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Benign catalysis with zinc: atom-economical and divergent synthesis of nitrogen heterocycles by formal [3+2] annulation of isoxazoles with ynol ethers

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Herein, we disclose an efficient zinc-catalyzed formal [3+2] annulation of isoxazoles with ynol ethers under exceptionally mild reaction conditions, leading to the atom-economical and divergent synthesis of 2-alkoxyl 1*H*-pyrroles and 3*H*-pyrroles, respectively. Importantly, this zinc-catalyzed protocol demonstrates the dramatically divergent reactivity from the relevant platinum catalysis, where the formal [4+2] annulation of isoxazoles with ynol ethers was involved. In addition, theoretical calculations provide further evidence for the feasibility of the proposed reaction mechanism, especially the distinct selectivity.

Introduction

Isoxazoles, as masked 1,3-dicarbonyl equivalents, have proven to be versatile building blocks and pivotal intermediates for the efficient construction of various valuable heterocycles.¹ As a result, numerous methods have been developed based on isoxazoles in recent years.² However, the relevant reactions of isoxazoles with alkynes have seldom been explored³⁻⁷ probably due to the relatively weak nucleophilicity of isoxazoles. In 2015, our group reported the first catalytic reaction of isoxazoles with alkynes, and this protocol has been utilized into the synthesis of various 2-aminopyrroles through a gold-catalyzed formal [3+2] annulation of isoxazoles with ynamides involving a presumable α -imino gold carbene intermediate.³ Interestingly, a formal [4+2] annulation of isoxazoles with ynol ethers occurred instead in the presence of platinum as catalyst, and the corresponding α -imino platinum carbene was presumably generated (Scheme 1a).⁴ Such a protocol has also been well exploited by Hashmi,⁵ Liu⁶ and others,⁷ and various efficient gold-catalyzed annulations have been established, allowing the facile synthesis of a range of valuable heterocycles. Despite these findings, these catalytic annulations have been mostly limited to noble-metal catalysts. Therefore, the exploration of non-noble metal-catalyzed protocol for such a generation of αimino metal carbenes is highly desirable, not only for making this protocol more practical, but also because it may result in a selectivity switch for the assembly of diverse heterocycles.

Electron-rich heterosubstituted alkynes have attracted increasing attention from the synthetic community in the past decade due to their use in the highly efficient and regioselective construction of valuable heterocycles. However, compared with the ynamide chemistry,⁸ the chemistry of alkynyl ethers and

thioethers has traditionally been far less exploited despite being readily accessed and robust.^{9,10} Very recently, our group disclosed that zinc could effectively catalyze the reaction of isoxazoles with thioynol ethers to afford β -keto enamides, and an unprecedented 1,2-sulfur migration was presumably involved.¹¹ Inspired by these results and our continuing effort on the use of heterosubstituted alkynes for heterocycle synthesis,¹² we envisioned that the reaction of isoxazoles with ynol ethers might also be achieved by this zinc catalysis. Herein, we wish to report the realization of such a zinc-catalyzed formal [3+2] annulation of isoxazoles with ynol ethers, leading to the atom-economical and divergent synthesis of 2-alkoxyl 1*H*-pyrroles and 3*H*-pyrroles, respectively (Scheme 1b). And

(a) Pt catalysis: [4+2] annulations



Scheme 1. Transition metal-catalyzed reaction of isoxazoles with ynol ethers

these *N*-heterocycles could be readily converted to valuable γ -lactams¹³ via one-pot synthesis and *N*-acyl 1*H*-pyrroles, respectively (Scheme 1b). Importantly, this zinc-catalyzed protocol demonstrates the dramatically divergent reactivity from the relevant platinum catalysis, where the formal [4+2] annulation of isoxazoles with ynol ethers was involved.⁴ Moreover, theoretical calculations provide further evidence for the feasibility of the proposed reaction mechanism, especially the distinct selectivity. In this paper, we wish to report the results of our detailed investigations of this zinc-catalyzed reaction of isoxazoles with ynol ethers, including substrate scope, synthetic applications and mechanistic studies.

Results and discussion

At the outset, we used ynol ether **1a** and commercial available 3,5-dimethylisoxazole **2a** as the model substrates, and some of the results are listed in Table 1.¹⁴ Although **1a** was decomposed in the presence of most non-noble metal catalysts (Table 1, entries 1–4), we were pleased to find that the treatment of ynol ether **1a** and isoxazole **2a** with $Zn(OTf)_2$ at 80 °C afforded the corresponding [3+2] annulation product **3a** rapidly in 66% yield (Table 1, entry 5). Notably, the formation of 2,5-dihydropyridine was not detected in this case, which is distinctively different from our previous protocol where the

Table 1. Optimization of reaction conditions ^a			
Ph—	OEt +	catalyst (10 mol %) conditions EtO 3a	O NH H A
Entry	Metal catalyst	Reaction conditions	Yield ^b (%)
1	Yb(OTf) ₃	DCE, 80 °C, 24 h	<1
2	Y(OTf) ₃	DCE, 80 °C, 24 h	<1
3	Sc(OTf) ₃	DCE, 80 °C, 24 h	<1
4	Cu(OTf) ₂	DCE, 80 °C, 24 h	<1
5	Zn(OTf) ₂	DCE, 80 °C, 10 min	66
6	ZnCl ₂	DCE, 80 °C, 1 h	60
7	ZnBr ₂	DCE, 80 °C, 0.5 h	48
8 ^c	Zn(OTf) ₂ /NaBAr ^F ₄	DCE, 80 °C, 10 min	87
9 ^c	NaBAr ^F 4	DCE, 80 °C, 24 h	<1
10 ^c	Zn(OTf) ₂ /NaBAr ^F ₄	DCE, rt, 1 h	89
11 ^c	ZnCl ₂ /NaBAr ^F 4	DCE, rt, 6 h	88
12	IPrAuNTf ₂	DCE, rt, 1 h	63
13	Cy-JohnPhosAuNTf ₂	DCE, rt, 6 h	47

^{*a*} Reaction conditions: [**1a**] = 0.05 M. ^{*b*} Measured by ¹H NMR using diethyl phthalate as the internal standard. ^{*c*} 20 mol % NaBAr^F₄ was added. DCE = 1,2-dichloroethane, NaBAr^F₄ = sodium tetrakis[3,5-bis(trifluoromethyl)phenyl] borate, Ipr = 1,3-bis(2,6-diisopropylphenyl) imidazol-2-ylidene, CyJohnPhos = 2-(dicyclohexylphosphanyl) biphenyl.

reaction of isoxazoles with ynol ethers under platinum catalysis predominantly afforded 2,5-dihydropyridines.⁴ Variation of the catalyst's counteranion by switching Zn(OTf)2 to ZnCl2 and ZnBr₂ failed to further improve the yield (Table 1, entries 6–7). To our delight, the reaction yield was substantially improved by employing 10 mol % Zn(OTf)₂ and 20 mol % NaBArF₄,¹⁵ and the desired 2-ethoxypyrrole 3a was formed in 87% yield (Table 1, entry 8). Of note, $NaBAr_{4}^{F}$ alone could not catalyze this annulation (Table 1, entry 9). Gratifyingly, 3a could be obtained at ambient temperature with a yield up to 89% (Table 1, entry 10). In addition, the use of 10 mol % $ZnCl_2$ and 20 mol % NaBAr^F₄ gave silimar yield but requiring longer reaction time (Table 1, entry 11). Finally, it should be mentioned that typical gold catalysts such as IPrAuNTf₂ and Cy-JohnPhosAuNTf₂ could also catalyze this reaction, but resulting in significantly decreased yields (Table 1, entries 12-13).





^{*a*} Reactions run in vials; [**1a**] = 0.05 M; isolated yields are reported. ^{*b*} 5 mmol scale, 5 mol % Zn(OTf)₂ and 10 mol % NaBAr^F₄ were used, [**1a**] = 0.15 M, 5 h. ^{*c*} -10 °C, 20 mol % Zn(OTf)₂ and 40 mol % NaBAr^F₄ were used, 12 h.

With the optimized reaction conditions in hand (Table 1, entry 10), we explored the scope of the reaction using different isoxazoles. As shown in Table 2, the zinc-catalyzed reaction of ynol ether **1a** with various 3,5-disubstituted isoxazoles **2** occurred efficiently, affording the desired 2-ethoxypyrroles **3** in moderate to excellent yields. It was found that different dialkyl-substituted isoxazoles were suitable substrates for this tandem annulation, and the corresponding 2-ethoxypyrroles **3a**–**3e** were formed in 63–88% yields (Table 2, entries 1–5). In addition, the functional groups such as chloride (Table 2, entry 6) and bromide (Table 2, entry 7) were well tolerated under this annulation. Then, different aryl-substituted isoxazoles

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were examined, and the reaction also proceeded well to deliver the corresponding products **3i–31** in 66-95% yields (Table 2, entries 9–12). This reaction was also extended to styrylsubstituted and heteroaryl-substituted isoxozoles, producing the anticipated **3h** (70%) and **3m** (76%), respectively (Table 2, entries 8 and 13). To further test the practicality of the current catalytic system, the reaction was carried out on a gram scale (5.0 mmol) in the presence of 5 mol % of $Zn(OTf)_2$ and 10 mol % NaBAr^F₄, and the desired **3a** was obtained in 83% yield (1.01 g), thus highlighting the synthetic utility of this transformation (Table 2, entry 1). Importantly, no formal [4+2] annulation was observed in all cases. The molecular structure of **3a** was further confirmed by X-ray diffraction.¹⁶



^{*a*} Reactions run in vials; [1] = 0.05 M; isolated yields are reported. ^{*b*} 20 mol % Zn(OTf)₂ and 40 mol % NaBAr^F₄ were used. ^{*c*} 17% of ynol ether was recoveried, 10 h.

We then extended the reaction to different ynol ethers 1 (Table 3). The reaction also proceeded smoothly with a variety of aryl-substituted ynol ethers 1 to produce the corresponding 2-alkoxylpyrroles 3 in generally good to excellent yields (Table 3, entries 1–10). Of note, heteroaryl-substituted ynol ether was also compatible with this transformation, delivering the desired 3x in 62% yield (Table 3, entry 11). In addition to ethoxyl ynol ethers, methoxy and phenoxy ynol ethers were also readily tolerated, leading to the efficient formation of products 3y-3z in 75–78% yields (Table 3, entries 12–13). Thus, this zinc-catalyzed formal [3+2] annulation protocol offers a highly efficient and practical way to construct the 2-alkoxylpyrroles.

Interestingly, when the scope of the above zinc catalysis was extended to the reaction of ynol ether **1a** with fully substituted isoxazoles **2**, only 3*H*-pyrroles **4a–4i** were formed in mostly high yields under similar reaction conditions (Table 4). Of note, this reaction could also worked smoothly with heteroaryl-substituted and alkyl-substituted isoxazoles, which were further transformed into the desired **4h** and **4i** in 72% and 33% yields, respectively (Table 4, entries 8–9). Importantly, such a zinc catalysis demonstrates unique reactivity dramatically divergent from the relevant platinum-catalyzed protocol as only the formation of 2,5-dihydropyridines was observed under platinum catalysis.⁴



Further synthetic transformations of the as-synthesized products were then explored, as outlined in Scheme 2. For example, the treatment of ynol ether **1a** with isoxazoles **2** under the optimal reaction conditions, followed by hydrolysis with MsOH, led to the one-pot synthesis of valuable γ -lactams¹² **5a**-**5c** in 66–87% yields. Thus, the ether directing group can be readily transformed into the useful carbonyl group. Moreover, *3H*-pyrrole **4a** could be facilely converted into the corresponding *N*-acyl-protected 1*H*-pyrrole **6a** in 82% yield via a presumable intermolecular migration^{3b} or intramolecular double 1,5-migration of acyl group.¹⁷



Scheme 2. Synthetic applications.



Scheme 3. Plausible mechanism for zinc-catalyzed reaction of isoxazoles with ynol ethers. Relative free energies(ΔG_{DCE}) of key intermediates and transition states were computed at the SMD-M06/6-31G(d,p)/LanL2DZ level of theory in DCE solvent at 298K. Key bond lengths were shown in italic (unit: Å).

On the basis of the above experimental observations and density functional theory (DFT) calculations,¹⁴ plausible mechanisms for this zinc-catalyzed annulation reaction are depicted in Scheme 3. Firstly, isoxazole **2a** nucleophilically attacks the Zn(II)-ligated ynol ether **A** to yield the vinyl zinc intermediate **B**, which is further converted into the phenyl-stabilized carbocation intermediate **C** upon cleavage of the isoxazole N-O bond. Subsequently, the intermediate **C** is subjected competitively to either intramolecular cyclization or 1,2-OEt migration¹¹ to furnish 5-membered ring intermediate **D**, 7-membered ring intermediate **D**2, and cyanide intermediate **D**1, respectively. Clearly, 1,5-cyclization (via **TS**_D) is highly exothermic ($\Delta G = 41.9$ kcal/mol) and kinetically accessible with an activation barrier of only 10.6 kcal/mol; 1,7-cyclization

(via TS_{D2}), though kinetically being the most favorable, is highly reversible with an activation barrier of only 15.6 kcal/mol for its reverse reaction; 1,2-OEt migration (via TS_{D1}) is endothermic and kinetically the most unfavorable. As such, the formation of formal [3+2] annulation product **3a** via 1,5cyclization is predominant and thermodynamically controlled, demonstrating the dramatically divergent reactivity from the relevant platinum-catalyzed protocol, where only the formation of formal [4+2] annulation product was observed.¹⁴

Conclusions

In summary, we have developed an efficient zinc-catalyzed formal [3+2] annulation of isoxazoles with ynol ethers under exceptionally mild reaction conditions, leading to the atomeconomical and divergent synthesis of 2-alkoxyl 1*H*-pyrroles and 3*H*-pyrroles, respectively. Importantly, this zinc-catalyzed protocol demonstrates the dramatically divergent reactivity from the relevant platinum catalysis, where the formal [4+2] annulation of isoxazoles with ynol ethers was involved. Moreover, the mechanistic rationale for this tandem reaction, in particular accounting for the distinct selectivity, is well supported by DFT computations.

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Graphical Abstract

An efficient zinc-catalyzed formal [3+2] annulation of isoxazoles with ynol ethers under room temperature has been developed, leading to the atom-economical and divergent synthesis of 2-alkoxyl 1*H*-pyrroles and 3*H*-pyrroles, respectively. Importantly, this zinc-catalyzed protocol demonstrates the dramatically divergent reactivity from the relevant platinum catalysis, where the formal [4+2] annulation of isoxazoles with ynol ethers was involved.

