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Synthesis of (*E*)-3-Alkylidene-1-pyrrolines by the Rhodium-Catalyzed Cyclization of Terminal Alkynes with Homopropargylic Amines

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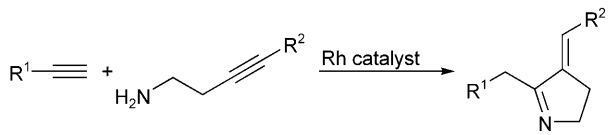
Abstract: The cyclization of terminal alkynes with homopropargylic amines in the presence of a rhodium complex as catalyst leads to the formation of (*E*)-3-alkylidene-1-pyrrolines. The reaction tolerates a wide range of functional groups on the terminal alkynes. The formation of a vinylidene-rhodium complex, followed by the intermolecular nucleophilic attack of a homopropargylic amine nitrogen on the α-carbon atom of the vinylidene-rhodium complex, is proposed as a key step in the catalytic reaction.

Keywords: homopropargylic amines; N-heterocycles; rhodium catalysis; terminal alkynes; vinylidene intermediates

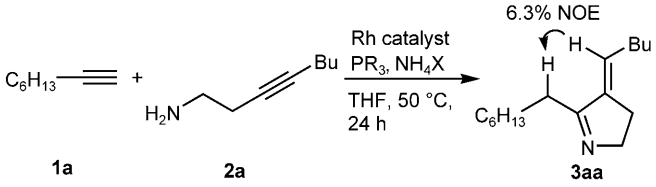
The 3-alkylidene-1-pyrroline framework is stable and is frequently found in natural products such as lanopylines[1] and lokysterolamines,[2] in synthetic biologically active molecules,[3] and in photoisomerization molecules.[4] This unique structure can be prepared by the condensation of 1-pyrrolines with aldehydes[5] or enamines[6] in the absence or presence of an acid catalyst. In most cases, however, product yields are low. Gawley reported that such compounds can be prepared by treating 4-alkenyl hydroximes with P_2O_5 or trimethylsilyl polyphosphate (PPSE). The reaction involves the formation of a nitrilium ion intermediate, followed by intramolecular cyclization.[7a–c] The same authors subsequently reported that nitrilium ions could also be generated from *N*-(3-alkenyl)amides under the same reaction conditions to give 3-alkylidene-1-pyrrolines,[7d,e] although the same type of transformation has been achieved by using $POCl_3$ in place of PPSE.[8] While these reactions are efficient, there are certain restrictions, in that the substituents on the alkene carbon are required to form more stable benzylic or tertiary carbocation intermediates.[9] Snider applied an intramolecular aza-Wittig reaction[10,11] of 3-(2-azidoehtyl)-3-eicocen-2-one with polymer-bound PPh_3 in the synthesis of lanopylin B_1.[12] We wish to report herein a novel approach to the synthesis of (*E*)-3-alkylidene-1-pyrrolines by the rhodium-catalyzed cyclization of terminal alkynes with homopropargylic amines (Scheme 1).

The cyclization of 1-octyne (**1a**) with oct-3-ynylamine (**2a**) was initially explored using conditions that were previously reported by us for the $RhCl(PPh_3)_3$/NH_4BF_4-catalyzed reaction of terminal alkynes with allylic amines,[13] except that a reaction temperature of 50 °C was used. Under these conditions, product **3aa** was obtained in 40% yield as a single stereoisomer, along with some by-products that included dimers and trimers of **1a**, and the cyclization product of **2a** itself (Table 1, entry 1). An NOE experiment confirmed the stereochemistry of **3aa** as being an *E*-isomer. Whereas the addition of NH_4BF_4 to the reaction mixture was required to afford **3aa** when $RhCl(PPh_3)_3$ was used as a catalyst (entry 2), $[Rh(cod)_2]BF_4/PPh_3$ catalyzed the reaction, even in the absence of the ammonium salt (entry 3). These results indicate that a cationic rhodium complex can serve as an active catalytic species.[14]



Scheme 1.

Table 1. Effect of catalyst, phosphine, and ammonium salt.[a]



Entry	Catalyst	PR_3	NH_4X	Yield [%][b]
1	$RhCl(PPh_3)_3$	–	NH_4BF_4	40
2	$RhCl(PPh_3)_3$	–	none	0
3	$[Rh(cod)_2]BF_4$	PPh_3	none	30
4	$[RhCl(cod)_2]_2$	none	NH_4BF_4	0
5	$[RhCl(cod)_2]_2$	PPh_3	NH_4BF_4	38
6	$[RhCl(cod)_2]_2$	$P(4\text{-}CF_3C_6H_4)_3$	NH_4BF_4	3
7	$[RhCl(cod)_2]_2$	$P(4\text{-}MeOC_6H_4)_3$	NH_4BF_4	56
8[c]	$[RhCl(cod)_2]_2$	$P(4\text{-}Et_2NC_6H_4)_3$	NH_4BF_4	68
9[d]	$[RhCl(cod)_2]_2$	$P(4\text{-}Et_2NC_6H_4)_3$	NH_4NO_3	73
10	$[RhCl(cod)_2]_2$	PCy_3	NH_4BF_4	0

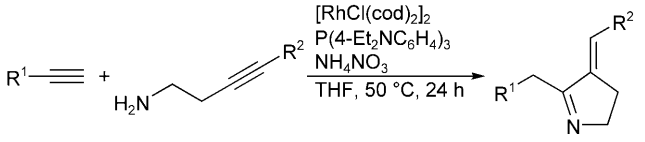
[a] *Reaction conditions:* 1-octyne (0.5 mmol), oct-3-ynylamine (1 mmol), Rh catalyst (0.05 mmol in entries 1–3 or 0.025 mmol in entries 4–9), PR_3 (0.15 mmol), NH_4X (0.06 mmol) in THF (1 mL), 50 °C, 6 h.
[b] Yields determined by GC with 1-undecane as an internal standard.
[c] THF (2 mL) for 30 h.
[d] THF (2 mL) for 24 h. Isolated yield was 69%.

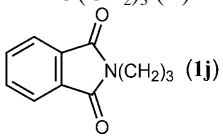
To examine the efficiency of phosphines, which are essential for the present reaction to proceed, as shown in Table 1, entries 4 and 5, $[RhCl(cod)]_2$ together with NH_4BF_4 was used as a catalyst precursor. A small amount of **3aa** was formed when a phosphine containing an electron-withdrawing group at the *para*-position was used (entry 6). In contrast, the yield was improved when electron-rich arylphosphines, e.g., tris(4-methoxyphenyl)phosphine (entry 7) and tris(4-diethylaminophenyl)phosphine (entry 8) were used. The addition of NH_4NO_3 in place of NH_4BF_4 gave the best result of 73% yield (entry 9).[15] No reaction occurred when PCy_3 was used (entry 10).

With the optimized reaction conditions in hand, the scope of the reactions of terminal alkynes with homopropargylic amines was investigated (Table 2). Some homopropargylic amines were tested in reactions with 1-octyne (**1a**). The reactions of methyl- and isopropyl-substituted homopropargylic amines afforded **3ab** and **3ac** in 76% and 67% yields, respectively (Table 2, entries 2 and 3). Although no reaction occurred in the case of the phenyl-substituted substrate **2d** under these reaction conditions, increasing the reaction temperature to 70 °C led to the formation of **3ad** in 68% yield.

The scope of this cyclization with regard to various terminal alkynes with **2b** was further examined. Not

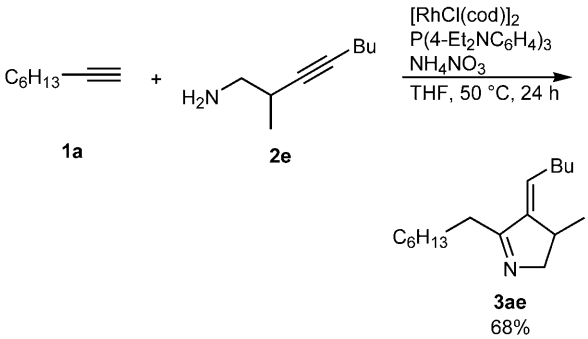
Table 2. Substrate scope.[a]



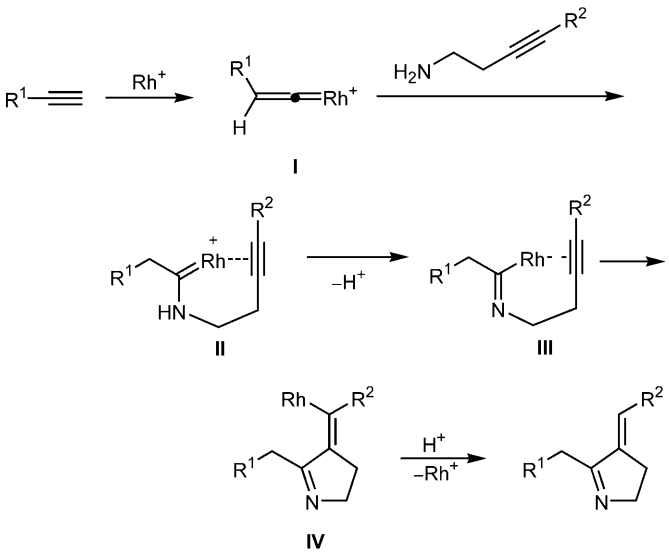
Entry	R^1	R^2	Yield [%][b]
1	C_6H_{13} (**1a**)	Bu (**2a**)	73 (**3ab**)
2	C_6H_{13} (**1a**)	Me (**2b**)	76 (**3ab**)
3	C_6H_{13} (**1a**)	*i*-Pr (**2c**)	67 (**3ac**)
4[c]	C_6H_{13} (**1a**)	Ph (**2d**)	68 (**3ad**)
5	$CyCH_2$ (**1b**)	Me (**2b**)	72 (**3bb**)
6	Cy (**1c**)	Me (**2b**)	55 (**3cb**)
7	*t*-Bu (**1d**)	Me (**2b**)	0
8	$Ph(CH_2)_2$ (**1e**)	Me (**2b**)	68 (**3eb**)
9	$MeO_2C(CH_2)_3$ (**1f**)	Me (**2b**)	65 (**3fb**)
10	$NC(CH_2)_3$ (**1g**)	Me (**2b**)	67 (**3gb**)
11	$t\text{-}BuMe_2SiO(CH_2)_3$ (**1h**)	Me (**2b**)	77 (**3hb**)
12	$THPO(CH_2)_3$ (**1i**)	Me (**2b**)	67 (**3ib**)
13	 (**1j**)	Me (**2b**)	66[d] (**3jb**)

[a] *Reaction conditions:* terminal alkyne (0.5 mmol), homopropargylic amine (1 mmol), $[RhCl(cod)]_2$ (0.025 mmol), $P(4\text{-}Et_2NC_6H_4)_3$ (0.15 mmol), NH_4NO_3 (0.06 mmol) in THF (2 mL) at 50 °C for 24 h.
[b] Yields determined by GC with 1-undecane as an internal standard.
[c] At 70 °C for 30 h.
[d] Isolated yield.

only primary but also secondary alkyl-substituted alkynes reacted to give **3bb** and **3cb** in preparatively useful yields. On the other hand, the use of *tert*-butylacetylene **1d** gave a small amount of dimerization product, along with unreacted **1d**. The reaction was compatible with functional groups such as ester (**1f**), nitrile (**1g**), siloxy (**1h**), THP (**1i**), and imide (**1j**). The reaction of **1a** with homopropargylic amine **2e** under the same reaction conditions gave trisubstituted N-heterocycle **3ae** in 68% yield [Eq. (1)]. However, the



(1)



Scheme 2. A plausible reaction mechanism.

use of non-4-ynylamine, leading to the formation of 6-membered ring, resulted in no cyclization product.

A proposed reaction mechanism is shown in Scheme 2 although the details are obscure at this time. A terminal alkyne reacts with a cationic rhodium complex to form the vinylidene complex **I**,[16] which undergoes nucleophilic attack by a homopropargylic amine at the α-carbon atom of **I** to afford an α-aminocarbene-rhodium complex **II**.[16,17] Deprotonation of **II** is followed by the insertion of a C≡C triple bond into the Rh-carbon bond of **III** to give a 5-membered heterocyclic intermediate **IV**. Lastly, the protonolysis of **IV** affords the product with regeneration of the cationic rhodium complex.[18] An attempted deuterium labeling experiment using 1-deuterio-1-octyne to obtain information concerning the reaction mechanism, especially the formation of the vinylidene-rhodium complex, resulted in rapid H/D scrambling, even at a temperature of 50 °C.

In summary, the findings reported herein demonstrate the rhodium-catalyzed cyclization of terminal alkynes with homopropargylic amines leading to (*E*)-3-alkylidene-1-pyrrolines as single stereoisomers. A cationic rhodium complex bearing electron-rich phosphines acts as the active catalytic species in the reaction. The formation of a vinylidene-rhodium complex followed by the intermolecular nucleophilic attack of a homopropargylic amine nitrogen on the α-carbon atom of the vinylidene-rhodium complex appears to be a key step in the catalytic reaction. Detailed mechanistic studies are currently underway in our laboratory.

Experimental Section

General Procedure for Rhodium-Catalyzed Cyclization of Terminal Alkynes with Homopropargylic Amines

A 10-mL reaction flask equipped with a reflux condenser was flame-dried under an N_2 atmosphere and then cooled to room temperature, after which, $[RhCl(cod)_2]_2$ (12.3 mg, 0.025 mmol), NH_4NO_3 (4.8 mg, 0.06 mmol), $P(4\text{-}Et_2NC_6H_4)_3$ (71.3 mg, 0.15 mmol), THF (2 mL), homopropargylic amine (1 mmol), and terminal alkyne (0.5 mmol) were sequentially added. The reaction mixture was heated at 50 °C for 24 h. After cooling to room temperature, the volatiles were removed under vacuum and the product was isolated by silica-gel column chromatography.

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References

[1] Y. Sakano, M. Shibuya, A. Matsumoto, Y. Takahashi, H. Tomoda, S. Ōmura, Y. Ebizuka, *J. Antibiot.* **2003**, *56*, 817–826.

[2] a) J. Jurek, P. J. Scheuer, M. Kelly-Borges, *J. Nat. Prod.* **1994**, *57*, 1004–1007; b) H. S. Lee, Y. Seo, J. R. Rho, J. Shin, V. J. Paul, *J. Nat. Prod.* **2001**, *64*, 1474–1476.

[3] a) R. Fisher, S. Lensky, C. Methfessel, K. Tietjen, C. Erdelen, U. Wachendorff-Neumann, DE Patent 19,622,353, **1997**; b) I. Ikeda, T. Utsunomiya, M. Sadamitsu, Y. Ozoe, K. Mochida, *J. Pestic. Sci.* **2006**, *31*, 417–419.

[4] a) D. Sampedro, A. Migani, A. Pepi, E. Busi, R. Basosi, L. Latterini, F. Elisei, S. Fusi, F. Ponticelli, V. Zanirato, M. Olivucci, *J. Am. Chem. Soc.* **2004**, *126*, 9349–9359; b) F. Lumento, V. Zanirato, S. Fusi, E. Busi, L. Latterini, F. Elisei, A. Sinicropi, T. Andruniów, N. Ferré, R. Basosi, M. Olivucci, *Angew. Chem.* **2007**, *119*, 418–424; *Angew. Chem. Int. Ed.* **2007**, *46*, 414–420; c) A. Sinicropi, E. Martin, M. Ryazantsev, J. Helbing, J. Briand, D. Sharma, J. Léonard, S. Haacke, A. Cannizzo, M. Chergui, V. Zanirato, S. Fusi, F. Santoro, R. Basosi, N. Ferré, M. Olivucci, *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 17642–17647.

[5] Y. Nomura, T. Bando, Y. Takeuchi, S. Tomoda, *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3199–3200.

[6] M. Komatsu, S. Takamatsu, M. Uesaka, S. Yamamoto, Y. Ohshiro, T. Agawa, *J. Org. Chem.* **1984**, *49*, 2691–2699.

[7] a) R. E. Gawley, E. J. Termine, K. D. Onan, *J. Chem. Soc. Chem. Commun.* **1981**, 568–569; b) R. E. Gawley, E. J. Termine, *Tetrahedron Lett.* **1982**, *23*, 307–308;

c) R. E. Gawley, E. J. Termine, *J. Org. Chem.* **1984**, *49*, 1946–1951; d) R. E. Gawley, S. Chemburkar, *Tetrahedron Lett.* **1986**, *27*, 2071–2074; e) R. E. Gawley, S. R. Chemburkar, *Heterocycles* **1989**, *29*, 1283–1292.

[8] S. Sugasawa, S. Ushioda, *Tetrahedron* **1959**, *15*, 48–52.

[9] Methylenecyclopropanes reacted with nitriles in the presence of TfOH to give 3-alkylidene-1-pyrrolines *via* the similar cationic intermediates. J.-W. Huang, M. Shi, *Synlett* **2004**, 2343–2346.

[10] P. H. Lambert, M. Vaultier, R. Carrié, *J. Chem. Soc. Chem. Commun.* **1982**, 1224–1225.

[11] Recent reviews on the aza-Wittig reaction, see: a) G. Hajós, I. Nagy, *Curr. Org. Chem.* **2008**, *12*, 39–58; b) F. Palacios, C. Alonso, D. Aparicio, G. Rubiales, J. M. de Los Santos, *Tetrahedron* **2007**, *63*, 523–575.

[12] B. B. Snider, J. Zhou, *J. Org. Chem.* **2005**, *70*, 1087–1088.

[13] Y. Fukumoto, F. Kinashi, T. Kawahara, N. Chatani, *Org. Lett.* **2006**, *8*, 4641–4643.

[14] a) M. J. Atherton, J. Fawcett, J. H. Holloway, E. G. Hope, A. Karaçar, D. R. Russell, G. C. Saunders, *J. Chem. Soc. Dalton Trans.* **1996**, 3215–3220; b) M. J. Atherton, J. Fawcett, J. H. Holloway, E. G. Hope, S. M. Martin, D. R. Russell, G. C. Saunders, *J. Organomet. Chem.* **1998**, *555*, 67–79; c) E. G. Hope, R. D. W. Kemmitt, A. M. Stuart, *J. Chem. Soc. Dalton Trans.* **1998**, 3765–3770.

[15] A cationic Rh(I) nitrate complex has been isolated and characterized, see: W. S. Han, S. W. Lee, *Inorg. Chim. Acta* **2003**, *348*, 15–24.

[16] Recent reviews on catalytic reactions that proceeded *via* vinylidene metal intermediate, see: a) C. Bruneau, P. H. Dixneuf, *Angew. Chem.* **2006**, *118*, 2232–2260; *Angew. Chem. Int. Ed.* **2006**, *45*, 2176–2203; b) K. Ohe, *Bull. Korean Chem. Soc.* **2007**, *28*, 2153–2161; c) R.-S. Liu, *Synlett* **2008**, 801–812; d) C. Bruneau, P. H. Dixneuf, *Metal Vinylidenes and Allenylidenes in Catalysis*, Wiley-VCH: Weinheim, Germany, **2008**; e) B. M. Trost, A. McClory, *Chem. Asian J.* **2008**, *3*, 164–194.

[17] Catalytic reactions involving an intermolecular attack of nitrogen nucleophiles to the α-carbon of the vinylidene-metal intermediate, see: a) Y. Fukumoto, T. Dohi, H. Masaoka, N. Chatani, S. Murai, *Organometallics* **2002**, *21*, 3845–3847; b) Y. J. Park, B.-I. Kwon, J.-A. Ahn, H. Lee, C.-H. Jun, *J. Am. Chem. Soc.* **2004**, *126*, 13892–13893; c) Y. Fukumoto, H. Asai, M. Shimizu, N. Chatani, *J. Am. Chem. Soc.* **2007**, *129*, 13792–13793.

[18] A reaction mechanism involving the formation of **V** from **II** followed by the insertion of a C≡C bond into the Rh-hydrogen bond of **V** to give 6-membered metallacycle **VI** cannot be ruled out.