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Synthesis of C3-alkenylated 2,3,4-trisubstituted pyrrole derivatives through cyclization of methylene isocyanides and ene–yne–ketones†

Shasha Li,‡[a] Gongruixue Zeng,‡[b] Xiaoqi Xing,[b] Zhiheng Yang,[a] Feiyun Ma,[a] Boxia Li,[a] Weiyan Cheng, *[a] Jiankang Zhang*[b] and Ruoyu He*[c]

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A mild, transition-metal-free and facile C3-alkenylated 2,3,4-trisubstituted pyrrole cyclization of methylene isocyanides with ene–yne–ketones in moderate to good yields was explored. The E-alkenylated products were isolated in moderate to exclusive selectivity in most cases. The investigated compounds in this work are expected to open up for use as potential medicinal agents or precursors for post-modification.

Introduction

Multi-substituted pyrroles have been exploited as important drugs or drug candidates, which are also present in diverse bioactive natural products.[1–7] Among various functional groups introduced into pyrroles, incorporation of the alkenyl group opens new opportunities for diversification of the scaffold to develop functionalized molecules with additional therapeutic potential.[8–12] Alkenylated pyrrole-containing biologically active drug like compounds have been well developed including multitarget tyrosine kinase inhibitor sunitinib and histone deacetylase inhibitor domatinostat (Fig. 1).[13–21]

Several approaches to obtain C-alkenylpyrroles have been reported including traditional methods the Wittig reaction and Knoevenagel condensation using aldehyde functionalized pyrroles as starting materials.[10,11,22–29] Recently, the described methods are mainly focused on direct alkenylation on the pyrrole ring (Fig. 2). Because of the instability of pyrroles in acidic and oxidative environments, alkenylation was mainly achieved on NH-protected pyrrole. Gaunt and colleagues reported a palladium-catalyzed oxidative alkenylation of N-triisopropylsilyl (TIPS) protected pyrrole with an activated alkene.[8] Notably, to explore more convenient methods, direct alkenylation on NH-free pyrrole was recently developed. Through a one-pot two-fold alkenylation strategy with aldehydes employed as alkenylating agents, Samrat *et al.* presented an alkenylation strategy with sulfone used as a starting precursor.[11] Additionally, Joydev *et al.* exploited a site-selective alkenylation of (NH)-pyrroles with an electron-withdrawing group, which also required expensive palladium as an oxidative reagent.[10] To avoid the negative effects caused by the active pyrrole, cycloaddition approaches for forming a pyrrole ring together with a vinyl substitution would be an efficient alternative option. Cyclization of active methylene isocyanides with diverse synthons yielding poly-substituted pyrroles has been performed.[27,30–36] Therefore, considering the synthetic utility of methylene isocyanides for constructing pyrroles and with our continuing effort in the synthesis of this five-membered heterocyclic ring, we herein describe a simple protocol providing 3-alkenylated 2,3,4-trisubstituted pyrroles *via* [3+2] cyclization of methylene isocyanides with ene–yne–ketones under basic conditions (Fig. 2).

Results and discussion

We commenced our investigation by exploring the reaction of 3-(3-phenylprop-2-yn-1-ylidene)pentane-2,4-dione (**1a**) with ethyl isocyanoacetate (**2a**) (Table 1). A base proved to be an essential influence factor for entry into alkenylated pyrroles. No reaction was observed in initial attempts with various attempted bases (entries 1–7), while product **3a** could only be obtained in 35%

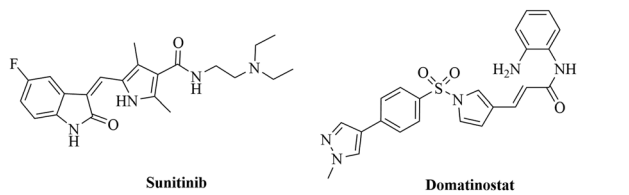

Fig. 1 Drugs or candidates with an alkenylated pyrrole.

[a] *Department of Pharmacy, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan, China. E-mail: fccchengwy@zzu.edu.cn*
[b] *School of Medicine, Zhejiang University City College, Hangzhou 310015, Zhejiang, China. E-mail: zjk0125@yeah.net*
[c] *Department of Pharmaceutical Preparation, Hangzhou Xixi Hospital, Hangzhou 310023, Zhejiang, China. E-mail: heruoyu_hry@hotmail.com*

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‡ These authors contributed equally.

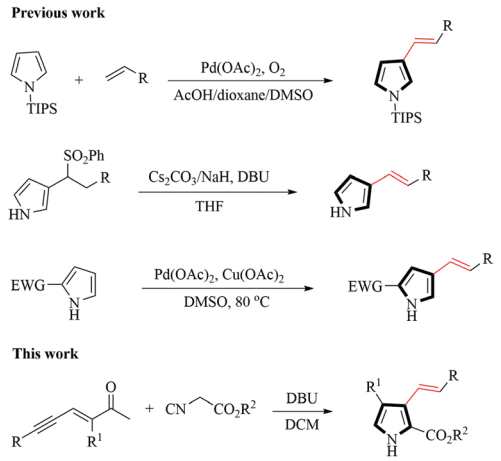


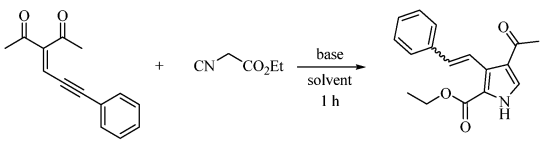
Fig. 2 Construction of alkenylated pyrroles.

yield with almost no stereoselectivity (1 : 1 *E*/*Z* ratio) in the presence of DBU with MeCN as a solvent (entry 8). Subsequently, the screening of diverse solvents showed DCM to be the most suitable one, furnishing product **3a** in 63% yield, while no product was observed with MeOH as a solvent (entries 9–14). Increasing the equivalency of **2a** to 1.5-fold did improve the yield to 68% (entry 15), while no obvious improvement was observed when further raised to 2- and 5-fold (entries 16 and 17). Similarly, alteration of the equivalency of DBU also had little positive influence on the yield (entries 18 and 19). To check the effect of the temperature on the outcome, we next conducted the reaction at various temperatures (entries 20 and 21). The yield got diminished at 0 °C, which was mainly attributed to the slower reaction velocity, while the yield was desirable at 50 °C with a shorter reaction period. However, with these optimized conditions changed, the *E*/*Z* selectivity of product **3a** remained the same.

With the optimized conditions in hand, we intended to investigate the scope of this method with respect to various ene–yne–ketones (Scheme 1). While the dione substrate with an unsubstituted phenyl ring (**1a**) gave **3a** in good yield, both electron-withdrawing and -donating groups in the *ortho*, *para* and *meta* positions on the phenyl group could be tolerated, furnishing the corresponding target compounds (**3a–3l**) in favorable yields. Besides, by replacing the phenyl group with a naphthyl group, **3m** could also be obtained in good yield. Various electron-withdrawing R^1 groups were also suitable reaction partners and provided products **3n–3p** in 62–84% yields. It is noteworthy that although no obvious regularity of the *E*/*Z* selectivity for the product was observed, the (*E*)-isomer was considered to be the preferential conformation, and only in a few cases was the (*E*)-isomer of the products isolated exclusively (**3c**, **3f**, **3g**, **3h**, and **3i**).

In order to check the endurance of various active methylene isocyanides, we next evaluated several isocyanoacetates with different ester moieties under the reaction parameters

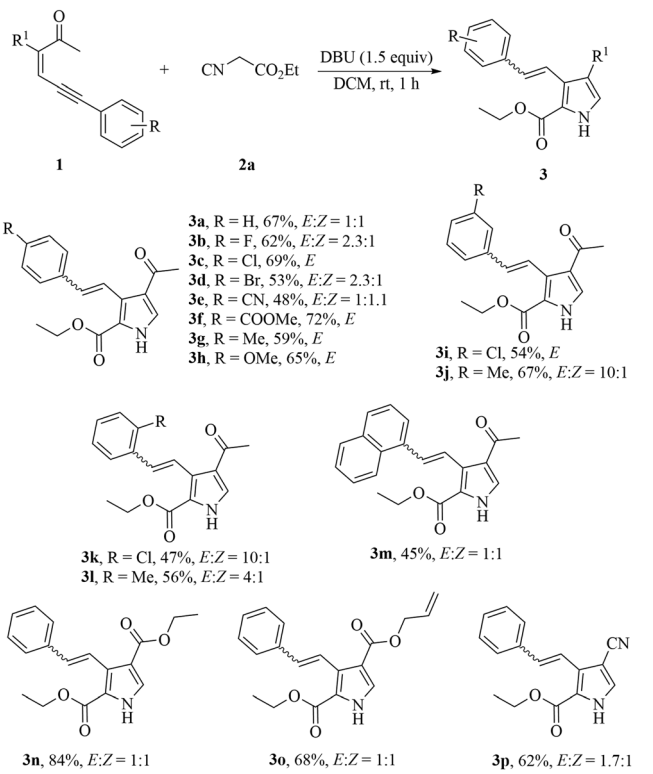
Table 1 Optimization of the reaction conditions[a]



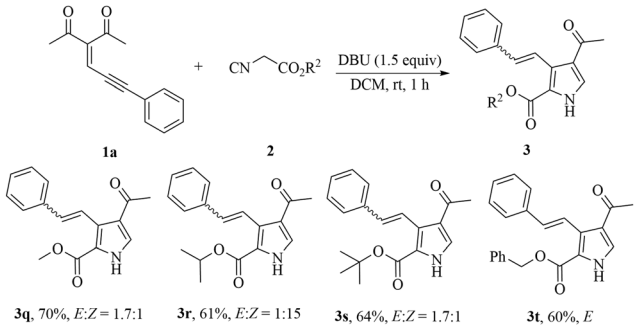
1a 2a 3a

Entry	Base	Solvent	Temp. (°C)	Yield[b]/(%)
1	NaOH	MeCN	r.t.	0
2	K_2CO_3	MeCN	r.t.	0
3	NaOAc	MeCN	r.t.	0
4	EtONa	MeCN	r.t.	<5
5	Et_3N	MeCN	r.t.	0
6	DIPEA	MeCN	r.t.	0
7	DABCO	MeCN	r.t.	0
8	DBU	MeCN	r.t.	35
9	DBU	THF	r.t.	52
10	DBU	MeOH	r.t.	0
11	DBU	Dioxane	r.t.	57
12	DBU	DMF	r.t.	31
13	DBU	DCE	r.t.	45
14	DBU	DCM	r.t.	63
15[c]	DBU	DCM	r.t.	68
16[d]	DBU	DCM	r.t.	65
17[e]	DBU	DCM	r.t.	64
18[f]	DBU	DCM	r.t.	55
19[g]	DBU	DCM	r.t.	53
20[h]	DBU	DCM	0	35
21[i]	DBU	DCM	50	60

[a] Reaction conditions unless otherwise specified: 0.5 mmol of **1a**, 0.55 mmol of **2a**, 1.5 equiv. base, 2 mL of solvent, r.t., 1 h, air. [b] Isolated yield. [c] 0.75 mmol of **2a**. [d] 1 mmol of **2a**. [e] 2.5 mmol of **2a**. [f] 2 equiv. DBU. [g] 5 equiv. DBU. [h] Reacted for 3 h. [i] Reacted for 0.5 h.



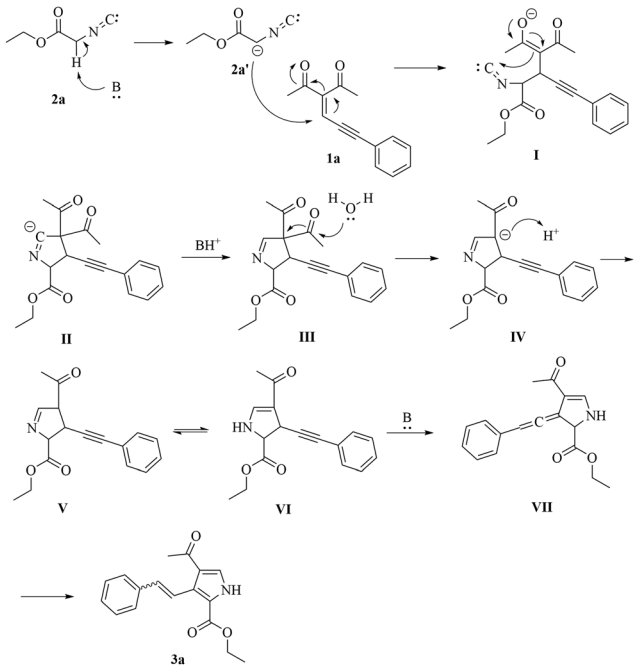
Scheme 1 Scope of the ene–yne–ketones. Reaction conditions unless otherwise specified: 0.5 mmol of **1a**, 0.75 mmol of **2a**, 1.5 equiv. DBU, 2 mL of solvent, r.t., 1 h, air. Isolated yield.



Scheme 2 Scope of the methylene isocyanides. Reaction conditions unless otherwise specified: 0.5 mmol of **1a**, 0.75 mmol of **2a**, 1.5 equiv. DBU, 2 mL of solvent, r.t., 1 h, air. Isolated yield.

(Scheme 2). Notably, different isocyanoacetates generated the corresponding products (**3q–3t**) in moderate to good yields. However, the *E*/*Z* selectivity for the isopropyl isocyanoacetate generated product (**3r**) was opposite to the other products, in which the (*Z*)-isomer of **3r** was more preferable with an *E*/*Z* ratio of 1 : 15, and the irregularity of the selectivity needs to be further evaluated.

On the basis of the observations, a plausible mechanism is proposed as illustrated in Scheme 3. Firstly, active methylene isocyanide was deprotonated by DBU to generate **2a′**, which reacted with **1a** to obtain intermediate **I.** Subsequently, intramolecular cyclization followed by protonation gave **III.** Then, deacetylation with the assistance of water afforded **IV**, which upon interconversion formed **VI.** Finally, in the presence of DBU, a 1,3-H shift took place in intermediate **VI** leading to the allene intermediate **VII**, which would further go through a tautomerism process to obtain the final product **3a.**



Scheme 3 Plausible reaction mechanism.

Conclusions

In conclusion, we have developed a valuable and wide-in-scope protocol for the synthesis of trisubstituted C3 alkenylated pyrroles *via* DBU mediated [3+2] cyclization of isocyanoacetates to ene–yne–ketone derivatives. The facile process occurs at room temperature and is transition-metal-free. We anticipate that this strategy would be helpful for searching for more complex molecules containing alkenylated pyrrole, which may have potential for further post-synthetic modifications or medicinal applications.

Conflicts of interest

There are no conflicts to declare.

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