

# Ruthenium(II)-Catalyzed Cycloaddition of 1,6-Diynes with Isocyanates Leading to Bicyclic Pyridones

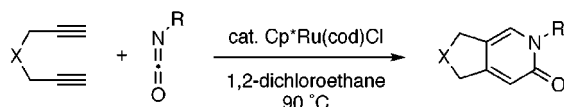
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Received May 9, 2001

## ABSTRACT



A ruthenium(II) complex possessing a planar Cp\* ligand, Cp\*Ru(cod)Cl, effectively catalyzed the [2 + 2 + 2] cycloaddition of 1,6-diynes with isocyanates to afford bicyclic pyridones in 58–87% yields.

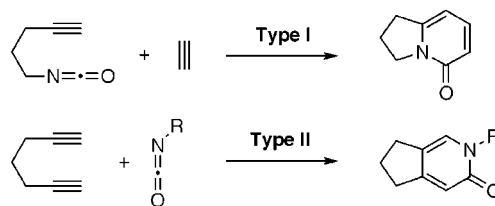
Transition-metal-catalyzed cyclocotrimerization of two molecules of an alkyne and an isocyanate is an efficient method to construct substituted 2-pyridone rings.<sup>1</sup> Such a catalytic pyridone formation has first been accomplished independently by Yamazaki using Co catalysts<sup>2</sup> and by Hoberg using Ni catalysts.<sup>3</sup>

The cobalt catalysis has further been extended to partially intramolecular versions utilizing isocyanatopentynes or  $\alpha,\omega$ -diynes by Vollhardt and co-workers.<sup>4</sup> The cycloadditions of isocyanatoalkynes with several silylalkynes effectively gave 2,3-dihydro-5(1*H*)-indolizinones (Figure 1, Type I), and this strategy was elegantly applied to the total synthesis of the antitumor agent Camptothecin.<sup>4</sup> In contrast, the related cycloadditions of  $\alpha,\omega$ -diynes with isocyanates (Figure 1, Type II) have been less attractive, although a wide variety of readily accessible diynes and isocyanates can be directly used for this type of cycloaddition. Actually, the reactions of 1,7-octadiyne with phenyl isocyanate or 1,6-heptadiyne

with  $\beta$ -phenethyl isocyanate were carried out in the presence of 15 mol % CpCo(CO)<sub>2</sub> by the same authors, but the expected pyridones were obtained only in 16% and 31% yields, respectively.<sup>4</sup> Moreover, no pyridone was formed as a result of the facile cyclotrimerization of the diyne substrate when the reaction was conducted with Ni(cod)<sub>2</sub> as the catalyst.<sup>4</sup>

With these facts in mind, we developed more efficient Type II cycloaddition using the ruthenium catalyst. Herein, we wish to report our preliminary results of the ruthenium-catalyzed cycloaddition of 1,6-diynes with isocyanates.

To search for a new catalytic system,<sup>5</sup> we first attempted the cycloaddition of a malonate-derived 1,6-diyne **1a** (X = C(CO<sub>2</sub>Me)<sub>2</sub>) and phenyl isocyanate (**2a**) in the presence of



**Figure 1.** Partially intramolecular [2 + 2 + 2] cyclocotrimerizations of alkynes and isocyanates.

(1) (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, Chapter 7.3, pp 741–770. (b) Shore, N. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, Chapter 9.4, pp 1129–1162.

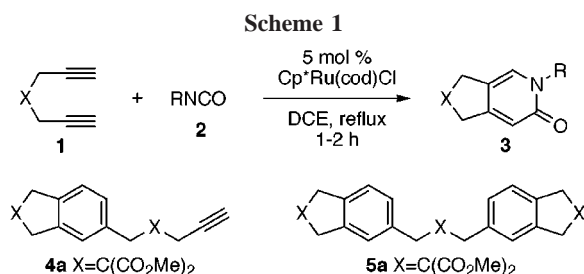
(2) Hong, P.; Yamazaki, H. *Tetrahedron Lett.* **1977**, 1333–1336.

(3) Hoberg, H.; Oster, B. W. *Synthesis* **1982**, 324–325.

(4) Earl, R. A.; Vollhardt, K. P. C. *J. Org. Chem.* **1984**, *49*, 4786–4800.

(5) For other examples, see: (a) Flynn, S. T.; Hasso-Henderson, S. E.; Parkins, A. W. *J. Mol. Catal.* **1985**, *32*, 101–105. (b) Diversi, P.; Ingrosso, G.; Lucherini, A.; Malquori, S. *J. Mol. Catal.* **1987**, *40*, 267–280.

a catalytic amount of Cp\*Ru(cod)Cl (Cp\* = pentamethylcyclopentadienyl, cod = 1,5-cyclooctadiene), which is the excellent catalyst for the related cycloaddition of 1,6-diynes with alkenes or monoalkynes.<sup>6</sup> A 1,2-dichloroethane (DCE) solution of **1a** was added to the solution of **2a** (2 equiv) and 10 mol % Cp\*Ru(cod)Cl in DCE at room temperature, and the resultant solution was then refluxed for 2 h to afford the desired bicyclic pyridone **3aa** and the diyne dimer **4a** in 45% and 18% yields, respectively (Scheme 1 and Table 1, run



1). The competitive formation of **4a** was effectively suppressed by improving the procedure as follows: to a refluxed

**Table 1.** Ru-Catalyzed Cycloaddition of 1,6-Heptadiyne **1a** with Isocyanate **2a**<sup>a</sup>

run	catalyst (mol %)	<b>2a</b> (equiv)	solvent <sup>b</sup>	time (h)	<b>3aa</b> yield (%) <sup>c</sup>
1	Cp*Ru(cod)Cl (10)	2	DCE	2	45
2	Cp*Ru(cod)Cl (10)	2 + 2 <sup>d</sup>	DCE	1	89
3	Cp*Ru(cod)Cl (10)	2 + 2 <sup>d</sup>	C <sub>6</sub> H <sub>6</sub>	20	34
4	Cp*Ru(cod)Cl (10)	2 + 2 <sup>d</sup>	AN	27	7 <sup>e</sup>
5	[Cp*RuCl <sub>2</sub> ] <sub>2</sub> (10)	2 + 2 <sup>d</sup>	DCE	1	74
6	Ru(cod)(AN) <sub>2</sub> Cl <sub>2</sub> (10)	2 + 2 <sup>d</sup>	DCE	3	35
7	C <sub>6</sub> Me <sub>6</sub> Ru(cod) (10)	2 + 2 <sup>d</sup>	DCE	18	0
8	Cp*Ru(cod)Cl (5)	2 + 2 <sup>d</sup>	DCE	1	87
9	Cp*Ru(cod)Cl (2)	2 + 2 <sup>d</sup>	DCE	2	65

<sup>a</sup> To a solution of a catalyst and **2a** (2 equiv) was added a solution of **1a**, and the solution was refluxed for the time indicated. <sup>b</sup> DCE = 1,2-dichloroethane; AN = acetonitrile. <sup>c</sup> Isolated yields. <sup>d</sup> To a refluxed solution of a catalyst and 2 equiv of **2a** in DCE was added dropwise a solution of **1a** and another 2 equiv of **2a** in DCE. <sup>e</sup> The diyne **2a** was recovered in 61% yield.

solution of the catalyst and 2 equiv of **2a** in DCE was added dropwise a solution of **1a** and another 2 equiv of **2a** in DCE. As a result, the yield of **3aa** was raised to 89% (run 2).<sup>7</sup> The yield was, however, considerably lowered in benzene (run 3), and the reaction hardly proceeded in acetonitrile even after 27 h (run 4).

We then examined other typical organoruthenium complexes with various oxidation states and ligand fields. A dinuclear ruthenium(III) complex having a Cp\* ligand,

(6) (a) Yamamoto, Y.; Ogawa, R.; Itoh, K. *Chem. Commun.* **2000**, 549–550. (b) Yamamoto, Y.; Kitahara, H.; Ogawa, R.; Kawaguchi, H.; Tatsumi, K.; Itoh, K. *J. Am. Chem. Soc.* **2000**, *122*, 4310–4319.

(7) An excess of the isocyanate **2a** was recovered as carbanilide.

[Cp\*RuCl<sub>2</sub>]<sub>2</sub>, also gave **3aa**, albeit in slightly lower yield (run 5). The importance of the planar Cp\* ligand was clearly elucidated by the fact that a ruthenium(II) complex without the Cp\* ligand, Ru(cod)(AN)<sub>2</sub>Cl<sub>2</sub>, gave **3aa** only in 35% yield along with an inseparable mixture of **4a** and unknown byproducts (run 6). On the other hand, a ruthenium(0) complex having a bulky planar hexamethylbenzene ligand, C<sub>6</sub>Me<sub>6</sub>Ru(cod), was found totally ineffective for the present cycloaddition (run 7). Finally, the catalyst amount was optimized using the best catalyst. A lower catalyst load of 5 mol % Cp\*Ru(cod)Cl gave **3aa** in similar high yield (run 8), although 2 mol % of the catalyst was not enough for the completion of the reaction (run 9).

Having optimized the reaction conditions, other isocyanates were subjected to the cycloaddition with the diyne **1a** as summarized in Table 2. In the same manner with **2a**,

**Table 2.** Cp\*Ru(cod)Cl-Catalyzed Cycloaddition of 1,6-Heptadiynes **1a–d** with Isocyanates **2a–f**<sup>a</sup>

run	diynes	isocyanates	pyridones yield (%) <sup>b</sup>
1	<b>1a</b>	<b>2b</b>	<b>3ab</b> (79)
2	<b>1a</b>	<b>2c</b>	<b>3ac</b> (87)
3	<b>1a</b>	<b>2d</b>	<b>3ad</b> (93)
4	<b>1a</b>	<b>2e</b>	<b>3ae</b> (85)
5	<b>1b</b>	<b>2a</b>	<b>3ba</b> (62)
6	<b>1c</b>	<b>2a</b>	<b>3ca</b> (58)
7	<b>1d</b>	<b>2a</b>	<b>3da</b> (82)

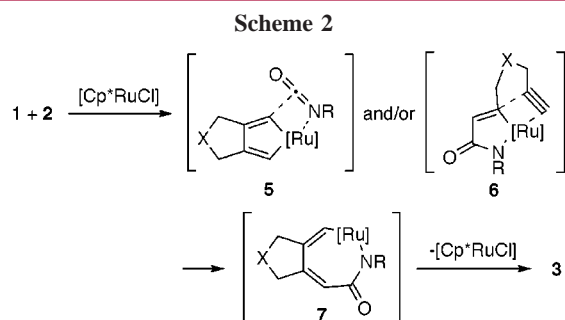
<sup>a</sup> To a refluxing solution of 5 mol % Cp\*Ru(cod)Cl and **2** (2 equiv) in DCE was added dropwise a solution of **1** and **2** (2 equiv) in DCE, and the solution was refluxed for 1 h (2 h for runs 6 and 7). <sup>b</sup> Isolated yields.

1-naphthyl isocyanate (**2b**) and 2-furyl isocyanate (**2c**) underwent the cycloaddition with **1a** to afford the corre-

sponding products **3ab** and **3ac** in 79% and 87% yields, respectively (runs 1 and 2). In addition to the aryl isocyanates, alkyl isocyanates can be employed in the present protocol. Isocyanates **2d** and **2e**, which possess a primary or secondary alkyl group on their nitrogen atom, effectively gave the desired *N*-alkyl pyridones **3ad** and **3ae** in high yields. Exceptionally, *tert*-butyl isocyanate **2f** gave no pyridone product under the same reaction conditions. This is probably because the coordination of its C=N bond to the ruthenium center was completely hindered by the bulky *tert*-butyl group on the nitrogen atom. In this case, the diyne cyclootrimerization products **4a** and **5a** were formed in 17% and 71% yields, respectively.

The generality of the present ruthenium catalysis was further examined with respect to the diyne substrate. Parent 1,6-heptadiyne (**1b**) and dipropargyl ether (**1c**), having no tertiary center on the tether chain, also reacted with **2a** to afford the expected *N*-phenyl pyridones **3ba** and **3ca** in 62% and 58% yields, respectively (runs 5 and 6), although these diynes were anticipated to be ineffective without the kinetic Thorpe–Ingold effect.<sup>8</sup> *N,N*-Dipropargyl *p*-toluenesulfonamide (**1d**) efficiently afforded a pyrroline-fused pyridone **3da** in high yield with the aid of the proximity effect caused by the bulky *p*-tosyl group (run 7).

Scheme 2 shows a plausible mechanism of the Ru(II)-catalyzed cycloaddition of 1,6-diynes **1** with isocyanates **2**.



Yamazaki has proposed that a cobaltacyclopentadiene is initially formed from the oxidative cyclization of two molecules of an alkyne, and the subsequent reaction of the cobaltacycle intermediate with an isocyanate affords a pyridone. Such a metallacyclopentadiene mechanism was

(8) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, 107, 1080–1106.

supported by the fact that isolated cobaltacyclopentadienes and isocyanates produced the corresponding pyridones.<sup>9</sup> On the other hand, an alternative mechanism, which starts with the formation of an azanickelacyclopentenone from an alkyne and an isocyanate, was proposed in Hoberg's nickel-catalyzed cyclocotrimerizations.<sup>10</sup> According to these claims, two mechanisms including ruthenacyclopentadiene intermediates<sup>11,12</sup> **5** or azaruthenacyclopentenones **6** can be assumed for our case. In either event, common intermediates **7** is consequently produced, and the reductive elimination of the [Cp\*RuCl] fragment from **7** gives the bicyclic pyridones **3**. The metallacyclopentadiene mechanism is, however, preferable to the ruthenium-catalyzed cycloaddition using diynes as alkyne components. Without exception, 1,6-diynes are essential substrates for our previously reported ruthenium-catalyzed [2 + 2 + 2] cycloadditions.<sup>6</sup> This is also true of the present pyridone annulation. A typical monoalkyne, 1-hexyne, did not undergo [2 + 2 + 2] cyclocotrimerization with **2a** under the same reaction conditions with the diyne cycloaddition. This is probably because the ruthenacyclopentadiene formation from a 1,6-diyne is entropically more favorable than that from two molecules of a monoalkyne. These facts supports the ruthenacyclopentadiene mechanism (**1** + **2** → **5** → **7** → **3**).

**Acknowledgment.** We gratefully acknowledge financial support (09750947, 09305059, 10132222, 12450360, and 13875174) from the Ministry of Education, Science, Sports, and Culture, Japan.

**Supporting Information Available:** Typical procedure for the cycloaddition of **1** and **2** and analytical data for the pyridones **3**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(9) Hong, P.; Yamazaki, H. *Synthesis* **1977**, 50–52.

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(11) For catalytic reactions involving ruthenacyclopentadiene intermediates, see: (a) Lidner, E.; Jansen, R.-M.; Mayer, H. A.; Hiller, W.; Fawzi, R. *Organometallics* **1989**, 8, 2355–2360. (b) Yi, C. S.; Torres-Lubian, J. R.; Liu, N.; Rheingold, A. L.; Guzei, I. A. *Organometallics* **1998**, 17, 1257–1259. (c) Chatani, N.; Fukumoto, Y.; Ida, T.; Murai, S. *J. Am. Chem. Soc.* **1993**, 115, 11614–11615. Also, see ref 6.

(12) For the formation of ruthenacyclopentadiene/ruthenacyclopentatriene complexes from alkynes, see: (a) Bruce, M. I.; Matisons, J. G. *J. Organomet. Chem.* **1983**, 251, 249–260. (b) Albers, M. O.; de Waal, D. J. A.; Liles, D. C.; Robinson, D. J.; Singleton, E.; Wiege, M. B. *J. Chem. Soc., Chem. Commun.* **1986**, 1680–1682. (c) Campion, B. K.; Heyn, R. H.; Tilley, T. D. *Organometallics* **1990**, 9, 1106–1112. (d) Bruce, M. I.; Koutsantonis, G. A. *Aust. J. Chem.* **1991**, 44, 207–217. (e) Ernst, C.; Walter, O.; Dinjus, E.; Görls, J. *Prakt. Chem.* **1999**, 341, 801–804. Also see refs 10a and 10b.