Synthesis of 2-substituted pyridines from pyridine N-oxides

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Abstract
The synthesis of substituted pyridines has drawn the attention of many chemists due to their importance as building blocks for biologically active compounds and materials. This mini-review focuses on recent developments relating to the synthesis of substituted pyridines from pyridine N-oxides, along with their interesting mechanism aspects. New developments including alkenylation, alkynylation, alkylation, arylation, amination and cyanation are discussed.

Keywords: Substituted pyridines, pyridine N-oxides

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1. Introduction

Substituted pyridines are an important class of compounds in organic synthesis. The structural framework of substituted pyridines is often seen in natural products, compounds possessing important biological activities, and functional materials. Substituted pyridines are usually prepared starting from halo- or metallated pyridyl compounds. However, this method is commonly accompanied with problems and the formation of by-products.

Pyridine N-oxides are very useful synthetic intermediates in the field of heterocyclic chemistry, since they are much more reactive towards both electrophilic and nucleophilic reagents than the heterocycles from which they are derived. Reactions of pyridine N-oxides is one of the most useful synthetic methods for the formation of various substituted pyridines and their derivatives. Over recent decades, pyridine N-oxides have drawn the attention of numerous research groups, and the number of new synthetic methodologies and modifications of traditional procedures has grown markedly, which has been reflected in the number of research publications in the literature. This mini-review focuses on recent developments relating to the synthesis of substituted pyridines from pyridine N-oxides along with their interesting mechanism aspects. Accordingly, we discuss only the most essential reactions here and summarize the recent contributions reported after 2002.

Figure 1. Pyridine N-oxide.

2. Transition Metal-catalyzed Alkenylation

Recently, Chang et al. reported highly promising oxidative protocol for the selective alkenylation of pyridine N-oxides using olefins relying on the palladium mediated C-H bond activation strategy (Scheme 1). Various alkenylated pyridine N-oxides were obtained in good to high yields. The resultant alkenylated pyridine N-oxides (e.g., 3a) were readily deoxygenated to give 2-alkenylpyridines, making the present alkenylation route a highly attractive alternative for the 2-functionalization of pyridine derivatives. In addition, Cui, Wu and co-workers revealed for the first time in Pd-catalyzed alkenylation of quinoline- and isoquinoline-N-oxides via C-H activation under external-oxidant-free conditions (Scheme 2).
Hiyama et al. reported nickel-catalyzed activation of C(2) - H bonds of pyridine N-oxides 1 under mild conditions followed by regio- and stereoselective insertion of alkynes 8 to afford (E)-2-alkenylpyridine N-oxides 9 in modest to good yields (Scheme 3). The resulting adducts were readily deoxygenated to give various substituted pyridines 10.
A plausible mechanism for the nickel-catalyzed alkenylation of pyridine N-oxides is shown in Scheme 4. Alkyne-coordinated nickel (0) species A underwent oxidative addition to the C2-H bond, giving the pyridyl(hydride)-nickel species B. Hydronickelation in a cis fashion then provided the alkenyl(pyridyl)nickel intermediate C. Coordination of the alkyne such that the steric repulsion between the bulkier R3 and the pyridyl group in B was avoided would be responsible for the observed regioselectivities. Reductive elimination followed by coordination of an alkyne afforded 2-alkenylpyridine-N-oxide 9 and regenerated the nickel (0) species A. The N-oxide moiety played an important role in directing the metal catalyst to the proximal C2-H bond and/or making the C-H bond acidic enough to undergo the oxidative addition to nickel (0).
3. Palladium-Catalyzed Arylation

Fagnou et al. reported palladium-catalyzed direct arylation reactions of pyridine N-oxides (azine and azole N-oxides) occur in excellent yield with complete selectivity for the 2-position with a wide range of aryl bromides. The resulting 2-arylpyridine N-oxides could be easily reduced to the free pyridine via palladium-catalyzed hydrogenolysis (Scheme 5).

![Scheme 5](image)

A recent report by the same author revealed that lower yields were encountered with substrates bearing methyl substituents adjacent to the N-oxide moiety, they developed site selective arylation reactions of both sp² and benzylic sp³ sites on pyridine N-oxide substrates and illustrate that reactivity could be performed both divergently and sequentially (Scheme 6). Furthermore, the N-oxide moiety could be used to introduce a wide range of other functional groups or could easily be deoxygenated under mild conditions.

![Scheme 6](image)

Direct arylation of pyridine N-oxides with aryl triflates can also be obtained. Fagnou et al. reported palladium-catalyzed direct arylation of pyridine N-oxides using aryl triflates to afford the corresponding 2-aryl pyridine N-oxides (Scheme 7). Differentially diarylated products could be obtained by carrying out the arylation reactions in sequence as shown in Scheme 8. Pyridine N-oxide was arylated with p-tolyl trifluoromethanesulfonate in 89% yield. This product
could then be resubmitted to arylation conditions with 4-methoxyphenyl trifluoromethanesulfonate under the more active conditions to generate the differentially diarylated compound 20 in 84% yield. Conditions A, which employed aryl triflates, resulted in not only higher yield than the previously reported conditions B (with aryl bromides) but also required less equivalents of intermediate 19. Therefore, it could be advantageous to employ aryl triflates when low yields were obtained with aryl bromides.

Scheme 7

Scheme 8
4. Amination

Yin *et al.* developed a general and efficient method to convert pyridine *N*-oxides to 2-aminopyridines 23 in a one-pot process in high yields and high regioselectivity. The process used commercially available reagents *t*-BuNH₂ and Ts₂O and showed good functional group compatibility (Scheme 9). The use of *t*-BuNH₂ was critical for shutting down side reactions such as dimerization and tosylation of the product as well as suppressing the reaction between the amine and the activating reagent Ts₂O. TFA treatment of the crude reaction mixture effectively removed the *t*-Bu group.

\[
\begin{align*}
1 & \xrightarrow{Ts_2O*tBuNH_2, \text{ Then TFA 71-92\%}} 23 \\
1 & \xrightarrow{Ts_2O} 21 & \xrightarrow{NH_2*tBu} 22
\end{align*}
\]

\(R^1 = \text{H, 3- or 4-Me, 4-Cl, 4-Ph, 4-MeO, 2- or 4-CO}_2\text{Me, 2-pyridiny1, 2-Methyl-3-Methoxy-4-Chloro} \)

Scheme 9

Londregan *et al.* reported a general and facile one-pot amination procedure for the synthesis of 2-aminopyridines from the corresponding pyridine *N*-oxides as a mild alternative to *S_N*Ar chemistry. The authors found that the phosphonium salt PyBroP (bromotripyrrolidinophosphonium hexafluorophosphate) functioned as a general and mild *N*-oxide activator for the regioselective addition of amine nucleophiles. In this reaction, unhindered aliphatic amines participated most effectively in the transformation, but aminations using heterocycles, such as imidazoles and pyrazoles, unexpectedly proceeded (Scheme 10). The mechanism of the reaction is shown in Scheme 11. The reaction proceeded via the activated pyridine complex 24. Subsequent basic rearomatization 25 afforded the desired 2-aminopyridine 23 and phosphoryltripyrrolidine 26, the only significant organic byproduct of the reaction. Recently, the same group also found that reactions could be expanded into broader classes of nucleophiles (such as phenol, sulfonamide, malonate, pyridone, thiol) after minimal reaction
optimization of original amination procedure. The presented reactions represented a very large and varied set of putative nucleophiles and N-oxides.\textsuperscript{17}

![Scheme 10](image1.png)

**Scheme 10**

A one-pot method for the generation of imidoyl chlorides and their subsequent in situ reaction with pyridine N-oxides was developed by Manley and Bilodeau (Scheme 12).\textsuperscript{18} The imidoyl chlorides were formed from the reaction of secondary amides with a stoichiometric amount of oxalyl chloride and 2,6-lutidine in CH$_2$Cl$_2$ at 0 °C. Upon warming of the reaction mixture to room temperature in the presence of pyridine N-oxides, a rapid conversion to 2-aminopyridine amides 28 was observed in moderate to excellent isolated yields.
Keith reported a convenient one-step procedure for the conversion of pyridine N-oxides to 2-imidazolopyridines 30 in fair to excellent yield through the action of sulfuryl diimadazole at elevated temperatures.\(^\text{19}\) A possible mechanism for the activation and substitution of pyridine N-oxides with potential side reactions is shown in Scheme 13.

```
\begin{align*}
\text{Scheme 12} \\
\text{Recently, same researcher also developed a method for the deoxygenative coupling of pyridine N-oxides with azoles through the use of preformed tosylazole reagents. The}
\end{align*}
```
methodology allowed for the introduction of 1,2,4- and 1,2,3-triazoles, imidazole, and electron-deficient pyrazoles on pyridine (Scheme 14).  

\[
\begin{array}{c}
\text{R}^1 \quad \text{Ts-triazole} \\
\text{or Ts-diazole} \\
\text{DIPEA, heat} \\
\text{Up to 93\%} \\
\text{DIPEA: disopropylethylamine}
\end{array}
\]

[R\textsuperscript{1} = H, 4-Ph, 3,5-dimethyl, 2-Me, 3- or 4-MeO, 4-NMe\textsubscript{2}]  

Scheme 14

5. Cyanation

Recently, Yamamoto et al. reported a convenient method for the direct synthesis of 2-cyanoisonicotinamide 35 from isonicotinic acid N-oxide using zinc cyanide as a cyanation reagent (Scheme 15). The reaction mechanism is shown in Scheme 16.

\[
\begin{array}{c}
\text{CONMe}_2 \\
\text{1b} \\
\text{Me}_2N\text{O} + \text{Zn(CN)}_2 \text{Cl} \to \text{CH}_3\text{CN} \\
\text{120 °C} \\
\text{35}
\end{array}
\]  

Scheme 15
Scheme 16

Furthermore, this strategy could be applied to the synthesis of FYX-051·TsOH (40), a xanthine oxidoreductase inhibitor (Scheme 17). Additionally, they reported a reaction of 4-amidopyridine N-oxide with dimethylcarbamoyl chloride and potassium cyanide in CH$_3$CN at 120 °C and gave the corresponding 2-cyano-4-amidopyridine 41 in a good yield (Scheme 18).$^{22}$

Scheme 17

Scheme 18
6. Transition-metal Free Regiospecific Alkylation

Recently, Almqvist and Olsson et al. reported on the transition-metal free regiospecific synthesis of 2-substituted alkyl, alkynyl, and arylpyridines, a class of compounds prominent in medicinal chemistry and materials. Sequential addition of Grignard reagents to pyridine N-oxides in THF at room temperature followed by treatment of the resulting 2,4-dienal oximes 42 with acetic anhydride at 120 °C afforded a range of 2-substituted pyridines 43 in good to high yields (Scheme 19).23

\[
R^1 = H, 4-\text{Ph}, 4-\text{BnO}, 4-\text{Cl} \\
R = \text{Bn, Ph, Me, } p-\text{MePh, } p-\text{MeOPh, } \text{PhCC, cy-propylCC, naphthalen-2-yl, thiophen-2-yl, iso-propyl}
\]

Scheme 19

Olsson and Almqvist et al. also developed a mild method for the selective 2-substitution pyridine N-oxides 44 via a directed ortho-metallation. Addition of \textit{i}-PrMgCl to pyridine N-oxides in THF at -78 °C generated selectively an ortho-metallated species, which could be trapped with various electrophiles, ranging from aldehydes, ketones and halogens, to generate 2-substituted pyridine N-oxides (Scheme 20).24 Additionally, Duan et al. also reported similar results. 2-Bromopyridine N-oxides were readily magnesiated with \textit{i}-PrMgCl\textsubscript{LiCl} via bromine-magnesium exchange. The bromine adjacent to pyridine N-oxide (at 2- or 6-position) could be selectively magnesiated in the presence of halogens substituted at other positions (Scheme 21).25
Recently, Itami and Li et al. reported transition-metal-free systems for the cross-coupling reactions of nitrogen heteroaromatics and alkanes. Under the influence of tBuOOtBu, pyridine N-oxide derivatives reacted with alkanes to furnish the corresponding cross-coupling products (alkylated nitrogen heterocycles) in good yields. The present oxidative cross-coupling reactions at two different C-H bonds not only contributed to the realization of “greener” synthesis, but also unlocks opportunities for markedly different strategies in chemical synthesis (Scheme 22).  

\[
\begin{align*}
R^1 &= H, 2- or 4-Me, 3,5-dimethyl, 2- or 3- or 4-MeO, 2- or 3-Cl, 4-OBn \\
\end{align*}
\]

Scheme 20

\[
\begin{align*}
1 & \xrightarrow{\text{1) } \text{PrMgCl or } n-\text{BuMgCl, THF, } -78 \, ^\circ\text{C}} 44 \\
1 & \xrightarrow{\text{2) } E^+, \text{THF, } -78 \, ^\circ\text{C-rt}} 44 \\
E &= \text{PhCHOH, I, aldehydes, ketones} \\
R^1 &= \text{H, Me, MeO, CN, CON'^Pr}_2, \text{etc} \\
\end{align*}
\]

Scheme 21

Recently, Itami and Li et al. reported transition-metal-free systems for the cross-coupling reactions of nitrogen heteroaromatics and alkanes. Under the influence of tBuOOtBu, pyridine N-oxide derivatives reacted with alkanes to furnish the corresponding cross-coupling products (alkylated nitrogen heterocycles) in good yields. The present oxidative cross-coupling reactions at two different C-H bonds not only contributed to the realization of “greener” synthesis, but also unlocks opportunities for markedly different strategies in chemical synthesis (Scheme 22).  

\[
\begin{align*}
1a & \xrightarrow{\text{Cy cycles}} 47 \\
1a & \xrightarrow{\text{Cy cycles}} 48 \\
Cy &= \text{5 or 6 or 7 or 8-member rings} \\
\end{align*}
\]

Scheme 22
7. Transition-metal Free Alkynylation

Chupakhin et al. reported a method for the direct introduction of acetylenes into heterocyclic systems using $S_N^H$ methodology. It provided a versatile tool for the synthesis of a series of ethynyl azines. The method requires no expensive reagents, and can be used as a complementary method to Sonogashira cross-coupling reactions (Scheme 23).27

![Scheme 23](image)

8. Palladium-catalyzed Direct (Hetero)arylation

You, Hu, and co-workers recently reported for the first time in Pd(II)-catalyzed, copper(I)-promoted oxidative cross-coupling between pyridine N-oxides and electron-rich heteroarenes such as furans and thiophenes, where Cu(OAc)$_2$H$_2$O was used as an oxidant (Scheme 24).28 Plausible catalytic cycle of oxidative C-H/C-H cross-coupling of heteroarenes with pyridine N-oxides is shown in Scheme 25. In the first metalation step, the abstraction of hydrogen from thiophene took place in the reaction system. Thus, thiophene would undertake a regioselective electrophilic C-H substitution ($S_E$Ar) of Pd(OAc)$_2$ to generate $\alpha$-thienylpalladium(II) intermediate 51. Then it reacted with N-oxide to form the key heterocoupling intermediate 52, which might be rate-determining in the entire reaction.

![Scheme 24](image)
Zhang, Li et al. reported a Pd(II)-catalyzed oxidative coupling between pyridine \( N \)-oxides and \( N \)-substituted indoles via two-fold C-H bond activation with high selectivity using \( \text{Ag}_2\text{CO}_3 \) as an oxidant (Scheme 26).\(^{29}\) Recently, Yamaguchi, Itami et al. also developed similar reactions of palladium-catalyzed C-H/C-H coupling reaction of indoles/pyrroles and pyridine \( N \)-oxides, proceeding selectively at the C3 position of the indoles/pyrroles and the C2 position of the pyridine oxides (Scheme 27).\(^{30}\)

\[
\begin{align*}
\text{(1) } & \quad \text{Pd(0)} & \quad \text{Cu(OAc)}_2 & \quad \text{Cu} \\
\text{Pd(0)} & \quad \text{Cu(OAc)}_2 & \quad \text{Cu} \\
\text{Pd(0)} & \quad \text{Cu(OAc)}_2 & \quad \text{Cu} \\
\text{Pd(0)} & \quad \text{Cu(OAc)}_2 & \quad \text{Cu} \\
\text{Pd(0)} & \quad \text{Cu(OAc)}_2 & \quad \text{Cu} \\
\text{Pd(0)} & \quad \text{Cu(OAc)}_2 & \quad \text{Cu} \\
\end{align*}
\]

**Scheme 25**

**Scheme 26**

\[R^1 = \text{H, 2- or 4-Me, 4-tBu, 3-Ph, 3-Br, 3-CN} \]

\[R^2 = \text{Bn, Me, Ph} \]

\[\text{TBAB} = \text{tetraethylammonium bromide} \]
Scheme 27

9. Conclusions

In summary, we have described some recent advances in the synthesis of various types of 2-substituted pyridines from pyridine N-oxides. The significance of development of synthetic methods is that it provides a useful alternative to classic approach, which has usually prepared starting from halo- or metallated pyridyl compounds. However, pyridine N-oxide is now being more popular because of its efficiency, and many new methods will probably be developed for the synthesis of 2-substituted pyridines in the near future.

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Zhibao Huo was born in Shenyang, China, in 1971. He completed his master and doctoral studies at Tohoku University in 2004 and 2007 under the guidance of Prof. Yoshinori Yamamoto. After working for about three years as a postdoctoral fellow in the same laboratory, in April 2010, he was appointed as Professor of Organic Chemistry at Shanghai Jiao Tong University, China. His research interests include transition metal- and Lewis acid-mediated development of new synthetic methods, asymmetric catalysis, and synthesis of biologically important natural and unnatural compounds.