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Substituted Pyrrololactams via Ring Expansion of Spiro-2*H*-pyrroles from Intermolecular Alkyne–Isocyanide Click Reactions

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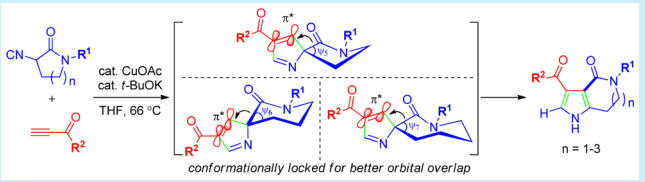
Supporting Information

ABSTRACT: The facile synthesis of 6- to 8-membered pyrrololactams has been developed using a ring expansion of spiro-2*H*-pyrroles, the products of intermolecular alkyne–isocyanide click reactions. The key to successful ring expansion of spiro-2*H*-pyrroles to pyrrololactams is the enforced orbital overlap between the internal alkene and the amide carbonyl group through the conformationally locked bicyclic structures. The newly disclosed α-isocyano lactams, substrates for click reactions, should find their utility in the synthesis of pharmaceutically important heterocyclic compounds.



Facile access to multisubstituted pyrroles has been of special interest to synthetic chemists engaged in the preparation of natural products, therapeutic agents, and materials with distinctive optoelectronic properties.[1] One of the bottlenecks in the synthesis of pyrroles appears to be a lack of general and direct methods for highly substituted fused pyrroles. Thus, while the syntheses of fused pyrroles have been typically achieved by multistep reactions,[2] the recent development of direct synthetic methods for fused pyrroles highlights the challenges and potential of cycloadditions,[3] tandem reactions,[4] and multicomponent reactions.[5] Among synthetic methods to fused pyrroles, the ring-expansion strategy can render a general solution to the difficulty associated with the direct preparation of highly substituted fused pyrroles. Thus, the laboratories of Toste,[6] Shi,[7] and You[8] demonstrated facile access to fused pyrroles using the ring expansion of elaborated substrates (Scheme 1a).

Cycloaddition reactions between alkynes and isocyanides provide a regiodivergent synthesis of highly substituted pyrroles.[9] Utilizing the "click chemistry" feature of the alkyne–isocyanide [3 + 2] cycloaddition reactions,[10] we have recently disclosed an angle strain-induced bond migration of 2,2-disubstituted-2*H*-pyrroles to the regioselective synthesis of pyrroles.[11] This approach readily allows for the facile regioselective synthesis of 2,3,4-substituted pyrroles with two different EWGs at the 3- and 4-carbon atoms. With an aim of developing an efficient synthetic method for pyrrololactams with interesting biological activities (Scheme 1b),[12] we describe herein a facile one-pot synthetic procedure to highly decorated pyrrololactams via an intermolecular alkyne–isocyanide click reaction followed by an angle strain induced ring expansion (Scheme 1c). The current method enables a one-pot synthesis of pyrrololactams from simple starting materials with structural diversity (6- to 8-membered pyrrololactams), high reaction efficiency (one-pot reaction in 50–80% yields), and controlled regioselectivity.[13]

To investigate the ring expansion of spiro-2*H*-pyrroles, we prepared hereto unknown α-isocyano lactams (see Supporting Information for details) and subjected them to the alkyne–isocyanide [3 + 2] cycloaddition reaction (Table 1). The use of Lewis bases such as Ph_3P and Cy_3P did not effect the desired transformation, only leading to a slow decomposition of both starting materials (entries 1 and 2). After the inactivity of CuOAc was confirmed (entry 3), the cooperative catalyst effect between Ph_3P and CuOAc was investigated (entries 4–6). Upon combining α-isocyano lactam **1a** and 1-phenylprop-2-yn-1-one **2a** in the presence of 10 mol % of Ph_3P and 5 mol % of CuOAc, the formation of pyrrololactam **3a** was observed at ambient temperature in a 20% yield (entry 4). The reaction at higher temperature increased the yield to 68% (entry 5); however, a further attempt to elevate the reaction temperature using 1,4-dioxane was not successful (entry 6). The change of counterions from −OAc to −OTf led to a dramatic deceleration of the reaction rate (entry 7), implying the possible role of OAc as a base.[14] Consequently, the screening of Brønsted bases was conducted (entries 8–11) and swiftly led to the identification of an optimal base, *t*-BuOK, where the desired pyrrololactam **3a** was isolated in a 82% yield (entry 8). The reaction time could be shortened from 3 to 1 h by increasing the reaction temperature to 100 °C in 1,4-dioxane (entry 12). Reactions in DMSO and $PhCH_3$ were not satisfactory (entries 13 and 14). Other copper salts were also tested; however, the reaction yields were largely held to 28–49% (entries 15 and 16). A control experiment confirmed the inactivity of *t*-BuOK in the formation of pyrrololactam **3a**. Interestingly, unlike the cases with 2,2-disubstituted 2*H*-pyrroles,[11] the products from alkyne–isocyanide [3 + 2] cycloaddition reactions, the

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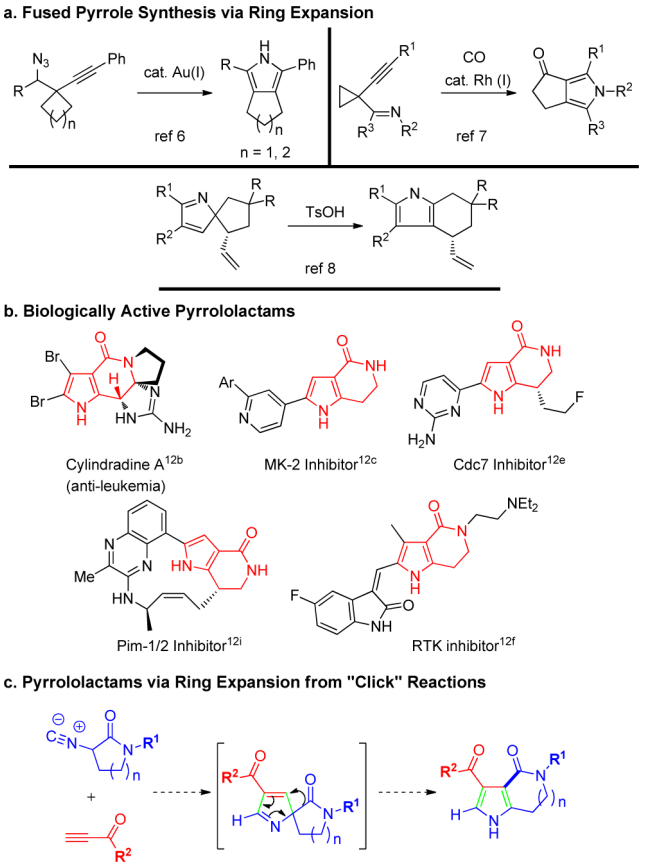
Scheme 1. Ring-Expansion Approaches to Fused Pyrroles and Pyrrololactams

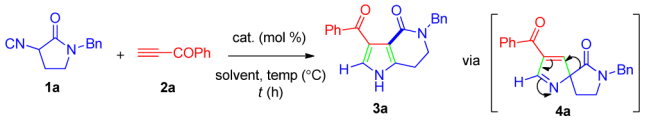


formation of spiro-2*H*-pyrrole **4a**, a possible precursor to **3a**, was not observed during the reaction.[15]

The optimized conditions for pyrrololactam via one-pot alkyne−isocyanide [3 + 2] cycloaddition followed by a ring expansion were further scrutinized using other *α*-isocyano lactams and alkynes (Scheme 2). The employment of electronically and sterically diverse alkyl- and arylalkynones smoothly provided 6-membered pyrrololactams **3a−i** in 54−82% yields. Generally, the arylalkynones with electron-donating groups (**3b−d**) and sterically demanding group (**3h**) required a longer reaction time of 12 h. The use of 6-membered *α*-isocyano lactam **1b** led to the formation of 7-membered pyrrololactams **3j−m** in comparable yields. Gratifyingly, the chemistry could be also applied to the synthesis of 8-membered pyrrololactams **3n−q** using 7-membered *α*-isocyano lactam **1c** and aryl/alkylalkynones. The *N*-benzyl group of *α*-isocyano lactams could be switched to *p*-methoxybenzyl (PMB) and *p*-methoxyphenyl (PMP) without a significant loss of yields and reaction times (**3r**-**3u**). The use of alkynyl esters could be also tolerated in the current pyrrololactam synthesis (**3v,w**). The limitation of the current method exists upon employing 4-membered *α*-isocyano lactam **1d**, where the decomposition of **1d** predominates over the formation of pyrrololactam products.

The one-pot functionlization of pyrrololactams was further explored using either an excess of alkynyl methyl ester or a sequential treatment with *tert*-butyl acrylate (Scheme 3). While the isolated yields of pyrrololactams were somewhat lower in 35−51% yields,[16] the one-pot synthesis of tetrasubstituted pyrrololactams (**3x−aa**) amply demonstrated the further synthetic potential of the current method.

Table 1. Optimization of the Synthesis of Pyrrololactam[a]



entry	cat. (mol %)	solvent	temp (°C)	time (h)	yield[b] (%)
1	Ph_3P (10)	THF	23	12	0
2	Cy_3P (10)	THF	66	12	0[c]
3	CuOAc (10)	THF	66	24	0[c]
4	CuOAc (5) Ph_3P (10)	THF	23	24	20
5	CuOAc (5) Ph_3P (10)	THF	66	3	68
6	CuOAc (5) Ph_3P (10)	1,4-dioxane	100	3	47
7	CuOTf (5) Ph_3P (10)	THF	66	3	<2[c]
8	CuOAc (5) *t*-BuOK (10)	THF	66	3	82
9	CuOAc (5) K_2CO_3 (10)	THF	66	5	73
10	CuOAc (5) Et_3N (10)	THF	66	12	0[c]
11	CuOAc (5) DBU (10)	THF	66	6	47
12	CuOAc (5) *t*-BuOK (10)	1,4-dioxane	100	1	79
13	CuOAc (5) *t*-BuOK (10)	DMSO	100	0.5	68
14	CuOAc (5) *t*-BuOK (10)	$PhCH_3$	100	4	38
15	$Cu(OAc)_2$ (5) *t*-BuOK (10)	THF	66	4	49
16	$Cu(OTf)_2$ (5) *t*-BuOK (10)	THF	66	4	28[c]

[a]Reaction conditions: **1** (0.2 mmol) and **2** (0.22 mmol) in solvents (0.10 M) under argon. [b]Isolated yield of products after column chromatography. [c]Partial decomposition of **1a**/**2a**.

The rate comparison experiments of lactams with different ring sizes suggested that the formation of pyrrololactams might be influenced by the cycloaddition reaction step (Scheme 4a). Thus, the use of acyclic *α*-isocyano amide also provided the corresponding pyrrole product without the 2*H*-pyrrole intermediate. The facile ring expansion of spiro-2*H*-pyrroles to pyrrololactams could be explained by invoking the conformational rigidity of spiro-2*H*-pyrroles that readily allows the orbital overlap between the $\pi^*_{C=C}$ bond of internal alkene and the $\pi_{C=O}$ bond of electron-withdrawing group.[17] Thus, unlike the 2*H*-pyrroles that were previously observed during the alkyne−isocyanide [3 + 2] cycloaddition reactions,[11] the spiro-2*H*-pyrroles could not be identified during the reactions between *α*-isocyano lactams and alkynes. These observations strongly imply that the conformational flexibility of 2*H*-pyrroles deters the 1,2-bond migration (Scheme 4b), whereas the conformationally locked spiro-2*H*-pyrroles undergo a facile ring expansion to pyrrololactams (Scheme 4c). The conformational rigidity of the spiro-2*H*-pyrroles would enforce the alignment between the internal alkene and the amide carbonyl group. In addition, since the large bond angle (ψ) facilitates the 1,2-bond migration of the spiro-2*H*-pyrroles, the 6-membered spiro-2*H*-pyrroles with a larger bond angle (114.4° ± 0.2°)[18] should

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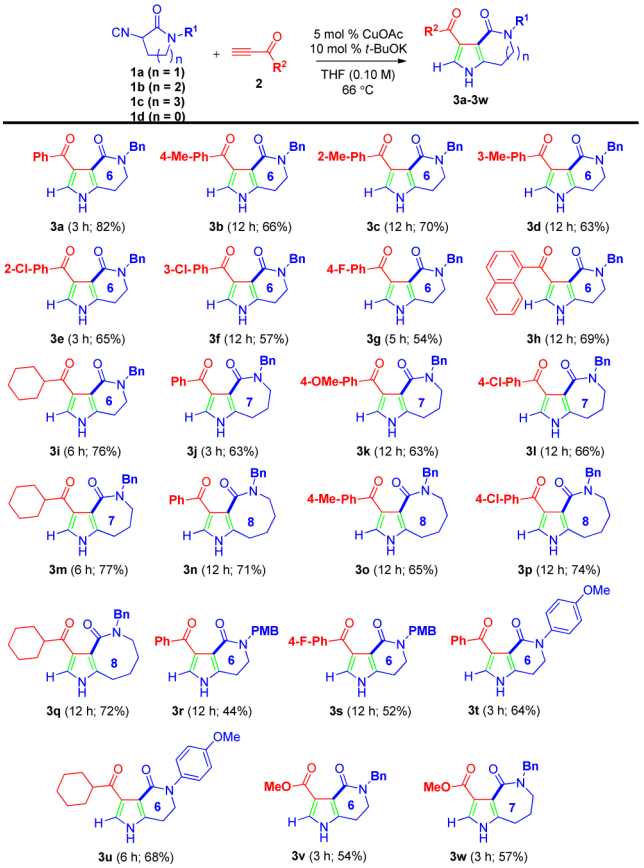
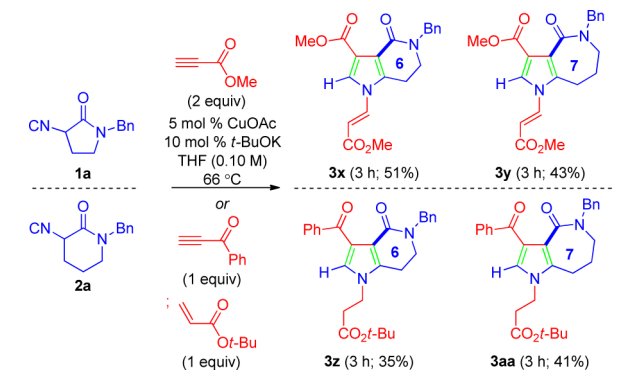
Scheme 2. Scope of the Synthesis of 6- to 8-Membered Pyrrololactams



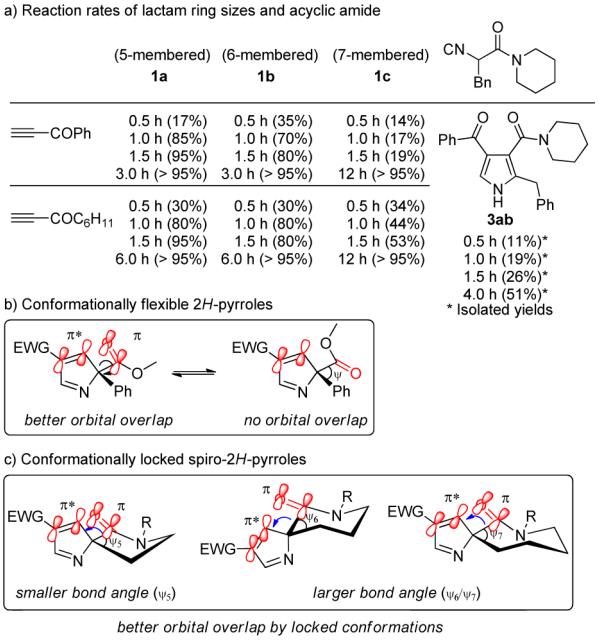
Scheme 3. One-Pot Synthesis of Tetrasubstituted Pyrrololactams



display a faster ring expansion aptitude over the 5-membered spiro-2*H*-pyrroles with a smaller bond angle (101−106.5°).[19]

In summary, we have developed a facile one-pot synthesis of 6- to 8-membered pyrrololactams using the intermolecular alkyne−isocyanide [3 + 2] cycloaddition reaction followed by a spontaneous ring expansion of spiro-2*H*-pyrrole intermediates. The conformationally locked spiro-2*H*-pyrroles are believed to enforce the alignment between the internal alkene and the amide carbonyl group for better orbital overlap that induces a subsequent ring expansion. Importantly, by utilizing newly disclosed α-isocyano lactams, the highly substituted pyrrolo-lactams are readily accessed. The extension of the 1,2-bond migration strategy to other heterocycles is currently being

Scheme 4. Facile Ring Expansion via Conformationally Locked Spiro-2*H*-pyrroles



investigated in our laboratory, and our results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03786.

Experimental procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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