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A two-step, one-pot procedure using acid chlorides and propargyl amines to form tri-substituted oxazoles via gold-catalyzed cyclization

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ABSTRACT

2,4-Disubstituted-5-methyl oxazoles were prepared from a 2-step, 1-pot procedure using acid chlorides and propargyl amines. These conditions lead to the formation of propargyl amides in situ followed by $AuCl_3$ catalyzed cyclization. We were interested in this novel formation of tri-substituted oxazoles and exploring the scope of the reaction using these mild conditions. A variety of aryl and aliphatic amides containing sensitive functional groups were tolerated giving good yields.

Oxazoles are important heterocycles that are abundant in natural products and pharmaceutically active compounds.[1] There are numerous protocols to form substituted oxazoles. A common method to prepare di-substituted oxazoles utilizes a multi-step synthesis which includes a Burgess dehydration and oxidation as shown in the synthesis of madumycin and hennoxazole natural products.[1a,b] Godfrey's tri-substituted oxazole for their dual PPARα/γ agonist program was prepared using the Dakin-West $POCl_3$ conditions.[1c] These are acidic reactions during which some functional groups may not be tolerated. Other classical methods to prepare oxazoles include strong acidic conditions (Fisher and Gabriel) or strong basic conditions (van Leusen).[2]

More recently, mercury, palladium, tungsten, and strong bases have been shown to cyclize *N*-propargylcarboxamides to oxazoles.[3] These conditions have limitations as some are toxic, air sensitive, and incompatible with some functional groups. For milder conditions, SiO_2, $CeCl_3$, $FeCl_3$, and Ru/Au metals are used to form substituted oxazoles.[4] More notably, Hashmi has pioneered more mild conditions using 5 mol % $AuCl_3$ to effectively cyclize terminal *N*-propargylcarboxamides to 5-methyl oxazoles in good yields through a proposed 5-*exo*-*dig* mechanism.[5]

Originally, we prepared 5-methyl oxazoles through cyclization of propargylic amide **1** using the Burgess reagent (Scheme 1, Route A). The Burgess cyclization conditions consistently afforded low yields. Therefore, we investigated and optimized $AuCl_3$-catalyzed cyclization of propargyl amide **3** (prepared via its corresponding carboxylic acid) giving improved yields (Scheme 1, Route B). The gold catalyzed cyclization route was encouraging and due to its operational ease we were interested in applying this method using acid chlorides to facilitate telescoping reaction conditions.

Although tri-substituted oxazoles containing aryl groups have been made by several methods, very few tri-alkyl substituted oxazoles have been prepared to date.[4] We became interested in Hashmi's gold-catalyzed method as it provided a good starting point to prepare a variety of tri-substituted oxazoles in a telescoping manner. We investigated a two-step, one-pot protocol starting from acid chlorides and propargyl amines forming the propargyl amides in situ. $AuCl_3$ would then catalyze the cyclization of the amides to form tri-substituted oxazoles. Based on the pi-acidity of gold and high tolerance of functional groups, this methodology was studied further.

A variety of acid chlorides with R_2 groups (aliphatic and aryl) were selected to probe the scope of the reaction (Scheme 2). Two propargyl amines were chosen due to their ease of availability, but-3-yn-2-amine and (*S*)-ethyl 3-aminopent-4-ynoate (R_1). The two-step, one-pot reaction procedures were straightforward. Propargyl amides were prepared in situ from acid chlorides and propargyl amines in the presence of triethylamine. After 30 min at ambient temperature, 5 mol % $AuCl_3$ was added and the reaction was stirred at 45 °C (unless indicated) under air. The reactions were performed in capped scintillation vials and reaction mixtures were filtered and purified to afford the cyclized products.[6]

The substrates in Scheme 2 gave moderate to good yields with little heat. Acid chlorides elaborated with heterocycles such as thiazoles or pyridines typically needed higher catalyst loading and

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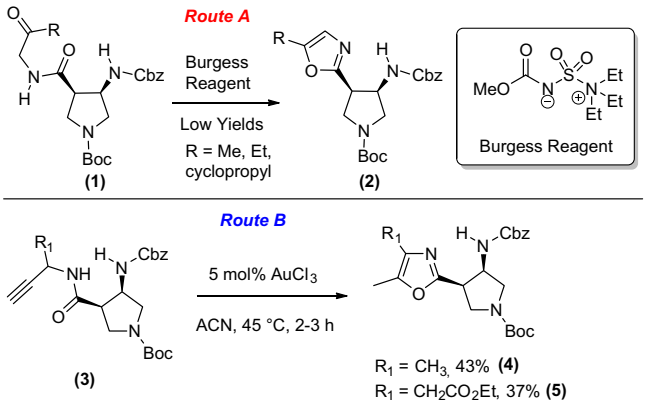
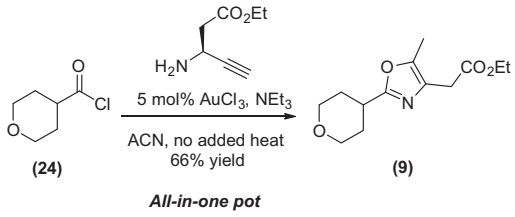
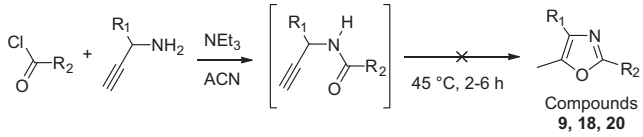


Scheme 1. Initial synthesis of di-and tri-substituted oxazoles using the Burgess reagent and catalytic $AuCl_3$.



Scheme 3. $AuCl_3$ introduced at the beginning of reaction.



Scheme 4. Absence of $AuCl_3$ catalyst did not give oxazoles.

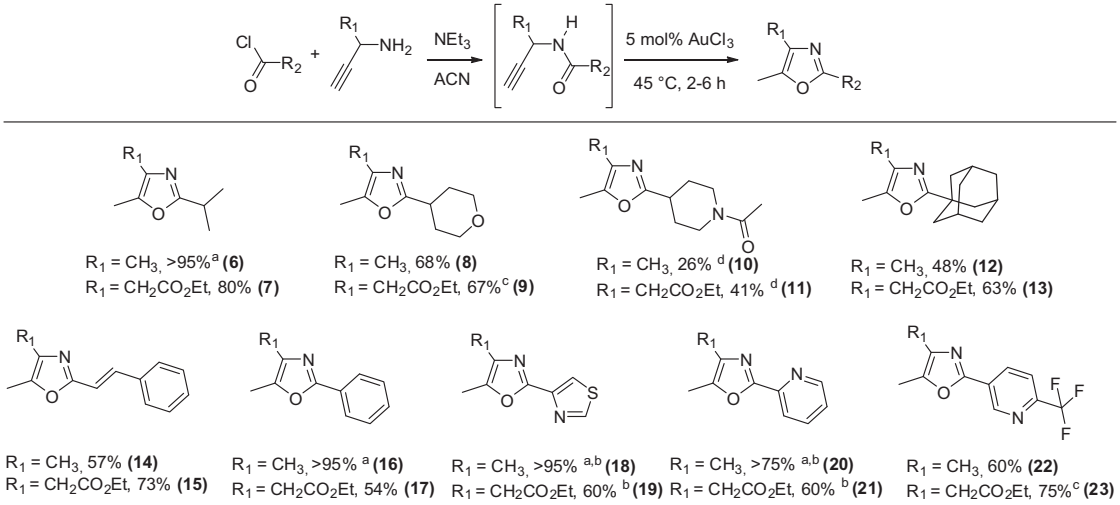
warmer conditions for full conversion (compounds **18**–**21**). In general, electron deficient systems gave lower yields,[7] however, the 2-trifluoromethoxy pyridine gave good yields under the standard conditions (compounds **22** and **23**). Aliphatic heterocycles were also shown to work under these conditions (compounds **8**–**11**). In addition, these conditions were robust on a ~3 mmol scale using a lower catalyst loading of 2 mol % which afforded comparable or better yields than at 0.5 mmol scale (compounds **9** and **23**). Overall, this two-step, one-pot, mild protocol displayed broad substrate scope along with good yields.

Although we typically added $AuCl_3$ after formation of the propargyl amide, the $AuCl_3$ can be introduced at the beginning of the reaction with acid chloride without any loss of yield. Due to the exotherm observed when adding triethylamine to the mixture of acid chloride and propargyl amine in ACN (generating the amide in situ), cyclization occurred without adding external heat giving comparable yields (Scheme 3).

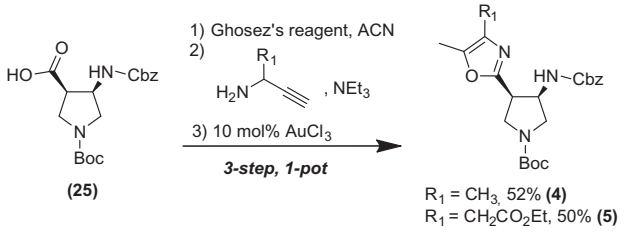
To ensure $AuCl_3$ was essential for the cyclization, control experiments were investigated without the catalyst. After prolonged heating of the aliphatic and aromatic systems without $AuCl_3$, cyclization to the oxazoles did not occur, forming only the intended propargyl amides (Scheme 4).

In drug discovery, multi-step telescoping reaction conditions with one purification are valuable in library productions as well as process scale chemistry. Generally, carboxylic acids are known to be more commercially available and stable than acid chlorides, therefore starting with these acids would be favorable. Based on our success with the two-step, one-pot protocol, we investigated a three-step, one-pot synthesis of tri-alkyl substituted oxazoles. Carboxylic acid **25** (the precursor to compound **3** prepared via a modified N,O-cyclization[8]) was selected for further studies as it contained both Boc and Cbz protecting groups, in which these labile groups would likely not survive under the harsh oxazole formation mentioned previously.[2,3]

To maintain neutral reaction conditions, Ghosez's reagent (tetramethyl-α-chloroenamine) was used to form the acid chlorides in situ from the carboxylic acid. Next propargyl amine and triethylamine were added, forming the propargyl amide in situ as well. Catalytic $AuCl_3$ was introduced and the reaction was heated at 45 °C for 2 h. A higher catalyst loading was needed to enhance the reaction rate. This three-step, one-pot procedure gave 50% yield of the desired product (Scheme 5, compound **5**) using (*S*)-ethyl 3-aminopent-4-ynoate on a 0.2 mmol scale. These conditions were robust on a 1.5 mmol scale which afforded a 52% yield (Scheme 5, compound **4**) using but-3-yn-2-amine.[9] This three-step, one-pot protocol gave better yields when compared to the



Scheme 2. Synthesis of tri-substituted oxazoles with $AuCl_3$ from a two-step, one-pot reaction using acid chlorides. Reagents and conditions: To the acid chloride (1 equiv) and propargyl amine (1.5 equiv) in 0.5 M ACN was added NET_3 (1.5 equiv). Stirred at room temperature for 30 min, then 5 mol % $AuCl_3$ was added and stirred at 45 °C, 2 h in scintillation vials. (a) Conversion of LCMS; (b) 4–6 h, 65 °C (with 30 mol % $AuCl_3$); (c) 2.4–3.4 mmol scale, 2 mol % $AuCl_3$ 2 h 45 °C; (d) purified by preparative HPLC.



Scheme 5. Three-step, one-pot synthesis gives tri-substituted oxazoles.

stepwise formation of the oxazole (Scheme 1, Route B) starting from compound **25**.

In summary, a robust and general gold-catalyzed cyclization methodology was developed to form tri-substituted oxazoles from propargylic amides prepared in situ from acid chlorides in a two-step, one-pot reaction procedure. Additionally, this was expanded to carboxylic acids in a three-step, one-pot protocol. These simple procedures are mild (45 °C–65 °C), atom-economical (2–30% catalyst loadings), air stable, and tolerate a broad range of functionalities. In addition, the described transformation does not require solvent exchanges nor isolation of intermediates and both procedures have only one simple purification to obtain tri-substituted oxazoles in good yields.

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6. *Representative procedure (Scheme 2, compound **8**)*: to a solution of tetrahydro-2*H*-pyran-4-carbonyl chloride (100 mg, 0.7 mmol) in ACN (1.5 mL, 0.5 M) was added but-3-yn-2-amine hydrochloride (107 mg, 1.01 mmol) followed by triethylamine (142 μL, 1.01 mmol). The reaction mixture was stirred at room temperature for 30 min. $AuCl_3$ (10 mg, 0.034 mmol) was added and the reaction mixture was stirred at 45 °C for 2–3 h until complete conversion to the product which was detected by LCMS. After filtration and concentration, the crude oil was purified directly on SiO_2 (12 g column eluted with 0–25% ethyl acetate-heptanes) to give a clear oil of 4,5-dimethyl-2-(tetrahydro-2*H*-pyran-4-yl)oxazole (83 mg, 68% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.02 (td, J = 3.60, 11.49 Hz, 2H), 3.51 (dt, J = 2.91, 11.18 Hz, 2H), 2.88–3.01 (m, 1H), 2.20 (s, 3H), 2.06 (d, J = 0.76 Hz, 3H), 1.87–1.99 (m, 4H). LCMS (APCI) m/z 182 $(M+1)^+$.
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9. *Representative procedure (Scheme 5, compound **4**)*: to a solution of (3*R*,4*R*)-4-(((benzyloxy)carbonyl) amino)-1-(*tert*-butoxycarbonyl)pyrrolidine-3-carboxylic acid (562 mg, 1.5 mmol) in ACN (4 mL, 0.25 M) was added Ghosez's reagent (tetramethyl-α-chloroenamine) (401 μL, 3 mmol) at 0 °C. The reaction was stirred for 1 h at room temperature. But-3-yn-2-amine hydrochloride (238 mgs, 2.25 mmol) and triethylamine (523 μL, 3.75 mmol) were added dropwise and stirred for 1 h. $AuCl_3$ (46 mg, 0.15 mmol) was added and the reaction mixture was stirred at 45 °C for 2–3 h until complete conversion to the product which was detected by LCMS. After filtration and concentration, the crude oil was purified directly on SiO_2 (25 g column eluted with 0–65% ethyl acetate-heptanes) to give a clear oil of (3*R*,4*R*)-*tert*-butyl 3-(((benzyloxy)carbonyl)amino)-4-(4,5-dimethyloxazol-2-yl)pyrrolidine-1-carboxylate (325 mg, 52% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.41 (m, 5H), 4.96–5.14 (m, 2H), 4.36–4.69 (m, 1H), 3.19–3.98 (m, 5H), 2.17 (s, 2H), 2.03 (s, 3H), 1.45 (s, 9H). LCMS (APCI) m/z 416 $(M+1)^+$.