Gold-catalyzed intermolecular reaction of ynamides with 3-indolyl azides via an unexpected 1,2-alkyl migration

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Abstract

A gold-catalyzed intermolecular reaction of ynamides with 3-indolyl azides via the presumable α-imino gold carbenes has been developed, providing an alternative and efficient way for the synthesis of valuable 3-amino-β-carbolines in generally good to excellent yields. Importantly, this new protocol involves an unexpected 1,2-alkyl migration pathway.

1. Introduction

Rearrangement [1–3] and migration [4–6] reactions as features in the chemistry field have been the focus of considerable attention in the past decades, as they could build surprising and unexpected structures, which are even difficult to synthesize by conventional methods. Among those, intramolecular cyclization of heteroaromatic compounds with alkynes involving alkyl migrations has received particular attention in recent years because this chemistry offers new ways for the efficient construction of synthetically useful heterocycles [7–13]. For example, Beller and co-workers [7,8] reported an elegant protocol for the platinum-catalyzed synthesis of pyrroloazepinones in 2009, involving a rearrangement of the amidocarbonyl group from the 2- to the 3-position of the pyrrole ring (Scheme 1a). In 2011, Hashmi and co-workers [9] reported a gold-catalyzed cyclization/2,3-alkyl shift of 3-silyloxy-1,5-enynes for the highly efficient synthesis of benzo[b]furan derivatives (Scheme 1b). In subsequent work by the same group, they successfully extended the scope of the reaction for the preparation of a variety of heterocycles such as benzo[b]thiophenes, dibenzothiophenes, and dibenzofurans [10]. In 2012, Hashmi and co-workers [11] disclosed another elegant example of gold-catalyzed synthesis of azeepino[3,4-b]indol-1-ones, where an unprecedented 3,2-shift of an acylamino group was involved (Scheme 1c). Very recently, elegant studies on the synthesis of iodocarbazoles through a tandem iodocyclization with migration and aromatization were demonstrated by Liang and co-workers (Scheme 1d) [12]. Despite these significant achievements, these migration reactions have been limited to intramolecular reactions, which may severely limit the molecular flexibility and its further synthetic applications, and such an intermolecular migration reaction has not been reported.

Recently, the generation of α-imino gold carbenes [14–22] through gold-catalyzed alkyne amination has gained significant attention, because this strategy offers easy access to a variety of valuable complex nitrogen-containing molecules [23–33]. In our recent study on the ynamide chemistry [34–48], we first disclosed that benzyl azides could serve as efficient nitrene transfer reagents to react with ynamides for the intermolecular generation of α-imino gold carbenes. As a result, this chemistry has evolved into a robust and reliable method for the construction of versatile 2-aminooindoles and 3-amino-β-carbolines (Scheme 2a) [49]. On the basis of this work, we further developed the relevant gold-catalyzed intermolecular ynamide amination initiated aza-Nazarov cyclization [50] and C–H functionalization [51], leading to the efficient synthesis of highly functionalized 2-aminopyrroles and 2-aza-1,3-butadienes, respectively. Inspired by these results, we envisioned that the synthesis of 2-amino-γ-carbolines might be accessed directly through such a gold-catalyzed intermolecular reaction of ynamides with 3-indolyl...
azides (Scheme 2b). Interestingly, the corresponding 3-amino-β-carbolines were obtained instead in this case. Herein, we would like to communicate this unexpected gold-catalyzed reaction of ynamides with 3-indolyl azides via the presumable α-imino gold carbenes, allowing the efficient synthesis of valuable 3-amino-β-carbolines under mild reaction conditions, particularly in an atom- and step-economic manner (Scheme 2b). Importantly, this new protocol involves an unexpected 1,2-alkyl migration pathway.

2. Materials and methods

Typical procedure for the amination reaction (3a as an example): IPrAuNTf₂ (9.0 mg, 0.01 mmol) was added to a solution of the N-phenyl-N-(phenylethynyl)methanesulfonamide 1a (54.3 mg, 0.20 mmol), tert-butyl 3-(azidomethyl)-1H-indole-1-carboxylate 2a (81.7 mg, 0.30 mmol), AgOAc (36.7 mg, 0.22 mmol), 4 Å MS (100 mg) in dry DCE (4.0 mL) at room temperature. The reaction
mixture was stirred at 60 °C and the progress of the reaction was monitored by thin-layer chromatography (TLC). The reaction typically took 24 h. Upon completion, the mixture was then concentrated and the residue was purified by chromatography on silica gel (eluent: hexanes/ethyl acetate) to afford the desired tert-butyl 4-phenyl-3-[(N-phenylmethylsulfonamido)-9H-pyrido[3,4-b] indole-9-carboxylate 3a as white solid in 97% yield. 

\[ ^1\text{H NMR (500 MHz, CDCl}_3 \] \( \delta \) 9.53 (s, 1H), 8.36 (d, \( J = 8.0 \) Hz, 1H), 7.50–7.38 (m, 4H), 7.23–7.16 (m, 2H), 7.14–7.07 (m, 3H), 7.06–6.95 (m, 3H), 6.87 (d, \( J = 8.0 \) Hz, 1H), 3.40 (s, 3H), 1.81 (s, 9H); 

\[ ^{13}\text{C NMR (125 MHz, CDCl}_3 \] \( \delta \) 150.2, 146.6, 140.2, 139.8, 135.7, 134.4, 133.1, 129.8, 129.6, 129.5, 128.6, 128.5, 128.2, 127.9, 127.0, 123.6, 123.2, 123.1, 116.2, 85.1, 39.9, 28.3.

3. Results and discussion

Ynamide 1a and 3-indolyl azide 2a were chosen as model substrates for our initial study, and some of the results are listed in Table 1. Initially, it was found that the reaction of ynamide 1a and 3-indolyl azide 2a afforded the corresponding 3-amino-β-carboline 3a in 50% yield under our previously developed conditions (Table 1, entry 1) [48]. Of note, neither 2-aminoindole nor background enamide formation was detected in this case [48]. Attempts to improve the yield of this reaction by the screening of other gold catalysts were unsuccessful (Table 1, entries 2–5). In addition, slightly improved yield could be achieved when the reaction was performed at 60 °C (Table 1, entry 6). Considering that a dehydrogenative oxidation was involved in this tandem reaction, several external oxidants were screened (Table 1, entries 7–12). To our delight, the desired 3a was formed in 90% yield by employing 1.1 equiv of AgOAc as oxidant (Table 1, entry 12). Of note, other molecular sieves such as 3 Å MS and 5 Å MS failed to improve the reaction (Table 1, entries 13 and 14).

With the optimized reaction conditions in hand (Table 1, entry 12), the scope of this gold-catalyzed formal [4+2] annulation reaction was then examined, as shown in Table 2. The reaction of 3-indolyl azide 2a with various R1-substituted ynamides 1 was first examined, and the corresponding 3-amino-β-carbolines 3a–3e were obtained in 84%–97% yields (Table 2, entries 1–5). In addition,
the reaction also proceeded smoothly with ynamides bearing different R² groups, delivering the desired 3f–3j in generally good to excellent yields (Table 2, entries 6–10). Finally, various 3-indolyl azides with different electronic nature on the indole ring were screened, and the reaction furnished the desired products 3k–3n in mostly excellent yields (Table 2, entries 11–14). This transformation thus makes it an alternative way for the efficient construction of the valuable 3-amino-[β]-carbolines, known as the lead compounds for anti-tumor agents, that conventionally demand rather tedious synthesis [52–56].

Based on the above experimental results and our previous work [49], a plausible mechanism of this gold-catalyzed formal [4+2]...
annulation was depicted in Scheme 3. The 3-indolyl azide 2 first attacked Au-activated ynamide 1, leading to the generation of vinyl gold intermediate A, which could be further transformed into the corresponding α-imino gold carbene intermediate B by extrusion of molecular nitrogen. The gold carbene could be then trapped by the highly nucleophilic 3-position of the indole ring, leading to intermediate C. Subsequently, the 1,2-alkyl migration from the 3- to 2-position occurred to form the intermediate D with a more stable carbonium ion. Intermediate D underwent subsequent protodeauration to generate intermediate E, and E could be finally converted into the product 3 through dehydrogenative oxidation.

4. Conclusions

In summary, a gold-catalyzed intermolecular reaction of ynamides with 3-indolyl azides via the presumable α-imino gold carbenes have been developed, providing an alternative and efficient way for the synthesis of various synthetically useful 3-amino-β-carbolines. Importantly, this new protocol involves an unexpected 1,2-alkyl migration pathway. Other significant features of this approach include the use of readily available precursors, high flexibility, simple procedure, and mild reaction conditions.

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Conflict of interest

The authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.scib.2017.08.020.

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