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Base-Mediated Regiospecific Cascade Synthesis of *N*-(2-Pyridyl)pyrroles from *N*-Propargylic β-Enaminones

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A KOH-promoted regiospecific synthesis of polysubstituted *N*-(2-pyridyl)pyrroles under transition metal-free conditions has been developed. The pyrrole and pyridine rings were simultaneously installed from acyclic enaminone precursors under mild conditions and generated 1 equiv of H_2O as the sole byproduct. A series of polysubstituted *N*-(2-pyridyl)pyrroles were provided in up to 91% yield for 21 examples.

N-(2-Pyridyl)pyrrole is an important heterocycle and key skeleton in natural products, pharmaceuticals and advanced functional materials,[1] which are exemplified by four examples shown in Figure 1. Consequently, developing mild and efficient access to *N*-(2-pyridyl)pyrroles is of great significance.

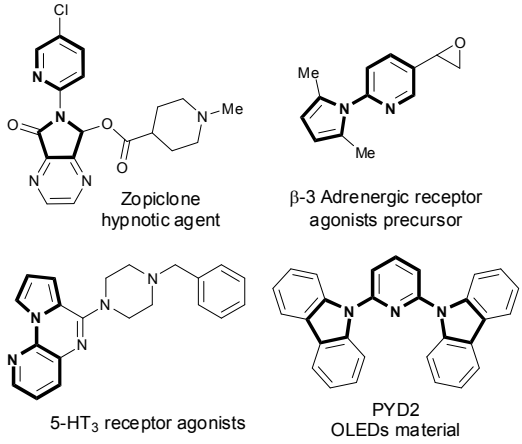
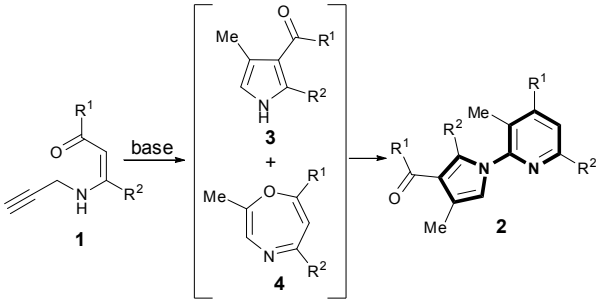


Fig. 1. Four examples illustrating the importance of the *N*-(2-pyridyl)pyrrole.

Conventionally, *N*-(2-pyridyl)pyrroles have been synthesized by the Paal-Knorr reaction from 2-amino-pyridines with 1,4-dicarbonyl compounds[2] (or 2,5-dimethoxytetrahydrofuran[3]). Recently, copper-catalysed Ullmann-type coupling of 2-halopyridines with pyrroles has been developed as a straightforward method to construct such a structure.[4] However, in this procedure the pyridine scaffold and the pyrrole ring need to be constructed in advance. Moreover, the requirement of a transition metal may cause contamination of the products that limits their applications, especially in the pharmaceutical industry.[5] Therefore, a general and metal-free procedure to synthesize *N*-(2-pyridyl)pyrroles under mild reaction conditions remains highly desirable.

Recently, cascade reactions have received much attention for the assembly of complicated molecules from relatively simple starting materials in an economically favourable process.[6] Among which, the interception of *in situ* generated reactive species has been perceived as a powerful shortcut for the discovery of new cascade reactions with high efficiency. Due to the presence of nucleo/electro-philic enaminone[7] and a highly reactive C≡C triple bond, *N*-propargylic β-enaminones **1** may be a potential precursor of cascade reactions and their utilization in organic synthesis remains a subject of great current interest.[8] In 2008, Cacchi and co-workers reported that *N*-propargylic β-enaminones **1** could be selectively transformed into pyrroles via a base-promoted *5-exo-dig* cycli-



Scheme 1. Proposed route to *N*-(2-pyridyl)pyrroles.

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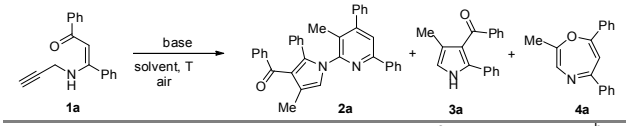
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

zation (Scheme 1, **3**).[9] According to our previous work,[10] 1,4-oxazepines can also be formed via a *7-exo-dig* cyclization under basic conditions (Scheme 1, **4**). We assumed that the highly reactive species **4** might be trapped by the pyrrole **3** (formed *in situ*) to give *N*-(2-pyrcidyl)pyrroles **2** in the presence of a suitable base. In continuation of our effort on enaminone chemistry,[11] herein we describe a base-mediated regiospecific synthesis of *N*-(2-pyridyl)pyrroles from *N*-propargylic enaminones (Scheme 1). As far as we know, this is the first report to simultaneously build pyrrole and pyridine rings from an acyclic precursor under metal-free conditions.[12]

1,3-Diphenyl-3-(prop-2-yn-1-ylamino)-2-propen-1-one **1a** was chosen as a model substrate to optimize the reaction parameters. Initially, the model reaction of **1a** was examined using KOH/ DMSO system, which was used as a base/solvent system for *N*-pyridylation of heteroarenes in our previous report.[10] To our delight, the desired *N*-(2-pyridyl)pyrrole product **2a** was obtained in 28% yield as well as pyrrole **3a** in 40% yield. The structure of **2a** was confirmed by single crystal X-ray diffraction (see ESI for details). Then a series of solvents was screened, and the results showed that aprotic solvents favoured the formation of the desired product **2a** and CH_3CN turned out to be the most effective solvent (Table 1, entries 1-7). The KOH/DMSO system, being of stronger basicity,[13] may

Table 1. Screening the reaction parameters.[a]



Entry	Base	Solvent	Temp (^oC)	Yield (%)[b] **2a**:**3a**:**4a**
1	KOH	DMSO	120	28:40:0
2	KOH	DMF	120	85:0:0
3	KOH	DMAc	120	86:0:0
4	KOH	Dioxane	reflux	trace:45:0
5	KOH	EtOH	reflux	0:12:0
6	KOH	Toluene	reflux	0:0:0
7	**KOH**	**CH_3CN**	**reflux**	**91:0:trace**
8	Cs_2CO_3	CH_3CN	reflux	85:trace:0
9	NaOH	CH_3CN	reflux	79:8:0
10	NaOtBu	CH_3CN	reflux	30:35:0
11	KOtBu	CH_3CN	reflux	23:43:0
12	K_2CO_3	CH_3CN	reflux	0:0:0
13	Et_3N	CH_3CN	reflux	0:0:0
14	DABCO	CH_3CN	reflux	0:0:0
15[c]	KOH	CH_3CN	reflux	82:0:10
16[d]	KOH	CH_3CN	reflux	62:0:16
17	KOH	CH_3CN	60	78:0:11
18[e]	KOH	CH_3CN	reflux	90:0:trace
19[f]	KOH	CH_3CN	reflux	90:0:trace
20	----	CH_3CN	reflux	0:0:0
21[g]	KOH	CH_3CN	reflux	92:0:trace

[a] Reaction conditions: **1a** (0.5 mmol), and base (1 mmol) in solvent (2 mL) at corresponding temperature for 30 min. [b] Isolated yield. [c] 0.75 mmol of base was used. [d] 0.15 mmol of base was used for 2 h. [e] 2.0 equiv of TEMPO (2,2,6,6-tetramethylpiperidinooxy) was added. [f] under N_2 atmosphere. [g] Use highly pure KOH (99.999% purity). DMF = N,N-dimethylformamide. DMSO = dimethylsulfoxide.

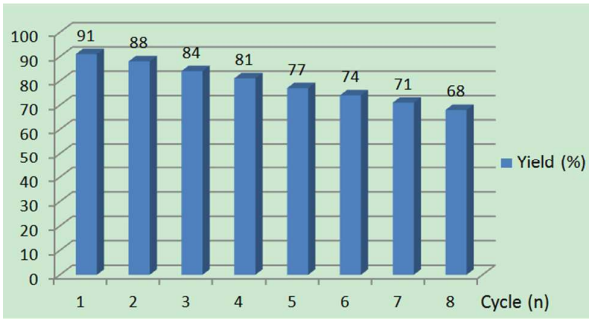
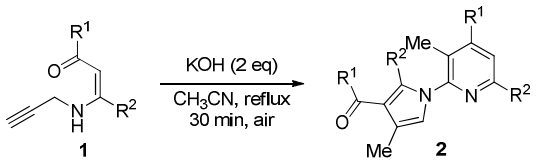


Fig. 2. Recycling KOH.

favour the formation of pyrrole **3a** through the *5-exo-dig* cyclization, which resulted in a lower yield of **2a**. Further investigation on the influence of base supported our hypothesis. An acceptable yield of **2a** was achieved in the presence of Cs_2CO_3 and NaOH (Table 1, entries 8-9). High-alkaline bases, such as NaO*t*Bu and KO*t*Bu, gave pyrrole **3a** as main product (35% and 43%, respectively, entries 10-11). In contrast, no reactions occurred when weaker bases, such as K_2CO_3, Et_3N or DABCO (1,4-diaza[2.2.2]bicyclooctane), were used (Table 1, entries 12-14). Decreasing the amount of KOH from 2 equiv to 1.5 equiv resulted in a lower yield of **2a** (Table 1, entry 15). Remarkably, a respectable 62% yield of **2a** was achieved using 0.3 equiv of KOH (entry 16). The requirement of high loading of base might be due to the low solubility of KOH in CH_3CN.[14] Decreasing reaction temperature resulted in a lower yield (Table 1, entry 17). When a radical-trapping reagent, 2,2,6,6-tetramethylpiperidinooxy (TEMPO), was added to the reaction, the yield of the product was not influenced significantly, indicating that the radical pathway is not likely to be involved in this transformation (Table 1, entry 18). Under N_2 atmosphere, the reaction provided a similar result (entry 19 *vs* 7). The starting substrate remains unreactive without base (Table 1, entry 20). To avoid the involvement of transition metals in the reaction, KOH (99.999% purity) was used instead of a purity of 98%, providing a similar yield (92%, entry 21 *vs* 7), indicating that the purity of KOH was irrelevant here. Importantly, the base could be simply recovered and reused by simple filtration after the reactions was finished. The reactivity of KOH gradually lost during the eight recycles (Figure 2).

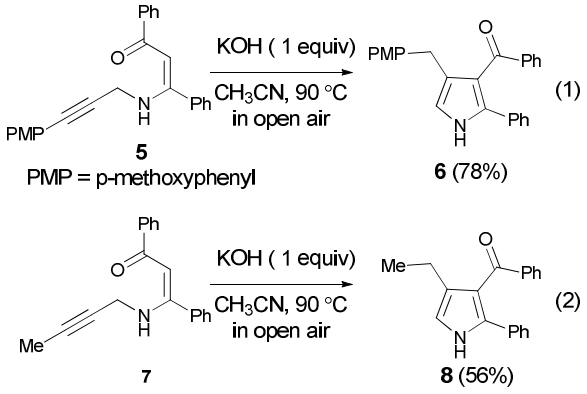
The scope and generality of the substrates for this process was next investigated under the optimized reaction conditions (Table 1, entry 7). As shown in Table **2,** R^1 in substrate **1** could be either electron-rich or electron-deficient aryl groups, and provided the corresponding *N*-(2-pyridyl)pyrroles in 64-89% yields (entries 1-10). Due to steric hindrance, the substrates with *para*-substitutents gave slightly higher yields than those with *ortho*-substitutents (entries 3, 5 *vs* entries 2, 4). Halogens, such as F, Cl and Br were all tolerated well, which made this reaction particularly attractive for increasing the molecular complexity by transition-metal-catalyzed coupling reactions. Moreover, when R^1 is a heteroaryl group, such as 2-thienyl, this transformation still could proceed smoothly and gave the multi-heterocycle product **2k** in 69% yield (entry 11). Alkyl groups, such as isopropyl- and cyclohexyl-, were also tolerated, although giving the desired products in declined yields (entries 12-13).

Table 2. Substrate scope.[a]

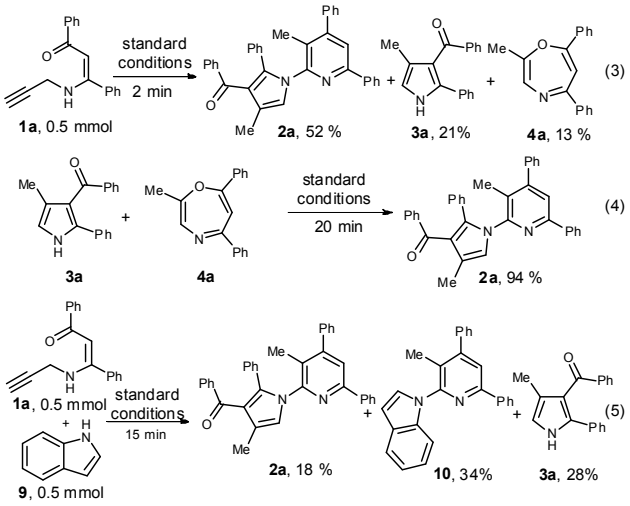


Entry	1	R^1	R^2	2	Yield (%)[b]
1	**1a**	Ph	Ph	**2a**	91
2	**1b**	2-MeC_6H_4-	Ph	**2b**	78
3	**1c**	4-MeC_6H_4-	Ph	**2c**	81
4	**1d**	2-BrC_6H_4-	Ph	**2d**	75
5	**1e**	4-BrC_6H_4-	Ph	**2e**	81
6	**1f**	4-ClC_6H_4-	Ph	**2f**	77
7	**1g**	4-FC_6H_4-	Ph	**2g**	76
8	**1h**	4-MeO$C_6H_4$4-	Ph	**2h**	80
9	**1i**	4-$CF_3C_6H_4$-	Ph	**2i**	70
10	**1j**	Naphthalen-2-	Ph	**2j**	85
11	**1k**	Thiophen-2-	Ph	**2k**	69
12	**1l**	Isopropyl-	Ph	**2l**	28
13	**1m**	Cyclohexyl-	Ph	**2m**	45
14	**1n**	Ph	2-MeC_6H_4-	**2n**	73
15	**1o**	Ph	3-MeC_6H_4-	**2o**	85
16	**1p**	Ph	4-MeC_6H_4-	**2p**	91
17	**1q**	Ph	4-BrC_6H_4-	**2q**	74
18	**1r**	Ph	4-ClC_6H_4-	**2r**	71
19	**1s**	Ph	4-FC_6H_4-	**2s**	88
20	**1t**	Ph	4-MeOC_6H_4-	**2t**	78
21	**1u**	Ph	Thiophen-2-	**2u**	75

[a] Reactions were carried out in open air on a 0.5 mmol scale using 2 equiv of KOH in 2 mL of CH_3CN under refluxing for 30 min. [b] Isolated yield.



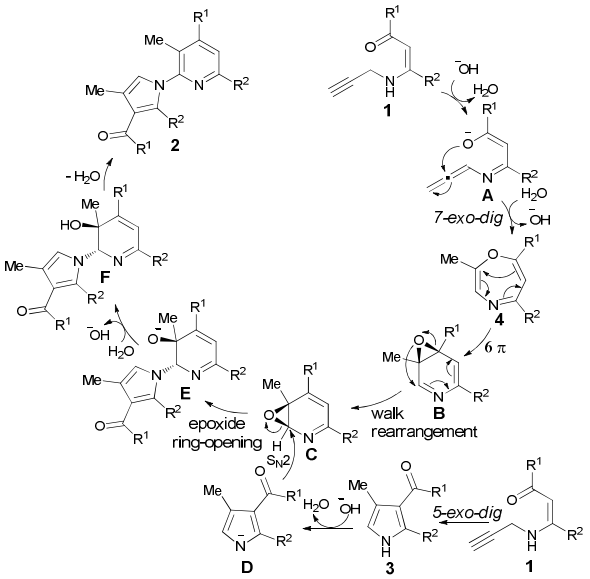
The scope of the R^2 group in the substrate was also investigated. In general, R^2 could be electron- rich or electron-deficient aryls or heteroaryls (entries 14-21). The steric hindrance did not significantly affect this reaction. Substrates with *ortho-*, *meta-*, or *para-* methyl substituents did not diminish the efficiency of this transformation (entries 14-16). Heterocyclic substituents are also suitable, albeit with slightly lower efficacy (entry 21). When R^2 is alkyl group, such as *n*-butyl, the substrate was decomposed. No main product could be obtained. Free acetylene group is essential to get the desired product. When phenyl and methyl-tethered *N*-propargylic β-enaminone, 3-((3-(4-methoxyphenyl)prop-2-yn-1-yl)amino)-1,3-diphenylprop-2-en-1-one **5** and 3-(but-2-yn-1-ylamino)-1,3-diphenylprop-2-en-1-one **7**, were employed as starting materials in this reaction, only pyrrole **6** and **8** were afforded *via* base-promoted *5-exo-dig* cyclization (Eq 1-2).



Scheme 2. Controlled experiment.

In order to gain insight into the mechanism, some controlled experiments were carried out (Scheme 2). When the reaction of *N*-propargylic β-enaminone **1a** under standard conditions was quenched by water after 2 min, besides the desired product **2a**, pyrrole **3a** and 1,4-oxazepine **4a** were obtained in 21% and 13% yields, respectively (Eq 3). The reaction of pyrrole **3a** and 1,4-oxazepine **4a** under the standard conditions gave the desired product **2a** in 94% yield (Eq 4), suggesting pyrroles **3** and 1,4-oxazepines **4** were generated *in situ* and involved in this cascade reaction. Moreover, when an external nucleophile **9** was added into the reaction of **1a** under the standard conditions, *N*-(2-pyridyl)pyrrole product **2a** was obtained in 18% yield, as well as *N*-(2-pyridyl)indole **10** in 34% yield and pyrrole **3a** in 28% yield (Eq 5), indicating that pyrrole **3a** and 1,4-oxazepine **4a** were formed in roughly equal amounts during the process of the reaction.

On the basis of the aforementioned observations and our previous work,[10] a tentative mechanism for the formation of functionalized *N*-(2-pyridyl)pyrroles **2** was proposed, as depicted in Scheme 3. On one hand, base-promoted *5-exo-dig* cyclization of **1** provided the substituted pyrrole scaffolds **3**. On the other hand, base-mediated propargyl–allenyl isomerisation and enolization of **1** generated iminoenolate intermediates **A**, followed by intramolecular 7-*exo-dig* cyclization to afford 1,4-oxazepines **4**, which subsequently underwent a 6π-electrocyclization, and a walk rearrangement to give epoxide intermediates **C**. S_N2 attack of pyrrole anions **D** resulted in an epoxide ring-opening of **C** to generate *trans*-2,3-dihydropyridine intermediates **E**. Finally, the protonation and dehydrative aromatization led to the desired products **2**.



Scheme 3. Plausible reaction mechanism.

Conclusions

In summary, we have described a novel and highly efficient base-promoted cascade reaction for the synthesis of the diverse *N*-(2-pyridyl)pyrroles from *N*-propargylic β-enaminones by tuning the basicity of reaction conditions. This procedure simultaneously facilitated the construction of a pyridine scaffold and generation of a pyrrole ring, and tolerated a wide range of functional groups. The formation of 1,4-oxazepines, and interception by the pyrroles generated *in situ* were key steps in this metal-free cascade reaction. This protocol only required 2 equiv of KOH as an additive, and it generated 1 equiv of H_2O as the sole byproduct, thereby making this process atom economic and environmentally friendly.

Acknowledgements

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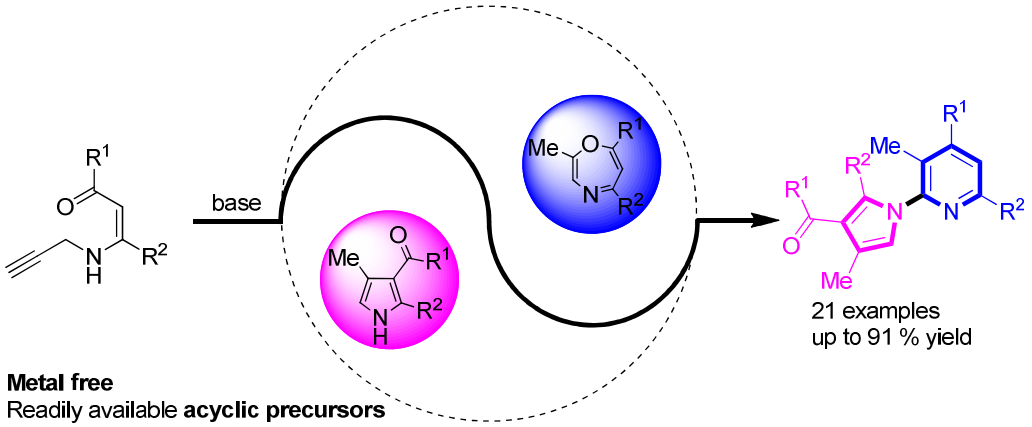

Metal free
Readily available **acyclic precursors**
Simultaneous construction of **pyrrole** and **pyridine** ring

Two birds with one stone: **Two** classical heterocycles, pyrrole and pyridine, were simultaneously installed from **one** acyclic enaminone precursor for the preparation of *N*-(2-pyridyl)pyrroles.