids synthesis.[2] There have been many approaches to the synthesis of hydantoin derivatives including the Urech method,[3] the Bucherer–Bergs type reaction,[4] and transformations via intramolecular cyclization.[5] Metal-promoted preparations of hydantoins have also been reported; iron-,[6] lead-,[7] and sodium-mediated[8] reactions, and ruthenium-[9] and palladium-catalyzed[10] reactions. Recently, fourth-row-transition-metal-catalyzed reactions have received much attention because they are abundant and cheap compared to fifth- or sixth-row transition metals. However, examples of fourth-row-transition-metal-catalyzed syntheses of hydantoin derivatives are still rare. We will report herein the manganese-catalyzed construction of hydantoin frameworks from terminal alkynes and isocyanates.

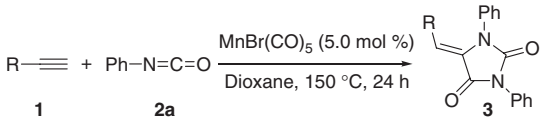
Treatment of phenylalkyne **1a** with phenyl isocyanate (**2a**) in the presence of a catalytic amount of a manganese complex, $MnBr(CO)_5$, in dioxane at 150 °C for 24 h in a sealed tube gave hydantoin derivative **3a** in 91% yield stereoselectively (eq 1).[11–13] We also found that a catalytic amount of a rhenium complex, $Re_2(CO)_{10}$ (2.5 mol %), or an iron complex, $Fe(CO)_5$ (5.0 mol %),[14] promoted the formation of hydantoin derivative **3a** under the same reaction conditions in 55% and 75% yields, respectively.



1a (1.0 equiv) **2a** (2.2 equiv) **3a** 91% (1)

Terminal aromatic alkynes having an electron-donating group at the para position, **1b** and **1c**, gave hydantoin derivatives **3b** and **3c** in 77% and 79% yields, respectively (Table 1, Entries 1 and 2). By using an alkyne bearing an electron-withdrawing group, **1d**, the yield was improved and hydantoin **3d** was obtained in 93% yield (Table 1, Entry 3). Aryl alkynes with a halogen atom at the para position, **1e** and **1f**, produced hydantoins **3e** and **3f** in good yields without loss of the halogen atom (Table 1, Entries 4 and 5). By the reaction of enyne **1g** with phenyl isocyanate (**2a**), hydantoin **3g** was also produced in moderate yield (Table 1, Entry 6). Terminal alkynes having primary alkyl groups, **1h**–**1j**, afforded hydantoins **3h** and **3i** in low yields (Table 1, Entries 7 and 8). In contrast, the reaction of secondary alkyl alkyne **1j** afforded hydantoin **3j** in 89% yield (Table 1, Entry 9). Internal alkynes, on the other hand, did not give hydantoin derivatives under the conditions. The iron complex, $Fe(CO)_5$, promoted the reactions; however, the yields of hydantoins **3b**–**3j** were moderate (See the Supporting Information, Table S1).[16] In the case of $Re_2(CO)_{10}$, the yields of **3b**–**3j** decreased considerably (See the Supporting Information, Table S1).[16]

Table 1. Reactions between several terminal alkynes **1** and phenyl isocyanate (**2a**)[a]



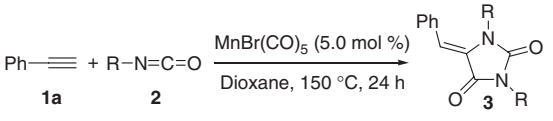
1 **2a** **3**

Entry	R			Yield/%[b]
1	*p*-$MeOC_6H_4$	**1b**	**3b**	77 (82)
2	*p*-MeC_6H_4	**1c**	**3c**	79 (85)
3	*p*-$CF_3C_6H_4$	**1d**	**3d**	93 (95)
4	*p*-ClC_6H_4	**1e**	**3e**	88 (90)
5	*p*-BrC_6H_4	**1f**	**3f**	89 (89)
6[c]		**1g**	**3g**	65 (70)
7[c]	*n*-$C_{10}H_{21}$	**1h**	**3h**	32 (40)
8[c]	$PhCH_2OCH_2$	**1i**	**3i**	15 (22)
9	*c*-C_6H_{11}	**1j**	**3j**	89 (90)

[a]**1** (1.0 equiv); **2a** (2.2 equiv). [b]Isolated yield. The yield determined by ^1H NMR is reported in parentheses. [c]**2a** (2.0 equiv).

Treatment of an aryl isocyanate bearing an electron-donating group, **2b** or **2c**, with phenylacetylene (**1a**) produced hydantoins **3k** and **3l** in 93% and 91% yields, respectively (Table 2, Entries 1 and 2). An aryl isocyanate having an electron-donating group, **2d**, gave hydantoin **3m** in 94% yield (Table 2, Entry 3). A secondary alkyl isocyanate **2e** provided hydantoin derivative **3n** in good yield (Table 2, Entry 4). Although $Re_2(CO)_{10}$ and $Fe(CO)_5$ promoted the reactions, the yields of hydantoins **3k**–

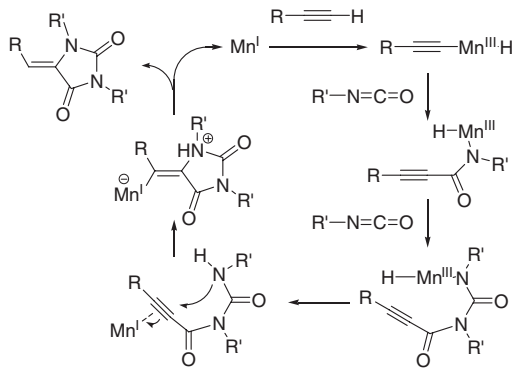
Table 2. Reactions between terminal alkyne **1a** and several isocyanates **2**[a]



1a **2** **3**

Entry	R			Yield/%[b]
1	*p*-$MeOC_6H_4$	**2b**	**3k**	93 (95)
2	*p*-MeC_6H_4	**2c**	**3l**	91 (94)
3	*p*-$CF_3C_6H_4$	**2d**	**3m**	94 (95)
4	*c*-C_6H_{11}	**2e**	**3n**	84 (90)

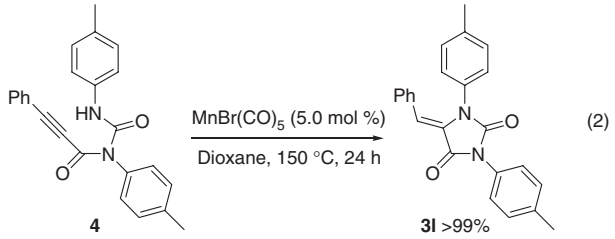
[a]**1a** (1.0 equiv); **2** (2.2 equiv). [b]Isolated yield. The yield determined by ^1H NMR is reported in parentheses.



Scheme 1. Proposed mechanism for the formation of hydantoin derivatives.

3n with the two catalysts were lower than those with $MnBr(CO)_5$ (See the Supporting Information, Table S2).[16] However, primary and tertiary alkyl isocyanates (2-phenylethyl isocyanate, octadecyl isocyanate, and 1-adamantyl isocyanate) did not provide the corresponding hydantoin derivative because of the trimerization of the isocyanates under the reaction conditions. The formation of hydantoin derivative did not proceed using trimethylsilyl isocyanate and tosyl isocyanate.

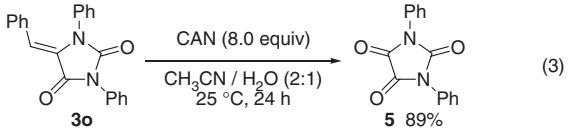
To elucidate the reaction mechanism, we carried out the reaction of **4** in the presence of a manganese catalyst, $MnBr(CO)_5$, at 150 °C for 24 h (eq 2). As a result, hydantoin **3l** was obtained quantitatively. This result suggests that hydantoin **3l** was formed via the formation of **4**.



(2)

Judging from the result in eq 2 and the geometry of the olefin moiety of the products, we propose the following mechanism for the hydantoin synthesis (Scheme 1):[15] (1) oxidative addition of a terminal alkyne to a manganese center; (2) insertion of an isocyanate into the manganese–carbon bond of the manganese acetylide; (3) insertion of another isocyanate into the manganese–nitrogen bond of the manganese amide intermediate; (4) reductive elimination and intramolecular cyclization.

By the treatment of hydantoin **3o** with cerium ammonium nitrate (CAN) at 25 °C for 24 h, oxidative carbon–carbon double bond cleavage took place, and imidazolidinetrione **5** was obtained in 89% yield (eq 3). In this reaction, benzaldehyde was obtained as a side product.



(3)

In summary, we have succeeded in $MnBr(CO)_5$-catalyzed synthesis of hydantoin derivatives from terminal alkynes and isocyanates. The reaction proceeds with a catalytic amount of a fourth-row-transition-metal complex, and has wide applicability.

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11 The structure of **3a** was determined by a comparison with the reported data in ref 6a, and by X-ray single-crystal structure analysis.

12 Investigation of temperature in the reaction between phenylacetylene (**1a**) (1.0 equiv) and *p*-methoxyphenyl isocyanate (**2b**) (2.0 equiv): 50 °C, 0%; 80 °C, 30%; 100 °C, 45%; 115 °C, 59%; 135 °C, 62%; 150 °C, 75%.

13 An iron complex, $Fe(acac)_3$ (5.0 mol %), provided hydantoin derivative **3a** in 8% yield. Only a trace amount of hydantoin **3a** was obtained in the presence of a ruthenium complex, $Ru_3(CO)_{12}$ or $RuH_2(CO)(PPh_3)_3$. The reaction did not proceed using $ReBr(CO)_5$, $[ReBr(CO)_3(thf)]_2$, $FeCl_3$, and $RhCl_3$.

14 In a reported paper (ref 6), the formation reaction of hydantoins proceeded stoichiometrically using an iron complex, $Fe(CO)_5$. However, as a result of our investigation, the iron complex promoted the reaction catalytically.

15 Another reaction mechanism can be considered: (1) the formation of a manganese–alkylidene intermediate; (2) nucleophilic addition of isocyanate to the intermediate; (3) addition of another isocyanate; (4) addition of a manganese–carbon bond of the alkenylmanganese moiety; (5) isomerization of an olefinic moiety.

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

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