A New Route to Tricyclic 2-Pyridone Frameworks via Formation of Bicyclic *N*-Alkenyl Alkynylamides Followed by Gold-catalyzed Cycloisomerization

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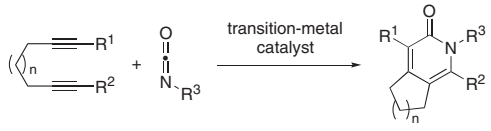
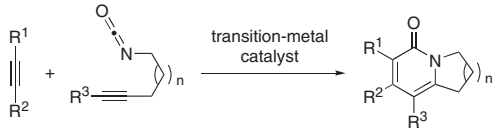
A cationic gold(I)/PPh_3 complex catalyzes cycloisomerizations of bicyclic *N*-alkenyl alkynylamides leading to tricyclic 2-pyridone derivatives at room temperature in good yields. The bicyclic *N*-alkenyl alkynylamides are readily prepared starting from commercially available 2-substituted cycloalkanones.

As 2-pyridone frameworks are important core units in biologically active compounds and functional organic materials, their efficient synthesis has been extensively pursued to date.[1] For the synthesis of bicyclic 2-pyridones, transition metal mediated [2 + 2 + 2] cycloadditions of diynes with isocyanates (eq 1)[2] and alkynylisocyanates with alkynes (eq 2)[3] are highly efficient and convergent methods.[4]

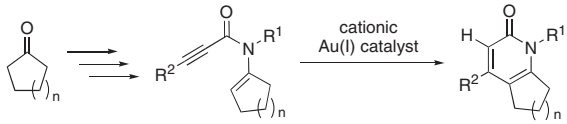


(1)

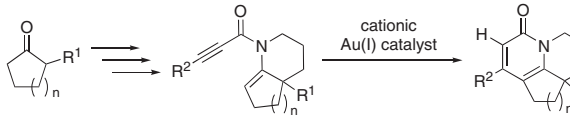


(2)

Recently, we have reported that a cationic gold(I)/PPh_3 complex catalyzes the cycloisomerization of *N*-alkenyl alkynylamides (amide-linked 1,5-enynes) that can be readily prepared starting from the corresponding cycloalkanones leading to 5–6 and 6–6 fused bicyclic 2-pyridones ($n = 1$ and 2, eq 3).[5–7] In this letter, we describe the synthesis of tricyclic 2-pyridones (pyridoquinolinone derivatives[8]) that cannot be synthesized by [2 + 2 + 2] cycloadditions via formation of bicyclic *N*-alkenyl alkynylamides starting from the corresponding 2-substituted cycloalkanones followed by the gold-catalyzed cycloisomerization (eq 4).



(3)

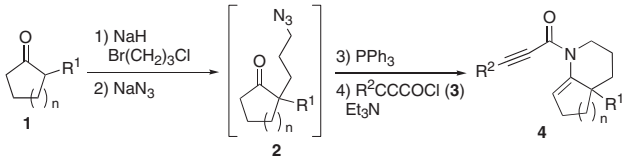


(4)

We first investigated the synthesis of bicyclic *N*-alkenyl alkynylamides **4** starting from the commercially available 2-substituted cycloalkanones **1**. After screening synthetic routes and optimization of reaction conditions, 1,5-enyne **4aa** was successfully prepared starting from ketone **1a** in four steps without purification of each intermediate (Table 1, Entry 1). Intermediate azide **2a** was prepared via alkylation of ketone **1a** with 1-bromo-3-chloropropane followed by treatment with NaN_3. The azide **2a** was treated with PPh_3 to form the corresponding imine,[10] which reacted with alkynoyl chloride **3a** to furnish the desired 1,5-enyne **4aa**. Various 1,5-enynes **4** were then prepared starting from 2-substituted cycloalkanones **1a**–**1d** by following the above optimized procedure. Both ethoxycarbonyl- (**1a** and **1b**, Entries 1–6) and phenyl-substituted cycloalkanones (**1d**, Entries 8 and 9) could be transformed to the corresponding 1,5-enynes in fair to good yields, while benzoyl-substituted cyclohexanone **1c** was transformed to the corresponding 1,5-enyne **4ca** in low yield due to the competitive aza-Wittig reaction in the benzoyl carbonyl group (Entry 7). With respect to alkynoyl chlorides, both aryl- (Entries 1–3 and 6–8) and alkyl-substituted alkynoyl chlorides (Entries 4, 5, and 9) could be employed.

Thus obtaining the bicyclic 1,5-enynes **4**, these were subjected to the cationic gold(I)/PPh_3 complex-catalyzed cycloisomerizations as summarized in Table 2. The cycloisomerizations of bicyclic 5–6 fused 1,5-enynes smoothly proceeded to give the desired tricyclic 2-pyridones in high yields (Entries 1–6). Not only 5–6 fused 1,5-enynes but also 6–6 fused 1,5-enynes (Entries 7–10) could participate in this reaction, although product yields were moderate and prolonged reaction times were required. With respect to the substituents (R^1) at the bridged carbon atom,

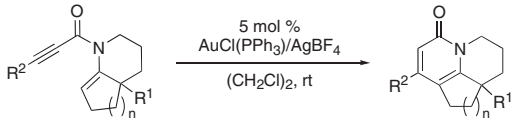
Table 1. Synthesis of bicyclic *N*-alkenyl alkynylamides **4**[a]



Entry	Substrate **1**	Substrate **3**[b]	Product **4**, Yield[c]/%
1	**1a** ($n = 1$, $R^1 = CO_2Et$)	**3a** ($R^2 = Ph$)	**4aa**, 35
2	**1a** ($n = 1$, $R^1 = CO_2Et$)	**3b** ($R^2 = 4\text{-}MeOC_6H_4$)	**4ab**, 36
3	**1a** ($n = 1$, $R^1 = CO_2Et$)	**3c** ($R^2 = 2\text{-}ClC_6H_4$)	**4ac**, 31
4	**1a** ($n = 1$, $R^1 = CO_2Et$)	**3d** ($R^2 = Me$)	**4ad**, 47
5	**1a** ($n = 1$, $R^1 = CO_2Et$)	**3e** ($R^2 = Cy$)	**4ae**, 57
6[d]	**1b** ($n = 2$, $R^1 = CO_2Et$)	**3a** ($R^2 = Ph$)	**4ba**, 51
7[d]	**1c** ($n = 2$, $R^1 = Bz$)	**3a** ($R^2 = Ph$)	**4ca**, 9
8	**1d** ($n = 2$, $R^1 = Ph$)	**3a** ($R^2 = Ph$)	**4da**, 45
9	**1d** ($n = 2$, $R^1 = Ph$)	**3d** ($R^2 = Me$)	**4dd**, 27

[a]See Supporting Information for detailed reaction conditions.[9] [b]Carboxylic acid chloride **3** were prepared in situ by the reaction of the corresponding carboxylic acid and 1-chloro-*N*,*N*,2-trimethyl-1-propenylamine. [c]Isolated yield. [d]1-Chloro-3-iodopropane was used instead of 1-bromo-3-chloropropane.

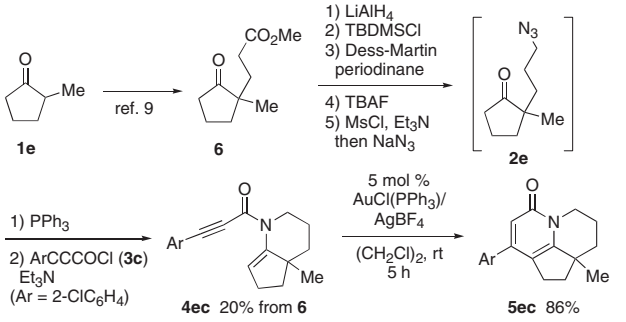
Table 2. Gold-catalyzed cycloisomerizations of bicyclic *N*-alkenyl alkynylamides **4**[a]



4 **5**

Entry	Substrate **4**	Time/h	Product **5**, Yield[b]/%
1	**4aa** ($n = 1$, $R^1 = CO_2Et$, $R^2 = Ph$)	5	**5aa**, 82
2[c]	**4aa** ($n = 1$, $R^1 = CO_2Et$, $R^2 = Ph$)	5	**5aa**, 81
3	**4ab** ($n = 1$, $R^1 = CO_2Et$, $R^2 = 4\text{-}MeOC_6H_4$)	1	**5ab**, 87
4	**4ac** ($n = 1$, $R^1 = CO_2Et$, $R^2 = 2\text{-}ClC_6H_4$)	4	**5ac**, 79
5	**4ad** ($n = 1$, $R^1 = CO_2Et$, $R^2 = Me$)	17	**5ad**, 71
6	**4ae** ($n = 1$, $R^1 = CO_2Et$, $R^2 = Cy$)	12	**5ae**, 86
7	**4ba** ($n = 2$, $R^1 = CO_2Et$, $R^2 = Ph$)	17	**5ba**, 71
8	**4ca** ($n = 2$, $R^1 = Bz$, $R^2 = Ph$)	30	**5ca**, 51
9	**4da** ($n = 2$, $R^1 = Ph$, $R^2 = Ph$)	15	**5da**, 64
10	**4dd** ($n = 2$, $R^1 = Ph$, $R^2 = Me$)	36	**5dd**, 60

[a]$AuCl(PPh_3)_3$ (0.010 mmol), $AgBF_4$ (0.010 mmol), **4** (0.200 mmol), and $(CH_2Cl)_2$ (1.0 mL) were used. See Supporting Information in detail.[9] [b]Isolated yield. [c]$(CH_2Cl)_2$ (reagent grade) was used.

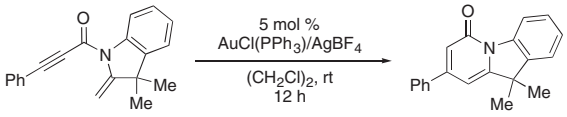


Scheme 1. Synthesis of tricyclic 2-pyridone **5ec** (See Supporting Information for detailed reaction conditions[9]).

the reactions of ethoxycarbonyl-substituted 1,5-enynes proceeded in higher yields than those of benzoyl- and phenyl-substituted 1,5-enynes (Entry 7 vs. Entries 8 and 9). With respect to the substituents (R^2) at the alkyne terminus, the reactions of aryl-substituted 1,5-enynes proceeded at higher reaction rates than those of alkyl-substituted 1,5-enynes (Entries 1, 3, and 4 vs. 5 and 6; Entry 9 vs. 10). Importantly, the present cycloisomerization could be conducted using a reagent grade solvent without erosion of the product yield (Entry 2).

Although elaborate operations are required, tricyclic 2-pyridone **5ec**, bearing a methyl group at the bridged carbon atom, could also be synthesized as shown in Scheme 1. 1,4-Addition of methyl methacrylate to 2-methylcyclopentanone (**1e**) furnished ester **6** following the literature procedure.[11] The ester **6** was transformed into azide **2e** in five steps. The azide **2e** was treated with PPh_3 followed by reaction with alkynoyl chloride **3c** to furnish the desired 1,5-enyne **4ec**. The gold-catalyzed cycloisomerization of **4ec** proceeded to give the desired 2-pyridone **5ec** in high yield.

The cycloisomerization of 1,5-enyne **7** that can be readily prepared from phenylpropiolic acid and 2,3,3-trimethylindolenine in one step leading to tricyclic 2-pyridone **8** was also investigated. Fortunately, the desired cycloisomerization proceeded at room temperature by using the cationic gold(I)/PPh_3 complex (5 mol %) to yield the expected tricyclic 2-pyridone **8** in 52% yield (eq 5).



7 **8** 52% (5)

In conclusion, a new route to tricyclic 2-pyridone derivatives has been developed via formation of bicyclic *N*-alkenyl alkynylamides followed by the gold-catalyzed cycloisomerization. Future work will focus on application of this methodology to the total synthesis of natural products.

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References and Notes

1 For recent reviews, see: a) M. Torres, S. Gil, M. Parra, *Curr. Org. Chem.* **2005**, *9*, 1757. b) I. Nakamura, Y. Yamamoto, *Chem. Rev.* **2004**, *104*, 2127. c) J. H. Rigby, *Synlett* **2000**, 1.

2 a) K. Tanaka, A. Wada, K. Noguchi, *Org. Lett.* **2005**, *7*, 4737. b) Y. Yamamoto, K. Kinpara, T. Saigoku, H. Takagishi, S. Okuda, H. Nishiyama, K. Itoh, *J. Am. Chem. Soc.* **2005**, *127*, 605. c) H. A. Duong, M. J. Cross, J. Louie, *J. Am. Chem. Soc.* **2004**, *126*, 11438. d) L. V. R. Bonaga, H.-C. Zhang, D. A. Gauthier, I. Reddy, B. E. Maryanoff, *Org. Lett.* **2003**, *5*, 4537. e) T. Takahashi, F.-Y. Tsai, Y. Li, H. Wang, Y. Kondo, M. Yamanaka, K. Nakajima, M. Kotora, *J. Am. Chem. Soc.* **2002**, *124*, 5059, and references therein.

3 R. A. Earl, K. P. C. Vollhardt, *J. Org. Chem.* **1984**, *49*, 4786.

4 For recent reviews of synthesis of azaheterocycles including 2-pyridones by transition metal mediated [2 + 2 + 2] cycloadditions, see: a) B. Heller, M. Hapke, *Chem. Soc. Rev.* **2007**, *36*, 1085. b) P. R. Chopade, J. Louie, *Adv. Synth. Catal.* **2006**, *348*, 2307. c) J. A. Varela, C. Saà, *Chem. Rev.* **2003**, *103*, 3787.

5 a) H. Imase, K. Noguchi, M. Hirano, K. Tanaka, *Org. Lett.* **2008**, *10*, 3563. b) H. Imase, T. Suda, Y. Shibata, K. Noguchi, M. Hirano, K. Tanaka, *Org. Lett.* **2009**, *11*, 1805.

6 For selected recent examples of cycloisomerizations of 1,5-enynes to form six-membered compounds, see: a) J. Sun, M. P. Conley, L. Zhang, S. A. Kozmin, *J. Am. Chem. Soc.* **2006**, *128*, 9705. b) B. D. Sherry, L. Maus, B. N. Laforteza, F. D. Toste, *J. Am. Chem. Soc.* **2006**, *128*, 8132. c) M. Movassaghi, M. D. Hill, *J. Am. Chem. Soc.* **2006**, *128*, 4592. d) T. Shibata, Y. Ueno, K. Kanda, *Synlett* **2006**, 411. e) C. Nieto-Oberhuber, M. P. Muñoz, S. López, E. Jiménez-Núñez, C. Nevado, E. Herrero-Gómez, M. Raducan, A. M. Echavarren, *Chem.—Eur. J.* **2006**, *12*, 1677. f) C. M. Grisé, L. Barriault, *Org. Lett.* **2006**, *8*, 5905. g) S. Datta, A. Odedra, R.-S. Liu, *J. Am. Chem. Soc.* **2005**, *127*, 11606. h) C. Fehr, J. Galindo, *Angew. Chem., Int. Ed.* **2006**, *45*, 2901. i) H. Imagawa, T. Iyenaga, M. Nishizawa, *Org. Lett.* **2005**, *7*, 451. j) V. Mamane, P. Hannen, A. Fürstner, *Chem.—Eur. J.* **2004**, *10*, 4556, and references therein.

7 For recent reviews of cycloisomerizations of 1,*n*-enynes, see: a) V. Michelet, P. Y. Toullec, J.-P. Genêt, *Angew. Chem., Int. Ed.* **2008**, *47*, 4268. b) L. Zhang, J. Sun, S. A. Kozmin, *Adv. Synth. Catal.* **2006**, *348*, 2271. c) C. Bruneau, *Angew. Chem., Int. Ed.* **2005**, *44*, 2328. d) L. Añorbe, G. Domínguez, J. Pérez-Castells, *Chem.—Eur. J.* **2004**, *10*, 4938.

8 a) A. Padwa, A. C. Flick, H. Lee, *Org. Lett.* **2005**, *7*, 2925. b) A. Padwa, S. R. Harring, M. A. Semones, *J. Org. Chem.* **1998**, *63*, 44. c) C. H. Heathcock, M. H. Norman, D. A. Dickman, *J. Org. Chem.* **1990**, *55*, 798. d) D. A. Dickman, C. H. Heathcock, *J. Am. Chem. Soc.* **1989**, *111*, 1528.

9 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

10 B. J. Neubert, B. B. Snider, *Org. Lett.* **2003**, *5*, 765.

11 H. O. House, W. L. Roelofs, B. M. Trost, *J. Org. Chem.* **1966**, *31*, 646.

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