DOI: 10.1002/adsc.201000292

Synthesis of Substituted 1,2-Dihydropyridines from Propargyl Vinyl Ethers and Allenic Vinyl Ethers by Gold-Catalyzed Claisen Rearrangement and 6π-Aza-electrocyclization

Hao Wei,[a] Yao Wang,[a] Bin Yue,[a] and Peng-Fei Xu[a,*]

[a] State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, People's Republic of China
Fax: (+86)-931-8915-557; e-mail: xupf@lzu.edu.cn

Received: April 14, 2010; Revised: July 26, 2010; Published online: September 23, 2010

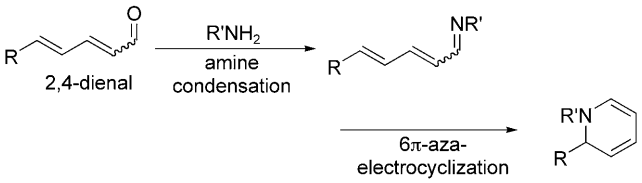
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201000292.

Abstract: An efficient synthetic method was developed for the construction of substituted 1,2-dihydropyridines by gold-catalyzed tandem reactions. The key intermediates 2,4-dienals were generated from propargyl vinyl ethers or allenic vinyl ethers with gold catalysts. These two reactions involved the process of gold-catalyzed [3,3]-sigmatropic rearrangement/isomerization/amine condensation/6π-aza-electrocyclization.

Keywords: 6π-aza-electrocyclization; Claisen rearrangement; 1,2-dihydropyridines; gold; heterocycles; tandem reactions

Nitrogen-containing heterocyclic systems are important core structures in organic chemistry because of their presence in many natural products[1] and pharmaceutically important small molecules. Dihydropyridines have been recognized as versatile synthetic intermediates[2] that provide access to a variety of heterocycles such as piperidines (by reduction)[3] and pyridines (by oxidation).[4]

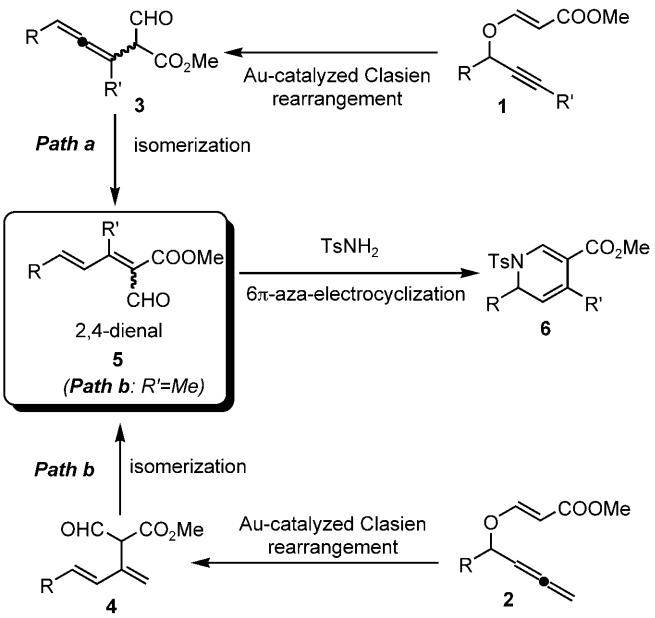
Considerable efforts have been directed toward the development of new and efficient methodologies for the synthesis of 1,2-dihydropyridines.[5] One of the approaches for synthesizing this class of compounds is the 6π-electrocyclization of 1-azatrienes,[6] which could be obtained by the reaction of primary amines and 2,4-dienals (Scheme 1).[7] Apparently, the key of this strategy is the chemical access to 2,4-dienals. We have discovered an alternative and more direct access to 2,4-dienals, based on the gold-catalyzed Claisen rearrangement of propargyl vinyl ethers **1** or allenic vinyl ethers **2** to allenes **3** or 1,3-dienes **4**, followed by isomerization.



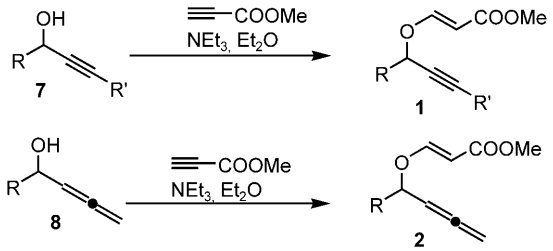
Scheme 1. 2,4-Dienals as the key intermediates to 1,2-dihydropyridines.

During this discovery, we first prepared 2,4-dienals **5** from easily accessible starting materials under mild conditions. Then the 2,4-dienal **5** was reacted with a primary amine to form the corresponding functionalized 1-azatrienes[10], which ultimately rearranged to 1,2-dihydropyridine **6** through a 6π-aza-electrocyclization (Scheme 2). Previously, transformations involving the metal-catalyzed rearrangement of propargyl vinyl ethers[11,12] had been reported to be able to reorganize to 2*H*-pyrans,[11b] furans,[11c] dihydropyans,[11d] or pyrroles and substituted pyrroles[11a] by further one-pot condensation with primary amine and subsequent 5-*exo*-dig cyclization. To the best of our knowledge, no metal-catalyzed rearrangement[13] of allenic vinyl ethers has been reported so far. Considering the possible compatibility of transition metal-catalyzed Claisen rearrangement[14] with primary amines, we anticipated that the tandem reaction could be carried out. Propargyl vinyl ethers **1** or allenic vinyl ethers **2** could be easily prepared from propargylic alcohols **7** or 2,3-allenols **8** in one step (Scheme 3).

At the beginning of the study, we started our investigation by using the propargyl vinyl ether **1a** (Table 1). Gold-related catalysts are superior reagents in activating alkyne, allene and alkene functionalities[15], and gold-catalyzed Claisen rearrangements have been reported by Toste and Kirsch[11]. Therefore we performed the experiments in the presence of var-



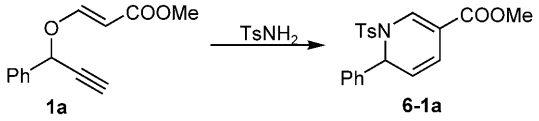
Scheme 2. Proposed tandem reactions to synthesis of 1,2-dihydropyrides.



Scheme 3. Synthesis of propargyl vinyl ethers **1** and allenic vinyl ethers **2** from propargylic alcohols **7** and 2,3-allenols **8**.

ious gold catalysts. No reaction occurred with $AuCl_3$ or $AuPPh_3Cl/AgOTf$ (5 mol% each) in CH_2Cl_2 at room temperature (entries 1 and 2). 1,2-Dihydropyridine was obtained in 84% yield when $AuPPh_3Cl/AgBF_4$ (5 mol%) was used (entry 3). To our delight, a 92% yield was realized by using $Au(PPh_3)Cl/AgSbF_6$ (5 mol%) at room temperature (entry 4). Ag(I) could serve to abstract the chloride from $Au(PPh_3)Cl$ to form a more electrophilic catalyst. On the contrary, when $Au(PPh_3)Cl$ or $AgSbF_6$ was used alone (entries 5 and 6), the tandem reaction did not take place at all. On the other hand, other transition metal catalysts such as $PtCl_2$ or $PdCl_2(CN)_2$ did not promote any transformation (entries 7 and 8). The investigation on the solvent effect showed that the best choice of the solvent was CH_2Cl_2 (entries 9–11). However, the yield decreased when the amount of $TsNH_2$ was reduced from 2.0 to 1.2 equivalents (entry 12). Thus the use of 5 mol% of $Au(PPh_3)Cl/AgSbF_6$, with 2.0 equivalents of $TsNH_2$ in CH_2Cl_2 at room temperature constituted the optimal reaction conditions.

Table 1. Optimization of reaction conditions.[a]

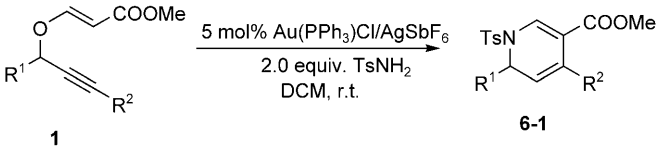


Entry	Catalyst [mol%]	Solution	$TsNH_2$ [mol%]	Yield [%]
1	$AuCl_3$	DCM	200	NR[b]
2	$PPh_3AuCl/AgOTf$	DCM	200	NR[b]
3	$PPh_3AuCl/AgBF_4$	DCM	200	84
4	$PPh_3AuCl/AgSbF_6$	DCM	200	92
5	PPh_3AuCl	DCM	200	NR[b]
6	$AgSbF_6$	DCM	200	NR[b]
7	$PdCl_2(CN)_2$	DCM	200	NR[b]
8	$PtCl_2$	DCM	200	NR[b]
9	$PPh_3AuCl/AgSbF_6$	toluene	200	trace[c]
10	$PPh_3AuCl/AgSbF_6$	CH_3CN	200	NR[b]
11	$PPh_3AuCl/AgSbF_6$	DCE	200	77
12	$PPh_3AuCl/AgSbF_6$	DCM	120	80

[a] Reactions were conducted with 0.4 mmol of **1a** in 3 mL of solvent at room temperature.
[b] No reaction.
[c] Most of the material decomposed.

With the optimized conditions in hand, we next explored the scope of this catalyzed tandem reaction by studying a wide variety of substrates (Table 2). Substrates containing electron-rich or electron-deficient aryl groups at the propargylic position gave good to excellent yields of desired 1,2- dihydropyridines (entries 2–9).

Table 2. Tandem synthesis of 1, 2-dihydropyridines from propargyl vinyl ethers and $TsNH_2$.[a]

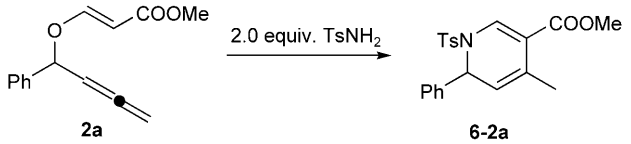


Entry	R^1	R^2	Product	Yield [%][b]
1	C_6H_5	H	**6-1a**	92
2	2-Me-C_6H_4	H	**6-1b**	90
3	4-Me-C_6H_4	H	**6-1c**	91
4	3-Me-C_6H_4	H	**6-1d**	80
5	3,4-di-Me-C_6H_3	H	**6-1e**	78
6	2-MeO-C_6H_4	H	**6-1f**	89
7	4-Cl-C_6H_4	H	**6-1g**	85
8	2-Cl-C_6H_4	H	**6-1h**	84
9	2-naphthyl	H	**6-1i**	88
10	*n*-hexyl	H	**6-1j**	82
11	C_6H_5	*n*-pentyl	**6-1k**	60

[a] Reactions were conducted with 0.4 mmol of **4a** in 3 mL of solvent.
[b] Isolated yield after column chromatograph.

An alkyl group at the propargyl position also afforded the desired product smoothly (entry 10). Substitution at the alkyne terminus was equally tolerated, such as an alkyl substituent (entry 11). Then we examined the possibility of using tertiary propargyl vinyl ether. However, no reaction was observed even with high catalyst loading (15 mol%) at an elevated temperature after a prolonged reaction time.

In light of our success in employing $AuPPh_3Cl/AgSbF_6$ for the former tandem reaction, we chose this catalyst system for allenic vinyl ether **2a**. However, only a 34% yield of the desired compound **6-2a** was obtained when the same conditions were used. In search of more effective conditions, we screened the combinations of $AuPPh_3Cl$ with different silver catalysts and found $AgBF_4$ gave the best result (69% yield). Additionally, $AuPPh_3Cl/AgOTf$ failed to afford the target compound, while $AuPPh_3Cl/AgNTf_2$ gave the product in 39% yield (Scheme 4).



$AuPPh_3Cl/AgSbF_6$	34%
$AuPPh_3Cl/AgOTf$	trace
$AuPPh_3Cl/AgNTf_2$	39%
$AuPPh_3Cl/AgBF_4$	69%

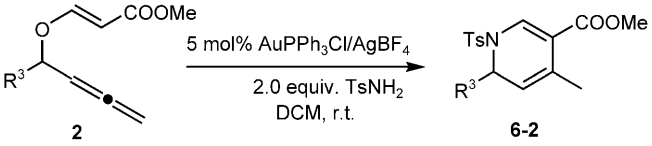
Scheme 4. Optimization of reaction conditions.

The substrate scope was also examined utilizing the optimized reaction conditions (Table 3). At first we investigated the effect of the substitution on the phenyl ring and discovered that a number of functional groups, including methyl, chloro and bromo were well tolerated. For substrates bearing a *para*- or *ortho*-methyl group, the reaction went smoothly in good yields (entries 2 and 3), while the one bearing a *meta*-methyl group gave a moderate yield (entry 4). The substrate containing a *para*-chloro or *para*-bromophenyl group successfully afforded the desired products in moderate yields (entries 5 and 6). The substrate with a naphthalene group was well-behaved (entry 7). Unfortunately, the reaction of **2h** containing an alkyl group at the propargyl position failed (entry 8).

When $TsNH_2$ reacted with **2i** containing a butyl group at the allene terminus, only an enamine was obtained as the final product, which was consistent with the previously proposed isomerization process (Scheme 5).

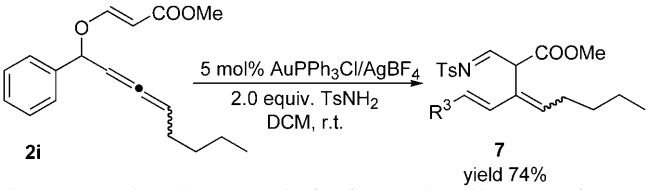
In order to prove the mechanism of the reaction, we investigated the reaction of compound **5a** with

Table 3. Tandem synthesis of 1, 2-dihydropyridines from allenic vinyl ethers and Ts-NH_2.[a]



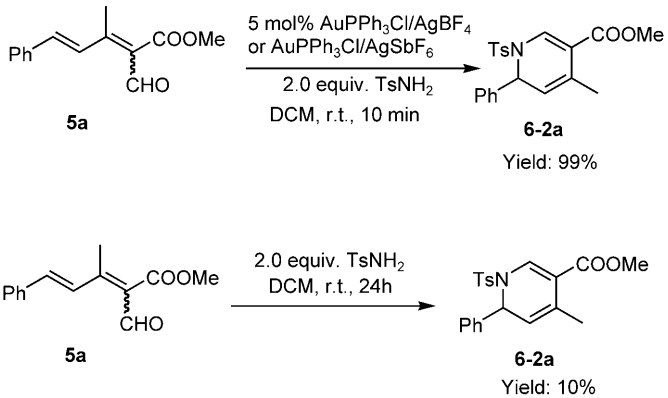
Entry	R^3	Product	Yield [%][b]
1	C_6H_5	**6-2a**	69
2	2-Me-C_6H_4	**6-2b**	67
3	4-Me-C_6H_4	**6-2c**	65
4	3-Me-C_6H_4	**6-2d**	56
5	4-Cl-C_6H_4	**6-2e**	55
6	4-Br-C_6H_4	**6-2f**	48
7	2-naphthyl	**6-2g**	62
8	*n*-hexyl	**6-2h**	NR[c]

[a] Reactions were conducted with 0.4 mmol of **4a** in 3 mL of solvent.
[b] Isolated yield after column chromatograph.
[c] No reaction.

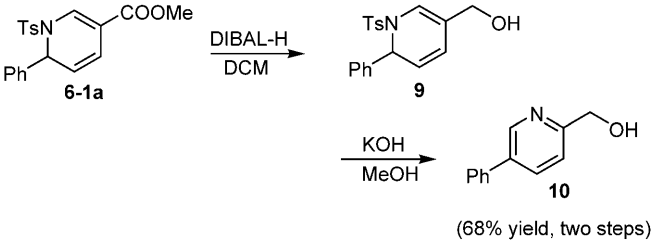


Scheme 5. The effect of substitution at the allene terminus.

2 equivalent of $TsNH_2$ in the presence of 5 mol% of $Au(PPh_3)Cl/AgBF_4$ or $Au(PPh_3)Cl/AgSbF_6$ in CH_2Cl_2 at room temperature (Scheme 6). 1,2-Dihydropyridine **6-2a** was obtained in quantitative yield after 10 min. However, the reaction rate became much slower if the reaction was attempted without catalysts. In our cases $Au(PPh_3)Cl/AgBF_4$ had a further specific quality of accelerating the condensation of aldehyde with primary amine[10].



Scheme 6. Support of the proposed mechanism.



Scheme 7. Conversion of 1,2-dihydropyidines to pyridines.

Next, we investigated the conversion of 1,2-dihydropyrodines to pyridines (Scheme 7). To simplify the purification, we reduced ester **6-1a** to acohol **9**. The tosyl group was removed by treatment with KOH in MeOH to give pyridine **10** in 68% yield.

In summary, we have reported our preliminary results on gold-catalyzed tandem reactions for the synthesis of substituted 1,2-dihydropyridines from propargyl vinyl ethers or allenic vinyl ethers and primary amines *via* gold-catalyzed [3,3]-sigmatropic rearrangement/isomerization/amine condensation/6π-aza-electrocyclization. 2,4-Dienals are the key intermediates in these two tandem reactions. This discovery is significant not only as a novel tandem reaction sequence but also as a mild, selective and efficient approach to synthesize 1,2-dihydropyridines.

Experimental Section

Synthesis of 1,2-Dihydropyridines 6-1

To a solution of propargyl vinyl ethers **1** (0.4 mmol) and $TsNH_2$ (136 mg, 0.8 mmol) in CH_2Cl_2 (3 mL) was added $(Ph_3P)AuCl$ (8 mg, 0.015 mmol) and $AgSbF_6$ (6 mg, 0.02 mmol) in this order at room temperature. The mixture was stirred at room temperature. When the reaction was complete as determined by TLC analysis, the resulting mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel.

Synthesis of 1,2-Dihydropyridines 6-2

To a solution of the allenic vinyl ethers **2** (0.4 mmol) and $TsNH_2$ (136 mg, 0.8 mmol) in CH_2Cl_2 (3 mL) was added $(Ph_3P)AuCl$ (8 mg, 0.02 mmol) and $AgBF_4$ (6 mg, 0.02 mmol) in this order at room temperature. The mixture was stirred at room temperature. When the reaction was complete as determined by TLC analysis, the resulting mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel.

Synthesis of Pyridines 10

To a solution of 1,2-dihydropyridine **6-1a** (180 mg, 0.5 mmol) in dry CH_2Cl_2 (10 mL), DIBAL-H (1.25 mL, 1 M in hexane, 1.25 mmol) was added at −78 °C under argon atmosphere. After being stirred for 1 h, the mixture was quenched with 10% aqueous potassium sodium tartrate (5 mL). The mixture was allowed to come to room temperature. After 3 h, the mixture was filtered, and the solution was extracted with CH_2Cl_2. After that, the organic layer was washed with brine, and dried over anhydrous Na_2SO_4, filtered and evaporated to give a residue.

The resulting crude material was used for the next step without future purification. In a 25-mL round-bottomed flask were placed the crude alcohol **9** and MeOH (5 mL), KOH (140 mg, 5 mmol) was added. The mixture was refluxed overnight and quenched by water. The mixture was extracted with CH_2Cl_2. Combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by flash column chromatography on silica gel and give pyridine **10**; yield: 63 mg (68%).

Acknowledgements

We are grateful for the National Basic Research Program of China (No. 2010CB833200), the NSFC (20772051, 20972058), the "111" program from MOE of P. R. China.

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