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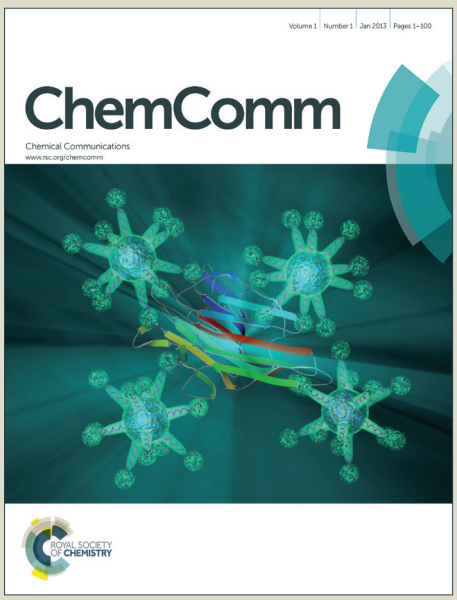

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Au(I)-Catalyzed Rearrangement/Cyclization Cascade Toward the Synthesis of 2-Substituted-1,4,5,6-tetrahydrocyclopenta[*b*]pyrrole†‡

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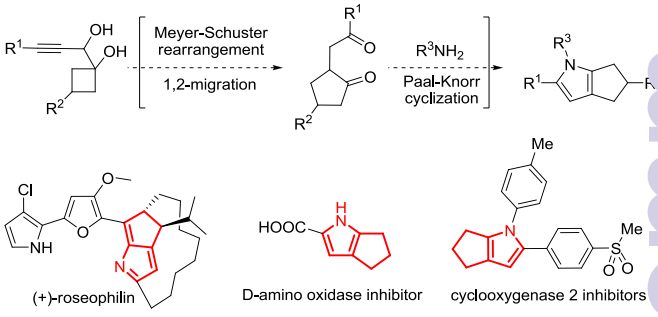
Xue-Qing Mou,[a] Zheng-Liang Xu,[a] Shao-Hua Wang,*[ab] Dao-Yong Zhu,[a] Jie Wang,[a] Wen Bao,[a] Shi-Jiang Zhou,[a] Chao Yang[a] and Di Zhang[a]

An Au(I)-catalyzed tandem reaction for the synthesis of 2-phenyl-1,4,5,6-tetrahydrocyclopenta[b]pyrrole derivatives from 1-(1-hydroxy-3-phenylprop-2-yn-1-yl)cyclobutanol and primary amine or NH_4OAc has been developed to afford a series of polysubstituted pyrroles in moderate to good yields.

Since its first detection by F. F. Runge in 1834 and structure elucidation by von Bayer in 1870's, pyrrole has been considered as one of the most important heterocycles due to its broad utilities.[1-4] Up to now, pyrroles and its derivatives not only present in lot of biological contexts, but also represent as the key structure components of many bioactive molecules[5-6] and some organic conducting materials,[7-8] e.g., vitamin B12, atorvastatin and polypyrroles. Therefore, developing synthetic methodologies toward the construction of pyrrole skeleton is always of considerable interest to synthetic chemists and has led to several classical strategies like Hantzsch pyrrole synthesis,[9] Knorr pyrrole synthesis,[10] Paal-Knorr pyrrole synthesis,[11] Van Leusen reaction,[12] Barton-Zard reaction[13] and Piloty-Robinson pyrrole synthesis.[14] Especially, in recent years, under the promotion of transition metal catalyzed annulation reactions,[15] a number of efficient methodologies toward the construction of pyrrole compounds have also been developed.[16] Despite of the results achieved, it is still highly desirable to further explore alternative approaches toward the synthesis of such an important heterocycle.

As we all known, the Paal–Knorr pyrrole synthesis utilizing 1,4-diketones and amines as starting materials is one of the most commonly used method to construct multi-substituted pyrroles. Therefore, it is likely that a similar type of reaction could take place between a 1,4-diketone intermediate generated *in situ* and an amine within a tandem process. Following this consideration and in connection with our interest in the transition metal catalyzed cyclization reactions and the development of synthetic methodologies toward the synthesis of heterocycles,[17,18] we envisioned that a facile and efficient tandem reaction procedure to pyrrole structures from 1-(1-hydroxy-3-phenylprop-2-yn-1-yl)-cyclobutanol and primary amine could be achieved through a Meyer-Schuster Rearrangement[19] / 1,2-migration[20] / Paal-Knorr cyclization cascade in the presence of proper catalyst, and would afford the products with a cyclopenta[*b*]pyrrole moiety, which is a common structural motif of many bioactive molecules, such as (+)-roseophilin,[21] D-amino oxidase inhibitor[22] and cyclooxygenase 2 inhibitors[23] (Scheme 1). To our knowledge, there is no report about such a reaction to give 1,4,5,6-tetrahydrocyclopenta[*b*]pyrrole via a tandem process, which is highly desirable in terms of reaction efficiency and atom economy. Herein, we present a new and unique strategy to construct 1,4,5,6-tetrahydrocyclopenta[*b*]pyrrole via an Au(I) catalyzed tandem reaction (Scheme 1).



Scheme 1 Proposed synthetic strategy and related bioactive molecules.

In order to realize such a tandem reaction, we first investigated systematically a variety of reaction conditions such as Lewis acid catalysts, solvents, reaction temperature and time with 1-(1-hydroxy-3-phenylprop-2-yn-1-yl)cyclobutanol (**1a**) and NH_4OAc (**2a**) as the model substrates. As summarized in Table 1, the desired reaction was attempted initially in the presence of Ph_3PAuCl (0.1 equiv) and AgOTf (0.

[a] School of Pharmacy & State Key Laboratory of Applied Organic Chemistry Lanzhou University, Lanzhou 730000, P. R. China. E-mail: wangshh@lzu.edu.cn;
[b] Key Laboratory of Drug Targeting and Drug Delivery System, Ministry of Education, Sichuan University, Chengdu, P. R. China.
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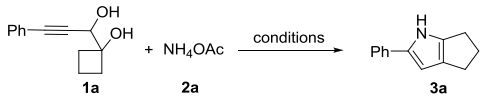
‡ Patent pending, Chinese patent application (No. 201510253806.6)

equiv) in DCM at room temperature, as similar type of catalysts has been used in the Meyer-Schuster Rearrangement.[24] To our delight, the desired product 2-phenyloctahydrocyclopenta[*b*]pyrrole (**3a**) was isolated in 26% yield (Table 1, entry 1). Inspired by this result, we next screened different solvents and reaction temperature. And it was found that nonpolar solvents usually gave better yields than polar ones. For example, when toluene, cyclohexane, *n*-hexane, or *n*-heptane were employed, the reaction could afford the expected product in higher yields than other solvents, like THF, DCE, 1,4-dioxane and DCM (Table 1, entries 1-9). Among the nonpolar solvents screened, the use of *n*-heptane could give the highest yield of 74% at 80 °C (Table 1, entry 9). And it was also observed that either decreasing or increasing temperature would cause a diminished yield of desired product (Table 1, entries 8-10). Next, different Lewis acid catalysts were further applied into the reaction, but none of them gave higher yields than the combination of Ph_3PAuCl and AgOTf (Table 1, entries 11 –21). Moreover, when Ph_3PAuCl or AgOTf alone was used as the catalyst, no desired product **3a** was detected except the decomposition of the substrate **1a** (Table 1, entries 18-19). Based on the information above, the loading of the catalyst, the reaction time were evaluated as well, and we were pleased to find that a lower amounts of catalyst (5 mol%) could catalyze the reaction well to give a yield of 75% by slightly prolonging the reaction time (Table 1, entry 22). Without catalyst, no conversion was observed (Table 1, entry 23), which indicated that the catalyst played a pivotal role in the reaction.

Table 1 Optimization of reaction conditions.[a]

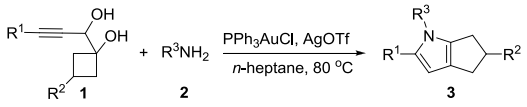


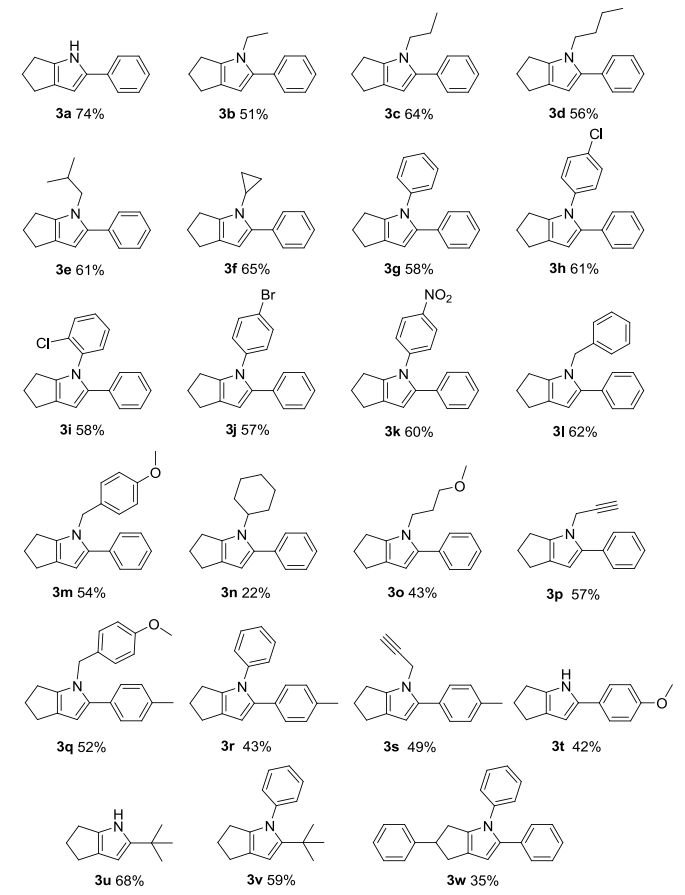
Entry	Catalyst (mol%)	Solvent	T (°C)	Yield[b] (%)
1	Ph_3PAuCl+AgOTf(10)	CH_2Cl_2	30	26
2	Ph_3PAuCl+AgOTf(10)	DCE	60	30
3	Ph_3PAuCl+AgOTf(10)	THF	60	25
4	Ph_3PAuCl+AgOTf(10)	dioxane	60	35
5	Ph_3PAuCl+AgOTf(10)	*c*-hexane[c]	60	32
6	Ph_3PAuCl+AgOTf(10)	toluene	110	54
7	Ph_3PAuCl+AgOTf(10)	*n*-hexane	80	48
8	Ph_3PAuCl+AgOTf(10)	*n*-heptane	60	65
9	Ph_3PAuCl+AgOTf(10)	*n*-heptane	80	74
10	Ph_3PAuCl+AgOTf(10)	*n*-heptane	100	69
11	Ph_3PAuCl+CF_3CO_2Ag(10)	*n*-heptane	80	trace
12	AuCl+AgOTf(10)	*n*-heptane	80	trace
13	AuCl+ CF_3CO_2Ag(10)	*n*-heptane	80	n.d.[d]
14	Ph_3PAuCl+$AgSbF_6$ (10)	*n*-heptane	80	42
15	IPrAuCl+AgOTf(10)	*n*-heptane	80	54
16	IPrAuCl+$AgSbF_6$(10)	*n*-heptane	80	46
17	SPhosAuCl+AgOTf(10)	*n*-heptane	80	23
18	Ph_3PAuCl(10)	*n*-heptane	80	n.d.[d]
19	AgOTf(10)	*n*-heptane	80	n.d.[d]
20	$Cu(OTf)_2$(10)	*n*-heptane	80	n.d.[d]
21	$AlCl_3$ (10)	*n*-heptane	80	n.d.
22[e]	Ph_3PAuCl+AgOTf(5)	*n*-heptane	80	75
23[e]	no catalyst	*n*-heptane	80	n.d.

[a] Reaction condition: without other notification, all of the reactions were performed with 1-(1-hydroxy-3-phenylprop-2-yn-1-yl)cyclobutanol (0.5 mmol), ammonium acetate (5 equiv.), catalyst in solvent (1 mL) at 80 °C under Ar for 4 h. [b] Isolated yield. [c] c-Hexane = cyclohexane. [d] n.d. = not detected. [e] The reaction time was 6 h.

With the optimized reaction conditions in hand (Table 1, entry 22), we subsequently investigated the substrate scope of such a transformation. Firstly, a series of amines were subjected to the tandem reaction with compound **1a**. As shown in Table 2, in most cases, the amines tested could proceed smoothly to transform into the polysubstituted pyrrole products in moderate yields (Table 2, **3a**–**3p**). Among them ammonium acetate as the amine source usually gave higher yield than aliphatic and aromatic amines. Among the aromatic amine investigated, the electronic effect of the substituents on phenyl ring was not clearly observed. The presence of electronic neutral or deficient substituent group like bromo, chloro and nitro could give the expected products in moderate yield leading to additional possibilities for further derivatization (Table 2, **3h**-**3k**). Besides, benzylamine and (4-methoxyphenyl)methanamine also could go through the reaction to give the desired products in moderate yield, which might simplify the synthesis process in case the pyrrole nitrogen needs pre-protection (Table 2, **3l**-**3m**). Additionally, when cyclic alkyl amine (**2f**, **2n**), alkoxy substituted alkyl amine (**2o**) and propargyl amine (**2s**) were subjected to the tandem reaction with compound **1a**, they all afforded the desired products. Encouraged by these results, we next applied the tandem reaction process to examine the scope of propargylic alcohols. It was found that introducing an additional electron donating group like methyl and methoxy group on the aromatic ring of substrate **1a** were well-tolerated, although they gave slightly lower yield than that of **1a** (for example, product **3g** and **3r**, **3p** and **3s**). Also, replacing the phenyl group of compound **1a** with a steric hindered *tert*-butyl group proved to be efficient under standard conditions, and therefore it revealed that the aromatic ring of propargylic alcohol substrate **1** is not a prerequisite in this reaction. With respect to R^2 component in propargylic alcohols substrate **1**, phenyl was also compatible to give corresponding product, albeit in low yield. It should be noted that when the substrates with a cyclopentanol moiety instead of cyclobutanol was applied to this tandem reaction, no desired products were obtained, which might be attributed to the low reactivity of such a five membered unit during the 1,2-migration step.

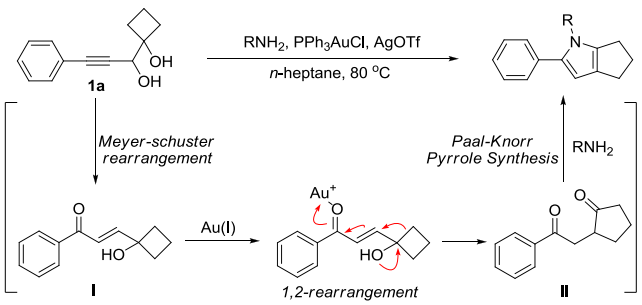
Table 2 Gold-catalyzed tandem synthesis of polysubstituted pyrrole.[a]





[a] Reaction conditions: without other notifications, all of the reactions were performed with substrate 1 (0.5 mmol), R^3NH_2 (3 equiv) or NH_4OAc (5 equiv), PPh_3AuCl (0.025 equiv), AgOTf (0.025 equiv) in *n*-heptane (1 mL) at 80 °C under Ar for 6h.

Based on above experimental results and related studies in this field, a plausible mechanism for this reaction was proposed with substrate **1a** as an example (Scheme 2). Firstly, in the presence of Au(I) catalyst, a Meyer-Schuster rearrangement reaction would take place to give α,β-unsaturated ketone intermediate **I**, which could go through an Au(I)-catalyzed 1,2-migration process to give 1,4-dicarbonyl intermediate **II**. Finally, a Paal-Knorr cyclization between intermediate **II** and amine would lead to the final product with a 1,4,5,6-tetrahydrocyclopenta[*b*]pyrrole skeleton.



Scheme 2 Plausible reaction mechanism.

In summary, an Au(I)-catalyzed tandem reaction, involving a Meyer-Schuster rearrangement / 1,2-migration / Paal-Knorr cyclization cascade has been successfully developed. Through the use of this methodology, a series of polysubstituted pyrroles were obtained in moderate to good yields, which might provide a simple and versatile procedure for the synthesis of 1,4,5,6-tetrahydrocyclopenta[*b*]pyrrole derivatives as well as related bioactivity screening.

Acknowledgements

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