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COMMUNICATION

Synthesis of Poly-Substituted Oxazoles by a Gold-Catalyzed Acid-Assisted Regioselective Cyclization

Qian Wang,[a] Stephanie Hoffmann,[a] Jasmin Schießl,[a] Matthias Rudolph,[a] Frank Rominger,[a] and A. Stephen K. Hashmi*[a]

Abstract: Poly-substituted oxazole derivatives are obtained via a regioselective gold-catalyzed reaction of α-alkynylamides and alkynoates in the presence of nitriles. The intermediary obtained gold carbenes are generated by an alkyne oxidation with a pyridine-*N*-oxide. Acidic conditions ensure that only one of the two carbonyl oxygen atoms in these intermediates selectively cyclizes to the products in excellent yields.

Introduction

Poly-substituted oxazoles are important motifs in natural products and pharmaceuticals, especially for the purpose of curing allergic diseases.[1] Many strategies for the synthesis of oxazoles have been established,[2] including the intermolecular reaction of α-diazo ketones with nitriles.[3] However, these approaches require a multi-step synthesis and/or harsh reaction conditions. In addition, often toxic metal salts such as mercury(II) compounds have to be used.[4] Therefore, the synthesis of poly-substituted oxazoles, from simple and commercially available substrates under mild reaction conditions, is of high priority. In the recent decades, gold complexes were established as powerful soft Lewis acids that efficiently activates alkynes towards the addition of nucleophiles.[5] Series of transformations such as 1,2-migrations[6] or X-H insertions[7] (X=O or N) with α-oxo gold carbenes became available. These species can be formed by an oxygen transfer from nucleophilic oxygen-atom donor groups onto π-activated alkynes.[8] Especially *N*-oxides in combination with alkynes turned out to be suitable alternatives for hazardous α-diazo ketones.[9,10] Herein, we report a gold-catalyzed annulation to give 2,4,5-trisubstituted oxazoles under mild conditions.

Liming Zhang and co-worker's ground-breaking synthesis of gold carbene intermediates from pyridine-*N*-oxides and alkynes completely avoids the use of diazo reagents (Scheme 1, a).[11] In such reactions, the intermediary formed α-oxo gold carbenes are intercepted by nitriles,[12] followed by a selective cyclization via the carbonyl moiety. The overall reaction offers a desirable [2+2+1] annulation as an expansion of the pioneering work of Zhang's group.[13] If the key carbenoid intermediate is derived from α-acyl alkynes, two carbonyl moieties are present. As a consequence two possible pathways leading to differently substituted oxazoles are reasonable. Controlling the selectivity of the reaction in the presence of additional functional groups attracted our attention.

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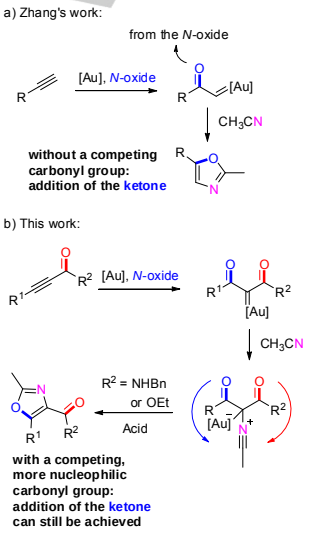
First we decided to use alkynones as test substrates (see the Supporting Information for details). The obtained mixture of isomeric products gave a hint that other functional groups might be feasible to switch the selectivity of the reaction. Inspired by that result we discovered that alkynamide derivatives [14] in addition with acid and alkynoates[15] (Scheme 1, b) as the starting materials deliver single products in perfect selectivity. The solid state molecular structure of the desired product **3d** is depicted in Figure 1. Based on the many applications of amide and ester[16] groups in medical compounds,[17] this protocol towards polysubstituted oxazoles offers a meaningful synthetic method.



Scheme 1. Gold-catalyzed oxidative oxazole synthesis: a) without competing carbonyl group, b) with a competing, more nucleophilic group.

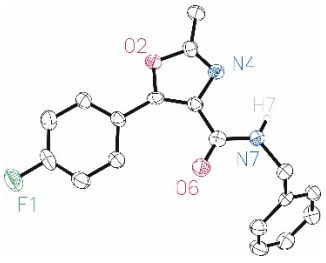


Figure 1. Solid-state molecular structure of **3d**.

Results and Discussion

When alkynamide **1a** was treated with 3,5-dibromopyridine *N*-oxide (1.5 equiv.) in the presence of [IPrAuCl]/$AgNTf_2$ in

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acetonitrile as solvent we still got a mixture of products **3a** and **4a** (Table 1, entry 1). However, to our surprise, only

Table 1. Optimization of the reaction conditions.[a]

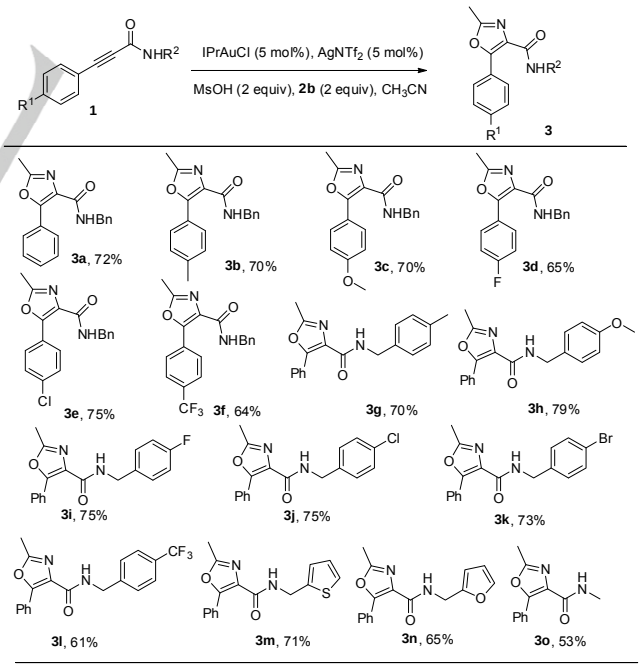
Entry	Catalyst	Acid	Temp.	**3a/4a**(%)[b]
1	[IPrAuCl]/$AgNTf_2$	-	80 °C	26/17
2	[IPrAuCl]/$AgNTf_2$	MsOH	80 °C	51/0
3	[IPrAuCl]/$AgNTf_2$	MsOH	50 °C	54/0
4	[IPrAuCl]/$AgNTf_2$	MsOH	50 °C	35/0
5	[IPrAuCl]/$AgNTf_2$	MsOH	50 °C	65/0
6	[IPrAuCl]/$AgNTf_2$	MsOH	50 °C	50/0
7	[IPrAuCl]/$AgNTf_2$	MsOH	50 °C	21/0
8	[PPh_3AuCl]/$AgNTf_2$	MsOH	50 °C	22/0
9	$KAuBr_4$	MsOH	50 °C	trace
10	[SPhosAuCl]/$AgNTf_2$	MsOH	50 °C	31/0
11	[Cy_3PAuCl]/$AgNTf_2$	MsOH	50 °C	30/0
12	[IPrAuCl]/$AgNTf_2$	TsOH	50 °C	55/0
13	[IPrAuCl]/$AgNTf_2$	TfOH	50 °C	58/0
14	[IPrAuCl]/AgOTf	MsOH	50 °C	53/0
15	[IPrAuCl]/$AgSbF_6$	MsOH	50 °C	51/0
16	**[IPrAuCl]/$AgNTf_2$**	**MsOH**	**50 °C**	**76 (72)**[d]/0
17	[IPrAuCl]/$AgNTf_2$	MsOH (0.2 eq.)	50 °C	37/0
18	[IPrAuCl]/$AgNTf_2$	$Zn(OTf)_2$ (2 eq.)	50 °C	11/0
19	[IPrAuCl]/$AgNTf_2$	$Sc(OTf)_3$ (2 eq.)	50 °C	trace
20	$AgNTf_2$	MsOH	50 °C	n.d.

[a] Unless otherwise noted, the reactions were carried out on a 0.1 mmol scale, [Au] (5 mol%), [Ag] (5 mol%), acid (2 equiv.) in 1 mL of CH_3CN with 1.5 equiv *N*-oxides overnight, entry 1-3 (**2c**), entry 4 (**2a**), entry 5 (**2b**), entry 6 (**2d**), entry 7 (**2e**), entry 8-20 (**2b**). [b] Yield was determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as the internal standard. Isolated yield of product in parentheses. [c] **2b** 2 equiv. [d] Isolated yield.

polysubstituted oxazole **3a** was obtained in 51% yield with MsOH (2 equiv) as an additive under the same conditions (Table 1, entry 2). Encouraged by this result, we further optimized the conditions. At first, different *N*-oxides were tested at 50 °C (Table 1, entry 3-7). 3,5-Dichloropyridine *N*-oxide **2b** was the best oxidant while quinoline *N*-oxide **2e** reached only 21 % yield. A small screening of other gold catalysts did not improve the yield (Table 1, entry 8-11). Even $KAuBr_4$ could not catalyze this reaction (Table 1, entry 9). TsOH and TfOH as additives were also effective leading to a single product **3a** in 55 % and 58 % respectively (Table 1, entry 12 and 13). A testing of different silver salts revealed only a minor effect of the counter ion onto the reaction (Table 1, entry 14 and 15). Increasing the amount of pyridine *N*-oxide to two equivalents significantly increased the yield to 76% (Table 1, entry 16). We also tested 0.2 equiv. MsOH as additives resulting in 37% yield (Table 1, entry 17). Other Lewis acids such as $Zn(OTf)_2$ and $Sc(OTf)_3$ as additives showed only poor activities (Table 1, entry 18 and 19). A control experiment demonstrated that the role of gold was pivotal for the reaction (Table 1, entry 20).

Under the optimized reaction conditions, we explored different *N*-substituted alkynamides **1** as precursor for polysubstituted oxazoles (Table 2). First, different substituents on the benzene core connected to the alkyne were examined. The effect of either electron-donating substituents like methyl- and methoxy-groups (**3b** and **3c**) or electron-withdrawing substituents like -F, -Cl, or -CF_3 (**3d**, **3e**, **3f)** were only minor with yields ranging from 64% to 75%. An only moderate effect of the substitution pattern onto the reaction was also observed for differently substituted benzylic moieties at the amide. Most of the products were gained in moderate yields (**3g-3k**) except of the electron-deficient trifluoromethyl-substituted **3l**, which was obtained in only 61 %. Notably, thiophene- and furan-substituted alkyneamides also performed well in this reaction (**3m** and **3n**). Moreover, an *N*-methyl amide derivative converted to the corresponding product **3o** in 53 % yield.

Table 2. Scope of the reaction from *N*-substituted alkynylamides.[a]



[a] **1** (0.1 mmol), [Au] (5 mol%), [Ag] (5 mol%), acid (2 equiv.), *N*-oxides (2 equiv.), 1 mL CH_3CN, 50 °C, overnight, yield of isolated product. [b] 80 °C, 16 h, MsOH (2 equiv.).

Table 3. Scope of the reaction for alkynoate starting materials.[a]

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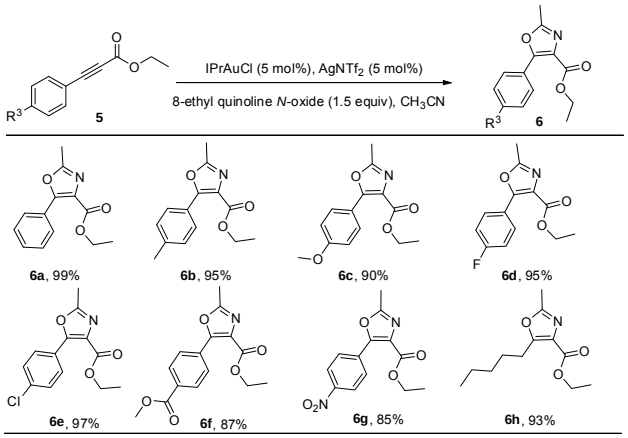
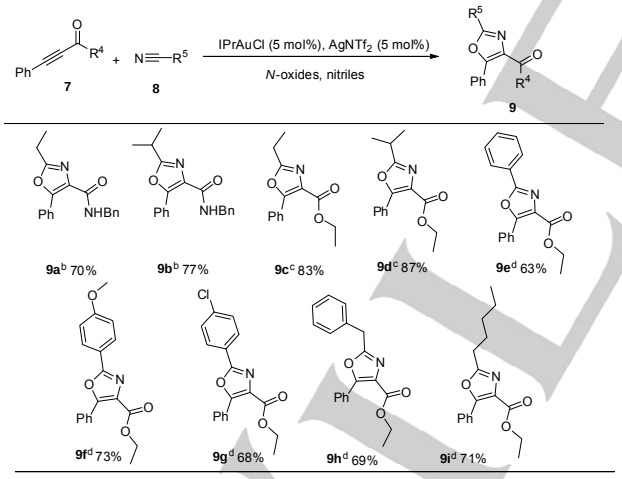


[a] **1** (0.2 mmol), [Au] (5 mol%), [Ag] (5 mol%), *N*-oxide (1.5 equiv), 1 mL CH_3CN, 80 °C, 3 h, yield of isolated product.

To our delight, alkynoates also reacted selectively. Noteworthy, even in the absence of an acid, a selective incorporation of the oxygen derived from the *N*-oxide was observed while the ester group remained in the final product (Table 3). 8-Ethylquinoline *N*-oxide (**2f**) was the best among the examined oxidants (see the Supporting Information for details). Phenylbenzoates bearing either electron-donating or electron-withdrawing groups afforded the corresponding products in excellent yield and perfect selectivity (**6a-6f**). Even with the strong electron-withdrawing effect of a nitro group, **6g** was still formed in 85 % yield. Furthermore, an alkyl alkynoate **5h** afforded product **6h** in 93 % yield.

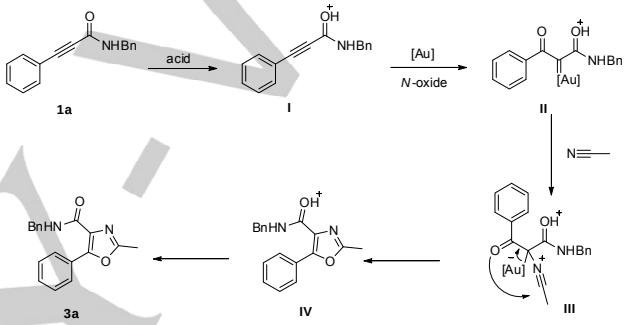
Table 4. Scope of the reaction for various nitriles.[a]



[a] **7** (0.1 mmol), [Au] (5 mol%), [Ag] (5 mol%) yield of isolated product. [b] **8** (1 mL), **2b** 2 equiv, 50 °C, overnight. [c] **8** (1 mL), **2f** 1.5 equiv, 80 °C, 3 h. [d] **8** 3 equiv., toluene (0.5 mL), **2f** 1.5 equiv, 80 °C, 3 h.

Next, we evaluated different nitriles in the reaction (Table 4). When propionitrile and isobutyronitrile were used as the reaction solvent, the proposed oxazoles were obtained in moderate to good yields (**9a**–**9d**). For expensive nitriles or nitriles with a high melting point, a different procedure was considered. With only three equivalents of benzonitrile in 0.5 mL toluene as the solvent (alkynoate concentration 0.4 M), **5a** performed an acceptable yield (**9e**, 63%) and the remaining benzonitrile could be recovered. Other nitriles were also used under the same reaction conditions. 4-Methoxybenzonitrile and 4-chlorobenzonitrile, led to a moderate yield of the desired products (**9f** and **9g**) which improves the diversity for an aryl substituent in the 2-position of the obtained oxazoles. Phenylacetonitrile and hexanenitrile also reacted with ethyl phenylpropiolate to generate **9h** and **9i** in good yield.

Based on the above results, we propose a mechanism as shown in Scheme 2. Alkynylamide **1a** undergoes a protonation leading to intermediate **I**. After that, in the presence of gold and *N*-oxide, an α-oxo gold carbene intermediate **II** is generated. Then the gold carbene intermediate **II** is captured by the nitrile to produce intermediate **III**. With the assistance of acid, the nucleophilicity of the amide decreases which promotes the ketone to react with the nitrile leading to the formation of intermediate **IV**. Furthermore, the final product **3a** is obtained by the loss of a proton.



Scheme 2. Proposed mechanism.

Conclusions

In conclusion, we have developed a one-step synthesis for polysubstituted oxazoles from alkynylamide derivatives and alkynoates. Acid as an additive was essential to give a selective reaction in the case of amides while esters reacted selectively even in the absence of an acid. The obtained products might serve as versatile building blocks as they represent substructures of biologically active compounds. The methodology could be useful for the synthesis of biologically or pharmaceutically active compounds. Further studies to expand the synthetic scope of this reaction are ongoing in our laboratories.

Experimental Section

Alkynamide **1** (0.10mmol), [IPrAuCl]/$AgNTf_2$ (0.005 mmol), *N*-oxide (0.15 mmol), and MsOH (0.20mmol) were mixed in nitriles (1 mL). The resulting mixture was heated in a closed flask at 50°C for 12 h. Then the solvent was removed under vacuum to give a residue, which was purified by silica gel chromatography (petroleum ether/ethyl acetate = 8:1) to yield the corresponding products **3**.

Acknowledgments

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Keywords: alkynes • gold • carbene • oxazoles • *N*-oxides

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Gold Carbene

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Synthesis of Poly-Substituted Oxazoles by a Gold-Catalyzed Acid-Assisted Regioselective Cyclization

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