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Synthesis of α-(4-Oxazolyl)amino Esters via Brønsted Acid Catalyzed Tandem Reaction

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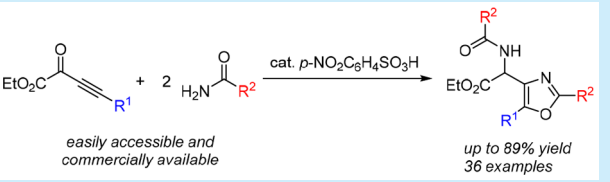
Supporting Information

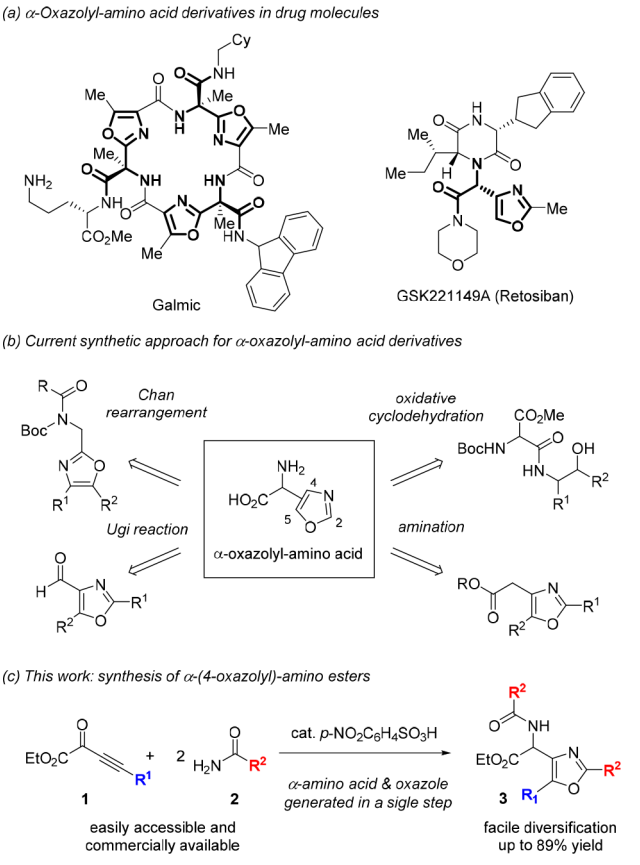
ABSTRACT: A one-step, Brønsted acid catalyzed tandem reaction for the synthesis of α-(4-oxazolyl)amino esters was developed. 4-Nitrobenzenesulfonic acid was found to be an efficient catalyst for the coupling of ethyl 2-oxobut-3-ynoates with amides to provide various α-(4-oxazolyl)amino esters. The experimental and X-ray crystallographic data suggest that a series of bond-forming reactions including imine formation, intermolecular Michael addition, and intramolecular Michael addition are involved to generate both the oxazole and amino acid functionalities.



Unnatural α-amino acids are an important class of building blocks continuously used in the synthesis of modified peptides to improve their bioactivity and metabolic stability.[1] Various α-amino acids with modified side chains are not recognized by enzymes, resulting in enhanced resistance toward enzyme-mediated biodegradation.[2] In addition, they have been widely used in bioconjugation chemistry, including in click or cross-coupling reactions for engineering proteins.[3] Given the biological importance of unnatural α-amino acids, there is strong interest in developing efficient synthetic methods for preparing them. The reported general synthesis of α-amino acids includes amination of carboxylic acids,[4] alkylation of glycine derivatives or oxazolones,[5] alkene hydrogenation,[6] and Strecker synthesis.[7]

In recent years, synthesis of unnatural α-amino acids with heteroaromatic groups has been developed to achieve various pharmacological and biological properties.[8] In particular, α-amino acids with oxazole side chains are found in drug molecules such as a nonpeptide galanin receptor agonist, galmic,[9] as well as an oxytocin receptor antagonist, GSK-221,149-A[10] (Scheme 1a). Because of the potent bioactivity of these structures, several strategies have been developed for their synthesis including Ugi reaction,[10,11] Chan rearrangement,[12] oxidative cyclodehydration,[13] and amination of α-oxazolyl esters[14] (Scheme 1b). However, the reported methods require a multistep procedure including preintroduction of the oxazole or the amino acid functionality. The structural variation of α-(oxazolyl)amino acids is thus quite limited. To address this challenge, the generation of oxazole and amino acid functional groups in a single step using commercially available or readily accessible starting materials is necessary to construct α-(oxazolyl)amino acid scaffolds with structural variation. Herein, we report a Brønsted acid catalyzed tandem reaction of ethyl 2-oxobut-3-ynoates **1**, synthesized through a one-step process from arylacetylene,[15] with commercially available amides **2** to access α-(4-oxazolyl)amino acid derivatives **3** (Scheme 1c). We believe that the development of a straightforward method to

Scheme 1. Bioactive Molecules and Their Synthesis



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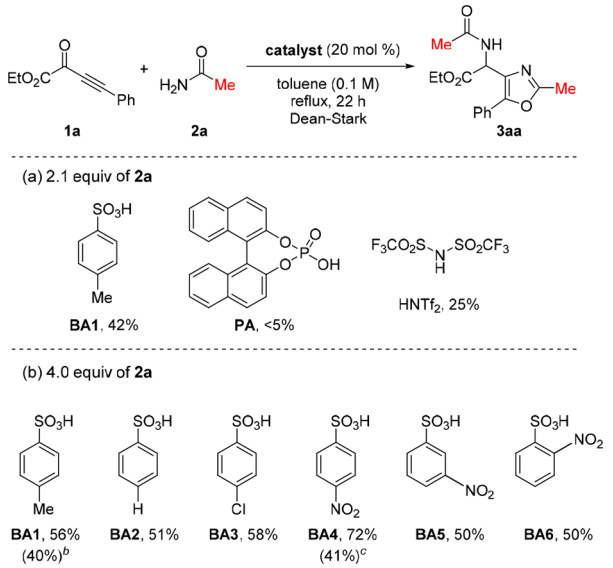
access α-(oxazolyl)amino acid derivatives will provide new opportunities for the discovery and development of biologically active compounds.

In our research on Rh-catalyzed conjugate additions of boronic acids,[16] we sought to prepare an unsaturated imino compound by the reaction of ethyl 2-oxo-4-phenylbut-3-ynoate **1a** and acetamide **2a**. In principle, the unsaturated carbonyl compound **1a** with two electrophilic sites could potentially undergo both 1,2- and 1,4-additions. According to previous studies using **1a** as an electrophile, we found that **1a** showed mostly 1,2-selectivity with a variety of nucleophiles.[17] Therefore, a reaction of **1a** with **2a** may provide a 1,2-adduct, leading to an imino ester. In our experiments, the reaction of **1a** with acetamide **2a** in the presence of catalytic *p*-toluenesulfonic acid **BA1** provided an unexpected product **3aa** in 42% yield (Scheme 2a). Because the product **3aa** contains two acetamide

Scheme 2. Catalyst Screening[a]



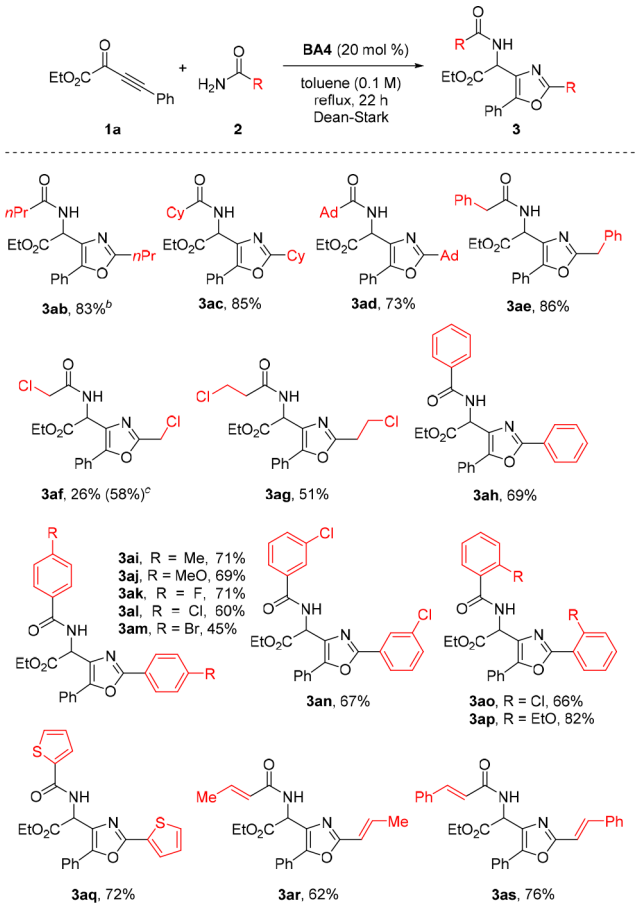
[a]Conditions: **1a** (0.5 mmol), **2a** (1.05 or 2.0 mmol), catalyst (20 mol %), and toluene (5.0 mL) were refluxed for 22 h with a Dean–Stark trap. Yield of isolated product. [b]Reaction was carried out without a Dean–Stark trap. [c]Reaction was carried out with **BA4** (10 mol %).

units, it appears that an additional addition reaction with **2a** takes place after the reaction between **1a** and **2a**. It is quite interesting that acetamide **2a** was selectively added to the β-position of the possible imino ester intermediate. Given the structural interest and potential of α-(4-oxazolyl)amino acids, we further explored this tandem reaction.

We optimized the reaction conditions by using various Brønsted acids. A phosphoric acid **PA** or $HNTf_2$ showed poor yields, indicating that significantly weaker or stronger Brønsted acids than **BA1** were inefficient (Scheme 2a).[18] As shown in Scheme 2b, the use of excess amount of **2a** and a Dean–Stark trap enhanced product yields. Based on these findings, we screened a variety of aryl sulfonic acids **BA2**–**BA6**. Notably, substituted sulfonic acids can be used in this process to increase the yields of **3aa**, where 4-nitrobenzenesulfonic acid **BA4** proved optimal, resulting in 72% yield. In addition, the reaction with low loading of **BA4** decreased the product yield.

Then we investigated the reaction scope of **1a** with a variety of amides **2** (Scheme 3). Aliphatic amides such as 1°, 2°, or 3° aliphatic amides **2b**–**d** and 2-phenylacetamide **2e** afforded

Scheme 3. Substrate Scope of Various Amides 2 with Ethyl 2-Oxo-4-phenylbut-3-ynoate 1a[a]



[a]Conditions: **1a** (0.5 mmol), **2** (2.0 mmol), **BA4** (20 mol %), and toluene (5.0 mL) were refluxed for 22 h with a Dean–Stark trap. [b]Yield of isolated product. [c]Reaction was carried out with **BA4** (100 mol %).

3ab–**ae** in good yields (73–86%). Although the reaction with 2-chloroacetamide **2f** provided the product **3af** in low yield (26%), the use of a stoichiometric amount of **BA4** increased the product yield to 58%. When 3-chloropropionamide **2g** was reacted with **1a** in the presence of 20 mol % of **BA4**, the desirable product **3ag** was obtained in 51% yield together with the dehalogenated product **3ag′** in 25% yield (see the Supporting Information).

The scope of aromatic amides was then explored. When aromatic amides with electronic and steric functional groups were reacted with **1a**, desirable α-amino esters **3ah**–**ap** were obtained in good yields (60–82%), but the reaction with 4-bromobenzamide **2m** gave the corresponding product **3am** with a somewhat decreased yield of 45%. In addition, the reactions with 2-thiophenecarboxamide **2q**, crotonamide **2r**, and cinnamamide **2s** gave the desired products **3aq**–**as** in good yields (62–76%).

The exact structure of the products was confirmed by the X-ray crystal structure analysis of **3aa** and **3ah** (Figure 1).[19] We demonstrated that this method is amenable to a gram-scale synthesis of amino ester **3ah** (2.28 g, 67% yield). Amino esters **3** were concisely deprotected to access unprotected amino acid derivatives with various oxazolyl side groups. Compound **3aa** was hydrolyzed to provide the *N*-acylamino acid and **3ah** was

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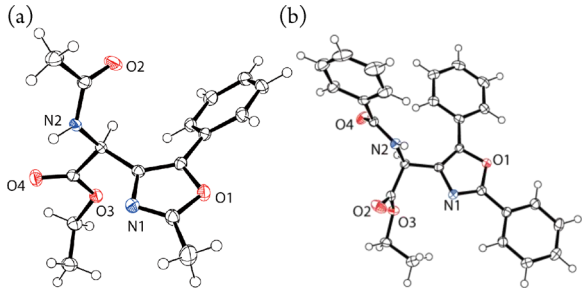
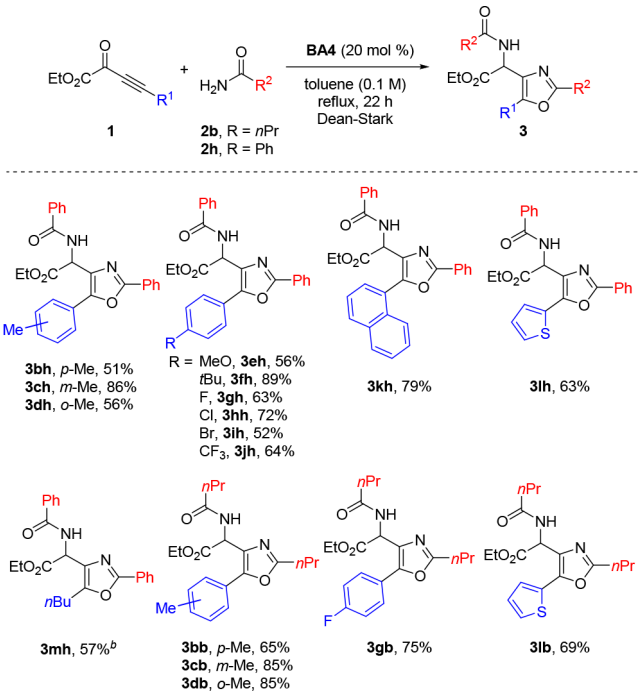


Figure 1. Crystal structures of (a) **3aa** and (b) **3ah**.

converted to the *N*-unprotected amino ester in 90 and 85% yields, respectively. In addition, DIBAL reduction of **3aa** provided the corresponding amino alcohols (see the SI).

Next, we evaluated the scope of ethyl 2-oxo-4-arylbut-3-ynoates **1**, as shown in Scheme 4. To examine the generality of

Scheme 4. Substrate Scope of Various Amides 2 with Ethyl 2-Oxo-4-arylbut-3-ynoate 1[a]

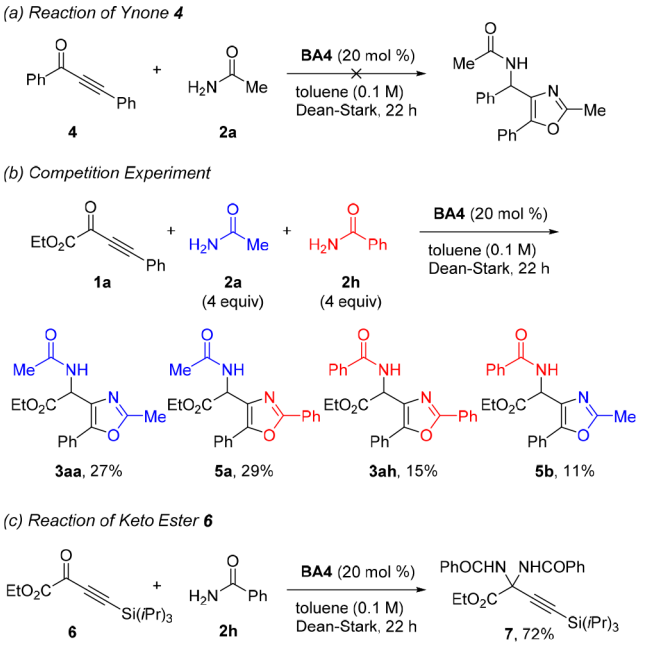


[a]Conditions: **1** (0.5 mmol), **2** (2.0 mmol), **BA4** (20 mol %), and toluene (5.0 mL) were refluxed for 22 h with a Dean–Stark trap. [b]Reaction was carried out with **1** (0.27 mmol), **2** (1.08 mmol), **BA4** (20 mol %), and toluene (2.7 mL).

the method, benzamide **2h** and butyramide **2b** were used for the reactions. First, reactions of **2h** with **1** substituted with electron-donating group such as Me, MeO, and *t*Bu groups as well as electron-withdrawing group such as F, Cl, Br, and CF_3 groups at the *para*, *meta*, and *ortho* positions provided desirable amino esters **3bh–jh** in moderate to good yields (51–89%). Good yields (79 and 63%) were observed for **1** containing either a 1-naphthyl (**1k**) or 2-thienyl group (**1l**). To our satisfaction, reaction of **1m** provided the desired amino ester **3mh** in 57% yield. Moreover, in reactions with butyramide **2b**, a variety of **1** afforded **3bb–3lb** in good to high yields (65–85%).

To gain insight into the reaction mechanism, we conducted several control experiments (Scheme 5). First, the ynone **4** did

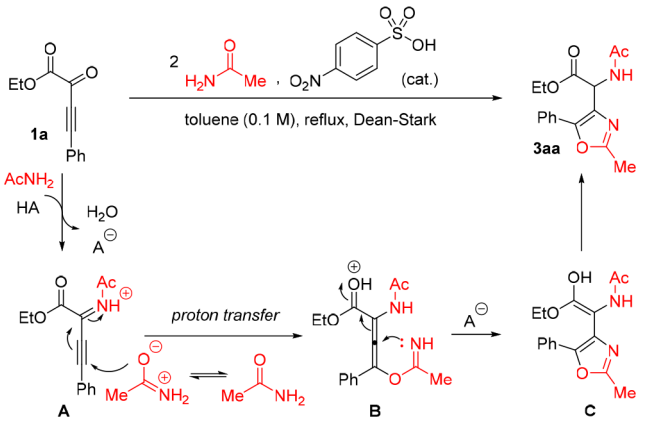
Scheme 5. Control Experiments



not react with acetamide **2a**, indicating the crucial role of the ester group for the desired reactivity (Scheme 5a). From the reaction of **1a** in the presence of both acetamide **2a** and benzamide **2h**, four compounds were obtained with 82% yield overall (Scheme 5b). The reactivity difference of the two amides **2a** and **2h** for 1,2-addition (**3aa** + **5a**/**3ah** + **5b** = 56%:26%) was more significant than that for 1,4-addition (**3aa** + **5b**/**3ah** + **5a** = 38%:44%). Therefore, the properties of the amides have more influence on the reactivity of 1,2-addition than 1,4-addition. In addition, reaction of **6** containing a bulky silyl group provided aminal product **7**, and thus, the 1,2 or 1,4-selectivity of the second amide addition can be controlled by the size of the keto ester substrates (Scheme 5c).

On the basis of the above observations, a proposed reaction mechanism is described in Scheme 6. On the basis of the previous reports[17] and our observations for the formation of aminal product **7** using **6** as an electrophile, substrate **1a** initially reacts with an amide to form the iminium ion **A** in the

Scheme 6. Proposed Mechanism



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presence of Brønsted acid catalysts. Intermediate **A** undergoes an intermolecular Michael addition of second amide and proton transfer to give the allene intermediate **B**. An intramolecular Michael addition of intermediate **B** then produces intermediate **C**, which undergoes tautomerization to form the desired product **3aa**.

In conclusion, a novel strategy to access a broad range of α-(4-oxazolyl)amino acids has been developed by a Brønsted acid catalyzed tandem reaction of ethyl 2-oxobut-3-ynoates with amides. We found that the catalytic amount (20 mol %) of 4-nitrobenzenesulfonic acid efficiently promoted the first imine formation between an ethyl 2-oxobut-3-ynoate and an amide, followed by inter- and intramolecular Michael addition with an amide to construct both the oxazole and amino acid functionalities. Starting with concisely accessible or commercially available materials, α-(4-oxazolyl)amino acids found in bioactive molecules were synthesized in a single step with 45–89% yields. We anticipate that α-(oxazolyl)amino acid derivatives will be used to discover new biologically active molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01212.

Experimental procedures, spectroscopic, and crystallographic details (PDF)

Accession Codes

CCDC 1835433–1835434 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(19) See the Supporting Information for X-ray data details.

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