JOC*Note*

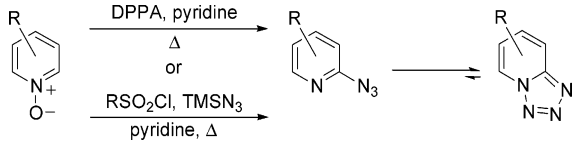
One-Step Conversion of Pyridine *N*-Oxides to Tetrazolo[1,5-*a*]pyridines

John M. Keith

Johnson & Johnson Pharmaceutical Research & Development, L.L.C. 3210 Merryfield Row, San Diego, California 92121

jkeith@prdus.jnj.com

Received September 1, 2006



Pyridine *N*-oxides were converted to tetrazolo[1,5-*a*]pyridines in good to excellent yield by heating in the presence sulfonyl or phosphoryl azides and pyridine in the absence of solvent. Various sulfonyl and phosphoryl azides were screened for reactivity under a standard set of conditions. Diphenyl phosphorazidate was the most convenient reagent and gave high yields. Reaction optimization, scope, and scalability are discussed.

Organic azides are especially versatile functional groups. Azides are commonly used as precursors to primary amines,[1] nitrenes,[2] and triazoles.[3] Azides adjacent to a heteroaromatic nitrogen atom exist in equilibrium with the corresponding tetrazole.[4] Substituents on the heteroaromatic ring can influence the ratio of products at equilibrium,[5] but in most instances, the tetrazole is the predominant species present. Despite the dominance of the tetrazole in the azide/tetrazole equilibrium, reactivity typical of azides can be observed. Tetrazolopyridines, Figure 1, can be converted to the pyridylnitrene under both thermal[6] and photochemical[7] conditions and can be reduced to the aminopyridine via a Staudinger reaction.[8] Cycloaddition with terminal alkynes[9] to give the corresponding triazole has also been demonstrated. Reactivity not typical of azides includes reduction of the pyridine ring to give aliphatic tetrazoles[10] and alkylation[11] or arylation[12] of the tetrazole to give otherwise difficult to access N-substituted bicyclic tetrazoles.

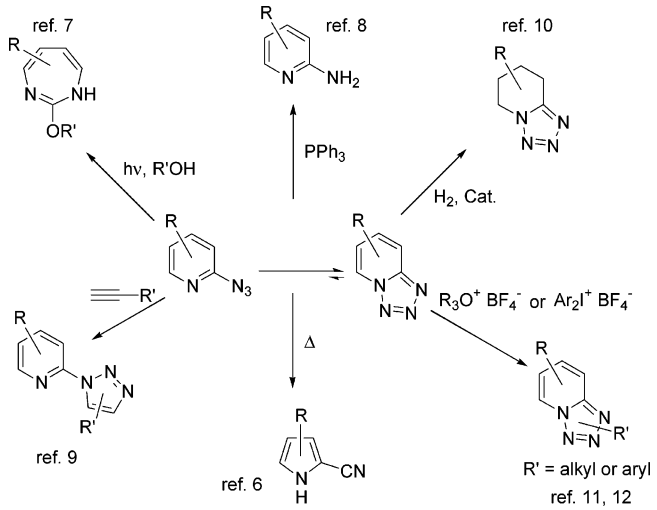


FIGURE 1. Tetrazolopyridines as intermediates.

Tetrazolopyridines are typically prepared by heating a 2-halopyridine in the presence of NaN_3 in a polar solvent.[13] The precursor halopyridine is typically prepared from the pyridone[14] or *N*-oxide[15] or by direct halogenation of the pyridine ring.[16] There were two reports of tetrazolopyridines prepared directly from the *N*-oxides using toluenesulfonyl azide (TsN_3)[17] and diphenyl phosphorazidate (DPPA),[18] but neither examined the reaction in any depth. We elected to reexamine the conversion of pyridine *N*-oxides to tetrazolopyridines with the goals of optimizing reaction conditions, determining substrate scope, and developing the process for multigram scale.

(1) (a) Boruah, A.; Baruah, M.; Prajapati, D.; Sandhu, J. S. *Synlett* **1997**, 1253−1254. (b) Vaultier, M.; Knouzi, N.; Carrie, R. *Tetrahedron Lett.* **1983**, *24*, 763−764. (c) Boyer, J. H. *J. Am. Chem. Soc.* **1951**, *73*, 5865−5866.

(2) (a) Tsao, M.-L.; Platz, M. S. *J. Am. Chem. Soc.* **2003**, *125*, 12014−12025. (b) Murata, S.; Yoshidome, R.; Satoh, Y.; Kato, N.; Tomioka, H. *J. Org. Chem.* **1995**, *60*, 1428−1434. (c) Albini, A.; Bettinetti, G.; Minoli, G. *J. Am. Chem. Soc.* **1991**, *113*, 6928−6934.

(3) (a) Lewis, W. G.; Green, L. G.; Grynszpan, F.; Radic, Z.; Carlier, P. R.; Taylor, P. R.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 1053−1057. (b) Angell, Y.; Burgess, K. *J. Org. Chem.* **2005**, *70*, 9595−9598.

(4) Brigas, A. F. *Sci. Synth.* **2004**, *13*, 861−915.

(5) (a) Karvellas, C.; Williams, C. I.; Whitehead, M. A.; Jean-Claude, B. J. *THEOCHEM* **2001**, *535* 199−215. (b) Kanyalkar, M.; Coutinho, E. C. *Tetrahedron* **2000**, *56*, 8775−8777. (c) Cmoch, P.; Stefaniak, L.; Webb, G. A. *Magn. Reson. Chem.* **1997**, *35*, 237−242. (d) Guimon, C.; Khayar, S.; Pfister-Guillouzo, G.; Claramunt, R. M.; Elguero, J. *Spectrosc. Lett.* **1981**, *14*, 747−753. (e) Boyer, J. H.; Miller, E. J., Jr. *J. Am. Chem. Soc.* **1959**, *81*, 4671−4673. (f) Denisov, A. Yu.; Krivopalov, V. P.; Mamatyuk, V. I.; Mamaev, V. P. *Magn. Reson. Chem.* **1988**, *26*, 42−46.

(6) (a) Simoni, D.; Rondanin, R.; Furno, G.; Aiello, E.; Invidiata, F. P. *Tet. Lett.* **2000**, *41*, 2699−2703. (b) Wentrup, C.; Winter, H. W. *J. Am. Chem. Soc.* **1980**, *102*, 6159−6161.

(7) (a) Reisinger, A.; Koch, R.; Wentrup, C. *J. Chem. Soc., Perkin Trans. 1* **1998**, *15*, 2247−2250. (b) Kuzaj, M.; Luerssen, H.; Wentrup, C. *Angew. Chem.* **1986**, *98*, 476−477.

(8) Sasaki, T.; Kanematsu, K.; Murata, M. *Tetrahedron* **1971**, *27*, 5359−5366.

(9) (a) Zhong, P.; Guo, S.-R. *Chin. J. Chem.* **2004**, *22*, 1183−1186. (b) Rogers, R. B.; Gerwick, B. C.; Egli, E. A. US Pat. 4474599, 1984.

(10) Boyer, J. H.; Chang, M. S.; Remisch, R. F. *J. Org. Chem.* **1960**, *25*, 286−287.

(11) (a) Cmoch, P.; Wiench, J. W.; Stefaniak, L.; Sitkowski, J. *J. Mol. Struct.* **1999**, *477*, 119−125. (b) Messmer, A.; Hajos, G.; Juhasz-Riedl, Z.; Sohar, P. *J. Org. Chem.* **1988**, *53*, 973−975.

(12) Messmer, A.; Hajos, G.; Fleischer, J.; Czugler, M. *Monatsh. Chem.* **1985**, *116*, 1227−1231.

(13) (a) Boyer, J. H.; Schoen, W. *J. Am. Chem. Soc.* **1956**, *78*, 423−425. (b) Carboni, S.; Da Settimo, A.; Ferrarini, P. L.; Pirisino, G. *Gazz. Chim. Ital.* **1966**, *96*, 1456−1469.

(14) (a) Seide, O. *Ber.* **1926**, *59B*, 2465−2473. (b) Henecka, H. *Ann.* **1953**, *583*, 110−128.

(15) Lee, C.-S.; Ohta, T.; Shudo, K.; Okamoto, T. *Heterocycles* **1981**, *16*, 1081−1084.

(16) Boudakian, M. M.; Frulla, F. F.; Gavin, D. F.; Zaslowsky, J. A. *J. Heterocycl. Chem.* **1967**, *4*, 375−376.

(17) Reddy, K. S.; Iyengar, D. S.; Bhalerao, U. T. *Chem. Lett.* **1983**, 1745−1748.

(18) Andrews, D. M.; Page, T. C. M.; Peach, J. M.; Pratt, A. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1045−1048.

10.1021/jo061819j CCC: $33.50
Published on Web 11/14/2006

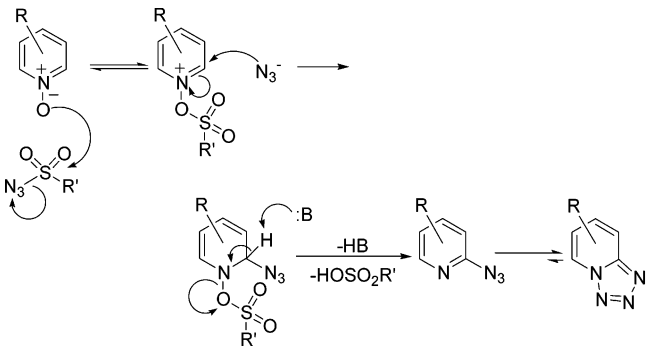


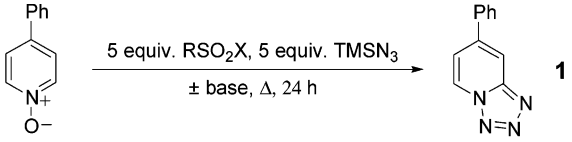
FIGURE 2. Reaction mechanism.

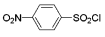
To affect the conversion of pyridine *N*-oxides to tetrazolo-[1,5-*a*]pyridines, we examined a number of activating groups (sulfonyl, sulfuryl, phosphonyl, and phosphoryl halides) in the presence of trimethylsilyl azide ($TMSN_3$). As we anticipated the reaction proceeding via a mechanism similar to that shown in Figure 2, we focused on electrophiles that could strongly activate the *N*-oxide to both nucleophilic attack and elimination.

Reactions were run neat at elevated temperature under a nitrogen atmosphere with a fixed reaction time of 24 h. Metathesis between $TMSN_3$ and the activating group was evident at 75 °C, as TMSCl would distill out (bp = 57−59 °C) of the reaction mixture. The reaction mixtures were typically kept at 75 °C for 30 min to 4 h to allow for distillation of the TMSCl. Table 1 shows the results with sulfur-based activating groups. Interestingly, most of the sulfur-based reagents affect the desired transformation to some degree. Reaction temperature and the presence of base had a large impact on reaction outcome. Reactions run at higher temperature (100 vs 75 °C) gave higher yields. Likewise, the addition of 2 equiv of pyridine was found to be beneficial to the yield in most[19] cases examined, but 5 equiv of pyridine did not result in higher yields (compare entries 7 vs 8, Table 1). *N*-Methylimidazole (NMI) was not an effective base for this reaction (compare entries 1−3, Table 1). The best chemical yields were obtained with toluenesulfonyl chloride (TsCl, entry 6, Table 1), 2-fluorophenylsulfonyl chloride (entry 18, Table 1), and phenylsulfonyl fluoride (entry 25, Table 1) as the activating reagents.

We next examined phosphoryl azides in the conversion of *N*-oxides to tetrazolopyridines. With the exception of commercially available diphenyl phosphorazidate, phosphoryl azides were prepared in situ from the corresponding phosphoryl chloride and $TMSN_3$. Most were effective mediators of the

TABLE 1. Influence of Temperature, Base, and Sulfonyl Activating Groups on the Yield of 7-Phenyltetrazolo[1,5-*a*]pyridine

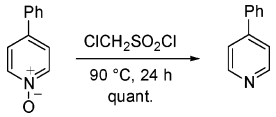


Entry	RSO_2X	Base	Temp (°C)	Yield (%)[a]
1	TsCl	none	75	36
2	TsCl	2 equiv. NMI	75	13
3	TsCl	2 equiv. pyridine	75	32
4	TsCl	none	100	36-47
5	TsCl	none	75-100[4]	51
6	TsCl	2 equiv. pyridine	100	67-73
7	TsCl	2 equiv. pyridine	75-100[4]	70
8	TsCl	5 equiv. pyridine	100	63
9	MsCl	none	75	15
10	MsCl	2 equiv. pyridine	75-100[30]	trace
11	CCl_3SO_2Cl	none	75-100[30]	12
12	CCl_3SO_2Cl	2 equiv. pyridine	75-100[30]	27[20]
13		none	75-100[30]	trace
14		2 equiv. pyridine	75-100[30]	44
15		none	75-100[30]	N.R.
16		none	75-100[30]	N.R.[21]
17		none	75-100[30]	53
18		2 equiv. pyridine	75-100[30]	72
19		none	75-100[30]	45
20		2 equiv. pyridine	75-100[30]	58
21	SO_2Cl_2	none	75-100[30]	24
22	SO_2Cl_2	2 equiv. pyridine	75-100[30]	38[22]
23	$C_4F_9SO_2F$	None/DCE	60	N.R.
24		none	75-100[30]	44
25		2 equiv. pyridine	75-100[30]	69

[a] All yields are post-chromatography: reactions run on a 100 mg scale relative to *N*-oxide: 75−100[30] = heating at 75 °C for 30 min before heating to 100 °C; 75−100[4] heating at 75 °C for 4 h before heating to 100 °C.

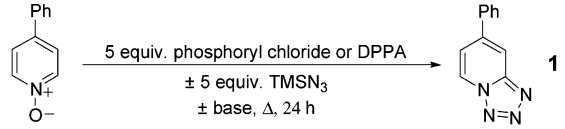
(19) Entries 1 and 3 showed small differences in yield; adding base to MsCl (entries 9 and 10) gave a tarry mixture containing some reduced product (see below).

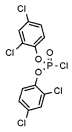
(20) Upon addition of $ClCH_2SO_2Cl$ to a mixture of *N*-oxide and $TMSN_3$, the mixture began to effervesce immediately. Analysis of the reaction mixture revealed the pyridine *N*-oxide was being reduced to the pyridine. Conducting the experiment in the absence of $TMSN_3$ and base at 90 °C, resulted in clean, quantitative reduction of the *N*-oxide. Such reductions have been seen previously with alkylsulfonyl chlorides in the presence of Et_3N, but $ClCH_2SO_2Cl$, like phenylmethanesulfonyl chloride, does not appear to require base to act as a reducing agent, possibly as a result of it more readily forming the sulfene. A small amount of reduced *N*-oxide was detected when MsCl was used as the activating group; see: Morimoto, Y.; Kurihara, H.; Shoji, T.; Kinoshita, T. *Heterocycles* **2000**, *53*, 1471−1474.



(21) The heterogeneity of the reaction mixture may have been responsible for the low to nonexistent yields obtained with the nitrophenylsulfonyl chlorides.

TABLE 2. Influence of Temperature, Base, and Phosphonyl Activating Groups on the Yield of 7-Phenyltetrazolo[1,5-*a*]pyridine

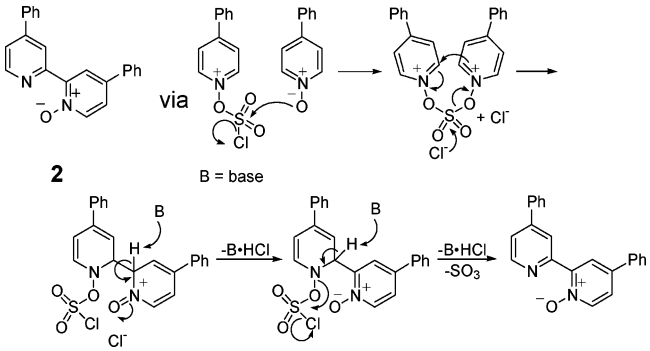


Entry	Phosphoryl compound	$TMSN_3$	Base	Temp. (°C)	Yield (%)[a]
1	DPPA	none	None	75	15
2	DPPA	none	None	100	57
3	DPPA	none	2 equiv. NMI	75	23
4	DPPA	none	2 equiv. pyridine	100	75
5	DPPA	none	2 equiv. pyridine	110	91
6	DPPA	none	2 equiv. pyridine	120	Quant.
7		yes	2 equiv. pyridine	100	3
8		yes	2 equiv. pyridine	100	81
9		yes	2 equiv. pyridine	100	80
10		yes	2 equiv. pyridine	100	38
11		yes	2 equiv. pyridine	100	N.R.

[a] All yields are post-chromatography: reactions run on a 100 mg scale relative to *N*-oxide.

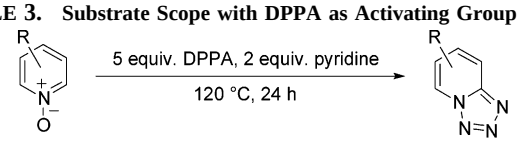
desired transformation except for diethyl chlorophosphate and chlorodiphenylphosphine oxide.[23] The three best reagents in this series were DPPA (entry 4), bis(2,2,2-trichloroethyl) chlorophosphate (entry 8), and bis(3,4-dichlorophenyl) chlorophosphate (entry 9), all giving comparable yields. We further examined the use of DPPA at higher temperatures (entries 5 and 6) and observed incremental increases in yield, with a quantitative yield obtained at 120 °C with our model substrate.

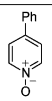
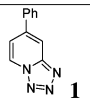
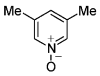
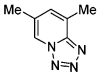
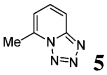
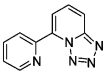
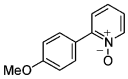
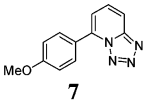
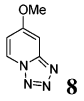
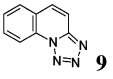
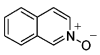
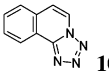
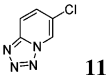
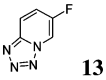
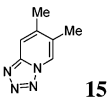
(22) Sulfuryl chloride (Table 1, entries 21 and 22) gave some desired product, but also a small amount (5 %) of the dehydratively coupled product (**2**), possibly arising via the mechanism shown below. Differentially functionalized bipyridyls could be very useful intermediates in the synthesis of metal ligands. We are presently pursuing the optimization of dehydratively coupling pyridine *N*-oxides.



(23) Diethyl chlorophosphate is probably succeptible to nucleophilic attack by azide ion to give EtN_3 and a less electrophilic monoalkyl azidophosphate. Chlorodiphenylphosphine oxide formed a chromatographically stable azide, but it was unreactive under our standard conditions.

TABLE 3. Substrate Scope with DPPA as Activating Group



Entry	*N*-Oxide	Product	Yield (%)[a]
1		 **1**	quant.
2		 **3**	90
3		 **4**	96
4		 **5**	71
5		 **6**	90
6		 **7**	85
7		 **8**	30 (53)[b]
8		 **9**	85
9		 **10**	86
10		 **11**	29
		 **12**	52
11		 **13**	21
		 **14**	55
12		 **15**	53
		 **16**	34

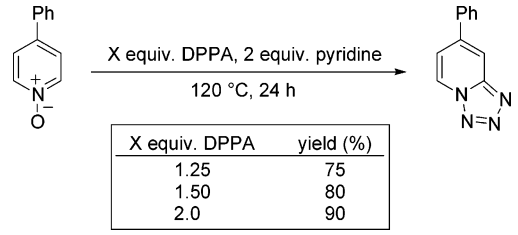
[a] All yields are post-chromatography: reactions run on a 100 mg scale relative to *N*-oxide. [b] The reaction was run for 48 h.

From the data in Tables 1 and 2, we elected to examine the scope of this reaction using DPPA as our activating agent and

azide source as it gave excellent yields[24] of product and was the most convenient to use.[25] The substrate scope is illustrated in Table 3.

Simple pyridine *N*-oxides were effective substrates for this reaction. Alkyl- and aryl-substituted pyridine *N*-oxides gave good to excellent yields of the corresponding tetrazolo[1,5-*a*]-pyridine. Much lower reactivity was observed with 4-methoxy-pyridine *N*-oxide, although allowing the reaction to proceed for 48 h did give useful yields of product (entry 7). Halides in the 3-position gave a mixture of products favoring substitution at the more electrophilic 2-position over the 6-position (pyridine numbering: entries 10 and 11). The converse was true when the 3-substituent was electron donating (entry 12). Halides in the 2- and 4-positions gave complex product mixtures, possibly resulting from competing S_NAr processes. As the stability of the products was a concern,[26] the thermal stability of each of the product tetrazolopyridines was examined by taking the melting point. All of the products exhibited narrow melting point ranges without any obvious sign (color change, gas evolution) of decomposition.

In anticipation of developing a multigram procedure for this transformation, we first examined the amount of DPPA required for the reaction. We recognized that 5 equiv of DPPA, while satisfactory for very small-scale reactions lacking solvent, would be undesirable for large-scale processes. Using 4-phenylpyridine *N*-oxide as our model substrate, we examined the reaction with reduced equivalents of DPPA (Figure 3). We found that 2 equiv of DPPA still gave excellent yields of product (90% vs quant with 5 equiv of DPPA) without extending the reaction time. With these results in hand, we examined the conversion of



X equiv. DPPA	yield (%)
1.25	75
1.50	80
2.0	90

FIGURE 3. Optimization for larger scale reactions. Reactions were run on a 0.5 g scale.

pyridine *N*-oxide to tetrazolo[1,5-*a*]pyridine on a 10 g scale. Gratifyingly, the reaction gave 10.92 g (86%) of the desired product as a readily crystallizable white solid.

In conclusion, we have developed a methodology for the direct conversion of pyridine *N*-oxides to tetrazolo[1,5-*a*]-pyridines in high yield under solvent free conditions. The process is easily scaled up without significant diminishment of yield.

Experimental Section

General Procedure Using DPPA. To a conical flask were added a stirbar, *N*-oxide (1 equiv), DPPA (2−5 equiv), and pyridine (2 equiv). The flask was purged with nitrogen and heated to 120 °C for 24 h. Direct chromatographic purification (0−2% of 2 N NH_3 in $MeOH/CH_2Cl_2$) of the reaction mixture gave the pure product.

Acknowledgment. We warmly thank DJ Tognarelli and Jiejun Wu for their effort in generating some of the analytical data for this project and Chris Mapes for generously providing a sample of 3,4-dimethylpyridine *N*-oxide.

Supporting Information Available: ^1H and ^{13}C NMR, HPLC, and IR spectra, 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.

JO061819J

(24) Though the sulfonyl halides gave comparable yields under some conditions, the products obtained from those reactions possessed trace amounts of color-imparting impurities making the products slightly yellow to orange as compared to bright white when DPPA was used.

(25) Trapping the TMSCl generated in the reaction mixture was a concern, especially for large-scale preparations.

(26) A reaction containing 4-nitropyridine *N*-oxide began to effervesce at 75 °C, and heating was stopped for perceived potential safety reasons.