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Mild Addition of Nucleophiles to Pyridine-*N*-Oxides

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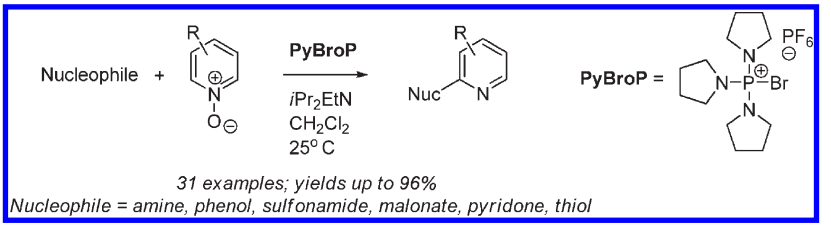
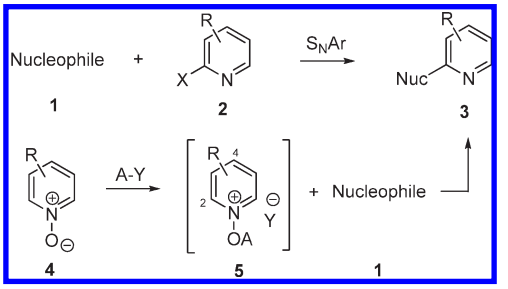
ABSTRACT



A general and facile one-pot procedure for the synthesis of 2-substituted pyridines from the corresponding pyridine-*N*-oxides and nucleophiles is presented as a mild alternative to S_NAr chemistry. A variety of nucleophiles and heterocyclic-*N*-oxides participate effectively in this transformation, which uses the phosphonium salt, PyBroP, as a means of substrate activation.

2-Substituted pyridines are a common structural feature in small molecule chemotherapeutics.[1] One method for their preparation is the direct displacement of the corresponding 2-halopyridines with nucleophiles (Scheme 1). Although amines are the most frequent reaction partner, there are many examples with alkoxy,[2] thiol,[3] and alkyl[4] nucleophiles. Yields for these transformations, particularly on unactivated 2-halopyridines, are commonly low and in most cases require metal catalysis and/or high temperature and pressure. Another approach to 2-substituted pyridines employs pyridine-*N*-oxides in place of the corresponding 2-halopyridines.[5] Treatment of a pyridine-*N*-oxide (**4**) with an activating agent (A-Y)[6] enhances the electrophilic character of the 2-position (**5**), thus allowing for nucleophilic addition under relatively mild conditions. Unfortunately, side reactions are quite common, including addition at the 4-position, counteranion (Y^-) addition at the 2 and 4-positions, and direct reaction of activating agent with the nucleophile. For the above reasons, general, mild, and selective methods for the preparation of 2-substituted pyridines are desirable.

Scheme 1. Syntheses of 2-Substituted Pyridines



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(6) Examples: Ts_2O, TsCl, Ac_2O, $POCl_3$.

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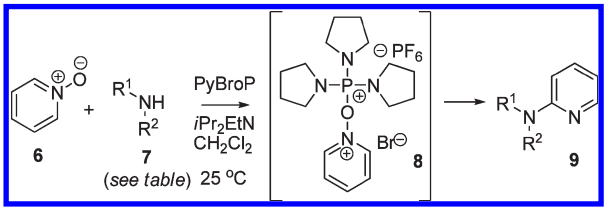
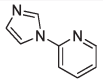
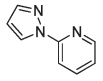
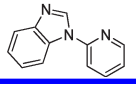
Our laboratory recently became interested in the N-oxide activation approach to selectively prepare 2-substituted pyridines. In a previous communication,[7] we demonstrated that the phosphonium salt PyBroP[8] (bromo-tris-pyrrolidino-phosphonium hexafluorophosphate) functioned as a general and mild N-oxide activator for the regioselective addition of amine nucleophiles. In that report, we described significant reaction optimization which resulted in an operationally simple amination procedure devoid of common side reactions mentioned above. In general, unhindered-aliphatic amines participated most effectively in the transformation. There were, however, a few exceptions to this paradigm (Table 1). Aminations using heterocycles, such as imidazoles and pyrazoles, unexpectedly proceeded in excellent yields (entries 1−3).

Table 1. Amination of Pyridine-*N*-Oxide with Heterocyclic Amines[a]



entry	amine **7**	product **9**	yield
1			95%
2			63%
3			86%

[a] Reaction Conditions: Combine N-oxide **6** (1.00 equiv), Amine **7** (1.25 equiv), *i*Pr$_2$EtN (3.75 equiv) in CH_2Cl_2 (0.25 M) and add PyBroP (1.30 equiv) and stir for 15 h at room temperature.

These results were contrary to our assumption that only nucleophilic amines would participate in the reaction. Under the mild reaction conditions, these heterocycles, although electron rich, are generally not considered strong nucleophiles. We therefore rationalized that other weakly nucleophilic substrates that share similar electronic and ionization properties to the heterocycles screened in Table 1 would function as effective nucleophiles in our reaction. We were encouraged by reports[9] in the literature on the direct addition of weak nucleophiles to tautomerizable carbon−oxygen bonds, which had been first activated by phosphonium salts.

We selected a number of nucleophiles to test under our standard protocol (Table 2). Presumably, these new substrates would function in place of the amines, for which the procedure was originally optimized. As a general guideline for selection, we chose nucleophiles within a pK_a range[10] of ∼10−20, as these would approximate the acidity of the heterocyclic amines in Table 1. When pyridine-N-oxide **6** was combined with each nucleophile (**1**) in dichloromethane and treated with *i*Pr$_2$EtN and PyBroP, we were pleased to obtain a variety of 2-substituted pyridines in modest to excellent yields. In none of these instances did we observe addition at the 4-position, a result consistent with our aforementioned amination procedure. As shown in Table 2, phenols (entries 1−5) were some of the most effective nucleophiles. Both aromatic and aliphatic sulfonamides (entries 6−8) underwent smooth N-addition in modest to excellent yields. A series of enolizable substrates (entries 9−12) also proceeded in moderate yields. In these cases, it was necessary to use a 3-fold excess of nucleophile with respect to N-oxide **6** in order to mitigate overaddition of the reaction product onto **6**. We were pleased with the reactivity of pyridones and pyrimidone (entries 13−16). In these examples, we observed chemoselective reaction at the nitrogen. For entry 15, we saw both a regioselective and chemoselective reaction at the 3-nitrogen. The relatively poor reactivity of the 1-nitrogen, as seen in entry 14, may explain this selectivity in part. Aliphatic thiols (entries 17−18) were also capable nucleophiles and afforded the desired 2-thiopyridines in good yields.

We further examined the reaction of select nucleophiles with various pyridine- and quinoline-N-oxides under our standard conditions (Table 3). With the exception of strongly electron deficient N-oxides (entries 7−9), we were pleased to observe good reactivity in all cases, regardless of the nucleophile. For entries 7−9, a change in reaction solvent to THF (*vide infra*), helped improve yields significantly. Although the examples in Table 3 are derived from commercially available N-oxides, the relative ease[11] of converting pyridines and quinolines to the corresponding pyridine- and quinoline-*N*-oxides facilitates considerable diversity in this methodology.

Analogous to amine nucleophiles, we propose that the reaction proceeds via the activated phosphonium complex (**8**) shown in Table 1. The strong regiochemical preference for 2-position addition in all cases is most likely attributed to a charge association[12] of **8** with the incoming nucleophile. Additionally, in certain examples (Table 3, entries

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(10) Equilibrium acidities discussed in this article are measured in DMSO, as reported by Bordwell. For a review, see: Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463.

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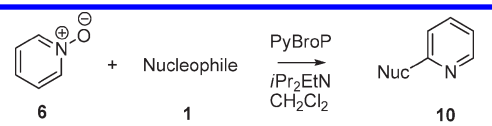
(12) For a review on the regioselectivity of nucleophilic addition onto activated pyridines, see: Poddubnyi, I. S. *Chem. Heterocycl. Compd.* **1995**, *31*, 682–714. Hard-hard/soft-soft interactions during the nucleophilic addition transition state are proposed to influence regioselectivity in additions onto activated pyridines, and may work in concert with the proposed charge interaction.

Table 2. Addition of Nucleophiles to Pyridine-*N*-Oxide*



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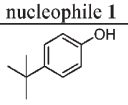
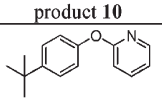
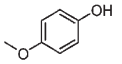
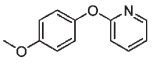
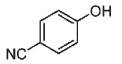
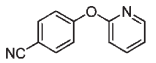
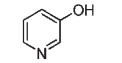
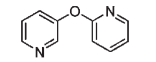
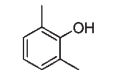
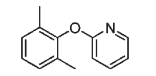
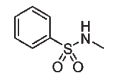
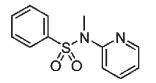
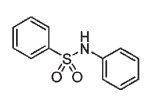
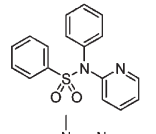
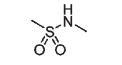
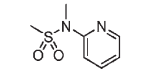
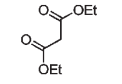
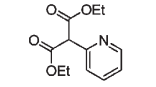
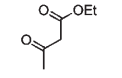
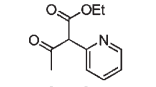
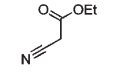
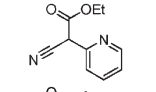
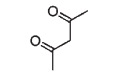
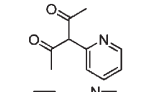
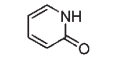
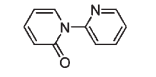
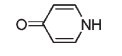
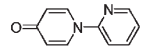
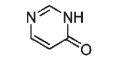
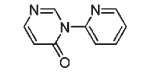
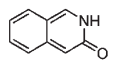
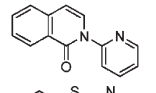
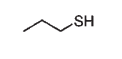
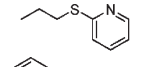
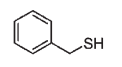
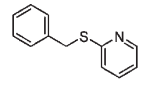
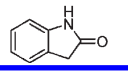
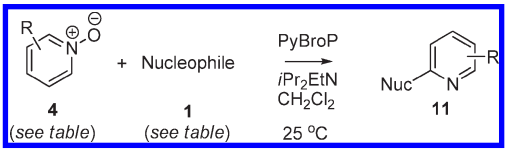
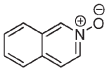
1			96%
2			90%
3			60%
4			56%
5			79%
6			63%
7[a]			84%
8			45%
9[b]			60%
10[b]			76%
11[b]			50%
12[b]			66%
13			72%
14			28%
15			55%
16			70%
17			68%
18			61%
19		n/r[c]	0%

* Reaction Conditions: Combine N-oxide **6** (1.00 equiv), Nucleophile **1** (1.25 equiv), iPr$_2$EtN (3.75 equiv) in CH_2Cl_2 (0.25 M) and add PyBroP (1.30 equiv) and stir for 15 h at room temperature. [a] Nucleophile **1** (0.75 equiv). [b] Nucleophile **1** (3.00 equiv). [c] No Reaction.

Table 3. Addition of Nucleophiles to Various Heterocyclic-*N*-Oxides*



entry	n-oxide **4**	nucleophile **1**	product **11**	yield
1				81%
2				64%
3[a]				71%
4				52%
5[b]				81%
6				84%
7				23% 53%[c]
8				46% 83%[c]
9				25% 60%[c]

* Reaction Conditions: Combine N-oxide **4** (1.00 equiv), Nucleophile **1** (1.25 equiv), iPr$_2$EtN (3.75 equiv) in CH_2Cl_2 (0.25 M) and add PyBroP (1.30 equiv) and stir for 15 h at room temperature. [a] Nucleophile **1** (0.75 equiv). [b] 2:1 3-methyl isomer: 5-methyl isomer. [c] THF (0.25 M) as solvent.

1−5), the LUMO electron density[13] of the N-oxide has a clear directing effect. As might be expected under the latter assumption, the steric bulk of vicinal substituents on said N-oxides has a limited influence on the product distribution, a result consistent with nucleophilic frontier density driven regioselectivity.

Overall, it would appear that the more electron-rich nucleophiles within each class perform most effectively in the transformation. Though not presented in Table 2, aliphatic alcohols,[14a] amides,[14a] and thiolphenols,[14b] regardless of relative acidity and electronic character, did not

(13) See the Supporting Information section for LUMO density calculations and further explanation. (a) Fukui, K.; Yonezawa, T.; Shingu, H. *J. Chem. Phys.* **1952**, *20*, 722–725. (b) Fukui, K.; Yonezawa, T.; Nagata, C.; Shingu, H. *J. Chem. Phys.* **1954**, *22*, 1433–1442.

participate in the reaction. The specific qualifications for an effective nucleophile in this reaction remain unclear. The appropriate balance of nucleophilicity, acidity and electronegativity appear to important. A pK_a range of ~10−20 can function as a general guideline for substrate selection, but is clearly not the exclusive predictor for reactivity, as 2-oxindole (Table 2, entry 19), with a N−H pK_a = 18.5, was inert. More electron-rich electrophilic partners seem to be preferred as well. The attenuated reactivity of strongly electron deficient N-oxides (Table 3, entries 7−9) in dichloromethane suggests that the stabilization of phosphonium complex **8** is critical to the successful reaction with the nucleophiles presented here. Indeed, by switching to a coordinating solvent (THF) in these examples, our yields greatly improved. This effect with THF was exclusive to examples with electron deficient N-oxides and did not help to improve the lower yielding examples from Table 1.

(14) (a) Alternative bases (NaH, NaOtBu) and solvent (THF) were screened. No reaction occurred. (b) Thiophenols react with the phosphorus center in **8** directly, cosuming the active species prior to 2-position addition.

In conclusion, we have presented a general and facile procedure for the synthesis of 2-substituted pyridines, which provides a mild alternative to traditional S_NAr chemistry. Minimal reaction optimization of our original amination procedure was necessary for expansion into broader classes of nucleophiles. The presented reactions represent a very large and varied set of putative nucleophiles and N-oxides. We believe a diverse substrate scope combined with an operationally simple procedure may make this a useful methodology. Research on further uses for this procedure will continue in our laboratory.

Acknowledgment. We thank Professor E. J. Corey (Harvard U.), David W. Piotrowski, David Price, David Hepworth, Jian Wang, and Geeta Yalamanchi (Pfizer Inc.) for their advice and support in our research.

Supporting Information Available. Experimental details, procedures and ^1H and ^{13}C NMR data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.