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Metal Free Quick Introduction of Azole in to Azine Nucleus: Acid Catalyzed Reissert-Henze Reaction

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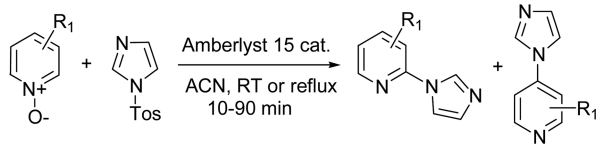
Imidazole appended heterocycle moieties are commonly encountered in biologically important molecules. Imidazole substituted in 2nd position of pyridine or quinoline moieties are prevalent in the SAR study of most drug discovery programs such as human neutrophil elastase,[1] gastric H+/K+-ATPase inhibitors,[2] NNRTIs (nucleoside Reverse Transcriptase Inhibitors),[3] HIV entry inhibitors,[4] CB1 antagonist[5] and AMPA receptors.[6] Further, 2-imidazolyl azabenzimidazole compounds have been reported as cardiotonic agents.[7] Introduction of imidazole or benzimidazole on to pyridine or quinoline ring at second position is generally carried out by reacting the corresponding azole with 2-halo pyridines or quinolines either with copper catalyst at elevated temperatures or ligand catalyzed coupling reactions.[8,9]

Earlier Katritzky *et al.* reported the introduction of benzotriazole on to the second position of the azine ring using *N*-tosylbenzotriazole in presence of base diisopropyl ethylamine (DIPEA).[10] This is similar to the Reissert-Henze reaction.[11,12] Later Keith reported the reaction of a *N*-oxide with *N,N'*-sulphuryldiimidazole to introduce imidazole (Im) on to the second position of the pyridine or quinoline in a similar manner.[13,14] However, drawback of this method is unsubstituted imidazole moiety could be introduced. Also, reaction requires high temperatures (> 100 °C) and longer reaction times for the reaction conversion. Moreover, halogen substituted pyridine *N*-oxides reacted very slowly and other substrates such as, cyano pyridine-*N*-oxides proved to be very sluggish in this methodology. In addition to the above drawback, formation of sulfur trioxide-pyridine complex, which in turn needs to be cleaved with base NaOH. Recently Keith reported base-catalyzed insertion of azoles on to azine nucleus by preformed *N*-tosylazoles,[14] wherein, it was claimed that *N,N'*-sulphuryldiimidazole was superior to *N*-tosyl imidazole in effecting the above insertion. Herein we report the quick introduction of imidazole, benzimidazole, benzotriazole and also sterically demanding 2-substituted imidazoles on to the 2nd or 4th position of pyridine or quinoline-*N*-oxides in a very fast method compared to prior conventional methods (Scheme 1).



Scheme 1

It has to be mentioned here that this is the first report on acid catalyzed Reissert-Henze reaction. Reports involving imidazole chemistry clearly specify the role of acid catalyst, which accelerates the leaving group ability of imidazole after quaternizing imidazole nitrogen.[16] Hence, we intended to execute this proposal with the Reissert-Henze reaction.

Initial study was carried out by reacting the quinoline *N*-oxide with *N*-tosylimidazole (TosIm) in the presence of catalytic *p*-toluenesulphonic acid (*P*TSA) (5-10 mol %) in acetonitrile (ACN) solvent. For our surprise, it was observed that the quinoline *N*-oxides reacted very rapidly with *N*-tosylimidazole even at room temperature and also, reaction was complete in 10 to 15 minutes. As a result, when the halogenated quinolines and isoquinolines were attempted under similar conditions, reaction was found to be working in the same way. But, the reaction of *N*-tosylimidazole with pyridine/quinoline-*N*-oxide proceeded only after a prolonged heating at higher temperatures (110 °C) in the absence of acidic catalyst.[10,13,14] Therefore, reaction of pyridine *N*-oxides was carried out using catalytic amount of acid and found to be working at 50 °C to obtain the desired product. However, excess of *N*-tosylimidazole and little longer time (3-7 h) were required in order to complete the reaction. Hence, this prompted us to change the conditions. Upon refluxing in acetonitrile, the reaction was completed in 90 min and also complete disappearance of the electrophile, *N*-tosylimidazole was observed by TLC. But, this indicated the decomposition of *N*-tosylimidazole in acidic medium. As a result, we attempted to screen some more acid catalysts such as aq.HCl (1 N), trifluoroacetic acid, silica-*P*TSA and acidic amberlyst-15 for this transformation. From the list of the above acid catalysts screened, minimum amount of decomposition of *N*-tosylimidazole was observed with amberlyst-15 catalyst. Hence, amberlyst-15 catalyst was the choice for our further study. In an effort to optimize the solvent, a weaker nucleophile 4-cyanopyridine *N*-oxide (entry 1) was

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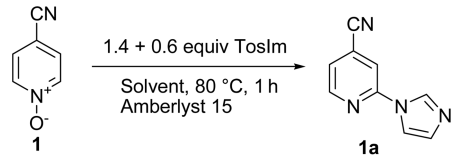
Table 1. Optimization of solvent



Sr.No	Solvent	Conversion by HPLC (%)
1	Xylene	32
2	Dioxane	47
3	Toluene	36
4	ACN	72
5	DMF	NR[b]
6	MIBK	25

[a]Reaction condition: Amberlyst-15-15 mg, *N*-oxide-0.46 mmol was used; MIBK-Methyl isobutyl ketone. [b]TosIm decomposed in DMF.

chosen as a model substrate, since reaction was very fast in quinolines and unsubstituted pyridines. 4-Cyanopyridine *N*-oxide (1.0 equiv.) and *N*-tosylimidazole (1.4 equiv.) was taken in solvent (3 mL), added Amberlyst-15 (15 mg). The reaction mixture was heated to 80 °C for 1 h. The reaction did not go to completion upon monitoring the reaction by TLC.

But, disappearance of *N*-tosylimidazole was observed. Therefore, additional quantity of 0.6 equiv of *N*-tosylimidazole was added and heated to reflux for another 30 min. The aliquots were submitted to HPLC and the ratio of conversion was calculated. It was found that the conversion to the desired product was moderate in solvents such as methyl isobutyl ketone (MIBK), xylene, toluene and dioxane. *N*-tosylimidazole was decomposed in *N,N*-dimethyl formamide (DMF) rapidly, and no product was observed. The use of acetonitrile afforded maximum conversion (72%).

Having optimized the solvent, we focused our attention towards optimizing the temperature.

As before, 4-cyanopyridine *N*-oxide was taken as a substrate in presence of amberlyst-15 in acetonitrile solvent. The reaction was carried out at different temperatures, and the corresponding results obtained are shown in Table 2. We found that pyridine *N*-oxides reacted with *N*-tosylimidazole at acetonitrile reflux temperature in the presence of acid catalyst with shorter reaction time. Quinoline and isoquinoline *N*-oxides were found to be highly reactive under the

Table 2. Temperature screening for acetonitrile solvent

Sr.No	Temp °C	Time	Unreacted S.M (**1**) (%)[a]	Product (**1a**) (%)[a]
1	RT	30 min	100	0
2	RT	1 h	100	0
3	50	30 min	74	26
4	50	1 h	55	45
5	reflux	30 min	37	63
6	reflux	1 h	22	78

[a]HPLC ratio.

Table 3. Synthesis of 2-Imidazol-1-yl pyridine/quinoline[a]

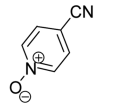
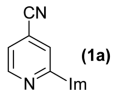
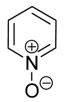
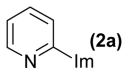
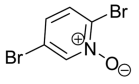
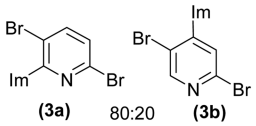
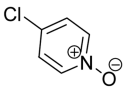
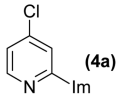
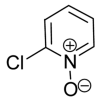
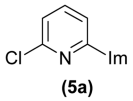
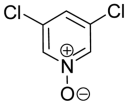
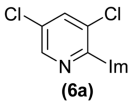
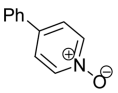
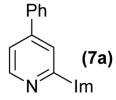
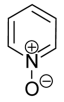
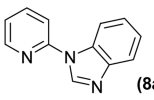
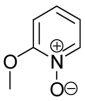
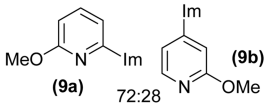
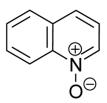
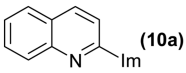
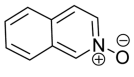
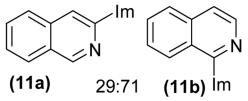
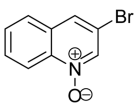
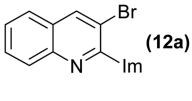
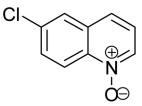
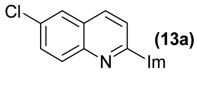
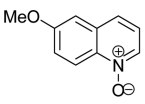
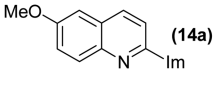
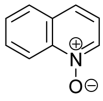
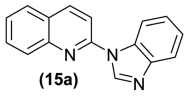
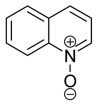
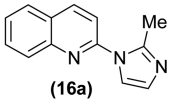
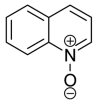
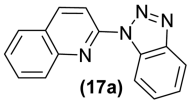
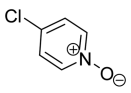
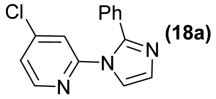
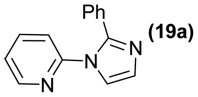
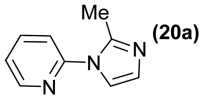
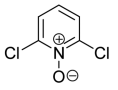
Entry	*N*-Oxide	Product	Yield[d]
1		 **(1a)**	61
2		 **(2a)**	63
3[b]		 **(3a)** 80:20 **(3b)**	45
4		 **(4a)**	60
5		 **(5a)**	58
6		 **(6a)**	45
7		 **(7a)**	68
8		 **(8a)**	65
9[b]		 **(9a)** 72:28 **(9b)**	53
10[c]		 **(10a)**	60
11[b,c]		 **(11a)** 29:71 **(11b)**	75
12[c]		 **(12a)**	35
13[c]		 **(13a)**	61
14[c]		 **(14a)**	40
15[c]		 **(15a)**	52

Table 3. Continued

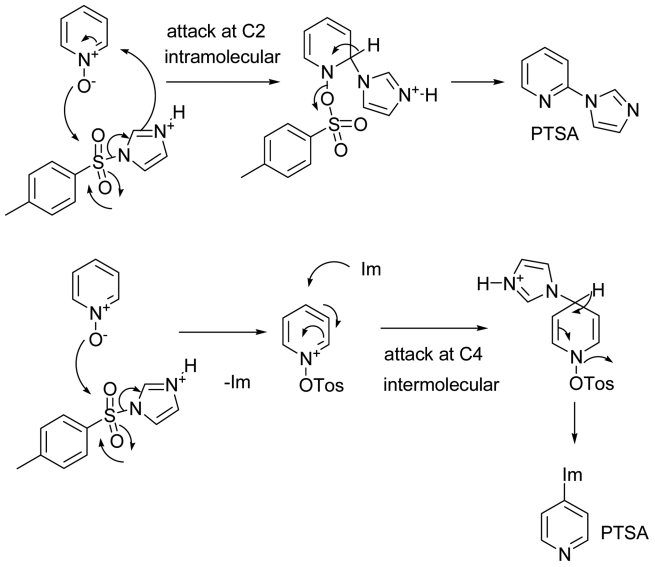
Entry	*N*-Oxide	Product	Yield[d]
16[c]		 **(16a)**	55
17[c]		 **(17a)**	71
18		 **(18a)**	48
19		 **(19a)**	49
20		 **(20a)**	53
21		NR	–
22		NR	–

[a]Reaction conditions: *N*-Oxide (1 equiv.), *N*-TosIm (1.4 equiv.), Amberlyst 15 (1% wt/wt) and acetonitrile (3 mL), reflux, 45 min. Additional *N*-TosIm (0.6 equiv.) was added and refluxed for additional 45 min. [b]Ratio by HPLC. [c]Reaction performed at RT for 10 min with *N*-TosIm (1.8 equiv). [d]Isolated yield.

optimized condition at room temperature. Reaction monitored by TLC and worked up quickly within 10 minutes. Prolonged reaction time gave poor yield. After optimizing the reaction conditions, we extended our studies to diverse *N*-oxide substrates (see Table 3).

We were delighted to observe the success of less reactive halogenated pyridine *N*-oxides (entries 3, 4, 5, 6, 12, 13) which gave good yields after heating the reaction mixture for 90 minutes with excess of *N*-tosylimidazole. Earlier reports for this halogenated pyridine *N*-oxides suggest that these substrates reacted slowly and time required for the reaction was 2-4 days when *N,N′*-sulphuryl diimidazole was used.[13] Pyridine *N*-oxides bearing cyano group (entry 1) also gave rise to good yield (61%). By and large, our method have resulted clean products, while *N,N′*-sulphuryl diimidazole gave mixture of products (imidate ester). Substituted *N*-oxides (entries 3, 9 and 11) gave mixture of products which were separated by preparative HPLC and characterized by ^{1}H NMR spectroscopy. 2,6-Lutidine-*N*-oxide (entry 21) and 2,6-dichloropyridine *N*-oxide (entry 22) failed to react in our conditions, which is complementary to Keith's work.[13]

Entries from 10-17 (Table 3) illustrate that quinoline/isoquinoline *N*-oxides reacted very smoothly with *N*-tosylazoles in 10 minutes at room temperature in the presence of catalytic amberlyst-15 in moderate yields (35 to 75%). All



Scheme 2. Possible mechanism

products were characterized by ^{1}H, ^{13}C NMR and HRMS analysis. Inspired by the results obtained, we broaden this methodology to substituted imidazoles. Sterically demanding 2-phenyl substituted tosylimidazole reacted as equally as unsubstituted imidazole (entries 18 and 19) to give moderate yield 48% and 49%. It is pertinent to mention here that, the displacement of Cl- group by imidazole in the 2nd or 4th position of pyridine ring was not observed in any of the examples (entry 4, 5 and 18). A probable mechanism of this reaction is illustrated in Scheme 2. Amberlyst-15 resin which is strongly acidic in nature due to sulfonic acid group in it.[17] The acidic proton from sulfonic acid group of amberlyst-15 protonates the imidazole nitrogen, thus making it a very good leaving group compared to the unprotonated imidazole. As discussed earlier in detail by Sarpong *et al.*[16c] the proton transfer from imidazole and pyridine is in equilibrium and coerce the reaction faster. The reaction does not require diisopropylethylamine (DIPEA) base for deprotonation which lead to the aromatization step.[10,13] The reaction proceeds without acid or base. The reaction between *N*-oxide and *N*-tosylimidazole was found to be slower (at least 24 h) with or without base.[10,13] The C2/C4 product selectivity was not achieved in both acid catalyzed (this work) or base catalyzed[13,14] transformations. C2 substituted product was observed in most cases arising out of intramolecular attack by imidazole leaving group. To achieve the selectivity of C2 substituted product (intramolecular reaction) over C4, a control experiment was performed at lower concentration of reactants in acetonitrile solvent at (0.01 M) which did not improve selectivity.

In conclusion we have demonstrated an expeditious synthesis of 2-imidazo-1-yl/benzimidazo-1-yl/benzotriazo-1-yl substituted pyridines or quinolines in moderate to good yields by Amberlyst-15 catalyst from *N*-oxides. This methodology worked very well for less reactive *N*-oxides *i.e.* ring containing electron withdrawing groups. This method completely avoids transition metals. Substituted imidazoles also

worked very well in our conditions with ease. In addition to the first report on acid catalyzed Reissert-Henze reaction, these results further demonstrate the value of acid catalysis in improving the leaving group ability of imidazole in organic synthesis. Though this methodology gives moderate yield, the faster reaction times will draw the attention of medicinal and combinatorial chemists.

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Supporting Information. Experimental details, general information and characterization data for all compounds and ^{1}H, ^{13}C, LCMS and HRMS spectra.

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