

Novel Syntheses of [6,7,*n*]-Benzazepinone and [6,6,*n*]-Benzophenanthridinone Derivatives by Rhodium-catalyzed Cyclization of *o*-(*n*-Cyanoalkynyl)benzaldehydes[†]

Chang Ho Oh* and Katta Venugopal Reddy

Department of Chemistry, Hanyang University, Seoul 133-791, Korea. *E-mail: changho@hanyang.ac.kr

Received May 30, 2007

Key Words : Benzazepinone, Phenanthridinone, Rhodium, Cyclization

Since transition metal catalysis allows simultaneous formation of more than one bond in a single step operation with high selectivity,¹ the exploitation of a model compound for nitrogen-containing polycyclic biologically active natural products has been a worthwhile contribution in synthetic and medicinal chemistry.²

Intramolecular hydroamidation of acetylenes, carbonylation of 2-alkylbenzenylamines, 1-aryl-3-hexen-1,5-diyne initiated by methoxide addition, fluoroarenes and nitriles *via* 1,2-arynes, nitroarylstannanes, radical dearomatization of benzene and hydrothermal reaction of *o*-phenylaniline, ullmann cross-coupling of 1-bromo-2-nitroarenes and 1,3-dipolarcycloaddition of nonstabilized azomethine ylide and photocycloaddition of phthalimide anion to alkenes have been used to synthesize benzazepinone, phenanthridine and benzophenanthridinone derivatives.³ However, these synthetic routes are often complicated and limited to only some substituents. Recently, we reported various cycloisomerization reactions with different unsaturated systems catalyzed by Au, Pt, Pd, and Rh.⁴ Our continued interest in the synthesis of polycyclic systems prompted us to develop the Rh-catalyzed cyclization of *o*-alkynylbenzaldehydes having a nitrile tether that produced tricyclic benzazepinones and benzophenanthridinone derivatives *via* [3+2] and [4+2] cycloaddition *via* pyrylium intermediates as shown in Scheme 1.

An initial study was tested with *o*-alkynylbenzaldehyde **1a** in the presence of various late transition metal catalysts (Table 1). PtCl₂ as a catalyst in refluxing 1,4-dioxane for 12 h converted **1a** to give a mixture of products, which were separated by column chromatography to give 2,3-dihydrobenzo[*e*]cyclopenta[*b*]azepin-5(*1H*)-one (**3a**) in 50% yield

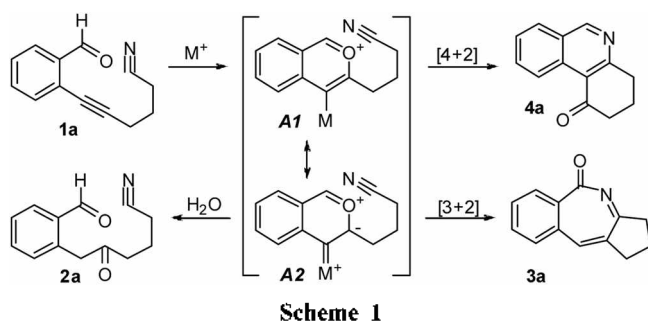


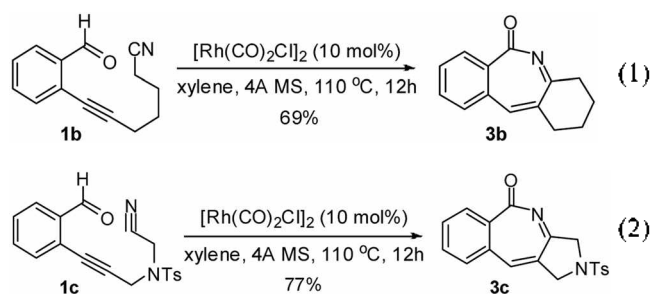
Table 1. Optimization of intramolecular [3 + 2] cyclization-cycloaddition under various reaction conditions with **1a**

Entry	Catalyst (mol %)	Solvent	T, °C/h	Products	Yield (%)
1	PtCl ₂ (10)	1,4-Dioxane	100/12	2a , 3a	30/50
2	PtCl ₂ (10)	1,4-Dioxane 4 Å MS	100/12	2a , 3a	10/59
3	AuBr ₃ (10)	EDC	RT/12	2a	91
4	AuCl ₃ (10)	EDC	RT/12	2a	78
5	AuCl(PPh ₃) ₂ (5) AgSbF ₆ (5)	EDC	RT/6	2a	89
6	AgSbF ₆ (10)	EDC	RT/12	2a	74
7	[Rh(cod)Cl] ₂ (10)	Xylene 4 Å MS	110/12	2a , 3a	10/71

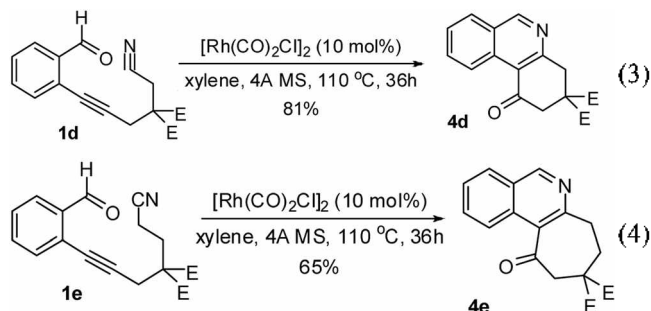
along with the hydrated product **2a** in 30% yield (entry 1). When this reaction was carried out in dry 1,4-dioxane in the presence of 4 Å molecular sieves, the reaction was dramatically accelerated to give the product **3a** in 59% yield still along with **2a** in 10% yield (entry 2). We presumed that a trace amount of water in the reaction medium or in solvent might generate a nucleophile which could undergo hydration to the metal-activated triple bond followed by tautomerization to the corresponding ketoaldehyde **2a**.

It was observed that gold(III) bromide in 1,2-dichloroethane (EDC) hydrated **1a** to afford **2a** even at room temperature exclusively (entry 3). This might be understood by the high reactivity of gold catalyst or the poor reactivity of the nitrile group toward the pyrylium intermediate **A**. We tried the same reaction with different catalysts, such as AuCl₃, AuCl(PPh₃)₂ with AgSbF₆, and AgSbF₆ itself, under dry reaction conditions, but led to hydration (entries 4-6). In fact, Zhu *et al.* reported that *o*-alkynylbenzaldehydes were hydrated in the presence of gold(+3) catalysts and trifluoroacetic acid to afford the corresponding ketoaldehyde.⁵ Finally, we found [Rh(COD)Cl]₂ as an optimal catalyst for the present [3+2] cyclization of pyrylium intermediate, generated *in situ* with alkynophilic metal cations, with a pendent nitrile. Thus, when the substrate **1a** in the presence of [Rh(COD)Cl]₂ (10 mol%) in dry xylene containing 4 Å molecular sieves was heated at 110 °C for 12 h, the product **3a** was isolated in 71% yield along with the ketoaldehyde **2a** in 10% yield. With this promising result, we further examined this [3+2] cycloaddition with structural alteration in the tether (eq. 1-2).

[†]This paper is dedicated to Professor Sang Chul Shim at Kyungpook National University on the occasion of his honorable retirement.

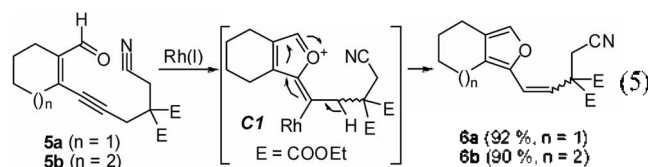
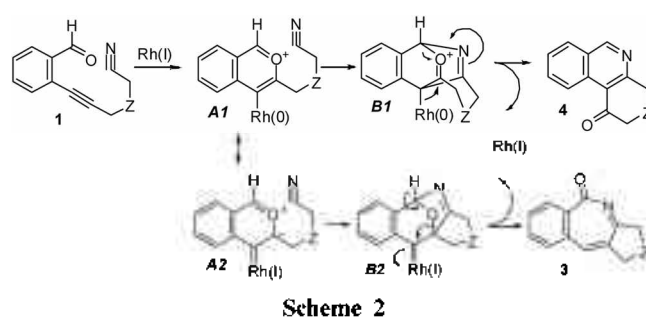


Substrate **1b**, an one-carbon longer homolog in the tether, underwent the present reaction to afford (4*aZ*,11*Z*)-3,4-dihydro-1*H*-dibenzo[*b,e*]azepin-6(2*H*)-one (**3b**) in 69% yield. The same reaction with the substrate **1c**, having -NTs group in the tether, also proceeded the same reaction to afford the corresponding product **3c**, (3*aE*,10*Z*)-2-tosyl-2,3-dihydrobenzo[*e*]pyrrolo[3,4-*b*]azepin-5(1*H*)-one in 77% yield. Interestingly, the similar substrate **1d** having a *gem*-diester group required longer time (36 h) for completion: the corresponding [4+2] cycloaddition product **4d**, diethyl 1-oxo-1,2-dihydrophenanthridine-3,3(4*H*)-dicarboxylate, was obtained in 81% yield (eq. 3). It is worth to note that the reaction proceeded smoothly with the substrate **1e**, one-carbon homolog of **1d**, to give the corresponding product **4e** in 65% yield (eq. 4).



Both structures of **3a** and **4d** were confirmed by 2D NMR. We should note that the present method could provide an easy access to [6,6,7]-tricyclic compounds without the *gem*-diester group and [6,6,6]-tricyclic compounds with the *gem*-diester group.

Mechanistic speculation was summarized in Scheme 2. The aromatic ring might form the pyrylium intermediate **A1** and its resonance form **A2**, which would undergo either [3+2] cycloaddition leading to **3** or [4+2] cycloaddition leading to **4**. A key factor associated with the chemoselectivity in cycloaddition should be related to group Z but is not uncovered yet. This method was applied to aliphatic systems **5a** and **5b**, where the aldehyde group and the triple bond were conjugated with cycloalkenes. These substrates were reactive toward Rh(I) even at room temperature but seemed to form **C1** intermediate which would be eliminated followed by protolysis to give the furan derivatives **6a** and **6b** in almost quantitative yields (eq 5).⁶



In conclusion, we have found a new and atom economical Rh-catalyzed cyclization reaction with *o*-alkynylbenzaldehydes having a nitrile tether leading to synthetically valuable nitrogen containing polycyclic compounds. Further studies to extend the scope of its synthetic utility and applications are in progress in our laboratory.

Acknowledgement. We wish to acknowledge the financial support of Korea Research Foundation (2004-C00197) and BK21.

References and Notes

- Trost, B. M. *Science* **1991**, *254*, 1471.
- (a) Pandey, G.; Banerjee, P.; Kumar, R.; Puranik, V. G. *Org. Lett.* **2005**, *7*, 3713. (b) Sha, C.-K.; Hong, A.-W.; Huang, C.-M. *Org. Lett.* **2001**, *3*, 2177. (c) Lee, P. H. *Bull. Korean Chem. Soc.* **2007**, *28*, 17. (d) Kim, Y.; Kang, J. *Bull. Korean Chem. Soc.* **2007**, *28*, 363.
- (a) Yu, Y.; Stephenson, G. A.; Mitchell, D. *Tetrahedron Lett.* **2006**, *47*, 3811. (b) Wu, M.-J.; Lin, C.-F.; Lu, W.-D. *J. Org. Chem.* **2002**, *67*, 5907. (c) Banwell, M. G.; Lupton, D. W.; Ma, S.; Renner, J.; Sydnese, M. O. *Org. Lett.* **2004**, *6*, 2741. (d) Fruta, T.; Kitamura, Y.; Hashimoto, A.; Fujii, S.; Tanaka, K.; Kan, T. *Org. Lett.* **2007**, *9*, 183.
- (a) Kim, N.; Kim, Y.; Park, W.; Sung, D.; Gupta, A. K.; Oh, C. H. *Org. Lett.* **2005**, *7*, 5289. (b) Oh, C. H.; Kim, A.; Park, W.; Park, D. I.; Kim, N. *Synlett* **2006**, 2781. (c) Oh, C. H.; Bang, S. Y.; Rhim, C. Y. *Bull. Korean Chem. Soc.* **2003**, *24*, 887. (d) Oh, C. H.; Rhim, C. Y.; Kim, M.; Park, D. I.; Gupta, A. K. *Synlett* **2005**, 2694. (e) Shin, S.; Gupta, A. K.; Rhim, C. Y.; Oh, C. H. *Chem. Commun.* **2005**, 4429.
- Zhu, J.; Germain, A. R.; Porco, Jr, J. A. *Angew. Chem. Int. Ed.* **2004**, *43*, 1239.
- (a) Asao, N.; Aikawa, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 7458. (b) Asao, N.; Sato, K.; Menggenbateer; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 3682.
- It was similar to Mike's report with *o*-alkynylcyclohexene aldehydes in the presence of chromium compounds, see: Koji, M.; Tomomi, Y.; Fumiaki, N.; Yumiko, K.; Yosuke, W.; Kouichi, O.; Sakae, U. *J. Org. Chem.* **2004**, *69*, 1557.