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One-Step Conversion of Azine *N*-Oxides to α-1,2,4-Triazolo-, 1,2,3-Triazolo, Imidazolo-, and Pyrazoloheteroarenes

John M. Keith*

Johnson & Johnson Pharmaceutical Research and Development, L.L.C., San Diego, California

jkeith@its.jnj.com

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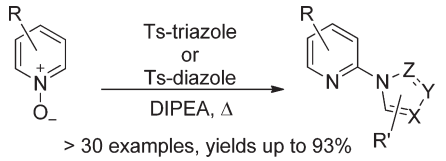

Pyridine, quinoline, isoquinoline, azaindole, and pyrimidine *N*-oxides were converted to their α-triazole and α-diazole derivatives by treatment with the corresponding *p*-toluenesulfonylazoles and Hunig's base at elevated temperatures.

With our continuing interest in the use of heteroaromatic *N*-oxides as scaffolds onto which various nitrogenous fragments may be appended,[1] we elected to investigate the possibility of introducing various triazoles and diazoles α to heteroarene nitrogens. Typically, azoles are introduced to electron-poor heteroarenes via substitution of a suitably placed halide at elevated temperatures[2] or through the use of a copper catalyst.[3,4] The heteroarene halides are typically prepared through conversion of an α-hydroxyl group with an oxyphilic halide source such as $SOCl_2$[5] or $POCl_3$,[6] by halogenation of *N*-oxide precursors[7] with subsequent deoxygenation[8−11] or deoxygenative halogenation,[12] or by direct metalation of an *N*-oxide followed by quenching with an electrophilic halide source.[13] In contrast, Katritzky installed benzotriazoles onto azine nuclei through activation of *N*-oxide precursors,[14] thus obviating the need for halide intermediates. It is this latter approach that we felt could be further developed to include other protic azoles.

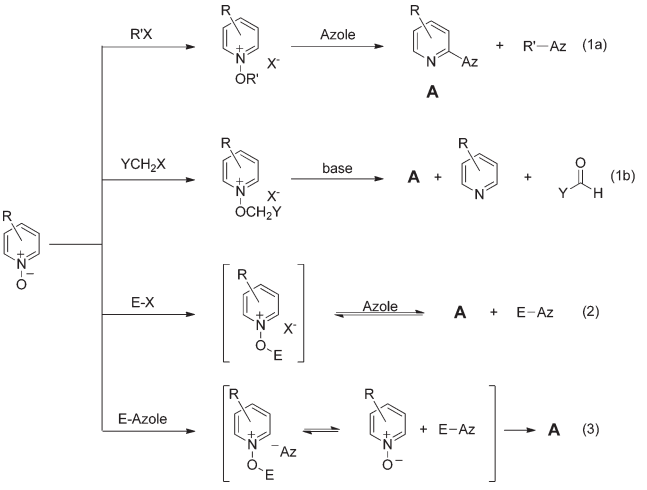

FIGURE 1. Possible strategies for the activation and substitution of *N*-oxides with azoles (Az) with potential side reactions shown.

Such deoxygenative substitution of *N*-oxides with azoles could be approached in several ways (Figure 1): (1) the *N*-oxide could be converted to a salt[15,16] and then treated with a nucleophilic azole or anionic azole salt; (2) the *N*-oxide could be activated in situ[17] and treated with an azole; or (3) the *N*-oxide could be treated with an electrophile having an azole as the labile substituent. There is literature precedent for each of these approaches, but they have different potential propensities to give side reactions. In eq 1a, the R′ group on the *N*-oxide could be transferred to the azole, thus consuming both the activating agent and nucleophile. In cases where R′ is a monosubstituted methyl (R′ = YCH_2-), the methylene can be oxidized to an aldehyde and in the process consume the *N*-oxide (Figure 1, eq 1b).[18] In eq 2, the azole may attack the electrophilic substituent on the *N*-oxide rather than the α-position on the arene ring. The resultant azole/electrophile complex could still be reactive, as in eq 3, though the reaction is likely to proceed more slowly or require more forceful

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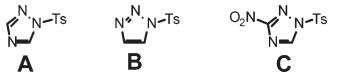
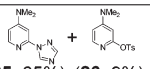
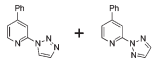
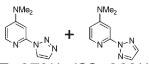
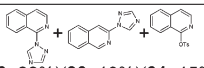
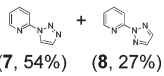
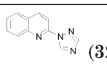
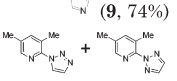
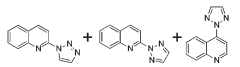
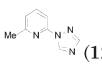
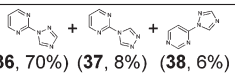
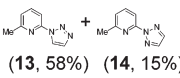
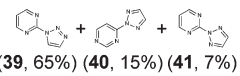
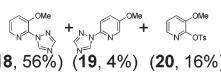
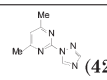
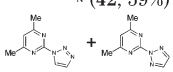
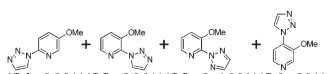
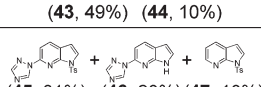
TABLE 1. Substrate Scope Using Preformed Tosyltriazoles A−C

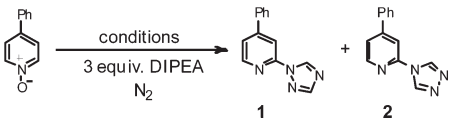


N-oxide (entry)	Rxn cond.	Product(s) + Yield(s)	N-oxide (entry)	Rxn cond.	Product(s) + Yield(s)
 1.	100 °C, 24 h, **A**	(**1**, 71%) + (**2**, 14%)	 7.	100 °C, 1 h, **A**	 (**25**, 65%) (**26**, 9%)
	100 °C, 24 h, **B**	 (**3**, 61%) (**4**, 28%)		80 °C, 4 h in ACN, **A**	(**25**, 88%)
	90 °C, 4 h in xylene, **C**	 (**5**, 93%)		100 °C, 1 h, **B**	 (**27**, 27%) (**28**, 38%)
				80 °C, 3.5 h in ACN, **B**	(**27**, 32%) + (**28**, 58%)
 2.	100 °C, 24 h, **A**	 (**6**, 84%)	 8.	100 °C, 17 h, **A**	 (**29**, 28%)(**30**, 13%)(**31**, 15%)
	130 °C, 1.5 h, **B**	 (**7**, 54%) (**8**, 27%)		100 °C, 17 h, **B**	complex mixture
 3.	100 °C, 7 h, **A**	 (**9**, 74%)	 9.	100 °C, 1.5 h, **A**	 (**32**, 73%)
	100 °C, 7 h, **B**	 (**10**, 44%) (**11**, 12%)		100 °C, 1.5 h, **B**	 (**33**, 45%) (**34**, 22%)(**35**, 8%)
 4.	130 °C, 3.5 h, **A**	 (**12**, 71%)	 10.	90 °C, 8 h, **A**	 (**36**, 70%) (**37**, 8%) (**38**, 6%)
	130 °C, 3.5 h, **B**	 (**13**, 58%) (**14**, 15%)		90 °C, 6.5 h, **B**	 (**39**, 65%) (**40**, 15%) (**41**, 7%)
 6.	90 °C, 4 h, **A**	 (**18**, 56%) (**19**, 4%) (**20**, 16%)	 11.	90 °C, 2 h, **A**	 (**42**, 59%)
				90 °C, 1 h, **B**	 (**43**, 49%) (**44**, 10%)
	90 °C, 4 h, **B**	 (**21**, 23%)(**22**, 23%)(**23**, 0.16%)(**24**, 2%)	 12.	90 °C, 2 h, **A**	 (**45**, 31%) (**46**, 20%)(**47**, 10%)

conditions.[19] The strategy found in eq 3 is similar to the undesired pathway in eq 2 in that the *N*-oxide is treated with a preformed azole/electrophile complex. It would be anticipated that such reactions would be slower than those shown in eqs 1 and 2, but it would also preclude the side reactions inherent to eqs 1a and 1b. We elected to screen reaction conditions related to eqs 2 and 3 using 4-phenylpyridine *N*-oxide as the substrate and 1,2,4-triazole as the nucleophile in the presence of DIPEA (diisopropylethylamine).

Initial reactions focused on activation of 4-phenylpyridine *N*-oxide (Scheme 1) with various electrophiles (strategy inherent to eq 2, Figure 1) in a high-boiling solvent such as chlorobenzene, followed by addition of 1,2,4-triazole.

SCHEME 1. Reactivity Screening



Utilization of TsCl, $(PhO)_2POCl$, $(2,4\text{-diCl-}C_6H_4O)_2$-POCl, and Ts_2O as electrophiles at temperatures ranging from 70 to 100 °C gave low conversions of *N*-oxide (39%, 27%, 9%, 20%, and 16%, respectively) after 16−20 h. Similarly, reaction of the *N*-oxide with preformed 1-tosyl-1,2,4-triazole (strategy inherent to eq 3) gave only a 38% yield of product after 3 days of heating at 130 °C. Interestingly, a 74% yield of (**1**) was obtained with Ts_2O when a reaction inadvertently ran dry. The reaction was repeated in the absence of solvent, and a similar yield (66%) of (**1**) was obtained along with a small amount of (**2**) (12%). We next heated a neat mixture of preformed 1-tosyl-1,2,4-triazole, DIPEA and 4-phenylpyridine-*N*-oxide for 23 h and obtained somewhat better yields of **1** and **2** (70% an 15%, respectively). We subsequently found that using as little as 1.2 equiv of 1-tosyl-1,2,4-triazole was sufficient to get good yields of product.

(19) Chen, Z.-C.; Stang, P. J. *Tetrahedron Lett.* **1984**, *25*, 3923–3926.

The likely mechanism for this transformation is similar to that of the Reissert−Henze reaction (Figure 2).[20]

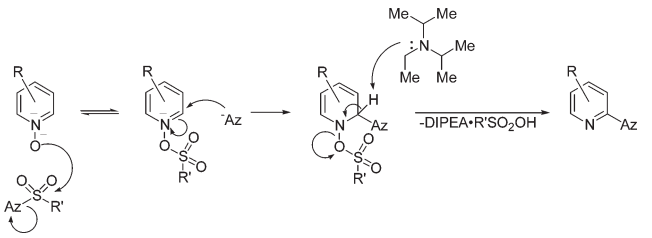


FIGURE 2. Likely mechanism for conversion of heteroarene *N*-oxides to α-azoloheteroarenes with sulfonyl azoles.

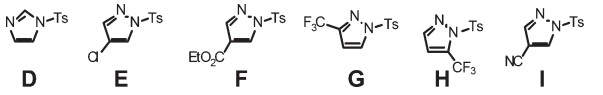
Having found that heating a neat mixture of *N*-oxide, preformed tosyltriazole, and DIPEA under a nitrogen atmosphere gave the best yields, we set out to determine the scope of the reaction. Two tosyl-1,2,4-triazoles (**A** and **C**) and 1-tosyl-1,2,3-triazole (**B**) were used in this study (Table 1). Reagents **A** and **B** were prepared by treating the corresponding triazole with Ts_2O and Et_3N in DCM, and reagent **C** was purchased from a commercial supplier. In most instances, only a slight excess of tosyltriazole is needed to obtain good yields of product, provided the *N*-oxide is dry. Unfortunately, many low molecular weight *N*-oxides are sold as hydrates or are strongly hygroscopic. In cases where drying the *N*-oxide is impractical, an excess (2−4 equiv) of the required tosyl triazole may be employed to facilitate its complete conversion. Fortunately, both **A** and **B** are easily separated from the product(s) of the reaction via chromatography, thus allowing excellent recovery of excess reagent.

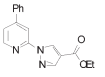
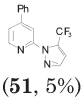
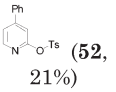
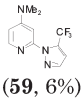
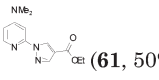
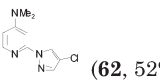
Generally, electronically neutral to electron-rich *N*-oxides were good substrates and electron-deficient *N*-oxides poor substrates for this reaction. Compounds bearing halide, cyano, and nitro groups were either of low reactivity or gave intractable mixtures of products (see the Supporting Information). The greater reactivity of electron-rich versus electron-deficient *N*-oxides makes this transformation complementary to S_NAr reactions and transition-metal-mediated couplings to halides, as such processes are more facile with electron-poor substrates.[21]

With all three reagents, substitution at the 1-position of the triazole was preferred. However, the selectivities for substitution at the 1-position of 1,2,3-triazole were somewhat less (1-position/2-position typically 2−5:1) than those obtained with 1,2,4-triazole (1-position/2-position typically ≫ 5:1). Interestingly, the reaction of **B** with 4-dimethylaminopyridine *N*-oxide (entry 7) resulted in a reversal of selectivity, with products favoring substitution in the 2-position of the triazole (2-position/1-position = 1.41:1).

The relative reactivity of the tosyl triazole reagents were found to be **C** > **B** and **A**, with **B** perhaps slightly more reactive than **A**. For highly reactive electron-rich *N*-oxides (entries 5 and 7), superior yields were obtained when the reactions were run in solution. Electron-rich *N*-oxides tended to yield varying amounts of tosylated products (**20**, **26**, and **31**) when subjected to neat reaction conditions.

TABLE 2. Evaluation of Tosyldiazoles as Electrophilic Reagents



N-oxide (entry)	Rxn Cond.	Product(s) + yield	
1.	100 °C, 24 h, **D**	 (**48**, 71%)	
	140 °C, 4 d, **E**	NR	
	130 °C, 4 d, **F**	 (**49**, 60%)	
	130 °C, 24 h, Ts_2O + 3-CF_3-pyrazole	 (**50**, 52%)	 (**51**, 5%)
	130 °C, 3 d, **G**	(**50**, 52%)	(**51**, 5%)
		 (**52**, 21%)	 (**53**, 13%)
	130 °C, 2 d, **H**	(**50**, 59%) (**52**, 13%)	(**51**, 14%) (**53**, 10%)
	120 °C, 24 h, **I**	 (**54**, 91%)	
 2.	130 °C, 24 h, **D**	 (**55**, 75%)	 (**56**, 18%)
 3.	100 °C, 3 h, **D**	 (**57**, 77%)	
 4.	80 °C, 4 h in xylenes, **G**	 (**58**, 77%)	 (**59**, 6%)
	80 °C, 4 h in xylenes, **I**	 (**60**, 74%)	
	130 °C, 4 h in xylenes, **F**	 (**61**, 50%)	(**26**, 50%)
	130 °C, 4 h in xylenes, **E**	 (**62**, 52%)	(**26**, 16%)

Consistent with previous studies,[22] 3-methoxypyridine *N*-oxide favored substitution in the 2- over the 6- and 4-positions, though a mixture of products was obtained. Isoquinoline *N*-oxide yielded a mixture of 1- and 3-substituted products, including the 1-tosylate, with reagent **A** and a complex mixture with reagent **B**. Contrary to expectations, reactions with pyrimidine *N*-oxide (entry 10) yielded product mixtures heavily favoring substitution in the 2- rather

(20) (a) Katritzky, A. R.; Lagowski, J. M. *Chemistry of the Heterocyclic N-Oxides*; Academic Press: London, 1971; p 300. (b) Abramovitch, R. A.; Smith, E. M. *Chem. Heterocycl. Compd.* **1974**, *14*, 114–117.

(21) (a) Zoltewicz, J. A. *Top. Curr. Chem.* **1975**, *59*, 33–64. (b) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992–4998.

(22) (a) Sakamoto, T.; Kaneda, S.; Nishimura, S.; Yamanaka, H. *Chem. Pharm. Bull.* **1985**, *33*, 565–571. (b) Yamanaka, H.; Araki, T.; Sakamoto, T. *Chem. Pharm. Bull.* **1988**, *36*, 2244–2247. (c) Reference 1a.

than the 4-position.[23] Reaction of **A** with 7-azaindole *N*-oxide (entry 12) gave a mixture of **47** (10%) and two products of substitution, one with a free N−H (**46**, 20%) as well as the *N*-tosyl product (**45**, 31%), suggesting activation of the *N*-oxide is competitive with tosylation of the azaindole nitrogen.

Introduction of diazoles onto azine nuclei was less facile than with triazoles. Tosylimidazole (**D**) was sufficiently reactive to affect the introduction of imidazole (Table 2, entries 1−3); however, it appears *N*,*N*′-sulfuryldiimidazole is a superior reagent for this transformation.[24] Tosylpyrazole and *N*,*N*′-sulfuryldipyrazole were ineffective reagents for the activation of *N*-oxides. If the pyrazole nucleus possessed a sufficiently electron-withdrawing substituent, modest to excellent reactivity could be attained with an *N*-tosylated derivative. Reagent **E** is at the boundary of reactivity for the tosylpyrazoles, being almost inert toward electron-neutral *N*-oxides (entry 1) but demonstrating moderate reactivity with the highly nucleophilic 4-dimethylaminopyridine *N*-oxide (entry 4). Reagent **F** was marginally more reactive than **E** (60% **49** after 4 days), but not noticeably so with 4-dimethylaminopyridine *N*-oxide. Reagents, or reagent mixtures, incorporating 3-trifluoromethylpyrazole (**G** and **H**) gave a pair of regioisomeric products with substitution at the 1-position predominating. Interestingly, the isomeric reagents **G** and **H** gave nearly identical ratios of products (thus precluding an intramolecular process), but the rates of the reactions, at least initially, were quite different. Reagent **H** was much more reactive than **G**, giving approximately 40−50% conversion of *N*-oxide within the first hour. However, the reaction slowed rather quickly, taking 2 days to go to completion. Isolation of the excess tosyl-3-trifluoromethylpyrazole from the reaction revealed that it had undergone isomerization to **G** under the reaction conditions. This would explain the initial rapid rate of reaction with the less stable **H**, but as **H** isomerized to the more stable **G**, the reaction rate decreased dramatically.

In an absolute sense, the relative reactivity of the six tosyldiazole reagents appears to be **H** > **D** > **I** > **G** > **F** > **E**.[25] However, the benefit obtained from the high reactivity of **H** lasts only until it converts into **G**, so in a practical sense the relative reactivity appears to be **D** > **I** > **H** > **G** > **F** > **E**. The reactivity trend observed with reagents **A**−**I** strongly suggests that the rate-limiting step involves nucleophilic attack of the tosyl group by the N-oxide substrate, because those reagents derived from relatively acidic azoles (better leaving groups), tended to be the most reactive.

In conclusion, we have developed a method for the deoxygenative coupling of azine *N*-oxides with azoles through the use of preformed tosylazole reagents. The methodology allows for the introduction of 1,2,4- and 1,2,3-triazoles, imidazole, and electron-deficient pyrazoles onto pyridine, pyrimidine, quinoline, isoquinoline, and azaindole scaffolds. The transformation is complementary to S_NAr and transition-metal-mediated reactions that introduce azoles onto azines.

Experimental Section

Preparation of 1 and 2. To a conical vial were added a spinvane, 102.1 mg (0.596 mmol) of 4-phenylpyridine *N*-oxide, 158.3 mg of 1-tosyl-1,2,4-triazole (0.709 mmol, 1.2 equiv), and 0.31 mL (1.78 mmol, 3 equiv) of DIPEA. The vial was thoroughly flushed with nitrogen, capped, and heated at 100 °C for 22.5 h. The reaction vessel was then cooled to rt and the residue chromatographed (CH_2Cl_2/EtOAc) to give 93.6 mg (71%) (**1**) and 19.0 mg (14%) (**2**), both as white solids. **1**: mp = 108−109 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.20 (s, 1H), 8.45 (d, J = 5.0 Hz, 1H), 8.11 (m, 2H), 7.70−7.68 (dd, J = 2.0, 8.5 Hz, 2H), 7.50−7.44 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.7, 151.9, 150.0, 148.7, 141.6, 137.1, 129.7, 129.2, 127.0, 120.9, 110.6; MS (ESI$^+$), found 223.1 $(M + H)^+$; HRMS (ESI$^+$) *m*/*e* calcd for $C_{13}H_{11}N_4$ 223.0984, found 223.0976 $(M + H)^+$. **2**: mp = 190−192 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.94 (s, 2H), 8.57−8.56 (dd, J = 0.5, 5.0 Hz, 1H), 7.68−7.66 (m, 2H), 7.56−7.52 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.6, 149.9, 147.3, 139.9, 136.8, 130.1, 129.4, 127.1, 121.6, 111.0; MS (ESI$^+$) found 223.1 $(M + H)^+$; HRMS (ESI$^+$) *m*/*e* calcd for $C_{13}H_{11}N_4$ 223.0984, found 223.0983 $(M + H)^+$.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra, 2D NMR spectra, HPLC chromatograms, melting points, experimental procedures, and tabulated analytical data for all prepared compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(23) Yamanaka, H.; Sakamoto, T.; Nishimura, S.; Sagi, M. *Chem. Pharm. Bull.* **1987**, *35*, 3119–3126.

(24) Reference 1a.

(25) The reaction times reported in the tables represent the total time reagents were in the flask, which was longer than the time it took the reactions to go to completion. The purely qualitative relative reactivity assessment of the reagents was based on time required for complete consumption of *N*-oxide. Unsurprisingly, except for **H**, the reactivity increases as the pK_a of the parent azole decreases.