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

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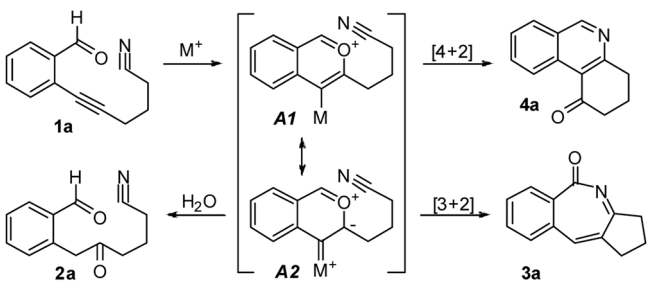
Since transition metal catalysis allows simultaneous formation of more than one bond in a single step operation with high selectivity,[1] the exploitation of a model compound for nitrogen-containing polycyclic biologically active natural products has been a worthwhile contribution in synthetic and medicinal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

Intramolecular hydroamidation of acetylenes, carbonylation of 2-alkylbenzenylamines, 1-aryl-3-hexen-1,5-diynes initiated by methoxide addition, fluoroarenes and nitriles *via* 1,2-arynes, nitroarylstannanes, radical dearomatization of benzene and hydrothermal reaction of *o*-phenylaniline, ullamann 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 benzophenathridinone 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 benzophenanthridine 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). $PtCl_2$ 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(1*H*)-one (**3a**) in 50% yield



Scheme 1

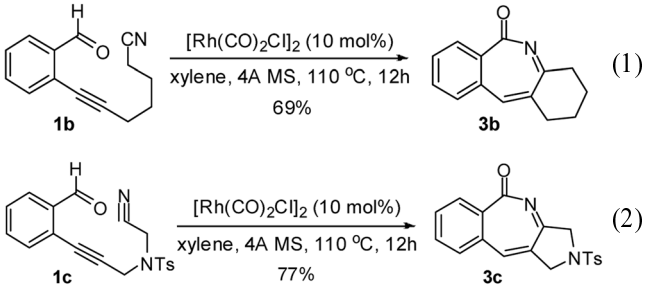
†This paper is dedicated to Professor Sang Chul Shim at Kyungpook National University on the occasion of his honorable retirement.

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

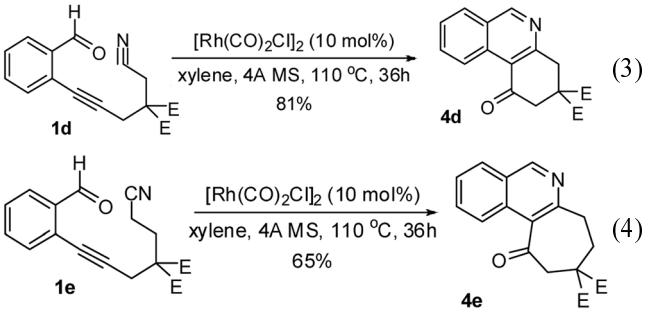
Entry	Catalyst (mol %)	Solvent	T, °C /h	Products	Yield (%)
1	$PtCl_2$ (10)	1,4-Dioxane	100/12	**2a**, **3a**	30/50
2	$PtCl_2$ (10)	1,4-Dioxane 4 Å MS	100/12	**2a**, **3a**	10/59
3	$AuBr_3$ (10)	EDC	RT/12	**2a**	91
4	$AuCl_3$ (10)	EDC	RT/12	**2a**	78
5	$AuCl(PPh_3)$(5) $AgSbF_6$ (5)	EDC	RT/6	**2a**	89
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 $AuCl_3$, $AuCl(PPh_3)$ with $AgSbF_6$, and $AgSbF_6$ itself, under dry reaction condtions, 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).

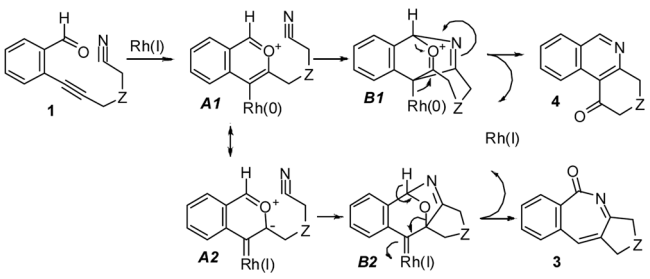


Substrate **1b**, an one-carbon longer homolog in the tether, underwent the present reaction to afford (4a*Z*,11*Z*)-3,4-dihydro-1H-dibenzo[*b*,*e*]azepin-6(2*H*)-one (**3b**) in 69% yield. The same reaction with the substrate **1c**, having -NTs group in the tether, also proceeded the same reaction to afford the corresponding product **3c**, (3a*E*,10*Z*)-2-tosyl-2,3-dihydrobenzo[*e*]pyrrolo[3,4-*b*]azepin-5(1*H*)-one in 77% yield. Interstingly, 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 proceded smoothly with the substrate **1e**, one-carbon homolog of **1d**, to give the corresponding product **4e** in 65% yield (eq. 4).

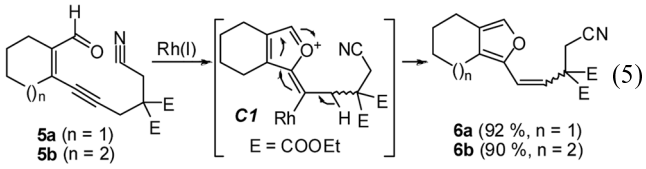


Both structures of **3a** and **4d** were confirmed by 2D NMR. We should note that the present method could provide an easy access to [6,6,7]-tricyclic compounds without the *gem*-diester group and [6,6,6]-tricyclic compounds with the *gem*-diester group.

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]



Scheme 2



In conclusion, we have found a new and atom economical Rh-catalyzed cyclization reaction with *o*-alkynylbezaldehydes 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.

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