ORGANIC LETTERS

2010
Vol. 12, No. 2
372−374

Synthesis of Pyrroles by Gold(I)-Catalyzed Amino−Claisen Rearrangement of *N*-Propargyl Enaminone Derivatives

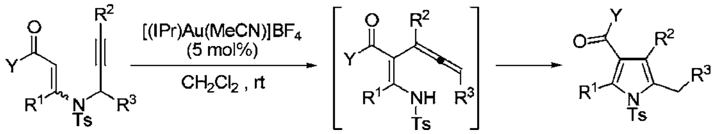
Akio Saito,* Tomoyo Konishi, and Yuji Hanzawa*

Laboratory of Organic Reaction Chemistry, Showa Pharmaceutical University,
3-3165 Higashi-tamagawagakuen, Machida, Tokyo 194-8543, Japan

akio-sai@ac.shoyaku.ac.jp; hanzaway@ac.shoyaku.ac.jp

Received November 24, 2009

ABSTRACT



The cationic N-heterocyclic carbene−gold(I) complex catalyzes the formation of tri- and tetrasubstituted pyrroles via the amino−Claisen rearrangement of *N*-propargyl *β*-enaminone derivatives and the cyclization of α-allenyl *β*-enaminone intermediates.

The pyrrole compound is not only prevalent in a wide variety of biologically and medicinally important compounds[1] but also used as a building block in organic synthesis.[2] The preparation of the pyrrole compound generally depends on the classical condensation such as the Paal−Knorr method[3] or the Hantzsch method,[4] albeit multistep synthetic operation. Although many studies have been reported on the synthesis of pyrroles through metal-catalyzed hydroamination or cycloisomerization of alkyne compounds possessing a nitrogen functional group,[5,6] a novel and efficient synthetic method remains an attractive goal.

The *β*-enaminone derivative is a versatile synthetic intermediate, and its utilities have received considerable attention in the field of heterocyclic synthesis.[7] In particular, the regioselective cyclization of *N*-propargyl *β*-enaminones

---

(1) For example: (a) Fürstner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3582. (b) Hoffmann, H.; Lindel, T. *Synthesis* **2003**, 1753. (c) Agarwal, S.; Cämmerer, S.; Filali, S.; Fröhner, W.; Knöll, J.; Krahl, M. P.; Reddy, K. R.; Knölker, H.-J. *Curr. Org. Chem.* **2005**, *9*, 1601. (d) Walsh, C. T.; Garneau-Tsodikova, S.; Howard-Jones, A. R. *Nat. Prod. Rep.* **2006**, *23*, 517. (e) Bellina, F.; Rossi, R. *Tetrahedron* **2006**, *62*, 7213.

(2) (a) Jones, R. A. *Pyrroles, Part II, The Synthesis, ReactiVity and Physical Properties of Substituted Pyrroles*; Wiley: New York, 1992. (b) Sundberg, R. J. *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier: Oxford, UK, 1996; Vol. 2, p 119. (c) Pelkey, E. T. *Prog. Heterocycl. Chem.* **2005**, *17*, 109.

(3) (a) Knorr, L. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 1635. (b) Paal, C. *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 367. For recent examples, see: (c) Trost, B. M.; Doherty, G. A. *J. Am. Chem. Soc.* **2000**, *122*, 3801. (d) Quiclet-Sire, B.; Quintero, L.; Sanchez-Jimenez, G.; Zard, S. Z. *Synlett* **2003**, 75. (e) Tracey, M. R.; Hsung, R. P.; Lambeth, R. H. *Synthesis* **2004**, 918.

(4) (a) Hantzsch, A. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 1474. For recent examples, see (b) Palacios, F.; Aparico, D.; de los Santos, J. M.; Vicario, J. *Tetrahedron* **2001**, *57*, 1961. (c) Trautwein, A. W.; Süssmuth, R. D.; Jung, G. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2381.

(5) Recent examples: (a) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074. (b) Kim, J. T.; Gevorgyan, V. *Org. Lett.* **2002**, *4*, 4697. (c) Gabriele, B.; Salerno, G.; Fazio, A. *J. Org. Chem.* **2003**, *68*, 7853. (d) Martín, R.; Rivero, M. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 7079. (e) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260. (f) Hiroya, K.; Matsumoto, S.; Ashikawa, M.; Ogiwara, K.; Sakamoto, T. *Org. Lett.* **2006**, *8*, 5349. (g) Larionov, O. V.; de Meijere, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 5664. (h) Kamijo, S.; Kanazawa, C.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 9260. (i) Arcadi, A.; Di Giuseppe, S.; Marinelli, F.; Rossi, E. *Adv. Synth. Catal.* **2001**, *343*, 443. (j) Arcadi, A.; Di Giuseppe, S.; Marinelli, F.; Rossi, E. *Tetrahedron: Asymmetry* **2001**, *12*, 2715.

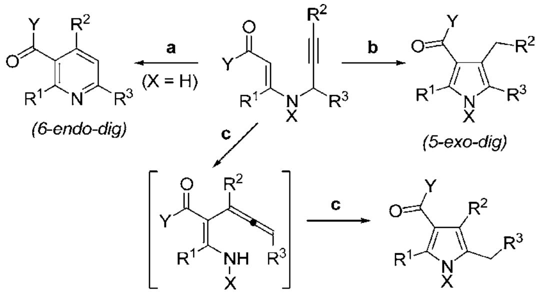
(6) Other examples for transition-metal-catalyzed synthesis of pyrroles: (a) Braun, R.; Zeitler, K.; Müller, T. J. J. *Org. Lett.* **2001**, *3*, 3297. (b) Balme, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 6238. (c) Siriwardana, A. I.; Kathriarachchi, K. K. A. D. S.; Nakamura, I.; Gridnev, I. D.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 13898. (d) Wurz, R. P.; Charette, A. B. *Org. Lett.* **2005**, *7*, 2313. (e) Lu, L.; Chen, G.; Ma, S. *Org. Lett.* **2006**, *8*, 835. (f) Cadierno, V.; Gimeno, J.; Nebra, N. *Chem.−Eur. J.* **2007**, *13*, 9973. (g) Yadav, J. S.; Reddy, B. V. S.; Srinivas, M.; Divyavani, C.; Basha, S. J.; Sarma, A. V. S. *J. Org. Chem.* **2008**, *73*, 3252.

(7) For reviews: (a) Elassar, A.-Z. A.; El-Khair, A. A. *Tetrahedron* **2003**, *59*, 8463. (b) Negri, G.; Kascheres, C.; Kascheres, A. J. *J. Heterocycl. Chem.* **2004**, *41*, 461. (c) Stanovnik, B.; Steve, J. *Chem. Rev.* **2004**, *104*, 2433.

10.1021/ol902716n

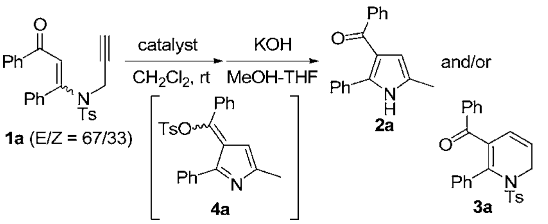
is a divergent construction of highly substituted pyridines or pyrroles (6-*endodig* or 5-*exo-dig*, Scheme 1).[8] Although the catalytic synthesis of pyridines via 6-*endodig* cyclization of the propargyl enaminone (path **a**) has been achieved, 5-*exo-dig* cyclization (path **b**) requires an excess amount of base.[8b] We recently developed the catalytic approach to the synthesis of indole compounds through amino−Claisen rearrangement of *N*-propargyl anilines.[9] As a part of our studies on the heterocyclic synthesis, we focused on the metal-catalyzed formation of pyrroles through the sequential reaction of amino−Claisen rearrangement and heterocyclization (path **c**). A similar approach such as the preparation of furan compounds from propargyl vinyl ethers was accomplished by cationic gold(I) catalyst,[10,11] which encourages us to examine the present project for the preparation of pyrroles. We herein describe the Au(I)-catalyzed formation of highly substituted pyrroles from *N*-propargyl *β*-enaminone derivatives.

Scheme 1. Formation of Heterocycles from *N*-Propargyl *β*-Enaminone Derivatives



In the preliminary studies on the formation of pyrrole from *N*-propargyl *β*-enaminone **1a** in the presence of Rh(I)-catalysts (10 mol %) in HFIP (hexafluoroisopropanol), which are the optimal conditions for the preparation of indole from *N*-propargyl anilines,[9] the formation of pyrrole was not observed (entries 1 and 2, Table 1). As our next efforts, the evaluation of Au catalysts was conducted for the reaction of **1a** in CH_2Cl_2 (entries 3−12). Although $(Ph_3P)AuCl/AgBF_4$ or $PtCl_2$ showed good results for the Claisen rearrangement of propargyl vinyl ethers,[10] **3a** was obtained through the 6-*endo-dig* cyclization of **1a** (entries 3 and 4). However, (IPr)AuCl (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) with Ag salts or $AuCl_3$ was found to give the pyrrole **2a** as a main product after the basic workup (KOH/MeOH-THF), which brought about the hydrolysis of **4a** (entries 7−11).[12,13] In particular, by the use of 5 mol % (IPr)AuCl/$AgBF_4$, **1a** was consumed at rt within 1 h giving rise to **2a** in 83% yield (entry 7). $[(IPr)Au(MeCN)]BF_4$,[14] which is generated by the mixture of (IPr)AuCl and $AgBF_4$ in CH_2Cl_2-MeCN, yielded a similar result to entry 7 (entry 12). It should be mentioned that other solvents instead of CH_2Cl_2 showed inferior results (HFIP−CH_2Cl_2(1:3):**2a** 20%, 1 h; HFIP:**2a** 4%, 1 h; MeCN: **3a** 40%, 18 h; THF: **3a** 40%, 18 h).

Table 1. Evaluation of Catalysts for the Formation of **2a** from **1a**

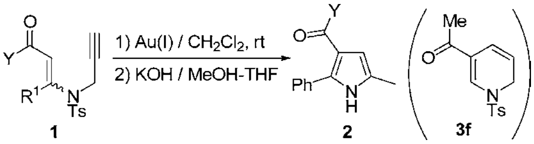


entry	catalyst (mol %)[c]	time (h)	yield (%)[a]		
			2a	**3a**	**1a**
1[b]	$[Rh(COD)_2]OTf$ (10)	6	–	–	71
2[b]	$RhH(CO)(Ph_3P)_3$ (10)	3	–	–	61
3	$PtCl_2$ (10)	5	–	40	48
4	$(Ph_3P)AuCl$ (5)/$AgBF_4$ (5)	20	–	6	–
5	$AgBF_4$ (10)	20	–	–	7
6	(IPr)AuCl (5)	20	–	–	87
7	(IPr)AuCl (5)/$AgBF_4$ (5)	1	83	1	–
8	(IPr)AuCl (5)/$AgSbF_6$ (5)	1	73	2	–
9	(IPr)AuCl (5)/$AgNTf_2$ (5)	1	57	19	–
10	(IPr)AuCl (5)/AgOTf (5)	1	65	21	–
11	$AuCl_3$ (5)	3	60	13	7
12	$[(IPr)Au(MeCN)]BF_4$ (5)	1	85[d]	–	–

[a] The yield was determined by ^1H NMR analysis using toluene as internal standard. [b] Solvent: HFIP (hexafluoroisopropanol). [c] IPr =*N*,*N′*-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene. [d] Isolated yield: 85%.

The scope of the Au(I)-catalyzed formation of various substituted pyrroles is summarized in Tables 2 and 3. The efficiency of $[(IPr)Au(MeCN)]BF_4$ showed in the reactions of enaminone **1a**−**e**, and the corresponding pyrroles were obtained in good yields after the basic workup. In all cases, the dihydropyridines **3a**−**e** were not detected. On the other

Table 2. Formation of Pyrroles **2** from Enaminones **1**[a]



1	Y	R^1	*E*/*Z*	time (h)	yield (%)[b]
1a	Ph	Ph	67/33	1	**2a** 85
1b	2-furyl	Ph	52/48	1	**2b** 61
1c	*p*-MeO-Ph	Ph	84/16	2	**2c** 61
1d	*p*-NO_2-Ph	Ph	74/26	4	**2d** 72
1e	*t*Bu	Ph	55/45	1	**2e** 76
1f	Me	H	100/0	4	(**3f** 38)

[a] Au(I): 5 mol % $[(IP)Au(MeCN)]BF_4$. [b] Isolated yield.

---

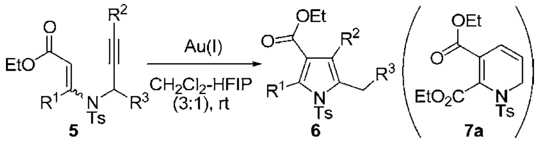
(8) (a) Abbiati, G.; Arcadi, A.; Bianchi, G.; Giuseppe, S. D.; Marinelli, F.; Rossi, E. *J. Org. Chem.* **2003**, *68*, 6959. (b) Cacchi, S.; Fabrizi, G.; Filisti, E. *Org. Lett.* **2008**, *10*, 2629.

(9) (a) Saito, A.; Kanno, A.; Hanzawa, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 3931. (b) Saito, A.; Oda, S.; Fukaya, H.; Hanzawa, Y. *J. Org. Chem.* **2009**, *74*, 1517.

(10) (a) Suhre, M. H.; Reif, M.; Kirsch, S. F. *Org. Lett.* **2005**, *7*, 3925. (b) Binder, J. P.; Kirsch, S. F. *Org. Lett.* **2006**, *8*, 2151.

(11) Au(I)-catalyzed Claisen rearrangement of propargyl enol ether: Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 15978.

Table 3. Formation of Pyrroles **6** from Enaminoesters **5**[a]



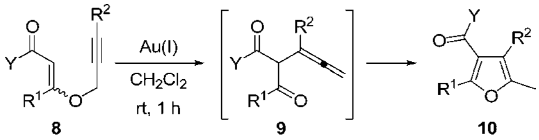
1	R¹	R²	R³	*E*/*Z*	time (h)	yield (%)[b]
5a	CO_2Et	H	H	69/31	22	(**7a** 86)[c]
5a					22	**6a** 38[d]
5a					22	**6a** 68[e]
5b	Ph	H	H	76/24	2	**6b** 81
5c	Me	H	H	100/0	1	**6c** 93
5d	Me	Me	H	100/0	2	**6d** 89
5e	Me	Ph	H	100/0	2	**6e** 85
5f	Me	H	n-C_5H_{11}	100/0	1	**6f** 87

[a] Au(I): 5 mol % $[(IP)Au(MeCN)]BF_4$. [b] Isolated yield. [c] Solvent: CH_2Cl_2. [d] Solvent: CH_2Cl_2−HFIP (1:1), **7a**: 58%. [e] Solvent: HFIP, **7a**: 13%.

hand, **1f** (R^1 = H) yielded **3f** as a main product (Table 2). Although the reaction of enaminoester **5a** in CH_2Cl_2 under the Au-catalyzed conditions afforded the dihydropyridine **7a** in 86% yield, the increase in the ratio of HFIP as a cosolvent improved the yield of pyrrole **6a** (Table 3). Thus, the effect of the employed solvent is very important for the formation of **6a**. In HFIP, the yield of **6a** was increased up to 68%.[15] Other esters **5b**−**f** ($R^1 \neq$ H and CO_2Et) in CH_2Cl_2−HFIP (3:1) were converted into the pyrroles **6b**−**f** in good yields without the formation of **7b**−**f**, respectively (Table 3).[16]

The present Au(I) catalyst could be applied to the formation of furan compounds **10** from vinyl ethers **8** (Table 4). On the basis of the previous report about the preparation of **10** from **8** catalyzed by $(Ph_3P)AuCl/AgBF_4$,[10] a plausible mechanism for such a furan formation would consist of (i) Au-catalyzed Claisen rearrangement of vinyl ethers **8**, which may proceed through a cyclization-induced rearrangement[11,17] (a *6-endo-dig* cyclization of **8** through Au(I)−alkyne complex, followed by the collapse of a six-membered intermediate into **9**), and (ii) the *5-exo-dig* cyclization of allenyl ketone **9** (or its tautomeric enol forms).

Table 4. Formation of Furans **10** from Vinyl Ethers **8**[a]

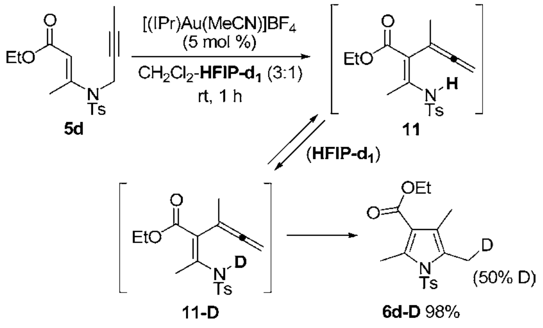


1	Y	R¹	R²	*E*/*Z*	yield (%)[b]
8a	Ph	Ph	Me	67/33	**10a** 89
8b	OEt	Me	H	100/0	**10b** 92
8c	OEt	Me	Me	100/0	**10c** 97
8d	OEt	Me	Ph	100/0	**10d** 99

[a] Au(I): 5 mol % $[(IP)Au(MeCN)]BF_4$. [b] Isolated yield.

The present pyrrole formation would take part in a process similar to the furan formation. This is supported by the formation of deuterated pyrrole **6d-D** as shown in Scheme 2. Although **6d-D** was not formed by the treatment of undeuterated **6d** with the present Au(I) catalyst in CH_2Cl_2−HFIP-d_1 [$(CF_3)_2CHOD$], the Au(I)-catalyzed reaction of **5d** in CH_2Cl_2−HFIP-d_1 yielded **6d-D** (50% D) quantitatively. The deuterium incorporation into **6d-D** from **5d** would be due to the cyclization of intermediate **11-D**, which was generated by the deuterium exchange between HFIP-d_1 and Claisen rearrangement intermediate **11**.

Scheme 2. Formation of Heterocycles from *N*-Propargyl *β*-Enaminone Derivatives



In conclusion, we have demonstrated the facile and mild preparation of tri- and tetrasubstituted pyrrole compounds from *N*-propargyl *β*-enaminone derivatives by the $[(IPr)Au(MeCN)]BF_4$ catalyst. The present catalyst also promoted the formation of furans from propargyl vinyl ethers efficiently. Since the propargyl enaminone derivatives or propargyl vinyl ethers as starting materials are easily available by the reactions of the corresponding propargyl *p*-tosylamides or propargyl alcohols with 2-propynoic acid derivatives (see Supporting Information), the present procedure would shed new light on the convenient approach for the preparation of pyrroles and furans. Synthetic applications and detailed mechanistic studies of the present reaction are underway.

Acknowledgment. This work was supported by a Grant-in-Aid for Young Scientists (B), MEXT Japan (No 21790024). A generous donation of HFIP by Central Glass Co., Ltd. is gratefully acknowledged.

Supporting Information Available: Experimental procedures and physical data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL902716N

---

(12) The isolated **4a** was hydrolyzed by KOH/MeOH−THF at rt for 1 h to give **2a** in 87% yield.

(13) Since the treatment of (2,5-dimethyl-1-tosyl-1*H*-pyrrol-3-yl)-(phenyl)-methanone with $[(IPr)Au(MeCN)]BF_4$ in CH_2Cl_2 showed no reaction, *N*-Ts-protected pyrrole may not take part in the formation of **4a**.

(14) de Frémont, P.; Stevens, E. D.; Fructos, M. R.; Díaz-Requejo, M. M.; Perez, P. J.; Nolan, S. P. *Chem. Commun.* **2006**, 2045.

(15) Although the effect of HFIP remains unclear at present, Brønsted acid (HBF_4), which might be generated from Au catalyst and HFIP during the reaction, did not catalyze the formation of **6a** in HFIP.

(16) In the Au(I)-catalyzed reactions of ester **5**, analogues of **4a** were not detected .

(17) Overman, L. E. *Angew. Chem., Int. Ed.* **1984**, *23*, 579.