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General and Mild Preparation of 2-Aminopyridines

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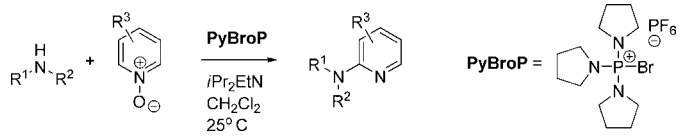
ABSTRACT

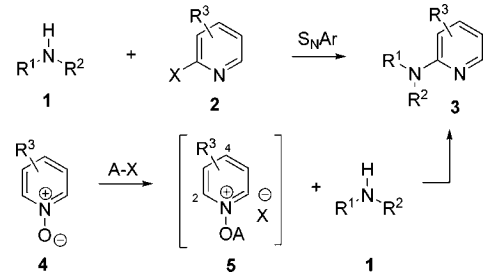


23 examples; yields up to 95%

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

2-Aminopyridines are ubiquitous features in small molecule chemotherapeutics.[1] Typical syntheses of 2-aminopyridines require a nucleophilic displacement of the corresponding 2-halopyridines with an amine (Scheme 1). Yields for this transformation, particularly on unactivated 2-halopyridines, are frequently low and in most cases require high temperatures and pressures.[2] Palladium- and copper-catalyzed aminations can enhance yields and do offer attractive alternatives to S_NAr chemistry, but these preparations usually require harsh reaction conditions as well as substrate-specific ligands.[3] Aminations at a late stage in a synthesis are often not possible due to substrate decomposition or incompatibility under the above conditions. For these reasons, new and mild methods for the preparation of 2-aminopyridines are desirable.

Scheme 1. Syntheses of 2-Aminopyridines



Another increasingly popular synthetic approach to 2-aminopyridines employs pyridine-*N*-oxides in place of the corresponding 2-halopyridines.[4] Treatment of pyridine-*N*-oxide (**4**) with an activating agent (A−X = Ts_2O, TsCl, Ac_2O, etc.) enhances the electrophilic character of the 2-position (**5**), thus allowing for nucleophilic addition of the

(1) (a) Hilton, S.; Naud, S.; Caldwell, J.; Boxall, K.; Burns, S.; Anderson, V. E.; Antoni, L.; Allen, C. E.; Pearl, L. H.; Oliver, A. W.; Aherne, G. W.; Garrett, M. D.; Collins, I. *Bioorg. Med. Chem.* **2010**, 459. (b) Yonezawa, S.; Tamura, Y.; Kooriyama, Y.; Sakaguchi, G. PCT Int. Appl. WO2010047372, 2010. (c) Steinig, A. G.; Mulvihill, M. J.; Wang, J.; Werner, D. S.; Weng, Q.; Kan, J.; Coate, H.; Chen, X. U.S. Pat. Appl. US2009197862, 2009. (d) Aicher, T. D.; Boyd, S. A.; Chicarelli, M. J.; Condroski, K. R.; Hinklin, R. J.; Singh, A. PCT Int. Appl. WO 2008118718, 2008.

(2) (a) Goldstein, D. M.; Gong, L.; Michoud, C.; Palmer, W. S.; Sidduri, A. PCT Int. Appl. WO 2008028860, 2008. (b) Kling, A.; Backfisch, G.; Delzer, J.; Geneste, H.; Graef, C.; Hornberger, W.; Lange, U. E. W.; Lauterbach, A.; Seitz, W.; Subkowski, T. *Bioorg. Med. Chem.* **2003**, *11*, 1319–1341.

(3) (a) Maiti, D.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 17423–17429. (b) Shen, Q.; Hartwig, J. F. *Org. Lett.* **2008**, *10*, 4109–4112.

(4) (a) Keith, J. M. *J. Org. Chem.* **2010**, *75*, 2722–2725. (b) Storz, T.; Bartberger, M. D.; Sukits, S.; Wilde, C.; Soukup, T. *Synthesis* **2008**, *2*, 201–214. (c) Yin, J.; Xiang, B.; Huffman, M. A.; Raab, C. E.; Davies, I. W. *J. Org. Chem.* **2007**, *72*, 4554–4557.

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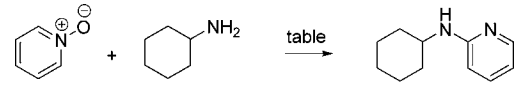
amine under relatively mild conditions. Unfortunately, side reactions are quite common, including addition at the 4-position, counteranion (X^-) addition at the 2- and 4-position, and amination of the activating agent directly with the amine nucleophile. Several clever solutions to these problematic side reactions appeared in the literature[4a,c] recently that carefully modulate reaction conditions to minimize side products. In these optimized cases, however, the amine substrate scope is narrow, thus limiting broad applicability.

We were interested in expanding and improving the reactivity of amines with pyridine-*N*-oxides while minimizing some of the more common side reactions. Since most of the reaction side products were due to the activating agent, we began our search for suitable alternatives. Phosphorus oxychloride and related reagents, when combined with pyridine-*N*-oxides, affect nonregioselective chlorination of the 2- and 4-position in a manner similar to the activating agents shown above.[5] In these cases, the strength of phosphorus−oxygen bond formation provides a strong thermodynamic drive for reaction completion. We surmised that we could take advantage of this same principle with more specific phosphonium salts. Although most commonly used as amide coupling reagents,[6] phosphonium salts (PyBroP,[7] BroP, PyBOP, and BOP)[8] have also been shown to activate carbon−oxygen bonds for nucleophilic displacement reactions.[9] Additionally, phosphorus activated carbon−oxygen bonds can function as effective partners in cross-coupling reactions.[10] To our knowledge, however, there have been no reports of phosphonium salt activation of pyridine-*N*-oxides.

To assess the feasibility of using phosphonium salts as a means to introduce amines onto pyridine-*N*-oxides, we attempted the coupling of pyridine-*N*-oxide **6** with cyclohexylamine **7** (Table 1). When a basic mixture of **6** and **7** was treated with PyBroP (bromo-tris-pyrrolidino-phosphonium hexafluorophosphate), we were delighted to obtain **8** as the major product of the reaction. Remarkably, no addition at the 4-position of the pyridine-*N*-oxide was observed. After reaction optimization, we found that Hunig's base (iPr$_2$EtN) and dichloromethane as a base/solvent pair worked most effectively (entry 1). PyBroP and the closely related BroP (entry 13) were the only phosphonium salts that afforded the desired product. Although BroP (83%) slightly outperformed PyBroP (82%), we chose not to use BroP due to the generation of carcinogenic HMPA as a byproduct (vide infra). Hydroxybenzotriazole-based phosphonium salts (entries 14 and 15) and bromo-triphenylphosphonium bromide

Table 1. Reaction Optimization for the Amination of Pyridine-*N*-oxide with Cyclohexylamine[a]



6 + 7 → 8

entry	additive	base	solvent	temp (°C)	yield
1	PyBroP	iPr$_2$EtN	CH_2Cl_2	25	82
2[b]	PyBroP	iPr$_2$EtN	CH_2Cl_2	25	75
3[c]	PyBroP	iPr$_2$EtN	CH_2Cl_2	25	41
4[d]	PyBroP	iPr$_2$EtN	CH_2Cl_2	25	69
5	PyBroP	iPr$_2$EtN	CH_2Cl_2	0→25	55
6	PyBroP	iPr$_2$EtN	DCE	70	53
7	PyBroP	iPr$_2$EtN	DMF	25	n/r[e]
8	PyBroP	iPr$_2$EtN	EtOAc	25	62
9	PyBroP	iPr$_2$EtN	THF	25	70
10	PyBroP	DBU	CH_2Cl_2	25	n/r
11	PyBroP	2,6-lutidine	CH_2Cl_2	25	40
12	PyBroP	NEt_3	CH_2Cl_2	25	78
13	BroP	iPr$_2$EtN	CH_2Cl_2	25	83
14	PyBop	iPr$_2$EtN	CH_2Cl_2	25	n/r
15	BOP	iPr$_2$EtN	CH_2Cl_2	25	n/r
16	Ph_3PBr_2	iPr$_2$EtN	CH_2Cl_2	25	n/r

[a] Unless otherwise noted, all reactions were conducted at 0.25 M concentration with **6** (1.00 equiv), **7** (1.25 equiv), base (3.75 equiv), and additive (1.30 equiv). [b] 1.00 equiv of **7**. [c] 5.00 equiv of **7**. [d] 0.10 M concentration. [e] No reaction.

(entry 16) were ineffective. Nontrialkylamine bases (entries 10 and 11) performed poorly under the reaction conditions. A solvent screen demonstrated that dichloromethane (0.25 M) gave the highest yields (entries 1, 4, and 7−9). Interestingly, elevated temperature (entry 6) had a detrimental effect on the observed yield. Under our optimized conditions, we used *N*-oxide **6** as the limiting reagent with a small excess of **7** (1.25 equiv), PyBroP (1.30 equiv), and a 3-fold excess of iPr$_2$EtN (3.75 equiv) compared to the amine nucleophile. The reactions were complete in 5−15 h at room temperature. The order of reagent addition had no impact on observed yields.

We next applied the optimized reaction conditions to a variety of amine nucleophiles (Table 2). When pyridine-*N*-oxide **6** was combined with each amine in dichloromethane and treated with iPr$_2$EtN and PyBroP, we were pleased to obtain the corresponding 2-aminopyridines in modest to excellent yields. In none of these instances did we observe reaction at the 4-position of the pyridine-*N*-oxide. As shown in Table 2, primary and secondary aliphatic amines were very effective nucleophiles (entries 1−6).[11] Ammonia (entry 15) also showed modest reactivity under our conditions. The steric bulk of the amine had little impact on the reaction outcome, as *t*-butylamine performed well (entry 12). Aminations with allylic and benzylic amines (entries 7 and 8) proceeded smoothly as did those with heterocyclic amines

(5) (a) Alcazar, J.; Alonso, J. M.; Bartolome, J. M.; Iturino, L.; Matesanz, E. *Tetrahedron Lett.* **2003**, *44*, 8983–8986. (b) Yamanaka, H.; Araki, T.; Sakamoto, T. *Chem. Pharm. Bull.* **1988**, *36*, 2244–2247.

(6) Han, S.; Kim, Y. *Tetrahedron* **2004**, *60*, 2447–2476.

(7) Castro, B.; Coste, J. PCT Int. Appl. WO90/10009, 1990.

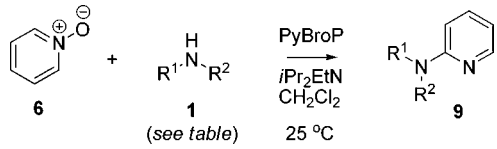
(8) Abbreviations: PyBroP = bromo-tris-pyrrolidino-phosphonium hexafluorophosphate; BroP = bromo-tris-dimethylamino-phosphonium hexafluorophosphate; PyBOP = benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate; BOP = benzotriazole-1-yl-oxy-tris-dimethylamino-phosphonium hexafluorophosphate.

(9) Wan, Z.; Wacharasindhu, S.; Levins, C. G.; Lin, M.; Keiko Tabei, K.; Mansour, T. S. *J. Org. Chem.* **2007**, *72*, 10194–10210.

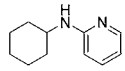
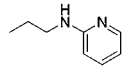
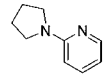
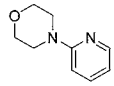
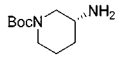
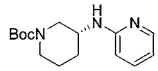
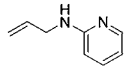
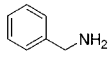
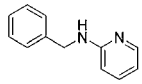
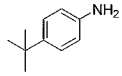
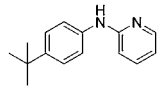
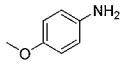
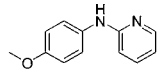
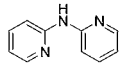
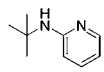
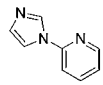
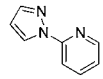
(10) Kang, F.; Sui, Z.; Murry, W. V. *J. Am. Chem. Soc.* **2008**, *130*, 11300–11302.

(11) For entry 6, as anticipated, no racemization and no protecting-group degredation occurred. Chiral purity was determined on a Chiralpak AD Column, 5% IPO/heptanes with 0.1% DEA, 210 nm, 1 mL/min flow rate, and compared to a racemic standard.

Table 2. Amination of Pyridine-*N*-oxide with a Variety of Amines[a]



6 + 1 (*see table*) → 9

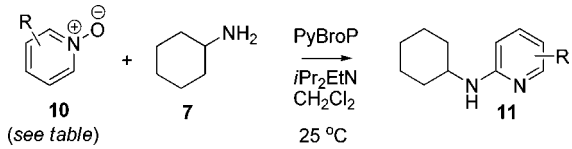
entry	amine **1**	product	yield
1			82%
2			73%
3[b]			83%
4			93%
5			58%
6			69%
7			85%
8			70%
9			44%
10			57%
11			36%
12			70%
13			95%
14			63%
15[c]	NH_3		58%

[a] Reaction Conditions: Combine *N*-oxide **6** (1.00 equiv), amine **1** (1.25 equiv), and 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. [b] 1.0 M $MeNH_2$ in THF. [c] 0.5 M NH_3 in 1,4-dioxane.

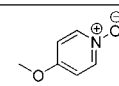
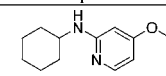
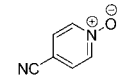
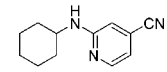
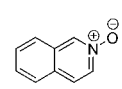
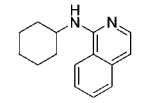
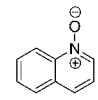
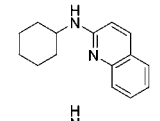
(entries 13 and 14). Although the yields were attenuated, we were pleased to observe reaction with electron-rich and electron-neutral anilines (entries 9 and 10). With the exception of entry 11, we observed little or no reactivity with electron-deficient anilines. To our knowledge, this is the only report of amidation with an aniline onto a 2,6-unsubstituted pyridine at room temperature.

We further examined the reaction of cyclohexylamine **7**, with a selection of pyridine- and quinoline-*N*-oxides under our optimized conditions (Table 3). We were pleased to observe modest to good reactivity in all cases examined. Electron-rich (entry 1) and electron-poor (entry 2) pyridine-*N*-oxides showed comparable reactivity. Quinoline-*N*-oxides worked well (entries 3 and 4), with isoquinoline-*N*-oxide affording the 1-substituted regioisomer only.[12] Reaction with 3-methylpyridine-*N*-oxide (entry 6) gave a 1:1 mixture of addition products at the 2- and 6-positions, with no apparent steric bias from the 3-methyl group. Although the majority of the examples in Table 3 is derived from commercially

Table 3. Amination of Various Heterocyclic-*N*-oxides with Cyclohexylamine[a]



10 (*see table*) + **7** → **11**

entry	N-oxide **10**	product	yield
1			65%
2			57%
3			71%
4			52%
5			50%
6[b]		+ isomer	64%
7		n/r[c]	0%

[a] Reaction Conditions: Combine *N*-oxide **7** (1.00 equiv), cyclohexylamine **7** (1.25 equiv), and 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. [b] 1:1 with 3-methyl isomer. [c] No reaction.

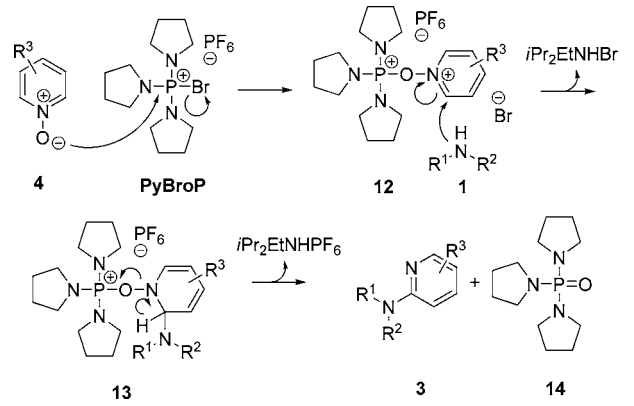
(12) Examples of 1-position regioselectivity with isoquinoline-*N*-oxides are known: (a) Manley, P. J.; Bilodeau, M. T. *Org. Lett.* **2002**, *4*, 3127–3129. (b) Abramovitch, R. A.; Rogers, R. B. *Tetrahedron Lett.* **1971**, *22*, 1951–1954.

(13) (a) Jain, S. L.; Sain, B. *Chem. Commun.* **2002**, 1040–1041. (b) Fields, J. D.; Kropp, P. J. *J. Org. Chem.* **2000**, *65*, 5937–5941. (c) Ferrer, M.; Sanchez-Baeza, F.; Messeguer, A. *Tetrahedron* **1997**, *53*, 15877–15888.

available *N*-oxides, the relative ease[13] of converting pyridines and quinolines to the corresponding pyridine- and quinoline-*N*-oxides facilitates even larger potential diversity.

The proposed mechanism for this transformation is outlined in Scheme 2. The reaction most likely proceeds via

Scheme 2. Proposed Reaction Mechanism



the activated pyridine complex **12**. Subsequent basic rearomatization (**13**) affords the desired 2-aminopyridine **3** and phosphoryltripyrrolidine **14**, the only significant organic byproduct of the reaction. The strong regiochemical preference for 2-position addition may be attributed to a charge association[14] of the activated phosphonium complex **12** with the incoming amine nucleophile **1**. Whatever the source of this effect, its strength cannot be overstated, as no addition at the 4-position of 2,6-dimethylpyridine-*N*-oxide (Table 3, entry 7) was observed under our standard reaction condtions. Preformation of **12**, as observed by the consumption of PyBroP and *N*-oxide, followed by the addition of amine and base, afforded the desired product as expected. Under no circumstances did we observe counteranion (Br^-, PF_6^-) addition onto the pyridine. In this transformation, the phosphonium salt works in excellent balance to activate and eliminate, while remaining unreactive toward the amine nucleophile.

In conclusion, we have presented a general and facile amination procedure for the synthesis of 2-aminopyridines, which provides a mild alternative to traditional S_NAr chemistry. A diverse substrate scope combined with an operationally simple procedure make this a useful methodology. Further optimization of this procedure will continue in our laboratory.

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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.

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(14) 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 addition to activated pyridines and may work in concert with the proposed charge interaction.