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COMMUNICATION

One-Pot Synthesis of Tetrasubstituted 2-Aminofurans via Au(I)-Catalyzed Cascade Reaction of Ynamides with Propargylic Alcohols

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One-pot synthesis of fully substituted 2-aminofurans via a Au(I)-catalyzed cascade reaction of ynamides and propargylic alcohol was realized. Hydroalkoxylation of ynamide with propargylic alcohol, Saucy-Marbet rearrangement, and cyclization of the resultant 3,4-dienamide sequentially proceeds in a one-pot reaction under highly mild conditions to give fully substituted 2-aminofurans.

Ynamides have received much attention, especially from synthetic organic chemists, owing to their unique reactivity that arises from a nitrogen functionality directly attached on the alkyne terminus.[1] That is, a β-carbon atom of ynamides has a partial negative charge due to the delocalization ability of a lone electron pair of nitrogen to the C-C triple bond, resulting in reactions of electrophiles occurring at the β-carbon atom while nucleophiles attack the α-carbon atom of ynamides in a stereoselective manner (Scheme 1a).

As the series of our continuous studies on the reactivity of ynamides toward transition-metal catalysts,[2] we recently reported a Au(I)-catalyzed hydroalkoxylation/Claisen rearrangement cascade of aryl ynol ethers and ynamides with allyl alcohols, stereoselectively giving γ,δ-unsaturated esters and amides, respectively.[3] In this context, we envisaged the use of propargylic alcohols instead of allyl alcohols in this reaction system. It has been known that the reaction of ynamides with propargylic alcohol in the presence of various catalysts such as Au(I), Ag(I), Zn(II), and Brønsted acids stereoselectively produced 3,4-dienamides **3** via Saucy-Marbet rearrangement[4,5] (Scheme 1b). The resulting 3,4-dienamides are very useful for synthesis of various cyclic compounds.[4b,4c,4d] With respect to the synthesis of furans from ynamides, Zhu reported that 3,4-dienamides **3**, which were prepared by Zn(II)-promoted reaction of ynamides and propargylic alcohols via Saucy-Marbet rearrangement, were transformed to tetrasubstituted 2-aminofurans by Pd(II)-catalyzed cyclization (Scheme 2a).[4d] On the other hand, although it is not an example of ynamides, Shi reported one-pot synthesis of tri-substituted furans from terminal alkynes and propargylic alcohols (Scheme 2b),[6] indicating that a Au(I) complex can catalyzed both steps of hydroalkoxylation of alkyne with the alcohol and cyclization of the resulting 3,4-diene-1-one. However, they applied only the case of terminal alkynes, probably because the regioselectivity at the stage of hydroalkoxylation of internal alkynes, which have two different substituents at the terminus, is generally difficult to control.[7,8] As mentioned above, the reaction of ynamides and propargylic alcohols stereoselectively proceeds due to the nature of ynamides. Thus, if one-pot synthesis of furans from ynamides and propargylic alcohols was realized, it would be an atom- and pot-economical[9] methodology for the synthesis of tetrasubstituted 2-aminofurans, which are known as a key structural motif for various biologically active substances.[10] Herein, we report one-pot synthesis of tetrasubstituted furans from ynamides and propargylic alcohols via a Au(I)-catalyzed hydroalkoxylation/Saucy-Marbet rearrangement/cyclization cascade (Scheme 2c).

Scheme 1. Reactivity of ynamides

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Scheme 2. Synthesis of furans

In order to check the feasibility of our plan, the reaction of ynamide **1a** and alcohol **2a** was tried with 1 mol% Au(IPr)Cl/AgNTf$_2$ in toluene at 80 °C, which are the optimized conditions of the Au(I)-catalyzed hydroalkoxylation/Claisen rearrangement cascade of ynamides with allyl alcohols previously reported by us.[3] As a result, 3,4-dienamide **3aa** and furan **4aa** were obtained in 35% and 38% yield, respectively (Figure 1).

Figure 1. Reaction of ynamide and propargylic alcohol in the presence of a Au(I) catalyst

We therefore decided to first screen the conditions for cyclization of **3aa** to **4aa**. The results are summarized in Table 1. The reaction of 3,4-dienamide **3aa** in the presence of 1 mol% of a Au(IPr) NTf$_2$ catalyst in toluene at 80 °C for 24 h gave the desired furan **4aa** in 42% yield along with unexpected by-product **8** in 42% yield (Table 1, entry 1). We speculated that **8** was formed via retro-Saucy-Marbet rearrangement followed by decomposition of the resultant **7** by a trace amount of H$_2$O or acids in situ. In order to both prevent the formation of **8** and promote cyclization from **3aa** to **4aa**, various additives were examined. Addition of MS 4A reduced the formation of **8**, but the yield of **4aa** was also decreased (entry 2). Addition of bases including DABCO and DBU were not effective for increasing the formation of **4aa** (entries 3 and 4). Interestingly, addition of the acids, TsOH and PPTS, improved the yields of **4aa** to 71% and 76%, respectively (entries 5 and 6). On the other hand, the reaction of **3aa** only by using PPTS in the absence of a Au(I) catalyst did not gave the desired product, indicating that the reaction actually proceeds by a Au(I) catalyst. It is thought that PPTS would assist the cyclization of **3aa** and/or prevent the formation of **8**, although the role of PPTS remains unclear.[11,12]

Table 1. Screening of reaction conditions of **3aa**[a]

entry	additive (mol%)	yield **4aa** (%)[b]	yield **8** (%)[b]	recov. **3aa** (%)[b]
1	none	42	42	-
2	MS 4A	12	27	13
3	DABCO (20)	3	13	67
4[c]	DBU (20)	-	-	-
5	TsOH·H$_2$O (5)	71	-	-
6	PPTS (5)	76	-	-
7[d]	PPTS (5)	-	-	78

[a] Reaction conditions: **3aa** (0.30 mmol), Au(IPr)NTf$_2$ (0.003 mmol) under N$_2$ at 80 °C for 24 h (entries 1-4, and 7) or for 3 h (entries 5 and 6). [b] Yields were calculated by ^{1}H-NMR using 1,1,2,2-tetrachloroethane as an internal standard. [c] 1,3-dienamide formed from **3aa** via isomerization was obtained in 90% yield. [d] The reaction was carried out without a Au(I) catalyst.

Next, we investigated one-pot reaction from **1a** and **2a** to furan **4aa** (Table 2). When the reaction of **1a** and **2a** was carried out under the above-mentioned optimized conditions for cyclization of **3aa**, expected products such as **3aa** and **4aa** were not obtained at all and only complex mixtures were obtained (entry 1). Surprisingly, decreasing the temperature tended to improve the yields of the products, and the isolated yield of **4aa** reached up to 97% in the reaction at room temperature (entries 2-4). The reaction of 1 mmol scale of the substrates smoothly proceeded without any problems, giving **4aa** in 91% isolated yield (entry 5). The reaction only by using PPTS in the absence of a Au(I) catalyst was again checked in this one-pot reaction,

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giving no products **3aa** and **4aa** along with recovery of the starting ynamide **1a** in 80% yield (entry 6).

Table 2. One-pot reaction of **1a** and **2a** to **4aa**[a]

entry	temp. (°C)	**4aa** (%)[b]	**3aa** (%)[b]
1	80	-	-
2	60	23	20
3	40	40	23
4	rt	97[c]	-
5[d]	rt	91[c]	-
6[e,f]	rt	-	-

[a] Reaction conditions: **1a** (0.30 mmol), **2a** (0.30 mmol), Au(IPr)NTf$_2$ (0.003 mmol), PPTS (0.015 mmol) under N_2 at the indicated temperature for 24 h. [b] Yields except for entry 4 were calculated by ^{1}H-NMR using 1,1,2,2-tetrachloroethane as an internal standard. [c] Isolated yield. [d] 1 mmol scale reactions. [e] The reaction was carried out without a Au(I) catalyst. [f] **1a** was recovered in 80% yield.

With the optimal conditions for one-pot synthesis of furan in hand, we next examined the scope and limitations of this reaction. First, the scope of ynamides using propargylic alcohol **2a** was investigated (Scheme 3). The reactions of ynamides **1b**-**1d**, having an aromatic ring with substituents at the *para*-position, gave the corresponding products **4ba**-**4da** in modest yields, suggesting that the electronic property of substituents on the aromatic ring does not obviously influence the reactivity. The existence of a bulky *tert*-butyl group on the terminus of alkyne retarded the reaction, giving **4ea** in 31% yield. Compared to the methyl-substituted substrate **1f**, substrates having a phenethyl group (**1g**) and a long alkyl chain with an oxygen functionality (**1h** and **1i**) gave the corresponding products in good yields. It is noteworthy that a bromo-substituted alkyl group, a phthalimide moiety, and an alkenyl moiety in the ynamides are tolerated in this reaction, affording the corresponding products **4ja**-**4la** in good yields. Not only a *p*-toluenesulfonyl (Ts)-amide but also 2-nitrobenzenesulfonyl (Ns)- and methanesulfonyl (Ms)-amides can be utilized as substrates, and **4ma** and **4na** were obtained in 89% and 92% yields, respectively.

Next, the scope of propargylic alcohols using ynamide **1a** was checked. The results are summarized in Scheme 4. The reaction of ynamide **1a** with propargylic alcohol **2b**, having a phenethyl group on the terminus, under the optimal conditions gave furan **4ab** in 92% yield. The reactions of substrates **2c**-**2e**, having a benzene ring with an electron-withdrawing or electron-donating group on the terminus, produced the corresponding furans **4ac**-**4ae** in good yields. The reaction of propargylic alcohol **2f**, having a long alkyl chain with an oxygen functionality, also proceeded, giving furan **4af** in a modest yield.[13]

[a] 1 mol% Au(IPr)NTf$_2$. [b] 5 mol% Au(IPr)NTf$_2$. [c] The reaction was carried out at rt. [d] The reaction was carried out at rt. 60 °C.

Scheme 3. Scope of the ynamides

[a] 1 mol% Au(IPr)NTf$_2$. [b] 5 mol% Au(IPr)NTf$_2$. [c] The reaction was carried out at rt. [d] The reaction was carried out at rt. 60 °C.

Scheme 4. Scope of the propargylic alcohols

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Plausible reaction mechanism for the formation of 2-aminofuran **4** from ynamide **1** and propargyl alcohol **2** is depicted in Scheme 5. Initially, the hydroalkoxylation by propargyl alcohol **2** would regioselectively occur at the α-position to afford **I** followed by Saucy-Marbet rearrangement, giving 3,4-dienamide **3**. Then, PPTS catalyzes the equilibrium between 3,4-dienamide **3** and its enol form **3'**, and the coordination of the diene moiety in **3'** to Au(I) catalyst takes place followed by nucleophilic attack of the oxygen atom at the center carbon on the diene moiety in **3'** to produce **II**. Finally, protodeauration of **II** occurs to give 2-amino furan **4** along with regeneration of Au(I) catalyst. Although PPTS seems to work in several steps of this cascade reaction, the role of PPTS in detail remains unclear at this stage.[12]

Scheme 5. Plausible reaction mechanism

The furan **4la** in Scheme 3 might be a suitable substrate for the intramolecular Diels-Alder reaction. We therefore chose **4la** for simple demonstration of the utility of tetrasubstituted 2-aminofurans synthesized by this reaction. When a solution of **4la** in *m*-xylene was heated at 160 °C for 48 hours, tetrahydroquinoline derivative **9** was obtained in 79% yield (Scheme 6). It was clear that tetrahydroquinoline **9** was produced via the Diels-Alder reaction of **4la** followed by aromatization of the adduct **10**.

Scheme 6. Intramolecular Diels-Alder reaction of furan **4la**

Conclusions

In summary, we have developed a one-pot synthesis of tetrasubstituted 2-aminofurans via a Au(I)-catalyzed cascade reaction of ynamides and propargylic alcohols. The remarkable features of this reaction are as follows: 1) multiple reactions (i.e., hydroalkoxylation, Saucy-Marbet rearrangement, and cyclization of 3,4-dienamide) proceeded in one-pot manner by using a Au(I) catalyst and PPTS under mild conditions, 2) the reaction is atom- and pot-economical, and 3) the reaction produced tetrasubstituted 2-aminofurans containing various functional groups, which should be useful for further transformation. Further investigations including synthetic application of this reaction are currently in progress.

Conflicts of interest

There are no conflicts to declare.

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