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Base-Promoted Intramolecular Cyclization of *N*-alkyl, *N*-propargylic

β -enaminones for the Synthesis of Polysubstituted Pyrroles

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Abstract: An efficient, mild, metal-free, base-mediated intramolecular cyclization of *N*-alkyl, *N*-propargylic β -enaminones has been realized for the generation of polysubstituted pyrrole derivatives. This synthetic transformation tolerates a range of substituted *N*-alkyl, *N*-propargylic β -enaminones in moderate to good yields.

Introduction

Polysubstituted pyrroles are an important class of nitrogen heterocycles, which are often found in numerous natural products, biologically pharmaceuticals and functional artificial materials.¹ Especially, highly functionalized pyrroles are occasionally observed as important structural units in chlorophyll, heme and pyrrole alkaloids in the nature.² Moreover, pyrroles are also widely employed as key synthetic intermediates to prepare drugs and biologically active compounds (Fig. 1):³ CB₁ antagonist can lower food intake and body-weight gain in mice without entering the brain or antagonizing central CB₁-dependent responses;^{3a} Hsp90 inhibitor exhibits nanomolar antiproliferative activities across multiple cancer cell lines;^{3b} and Atorvastatin (Lipitor) is used primarily for lowering blood cholesterol and for the prevention of events associated with cardiovascular disease.^{3c}

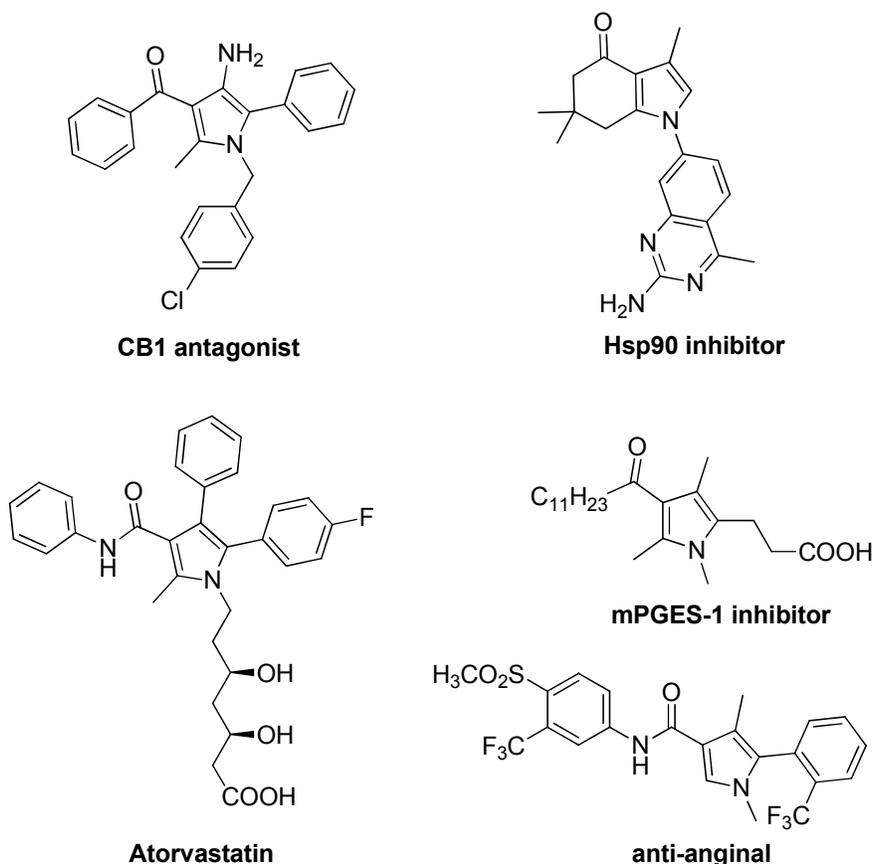
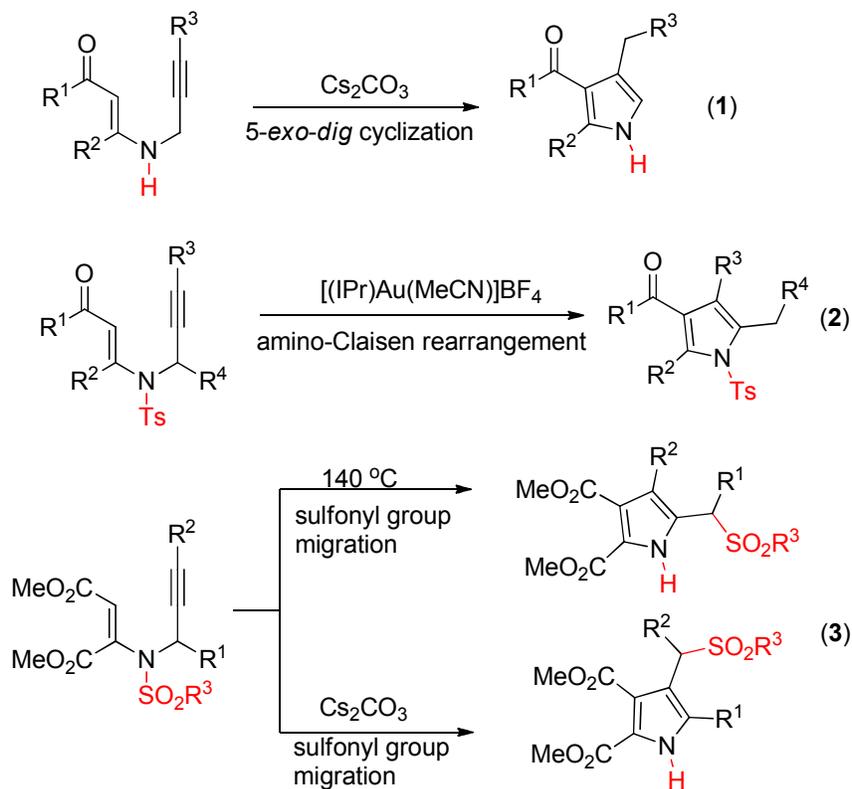


Fig.1 Examples of biologically important polysubstituted pyrrole derivatives

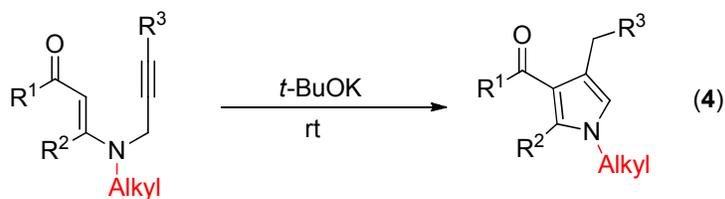
Motivated by these practical applications, strong efforts have been inputted to develop efficient methodologies to construct polysubstituted pyrroles during the past decades.⁴ In general, the classic methods to prepare pyrrole derivatives include Knorr reactions,⁵ Paal-Knorr method⁶ and Hantzsch synthesis.⁷ Although transition metal-catalysed processes have been proven to be a highly efficient strategy to synthesize pyrrole derivatives,⁸ unfortunately, all these reactions have significant drawbacks such as limited starting materials, the use of stoichiometric amounts of strong bases, potential contamination of pharmaceuticals because of expensive, poisonous, environmentally unfriendly transition-metal reagents, harsh reaction conditions and formation of undesired by-products.⁹ All these negative factors strongly encourage scientists to develop metal-free methods to approach pyrrole derivatives. On the other hand, *N*-propargylic β -enaminone has received more attention and have been recognized as versatile synthetic intermediates to construct heterocyclic molecules¹⁰ including pyrroles,¹¹ dihydropyrroles,¹² pyridines,¹³ dihydropyridines¹⁴ and 1,4-oxazepines.¹⁵ In 2008, Cacchi et al reported the selective cyclization of *N*-propargylic β -enaminone in to pyrroles by using an excess amount of base via 5-*exo-dig* cyclization (Scheme 1, eq 1).^{11a} Au(I)-catalyzed amino-Claisen rearrangement of *N*-tosyl, *N*-propargylic β -enaminones to pyrroles was developed by Saito et al (Scheme 1, eq 2).^{11b} Xin et al described that the similar structure, 3-aza-1,5-enyne, was selectively transformed into two kinds of functionalized

pyrroles via regioselective sulfonyl group migration under thermal or base conditions (Scheme 1, eq 3).^{11c} It is worthy to note that all of these works seldom employed *N*-alkyl, *N*-propargylic β -enaminones as building blocks for the synthesis of pyrroles.^{11d} Therefore, the development of new kind of *N*-substituted, *N*-propargylic β -enaminones to construct functionalized and polysubstituted pyrroles is of great interest. Herein, we present the novel base-promoted intramolecular cyclization of *N*-alkyl, *N*-propargylic β -enaminones to prepare polysubstituted *N*-alkyl pyrroles without using transition-metal reagents as catalyst (Scheme 1, eq 4).

Previous:



This work:



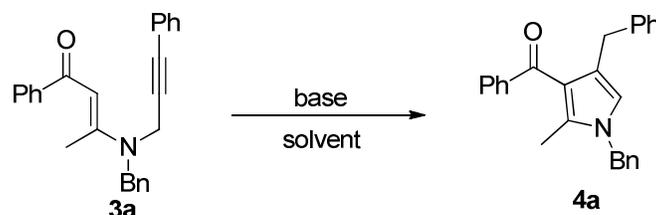
Scheme 1 Conversion of substituted *N*-propargylic β -enaminones to pyrroles

Results and discussion

In our initial attempt, **3a** (3-(benzyl(3-phenylprop-2-yn-1-yl)amino)-1-phenylbut-2-en-1-one) was selected as a model substrate for the intramolecular cyclization to prepare the corresponding pyrrole derivative **4a**. Initially, the cyclization reaction of

3a in the presence of NaOH or KOH with DMF as solvent at room temperature, only a trace of the cyclized products were formed (Table 1, entries 1 and 2). Importantly, the desired pyrrole **4a** was successfully obtained in 49% yield when the base was changed to stronger base MeONa (Table 1, entry 3). Encouraged by this result, other strong bases, such as EtONa, *t*-BuOLi, *t*-BuONa, *t*-BuOK and NaH were screened (Table 1, entries 4–8). It was found that *t*-BuOK in DMF for 30 minutes gave the best result, affording pyrrole **4a** in 69% yield (Table 1, entry 7). We then tested the effect of polar aprotic solvents on the intramolecular cyclization of **4a** in the presence of *t*-BuOK (Table 1, entries 9–15). Among the evaluated solvents, only THF gave a comparable result (Table 1, entry 11). Protonic solvent *t*-BuOH was proven to be ineffective for this transformation and the desired pyrrole **4a** was only obtained in 20% yield (entry 16). Furthermore, the amounts of *t*-BuOK were also investigated and all the reactions could proceed smoothly, albeit with slightly decreased yields (Table 1, entries 17 and 18). Finally, lower temperature (0 °C) has been employed to conduct this reaction. The result suggests that a relatively longer reaction time is needed at low temperature (0 °C) than at rt (Table 1, entry 19).

Table 1 Optimization of the reaction conditions for the synthesis of **4a**^a



entry	base (equiv)	solvent	time (min)	yield ^b (%)
1	NaOH (1.0)	DMF	60	traces
2	KOH (1.0)	DMF	30	traces
3	MeONa (1.0)	DMF	30	49
4	EtONa (1.0)	DMF	30	48
5	<i>t</i> -BuOLi (1.0)	DMF	30	30
6	<i>t</i> -BuONa (1.0)	DMF	30	60
7	<i>t</i> -BuOK (1.0)	DMF	30	69
8	NaH (1.0)	DMF	60	traces
9	<i>t</i> -BuOK (1.0)	DMAC ^c	30	51
10	<i>t</i> -BuOK (1.0)	DMSO	30	53
11	<i>t</i> -BuOK (1.0)	THF	30	65
12	<i>t</i> -BuOK (1.0)	1,4-dioxane	30	59
13	<i>t</i> -BuOK (1.0)	DCM	30	55
14	<i>t</i> -BuOK (1.0)	CH ₃ CN	30	60
15	<i>t</i> -BuOK (1.0)	toluene	60	nr ^d
16	<i>t</i> -BuOK (1.0)	<i>t</i> -BuOH	30	20
17	<i>t</i> -BuOK (2.0)	DMF	30	58

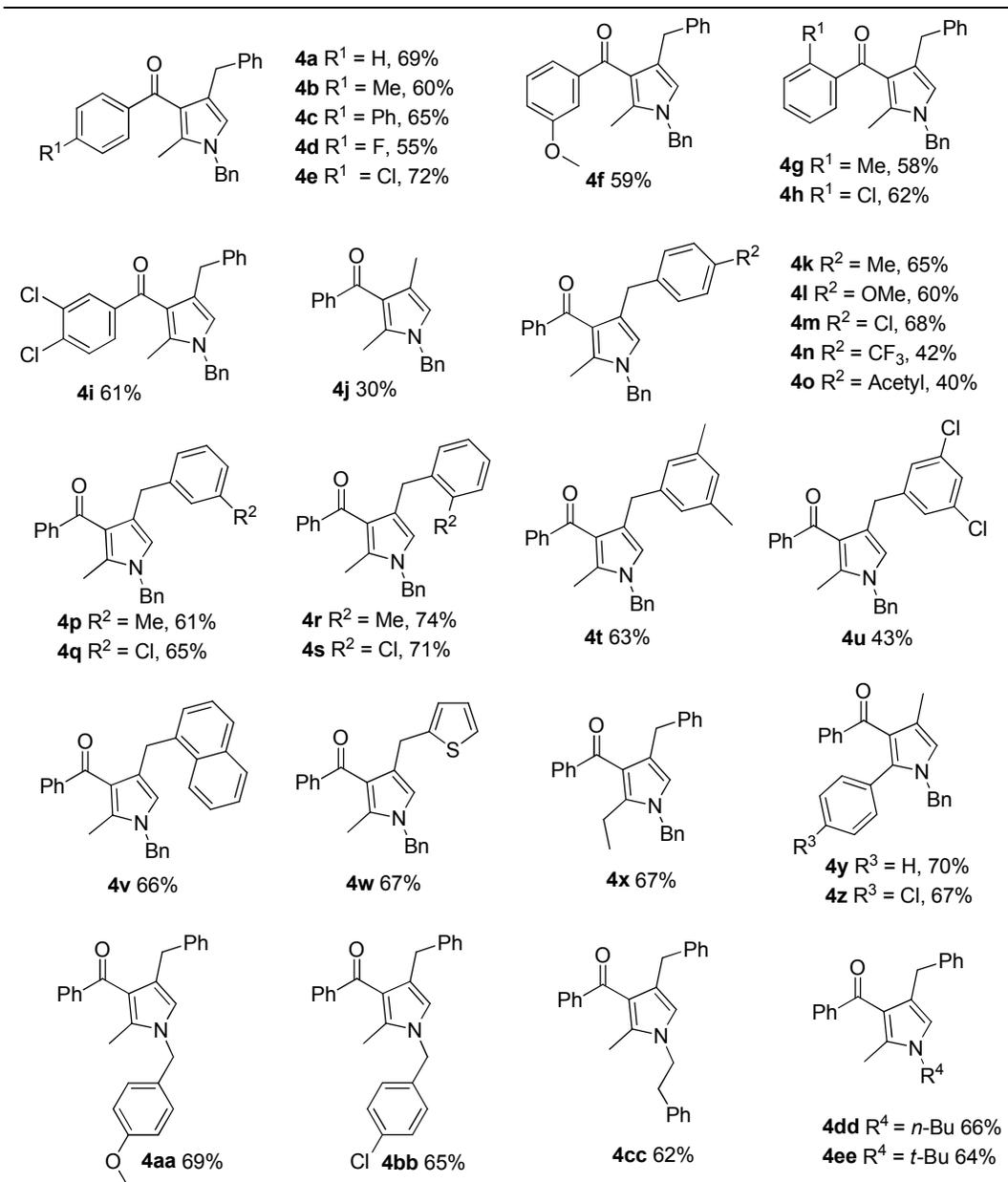
18	<i>t</i> -BuOK (0.5)	DMF	30	48
19 ^c	<i>t</i> -BuOK (1.0)	DMF	120	60

^aReaction conditions: **3a** (0.5 mmol 1.0 equiv), base (0.5-2.0 equiv), in 3 mL solvent, rt. ^bIsolated yields. ^cDMAC: *N,N*-dimethylacetamide. ^dnr: no reaction. ^eReaction performed at 0 °C.

On the basis of the optimal reaction conditions established (Table 1, entry 8), the generality of this reaction and the scope of *t*-BuOK-promoted intramolecular cyclization of various substituted pyrroles have been tried and all results are summarized in Table 2. Neutral, electron-donating, or electron-withdrawing groups on the ring of the aromatic β -enaminones could be tolerated to deliver the corresponding pyrrole derivatives (**4a-4i**) in 55–72% yields. The desired product **4j** could be obtained only in 30% yield and with 35% yield of isomeric product **4j'** (Scheme 2, eq 1) under the same conditions when substrate with terminal alkyne was employed. By the way, the structure of pyrrole **4j** was further confirmed by X-ray crystal structure analysis (Fig. 2). Aryl group substitutions on *N*-propargylic β -enaminones substrates with internal alkyne proceed smoothly to give pyrroles (**4k-4m** and **4p-4t**) in excellent yields (60–74%), regardless of electron-donating and weak electron-withdrawing groups on the ring. In contrast, substrates with stronger electron-donating groups (4-CF₃-C₆H₄, 4-Acetyl-C₆H₄ and 3,5-Cl₂-C₆H₃) provided products in relatively lower yields. Pleasingly, substrates with naphthalene and thiophene substituents could be employed successfully in this system, affording **4v** and **4w** in 66% and 67% yields, respectively. Varying the β -substituted groups from methyl to ethyl and aryl led to full substrate conversions with product **4x-4z** in high yields. The N1 position including 4-methoxybenzyl, 4-chlorobenzyl phenethyl, *n*-butyl and *t*-butyl groups also worked well, furnishing pyrroles in 62-69% yields.

Table 2 Scope of the synthesis of pyrrole derivatives^{a,b}





^aReaction conditions: **3** or **2a** (0.5 mmol 1.0 equiv), *t*-BuOK (0.5 mmol, 1.0 equiv), in DMF (3 mL) at room temperature for 30 min. ^bIsolated yields.

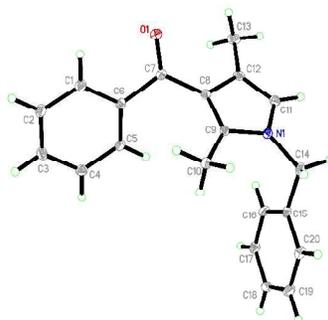
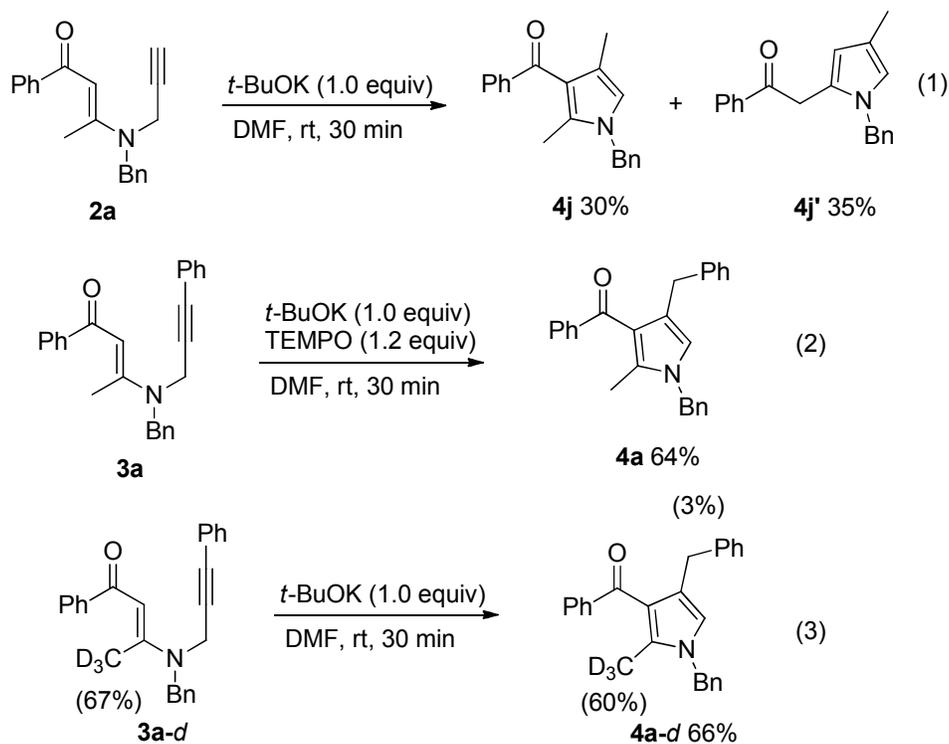


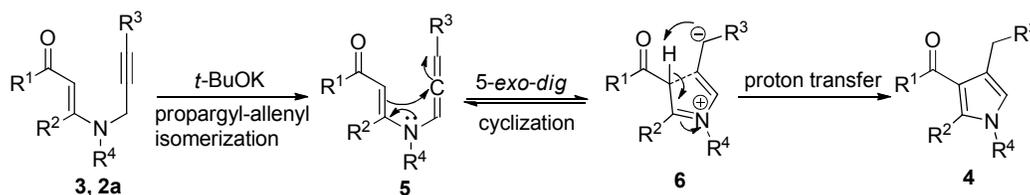
Fig. 2 ORTEP diagram of compound **4j** (CCDC 1470929)

To investigate the possible mechanism of this transformation, a series of control experiments were carried out, and the results are shown in Scheme 2. When subjecting substrate **2a** with terminal alkyne under the standard conditions, two products **4j** and **4j'** were generated in 30% and 35% yield (Scheme 2, eq 1). The **4j'** was probably due to an attack of the anion generated *in situ* from the CH₃ at the β-position on the carbon of allene (**5**) generated in the presence of *t*-BuOK (Scheme 3). Moreover, only a trace amount of decrease in yield was detected when 1.2 equiv of TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl), a radical inhibitor, was introduced into the standard reaction system (Scheme 2, eq 2). Furthermore, when the 67% deuterated substrate **3a-d** was used to react under the optimal condition, no deuterium incorporation was observed at the methylene group (Scheme 2, eq 3). This proves that the protonation of the anion is carried out by the hydrogen of α-carbon and not by the CH₃ group at the β-position in **2a** or **3a**.



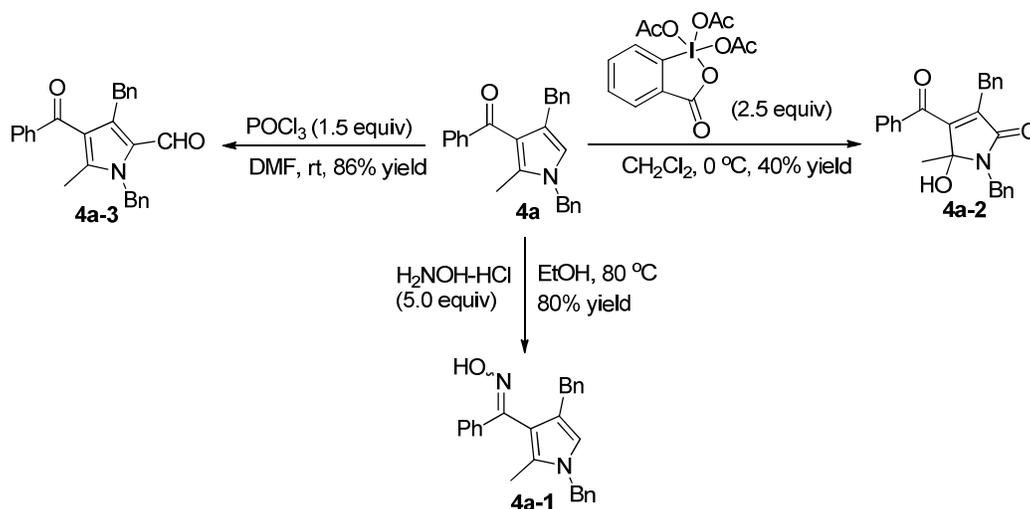
Scheme 2 Preliminary mechanistic studies

On the basis of the above-mentioned results, a plausible mechanism is proposed in Scheme 3. First, the propargyl moiety of **3** or **2a** would transform into the allene intermediate **5**¹⁹ in the presence of *t*-BuOK. Subsequently, a 5-*exo-dig* cyclization via an intramolecular nucleophilic attack to the allene bond would take place.²⁰ The proton of intermediate **6** at α -position would be transferred intramolecularly to furnish the final pyrroles **4**.



Scheme 3 Plausible reaction mechanism for the formation of polysubstituted pyrroles **4**

Finally, we converted the tetrasubstituted pyrrole **4a** to the corresponding oxime **4a-1** (80% yield) through a condensation process with hydroxylamine hydrochloride.¹⁶ The oxidation of pyrrole **4a** with Dess-Martin periodinane proceeded to give the γ -lactam **4a-2** in 40% isolated yield.¹⁷ Meanwhile, pentasubstituted pyrrole **4a-3** was obtained in 86% yield by the introduction of an aldehyde group at the 5-position¹⁸ (Scheme 4). These derivatives could be further used for building more complex organic molecules.



Scheme 4 Synthetic application for this transformation

Experimental

General experimental information

All of the chemicals were obtained from commercial sources or prepared according to standard methods. ¹H, ¹⁹F and ¹³C NMR spectra were recorded using a Bruker AV 400 MHz NMR spectrometer. TMS was used as an internal standard. Chemical shifts are reported in ppm downfield from CDCl₃ (δ = 7.26 ppm) for ¹H NMR and relative to

the central CDCl₃ resonance ($\delta = 77.0$ ppm) for ¹³C NMR spectroscopy. Multiplicities were reported as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), dd (doublet of doublets) and dt (doublet of triplets). Coupling constants were reported in Hertz (Hz). Melting points were measured on a RY-I apparatus and uncorrected. HRMS were recorded on an IonSpec FT-ICR mass spectrometer with Electron Spray Ionization (ESI) resource.

Typical procedure for the preparation of 1,2,3,4-tetrasubstituted pyrroles (4)

A mixture of *N*-alkyl, *N*-propargylic β -enaminones **3** or **2a** (0.5 mmol, 1.0 equiv), *t*-BuOK (56.1 mg, 0.5 mmol, 1.0 equiv) and DMF (3 mL) was stirred at room temperature for 30 min. After this time, ethyl acetate was added and the resulting mixture was washed with a saturated NH₄Cl solution and subsequently with a saturated NaCl solution. The organic phase was separated, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, hexane/ethyl acetate = 100:1) to give desired compound **4**.

Conclusions

In conclusion, a novel strategy has been developed for the synthesis of tetrasubstituted pyrroles in moderate to good yields from *N*-alkyl, *N*-propargylic β -enaminones in the presence of *t*-BuOK under mild reaction conditions. Many functional groups have been tried to produce a series of synthetically relevant pyrroles via an intramolecular 5-*exo-dig* cyclization. This method is very efficacious due to its metal-free mediation and high atom economy.

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Supporting Information Available

Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic data for all new compounds. X-ray crystallographic analysis for product **4j**. CCDC 1470929. For ESI and crystallographic data in CIF or other electronic format see DOI:

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