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Base-Promoted N-Pyridylation of Heteroarenes Using *N*-Propargyl Enaminones as Equivalents of Pyridine Scaffolds

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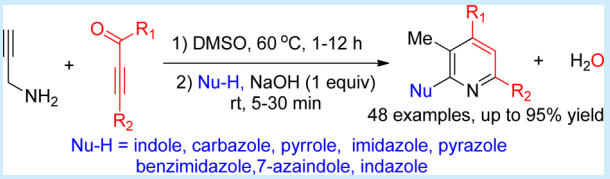
Supporting Information

ABSTRACT: N-Pyridylation of various N-heteroarenes, including N-heteroarene-containing peptides, was achieved using *N*-propargyl enaminones (isolated or generated in situ from propargyl amine and propynones) as masked polysubstituted pyridine cores. This metal-free procedure proceeds under mild reaction conditions and generates 1 equiv of H_2O as the sole byproduct.

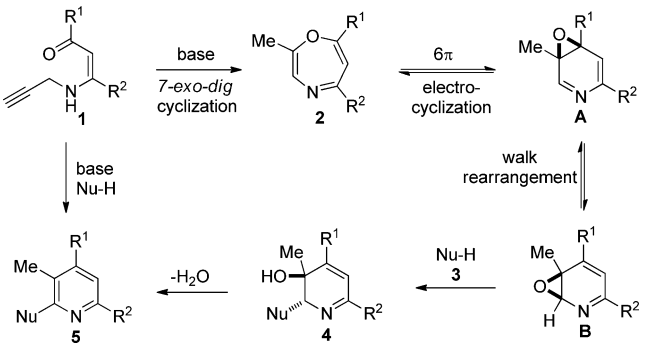


Pyridines represent one of the most important classes of heterocyclic compounds.[1] Among them, heteroaryl-containing pyridines have attracted much research interest due to their prevalence in agrochemicals,[2] pharmaceuticals,[3] and advanced materials.[4] Over the past decade, various synthetic methods,[5] including transition-metal-catalyzed reactions,[6] organocatalyzed reactions,[7] and the metal-free reactions,[8] have been developed to selectively synthesize highly functionalized pyridine derivatives. Despite these advances, the Ullman-type N-pyridylation of heteroarenes is still the most commonly used method for constructing *N*-pyridyl heteroarenes, which requires functionalized pyridine cores as the starting materials.[9] Novel approaches to these motifs are rare and remain to be explored.[10]

In organic synthesis, the cascade reactions are used to reduce waste, avoid isolating intermediates, and improve the reaction efficiency. We recently have described a cascade reaction for the synthesis of 1,5-disubstituted 1,2,3-triazoles from enaminones.[11a] In the exploration of this reaction, an unexpected seven-membered ring 1,4-oxazepine **2** was observed from *N*-propargyl enaminones **1**.[12] It was considered that an equilibrium might exist between 1,4-oxazepines **2** and the epoxide intermediates **B** through a 6π-electrocyclization/walk rearrangement cascade reaction.[13] Intermediate **B** is proposed to be trapped by a suitable nucleophile to form 2,3-dihydropyridines **4**, which would be further aromatized to give substituted pyridines **5** (Scheme 1).

In our initial survey, indole **3a** and 1,3-diphenyl-3-(propargylamino)-2-propen-1-one **1a** were used as substrates to verify the above hypothesis (Table 1). To our delight, the desired product **5aa** was isolated in 35% yield when the mixture of **3a** and **1a** in DMSO was treated with LiO*t*Bu for 5 min (entry 1).[14] Its molecular structure was confirmed by single crystal X-ray diffraction. Acceptable yields were achieved in the presence of other strong bases, such as NaO*t*Bu, KO*t*Bu, NaOEt, KOH, and NaOH (entries 2−6). NaOH gave the best result, affording **5aa** in 90% yield (entry 6). In contrast, no reactions occurred when weak bases, such as K_2CO_3 or Et_3N, were used (entries 7, 8). Further investigation showed that

Scheme 1. A Proposed Route to Pyridine Derivatives from *N*-Propargyl Enaminones



polar aprotic solvents favored this transformation (entries 9−13). However, no better result was obtained than DMSO. Remarkably, a respectable 76% yield of **5aa** was achieved using 0.3 equiv of NaOH (entry 14).

With the optimal reaction conditions established, we started our investigation by reacting enaminone **1a** with different indoles (Scheme 2). A diverse set of functional groups, such as alkoxy, halogen, cyano, formyl, and nitro, were tolerated in this procedure owing to the mild reaction conditions. Electron-donating groups in the indole ring **5ab**, **5ac** led to higher yields than stronger electron-withdrawing groups **5ah**−**aj**, probably because electron-donating substituents enhanced the nucleophilicity of N atom of indole. It was obviously observed that the steric hindrance on the C2- or C7-position of indole lowered the nucleophilicity of the N atom and affected the reaction efficiency **5al**−**ao**. Notably, double N-pyridylation of bis-(indole) could afford the desired product **5ap** in 55% yield. This heteroaryl-containing pyridine with C_2 symmetry is expected to be developed as a new functional material or ligand in an organic reaction. Next, we focused our attention on

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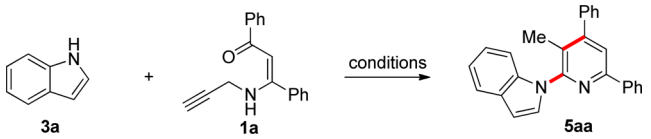
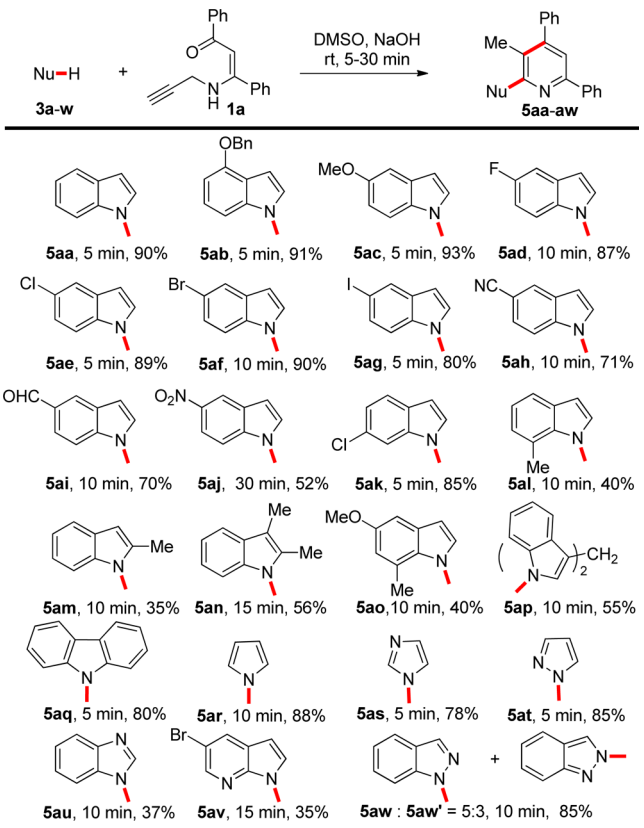
Table 1. Optimizing the Reaction Conditions for the Cascade Reaction of Indole 3a with 1,3-Diphenyl-3-(propargylamino)-2-propen-1-one 1a[a]



entry	solvent	base	time (min)	yield (%)[b]
1	DMSO	LiO*t*Bu	5	35
2	DMSO	NaO*t*Bu	5	86
3	DMSO	KO*t*Bu	5	78
4	DMSO	NaOEt	60	60
5	DMSO	KOH	5	87
6	**DMSO**	**NaOH**	**5**	**90**
7	DMSO	K_2CO_3	60	0
8	DMSO	Et_3N	60	0
9	DMF	NaOH	5	88
10	NMP	NaOH	5	89
11	MeOH	NaOH	60	0
12	THF	NaOH	60	0
13	toluene	NaOH	60	0
14[c]	DMSO	NaOH	60	76

[a]Reaction conditions: **3a** (0.5 mmol), **1a** (0.5 mmol), base (0.5 mmol), in 1 mL solvent, rt. [b]Isolated yields. [c]0.15 mmol base. DMSO = dimethyl sulfoxide. DMF = *N*,*N*-dimethylformamide. NMP = *N*-methyl-2-pyrrolidone. THF = tetrahydrofuran.

Scheme 2. Scope of N-Nucleophiles[a]

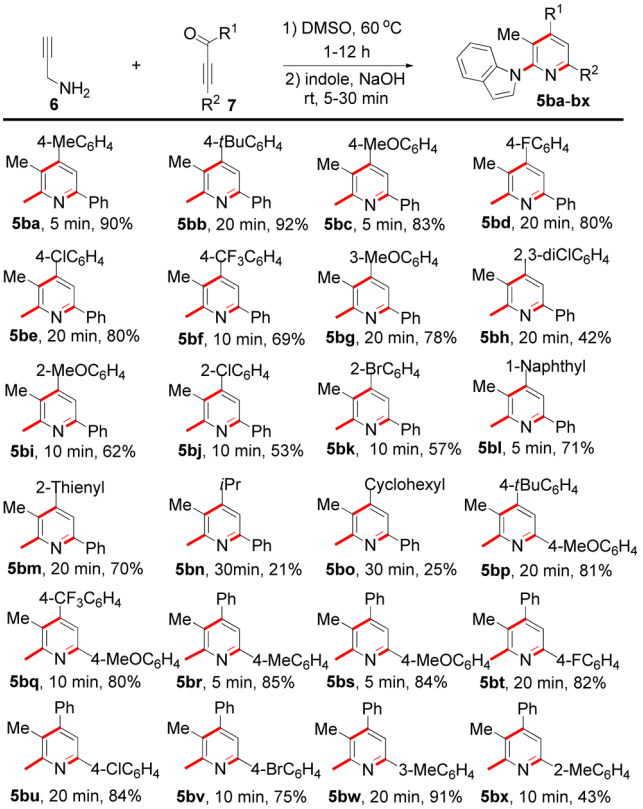


[a]Reaction conditions: **3a** (0.5 mmol), **1a** (0.5 mmol), NaOH (0.5 mmol), DMSO (1 mL), rt.

investigating the scope of other N-heteroarenes. Delightfully, various N-heteroarenes, including carbazole, pyrrole, imidazole, and pyrazole, furnished the corresponding products **5aq–at** in good yields. Benzimidazole and 7-azaindole were less reactive and gave the corresponding products in lower yields. Moreover, indazole could be employed in this process with good efficiency. A mixture of 1*H*-indazole **5aw** and 2*H*-indazole **5aw′** was generated in 85% total yield. In all cases, these rapid reactions were completed within 30 min. Furthermore, other nucleophiles, such as benzylamine, aniline, acetanilide, succinimide, and benzyl thiol, were also tested. No desired products were observed.

Our previous works have indicated that *N*-propargyl enaminones **1** could be easily prepared from propargyl amine **6** and propynones **7**.[11] Thus, a "one pot" two-step strategy to construct 2-(1-indolyl)pyrindes **5ba–bx** starting from **6** and **7a–x** was examined (Scheme 3). It was worth noticing that the

Scheme 3. Scope of Propynones[a]



[a]Reaction conditions: **6** (0.55 mmol), **7** (0.5 mmol), DMSO (1 mL), 60 °C. After the reaction mixture was cooled to rt, indole (0.5 mmol) and NaOH (0.5 mmol) were added. Isolated yields based on **7**.

reaction was equally successful with both isolated and *in situ* generated **1**. As illustrated in Scheme 3, the reaction was not significantly affected by the electronic effects of the substituents. Propynones **7** bearing electron-rich or electron-deficient groups on R^1- or R^2- were both effective. When sterically hindered propynones were used as substrates, the corresponding products **5bh–bk**, **5bx** were furnished in lower yields. Remarkably, 1-naphthalenyl and 2-thienyl propynones were suitable substrates, affording **5bl**, **5bm** in 71% and 70% yields, respectively. However, alkyl groups on R^1- affected the reaction efficiency. No desired product was formed when R^2-

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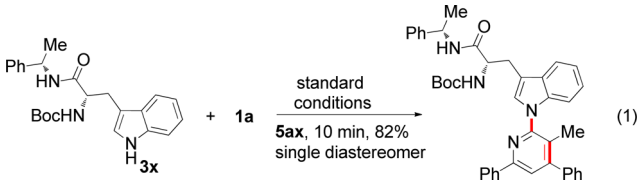
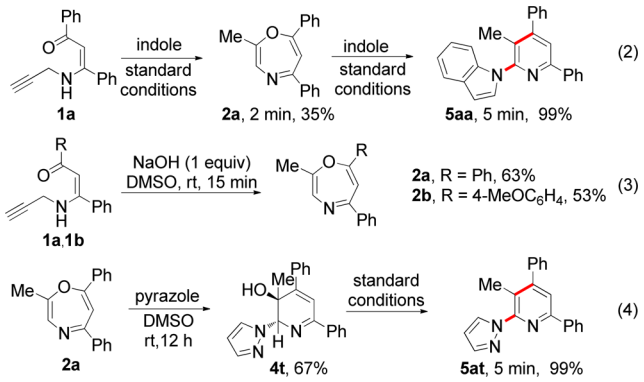
was an alkyl group. 3-Phenylprop-2-yn-1-amine **8** was also used instead of **6** to further explore the substrate scope; however, the desired product was not formed.

The Ullman-type N-pyridylation of heteroarenes is often carried out at elevated temperatures (100−190 °C), in the presence of copper salts and bases.[9] The harsh reaction conditions of Ullman reactions limited its application in the pharmaceutical industry and life science because of the metal contamination and the racemization of chiral compounds. These challenges prompted us to explore our procedure in the modification of complex molecules, especially peptides. As expected, L-tryptophane-containing dipeptide **3x** could be modified, affording **5ax** in 82% yield as a single diastereomer (eq 1).



(1)

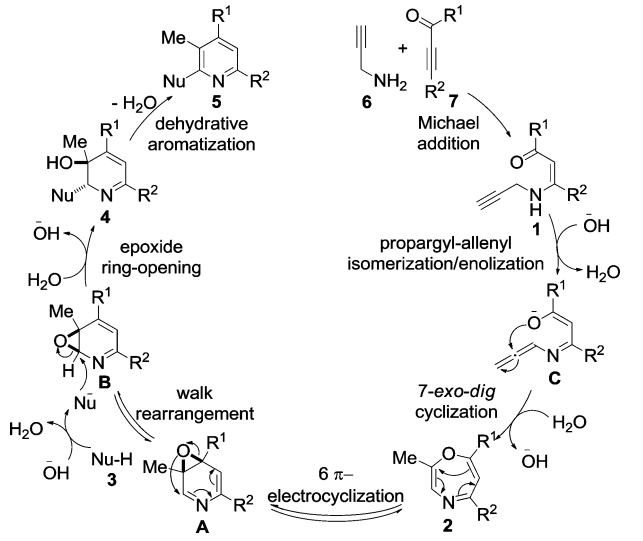
To understand the mechanism of this cascade reaction, some experiments were carried out. When the standard reaction of **1a** with indole was quenched with water after 2 min, the 1,4-oxazepine intermediate **2a** was isolated in 35% yield, which could be further transformed into the desired product **5aa** in nearly quantitative yield (eq 2). As expected, **2a** and **2b** could



be obtained from **1a** and **1b**, respectively, under standard conditions in the absence of indole (eq 3).[14] The tentative 2,3-dihydropyridine intermediate **4** was not observed during the reaction, presumably because the dehydrative aromatization rate of **4** is faster than the formation rate of **4** under basic conditions. Thus, various N-heteroarenes were tested to generate intermediate **4** in the absence of a base. To our delight, when pyrazole was used as a nucleophile, the desired intermediate **4t** was formed in 67% yield. The configurations of **4t** were assigned based on the 2D-NOESY NMR spectroscopy, where the pyrazole group is *trans* to the hydroxyl group. In this case two adjacent stereocenters were created simultaneously and no diastereoisomer was formed. Finally, **5at** could be generated in almost quantitative yield from **4t** under the standard conditions (eq 4).

Based on the experimental results obtained, the reaction mechanism was proposed. As shown in Scheme 4, an initial propargyl−allenyl isomerization/enolization cascade reaction of enaminones **1** formed iminoenolate intermediates **C**.[15] The intramolecular 7-*exo*-*dig* cyclization of **C** provided 1,4-

Scheme 4. Proposed Reaction Mechanism



oxazepines **2**, which subsequently isomerized to give epoxide intermediates **B** via a 6π-electrocyclization/walk rearrangement cascade reaction.[16] Epoxide ring opening of **B** with N-heteroarenes proceeds via S_N2 substitution, generating *trans*-2,3-dihydropyridine intermediates **4**. At last, the dehydrative aromatization of **4** leads to the final products **5**.

In conclusion, we have described a general and operationally simple method to construct diverse 2-(1-heteroaryl) pyridines from the reaction of *N*-propargyl enaminones with N-heteroarenes. This procedure allowed the formation of one pyridine core and one C−N bond in "one pot", and it showed a wide range of functional group tolerance. This protocol only required 1 equiv of NaOH as an additive, and it generated 1 equiv of H_2O as the sole byproduct, thereby making this process environmentally friendly and atom economic. Moreover, this new process could be applied to modify heteroarene-containing complex molecules, such as peptides.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H NMR and ^{13}C NMR for all synthesized compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01733.

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Notes

The authors declare no competing financial interest.

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(16) We cannot deny the following pathway: a conjugate addition of the nucleophile **3** to intermediate **A** directly delivers compound **4**.

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