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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 7107–7111

Selective synthesis of 2-pyridones and pyrimidine-2,4-diones by neutral rhodium(I) complex-catalyzed cyclocotrimerization of alkynes and isocyanates

Teruyuki Kondo,* Masato Nomura, Yasuyuki Ura, Kenji Wada and Take-aki Mitsudo

Department of Energy and Hydrocarbon Chemistry, Graduate School of Engineering, Kyoto University, Nishikyo-ku, Kyoto 615-8510, Japan

Received 14 June 2006; revised 10 July 2006; accepted 13 July 2006
Available online 8 August 2006

Abstract—A neutral rhodium(I) complex, '$RhCl(PPh_3)_2$' generated by the combination of $[RhCl(C_2H_4)_2]_2$ with a fourfold amount of PPh_3, effectively catalyzed the cyclocotrimerization of alkynes (**1**) and isocyanates (**2**) to give 2-pyridones (**3**) and/or pyrimidine-2,4-diones (**4**), selectively, by controlling the molar ratio of alkynes (**1**) and isocyanates (**2**).
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Many naturally occurring and synthetic compounds containing the 2-pyridone scaffold possess interesting pharmacological properties.[1] Recent interest in the 2-pyridone ring system has led to several new procedures for its preparation.[2] A highly convergent and atom-economical approach is the transition metal complex-catalyzed cyclocotrimerization of two alkynes with an isocyanate.[3] Since this methodology was first reported independently by Yamazaki using cobalt catalysts[4] and by Hoberg using nickel catalysts,[5] a remarkable progress has been made with these catalysts.[6,7] On the other hand, Takahashi succeeded in preparing various 2-pyridones from two different internal alkynes and an isocyanate via the formation of an azazirconacyclopentenone intermediate, followed by transmetallation with $Ni(PPh_3)_2Cl_2$; however this reaction requires *stoichiometric* amounts of both Ni and Zr complexes.[8] Recently, Itoh developed the first ruthenium-catalyzed synthesis of bicyclic 2-pyridones by the partial intermolecular cycloaddition of diynes with isocyanates.[9]

Notably, there has been much less progress in the development of rhodium catalysts compared to cobalt and nickel catalysts. To the best of our knowledge, the rhodium complex-catalyzed cyclocotrimerization of alkynes and isocyanates has thus far been investigated by only two research groups. Flynn reported that 1-(4-chlorophenyl)-3,5-dimethoxycarbonyl-4,6-dimethylpyrid-2-one was obtained in only 13% yield when a rhodacyclic complex was used as a neutral rhodium catalyst for the cyclocotrimerization of methyl tetrolate with 4-chlorophenylisocyanate.[10] Tanaka reported the chemo-, regio-, and enantioselective cycloaddition of diynes or terminal alkynes with isocyanates to give 2-pyridones catalyzed by a cationic rhodium complex, $[Rh(cod)_2]BF_4$, with H8-BINAP.[11] Since various neutral rhodium complexes are highly effective for cyclotrimerization and related reactions of alkynes,[12,13] we reinvestigated the catalytic activities of several neutral rhodium complexes combined with phosphine ligands in detail.

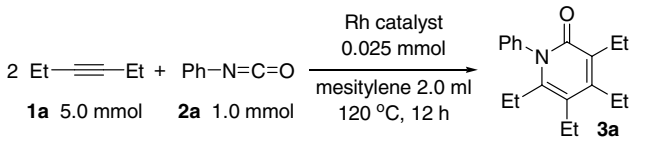
We report here that a neutral rhodium(I) complex, '$RhCl(PPh_3)_2$' generated by the combination of $[RhCl(C_2H_4)_2]_2$ with a fourfold amount of PPh_3, effectively catalyzed the cyclocotrimerization of alkynes and isocyanates to give 2-pyridones and/or pyrimidine-2,4-diones, selectively, by controlling the molar ratio of alkynes and isocyanates. Another advantage of the present rhodium-catalyzed cyclocotrimerization of alkynes and isocyanates is stability of the catalyst as compared to the reported cationic rhodium[11] and nickel(0)[5] catalysts.

First, the catalytic activities of several rhodium as well as ruthenium complexes[14] were examined in the synthesis of 3,4,5,6-tetraethyl-1-phenyl-2-pyridone (**3a**) by the

Keywords: Ruthenium; Catalyst; Cyclocotrimerization; 2-Pyridone; Pyrimidine-2,4-dione.
* Corresponding author. Tel.: +81 75 383 2508; fax: +81 75 383 2510; e-mail: teruyuki@scl.kyoto-u.ac.jp

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.07.105

cyclocotrimerization of 3-hexyne (**1a**) and phenyl isocyanate (**2a**) (Eq. 1).



(1)

Among the catalysts examined, $RhCl(CO)(PPh_3)_2$ (**3a** 23%), $[RhCl(CO)_2]_2$ (**3a** 11%), and $[RhCl(C_2H_4)_2]_2$ (**3a** 10%) as well as $RhCl(PPh_3)_3$ (**3a** 44%) were effective. However, ruthenium complexes, such as $RuCl_2(PPh_3)_3$, $CpRuCl(PPh_3)_2$ [Cp = cyclopentadienyl], $Cp^*RuCl(cod)$ [Cp^* = pentamethylcyclopentadienyl, cod = 1,5-cyclooctadiene], and $[RuCl_2(CO)_3]_2$, were totally ineffective.

The effect of phosphine ligands was examined in the $[RhCl(C_2H_4)_2]_2$-catalyzed synthesis of **3a** from **1a** and **2a**. As shown in Table 1, the concomitant use of PPh_3 ligand as well as its amount relative to $[RhCl(C_2H_4)_2]_2$ catalyst are highly important for the present reaction (entries 1–3). The use of *two equivalents of PPh*$_3$ *per rhodium atom* (i.e., $[RhCl(C_2H_4)_2]_2$ (0.025 mmol) and PPh_3 (0.10 mmol)) gave the best result (**3a**, 60%), which suggests that the catalytically active rhodium species would be a coordinatively unsaturated (14e) and sterically less hindered '$RhCl(PPh_3)_2$'. In contrast, catalyst systems combined with other monodentate phosphines, such as $P(C_6H_4Me\text{-}p)_3$, $P(C_6H_4F\text{-}p)_3$, PCy_2Ph, PCy_3 [Cy = cyclohexyl], and P^nBu_3, as well as bidentate phosphines, such as 1,4-bis(diphenylphosphino)butane (dppb) and 1,1′-bis(diphenylphosphino)ferrocene (dppf), gave **3a** in moderate to poor yields (entries 4–10). Consequently, when the reaction of 3-hexyne (**1a**, 5.0 mmol) with phenyl isocyanate (**2a**, 1.0 mmol) was carried out in the presence of a catalytic amount of $[RhCl(C_2H_4)_2]_2$ (0.025 mmol) and PPh_3 (0.10 mmol) in mesitylene (2.0 ml) at 120 °C for 12 h under an argon atmosphere, the corresponding 2-pyridone, 3,4,5,6-tetraethyl-1-phenyl-2-pyridone (**3a**), was obtained in 60% yield (isolated yield, 50%; entry 2).[15]

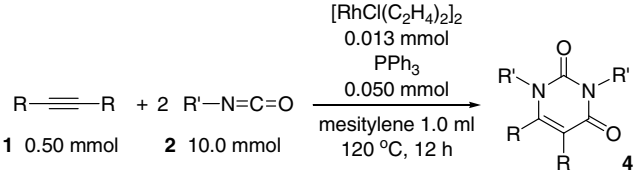
Table 1. The effect of phosphine ligands in the $[RhCl(C_2H_4)_2]_2$-catalyzed synthesis of **3a** from **1a** and **2a**[a]

Entry	Ligand	Yield of **3a**[b] (%)
1	—	10
2	PPh_3	60
3[c]	PPh_3	40
4	$P(C_6H_4Me\text{-}p)_3$	7
5	$P(C_6H_4F\text{-}p)_3$	33
6[d]	PCy_2Ph	14
7[d]	PCy_3	22
8	P^nBu_3	23
9[e]	dppb	32
10[f]	dppf	27

[a] 3-Hexyne (**1a**) (5.0 mmol), phenyl isocyanate (**2a**) (1.0 mmol), $[RhCl(C_2H_4)_2]_2$ (0.025 mmol), phosphine (0.10 mmol as a P atom), and mesitylene (2.0 ml) at 120 °C for 12 h under an argon atmosphere.
[b] GLC yield.
[c] PPh_3 (0.15 mmol) was used.
[d] Cy = cyclohexyl.
[e] 1,4-Bis(diphenylphosphino)butane.
[f] 1,1′-Bis(diphenylphosphino)ferrocene.

The results obtained from the reaction of several isocyanates with 3-hexyne (**1a**) under optimum reaction conditions are summarized in Table 2. Both aromatic and aliphatic isocyanates were readily converted into the corresponding 2-pyridones. No significant effect was observed for the electron-donating (*p*-Me (**2b**)) and electron-withdrawing substituents (*p*-Cl (**2c**)) on a phenyl ring in aromatic isocyanates. The reactions of *n*-hexyl isocyanate (**2d**) and cyclohexyl isocyanate (**2e**) with 3-hexyne (**1a**) gave the corresponding 2-pyridones, **3d** and **3e**, in isolated yields of 56% and 34%, respectively, while more bulky aliphatic isocyanates, such as *tert*-butyl isocyanate (**2f**) and adamantyl isocyanate (**2g**), could not be used in the present reaction. As for alkynes, 4-octyne (**1b**) was applicable to give the corresponding 2-pyridone (**3f**) in an isolated yield of 30%, while no 2-pyridones were obtained from the reactions of diphenylacetylene (**1c**), 1-phenyl-1-propyne (**1d**) or dimethyl acetylenedicarboxylate (**1e**) with phenyl isocyanate (**2a**).

On the other hand, treatment of alkynes (**1**) with a large excess amount of isocyanates (**2**, 20 equiv)[16] under the same catalytic reaction conditions gave pyrimidine-2,4-diones (**4**) in high yields, which were obtained by the cyclocotrimerization of two isocyanates with an alkyne (Eq. 2).

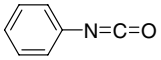
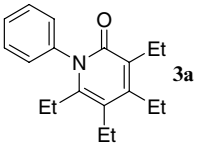
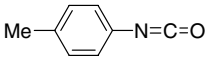
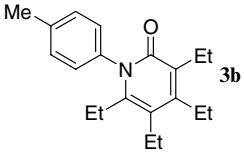
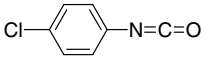
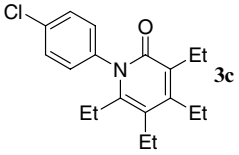
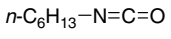
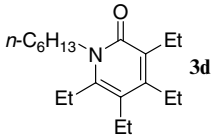
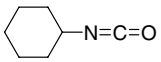
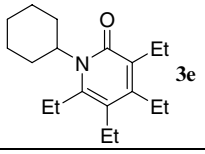


(2)

The results obtained from the cyclocotrimerization of alkynes (**1a**, **1c**, and **1d**, 0.50 mmol) and *n*-hexyl isocyanate (**2d**, 10 mmol) in the presence of a catalytic amount of $[RhCl(C_2H_4)_2]_2$ (0.013 mmol) and PPh_3 (0.050 mmol) in mesitylene (1.0 ml) at 120 °C for 12 h under an argon atmosphere are summarized in Table 3. For example, 5,6-diethyl-1,3-dihexyl-1,3-dihydropyrimidine-2,4-dione (**4a**) was obtained from **1a** and **2d** in an isolated yield of 86% (entry 1). No 2-pyridone was obtained at all, as confirmed by careful GC–MS analysis. In contrast to the synthesis of 2-pyridones, diphenylacetylene (**1c**) and 1-phenyl-1-propyne (**1d**) can be used in the present reaction (entries 2 and 3).

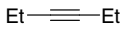
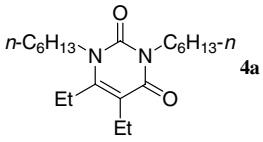
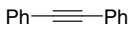
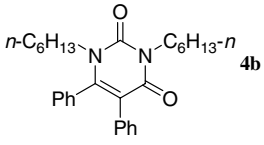
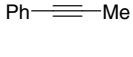
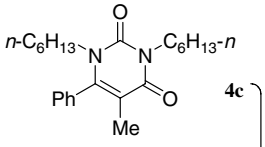
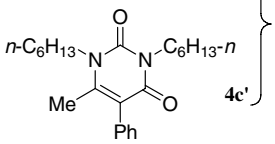
Considering the results obtained above, the most plausible mechanism is illustrated in Scheme 1. We now believe that an azarhodacyclopentenone derived from the oxidative cyclization of an alkyne (**1**) and an isocyanate (**2**) on an active rhodium center is the key intermediate for the present reaction.[17] Since cocyclization of 1,6-heptadiyne (**5a**) and phenyl isocyanate (**2a**) did not proceed at all by the present catalyst system,[9a,b] the

Table 2. $[RhCl(C_2H_4)_2]_2$/PPh_3-catalyzed synthesis of 2-pyridones (**3**) from 3-hexyne (**1a**) with isocyanates (**2**)[a]

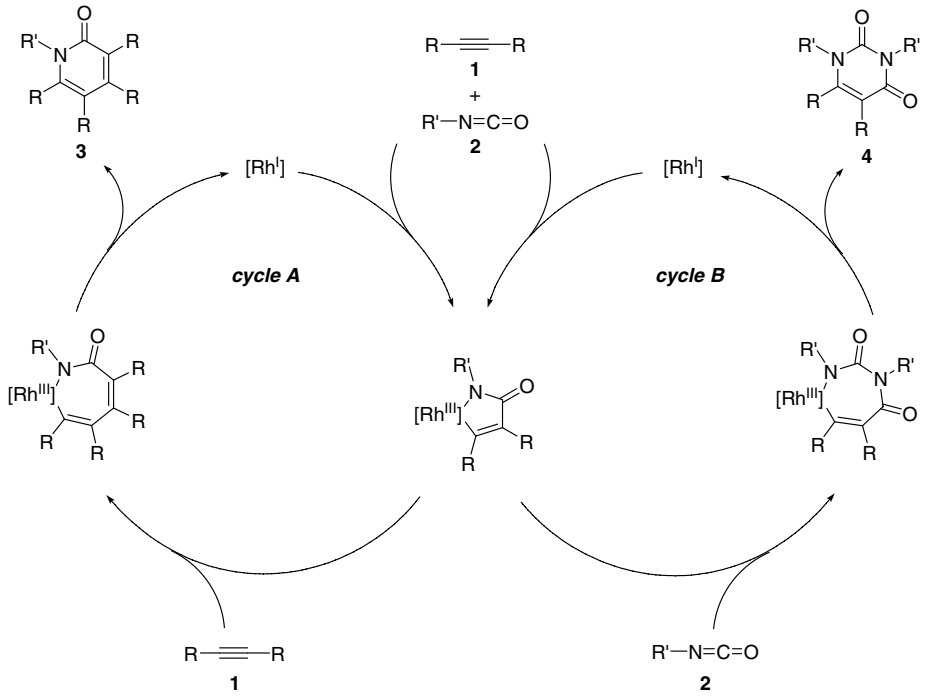
Entry	Isocyanate	Product	Isolated yield (%)
1	 **2a**	 **3a**	50 (60)[b]
2	 **2b**	 **3b**	59
3	 **2c**	 **3c**	63
4	 **2d**	 **3d**	56
5[c]	 **2e**	 **3e**	34

[a] 3-Hexyne (**1a**) (5.0 mmol), isocyanate (**2**) (1.0 mmol), $[RhCl(C_2H_4)_2]_2$ (0.025 mmol), PPh_3 (0.10 mmol), and mesitylene (2.0 ml) at 120 °C for 12 h under an argon atmosphere.
[b] GLC yield.
[c] For 26 h. Cyclohexyl isocyanate was recovered in 58%.

Table 3. $[RhCl(C_2H_4)_2]_2$/PPh_3-catalyzed synthesis of pyrimidine-2,4-diones (**4**) from alkynes (**1**) with *n*-hexyl isocyanate (**2d**)[a]

Entry	Alkyne	Product	Isolated yield (%)
1	 **1a**	 **4a**	86
2	 **1c**	 **4b**	62
3	 **1d**	 **4c**  **4c'**	63[b] (**4c**/**4c'** = 4/1)[c]	63[b]

[a] Alkyne (**1**) (0.50 mmol), *n*-hexyl isocyanate (**2d**) (10.0 mmol), $[RhCl(C_2H_4)_2]_2$ (0.013 mmol), PPh_3 (0.050 mmol), and mesitylene (1.0 ml) at 120 °C for 12 h under an argon atmosphere.
[b] Determined by GLC and ^1H NMR.



Scheme 1. Possible mechanism for Rh-catalyzed synthesis of 2-pyridones **3** and pyrimidine-2,4-diones **4** from alkynes **1** and isocyanates **2**.

mechanism involving a rhodacyclopentadiene derived from the oxidative cyclization of two alkynes can be ruled out. In cycle A, an azarhodacycloheptadienone could be formed by the selective insertion of an alkyne into the rhodium–carbon bond in an azarhodacyclopentenone,[17] and the subsequent reductive elimination gives 2-pyridone (**3**). On the other hand, insertion of an isocyanate in place of an alkyne into the rhodium–nitrogen bond rather than the rhodium–carbon bond in an azarhodacyclopentenone proceeded,[18] when a large excess amount of isocyanates was used, to give a diazarhodacycloheptenedione, and subsequent reductive elimination gives pyrimidine-2,4-diones (**4**) according to cycle B.

In conclusion, we have developed a 'neutral' rhodium complex-catalyzed cyclocotrimerization of alkynes and isocyanates to 2-pyridones. Although Flynn[10] and Tanaka[11] claimed that neutral rhodium complexes have extremely low catalytic activity in the cyclocotrimerization of alkynes and isocyanates, we found that a coordinatively unsaturated and sterically less hindered '$RhCl(PPh_3)_2$' generated by the combination of $[RhCl(C_2H_4)_2]_2$ with a fourfold amount of PPh_3 showed good to high catalytic activity. In addition, the selective synthesis of pyrimidine-2,4-diones in place of 2-pyridones was realized by controlling the molar ratio of alkynes and isocyanates.

Acknowledgements

This work was supported in part by Grants-in-Aid for Scientific Research (B), Scientific Research on Priority Areas, and the 21st-century COE program, COE for a United Approach to New Materials Science, from the Japan Society for the Promotion of Science and the Ministry of Education, Culture, Sports, Science and Technology, Japan. T.K. acknowledges financial support from the Japan Chemical Innovation Institute. This research (project) was conducted in part at the Advanced Research Institute of Environmental Material Control Engineering, Katsura-Int'tech Center, Graduate School of Engineering, Kyoto University.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.07.105.

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15. After the reaction of entry 2 in Table 1, phenyl isocyanate (**2a**) still remained, however, longer reaction time did not improve both the conversion of **2a** and the yield of **3a**. In the present reaction, decarbonylation of isocyanates occurred to some extent. The generated carbon monoxide may coordinate to an active rhodium species leading to deactivation of the rhodium catalyst, which accords well with the low catalytic activity of $RhCl(CO)(PPh_3)_2$ (vide supra).
16. Since the reactivity of an alkyne is higher than that of an isocyanate under the present catalytic reaction conditions, treatment of 3-hexyne (**1a**) with an equal amount of *n*-hexyl isocyanate (**2d**) predominantly gave the corresponding 2-pyridone (**3d**). In order to obtain pyrimidine-2,4-dione (**4a**), a *large excess* amount (at least, 20 equiv) of *n*-hexyl isocyanate (**2d**) is needed.
17. Hoberg and co-workers isolated the corresponding nickelacycles in the nickel-catalyzed cyclocotrimerization of alkynes and isocyanates, in which the insertion of an alkyne into the nickel–carbon bond rather than the nickel–nitrogen bond in an azanickelacyclopentenone proceeded. See: Ref. 5b and 5c.
18. For example, see: Rais, D.; Bergman, R. G. *Chem. Eur. J.* **2004**, *10*, 3970–3978.