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Accessing 1,8-Naphthyridones by Metal-Free Regioselective Amination of Pyridine *N*-oxides/Acid-Mediated Cyclization

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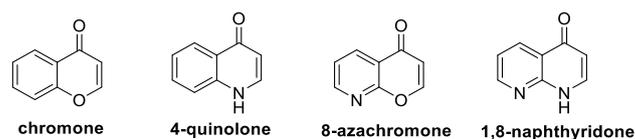
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Abstract. A concise and practical method for the metal-free synthesis of 1,8-naphthyridones is described using a two-step approach involving regioselective amination of pyridine *N*-oxides and acid-mediated cyclization. This is the first synthesis of 1,8-naphthyridones utilizing easily accessible pyridine *N*-oxides as substrates. Compared to previous reports, this method benefits from simple operation, easy access to starting materials, and a wide substrate scope, providing a variety of novel 1,8-naphthyridones.

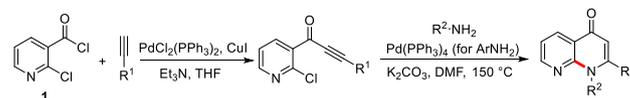
Keywords: Nitrogen heterocycles; Synthetic methods; Amine *N*-oxides; Amination; Naphthyridone

Isosteric replacement is a vital and practical tool in medicinal chemistry. The importance of this technique is easily observed through the isosteres of chromone (Scheme 1). Natural and synthetic chromone derivatives exhibit various biological and pharmaceutical properties, including antimicrobial, anticancer, antioxidant, and anti-inflammatory activities.^[1] For example, replacing the pyran “O” with “NH” gives the pharmacologically active 4-quinolone.^[2] Substituting the phenyl ring of chromone or 4-quinolone with a pyridyl ring affords two desirable pyridine derivatives, 8-azachromone^[3] and 1,8-naphthyridone^[4] (Scheme 1). This latter replacement is particularly valuable as 1,8-naphthyridone is among the most prominent scaffolds used for modern antibacterial agents, including amfonelic acid, enoxacin, gemifloxacin, and trovafloxacin. Unfortunately, there are a limited number of studies involving 1,8-naphthyridone, likely due to the difficulties associated with accessing this structure.

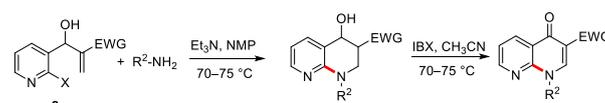


Scheme 1. Chromone, 4-Quinolone, and Their Aza Isosteres

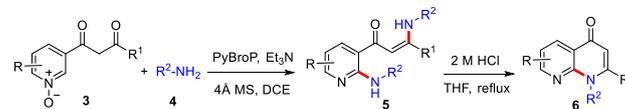
A. [Iaroshenko & Langer, 2012](#); Sonogashira coupling-Pd catalyzed amination/conjugate addition



B. [Muraleedharan, 2014](#); Michael addition-S_NAr cyclization-oxidation



C. **This work**; amination of pyridine *N*-oxides-enamine formation/acid mediated cyclization



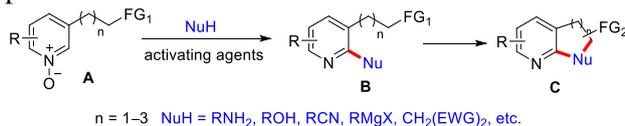
Scheme 2. Synthetic Approaches to 1,8-Naphthyridones

Previous reports achieved the key C2-N bond formation of the 1,8-naphthyridone via nucleophilic aromatic substitution (S_NAr) between 2-halogen substituted pyridines (**1** or **2**) and amines (Scheme 2A & 2B).^[5] However, few 1,8-naphthyridones have actually been prepared by either of these approaches as they each suffer from inherent limitations. The inclusion of the halogen atom requires additional steps and generates halide waste. Moreover, both methods are only suitable for a limited number of targets because the substituents on the pyridine rings

render their corresponding starting materials almost inaccessible. Therefore, a general synthetic method for preparing diversely functionalized 1,8-naphthyridones is still needed.

Our group sought to depart from traditional methods and envisioned new synthetic strategies to access these fused pyridine derivatives.^[6] We propose that C3-substituted pyridine *N*-oxide **A** can react with various nucleophiles under the proper activating conditions to give functionalized intermediates **B**, which can then be converted to the desired fused pyridine derivatives **C** (Scheme 3). As previous studies have reported that various nucleophiles can react with pyridine *N*-oxides to afford C2-functionalized pyridine derivatives, our modified approach will allow for the general synthesis of the fused heterocycles.^[7]

Continuing our research on the efficient synthesis of drug-like nitrogen heterocycles,^[8] we now describe a practical method for the synthesis of functionalized 1,8-naphthyridones using easily accessible, non-C-2-substituted pyridine *N*-oxides (**3**) as the key precursor (Scheme 2C). As the electrophilic character of the C-2 position is enhanced in **3**, it can be attacked by amines (**4**) under PyBroP activating conditions,^[9] leading to aminated intermediate **5**, which can be cyclized to afford the desired product **6**. Although metal-free regioselective amination of simple pyridine *N*-oxides has been established,^[10] the application of these methods to prepare complex pyridine derivatives remains underexplored. To the best of our knowledge, this general approach to naphthyridones based on *N*-oxide chemistry is unprecedented. In comparison with previously reported methods, our method benefits from the use of commercially available and inexpensive nicotines as the starting material that is easily converted to **3** in good yields using our published procedure.^[6b]



Scheme 3. Synthesis of Fused Pyridine Derivatives

We initially selected **3a** and benzylamine as substrates for optimization of the reaction conditions. Unfortunately, **5aa** was formed as the major product using the reported amination conditions^[9] rather than the expected amination product **5aa-1** or the desired product **6aa** (Table 1, entry 1). From this finding, we concluded that along with the expected amination reaction, benzylamine also reacted with the carbonyl group of **3a** to form an enamine, preventing intramolecular cyclization leading to **6aa**. Notably, the reaction was highly regioselective with no C6-amination product **5aa-2** detected. This idealized regioselectivity likely results from the electron-withdrawing effect of the C3-carbonyl group, which enhances the electrophilicity of the C2 position above that of the C6 atom. Both the base (entries 2-8) and solvent (entries 9-13) were found to be critical for the

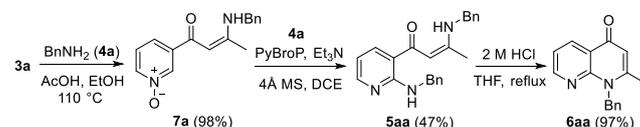
transformation, with Et₃N identified as the optimal base among organic and inorganic bases. Although both EtOAc and THF are suitable solvents for the amination of simple pyridine *N*-oxides,^[9] both were deemed unsuitable (entries 9-10) while DCE was determined to be ideal for this reaction (entry 12). Interestingly, using more dilute (entry 14) or concentrated reaction conditions (entry 15) decreased the yield. Despite the moderate yield and presence of several polar byproducts, **5aa** could be easily isolated by flash column chromatography.

Table 1. Reaction Optimization*

Entry	Base	Solvent	[M]	Yield, % ^{a)}
1 ^{b)}	DIEA	DCM	0.25	17
2	DIEA	DCM	0.25	23
3	Et ₃ N	DCM	0.25	40
4	DBU	DCM	0.25	N/A
5	2,6-lutidine	DCM	0.25	12
6	K ₂ CO ₃	DCM	0.25	11
7	Na ₂ CO ₃	DCM	0.25	26
8	Cs ₂ CO ₃	DCM	0.25	trace
9	Et ₃ N	EtOAc	0.25	N/A
10	Et ₃ N	DMF	0.25	N/A
11	Et ₃ N	THF	0.25	N/A
12	Et ₃ N	DCE	0.25	44
13	Et ₃ N	toluene	0.25	34
14	Et ₃ N	DCE	0.125	30
15	Et ₃ N	DCE	0.5	38

*All reactions were performed at rt at a concentration of 0.25 M with respect to the *N*-oxide SM (200 mg, 1.0 equiv) using BnNH₂ (2.5 equiv), PyBroP (1.3 equiv), base (3.0 equiv), and 4Å molecular sieves in solvent. ^{a)} Purified yield of **5aa**. ^{b)} BnNH₂ (1.25 equiv) was employed.

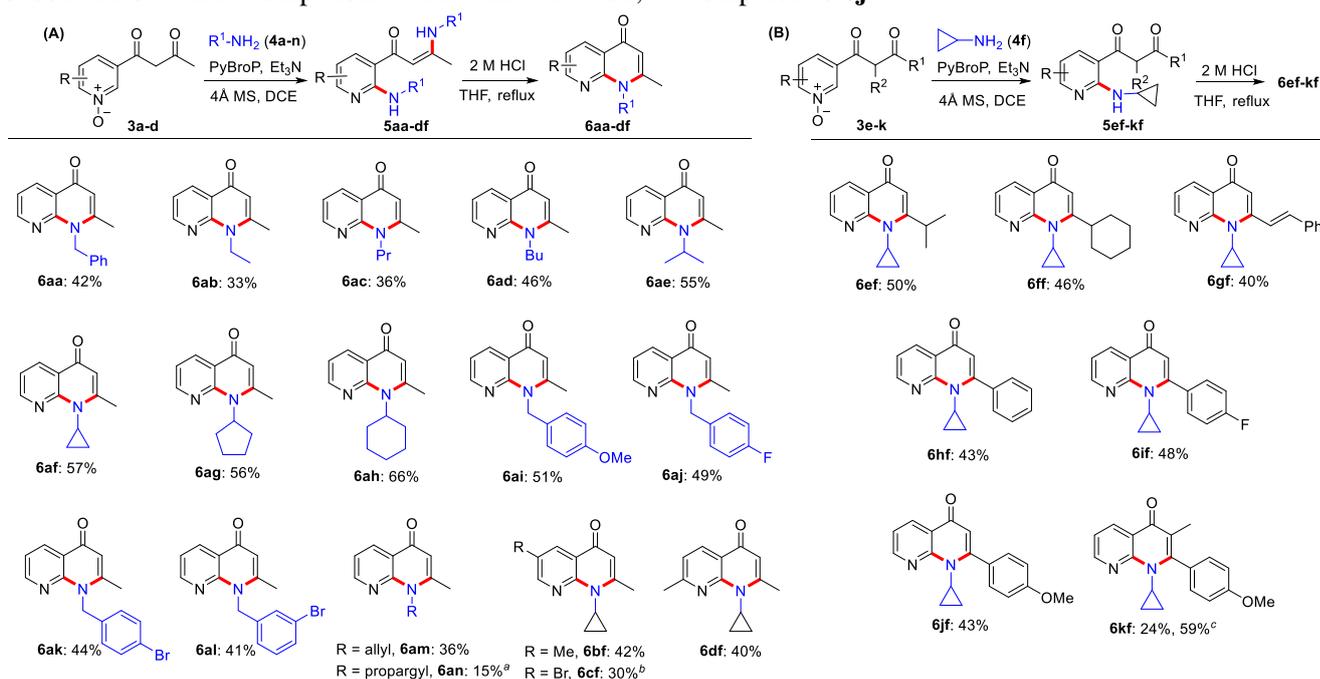
As the 1,3-dicarbonyl functionality is particularly reactive under basic conditions, the desired amination could be improved by first protecting the carbonyl. Therefore, **3a** was first reacted with benzylamine (**4a**) under acidic conditions to produce enamine **7a**, which was then subjected to the established amination conditions to afford **5aa** in 47% yield (Scheme 4), similar to the one-step transformation described above. Next, **5aa** underwent intramolecular conjugate addition and elimination of the benzylamine group under acidic conditions to afford the desired product **6aa** in 97% yield (Scheme 4). Notably, the product was obtained in analytically pure form without the need for further purification.



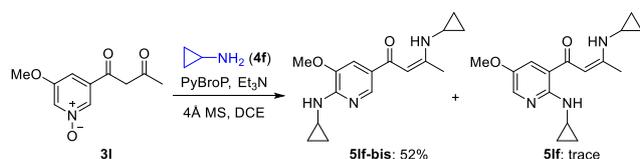
Scheme 4. Dicarbonyl-Protection and Acid-Mediated Cyclization

Under the optimized conditions (Table 1, entry 12), the substrate scope of the reaction was explored using a set of pyridine *N*-oxides and alkyl amines (Scheme 5). A variety of functionalized 1,8-naphthyridones were accessible in moderate yields with excellent regioselectivity (C2 vs. C4 and C6) using this method. Straight-chain amines (**6aa-ad**), sterically hindered amines (**6ae**), cycloalkylamines (**6af-ah**), allylic (**6am**), and benzylic amines (**6ai-al**) were all found to be good substrates. Owing to their stronger nucleophilicity, isopropyl amines and cycloalkylamines provided higher yields than straight-chain amines. Pyridine rings carrying C5, or C6-methyl (**6bf**, and **6df**) or allylic methyl (**6kf**) substituents were compatible with the reaction,

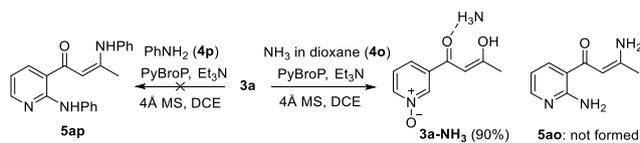
providing additional handles for further functionalization at the C(sp³)-H positions via cross-coupling or radical halogenation reactions. Surprisingly, the C6-aminated product **5lf-bis** predominated for electron rich pyridine *N*-oxide (Scheme 6). Interestingly, compounds **5ef-kf** were formed on substrates with non-methyl R¹ groups (Scheme 5B), likely due to steric hindrance precluding enamine formation. This transformation is compatible with various R¹ groups, including alkyl (**6ef**), cycloalkyl (**6ff**), alkenyl (**6gf**), and phenyl (**6hf-kf**, Scheme 5B) functionalities. Interestingly, the reaction was particularly sensitive to the identity of the R² group, with little reaction observed for **6kf** as compared to **6jf**.



Scheme 5. Substrate Scope for the Preparation of 1,8-Naphthyridones with Aliphatic Amines. Reaction conditions: 1st step: *N*-oxide (1.0 equiv), amine (2.5 equiv), PyBroP (1.3 equiv), Et₃N (3.0 equiv), 4Å molecular sieves, DCE (0.25 M), rt. 2nd step: **5** (1.0 equiv), 2 M HCl (2.0 equiv), THF (0.20 M), reflux. Yield reported after two steps. ^a Multiple byproducts were observed. ^b Na₂CO₃ was used to replace Et₃N in the first step. ^c Yield based on recovered starting material (BRSM).



Scheme 6. Amination with electron-rich pyridine *N*-oxide.



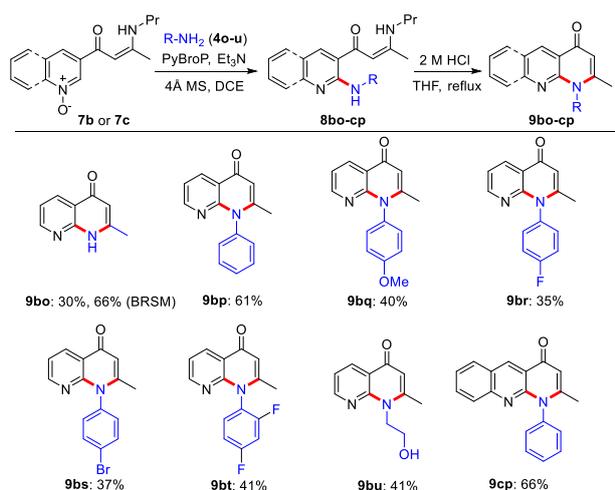
Scheme 7. Attempted Amination with Ammonia or Aniline

Owing to their medicinal and synthetic importance, we sought to show the applicability of this reaction to the development of halogenated 1,8-naphthyridones. Although low yields of **5cf** were obtained under the

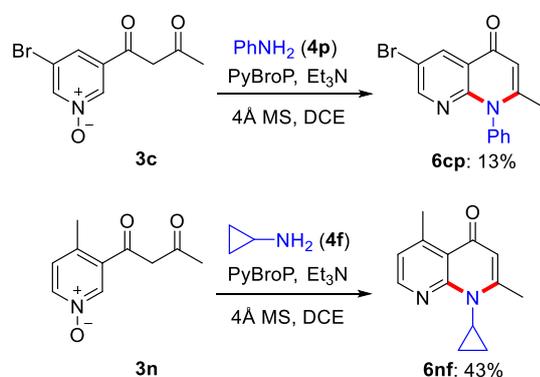
standard conditions, we dramatically improved these yields by replacing triethylamine with sodium carbonate (see the Supporting Information for details). Sodium carbonate likely increases the lifetimes of both PyBroP and the activated intermediate.

To further demonstrate the synthetic utility of this reaction, we sought to employ aniline or ammonia as the aminating agent. Unfortunately, a complex mixture was obtained when aniline was used as the reagent (Scheme 7). In addition, treatment with ammonia resulted in the precipitation of complex **3a-NH₃** rather than the desired product **5ao** (Scheme 7). Based on these results, a protecting group strategy was necessary to obtain these 1,8-naphthyridones. To maximize atom economy, benzylamine (**7a**) was exchanged with propylamine (**7b**) as the protecting group (Scheme 8). Gratifyingly, this condition was amenable with a broad range of amines, including ammonia (**9bo**), phenylamine derivatives (**9bp-bt**), and ethanolamine (Scheme 8, **9bu**). Excellent

regioselectivity was observed across these reactions. Although the low solubility of ammonia gas in DCE resulted in a low formation of **9bo**, most substrates were recovered in moderate yield (66% BRSM). Unfortunately, no general conclusion could be obtained concerning the effect of electron density on the reactivity of phenylamine derivatives because the electron-rich amines afforded similar yields to the electron-poor ones (**9bq** vs. **9br**, **9bq** vs. **9bt**). Notably, products containing bromo (**6ak**, **6cf**, **9bs**) or hydroxy (**9bu**) groups are suited for further functionalization. Moreover, this method affords good yields with quinoline *N*-oxide (**9cp**, 66%), indicating its wide applicability for the synthesis of nitrogen-containing heterocycles.



Scheme 8. Substrate Scope for the Preparation of 1,8-Naphthyridones with Other Amines. Yields after two steps.



Scheme 9. One-pot Synthesis of 1,8-Naphthyridones

Finally, it should be noted that the amination and cyclization reactions can be realized in one-pot for some specific substrates. Instead of the expected amination products, the desired 1,8-naphthyridones **6cp** and **6nf** were obtained under the standard amination conditions (Scheme 9).

In this work, we described a metal-free synthesis of diversely functionalized 1,8-naphthyridones via regioselective amination of pyridine *N*-oxides and acid-mediated cyclization. Although this is a two-step process, the second step provides the product in almost quantitative yield without the need for purification. This is the first synthetic approach to 1,8-naphthyridones utilizing easily accessible

pyridine *N*-oxides as substrates. This method improves upon previous syntheses through its simple operation, easily accessible starting materials, and wide substrate scope. While the 34 naphthyridones prepared in this work represent simple substitutions, 33 of these compounds are novel^[11] and may be valuable resources in medicinal chemistry. This route furnishes an updated strategy to prepare drug-like complex pyridine derivatives via conventional methods.

Experimental Section

General Procedure I: Synthesis of Compound 7. Amine (1.1 equiv) and AcOH (0.1 equiv) were added to a solution of pyridine *N*-oxides (**3**) (1.0 equiv) in EtOH (0.25 M). The resulting mixture was refluxed for several hours until complete, as indicated by TLC. After cooling to rt, the reaction solution was concentrated in vacuo and purified by silica gel column chromatography using DCM/MeOH (50:1–30:1) to give product **7**.

General Procedure II: Amination of *N*-oxides. Et₃N (3.0 equiv), 4 Å molecular sieves (of the same mass as pyridine *N*-oxides), and PyBroP (1.3 equiv) were sequentially added to a solution of pyridine *N*-oxides (1.0 equiv) and amine (2.5 equiv) in dry DCE (0.25 M). The resulting mixture was stirred at rt for several hours until complete, as indicated by TLC. The reaction mixture was filtered, and the mother liquor was diluted with sat. aqueous NH₄Cl and extracted with EtOAc. The combined organic phases were dried over Na₂SO₄, concentrated in vacuo, and the crude product was purified by flash column chromatography using pet. ether/EtOAc (100:1–50:1) to afford the product.

General Procedure III: Synthesis of 1,8-Naphthyridones. A 2 M HCl (2.0 equiv) was added to a solution of the amination product (1.0 equiv) in THF (0.25 M). The resulting mixture was refluxed until complete, as indicated by TLC. After cooling to rt, the reaction solution was diluted with H₂O and extracted with DCM. The combined organic phases were washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford the product.

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