ORGANIC LETTERS

2009
Vol. 11, No. 21
5002−5005

Cationic Gold(I)-Mediated Intramolecular Cyclization of 3-Alkyne-1,2-diols and 1-Amino-3-alkyn-2-ols: A Practical Route to Furans and Pyrroles

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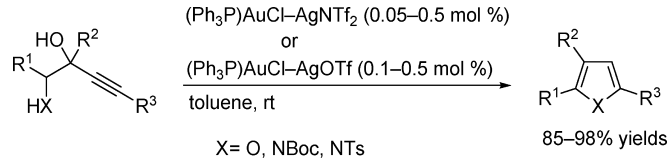
Received August 21, 2009

ABSTRACT



The intramolecular cyclizations of the 3-alkyne-1,2-diols and the 1-amino-3-alkyn-2-ols with a low catalyst loading (0.05−0.5 mol %) of $(Ph_3P)AuCl-AgNTf_2$ or $(Ph_3P)AuCl-AgOTf$ proceeded at room temperature to provide a variety of substituted furans and pyrroles in excellent yields (85−98% yields). This method is also fully applicable to the conversion of several dozen grams of the substrate using only 0.05 mol % each of the Au and Ag catalysts.

Furans and pyrroles have been found to be key structural components in abundant naturally occurring products.[1] They are also important intermediates in industrial organic syntheses, such as pharmaceuticals, flavors, and material sciences. For these extensive utilities, a huge number of synthetic methods of furans and pyrroles have been developed, including classical procedures under either acidic or basic conditions, such as the Paal−Knorr,[2] Hantzsch,[3] and Feist−Bénary syntheses.[4] Recently, from the viewpoint of atom economy or environmental concern, the transition-metal-catalyzed intramolecular cyclizations have attracted increasing attention,[5] in which various metal compounds, including copper,[6] zinc,[7] palladium,[6d,8] and silver,[6b,9] have been utilized. While these reactions are useful, most of the methods still need improvement in terms of catalyst loadings, yields, scope limitations, and/or vigorous reaction conditions. On the other hand, the gold catalysts work under relatively

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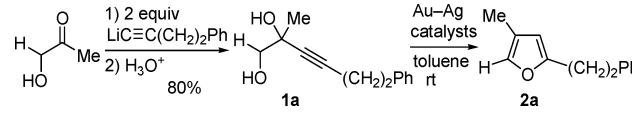
10.1021/ol901942t CCC: $40.75
Published on Web 09/25/2009

mild conditions for the synthesis of furans from allenyl ketones,[10] 2-(1-alkynyl)-2-alken-1-ones,[11] 1-(1-alkynyl)cyclopropyl ketones,[12] or alkynyl epoxides[13,14] and of pyrroles from homopropargyl azides.[15] In these approaches, however, expensive gold catalysts usually require high loadings (1−5 mol %). We now describe that the combinations of $(Ph_3P)AuCl$ with either $AgNTf_2$ or AgOTf (each as low as 0.05−0.5 mol %) present a highly powerful catalyst for the intramolecular cyclizations of the 3-alkyne-1,2-diols **1** and the 1-amino-3-alkyn-2-ols **3**. This method offers advantages over the known methods for the production of a wider range of substituted furans **2** and pyrroles **4** in excellent yields and the ready availability of the substrates (**1** and **3**).

The use of gold catalysts for organic synthesis has been an ever growing research area for the past decade, and a variety of reactions have already been developed.[16] For instance, propargyl alcohols are known to cause Meyer−Schuster rearrangements,[17] nucleophilic substitutions,[18] and the addition of alcohols.[19] During the course of our studies on the gold-mediated Meyer−Schuster rearrangement,[17a] we happened to disclose that the cationic Au(I) complex (0.5 mol %), generated in situ from an equimolar mixture of $(Ph_3P)AuCl$ and AgOTf, converted the propargyl alcohol **1a** having another hydroxyl group into the furan **2a** in 90% yields (entry 3, Table 1)[20,21] and the Meyer−Schuster rearrangement product was not obtained at all. In search of more effective conditions, we screened the combinations of gold and silver catalysts. Among a variety of gold compounds, $(Ph_3P)AuCl$ and $(Me_2S)AuCl$ gave comparably good results, which produced **2a** in 90 and 87% yields, respectively (entries 3 and 4). Additionally, AgOTf and $AgNTf_2$ proved to be good choices as silver catalysts. These combined catalysts could reduce the catalyst loading to 0.1 mol % giving **2a** almost quantitatively within 1−2.5 h (entries 6 and 7). On the contrary, when the gold or silver compound alone was used, the intramolecular cyclization did not take place at all (entries 1 and 2). Because the substrate **1a** is readily available by the reaction of hydroxyacetone with a lithium acetylide in 80% yield, the developed method offers a convenient and high-yielding means for the preparation of the substituted furan **2a**.

Table 1. Preliminary Survey for the Cyclization of 3-Alkyne-1,2-diol **1a** into **2a**



entry	Au cat.	Ag cat.	mol %	time	yield of **2a** (%)
1	$(Ph_3P)AuCl$	none	1.0	30 min	no reaction[a]
2	none	AgOTf	1.0	30 min	trace[a]
3	$(Ph_3P)AuCl$	AgOTf	0.5	20 min	90
4	$(Me_2S)AuCl$	AgOTf	0.5	20 min	87
5	$(Ph_3P)AuCl$	$AgNTf_2$	0.5	15 min	96
6	$(Ph_3P)AuCl$	AgOTf	0.1	2.5 h	94
7	$(Ph_3P)AuCl$	$AgNTf_2$	0.1	1 h	97

[a] NMR yield using *p*-dimethoxybenzene as the internal standard.

The optimized conditions were applicable to various alkynyldiols bearing a proton **1b**−**d**, aromatic **1e**,**f**, and heteroaromatic ring **1g** at the end of the acetylene functionality, which were readily prepared via the alkynylation of α-hydroxy carbonyl compounds in 52−84% yields,[22] to give the furans **2b**−**g** in excellent yields (Table 2). The combination of $(Ph_3P)AuCl$ and $AgNTf_2$ generally provided better results for **2** with lower catalyst loading compared to the $(Ph_3P)AuCl$−AgOTf catalyst (entries 3 vs 4 and 5 vs 6). It is worth noting that the intramolecular cyclization of the less reactive terminal alkynes **1b**−**d** was achieved to give the corresponding furans **2b**−**d** in 85−91% yields (entries 1−3), while the known transformations of a similar 3-alkyne-1,2-diol required the higher catalyst loadings (5−100 mol %) with scope limitations or did not proceed at all.[21] The reaction of **1g** having the unstable thienyl moiety was also ac-

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(13) Blanc et al. reported the intramolecular cyclization of alkynyl epoxides in CH_2Cl_2/MeOH, which was expected to proceed via 3-alkyne-1,2-diol derivatives to afford the corresponding furans; see: Blanc, A.; Tenbrink, K.; Weibel, J.-M.; Pale, P. *J. Org. Chem.* **2009**, *74*, 5342–5348.

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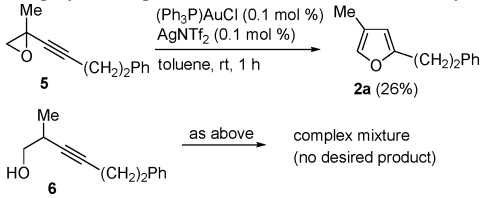
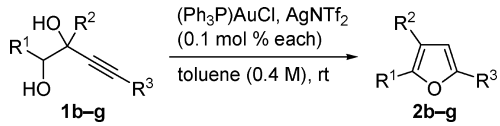
(20) The epoxide **5** reacted with $(Ph_3P)AuCl$−$AgNTf_2$ within 1 h to give **2a** albeit in low yield. A similar reaction of the alcohol **6** resulted in the formation of complex mixtures of products which included no furan compound. Hence, it was found that the hydroxyl group at the propargyl position of **1** plays an important role in this intramolecular cyclization.



(21) The related intramolecular cyclizations of 3-alkyne-1,2-diols to the substituted furans using Ag, Pd, Ru, and Mo catalysts have been reported; see: (a) Knight, D. W. Patent Application No. PCT/GB2006/001048. (b) Hayes, S. J.; Knight, D. W.; Menzies, M. D.; O'Halloran, M.; Tan, W.-F. *Tetrahedron Lett.* **2007**, *48*, 7709–7712. (c) Wakabayashi, Y.; Fukuda, Y.; Shiragami, H.; Utimoto, K.; Nozaki, H. *Tetrahedron* **1985**, *41*, 3655–3661. (d) Yada, Y.; Miyake, Y.; Nishibayashi, Y. *Organometallics* **2008**, *27*, 3614–3617. (e) McDonald, F. E.; Connolly, C. B.; Gleason, M. M.; Towne, T. B.; Treiber, K. D. *J. Org. Chem.* **1993**, *58*, 6952–6953.

(22) For synthesis of starting materials, see the Supporting Information.

Table 2. Au−Ag-Catalyzed Intramolecular Cyclization of **1b−g** into Furans **2b−g**[a]



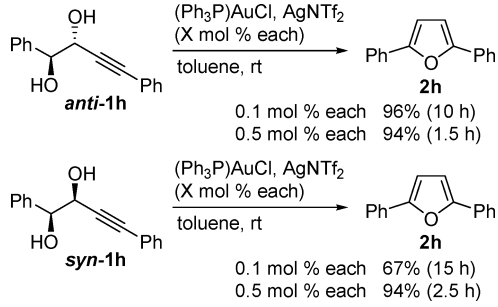
	substrate **1**					product **2**	
entry		R^1	R^2	R^3	time (h)		isolated yield (%)
1	**1b**	H	Ph	H	8	**2b**	85
2	**1c**	Ph	Ph	H	10	**2c**	91
3[b]	**1d**	H	$Ph(CH_2)_2$	H	1.5	**2d**	90
4[b,c]	**1d**	H	$Ph(CH_2)_2$	H	0.25	**2d**	73
5	**1e**	H	H	Ph	5	**2e**	90
6[c]	**1e**	H	H	Ph	0.67	**2e**	83
7	**1f**	$-(CH_2)_4-$		Ph	3	**2f**	97
8	**1g**	H	Me	2-thienyl	5	**2g**	90

[a] Standard condition: substrates (2.5 mmol) were employed. [b] Run at 60 °C. [c] Using 0.5 mol % each of $(Ph_3P)AuCl$ and AgOTf.

complished to afford **2g** in 90% yield (entry 8).[21b] Due to the poor solubility of **1d** in toluene, its reaction was conducted at 60 °C without inducing any side reactions (entry 3). The reactions of the alkynyldiols **1e−g** having internal acetylene groups were completed in a shorter time (entries 5, 7, and 8).[23]

Interestingly, the diastereomers (***anti-*** and ***syn-*****1h**)[22] were found to have different reactivities (Scheme 1), while the

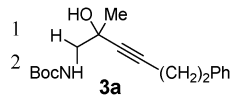
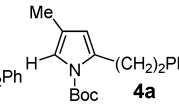
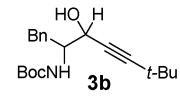
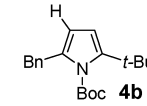
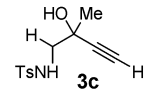
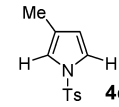
Scheme 1. Influence of Diastereomeric Conformations



Ru-catalyzed cyclizations of a pair of similar diastereomers were reported to give the same yields of the product for the same reaction time.[21d] Using 0.1 mol % each of the Au and Ag catalysts, the ***anti-*****1h** was completely converted into **2h** within 10 h, while the cyclization of ***syn-*****1h** was slightly slower to obtain a 67% yield of **2h** with the recovery of ***syn-*****1h** after 15 h. We found, however, using 0.5 mol % each of the same reagents, both diastereomers were almost quantitatively converted into **2h**, albeit at different reaction rates.

Moreover, the developed method was found to be effective for the intramolecular cyclization of the 1-amino-3-alkyn-2-ols **3a−c** to form the synthetically useful *N*-Boc or *N*-Ts pyrroles **4a−c** in excellent yields (Table 3).[21a] Only a few

Table 3. Conversion of **3a−c** into Pyrroles **4a−c** Using the Combination of Au and Ag Catalysts

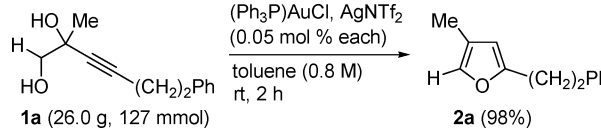
entry	substrate	product	time (h)	method[a]	mol %[b]	yield (%)
1	 **3a**	 **4a**	1	A	0.1	96
2			1	B	0.1	91
3	 **3b**	 **4b**	4	A	0.5	88
4			4	B	0.5	64
5	 **3c**	 **4c**	9	A	0.1	95

[a] All reactions were conducted in toluene (0.4 M) at room temperature. Method A: Using $(Ph_3P)AuCl-AgOTf$. Method B: Using $(Ph_3P)AuCl-AgNTf_2$. [b] Each loading of the Au and Ag catalysts.

gold-catalyzed preparations of pyrroles by inter- and intramolecular cyclizations have been previously reported.[15,24] Our protocol features the production of various pyrroles having substituents at the 2-, 3-, or 5-positions and the use of readily available substrates.[22] Generally, AgOTf as a silver catalyst more effectively facilitated the reaction than $AgNTf_2$ in this pyrrole synthesis. For example, in the case of **3b** having a bulky *tert*-butyl group at the acetylenic terminus, the reaction employing $(Ph_3P)AuCl$ and AgOTf smoothly proceeded at room temperature to give the corresponding pyrrole **4b** in 88% yield (entry 3), while a similar reaction catalyzed by $(Ph_3P)AuCl-AgNTf_2$ for the same time provided **4b** in 64% yield, accompanied by the recovery of **3b** (entry 4).

Worthy of note was the fact that this method was applicable for a larger scale reaction (Scheme 2). Only 0.05

Scheme 2. Larger Scale Preparation of Furan **2a** with Low Catalyst Loadings



mol % each of $(Ph_3P)AuCl$ and $AgNTf_2$ were enough to convert **1a** (26.0 g, 0.127 mol) into **2a** at room temperature in 98% yield.

In conclusion, we have found that the combination of $(Ph_3P)AuCl$ with either $AgNTf_2$ or AgOTf provides a highly powerful catalyst for the intramolecular cyclization

(23) The terminal alkynes **1b−d** have low solubilities in toluene at room temperature, which then required longer reaction times.

of readily available 3-alkyne-1,2-diols **1** and 1-amino-3-alkyn-2-ols **3**.[25] The advantages of this method include the extremely low catalyst loadings (0.05−0.5 mol %), rapid and clean reactions at room temperature, and production of a variety of substituted furans and pyrroles in excellent yields (85−98% yields). Although we have not yet conducted detailed mechanistic studies, we consider the following mechanism. Coordination of the acetylene bond of **1** or **3** to a cationic Au species, generated from Au and Ag compounds, enhances its electrophilicity and facilitates the 5-endo cyclization of homopropargylic hydroxyl or amino group to afford the cyclic intermediates. After dehydration, the furans **2** and pyrroles **4** were obtained. Further investigation of a practical extension of this method is now in progress.

Acknowledgment. This work was supported by a Grant-in-Aid for Young Scientists (B) from MEXT and The Uehara Memorial Foundation (for M.E.).

Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

OL901942T

(24) (a) Harrison, T. J.; Kozak, J. A.; Corbella-Pané, M.; Dake, G. R. *J. Org. Chem.* **2006**, *71*, 4525–4529. (b) Binder, J. T.; Kirsch, S. F. *Org. Lett.* **2006**, *8*, 2151–2153. (c) Shu, X.-Z.; Liu, X.-Y.; Xiao, H.-Q.; Ji, K.-G.; Guo, L.-N.; Liang, Y.-M. *Adv. Synth. Catal.* **2008**, *350*, 243–248. (d) Arcadi, A.; Giuseppe, S. D.; Marinelli, F.; Rossi, E. *Adv. Synth. Catal.* **2001**, *343*, 443–446.

(25) **Typical Experimental Procedure.** To a solution of the 2-methyl-6-phenyl-3-hexyne-1,2-diol **1a** (528 mg, 2.6 mmol) in toluene (6.5 mL, 0.4 M) were added $(Ph_3P)AuCl$ (1.3 mg, 0.0026 mmol) and $AgNTf_2$ (1.0 mg, 0.0026 mmol) in this order at room temperature. The reaction mixture was stirred at room temperature for 1 h and then quenched with saturated aqueous NH_4Cl. The organic materials were extracted with Et_2O, and the combined organic extracts were washed with brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography (silica gel, hexanes) to give 4-methyl-2-(2-phenylethyl)furan **2a** (469 mg, 97%).