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A General and Efficient 2-Amination of Pyridines and Quinolines

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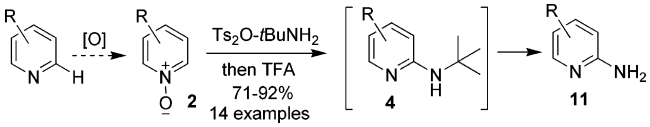

Pyridine *N*-oxides were converted to 2-aminopyridines in a one-pot fashion using Ts_2O-*t*-$BuNH_2$ followed by in situ deprotection with TFA. The amination proceeded in high yields, excellent 2-/4-selectivity, and with good functional group compatibility. 2-Amino (iso)quinolines were also obtained in the same manner. Combined with the simple oxidation of pyridines to pyridine *N*-oxides, this method provides a general and efficient way for amination of 2-unsubstituted pyridines.

2-Aminopyridines and analogues constitute an important class of compounds in organic synthesis and drug discovery.[1] During SAR investigations in the drug discovery process, derivatization of a 2-unsubstituted pyridine moiety in a complex molecule to the corresponding 2-aminopyridine is often desired but only achieved with a long sequence and low efficiency.[2] One of the most widely used amination methods is substitution of 2-halopyridines and analogues with ammonia or an equivalent under high temperature (150−250 °C) and pressure[3] or under Pd[4]- or Cu[5]-catalyzed conditions. However, to use this approach, a halogen atom must be installed at the 2-position first, and this is usually done by chlorination of pyridine *N*-oxides with poor 2,4-regioselectivity and/or low yields.[6,7] The most direct approach would start with 2-unsubstituted pyridines. The Chichibabin reaction[1b,c,8] gives 2-aminopyridines directly from sodium amide and pyridines, but it is very limited in scope with unsatisfactory yields and poor functional group tolerance due to the strongly basic conditions and high temperatures.[9]

Pyridine *N*-oxides **2** are readily available via oxidation of pyridines under a variety of different conditions.[10] Abramovich first reported use of imidoyl chlorides to convert pyridine *N*-oxides to 2-*amido*pyridines.[11] Synthesis of 2-amidopyridines from secondary amides or 2-amido(iso)quinolines from primary amides via in situ generation of imidoyl chlorides or benzoyl isocyanates has also been reported recently.[12] For the synthesis of 2-*amino*pyridines, 4-chloro-2,2-dimethyl-2*H*-1,3-benzoxazine can be used because the resulting amidopyridine product can be readily converted to 2-aminopyridines.[13] However, this reagent requires a two-step synthesis,[13b] and the release of the 2-amino group requires a separate step.

On the other hand, after reacting with an electrophile to form **3**, the 2-position is highly activated for nucleophile addition. If ammonia serves as the nucleophile, 2-aminopyridines **4** could be obtained. Very few examples of direct conversion of (iso)-quinoline *N*-oxides to *2-amino(iso)quinolines* are known, and they give 60−70% yields mostly using NH_4OH−TsCl.[14]

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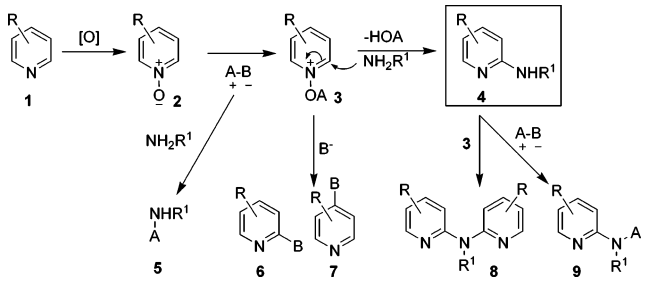
SCHEME 1

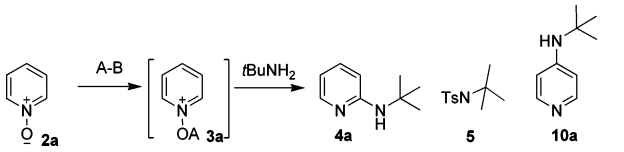


However, the corresponding reaction with pyridine N-oxides has failed (vide infra).[15] The inefficiency of this process is due to multiple side reactions. First, it is difficult to efficiently form the highly activated species **3** as a stable intermediate.[16] Once formed, **3** is exposed to the attack of the counterion B^- (B = Cl,[6] TsO,[6d,17] AcO[18]) at the 2- and 4-positions to give **6** and **7** as byproducts (vide infra). If the amine nucleophile is added before the activating reagent, reaction between the two reagents to give **5** becomes a major side reaction. Additionally, further reaction of product **4** with **3** or the activating reagent significantly lowers the yield.[15]During the course of the process development of a drug candidate, we needed an efficient and convenient method to convert a 2-unsubstituted pyridine moiety to a 2-aminopyridine moiety. Here we wish to report a general and efficient method to introduce a 2-amino group to 2-unsubstituted pyridines and (iso)quinolines.

Not surprisingly,[15] when we attempted the amination of pyridine *N*-oxide with TsCl−NH_4OH in $CHCl_3$ or CH_2Cl_2,[14] only ∼10% of the desired product was obtained with a large amount of $TsNH_2$ and Py_2NTs due to dimerization and further tosylation of the product. We set out to study the reaction parameters, such as the activating reagent, solvent, and particularly the ammonia surrogate R^1NH_2, hoping a bulky yet cleavable R^1 group such as *tert*-butyl would disfavor the undesired byproducts **5**−**9** (Table 1).

Indeed, when pyridine *N*-oxide was treated with 1.75 equiv of TsCl and 4.5 equiv of *t*-$BuNH_2$ in CH_2Cl_2, a clean reaction was observed with ∼61% conversion. Very little dimerization or tosylation byproduct was observed. Note that the inexpensive *t*-$BuNH_2$ also served as the base for this reaction. Very importantly, in contrast to poor 2-/4-selectivity in chlorination reactions,[6] a very good 2-/4-regioselectivity was obtained with this amination (entry 1). The only major side reaction is direct reaction between activating reagent and the amine to form **5**, so the ratio between the desired product **4a** and **5** was used to monitor the efficiency under different conditions. Unfortunately, the **4a/5** ratio was only 0.46 in this case. Use of Ts_2O[19] gave similar results (entry 2). To minimize the reaction between two reagents, we attempted to form activated species **3** in the absence of amine nucleophile, but premixing the *N*-oxide with TsCl or Ts_2O followed by amine addition gave no improvement (entries 3−5).[20] Other activating species such as AcCl, MsCl, or Ms_2O were ineffective (entries 6−9).

TABLE 1. Amination of Pyridine *N*-Oxide[a]



entry	A−B	solvent	conv (%)	**4a/5**	**4a/10a**
1	TsCl	CH_2Cl_2	61	0.46	19
2	Ts_2O	CH_2Cl_2	60	0.48	14
3[b]	TsCl	CH_2Cl_2	61	0.46	12
4[b]	Ts_2O	CH_2Cl_2	25	0.17	3.8
5[c]	Ts_2O	CH_2Cl_2	27	0.18	4.5
6[b]	AcCl	CH_2Cl_2	0	0	−
7	AcCl	CH_2Cl_2	0	0	−
8	MsCl	CH_2Cl_2	0	0	−
9	Ms_2O	CH_2Cl_2	16	−	8.6
10	Ts_2O	THF	68	0.58	12
11	Ts_2O	MeCN	5	0.02	−
12	Ts_2O	DMF	8	0.05	−
13	Ts_2O	EtOAc	87	0.80	18
14[d]	Ts_2O	EtOAc	74	0.76	43
15[d]	TsCl	EtOAc	20	0.15	48
16	TsCl	$CHCl_3$	79	0.80	14
17	TsCl	DCE	55	0.38	16
18	TsCl	$PhCF_3$	74	0.61	30
19	Ts_2O	$PhCF_3$	84	1.3	22
20[e]	Ts_2O	$PhCF_3$	60	0.66	25
21[d,e,f]	Ts_2O	$PhCF_3$	100	0.83	59

[a] Reaction conditions: to a solution of 0.25 mmol of **2a** and 4.5 equiv of *t*-$BuNH_2$ in 2.5 mL of solvent was added 1.75 equiv of activating reagent A−B at rt. Most reactions gave no further conversion after 15 min (those with TsCl took a few hours). [b] Activating reagent was added before *t*-$BuNH_2$. [c] Ts_2O was aged with **2a** for 30 min before adding *t*-$BuNH_2$. [d] Run at 0 °C. [e] 5 mL of solvent/mmol **2a**. [f] 6 equiv of *t*-$BuNH_2$ and 2.5 equiv of Ts_2O were used.

A solvent screen revealed that EtOAc gave a high **4a/5** ratio, while MeCN or DMF was ineffective (entries 10−13). The 2-/4-amination selectivity was improved to >40/1 when the reaction was run at 0 °C with Ts_2O or TsCl, but this also resulted in lower ratios of **4a/5**, likely due to limited solubility of **2a** in EtOAc (entries 14 and 15). Combination of TsCl and $CHCl_3$ also gave a high **4a/5** ratio (entry 16). The highest **4a/5** ratio was achieved at 1.3/1 with Ts_2O−$PhCF_3$ (entry 19). Complete conversion and high 2-/4-selectivity (∼59/1)[21] were finally achieved at 0 °C with larger amounts of reagents (entry 21). Lower **4a/5** ratio was due to the higher concentration (entry 19 vs 20), which is important for a more efficient one-pot process.

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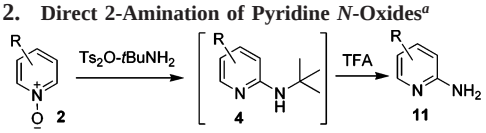
(19) Ts_2O is readily available on both small and large scales.

(20) This might indicate a reversible activation of **2a** by TsCl/Ts_2O or a preferred amine attack at the sulfur atom of activated species **3a**. In the case of Ts_2O, small amounts of water might cause decomposition of Ts_2O and low conversion.

(21) The 2-/4-amination selectivity was improved significantly by lowering the temperature from rt to 0 °C, but it is not clear how it was affected by solvents and activating reagents.

TABLE 2. Direct 2-Amination of Pyridine *N*-Oxides[a]



entry	*N*-oxide	product	yield(%)
1	**2a**	**11a**	84
2	**2b**	**11b**	88
3	**2c**	**11c1** 1.7:1 **11c2**	83[b]
4	**2d**	**11d**	71
5	**2e**	**11e**	92
6	**2f**	**11f**	90
7	**2g**	**11g**	92
8	**2h**	**11h**	80
9	**2i**	**11i**	81
10	**2j**	**11j**	82

[a] Reaction conditions: to a solution of 2.0 mmol of pyridine *N*-oxide and *t*-$BuNH_2$ (5−9 equiv) in $PhCF_3$ (CH_2Cl_2 or $CHCl_3$ might be added to dissolve the substrates) at 5−12 °C (20 °C for entry 5) was added 2.0−4.3 equiv of Ts_2O, 15 min; then TFA, 70 °C, 2−6 h (12 h for entry 9). Isolated yields are reported. [b] Combined yield of inseparable isomers.

Compound **4a** could be isolated at this point in 92% yield. 2-Aminopyridine was readily obtained by deprotection in neat TFA. However, a more efficient one-pot process was realized by adding TFA (2.5 mL/mmol) to the reaction mixture after completion of *tert*-butyl amination followed by heating at 70 °C to provide 2-aminopyridine in 84% yield.

We also used $HN(SiMe_3)_2$ instead of *t*-$BuNH_2$ as a more readily cleavable ammonia surrogate, but the product was hydrolyzed under the amination conditions to give the 2-aminopyridine that reacted further with the *N*-oxide to give significant amounts of dimers.[22]

Using the above optimized one-pot conditions, a variety of substituted pyridine *N*-oxides could be directly aminated at the 2-position in high yields (Table 2). Functional groups such as 2- and 4-ester groups, chloro, methoxy, and pyridyl groups were well tolerated. Amination of pyridine *N*-oxides with an electron-rich and an electron-withdrawing group proceeded well. In general, very little, if any, 4-amination was observed. In the case of 3-picoline *N*-oxide, 2- and 6-amination products were obtained in a 1.7/1 ratio (entry 3). A trisubstituted pyridine *N*-oxide was also aminated very efficiently (entry 10). The amination step typically took just a few minutes for completion; the in situ deprotection with TFA required 2−6 h.

TABLE 3. Direct 2-Amination of (Iso)quinoline *N*-Oxides[a]

entry	*N*-oxide	product	yield(%)
1	**2k**	**11k**	91
2	**2l**	**11l**	92
3	**2m**	**11m**	83
4	**2n**	**11n**	75

[a] Reaction conditions: same as in Table 2 but with 2.0−2.3 equiv of Ts_2O.

The one-pot amination method was readily expanded to quinoline *N*-oxides and isoquinoline *N*-oxide (Table 3). Substituted quinoline *N*-oxides were selectively aminated at the 2-position in high yields (entries 1−3). These *N*-oxides typically required slightly less Ts_2O than the simple pyridine *N*-oxides. For the isoquinoline *N*-oxide, if Ts_2O was added for activation in the absence of *t*-$BuNH_2$, significant amounts of the tosylation product (**6**) and other byproducts were observed within minutes at rt. These byproducts were mostly eliminated if Ts_2O was added after *t*-$BuNH_2$ (entry 4). Note that quinoline *N*-oxide **2k** was obtained via oxidation of quinoline with MCPBA, so the sequence represents an efficient 2-amination of 2-unsubstituted quinoline.

In summary, we have developed a general and efficient method to convert pyridine *N*-oxides to 2-aminopyridines in a one-pot process in high yields and high 2-/4-regioselectivity (>50/1). The process uses commercially available reagents *t*-$BuNH_2$ and Ts_2O and shows good functional group compatibility. The use of *t*-$BuNH_2$ 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 Ts_2O. TFA treatment of the crude reaction mixture effectively removed the *t*-Bu group. Starting with 2-unsubstituted pyridines or quinolines, simple oxidation followed by this amination provides an efficient synthesis of 2-aminopyridines or 2-aminoquinolines.

Experimental Section

Representative Procedure for 2-Amination: To a solution of pyridine *N*-oxide (190 mg, 2 mmol, 1.0 equiv) and *tert*-butylamine (1.05 mL, 10 mmol, 5.0 equiv) in $PhCF_3$ (10 mL)

(22) To prevent cleavage of TMS groups under reaction conditions, a stronger organic base (e.g., *i*-Pr_2NEt) was added to quench the TsOH, but this resulted in unidentified impurities, possibly from the organic base adding to the pyridine. We also noticed that NEt_3 added to the 2-position when combined with a pyridine *N*-oxide and Ts_2O.

at 0 °C was added Ts_2O (1.30 g, 4.0 mmol, 2.0 equiv) as a solid in portions while maintaining the reaction temperature at <5 °C. LC revealed incomplete conversion after 10 min. More *tert*-butylamine (0.21 mL, 2.0 mmol, 1.0 equiv) was added followed by Ts_2O (0.33 g, 1.0 mmol, 0.5 equiv). Complete conversion was obtained in 10 min. TFA (5 mL) was added to the reaction mixture, which was then aged at 70 °C for 5 h. The solution was concentrated to oil and diluted with water (5 mL) and CH_2Cl_2 (10 mL). The pH was adjusted to ∼10 with 50% aq NaOH (∼4 mL). The top aqueous layer was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic layers were concentrated and chromatographed (SiO_2, 2 × 20 cm, 1−3% MeOH/CH_2Cl_2) to give 2-aminopyridine (158 mg, 84% yield). NMR data matched those of commercial material. Note that, if desired, it is also possible to crystallize the HCl salt of the product from the crude product. See details in Supporting Information.

Supporting Information Available: Experimental procedures and characterization data for amination products (Tables 2 and 3). This material is available free of charge via the Internet at http://pubs.acs.org.

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