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# Intermolecular coupling of alkynes, isocyanates, and acyl chlorides: an efficient method for the synthesis of 5-hydroxypyrrol-2(5*H*)-ones

Ken-ichiro Kanno,[a] Shenyong Ren,[a] Yanzhong Li,[a] Kiyohiko Nakajima[b] and Tamotsu Takahashi[a,*]

[a]*Catalysis Research Center and Graduate School of Pharmaceutical Sciences, Hokkaido University, and SORST, Japan Science and Technology Corporation (JST), Kita-ku Sapporo 001-0021, Japan*
[b]*Department of Chemistry, Aichi University of Education, Igaya, Kariya, Aichi 448-8542, Japan*

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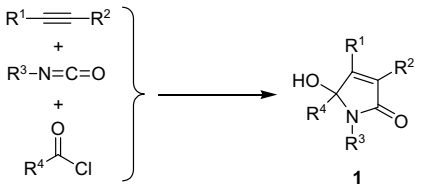
**Abstract**—New insights into the reaction of diethylzirconocene with an alkyne, an isocyanate, and an acyl chloride in this order are reported. The products of 5-hydroxypyrrol-2(5*H*)-ones are obtained in good yields after hydrolysis. It is an efficient method for the synthesis of 5-hydroxypyrrol-2(5*H*)-ones.


5-Hydroxypyrrol-2(5*H*)-ones are a class of very attractive heterocycles due to their wide range of interesting biological activities.[1,2] Within the last several decades, 5-hydroxypyrrol-2(5*H*)-ones have been evaluated for antineoplastic activity in tumor cells of white mice.[3] In some cases, these functional 5-membered lactams have shown antitumor activity.[4] Many methods have been developed to synthesize these useful functional heterocycles. For example, oxidative bromination reaction of nicotine,[5] amination of the corresponding lactones,[6] metal-catalyzed condensation–cyclization reaction of acyl cyanides with 3-oxoamides,[7] Ni-catalyzed cyanation of α-ketoalkynes in $H_2O$,[8] halolactamization–hydroxylation of 2,3-allenamides with $CuX_2$,[9] and regioselective reduction of 3-methoxymaleimides[10] can give 5-hydroxypyrrol-2(5*H*)-one derivatives. However, development of a highly efficient methodology for the synthesis of 5-hydroxypyrrol-2(5*H*)-ones with diversity is still of high interest.

So far, our group has developed zirconium-mediated cycloaddition reactions of unsaturated compounds such as alkynes, alkenes, nitriles, and isocyanates. In the case of the benzene formation reaction, highly selective cyclization of three different alkynes was achieved.[11] Similarly, selective synthesis of pyridine derivatives from two alkynes and a nitrile was also possible with zirconocene complexes.[12] Furthermore, the zirconium-mediated reactions with isocyanates could produce pyridone and cyclopentenone derivatives.[12b,13,14] During the course of our study on the chemistry of zirconocene-mediated cycloaddition reaction, we envisioned that 5-hydroxypyrrol-2(5*H*)-ones may be synthesized by the coupling reaction of an alkyne, an isocyanate, and an acyl chloride (Scheme 1). Herein we would like to report this reaction.[15]




**Scheme 1.**

A typical procedure for the synthesis of 5-hydroxypyrrol-2(5*H*)-one from alkyne, isocyanate, and acyl chloride is as follows (Scheme 2). Zirconacyclopentene **2** was prepared by the reaction of an alkyne with $Cp_2ZrEt_2$ in THF at 0 °C.[16] To the solution was added

* Corresponding author. Tel.: +81 11 706 9149; fax: +81 11 706 9150; e-mail: tamotsu@cat.hokudai.ac.jp

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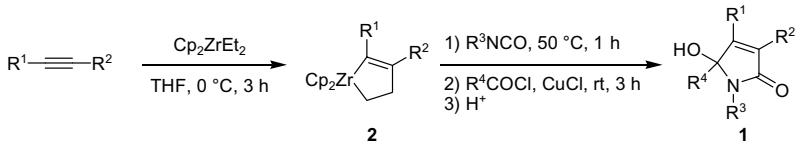
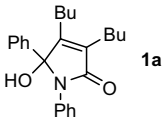
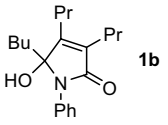
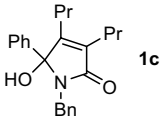
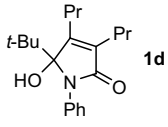
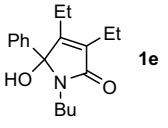
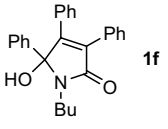
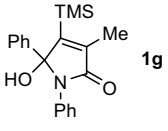
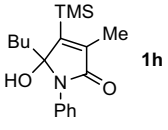
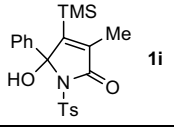



**Scheme 2.** Synthesis of 5-hydroxypyrrol-2(5*H*)-ones.

1.2 equiv of an isocyanate, and the reaction mixture was stirred for 1 h at 50 °C. Then CuCl and an acyl chloride were added at room temperature, and the reaction mixture was stirred for 3 h at the same temperature. After usual work-up and purification by a silica gel column chromatography, the corresponding 5-hydroxypyrrol-2(5*H*)-one was obtained in high yield.

The results of the reactions with various substrates are summarized in Table 1. The reaction using symmetrical alkynes proceeded smoothly with aryl or aliphatic isocyanates and acyl chlorides to afford the corresponding 5-hydroxypyrrol-2(5*H*)-ones in good yields (entries 1–6). When unsymmetrical alkyne such as 1-trimethylsilyl-1-propyne was employed, the corresponding products

**Table 1.** Formation of 5-hydroxypyrrol-2(5*H*)-one derivatives

| Entry | Alkyne | Isocyanate | Acylchloride | Product | Yield[a] (%) |
|---|---|---|---|---|---|
| 1 | Bu—≡—Bu | PhNCO | PhCOCl |  **1a** | 90 (75) |
| 2 | Pr—≡—Pr | PhNCO | BuCOCl |  **1b** | 71 (58) |
| 3 | Pr—≡—Pr | BnNCO | PhCOCl |  **1c** | 68 (51) |
| 4 | Pr—≡—Pr | PhNCO | *t*-BuCOCl |  **1d** | 75 (63) |
| 5 | Et—≡—Et | BuNCO | PhCOCl |  **1e** | 57 (43) |
| 6 | Ph—≡—Ph | BuNCO | PhCOCl |  **1f** | 77 (71) |
| 7 | TMS—≡—Me | PhNCO | PhCOCl |  **1g** | 56 (36) |
| 8 | TMS—≡—Me | PhNCO | BuCOCl |  **1h** | 68 (47) |
| 9 | TMS—≡—Me | TsNCO | PhCOCl |  **1i** | 81 (68) |

[a] NMR yields; isolated yields are given in parentheses.

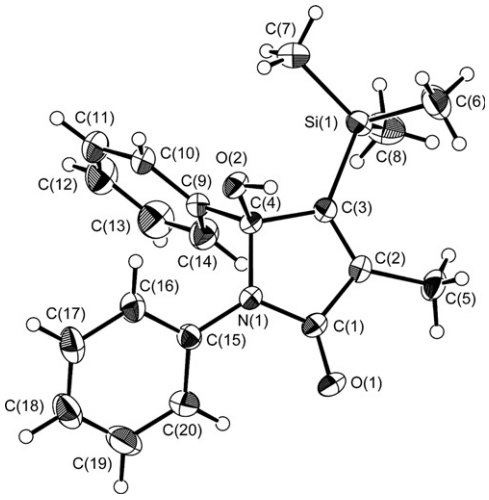


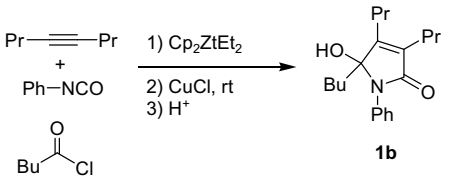

**Figure 1.** Molecular structure of **1g**.

were obtained as single isomers in high yields (entries 7–9). The structure of silylated 5-hydroxypyrrol-2(5*H*)-one **1g** was unambiguously confirmed by X-ray crystallography (Fig. 1). Isocyanates with functional groups such as benzyl and tosyl groups could also be used in the reaction (entries 3 and 9) to form the desired products **1c** and **1i**, respectively. Even with sterically congested pivaloyl chloride, the corresponding *tert*-butylated compound **1d** was obtained without significant loss of the yield (entry 4). However, the reaction with *tert*-butyl isocyanate gave no desired product.

In Scheme 3, a plausible reaction mechanism of the 5-hydroxypyrrol-2(5*H*)-one formation was proposed. At the beginning, $Cp_2ZrEt_2$ reacts with an alkyne to afford zirconacyclopentene **2**. And an isocyanate reacts with **2** to form either aza- or oxazirconacyclopentene **3** or **4**, which we have already reported in the similar reactions.[13,14] Transmetalation of zirconacycle **3** or **4** to CuCl gives **5** or **6**, which reacts with an acyl chloride to give **7** or **8** and releases CuCl. Finally, the intramolecular addition of the nitrogen atom to the carbonyl group followed by hydrolysis affords the corresponding 5-hydroxypyrrol-2(5*H*)-one **1**.

This mechanism suggested the catalytic nature of CuCl. In fact, as shown in Table 2, the reaction also proceeded

**Table 2.** Formation of hydroxypyrrolone **1b** with a catalytic amount of CuCl




**1b**

| Entry | CuCl (equiv) | Time (h) | Yield of **1b**[a] (%) |
|---|---|---|---|
| 1 | 2 | 3 | 71 |
| 2 | 0.5 | 12 | 81 |
| 3 | 0.1 | 24 | 72 |

[a] NMR yield.

with a catalytic amount of CuCl. When the reaction was carried out with 0.1 equiv of CuCl, product **1b** was obtained without significant loss of the yield. However, it takes one day to complete the reaction.

In summary, we developed the synthetic methodology of 5-hydroxypyrrol-2(5*H*)-ones **1** through an intermolecular coupling of alkynes, isocyanates, and acyl chlorides mediated by zirconium and copper. This method could be used for a variety of substrates and gave a number of the derivatives of **1** in one-pot reaction from the ordinary and commercially available starting materials.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.10.096.

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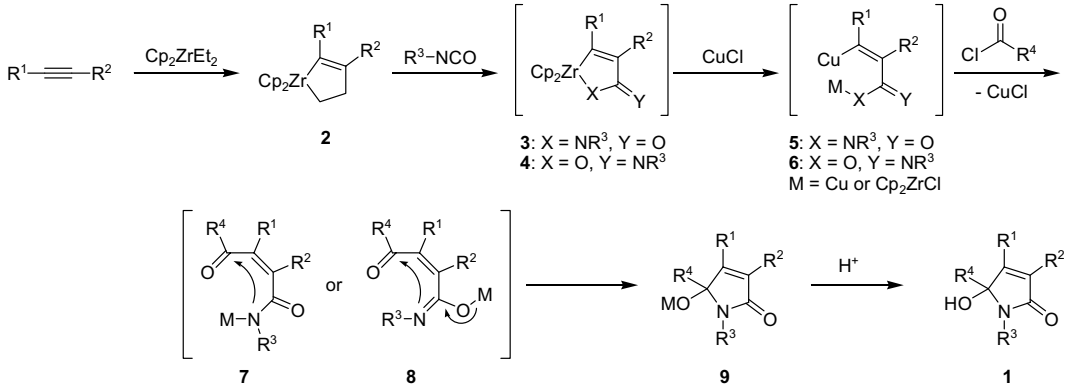


**Scheme 3.** Mechanism of formation 5-hydroxypyrrol-2(5*H*)-ones.

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