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One Step Conversion of Heteroaromatic-*N*-Oxides to Imidazolo-Heteroarenes

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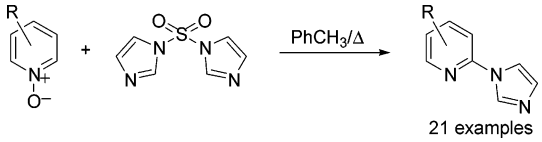

Various pyridine-, quinoline-, isoquinoline-, and pyrimidine-*N*-oxides were converted to their corresponding α-imidazoloheteroarenes in good yield by treatment with sulfuryl diimidazole in nonpolar solvents at elevated temperatures.

With our continuing interest in transformations of potential use to the pharmaceutical industry,[1] we wished to develop an alternate method for the introduction of imidazole functionality α- to heteroarene nitrogens. Typically, imidazole is introduced to electron-poor heteroarenes via substitution of a halide at elevated temperatures[2] or through the use of a copper catalyst.[3,4] The heteroarene halide, in turn, can be prepared by halogenation of an *N*-oxide precursor[5] with subsequent deoxygenation,[6−9] deoxygenative halogenation,[10] direct metalation of an *N*-oxide followed by quenching with an electrophilic halide source,[11] or through the conversion of an α-hydroxyl group with an oxyphilic halide source such as $SOCl_2$[12] or $POCl_3$.[13] We felt it was feasible to circumvent the need for the halide through activation of heteroarene-*N*-oxides to nucleophilic attack with concomitant elimination of the oxygen functionality, giving both a more concise and orthogonal approach to the introduction of imidazole. Such a transformation could be approached in several ways (Figure 1): (1) the *N*-oxide could be converted to an isolable salt[14,15] and then treated with imidazole; (2) the *N*-oxide could be activated *in situ*[16] and treated with imidazole; or (3) the *N*-oxide could be treated with an electrophile with imidazole as a labile substituent. Each of these approaches is precedented in the literature, but they have different potential propensities to give side products. Activation of an *N*-oxide by either approach (1) or (2) has the potential to give alternate products incorporating imidazole. In eq 1, the R′ group on the *N*-oxide could be transferred to imidazole thus consuming the activating agent and nucleophile. In other instances, the nucleophile may be basic enough to promote the oxidation of the R′ group, thus consuming the *N*-oxide.[17] In eq 2, the electrophilic substituent on the *N*-oxide could be transferred

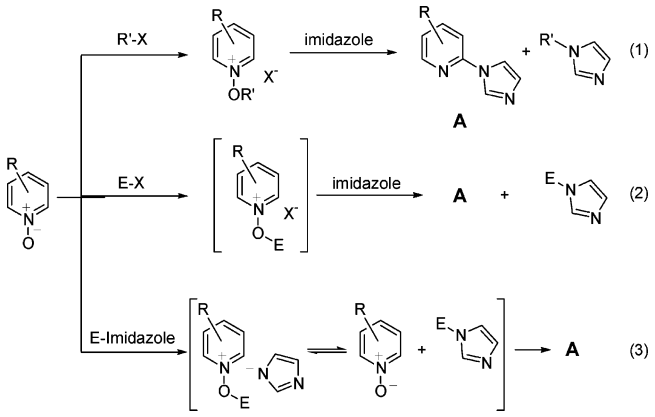

FIGURE 1. Possible strategies for the activation and substitution of *N*-oxides with potential side reactions shown.

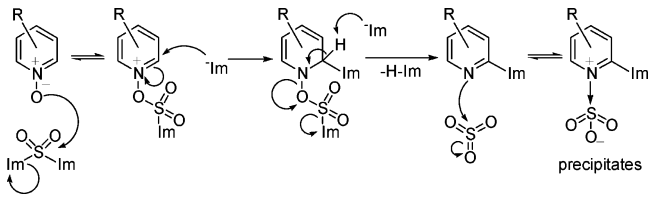

FIGURE 2. Possible mechanism for conversion of heteroarene-*N*-oxides to α-imidazolo-heteroarenes with sulfuryl diimidazole.

(1) (a) Keith, J. M. *J. Org. Chem.* **2006**, *71*, 9540−9543. (b) Letavic, M. A.; Ly, K. S. *Tetrahedron Lett.* **2007**, *48*, 2339−2343. (c) Dvorak, C. A.; Rudolph, D. A.; Ma, S.; Carruthers, N. I. *J. Org. Chem.* **2005**, *70*, 4188−4190. (d) Deng, X.; Mani, N. S. *Org. Lett.* **2006**, *8*, 3505−3508.

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(15) Traynelis, V. J.; Kimball, J. P. *J. Org. Chem.* **1975**, *40*, 2365−9.

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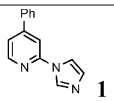
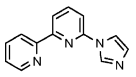
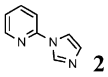
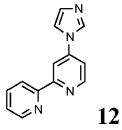
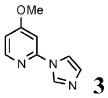
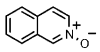
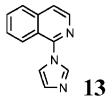
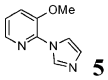
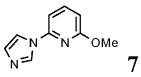
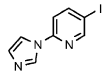
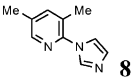
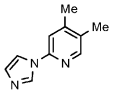
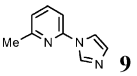
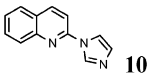
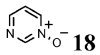
TABLE 1. Substrate Scope

Entry	Substrate	Temp (°C)	Reaction Time	Product(s)	Yield (%)	Entry	Substrate	Temp (°C)	Reaction Time	Product(s)	Yield (%)
1		110	6 h	 **1**	76	9		130	2 d	 **11**	74
2		100	4 h	 **2**	78					 **12**	13
3		100	2 h	 **3**	78	10		100	7.5 h	 **13**	62
4[24]	 **4**	100	9 h	 **5**	90	11		100	3 d	 **14**	28
5	 **6**	100	1d	 **7**	42					 **15**	56
6		110	6 h	 **8**	86	12		100	21 h	 **16**	44
7		100	1 d	 **9**	83					 **17**	34
8		100	1 d	 **10**	75	13[25]	 **18**	130	1 d	 **19**	76

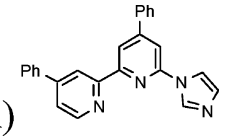
to the nucleophile, thus slowing or shutting down the reaction.[18] The strategy found in eq 3 should avoid the possible side reactions found in eqs 1 and 2, but the reaction may proceed more slowly because the leaving group on the electrophile is imidazole, a less labile substituent than a halide, sulfonate, or phosphate.

With the above issues in mind, we elected to explore the strategy inherent to eq 3 (Figure 2). Fortunately, the commercially available sulfuryl diimidazole is an electrophilic, easily handled solid and has imidazole as the only putative counterion, thus obviating the need for an exogenous base. For these reasons, we elected to use sulfuryl diimidazole for the studies described herein.

Initial optimization of reaction conditions was conducted using 4-phenylpyridine-*N*-oxide as the substrate. Heating a solution of 4-phenylpyridine-*N*-oxide and sulfuryl diimidazole in toluene at reflux resulted in complete consumption of starting material after 6 h, giving a good yield (76%) of **1**.[19] During the course of reaction, a dark oily residue formed on the sides of the flask. The residue hardened upon cooling and was insoluble in nonpolar organic solvents (CH_2Cl_2, EtOAc, CH_3CN, etc.) but dissolved readily in MeOH or water. We believe the residue is likely to be a complex between the product (and, in some cases, the starting material) and sulfur trioxide. Several pieces of data support this possibility: no gas evolution is apparent during the course of reaction;[20] pyridine/sulfur trioxide complexes are known;[21] and we isolated and characterized a chromatographically stable product/SO_3 complex.[22] The overall mechanism of the reaction likely resembles the one shown in Figure 2.[23]

(18) Chen, Z-C.; Stang, P. *Tett. Lett.* **1984**, *25*, 3923−3926.

(19) We also obtained a small amount (1%) of dimeric product (**A**). A similar product was obtained in a previous project (ref 1a) utilizing sulfuryl chloride.



(A)

(20) Heating a mixture of solid *N*-oxide with sulfuryl diimidazole to melting (120 °C) resulted in sudden reaction with potentially dangerous concomitant release of gas (presumably SO_3). Although product was formed under these conditions (54%), such neat preparations should be avoided.

(21) Barnes, R. S.; Harris, J. E. G.; Thomas, J. U.S. Patent 1921497, 1933.

TABLE 2. Substrates Giving Atypical Products

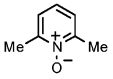
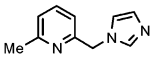
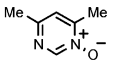
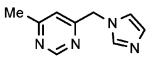
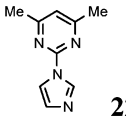
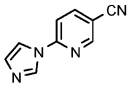
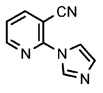
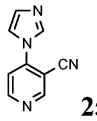
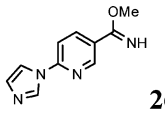
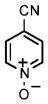
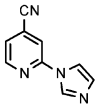
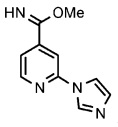
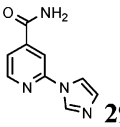
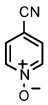
Entry	Substrate	Reaction Time at 130 °C	Product(s)	Yield (%)
1		7 d	 **20**	51
2		1 d	 **21**	17
			 **22**	24
3		17 h	 **23**	33
			 **24**	17
			 **25**	11
			 **26**	4
4		3 d	 **27**	43
			 **28**	18
			 **29**	0.9
5		3 d	**27**	79

Table 1 shows the results and reaction conditions for a variety of non-, mono-, and disubstituted heteroarene-*N*-oxides. Most electron-rich *N*-oxides went to completion within 24 h whereas electron poor and sterically encumbered substrates required longer reaction times and higher temperatures. Chlorobenzene and *m*-xylene worked equally well as solvents for reactions run at 130 °C. Imidazole generally substituted the position α to the ring nitrogen. Pyridine-*N*-oxides possessing alkyl and halide substitution in the 3-position moderately favored substitution at the 6-position (entries 11 and 12). When the 3-position possesses a methoxy group, substitution at the 2-position is favored (entry 4). Functionality in the 2-position of the *N*-oxide results in slower reaction (entries 5 and 7) while retaining selectivity for substitution at the 6-position. Only 2-(2-pyridyl)-pyridine-*N*-oxide (entry 9) yielded a small amount of product resulting from substitution of the 4-position (**12**). Quinoline-, isoquinoline-, and pyrimidine-*N*-oxide (entries 8, 10 and 13) were each effectively substituted under the standard reaction conditions.

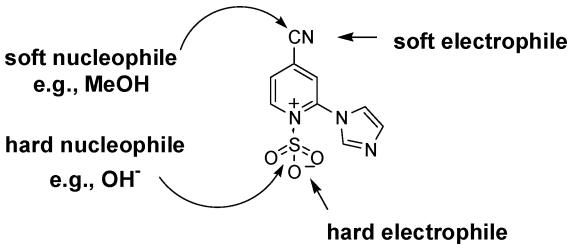


FIGURE 3. Proposed explanation of product distribution based on work up procedure.

Some substrates gave atypical products or product mixtures (Table 2).[24] An attempt to force substitution to the 4-position of 2,6-lutidine-*N*-oxide instead resulted in very slow substitution of one of the methyl groups (Table 2, entry 1). Similarly, with both the 4- and the 6-positions of pyrimidine-*N*-oxide blocked by methyl groups (Table 2, entry 2), methyl group substitution (**21**) competed with substitution of the 2-position (**22**). 3-Cyanopyridine-*N*-oxide gave substitution products **23**−**25** in all but the 5-position due to the strong directing effects of the nitrile (entry 3). Additionally, a small amount of methyl imidate ester (**26**) was isolated chromatographically. This product was initially something of a mystery as we were uncertain whether methanolysis was occurring during the purification process or, seemingly less likely, during workup. Methanolysis was even more pronounced with 4-cyanopyridine-*N*-oxide (Table 2, entry 4) as the substrate. Both the methyl imidate (**28**) and its hydrolysis product, the primary amide (**29**), were obtained. In this case, we were able to determine **28** was formed during the workup procedure in which we rinsed the reaction vessel with methanol and added the mixture to 1 N NaOH. The formation of products resulting from methanolysis could be avoided by rinsing the flask with 1 N NaOH, giving rise to greatly improved yields of **27** (entry 5). We suspect the products obtained after workup reflect the electronic nature of the product/SO_3 complex (Figure 3). The nitrile in the product/SO_3 complex should be more electrophillic relative to product alone. As a result of this activation, the relatively soft nucleophile methanol reacts with the nitrile (a soft electrophile) to give the methyl imidate ester. Conversely, treatment of the crude reaction mixture with NaOH (a hard nucleophile) most likely results in hydroxide ion attacking the highly electrophillic (i.e., hard) sulfur atom giving

(22) Only the SO_3 complex of product **5** was isolated and characterized, but such complexes were detected by M.S. with many of the substrates examined.

(23) See ref 1a.

(24) For discussion and examples of poor substrates, please see the Supporting Information.

sulfate ion thus freeing the desired product. Once the product has been decomplexed from SO_3, the nitrile becomes more resistant to solvolysis.

In conclusion, we have developed a convenient 1-step procedure for the conversion of heteroarene-*N*-oxides to α-imidazoloheteroarenes in fair to excellent yield through the action of sulfuryl diimidazole at elevated temperatures.

Experimental Section

Procedure for Preparing Compound 27. To a 100 mL round-bottomed flask were added 507 mg (4.22 mmol) of 4-cyanopyridine-*N*-oxide, 1.239 g (6.25 mmol; 1.5 equiv) of sulfuryl diimidazole, and an appropriate solvent (41 mL chlorobenzene; 0.1 M). The flask was fitted with a reflux condenser, the system was purged with nitrogen, and the mixture was heated with stirring at 130 °C until consumption of *N*-oxide was complete (3 days) as determined by TLC or HPLC. As the reaction proceeded, a dark precipitate formed on the sides of the flask. Once conversion of *N*-oxide was complete, the reaction mixture was added to a separatory funnel containing 1 N NaOH. The residue in the flask was taken up in 1 N NaOH[25] and added to the separatory funnel. The mixture in the separatory funnel was then mixed vigorously and then extracted with methylene chloride (300 mL × 2), and the organic layer was dried ($MgSO_4$), filtered, and evaporated to dryness to give the crude product. Chromatographic purification (silica gel, eluting with 0−5% 2 N NH_3 in MeOH/CH_2Cl_2) gave 565.1 mg (79%) of reasonably pure desired product. Further purification by HPLC (X-Terra C_{18}, 10−100% CH_3CN/H_2O w/0.05% TFA) gave product as a TFA salt.

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Supporting Information Available: ^1H and ^{13}C NMR spectra, HPLC chromatographs, melting points, experimental procedures, and tabulated spectral data for all prepared compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) Alternatively, the flask may be rinsed with MeOH when the *N*-oxide substrate does not possess a nitrile.