ORGANIC
LETTERS

2013
Vol. 15, No. 1
168–171

An Efficient, Regioselective Amination of 3,5-Disubstituted Pyridine *N*-Oxides Using Saccharin as an Ammonium Surrogate

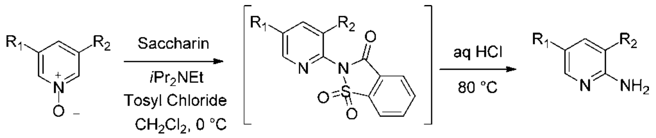
Robert P. Farrell,* Maria Victoria Silva Elipe, Michael D. Bartberger, Jason S. Tedrow, and Filisaty Vounatsos

*Chemical Process Research and Development, Amgen Inc., One Amgen Center Drive,
Thousand Oaks, California 91320, United States*

rfarrell@amgen.com

Received November 21, 2012

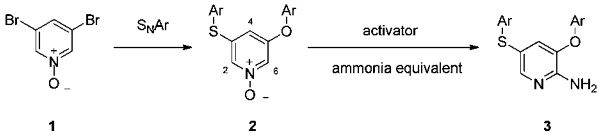
ABSTRACT



A process for the regioselective amination of unsymmetrical 3,5-substituted pyridine *N*-oxides has been developed utilizing cheap, readily available saccharin as an ammonium surrogate. High conversions of the corresponding saccharin adducts have been achieved under mild reaction conditions. *In situ* deprotection under acidic conditions allows for a one-pot process to substituted aminopyridines. High regioselectivities were obtained from a variety of 3,5-disubstituted pyridine *N*-oxides.

Aminopyridines are common structural motifs in molecules of high interest to the pharmaceutical industry.[1] An attractive, direct approach to 2-aminopyridines is *via* their corresponding pyridine *N*-oxides. The development of conditions for the reaction of pyridine *N*-oxides with various activating agents[2] and nitrogen nucleophiles to obtain 2-amino,[3] 2-amido,[4] and 2-*N*-hetero[5] pyridines has improved access to 2-aminopyridines and derivatives. While seeking an efficient, lower cost manufacturing route for a clinical candidate, we explored a regioselective amination of a 3-arylthio, 5- aryloxy pyridine *N*-oxide (**2**) readily prepared from dibromopyridine *N*-oxide (**1**) to obtain compound **3** (Scheme 1).

Scheme 1. Process Development Route to a 3-Arylthio, 5-Aryloxy Aminopyridine



A few examples of regioselective additions to pyridine *N*-oxides using a variety of C, N, and O based nucleophiles

---

[1] (a) Cui, J.; Tran-Dube, M.; Shen, H.; Nambu, M.; Kung, P.; Pairish, M.; Jia, L.; Meng, J.; Funk, L.; Botrouis, I.; McTique, M.; Grodsky, N.; Pyan, K.; Padrique, E.; Alton, G.; Timofeevski, S.; Yamazaki, S.; Li, Q.; Zou, H.; Christensen, J.; Mroxzkowski, B.; Bender, S.; Kania, R.; Edwards, M. *J. Med. Chem.* **2011**, *54*, 6342–6363. (b) May, B.; Zorn, J.; Witkop, J.; Sherrill, J.; Wallace, G.; Prusiner, S.; Cohen, F. *J. Med. Chem.* **2007**, *50*, 65–73. (c) Malamas, M.; Barnes, K.; Hui, Y.; Johnson, M.; Lovering, F.; Condon, J.; Fobare, W.; Solvibile, W.; Turner, J.; Hu, Y.; Manas, E.; Fan, K.; Olland, A.; Chopra, R.; Bard, J.; Pangalos, M.; Reinhart, P.; Robichaud, A. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2068–2073. (d) Zhang, D.; Ai, J.; Liang, Z.; Li, C.; Peng, X.; Ji, Y.; Jiang, H.; Geng, M.; Luo, C.; Liu, H. *Bioorg. Med. Chem.* **2012**, *20*, 5169–5180.

[2] Activating agent examples include Ts_2O, TsCl, $POCl_3$, oxalyl chloride, Ac_2O, trifluoroacetic anhydride, and PyBroP.

[3] (a) Yin, J.; Xiang, B.; Huffman, M.; Raab, C.; Davies, I. *J. Org. Chem.* **2007**, *72*, 4554–4557. (b) Londregan, A.; Jennings, S.; Wei, L. *Org. Lett.* **2010**, *12* (22), 5254–5257. (c) Wachi, K.; Terada, A. *Chem. Pharm. Bull.* **1980**, *28* (2), 465–472.

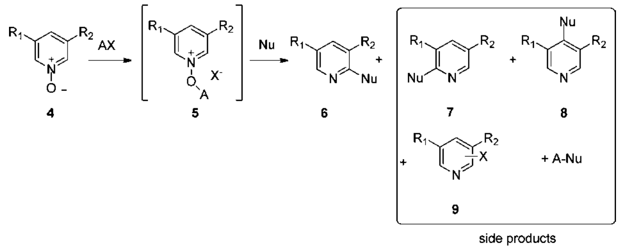
[4] (a) Abramovitch, R.; Singer, G. *J. Am. Chem. Soc.* **1969**, *91* (20), 5672–5673. (b) Abramovitch, R.; Rogers, R. *J. Org. Chem.* **1974**, *39* (13), 1802–1807. (c) Manley, P.; Bilodeau, M. *Org. Lett.* **2002**, *4* (18), 3127–3129.

[5] (a) Keith, J. *J. Org. Chem.* **2008**, *73*, 327–330. (b) Keith, J. *J. Org. Chem.* **2010**, *75*, 2722–2725. (c) Londregan, A.; Jennings, S.; Wei, L. *Org. Lett.* **2011**, *13* (7), 1840–1843.

10.1021/ol303218p

have been reported;[3c,4b,5a,b,6,7] however the substrate scope for such transformations has not been well-defined nor has a clear understanding been made of what key elements drive regioselectivity (e.g., substrate, nucleophile, activator). For our purposes, regioselective aminations of 3,5-disubstituted pyridine *N*-oxides have not been reported in the literature. Coupled with the challenge to develop a highly regioselective amination, it was vital to our process to minimize reaction side products commonly observed with direct aminations of pyridine *N*-oxides which often lead to lower yields and complicated isolations. These side products arise from the inherent reactivity of the amine nucleophile with the activator as well as from counterion attack of the activated species **5** leading to side product **9** (Scheme 2). It was recently reported that utilization of PyBroP[3b] mitigates the side reaction of the activator reacting with the nucleophile; however, the high cost and instability of the phosphonium reagent[8] make this approach undesirable for large scale development.

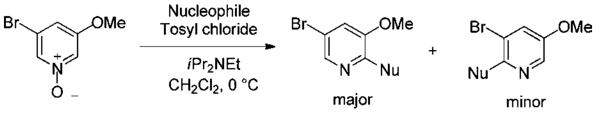
Scheme 2. Side Products Observed During Development of a Regioselective Direct Amination



We thus examined alternative literature conditions[3a] in which we treated our substrate with *tert*-butyl amine (4.0 equiv) and Ts_2O (2.0 equiv) in CH_2Cl_2 at 0 °C. Unfortunately, despite the excess of reagents, we obtained low conversions to product and observed many reaction impurities leading to a complex reaction mixture upon TFA deprotection. However, switching to HMDS (4.0 equiv) as the nucelophile with the otherwise same reaction conditions gave our desired 6-substituted product in 45% assay yield.[9] While the 2-substituted regioisomer was also observed, substitution at the 4-position was only detected in very trace quantities (< 0.5%) presumably due to the steric bulk of the 3,5-substituents. Despite this initial success, we were unable to overcome problems with formation of the 6-tosylated side product and low reaction conversions.

Having observed improved results with sterically bulky, less nucleophilic HMDS we began to screen alternative ammonia surrogates with similar characteristics but which surprisingly have not been published as nucleophiles for this application. A major breakthrough was achieved using *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide as the nucleophile under Ts_2O activation[10] affording > 99% conversion to the corresponding aminated product in a 11.6:1 ratio of the 6 and 2 regioisomer respectively. Removal of the sulfonamide group to generate the aminopyridine was problematic leading us to evaluate other Gabriel-type reagents[11] including saccharin, phthalimide, and diethyl-*N*-(*tert*-butoxycarbonyl)phosphoramidate. Gratifyingly, saccharin also displayed excellent reactivity toward our activated starting material (> 99% conversion) with good regioselectivity under unoptimized conditions (5.8:1). Furthermore, direct treatment of the unisolated saccharin adduct with aqueous HCl at 80 °C resulted in clean deprotection to the desired aminopyridine. After initial reaction optimization we also found both phthalimde and diethyl-*N*-(*tert*-butoxycarbonyl)phosphoramidate to give high conversion to their corresponding adducts although, importantly, regioselectivity was significantly impacted by the choice of nucleophile. This variability is highlighted on a model substrate (Table 1). Although diethyl-*N*-(*tert*-butoxycarbonyl)-phosphoramidate[12]delivers excellent regioselectivity, its relatively high cost made it unattractive for our purposes, and thus saccharin was chosen for further development.

Table 1. Effect of Nucleophile on Amination Regioselectivity



entry	nucleophile	regioselectivity[a]	conversion
1	saccharin	11.8:1	97%
2	diethyl-*N*-(Boc)phosphoramidate	17.0:1[b]	99%
3	phthalimide	2.6:1	100%

[a] Reaction conditions: Combined *N*-oxide (1.0 equiv) with nucleophile (1.1.equiv), and the mixure was slurried in CH_2Cl_2 (10 mL/g starting material). Added iPr$_2$EtN (2.0 equiv) with subsequent cooling to 0 °C. Added tosyl chloride (1.2 equiv) as a solid in one portion followed by stirring at 0 °C for 3−16 h. Regioselectivity and conversions were calculated by analysis of HPLC/MS peak area%. [b] Regioselectivity after deprotection to aminopyridine.

In an effort to maximize regioselectivity, optimization of our saccharin process included evaluation of base, activator, solvent, and reaction temperature.[13]

---

(6) Ujjainwalla, F.; Walsh, T. *Tett. Lett.* **2001**, *42*, 6441–6445.

(7) For a regioselective cyanation of a 3-alkoxy, 5-thiazole pyridine *N*-oxide using TMSCN/Et_3N, see: Umemura, K.; Noda, H.; Yoshimura, J.; Konn, A.; Yonezawa, Y.; Shin, C. *Tetrahedron Lett.* **1997**, *38* (20), 3539–3542.

(8) Bromotripyrrolidinophosphonium hexafluorophosphate PyBroP: CAS# 132705-51-2: Available from Aldrich: 25 g, $671. Storage conditions: −20 °C. Decomposition of PyBroP over prolonged storage generates pyrrolidine which can act as a nucleophile under the reaction conditions.

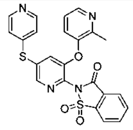
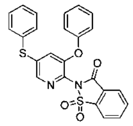
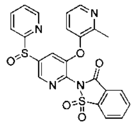
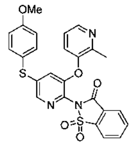
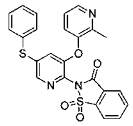
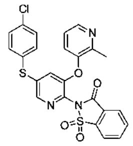
(9) Under the reaction conditions the TMS groups cleaved to give the unprotected aminopyridine in 45% solution assay yield with 6 HPLC area % tosylated side product and 31 HPLC area % unreacted starting material. 2-Aminopyridine regioisomer content was not quantified due to overlap with the starting material.

(10) Conditions: 2 equiv of Ts_2O, 1.3 equiv of DBU, 1.1 equiv of *N*-(*tert*-butoxycarbonyl)-P-toluenesulfonamide, CH_2Cl_2 (10 mL/g starting material), 0 °C.

(11) For a review of Gabriel reagents see: Ragnarsson, U.; Grehn, L. *Acc. Chem. Res.* **1991**, *24*, 285–289.

(12) Diethyl-*N*-(*tert*-butoxycarbonyl)phosphoramidate (CAS# 85232-02-6) avialable from TCI America: 5 g, $260.

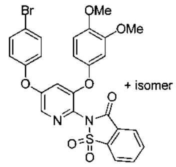
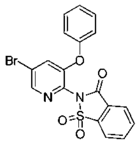
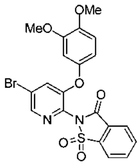
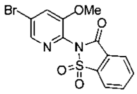
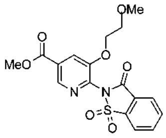
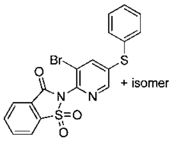
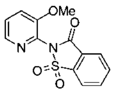
Table 2. 3-Arylthio, 5-Aryloxy Pyridine *N*-Oxide Aminations Using Saccharin

entry	major product	conversion	regioisomer ratio[a]	yield (%)[b]
1		100%	27.8:1	97[c]
2		99.6%	8.0:1	68
3		100%	6.7:1	46
4		98%	2.9:1	36
5		100%	5.6:1	70
6		97%	10.8:1	82

[a] Reaction conditions: Combined *N*-oxide (1.0 equiv) with saccharin (1.1equiv), and the mixture was slurried in CH_2Cl_2 (6 mL/g *N*-oxide). Added $i$$Pr_2EtN$ (2.0 equiv) with subsequent cooling to 0 °C. Added tosyl chloride (1.2 equiv) as a solution in CH_2Cl_2 (4 mL/g *N*-oxide) followed by stirring at 0 °C for 3 h. Regioisomer ratio refers to 2 and 6 substituted isomers. Regioisomer ratio and conversions were calculated by analysis of HPLC/MS peak area%. [b] Reported yields are for a single regioisomer using an unoptimized crystallization. [c] Isolated as the 6-aminopyridine derivative (Table 4, entry 1).

Of these variables, the choice of electrophilic activator was the most influential in the regioselective outcome. The highest regioselectivities were obtained using alkyl substituted benzenesulfonyl chlorides such as 4-*tert*-butylsulfonyl chloride (6.7:1), while remarkably little regioselectivity was observed with triflic anhydride (1.3:1).[14] Tosyl chloride (5.9:1) possessed the best mix of performance and price for our purposes.[15] The choice of solvent[16] was another important parameter, with CH_2Cl_2 delivering significantly higher regioselectivity for the desired isomer than THF, acetone, DMF, and DME. Due to the high polarity of the starting material, other less polar solvents were not evaluated. $i$$Pr_2NEt$ slightly outperformed pyridine, DBU, NMM, and Et_3N. Theoretically, 2 equiv of base are necessary for deprotonation of the nucleophile and scavenging the TsOH byproduct from rearomatization. During initial screening, we evaluated the use of less than 2 equiv of base allowing our substate, which contains a basic nitrogen, to also serve as a base (see closely related structure entry 1, Table 2). However, the unintended consequence of protonating our substrate was lower regioselectivity (6.7:1 vs 9.4:1) using 1.3 and 2.3 equiv of $i$$Pr_2NEt$ respectively. This result implied substrate electronics is an important

Table 3. Regioselective Amination of 3,5 Disubstituted Pyridine *N*-Oxides[a]

entry	major product	conversion	regioisomer ratio[a]	yield (%)[b]
1		94%	2.0:1	91%[c] mixture
2		100%	5.8:1	69%
3		95%	84:1	73%
4		97%	11.8:1	77%
5		100%	7.6:1	66%
6		100%	2.9:1	79% mixture
7		65%	3:1	21%

[a] Refer to Table 2 for conditions and footnotes.

---

(13) Regioselectivity was improved from 9.4:1 to 11.1:1 with our development substrate by lowering the reaction temperature from 0 to −15 °C. Reaction completion time in this case required 6 h.

(14) The following relative regioselectivities were observed using our development substrate: T_fO, 1.3:1; Ms_2O, 3.9:1; 4-NO_2-benzenesulfonyl chloride, 4.3:1; Ts_2O, 5.4:1; 4-MeO-benzenesulfonyl chloride, 5.5:1; tosyl chloride, 5.9:1; mesitylene sulfonyl chloride, 6.4:1; 4-*tert*-butylbenzenesulfonyl chloride, 6.7:1 (All reactions were carried out with 1.1 equiv of saccharin, 2.0 equiv of $i$$Pr_2NEt$, in CH_2Cl_2 (10 mL/g starting material) at 0 °C).

(15) Aldrich pricing: *p*-Toluenesulfonyl chloride, 1 kg = $66; 4-*tert*-butylbenzenesulfonyl chloride, 50 g = $127.

(16) It is noteworthy that these amination conditions are tolerant of water with full conversions realized using a 9:1 acetone/water solvent system.

factor for regioselectivity. To test this hypothesis, a series of analogous 3-aryloxy, 5-arylthio pyridine *N*-oxides were prepared. Their performance under the optimized amination conditions is shown (Table 2).

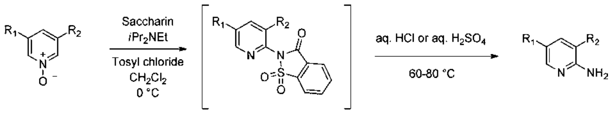
While for all these examples substitution is favored ortho to the aryl oxy substituent (see entries 1–6, Table 2), the regioselectivity is indeed highly influenced by altering the electronics of the substituents as highlighted in entries 4–6, Table 2. From these findings we reasoned that the scope of our regioselective amination protocol may well apply to other electronically differentiated 3,5-disubstituted pyridine *N*-oxides (Table 3). In the case of 3,5-diaryl ethers, marginal regioselectivity was observed ortho to the more electron-rich aryloxy substituent (entry 1, Table 3).

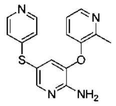
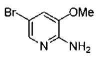
3-Bromo, 5-aryloxy, and alkyloxy substrates (readily prepared from dibromopyridine *N*-oxide) aminate predominately ortho to the electron-rich 5-substituent (entries 2–4, Table 3) making for a useful class of intermediates. Curiously, in the case of 3-bromo, 5-arylthio pyridine *N*-oxide (entry 6, Table 3) substitution was modestly favorable ortho to the bromine substituent. These amination conditions gave both lower selectivity and conversion when applied to monosubstituted substrates such as 3-methoxy pyridine *N*-oxide (entry 7, Table 3).

With acid soluble substrates, deprotection of the saccharin adducts can be achieved by direct addition of aqueous HCl or H_2SO_4 to the reaction mixture. In this way, primary aminopyridines were obtained in a single isolation (Table 4).

In a recent publication, various electrophilicity indices computed *via* quantum mechanics for *unactivated* substrates have been found to correspond well to experimentally observed regiochemical ratios,[5c] and we observed the same phenomenon. Curiously, however, our own calculations of both electrophilic Fukui indices and the LUMO distribution for *activated* (tosyl, triflyl) substrates suggest a significant decrease in inherent 2- versus 6-position reactivity far below that which is experimentally observed. This result may be suggestive of other, nonobvious mechanistic factors beyond the relative electrophilicity of the competing reactive centers upon substrate activation (refer to the Supporting Information for experimental details and results).

Table 4. Through Process Amination/Deprotection to 3,5-Disubstituted Aminopyridines



entry	major product	conversion	regioisomer ratio	yield (%)
1		100%	27.8:1	97%
2		97%	11.8:1	66%

In conclusion, an efficient and regioselective amination of electronically differentiated 3,5-pyridine *N*-oxides has been developed using novel amination reaction conditions. Saccharin is ideally suited as an ammonia surrogate for this application, delivering both high conversions and high regioselectivity. This protocol overcomes challenges associated with direct amination of pyridine *N*-oxides caused by the competetive reaction of the nucleophile with the activator. Cleavage of the saccharin intermediates has been achieved in a one-pot fashion upon treatment with aq. HCl or H_2SO_4. The substrate examples presented offer insight into the applicability of this protocol toward related 3,5-disubstituted pyridine *N*-oxides.

Acknowledgment. The authors thank our Amgen research colleagues Eric Bercot, Matthew Bio, Andrew Cosbie, Kelly Hu, and Kevin Turney for support and helpful discussions.

Supporting Information Available. General experimental procedures and spectral data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.