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Article

Catalytic nucleophilic addition of terminal alkynes to α,β-unsaturated-γ-lactams

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ABSTRACT

A novel catalytic reaction has been developed for the nucleophilic addition of terminal alkynes to α,β-unsaturated-γ-lactams via a cyclic *N*-acyliminium ion intermediate. This simple reaction proceeds rapidly under mild conditions, and provided a practical approach for the synthesis of a wide range of 5-alkynyl-2-pyrrolidinones in moderate to good yields (45%–76%).

1. Introduction

Pyrrolidin-2-one is an important five-membered heterocycle that can be found in a wide range of natural products, bioactive molecules and polymers [1–5]. Among the various pyrrolidin-2-one derivatives reported in the literature, 5-alkynyl-2-pyrrolidinones have attracted considerable interest because this substructure is prevalent in several potential therapeutic compounds, including the ocular hypotensive agent **1** [6], α7 nicotinic acetylcholine receptor agonist **2** [7] and anticonvulsant and anti-inflammatory agent **3** [8]. This scaffold has also been found in many natural products, including the erythrina alkaloid **4** [9] and polycyclic alkaloid **5** [10] (Fig. 1).

In light of their importance, considerable research efforts have been directed toward the development of synthetic methods for the construction of 5-alkynyl-2-pyrrolidinones in both the racemic and scalemic sense. One of the most popular and well-documented strategies for the construction of 5-alkynyl-2-pyrrolidinones involves the nucleophilic attack of an alkynylide to a pyrrolidin-2-one substrate bearing a leaving group at its 5-position, as exemplified by the reaction of a terminal alkyne with 5-phenylthio-2-pyrrolidinone (Scheme 1, path A) [11,12]. However, this strategy leads to the formation of numerous unwanted by-products because it requires multiple steps and involves the use of hazardous solvents. Another approach for the synthesis of 5-alkynyl-2-pyrrolidinones involves the addition of alkynyl Grignard reagents to 5-(1H-benzotriazol-1-yl)-2-pyrrolidinones (Scheme 1, path B) [13]. However, this reaction has been limited by the lack of a diverse range of commercially available Grignard reagents, which must therefore be synthesized prior to the reaction. Furthermore, this reaction typically requires a long reaction time of 48 h. Last, the reaction of alkynes with 5-methoxy-2-pyrrolidinone has also been used as a strategy for the synthesis

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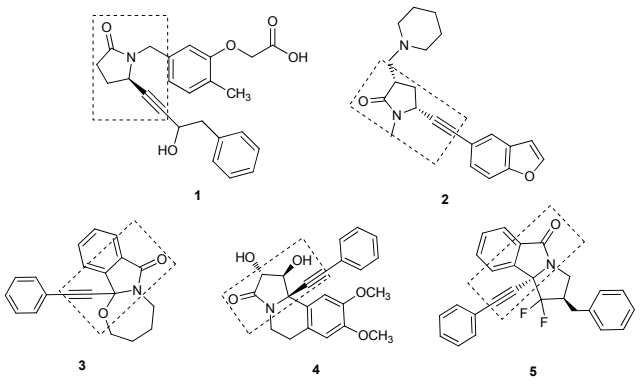
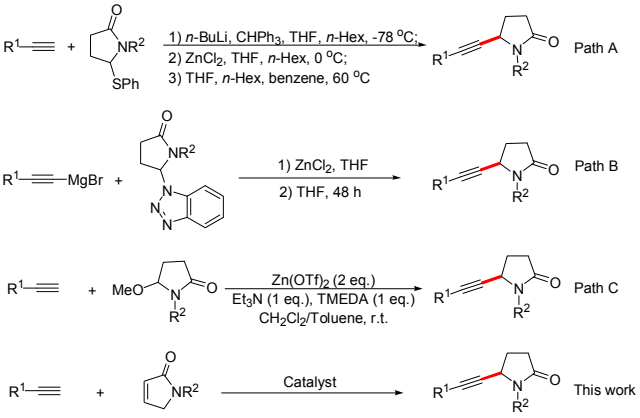


Fig. 1. Pharmaceutical and bioactive 5-alkynyl-2-pyrrolidinone derivatives.



Scheme 1. Synthetic methods of 5-alkynyl-2-pyrrolidinones.

of 5-alkynyl-2-pyrrolidinones. However, this reaction requires a super stoichiometric amount of Lewis acid and an organic base, making it inefficient (Scheme 1, path C) [14]. Consideration of these three strategies reveals that they all require multiple steps and generate numerous by-products. The development of an efficient, general and atom-economic strategy for the synthesis of 5-alkynyl-2-pyrrolidinones is therefore highly desirable. In 2002, Li and co-workers [15] developed a microwave-assisted stoichiometric CuBr-promoted nucleophilic addition reaction for the synthesis of 5-alkynyl-2-pyrrolidines from a terminal alkyne and 2-methoxypyrrolidines at 40–50 °C in water.

Herein, we describe a novel Brönsted acid-catalyzed reaction for the nucleophilic addition of terminal alkynes to α,β-unsaturated-γ-lactams to afford 5-alkynyl-2-pyrrolidinones via a cyclic *N*-acyliminium intermediate under mild conditions (Scheme 1) [16–23]. To the best of our knowledge, this work represents the most atom-economical synthesis of 5-alkenyl-2-pyrrolidinones reported to date via the nucleophilic addition reaction of terminal alkynes to α,β-unsaturated-γ-lactams.

Cyclic *N*-acyliminium ions are highly reactive electrophiles, which have been used extensively for the construction of nitrogen-containing ring systems via C–C bond-forming reactions [24–29]. For example, the research groups of Jacobsen and Dixon independently reported the successful use of this strategy for the installation of pyrrolidinone moieties at the C2- and C3-positions of an indole ring, respectively [30–32]. Previous work in our group has also focused on the use of *N*-acyliminium ion intermediates in organic synthesis [33]. We recently developed a novel and efficient reaction involving the nucleophilic addition of olefinic C–H bonds to α,β-unsaturated-γ-lactams (Scheme 2, path **I**) [23]. Based on the success of this study, it was envisaged that a Brönsted acid could also be used to promote the reaction of a terminal alkyne with an α,β-unsaturated-γ-lactam [33]. As shown in Scheme 2, the reaction of *N*-benzyl-α,β-unsaturated-γ-lactam with a Brönsted acid would lead to the formation of the corresponding *N*-acyliminium ion intermediate **A**. The subsequent nucleophilic addition reaction of terminal alkyne **2** to **A** would lead to the formation of the 5-alkynyl-2-pyrrolidinoneaddition product.

2. Experimental

2.1. General

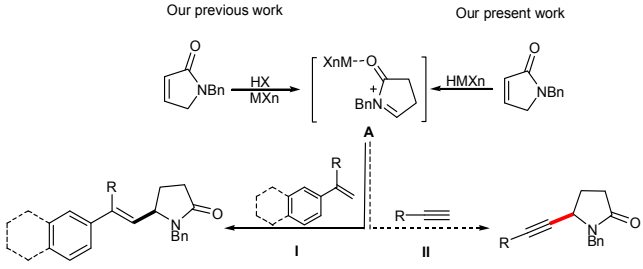
All of the non-aqueous reactions and manipulations conducted in the current study were performed under an atmosphere of N_2 using standard Schlenk techniques. All of the solvents used in the current study were dried using standard methods [34] and stored under N_2 prior to use. All of the reactions were monitored by thin-layer chromatography (TLC) using silica gel-coated plates.

NMR spectra were recorded on Bruker Avance III (400 MHz) spectrometers (Bruker). Chemical shifts (δ) were reported in parts per million down field of tetramethylsilane (TMS), which was used as an internal reference standard. Coupling constants (J) were reported in Hz together with their apparent peak multiplicities. High-resolution mass spectrometry (HRMS) analyses were recorded on a Bruker Micro TOF–QII mass instrument with electrospray ionization (ESI) in the positive ionization mode.

The *N*-benzyl-α,β-unsaturated-γ-lactam starting material **1** was synthesized according to procedures from the literature [35–37]. Phenylacetylene (**2a**) and 1-decyne (**2p**) were purchased from Energy Chemical. All of the other terminal alkynes **2b**–**2o** were synthesized using known methods [38–40].

2.2. General procedure for the nucleophilic addition reaction

A flame-dried Schlenk tube was charged with *N*-benzyl-α,β-unsaturated-γ-lactam **1** (0.5 mmol). The tube was then transferred to a glove box, where it was charged with Brönsted acid



Scheme 2. Synthetic strategies of 5-functionalized-2-pyrrolidinones.