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# An Efficient Rhodium-Catalyzed Double Hydroaminocarbonylation of Alkynes with Carbon Monoxide and Amines Affording 1,4-Diamide Derivatives

Qiufeng Huang[a] and Ruimao Hua[a,*]

[a] Department of Chemistry, Tsinghua University, Innovative Catalysis Program, Key Laboratory of Organic Optoelectronics & Molecular Engineering of Ministry of Education, Beijing 100084, People's Republic of China
Fax: (+86)-10-62792596; e-mail: ruimao@mail.tsinghua.edu.cn

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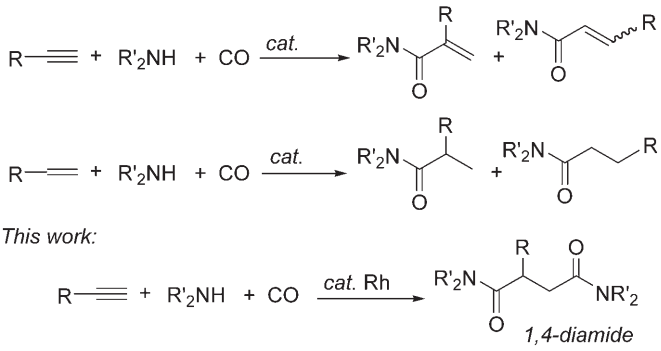
**Abstract:** The hydroaminocarbonylation of terminal alkynes with carbon monoxide and pyrrolidine or piperidine catalyzed by rhodium complexes affords 1,4-diamide derivatives in good to high yields.

**Keywords:** alkynes; amines; aminocarbonylation; carbon monoxide; rhodium

The transition metal-catalyzed carbonylation of unsaturated compounds is a versatile synthetic tool for the preparation of carbonyl compounds. In the past three decades, a variety of efficient catalyst systems and carbonylation reactions have been developed.[1] Among them, the hydroaminocarbonylation of alkynes,[2] allenes,[3] and alkenes[4] with carbon monoxide and amines has provided an easy access to acrylamides and amides. In the existing catalyst systems for the hydroaminocarbonylation of alkynes, the selectivity of the adducts depends on the reaction conditions employed, in most cases, a mixture of adducts was obtained. After surveying the efficient catalytic systems with high regioselectivity for hydroaminocarbonylation of terminal alkynes, we performed the reaction of phenylacetylene (**1a**) with pyrrolidine (**2a**) under a CO atmosphere in the presence of $RhCl(PPh_3)_3$ in toluene at 120 °C for 15 h. GC and GC-MS analysis of the reaction mixture disclosed that an unexpected new compound 2-phenyl-1,4-dipyrrolidin-1-yl-butane-1,4-dione (**3aa**) ($M^+ = 300$) was formed in low yield (10% by $^1H$ NMR).[5] The formation of this new compound is considered to be derived from the double hydroaminocarbonylation of **1a**. These interesting results encouraged us to develop an efficient catalyst system for this novel, one-pot, double hydroaminocarbonylation of terminal alkynes. In this communication, we report the results of the double hydroaminocarbonylation of terminal alkynes in the presence of rhodium complexes affording 2-substituted 1,4-diamides (Scheme 1).[6]

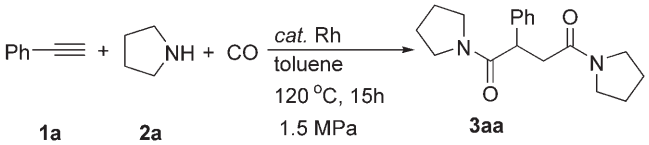



**Scheme 1.** Hydroaminocarbonylation of terminal alkynes and alkenes.

We examined the reaction of **1a** with **2a** in detail with various rhodium catalysts under different reaction conditions to optimize the formation of **3aa**, and the results are summarized in Table 1 and Table 2. The results in Table 1 reveal that rhodium complexes could catalyze the double hydroaminocarbonylation of **1a**, but the catalytic activity greatly depends on the structure of the complexes. Under identical reaction conditions, $RhCl(PPh_3)_3$ was found to be the best and showed high catalytic activity to give **3aa** in 83% GC yield (Table 1, entry 1).[7] The reaction with other rhodium complexes having the ratio of Rh/P = 2 or 4, and phosphine-free gave **3aa** in moderate or low yields (Table 1, entries 4–12). An increase of the CO pressure could slightly improve the yield of **3aa** (e.g., 11.0 MPa, 90% GC yield) (Table 1, entry 2). On the other hand, the reaction also depends on the reaction temperature, at 80 °C for 15 h, the yield of **3aa** decreased significantly (Table 1, entry 3). Furthermore,

**Table 1.** Rhodium-catalyzed double hydroaminocarbonylation of phenylacetylene (**1a**) with pyrrolidine (**2a**).[a]




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

| Entry | Catalyst | Yield of **3aa** [%][b] |
|---|---|---|
| 1 | $RhCl(PPh_3)_3$ | 83(70) |
| 2[c] | $RhCl(PPh_3)_3$ | 90 |
| 3[d] | $RhCl(PPh_3)_3$ | 30 |
| 4 | $RhCl(CO)(PPh_3)_2$ | 54 |
| 5 | $RhCl(CO)(PCy_3)_2$ | 60 |
| 6[e] | RhCl(CO)(dppe) | 34 |
| 7[f] | RhCl(CO)(dppb) | 28 |
| 8[g] | RhCl(CO)(dppp) | 33 |
| 9[h] | RhCl(CO)(dppf) | 25 |
| 10[f] | $RhCl(dppb)_2$ | 10 |
| 11[i] | $Rh(acac)(CO)_2$ | 40 |
| 12 | $Rh(acac)(CO)(PPh_3)$ | 50 |

[a] Reactions were carried out at 120 °C for 15 h by using 1.0 mmol of **1a**, 4.0 mmol of **2a** and 0.05 mmol of catalyst in 2.0 mL of toluene in a 25 mL autoclave.
[b] GC yield (isolated yield) based on **1a** used.
[c] 11.0 MPa.
[d] 80 °C.
[e] dppe = 1,2-bis(diphenylphosphino)ethane.
[f] dpp*b* = 1,4-bis(diphenylphosphino)butane.
[g] dppp = 1,5-bis(diphenylphosphino)propane.
[h] dppf = 1,1′-bis(diphenylphosphino)ferrocene.
[i] acac = acetylacetonato.

either an increase (6.0 mmol) or a decrease (2.0 mmol) in the amount of **2a** resulted in the formation of **3aa** in somewhat lower yields (77 % and 59 % GC yields, respectively).

Table 2 shows the effect of the solvent on the formation of **3aa**, in anisole, the reaction proceeded as smoothly as in toluene (Table 2, entry 1). However, the use of other solvents resulted in significant decreases of the yield.

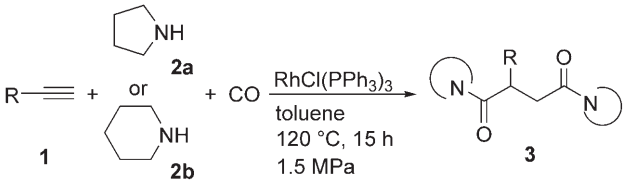
Table 3 includes representative results of $RhCl(PPh_3)_3$-catalyzed double hydroaminocarbonylation of other terminal alkynes with **2a** or piperidine (**2b**). As shown in Table 3, the present reaction seems to be suitable for both aliphatic and substituted aromatic alkynes to produce the corresponding adducts in good to high isolated yields. However, It should be especially noted that, in contrast to **2a** or **2b**, under the same reaction conditions, the use of $Bu_2NH$ did not furnish the corresponding **3aa**-type adducts (confirmed by GC-MS). For example, no carbonylated

**Table 2.** Effect of solvent on the formation of **3aa**.[a]

| Entry | Solvent | Yield of **3aa** [%][b] |
|---|---|---|
| 1 | $PhOCH_3$ | 85 |
| 2 | 1,4-dioxane | 30 |
| 3 | cyclohexone | < 5 |
| 4 | $CH_3CN$ | 37 |
| 5 | $CHCl_2CHCl_2$ | 28 |
| 6 | DMSO | < 5 |
| 7 | DMF | < 5 |
| 8 | NMP | < 5 |

[a] Reactions were carried out at 120 °C for 15 h by using 1.0 mmol of **1a**, 4.0 mmol of **2a** and 0.05 mmol of catalyst in 2.0 mL of toluene in a 25 mL autoclave.
[b] GC yield (isolated yield) based on **1a** used.

**Table 3.** $RhCl(PPh_3)_3$-catalyzed double hydroaminocarbonylation of terminal alkynes.[a]



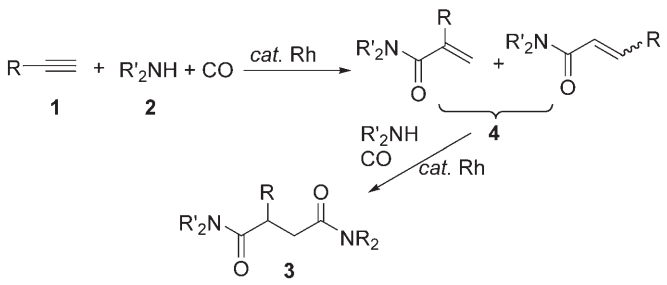

| Entry | R | Amine | | Product No. | Yield [%][b] |
|---|---|---|---|---|---|
| 1 | $C_6H_5$ | **1a** | **2b** | **3ab** | 61 |
| 2 | $p$-$CH_3C_6H_4$ | **1b** | **2a** | **3ba** | 75 |
| 3 | $p$-$CH_3C_6H_4$ | **1b** | **2b** | **3bb** | 59 |
| 4 | $p$-$ClC_6H_4$ | **1c** | **2a** | **3ca** | 55 |
| 5 | $p$-$ClC_6H_4$ | **1c** | **2b** | **3cb** | 58 |
| 6 | $p$-$CF_3OC_6H_4$ | **1d** | **2a** | **3da** | 75 |
| 7 | $p$-$CF_3OC_6H_4$ | **1d** | **2b** | **3db** | 67 |
| 8 | 3,4 - $F_2C_6H_3$ | **1e** | **2a** | **3ea** | 65 |
| 9 | 3,4 - $F_2C_6H_3$ | **1e** | **2b** | **3eb** | 50 |
| 10 | $n$-$C_6H_{13}$ | **1f** | **2a** | **3fa** | 78 |
| 11 | $n$-$C_6H_{13}$ | **1f** | **2b** | **3fb** | 83 |
| 12 | $NCCH_2CH_2CH_2$ | **1g** | **2a** | **3ga** | 72 |
| 13 | $NCCH_2CH_2CH_2$ | **1g** | **2b** | **3gb** | 81 |

[a] Reactions were carried out at 120 °C for 15 h by using 1.0 mmol of **1a**, 4.0 mmol of **2a** and 0.05 mmol of catalyst in 2.0 mL of toluene in a 25 mL autoclave.
[b] Isolated yield based on **1a** used.

products could be found from the reaction of **1a**, $Bu_2NH$ and carbon monoxide and **1a** was recovered.

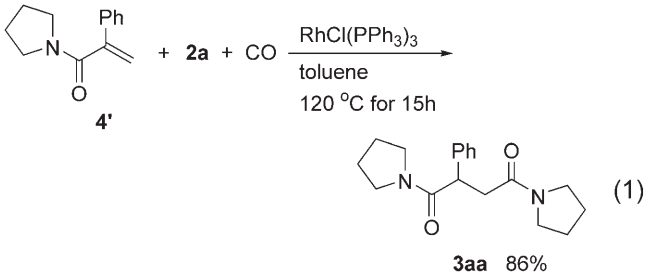
The present double hydroaminocarbonylation of terminal alkynes can be rationalized by the sequence




**Scheme 2.** Reaction route for the formation of 2-substituted 1,4-diamide **3**.

reactions depicted in Scheme 2. It includes the hydroaminocarbonylation of alkynes affording Markovnikov and/or *anti*-Markovnikov adducts **4**. Adduct **4** then undergoes the second hydroaminocarbonylation to furnish **3**. Because **3** was the exclusive isolated diamide product, we consider that the Markovnikov-type adduct **4′** is the major intermediate. Therefore we examined the reaction of **4′** with **2a** and CO under the reaction conditions indicated in Table 3. As expected, **3aa** was formed in high yield [Eq. (1)].




In summary, we describe in this communication a novel and unprecedented rhodium-catalyzed double hydroaminocarbonylation of terminal alkynes with carbon monoxide and pyrrolidine or piperidine to afford 1,4-diamides which are an important moiety for the synthesis of physiologically and biologically active molecules.[8] These findings have revealed the important carbonylative procedure of terminal alkynes with the following two aspects: (1) sequential double hydroaminocarbonylation reactions take place under the same catalyst system, and (2) a novel method for synthesizing 1,4-diamides has been developed. Further studies for extending the generality of the reaction are underway in our laboratory.

## Experimental Section

### Typical Procedure for $RhCl(PPh_3)_3$-Catalyzed Double Hydroaminocarbonylation of Phenylacetylene (1a) with Pyrrolidine (2a) Affording 2-Phenyl-1,4-dipyrrolidin-1-yl-butane-1,4-dione (3aa; Table 1, entry 1)

Phenylacetylene (**1a**; 1.0 mmol), pyrrolidine (**2a**; 4.0 mmol), $RhCl(PPh_3)_3$ (0.05 mmol) and toluene (2.0 mL) were placed in a 25-mL autoclave under nitrogen. Carbon monoxide was introduced at an initial pressure of 1.5 MPa at room temperature, and then the autoclave was heated in an oil bath at 120 °C with stirring for 15 h. After the autoclave had cooled to room temperature, CO was released slowly, and the crude reaction mixture was diluted with $CH_2Cl_2$ to 10 mL and $C_{28}H_{58}$ (0.2 mmol) was added as an internal standard for GC analysis. After GC and GC-MS analyses, the mixture was concentrated under vacuum. Product **3aa** was isolated by column chromatography ($Al_2O_3$, eluted with petroleum/acetone/triethylamine = 100:5:1); yield: 70%. The results of GC analysis of the reaction mixture revealed that **3aa** was formed in 83% GC yield.

Characterization data of products **3aa–3gb** and their $^1H$ and $^{13}C$ NMR spectra are given in the Supporting Information.

## Acknowledgements

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[5] In this case, small amount (<5%) of mono-hydroaminocarbonylated product **4** (as shown in Scheme 2) was formed, which was confirmed by GC-MS.

[6] Very recently, the direct selective hydroamidation of alkynes with amides has been reported, see for intermolecular hydroamidation: a) L. J. Gooβen, J. E. Rauhaus, G. Deng, *Angew. Chem. Int. Ed.* **2005**, *44*, 4042–4045; for intramolecular hydroamidation: b) Y. Yu, G. A. Stephenson, D. Mitchell, *Tetrahedron Lett.* **2006**, *47*, 3811–3814; c) N. T. Patil, Z. Hua, G. B. Bajracharya, Y. Tamamoto, *J. Org. Chem.* **2006**, *71*, 3612–3614.

[7] In the present catalytic hydroaminocarbonylation of terminal alkynes, the major by-products are the adduct(s) of **4** as shown in Scheme 2. The total yield of the carbonylated by-product **4** is in the range of 4–10%.

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