Gold-catalyzed tandem reactions of amide–aldehyde–alkyne coupling and cyclization-synthesis of 2,4,5-trisubstituted oxazoles†

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We report the first cationic gold(Ⅰ)-catalyzed one-pot reaction of amide, alkyne and aldehyde followed by cyclization, to successfully access highly substituted oxazoles derivatives in good yields. A single catalyst allows the occurring of this multi-step reaction atom- and step-economically, with water as the only theoretical side product.

Introduction

Oxazoles are important heterocyclic motifs present in a wide range of bioactive molecules,¹ natural products,² advanced materials,³ and ligand frameworks⁴ (Fig. 1). They exhibit highly variable properties and their structures are extremely diverse. As such, efficient synthetic methods accessing highly functionalized oxazoles are of great interest, yet remain challenging. Functionalization of pre-existing oxazole skeletons is one important strategy to access highly functionalized derivatives, but regioselectivity issues can limit such methods.⁵ More general synthetic pathways such as the Robinson–Gabriel⁶ and the van Leusen synthesis⁷ exploit a divergent strategy, consisting in the synthesis of acyclic oxazole precursors followed by a cyclisation.⁸ From an atom-economy perspective, such intramolecular cyclizations from acyclic precursors represent an attractive strategy for the preparation of substituted oxazoles. In the past decades, various transition metals have been reported to catalyze the cyclization of acetylenic precursors. Among these different methods, some use strong Brønsted acids or Lewis acid reagents which restrict the functional group tolerance.⁹ Thus, it is desirable to develop a simple approach to synthesize a broad variety of useful derivatives bearing diverse functionalities. Herein, we report a novel strategy for the multicomponent, one-pot synthesis of highly substituted oxazoles from simple amides, aldehydes and alkynes.

By furnishing complex products from simple building blocks in a minimum number of steps, multicomponent reactions represent efficient and rapid alternatives to traditional stepwise syntheses.¹⁰ One such reaction that has proven highly versatile and useful is the aldehyde–alkyne–amine coupling (A³ coupling) for the formation of propargylamines.¹¹ Since its discovery,¹² the multicomponent A³-coupling has been extensively developed by numerous authors, and shown great promise as a tool for the synthesis of complex molecules. In particular, its amenability to tandem transformations, especially cyclization, makes it an attractive technique for the synthesis of drug-like molecules. We envisioned that oxazoles might be accessed through such a tandem A³-coupling–cyclization, making use of amides instead of amines (Scheme 1). However, to the best of our knowledge, the formation of propargylamides via the coupling of amides, aldehydes and alkynes has never been reported before.¹³ Coinage transition-metal catalysts, such as gold, have shown excellent activity for the A³-coupling,¹⁴ and have been highly effective for the cyclization of acetylenic compounds.¹⁵ Thus, we envisioned that a judicious choice of gold catalyst might effectively catalyze both the A³-coupling and the tandem cyclization steps, providing access to highly functionalized oxazoles in a single pot.¹⁶

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† Electronic supplementary information (ESI) available: Experimental procedures and data for new compounds. See DOI: 10.1039/c5sc02933c

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Results and discussion

Inspired by our previous work on gold-catalyzed A₃ reactions, we began our investigation using aryl amide 1a, alkyl aldehyde 2a and phenylacetylene 3a as substrates (Table 1). While triphenylphosphinogold(i) chloride on its own did not generate any desired product, the addition of silver(i) triflate furnished product 4a in 30% yield (entry 2). The counter-anion of silver salt dramatically influenced the yields of the reaction, with triflate giving the best result (entries 2–5). When Ph₃PAuCl/AgOTf was used in toluene at 100 °C, a significant amount of 3-acylamidoketone 5a was detected, as well as its regioisomer 5b in a trace amount (<10%, see Scheme 2). To investigate the influence of water on the formation of this side-product, 4 Å molecular sieves were added (entry 6), which resulted in the complete inhibition of the desired reaction possibly due to gold poisoning from the molecular sieves. While it has been reported that a suitable acid activator (i.e. AgOTf) prevents the degradation of the gold catalyst, the addition of 50 mol% AgOTf was not beneficial to the reaction (entry 7). Although only a slight improvement of the reaction yield was observed at 130 °C, increasing the reaction temperature to 150 °C drastically accelerated the reaction, leading to complete conversion and excellent yield of the desired product (entries 8 and 9). In the absence of metal catalyst or additive, no desired product was observed (entry 10–12). The silver chloride formed during the catalyst preformation likewise showed no activity in the reaction (entry 12).

With the optimized conditions in hand, we investigated the reaction scope (Table 2). We were pleased to find that both aliphatic and aromatic aldehydes delivered the corresponding oxazoles in moderate to excellent yields.

Cyclohexanecarboxaldehyde 2a reacted with the coupling partners to afford the substituted oxazole 4a in a significantly better yield (95% isolated yield) than acyclic aliphatic aldehyde 2b (4b). Aromatic aldehydes with various functional groups were well tolerated and the corresponding products were isolated in good to excellent yields (4c and 4d). While aromatic aldehydes with both electron-withdrawing groups (EWG) and -donating groups (EDG) were well tolerated under the reaction conditions, aldehydes bearing EWGs such as chloride and ester substituents generally provide the desired product (4e and 4f). Aromatic amides possessing different EWGs and EDGs were also evaluated, and resulted in good reaction yields (4g–4n). It is noteworthy that even a boronic ester was tolerated under the reaction conditions, providing a handle for further functionalization via Suzuki coupling (4o). Impressively, our method can be further extended to the substrate bearing heterocyclic compound. The reaction of 4-chloronicotinamide afforded the oxazole product 4p in 62% yield. Fortunately, subjecting the substrate trisopropylsilyl acetyle 3q to the standard reaction conditions could

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**Table 1** Optimization of reaction conditions

<table>
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<tr>
<th>Entry</th>
<th>Catalyst (10 mol%)</th>
<th>Additive (20 mol%)</th>
<th>T (°C)</th>
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<th>4a</th>
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<tr>
<td>1</td>
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<tr>
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<td>—</td>
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<td>—</td>
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</table>

a Reaction conditions: benzamide (0.1 mmol), cyclohexanecarboxaldehyde (0.15 mmol), phenylacetylene (0.15 mmol), toluene (0.5 mL), under argon atmosphere. b 4 Å molecular sieves were added. c 50 mol% of additive was used. All reported yields were determined by 1H NMR spectroscopy of the crude reaction mixture using dibromomethane as internal standard. Yields in brackets are isolated.
Table 2 Amide, aldehyde, alkyne coupling – formation of 2,4,5 tri-substituted oxazoles[^6]

The coordination of cationic gold species to alkyne can further assist either the intramolecular 5-exo-dig cyclization (towards the formation of cyclic organogold complex V), or the formation of hydrated side products 5ₙ and 5ₚ.[^7] It is noteworthy that in our experiments, these hydrated side-products were produced exclusively at lower temperature. To determine the fate of these side-products, control experiments with and without gold catalyst were conducted under our optimized reaction conditions. We observed that compounds 5ₙ and 5ₚ did not lead to the formation of the corresponding oxazoles. Finally, succeeding the formation of V, the oxazoline intermediate VI is obtained via protodeauration, which further tautomerizes into the desired tri-substituted oxazole product 4.

Conclusions

In summary, we have successfully developed a highly efficient one-pot coupling method for the direct synthesis of tri-substituted oxazoles via an unprecedented amide, aldehyde and alkyne coupling (AA²). Using the tool of a single cationic gold(I) catalyst in one-pot to accomplish both the AA² and the cyclo-addition reactions, provides a novel atom-economical and practical alternative to construct important heterocyclic compounds, with water as the only side product. We further envisioned that this tandem reaction could be extended towards many other synthetically useful motifs and the expansion of the scope of simple starting material is currently undergoing in our laboratory.

Acknowledgements

We are grateful to the Canada Research Chair (Tier 1) foundation (to C.-J.L.), NSERC, CFI, and FQRNT (CCVC) for their support of our research.

Notes and references

[^6]: Conditions: amides (0.2 mmol), aldehydes (0.3 mmol), alkynes (0.3 mmol), Ph₃PAuCl (10 mol%), AgOTf (20 mol%), 0.5 mL of toluene, 6 h, under argon. Isolated yields reported.


17 For additional screening results, see ESI Tables S1–S4. For control experiments, see Schemes S1–S2†.

18 M. Kumar, G. B. Hammond and B. Xu, *Org. Lett.*, 2014, **16**, 3452. For influence of desiccants see Table S3 in ESI†.