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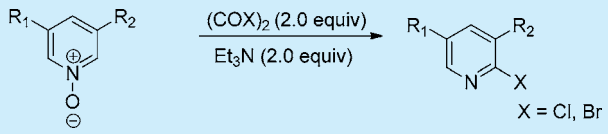
Highly Regioselective Halogenation of Pyridine *N*-Oxide: Practical Access to 2-Halo-Substituted Pyridines

Ying Chen,* Jinkun Huang,† Tsang-Lin Hwang, Maosheng J. Chen, Jason S. Tedrow, Robert P. Farrell, Matthew M. Bio, and Sheng Cui*

Drug Substance Technologies, Amgen, Inc., One Amgen Center Drive, Thousand Oaks, California 91320, United States

Supporting Information

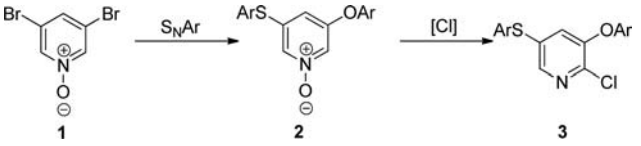
ABSTRACT: A highly efficient and regioselective halogenation reaction of unsymmetrical pyridine *N*-oxide under mild conditions is described. The methodology provides a practical access to various 2-halo-substituted pyridines, which are pharmaceutically important intermediates.



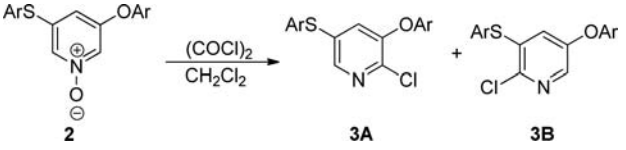
Substituted pyridines, particularly 2-aminopyridyl and heteroarene derivatives, constitute an important class of bioactive compounds that possess a range of physiological activities.[1] C2-Halogenated pyridines have been proven to be common precursors to prepare many of these compounds through S_NAr or cross-coupling reactions. However, direct access to those useful precursors by halogenation on substituted pyridine rings is particularly difficult mainly due to poor regioselectivity and reactivity. Alternatively, halogenation of pyridine *N*-oxide using POX_3,[2] SOX_2,[3] SO_2Cl_2,[4] or phosgene[5] still remains an attractive approach to install a halogen atom at the C2 position of a pyridine ring for a number of reasons, including the easy preparation of *N*-oxide, the functional group tolerance of the oxidation reaction, and the crystallinity of many pyridine *N*-oxides. However, this halogenation approach has not been widely used, mainly because existing procedures often suffer from limited or highly substrate-dependent regioselectivity (2, 4, and 6 positions) and harsh reaction conditions, such as elevated temperature, long reaction time, and the necessity of using a large excess of the halogenation reagents, which generally results in a poor yield. The functional group comparability is another issue that is difficult to overcome. In addition, those harsh conditions are not deemed ideal for the large scale manufacture involving highly energetic pyridine *N*-oxide substrates due to the potential safety issues. Recently, a mild method for the regioselective C2-bromination of fused azine *N*-oxide was reported by Bristol-Myers Squibb and the Baran group, but unfortunately, this method is not applicable to pyridine derivatives.[6] Recently, we sought a cost-effective and safe manufacturing process to prepare 2-chloro-3,5-trisubstituted pyridine intermediate (**3**), a key intermediate for a clinical candidate, for which a very attractive approach (Scheme 1) was envisioned to be the sequential S_NAr reaction of the readily available pyridine *N*-oxide followed by a regioselective chlorination of the resulting *N*-oxide (**2**).

Although the issue of regiocontrol (Scheme 2) was expected to be challenging for the substrate **2** mainly due to subtle electronic and steric differences between 3-arylthio and 5-aryloxy, the potential benefits of this regioselective transformation including efficiency of the route and the potential for extension to SAR studies warranted investigation. Not surprisingly, our initial attempts to use commonly used chlorination conditions (e.g., PCl_5, SO_2Cl_2, $SOCl_2$, NCS, benezenesulfonic chloride, trichloroacetyl chloride, and oxalyl chloride with or without the activator Ts_2O) afforded a mixture of two regioisomers (**3A** and **3B**) with negligible C2/C6 selectivity. Interestingly, very little C4 isomer was observed in most cases. The key breakthrough arose from the subsequent screening of bases and solvents using $POCl_3$ as the chlorinating agent.[7] Synthetically useful regioselectivity and reaction yield (**3A**:**3B** = 93:7, 63% yield) were obtained with 2,6-lutidine as the base and dichloromethane as solvent under very mild conditions (0 °C). This initial hit prompted further investigation on combinations of bases, chlorination reagents, and solvents in order to improve the reactivity and selectivity by presumably tuning the course of *N*-oxide activation and electrophile attack. To our delight, the choice of combination did play an important role in determining both C2/C6 selectivity and reactivity. A >99:1 C2/C6 selectivity and 76%

Scheme 1. Potential Process to a Key Intermediate (3)



Scheme 2. Regioselective Chlorination



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assay yield were achieved by using oxalyl chloride and Et_3N at 0 °C (Table 1, entry 1). Moreover, it was found that of all

Table 1. Base Effects on Chlorination[a]

entry	base	assay yield (3A, %)[b]	ratio 3A/3B[c]
1	triethylamine	76	99.1/0.9
2	diisopropylethylamine	63	88.5/11.5
3	DBU	57	64.5/35.5
5	2,6-lutidine	52	67.3/32.7
6	pyridine	31	65.7/34.3
7	K_2CO_3	31	58.7/41.3
8	no base	66	59.2/40.8

[a]Reaction conditions: **2** (1.0 mmol), oxalyl chloride (2.0 mmol), and base (2.0 mmol) at 0 °C for 30 min. The resulting mixture was analyzed by HPLC directly without purification. [b]Assay yield was determined by HPLC using a pure sample as an external reference standard. The weight assay of the pure sample was determined by quantitative NMR analysis. [c]The ratio was determined by HPLC using both isomers as reference standards.

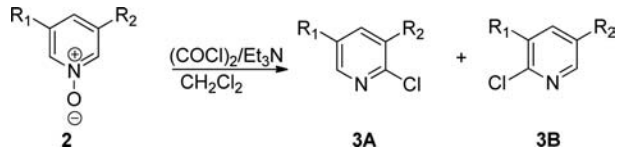
variables, the base played the most crucial role in both the selectivity and reaction yield (Table 1). For instance, diisopropylethylamine, a similar base to Et_3N, gave vastly inferior selectivity (Table 1, entry 2).

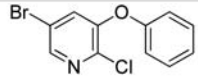
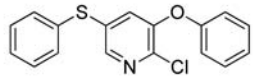
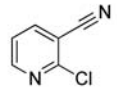
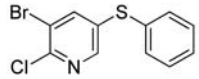
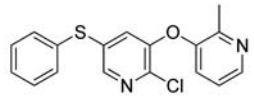
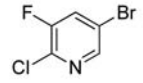
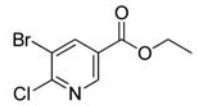
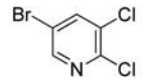
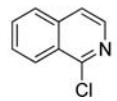
Further optimization was performed to make the process more amenable to large-scale manufacturing. The reaction yield could be improved to 86% by further decreasing the reaction temperature. At −70 °C, the reaction was instant and complete upon completion of oxalyl chloride charge.[8] While 1.1 equiv of both triethylamine and oxalyl chloride is sufficient to achieve a full conversion, to ensure consistent reaction yield and kinetics 2.0 equiv of both reagents were selected as the optimal conditions for the further optimization. In addition, the reaction could be run at high concentration, 100 g/L (substrate/solvent), without diminishing the reaction performance. Purification and isolation of the desired product could be achieved by crystallizing the *p*-toluenesulfonic acid (PTSA) salt of **3A** from 2-propanol, which provided >99% purity of a single isomer in 75% overall yield.

Having established an optimal protocol, we next investigated the generality and scope of the reaction. As shown in Table 2, the reaction conditions could be applied to a range of *N*-oxide derivatives.[9] In general, excellent C2/C6 selectivity was observed in almost all cases, and in several cases (entries 3, 5, 6, and 9) only a single isomer was detected at the end of reaction. In addition, both electron-rich and electron-poor substrates performed well, and sensitive functional groups including nitrile and ester (entries 3 and 7) were well tolerated. The regioselectivity was seemingly dominated by an electronic effect with the chloride being incorporated at the electron-deficient side for most of substrates. It is of particular interest that ca. 3/1 selectivity was obtained from 3-chloro-5-bromopyridine oxide (entry **8**) despite negligible electronic difference between chloride and bromide.

We envisioned that our findings in the regioselective chlorination reaction might be applied to bromination of pyridine *N*-oxide providing access to more valuable building blocks, 2-bromopyridines, in some circumstances. Compared to chlorination, there are even fewer reports on the practical and regioselective bromination of pyridine *N*-oxide. To our delight, the bromination was performed as efficiently as the chlorination reaction under similar reaction conditions, affording a variety of

Table 2. Scope of Chlorination on Pyridine *N*-Oxide



entry	major product	regioselectivity[a]	yield[b]
1		93.6:6.4	93.3%
2		98.3:1.7	84.4%
3		100:0	90.3%
4		77.9:22.1	77.4%
5		100:0	86.9%
6		100:0	84.4%
7		99.4:0.6	87.9%
8		73.5:26.5	74.9%
9		100:0	87.5%

[a]Ratio determined by 1D ^1H and 2D NMR ($^1H-^{13}C$ HMBC and 1,1-ADEQUATE). [b]Isolated yield for both isomers.

pharmaceutically important substituted pyridine building blocks in useful yield and selectivity (Table 3).[10]

Interestingly, when the bromination reaction was performed using oxalyl bromide in dichloromethane, a mixture of chloropyridine and bromopyridine in a 1/3 ratio was observed. Comparatively, a 1/1.2 ratio of bromopyridine and chloropyridine mixture was obtained in the case of chlorination with oxalyl chloride in dibromomethane. These results clearly suggested that both oxalyl halide and halogen solvents serve as the halide sources.[11] Further investigation indicated that a series of solvent adducts were observed when bromination reactions were carried out in acetonitrile or tetrahydrofuran. These results may be indicative of the formation of very reactive electrophilic species during the reaction; therefore, even a very weak nucleophilic solvent such as acetonitrile could be reactive. This phenomenon has been observed previously in the halogenation reaction of pyridine *N*-oxide.[12]

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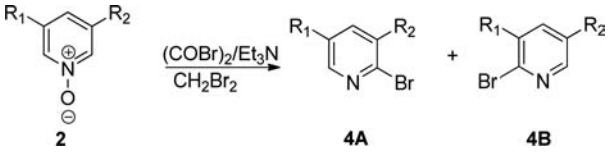
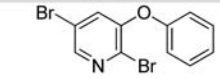
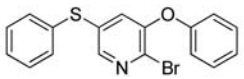
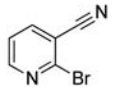
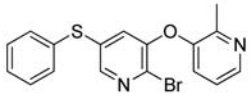
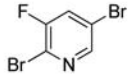
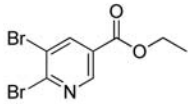
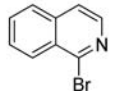
Table 3. Scope of Bromination on Pyridine *N*-Oxide

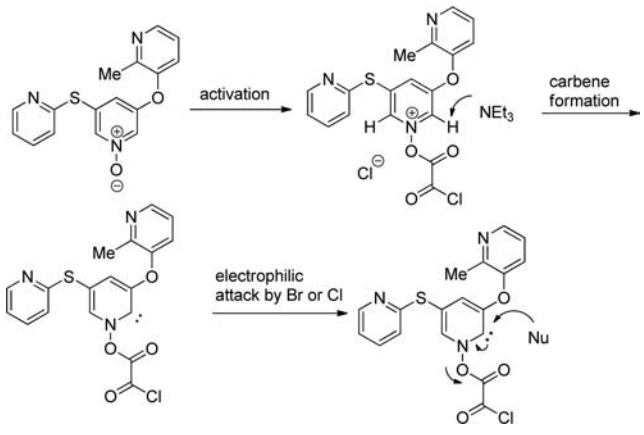


entry	major product	regioselectivity[a]	yield[b]
1		93.7:6.3	85.7%
2		82.9:17.1	72.9%
3		100:0	77.7%
4		98.4:1.6	81.2%
5		100:0	84.4%
6		98.8:1.2	76.1%
7		100:0	81.2%

[a]Ratio determined by 1D ^{1}H and 2D NMR (^{1}H−^{13}C HMBC and 1,1-ADEQUATE). [b]Isolated yield for both isomers.

On the basis of these experimental results, a plausible and likely simplistic mechanism can be proposed in which the *N*-oxide is first activated by oxalyl chloride and then the C2 proton in the resulting pyridinium chloride is extracted by triethylamine to generate a highly active electrophilic species such as a carbene. The presence of electrophiles may also explain the observed regioselectivity dominated by electron-withdrawing groups in most cases. Both solvents and halogenation reagents can act as nucleophiles in the system (Scheme 3). The nucleophilic reaction through a carbene intermediate have been known with *N*-fluoropyridinium salts.[12]

Scheme 3. Proposed Mechanism



In conclusion, we have developed a highly regioselective and efficient protocol for accessing a variety of 2-chloro or bromo-3,5-trisubstituted pyridines, which otherwise are challenging for synthesis. The mild reaction conditions, simple setup, and high process efficiency (high regioselectivity and yield) make this method suitable for large-scale production.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all products in Tables 2 and 3. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01057.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: ying@amgen.com.
*E-mail: scui@amgen.com.

Present Address

[†](J.H.) Jiangshu Hengrui Medicine CO., Ltd., Chengdu R&D Center, 88 S. Keyuan Route, B4 Suite 903, Tianfu Life Science Park, Chengdu Hi-Tech Zone, Chengdu, Sichuan 610000, China.

Notes

The authors declare no competing financial interest.

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(5) Schirok, H.; Figueroa-Perez, S.; Thutewohl, M.; Paulsen, H.; Kroh, W.; Klewer, D. *Synthesis* **2007**, *2*, 0251−0258.

(6) Wengryniuk, S. E.; Weickgenannt, A.; Reiher, C.; Strotman, N. A.; Chen, K.; Easrgate, M. D.; Baran, P. S. *Org. Lett.* **2013**, *15*, 792−795 and references cited therein.

(7) Base screening (Et_3N, $^{i}Pr_2EtN$, DBU, DABCO, 2,6-lutidine, pyridine, K_2CO_3, Cs_2CO_3) and solvent screening (DCM, toluene, MeCN, $CHCl_3$, DMF, pyridine).

(8) A continuous flow process for the reaction and workup has been developed to increase the manufacture throughput and reduce the

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manufacturing footprint. This work will be reported in a separate paper in the near future.
(9) Starting pyridine *N*-oxides were either purchased from Sigma-Aldrich without further purification or prepared from 3,5-dibromopyridine *N*-oxide based on the literature procedure. (Farrell, R. P.; Silva Elipe, M. V.; Bartberger, M. D.; Tedrow, J. S.; Vounatsos, F. *Org. Lett.* **2013**, *15*, 168−171).
(10) The reaction has to be operated at −55 °C instead of −70 °C because of the higher mp of the solvent dibromethane (−53 °C).
(11) The ratio of chloride and bromide was determined by NMR analysis of the crude product mixture after aqueous workup.
(12) (a) Hebel, D.; Rozen, R. *J. Org. Chem.* **1991**, *56*, 6298−6301. (b) Tagawa, Y.; Tanaka, J.; Hama, K.; Goto, Y.; Hamana, M. *Tetrahedron Lett.* **1996**, *37*, 69−72.

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