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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%).

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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], $\alpha 7$ 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-(1*H*-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 Brønsted 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 Brønsted 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 Brønsted 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-pyrrolidinone addition 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 Brønsted acid

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

(0.05 mmol). The tube was removed from the glove box and attached to a Schlenk line, where it was charged with terminal alkyne **2** (1.5 mmol) and solvent (2.0 mL) via a syringe under a N₂ atmosphere. The tube was then sealed and the reaction mixture was stirred at 50 °C for 15 h. The reaction was cooled to room temperature and evaporated to dryness under vacuum to give a residue, which was purified by flash column chromatography over silica gel (EA:PE = 1:100 to 1:3, v/v) to afford the desired product **3**.

2.3. Experimental characterization data for some substrates and products

Some of the substrates and all of the products described in this study are novel compounds. The structures and purities of these compounds have therefore been fully characterized by NMR spectroscopy. Analytical data for these compounds have been listed below.

1-Benzyl-1H-pyrrol-2(5H)-one (1). This compound was prepared using the general procedure described above and purified by flash column chromatography to give a pale-yellow solid, 7.0 g, 20% yield. ¹H NMR (400 MHz, CDCl₃): δ 3.88 (t, *J* = 2.0 Hz, 2H), 4.64 (s, 2H), 6.23 (dt, *J*₁ = 2.0 Hz, *J*₂ = 6.0 Hz, 1H), 7.05 (dt, *J*₁ = 2.0 Hz, *J*₂ = 6.0 Hz, 1H), 7.23–7.35 (m, 5H); ¹³C NMR (100 MHz, CDCl₃): δ 46.0, 52.3, 127.6, 127.9, 128.0, 128.8, 137.3, 142.8, 171.4.

4-Ethynyl-1,2-dimethylbenzene (2e). This compound was prepared using the general procedure described above and purified by flash column chromatography to give a pale-yellow liquid, 0.9 g, 70% yield. ¹H NMR (400 MHz, CDCl₃): δ 2.23 (s, 3H), 2.25 (s, 3H), 3.00 (s, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 1H), 7.27 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 19.5, 19.8, 76.2, 84.0, 119.3, 129.6, 129.6, 133.2, 136.7, 137.8.

4-Ethynyl-1,2-dimethoxybenzene (2i). This compound was prepared using the general procedure described above and purified by flash column chromatography to give the white solid, 2.2 g, 70% yield. ¹H NMR (400 MHz, CDCl₃): δ 3.00 (s, 1H), 3.88 (s, 3H), 3.89 (s, 3H), 6.81 (d, *J* = 8.4 Hz, 1H), 6.99 (d, *J* = 2.0 Hz, 1H), 7.12 (dd, *J*₁ = 1.6 Hz, *J*₂ = 8.0 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 55.9, 75.7, 83.8, 110.9, 114.2, 114.7, 125.5, 148.6, 149.9.

4-Ethynyl-1,2,3-trimethoxybenzene (2j). This compound was prepared using the general procedure described above and purified by flash column chromatography to give a white solid, 1.7 g, 88% yield. ¹H NMR (400 MHz, CDCl₃): δ 3.04 (s, 1H), 3.86 (s, 9H), 6.73 (s, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 56.1, 61.0, 76.2, 83.7, 109.3, 117.0, 153.1.

1-Ethynyl-naphthalene (2m). This compound was prepared using the general procedure described above and purified by flash column chromatography to give an orange-red liquid, 2.1 g, 87% yield. ¹H NMR (400 MHz, CDCl₃): δ 3.47 (s, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.51 (t, *J* = 6.8 Hz, 1H), 7.58 (d, *J* = 7.2 Hz, 1H), 7.74 (d, *J* = 7.2 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 2H), 8.37 (d, *J* = 8.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 81.8, 82.0, 119.8, 125.1, 126.1, 126.5, 127.0, 128.3, 129.3, 131.3, 133.1, 133.5.

5-Ethynylbenzo[d][1,3]dioxole (2p). This compound was prepared using the general procedure described above and

purified by flash column chromatography to give a pale-yellow liquid, 1.1 g, 75% yield. ¹H NMR (400 MHz, CDCl₃): δ 2.97 (s, 1H), 5.97 (s, 2H), 6.75 (d, *J* = 8.4 Hz, 1H), 6.93 (d, *J* = 1.2 Hz, 1H), 7.03 (dd, *J*₁ = 1.2 Hz, *J*₂ = 8.0 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 75.6, 83.6, 101.4, 108.4, 112.0, 115.3, 126.9, 147.4, 148.3.

1-Benzyl-5-(phenylethynyl)pyrrolidin-2-one (3a). This compound was prepared according to the general procedure described above and purified by flash column chromatography to give a colorless oil, 82 mg, 60% yield. ¹H NMR (400 MHz, CDCl₃): δ 2.16–2.24 (m, 1H), 2.31–2.40 (m, 1H), 2.42–2.50 (m, 1H), 2.59–2.71 (m, 1H), 4.15 (d, *J* = 14.8 Hz, 1H), 4.36 (dd, *J*₁ = 5.2 Hz, *J*₂ = 8.0 Hz, 1H), 5.12 (d, *J* = 14.8 Hz, 1H), 7.27–7.37 (m, 8H), 7.40–7.42 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 26.2, 30.1, 44.7, 49.1, 85.7, 86.4, 122.2, 127.7, 128.4, 128.6, 128.7, 128.9, 131.7, 136.3, 174.1; HRMS (ESI): *m/z* 298.1202 for [M+Na]⁺, Calcd. for C₁₉H₁₇NONa = 298.1202.

1-Benzyl-5-(2-tolylethynyl)pyrrolidin-2-one (3b). This compound was prepared using the general procedure described above and purified by flash column chromatography to give a colorless oil, 73 mg, 51% yield. ¹H NMR (400 MHz, CDCl₃): δ 2.17–2.25 (m, 1H), 2.33–2.40 (m, 1H), 2.42 (s, 3H), 2.45–2.51 (m, 1H), 2.60–2.68 (m, 1H), 4.14 (d, *J* = 14.4 Hz, 1H), 4.40 (dd, *J*₁ = 5.2 Hz, *J*₂ = 8.0 Hz, 1H), 5.17 (d, *J* = 14.4 Hz, 1H), 7.13–7.39 (m, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 20.8, 26.4, 30.1, 44.7, 49.2, 84.5, 90.3, 122.0, 125.7, 127.7, 128.6, 128.7, 129.5, 132.1, 136.2, 140.2, 174.1; HRMS (ESI): *m/z* 290.1545 for [M+H]⁺, Calcd. for C₂₀H₂₀NO = 290.1539.

1-Benzyl-5-(3-tolylethynyl)pyrrolidin-2-one (3c). This compound was prepared using the general procedure described above and purified by flash column chromatography to give a colorless oil, 77 mg, 53% yield. ¹H NMR (400 MHz, CDCl₃): δ 2.15–2.23 (m, 1H), 2.30–2.39 (m, 4H), 2.42–2.50 (m, 1H), 2.59–2.67 (m, 1H), 4.15 (d, *J* = 14.8 Hz, 1H), 4.35 (dd, *J*₁ = 5.2 Hz, *J*₂ = 8.0 Hz, 1H), 5.12 (d, *J* = 14.8 Hz, 1H), 7.15–7.18 (m, 1H), 7.22 (d, *J* = 5.2 Hz, 3H), 7.29–7.34 (m, 5H); ¹³C NMR (100 MHz, CDCl₃): δ 21.2, 26.2, 30.1, 44.7, 49.1, 85.8, 86.0, 122.0, 127.6, 128.3, 128.6, 128.7, 128.8, 129.6, 132.3, 136.3, 138.1, 174.1; HRMS (ESI): *m/z* 312.1373 for [M+Na]⁺, Calcd. for C₂₀H₁₉NONa = 312.1359.

1-Benzyl-5-(4-tolylethynyl)pyrrolidin-2-one (3d). This compound was prepared using the general procedure described above and purified by flash column chromatography to give a colorless oil, 72 mg, 50% yield. ¹H NMR (400 MHz, CDCl₃): δ 2.14–2.22 (m, 1H), 2.29–2.38 (m, 4H), 2.41–2.49 (m, 1H), 2.59–2.70 (m, 1H), 4.15 (d, *J* = 14.4 Hz, 1H), 4.35 (dd, *J*₁ = 5.2 Hz, *J*₂ = 8.0 Hz, 1H), 5.12 (d, *J* = 14.4 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.26–7.33 (m, 7H); ¹³C NMR (100 MHz, CDCl₃): δ 21.5, 26.2, 30.1, 44.7, 49.1, 85.7, 85.8, 119.1, 127.6, 128.6, 128.7, 129.1, 131.6, 136.3, 138.9, 174.1; HRMS (ESI): *m/z* 312.1355 for [M+Na]⁺, Calcd. for C₂₀H₁₉NONa = 312.1359.

1-Benzyl-5-((3,4-dimethylphenyl)ethynyl)pyrrolidin-2-one (3e). This compound was prepared using the general procedure described above and purified by flash column chromatography to give a colorless oil, 78 mg, 52% yield. ¹H NMR (400 MHz, CDCl₃): δ 2.14–2.22 (m, 1H), 2.25 (s, 3H), 2.27 (s, 3H), 2.29–2.38 (m, 1H), 2.41–2.49 (m, 1H), 2.58–2.66 (m, 1H), 4.14

(d, $J = 14.4$ Hz, 1H), 4.34 (dd, $J_1 = 5.2$ Hz, $J_2 = 8.0$ Hz, 1H), 5.11 (d, $J = 14.4$ Hz, 1H), 7.10 (d, $J = 7.6$ Hz, 1H), 7.14–7.18 (m, 2H), 7.27–7.36 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 19.8, 26.2, 28.2, 30.1, 44.7, 49.2, 85.4, 86.0, 119.4, 127.6, 128.6, 128.7, 129.1, 129.7, 132.8, 136.4, 136.8, 137.7, 174.2; HRMS (ESI): m/z 326.1507 for $[\text{M}+\text{H}]^+$, Calcd. for $\text{C}_{21}\text{H}_{21}\text{NO}_2\text{Na} = 326.1515$.

1-Benzyl-5-((2-methoxyphenyl)ethynyl)pyrrolidin-2-one (**3f**). This compound was prepared using the general procedure described above and purified by flash column chromatography to give a colorless oil, 85 mg, 55% yield. ^1H NMR (400 MHz, CDCl_3): δ 2.17–2.26 (m, 1H), 2.31–2.38 (m, 1H), 2.40–2.49 (m, 1H), 2.58–2.71 (m, 1H), 3.89 (s, 3H), 4.19 (d, $J = 14.8$ Hz, 1H), 4.39 (dd, $J_1 = 5.6$ Hz, $J_2 = 8.0$ Hz, 1H), 5.16 (d, $J = 14.8$ Hz, 1H), 6.88–6.94 (m, 2H), 7.28–7.39 (m, 7H); ^{13}C NMR (100 MHz, CDCl_3): δ 26.1, 30.2, 44.5, 49.3, 55.7, 82.2, 90.4, 110.7, 111.4, 120.4, 127.6, 128.6, 128.8, 130.1, 133.5, 136.4, 160.3, 174.0; HRMS (ESI): m/z 328.1294 for $[\text{M}+\text{Na}]^+$, Calcd. for $\text{C}_{20}\text{H}_{19}\text{NO}_2\text{Na} = 328.1308$.

1-Benzyl-5-((4-methoxyphenyl)ethynyl)pyrrolidin-2-one (**3g**). This compound was prepared using the general procedure described above and purified by flash column chromatography to give a colorless oil, 79 mg, 52% yield. ^1H NMR (400 MHz, CDCl_3): δ 2.14–2.22 (m, 1H), 2.29–2.38 (m, 1H), 2.41–2.49 (m, 1H), 2.58–2.66 (m, 1H), 3.82 (s, 3H), 4.15 (d, $J = 14.8$ Hz, 1H), 4.35 (dd, $J_1 = 5.2$ Hz, $J_2 = 8.0$ Hz, 1H), 5.11 (d, $J = 14.8$ Hz, 1H), 6.86 (d, $J = 8.8$ Hz, 2H), 7.27–7.36 (m, 7H); ^{13}C NMR (100 MHz, CDCl_3): δ 26.3, 30.1, 44.7, 49.2, 55.3, 85.0, 85.6, 114.0, 114.3, 127.6, 128.6, 128.7, 133.2, 136.4, 159.9, 174.1; HRMS (ESI): m/z 328.1305 for $[\text{M}+\text{Na}]^+$, Calcd. for $\text{C}_{20}\text{H}_{19}\text{NO}_2\text{Na} = 328.1308$.

1-Benzyl-5-((3,4-dimethoxyphenyl)ethynyl)pyrrolidin-2-one (**3h**). This compound was prepared using the general procedure described above and purified by flash column chromatography to give a colorless oil, 75 mg, 45% yield. ^1H NMR (400 MHz, CDCl_3): δ 2.15–2.23 (m, 1H), 2.30–2.40 (m, 1H), 2.42–2.50 (m, 1H), 2.60–2.71 (m, 1H), 3.89 (s, 3H), 3.90 (s, 3H), 4.17 (d, $J = 14.8$ Hz, 1H), 4.36 (dd, $J_1 = 5.2$ Hz, $J_2 = 8.0$ Hz, 1H), 5.10 (d, $J = 14.8$ Hz, 1H), 6.82 (d, $J = 8.4$ Hz, 1H), 6.88 (d, $J = 2.0$ Hz, 1H), 7.03 (dd, $J_1 = 1.6$ Hz, $J_2 = 8.0$ Hz, 1H), 7.27–7.36 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 26.3, 30.1, 44.7, 49.2, 55.9, 56.0, 84.9, 85.6, 111.0, 114.3, 125.1, 127.6, 128.5, 128.7, 136.4, 148.7, 149.8, 174.1; HRMS (ESI): m/z 358.1509 for $[\text{M}+\text{Na}]^+$, Calcd. for $\text{C}_{21}\text{H}_{21}\text{NO}_3\text{Na} = 358.1514$.

1-Benzyl-5-((3,4,5-trimethoxyphenyl)ethynyl)pyrrolidin-2-one (**3i**). This compound was prepared using the general procedure described above and purified by flash column chromatography to give a colorless oil, 91 mg, 50% yield. ^1H NMR (400 MHz, CDCl_3): δ 2.16–2.24 (m, 1H), 2.31–2.41 (m, 1H), 2.43–2.51 (m, 1H), 2.61–2.71 (m, 1H), 3.87 (s, 9H), 4.18 (d, $J = 14.4$ Hz, 1H), 4.37 (dd, $J_1 = 4.8$ Hz, $J_2 = 8.0$ Hz, 1H), 5.09 (d, $J = 14.4$ Hz, 1H), 6.62 (s, 2H), 7.27–7.36 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 26.2, 30.1, 44.8, 49.2, 56.2, 61.0, 85.5, 85.6, 109.0, 117.1, 127.6, 128.5, 128.7, 136.4, 139.2, 153.1, 174.1; HRMS (ESI): m/z 388.1517 for $[\text{M}+\text{Na}]^+$, Calcd. for $\text{C}_{22}\text{H}_{23}\text{NO}_4\text{Na} = 388.1519$.

1-Benzyl-5-((4-fluorophenyl)ethynyl)pyrrolidin-2-one (**3j**). This compound was prepared using the general procedure

described above and purified by flash column chromatography to give a colorless oil, 89 mg, 60% yield. ^1H NMR (400 MHz, CDCl_3): δ 2.14–2.23 (m, 1H), 2.31–2.40 (m, 1H), 2.42–2.50 (m, 1H), 2.59–2.71 (m, 1H), 4.15 (d, $J = 14.8$ Hz, 1H), 4.35 (dd, $J_1 = 5.2$ Hz, $J_2 = 8.0$ Hz, 1H), 5.10 (d, $J = 14.8$ Hz, 1H), 7.00–7.05 (m, 2H), 7.26–7.41 (m, 7H); ^{13}C NMR (100 MHz, CDCl_3): δ 26.1, 30.0, 44.8, 49.1, 84.6, 86.1, 115.6, 127.7, 128.5, 128.7, 133.6, 133.7, 136.3, 161.5, 174.1; ^{19}F NMR (376 MHz, CDCl_3): δ –110.2; HRMS (ESI): m/z 316.1106 for $[\text{M}+\text{Na}]^+$, Calcd. for $\text{C}_{19}\text{H}_{16}\text{FNONa} = 316.1108$.

1-Benzyl-5-(naphthalen-1-ylethynyl)pyrrolidin-2-one (**3l**). This compound was prepared using the general procedure described above and purified by flash column chromatography to give a colorless oil, 97 mg, 60% yield. ^1H NMR (400 MHz, CDCl_3): δ 2.29–2.35 (m, 1H), 2.42–2.49 (m, 1H), 2.52–2.56 (m, 1H), 2.67–2.75 (m, 1H), 4.24 (d, $J = 14.8$ Hz, 1H), 4.52 (dd, $J_1 = 4.8$ Hz, $J_2 = 7.6$ Hz, 1H), 5.21 (d, $J = 14.8$ Hz, 1H), 7.30–7.38 (m, 5H), 7.46 (t, $J = 8.0$ Hz, 1H), 7.52–7.61 (m, 2H), 7.66 (dd, $J_1 = 0.8$ Hz, $J_2 = 7.2$ Hz, 1H), 7.88 (dd, $J_1 = 3.6$ Hz, $J_2 = 7.2$ Hz, 2H), 8.21 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 26.4, 30.2, 44.8, 49.3, 83.8, 91.3, 119.8, 125.2, 125.8, 126.5, 127.0, 127.7, 128.4, 128.6, 128.8, 129.2, 130.8, 133.2, 133.2, 136.3, 174.1; HRMS (ESI): m/z 348.1355 for $[\text{M}+\text{Na}]^+$, Calcd. for $\text{C}_{23}\text{H}_{19}\text{NONa} = 348.1359$.

1-Benzyl-5-(naphthalen-2-ylethynyl)pyrrolidin-2-one (**3m**). This compound was prepared using the general procedure described above and purified by flash column chromatography to give a colorless oil, 79 mg, 49% yield. ^1H NMR (400 MHz, CDCl_3): δ 2.20–2.28 (m, 1H), 2.34–2.42 (m, 1H), 2.43–2.52 (m, 1H), 2.63–2.71 (m, 1H), 4.22 (d, $J = 14.8$ Hz, 1H), 4.42 (dd, $J_1 = 5.2$ Hz, $J_2 = 8.0$ Hz, 1H), 5.14 (d, $J = 14.8$ Hz, 1H), 7.28–7.39 (m, 5H), 7.45 (dd, $J_1 = 1.6$ Hz, $J_2 = 8.4$ Hz, 1H), 7.49–7.53 (m, 2H), 7.78–7.84 (m, 3H), 7.92 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 26.2, 30.1, 44.8, 49.2, 86.0, 86.7, 119.4, 126.7, 126.9, 127.7, 127.8, 127.8, 128.1, 128.2, 128.6, 128.7, 131.8, 132.9, 133.0, 136.3, 174.2; HRMS (ESI): m/z 348.1350 for $[\text{M}+\text{Na}]^+$, Calcd. for $\text{C}_{23}\text{H}_{19}\text{NONa} = 348.1359$.

1-Benzyl-5-(thiophen-2-ylethynyl)pyrrolidin-2-one (**3n**). This compound was prepared using the general procedure described above and purified by flash column chromatography to give a colorless oil, 106 mg, 76% yield. ^1H NMR (400 MHz, CDCl_3): δ 2.14–2.22 (m, 1H), 2.29–2.38 (m, 1H), 2.41–2.49 (m, 1H), 2.58–2.69 (m, 1H), 4.12 (d, $J = 14.8$ Hz, 1H), 4.36 (dd, $J_1 = 5.2$ Hz, $J_2 = 8.0$ Hz, 1H), 5.11 (d, $J = 14.8$ Hz, 1H), 6.99 (dd, $J_1 = 3.6$ Hz, $J_2 = 5.2$ Hz, 1H), 7.20 (dd, $J_1 = 0.8$ Hz, $J_2 = 3.6$ Hz, 1H), 7.26–7.36 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 26.0, 30.0, 44.8, 49.2, 79.0, 90.3, 122.0, 127.0, 127.6, 127.7, 128.6, 128.7, 132.5, 136.2, 174.0; HRMS (ESI): m/z 304.0764 for $[\text{M}+\text{Na}]^+$, Calcd. for $\text{C}_{17}\text{H}_{15}\text{NOSNa} = 304.0767$.

5-(Benzo[d][1,3]dioxol-5-ylethynyl)-1-benzylpyrrolidin-2-one (**3o**). This compound was prepared using the general procedure described above and purified by flash column chromatography to give a colorless oil, 76 mg, 48% yield. ^1H NMR (400 MHz, CDCl_3): δ 2.13–2.21 (m, 1H), 2.29–2.38 (m, 1H), 2.41–2.49 (m, 1H), 2.58–2.66 (m, 1H), 4.14 (d, $J = 14.4$ Hz, 1H), 4.33 (dd, $J_1 = 5.2$ Hz, $J_2 = 8.0$ Hz, 1H), 5.10 (d, $J = 14.4$ Hz, 1H), 5.99 (s, 2H), 6.77 (d, $J = 8.0$ Hz, 1H), 6.84 (d, $J = 1.6$ Hz, 1H), 6.94 (dd, $J_1 = 1.6$

Hz, $J_2 = 8.0$ Hz, 1H), 7.28–7.36 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 26.2, 30.1, 44.7, 49.1, 84.7, 85.5, 101.4, 108.5, 111.7, 115.3, 126.4, 127.6, 128.5, 128.7, 136.3, 147.5, 148.2, 174.1; HRMS (ESI): m/z 342.1097 for $[\text{M}+\text{Na}]^+$, Calcd. for $\text{C}_{20}\text{H}_{17}\text{NO}_3\text{Na}$ = 342.1101.

3. Results and discussion

3.1. Optimization of reaction conditions

We initially investigated the reaction of *N*-benzyl- α,β -unsaturated- γ -lactam (**1**) with phenylacetylene (**2a**) in the presence of catalytic quantities of Lewis and Brønsted acids to allow for the optimization of the reaction conditions (Table 1). Pleasingly, when $\text{Zn}(\text{OTf})_2$ and TsOH were used as the Lewis and Brønsted acid catalysts, respectively, the reaction proceeded successfully at 50 °C in TTCE to deliver the desired product **3a** in 33% yield (Table 1, entry 1). Encouraged by this result, we screened an extensive series of Lewis acid catalysts and found that $\text{Y}(\text{OTf})_3 \cdot x\text{H}_2\text{O}$ and $\text{Al}(\text{OTf})_3$ could also catalyze this transformation to afford the desired product **3a** in 45% and 52% yields, respectively (Table 1, entries 2 and 3). It is noteworthy that only trace quantities of the desired product were obtained

Table 1

Optimization of the reaction conditions.

Entry	Lewis acid	Brønsted acid	Solvent	T (°C)	Isolated yield (%)
1	$\text{Zn}(\text{OTf})_2$	TsOH	TTCE	50	33
2	$\text{Y}(\text{OTf})_3 \cdot x\text{H}_2\text{O}$	TsOH	TTCE	50	45
3	$\text{Al}(\text{OTf})_3$	TsOH	TTCE	50	52
4	None	TsOH	TTCE	50	Trace
5	$\text{Al}(\text{OTf})_3$	$\text{HO}_2\text{CCO}_2\text{H}$	TTCE	50	45
6	$\text{Al}(\text{OTf})_3$	TFA	TTCE	50	45
7	$\text{Al}(\text{OTf})_3$	$\text{NH}_2\text{SO}_3\text{H}$	TTCE	50	32
8	$\text{Al}(\text{OTf})_3$	PivOH	TTCE	50	25
9	$\text{Al}(\text{OTf})_3$	$\text{HAuCl}_4 \cdot 4\text{H}_2\text{O}$	TTCE	50	54
10	$\text{Al}(\text{OTf})_3$	None	TTCE	50	Trace
11	None	$\text{HAuCl}_4 \cdot 4\text{H}_2\text{O}$	TTCE	50	55
12	None	$\text{HAuCl}_4 \cdot 4\text{H}_2\text{O}$	CH_3NO_2	50	28
13	None	$\text{HAuCl}_4 \cdot 4\text{H}_2\text{O}$	Toluene	50	19
14	None	$\text{HAuCl}_4 \cdot 4\text{H}_2\text{O}$	DCE	50	31
15	None	$\text{HAuCl}_4 \cdot 4\text{H}_2\text{O}$	CH_2Cl_2	50	51
16	None	$\text{HAuCl}_4 \cdot 4\text{H}_2\text{O}$	CHCl_3	50	47
17	None	$\text{HAuCl}_4 \cdot 4\text{H}_2\text{O}$	TTCE	40	45
18	None	$\text{HAuCl}_4 \cdot 4\text{H}_2\text{O}$	TTCE	60	55
19 ^a	None	$\text{HAuCl}_4 \cdot 4\text{H}_2\text{O}$	TTCE	50	60
20 ^b	None	$\text{HAuCl}_4 \cdot 4\text{H}_2\text{O}$	TTCE	50	58
21	None	None	TTCE	50	NR

Reaction conditions: **1** (0.4 mmol), **2a** (1.2 mmol), Lewis acid (5 mol%) and Brønsted acid (5 mol%) in solvent (2.0 mL) under N_2 at 50 °C for 6 h. ^a $\text{HAuCl}_4 \cdot 4\text{H}_2\text{O}$ (10 mol%) was used for 15 h. ^b $\text{HAuCl}_4 \cdot 4\text{H}_2\text{O}$ (20 mol%) was used for 15 h.

TsOH = *p*-Toluenesulfonic acid; TFA = Trifluoroacetic acid; PivOH = 2,2-Dimethylpropanoate; TTCE = 1,1,2,2-Tetrachloroethane; DCE = 1,2-Dichloroethane.

when TsOH was used as a single agent catalyst (Table 1, entry 4). We then proceeded to investigate the effect of several different Brønsted acids, and the results revealed that $\text{HAuCl}_4 \cdot 4\text{H}_2\text{O}$ afforded the best yield of all of the Brønsted acids tested in the current study (Table 1, entries 5–9). When $\text{Al}(\text{OTf})_3$ was used in the absence of a Brønsted acid catalyst, the reaction provided only trace amounts of the desired product (Table 1, entry 10). Pleasingly, however, the use of $\text{HAuCl}_4 \cdot 4\text{H}_2\text{O}$ in the absence of a Lewis acid catalyst afforded **3a** in 55% yield (Table 1, entry 11). We then proceeded to investigate the effect of the solvent on the outcome of the reaction. The results revealed that the reaction proceeded more efficiently in polar solvents than it did in non-polar solvents, with TTCE providing the best results of all of the solvents tested in the current study (Table 1, entries 11–16). The temperature of the reaction was also evaluated but the results revealed that increasing or decreasing the temperature had no discernible impact on the yield (Table 1, entries 17 and 18). It is noteworthy that the desired product **3a** was produced in 60% yield when the amount of $\text{HAuCl}_4 \cdot 4\text{H}_2\text{O}$ was increased to 10 mol% and the reaction time was extended to 15 h (Table 1, entry 19). However, further increasing the charge of $\text{HAuCl}_4 \cdot 4\text{H}_2\text{O}$ to 10 mol% did not lead to a further increase in the yield (Table 1, entry 20). Finally, we conducted a control reaction containing no Lewis acid or Brønsted acid catalyst, which gave only trace quantities of the desired product **3a**, thereby highlighting the importance of the catalyst to the success of this reaction (Table 1, entry 21).

3.2. Substrate scope of the terminal alkyne

With the optimized reaction conditions in hand, we proceeded to evaluate the scope of this nucleophilic addition reaction using a variety of different substituted terminal alkynes (Table 2). In general, terminal alkynes bearing an electron-donating group on their aryl ring exhibited high reactivity to give the corresponding products in moderate to good yields. For example, *o*-, *m*- and *p*-tolylethyne all reacted smoothly under the optimized conditions to afford the corresponding 5-alkynyl-2-pyrrolidinones **3b**, **3c**, and **3d**, respectively, in moderate yields (Table 2, entries 2–4). The *o*- and *p*-methoxyl-1-ethynylbenzene substrates **2f** and **2g** also reacted successfully to give the corresponding addition products **3f** and **3g** in moderate yields (Table 2, entries 6 and 7). 1,2-Dimethyl-4-ethynylbenzene (**2e**), 1,2-dimethoxyl-4-ethynylbenzene (**2h**) and 1,2,3-trimethoxy-5-ethynylbenzene (**2i**) also furnished the target products **3e**, **3h** and **3i** in 52%, 45% and 50% yields, respectively (Table 2, entries 5, 8 and 9). Terminal alkynes bearing an electron-withdrawing group on their aryl ring also exhibited high reactivity. For example, 4-fluoro-1-ethynylbenzene (**2j**) afforded the corresponding addition product **3j** in 60% yield (Table 2, entry 10). However, 4-nitro-1-ethynylbenzene (**2k**) did not afford any of the desired product **3k** under these conditions (Table 2, entry 11). We also investigated the potential for steric hindrance from the substituents on the phenyl ring of the alkyne substrate, but found these groups had no discernible impact on the product yield. For example,

Table 2Substrate scope of catalytic nucleophilic addition of terminal alkynes to α,β -unsaturated- γ -lactams.

Entry	Alkyne (2)	Product (3)	Yield* (%)	Entry	Alkyne (2)	Product (3)	Yield* (%)
1			60	9			50
2			51	10			60
3			53	11			0
4			50	12			60
5			52	13			49
6			55	14			76
7			52	15			48
8			45	16			0

Reaction conditions: **1** (0.5 mmol), **2** (1.5 mmol) and H[AuCl₄·4H₂O] (10 mol%) in TTCE (2.0 mL) under N₂ at 50 °C for 15 h.

* Isolated yield.

o-tolylethyne (**2b**) and *o*-methoxyl-1-ethynylbenzene (**2f**) both reacted smoothly to provide the corresponding products in moderate yields (Table 2, entries 2 and 6). Furthermore, terminal alkynes bearing a bulky naphthalene moiety such as 1-ethynynaphthalene (**2l**) and 2-ethynynaphthalene (**2m**) gave the corresponding products in 60% and 49% yields (Table 2, entries 12 and 13). Heteroaryl alkynes, such as **2n** and **2o**, underwent the nucleophilic addition reaction to afford the desired addition products in 76% and 48% yields, respectively (Table 2, entries 14 and 15). However, the reaction of the simple aliphatic terminal alkyne 1-decyne (**2p**) failed to afford any of the desired product (Table 2, entry 16).

3.3. Mechanistic consideration for the nucleophilic addition

Based on the results of the experiments reported above and those of our previous mechanistic studies [19,21,23,33], we have proposed a tentative mechanism for this nucleophilic addition reaction, which is shown in Scheme 3. According to this mechanism, the reaction would proceed via the cyclic *N*-acyliminium ion intermediate **A**, which would be created in situ by the reaction of *N*-benzyl- α,β -unsaturated- γ -lactam **1** with H[AuCl₄] [37,41,42]. The subsequent conjugate base (AuCl₄[−])-mediated abstraction of a proton from phenylacetylene (**2a**) would lead to the formation of the corresponding

Scheme 3. Plausible reaction mechanism for this transformation.

alkynyl anion **B** [43–45] and regenerate HAuCl_4 to the next catalytic cycle. Finally, the nucleophilic attack of alkynyl anion **B** to *N*-acyliminium ion **A** would yield the desired product **3a**.

4. Conclusions

In summary, we have developed a novel reaction for the nucleophilic addition of terminal alkynes to *N*-benzyl- α,β -unsaturated- γ -lactam for the synthesis of 5-alkynyl-2-pyrrolidinones using $\text{HAuCl}_4 \cdot 4\text{H}_2\text{O}$ as a catalyst. This reaction proceeded smoothly under mild conditions to give the desired products in moderate to good yields. Further studies toward the synthesis of chiral 5-alkynyl-2-pyrrolidinones are currently underway in our group.

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Graphical Abstract

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

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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 under mild conditions, and represents a practical approach for the construction of a wide range of 5-alkynyl-2-pyrrolidinones in moderate to good yields (45%–76%).

- Atom economy
- Mild reaction conditions
- Broad substrate scope

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催化的端炔C–H键与 α,β -不饱和- γ -内酰胺的亲核加成反应

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摘要: 吡咯啉酮是一类重要的五元杂环, 广泛存在于许多天然产物、生物活性分子和高聚物中。在众多吡咯啉酮衍生物中, 5-炔基-2-吡咯啉酮引起了化学家们广泛的关注。因为这种分子结构不仅存在于具有潜在治疗作用的药物分子(如眼部降压药、 α 7乙酰胆碱受体激动剂、抗惊厥和消炎药物)中, 也存在于许多天然产物中, 例如刺桐类生物碱和多环类生物碱。鉴于此, 人们发展了许多合成这类化合物的方法。目前文献报道最多的方法是炔基负离子对5-位具有离去基团的吡咯啉酮化合物的亲核取代反应。离去基团主要有苯硫基、1-苯并咪唑基和烷氧基等。但是这些方法操作步骤繁琐, 产生大量的副产物, 原子经济性不高。

本课题组发展了一例新型的端炔C–H键与 α,β -不饱和- γ -内酰胺的亲核加成反应, 合成了一系列5-炔基-2-吡咯啉酮衍生物。该反应以环状N-酰亚胺正离子为反应活性中间体, 反应条件温和, 操作简便。据我们所知, 这是一例原子经济地合成5-炔基-2-吡咯啉酮衍生物的新方法。环状N-酰亚胺正离子是一类高活性的亲电试剂, 广泛应用于构建含氮杂环体系。本课题组利用这一策略实现了一系列C–C和C–N成键反应。基于此, 本文原位形成环状N-酰亚胺正离子, 以端炔作为亲核试剂, 与其发生亲核加成反应, 合成了一系列5-炔基-2-吡咯啉酮衍生物, 原子经济性为100%。

首先, 我们以5 mol% TsOH 为Brønsted酸, 考察了Lewis酸效应对反应收率的影响。结果表明, Al(OTf)₃给出最好的反应收率, 不加Lewis酸没有亲核加成产物生成。然后, 我们以5 mol% Al(OTf)₃为Lewis酸, 考察了Brønsted酸效应对反应收率的影响。结果表明, HAuCl₄·4H₂O给出最佳的反应收率54%, 不加Brønsted酸也没有亲核加成产物生成。值得一提的是, 当HAuCl₄·4H₂O为单一催化剂, 不加Al(OTf)₃时, 反应收率也达到55%。然后, 我们以HAuCl₄·4H₂O为催化剂, 考察了溶剂效应和反应温度对反应收率的影响。结果表明, 四氯乙烷(TTCE)为反应最佳的溶剂, 50 °C反应最佳。为了进一步提高反应收率, 我们又考察了催化剂用量对反应收率的影响。结果表明, 10 mol%的催化剂给出最佳的反应收率60%。进一步优化反应条件, 我们没有得到更好的结果。因此最佳的反应条件: N-苄基- α,β -不饱和- γ -内酰胺 **1** (0.4 mmol), 苯乙炔 **2a** (1.2 mmol), HAuCl₄·4H₂O (10 mol%), TTCE (2.0 mL), 50 °C下反应15 h。

在确定了最佳的反应条件后, 我们对端炔类底物的适用性进行了考察。结果表明, 给电子的苯乙炔表现出较高的反应活性; 弱吸电子的苯乙炔也表现出较高的反应活性; 强吸电子的苯乙炔则抑制反应的发生; 位阻效应对该反应没有明显影响; 杂环端炔也给出中等以上的收率; 然而, 简单脂肪端炔不能给出相应的亲核加成产物。

本文发展了一例催化的端炔C–H键与 α,β -不饱和- γ -内酰胺的亲核加成反应。该反应以环状N-酰亚胺正离子为关键中间体。反应条件温和, 操作简便。构建了一种以中等的收率(45%–76%)合成一系列5-炔基-2-吡咯啉酮衍生物的方法。

关键词: 碳-氢加成; Brønsted酸; N-酰亚胺正离子; 端炔; 吡咯啉酮

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