

# Chemistry Chat

## My Familiar Compound Family – Heterocyclic Compounds –

Nagatoshi Nishiwaki

Kochi University of Technology, School of Engineering Science

Heterocyclic compounds are lightly treated in textbooks, even though they account for one-third of all organic compounds. In addition, many people feel that the mere mention of the term "heterocyclic chemistry" makes it sound difficult. For me, benzene chemistry is more difficult than heterocyclic chemistry because I have no clue about it. There are two reasons why people feel heterocyclic chemistry is difficult; first, because it has a long history and, as in the field of fatty acids, common names are widely used. It is natural that people cannot understand a compound name unless they can recall its structure. Another is that different ring sizes and different types, positions, and numbers of heteroatoms can cause completely different behavior.

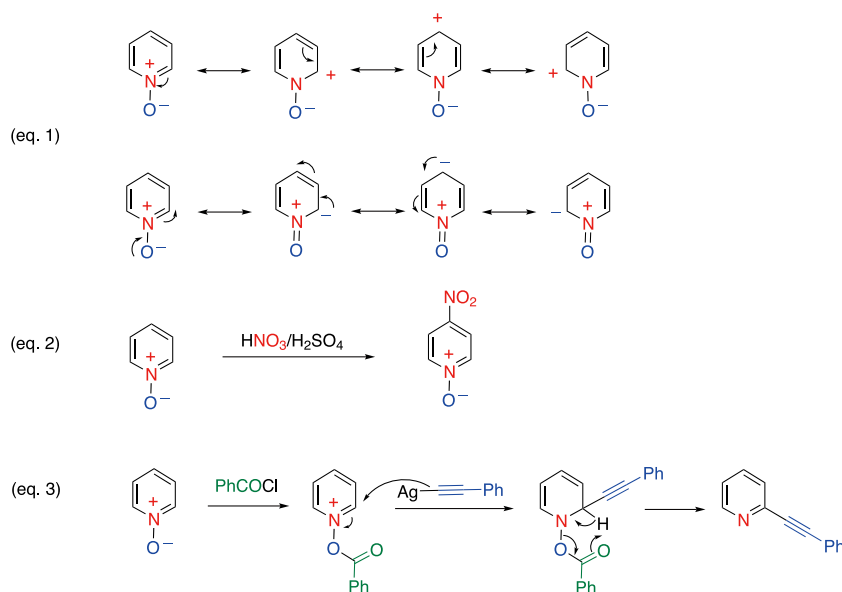
When I was young, I once attended an international conference on heterocyclic chemistry held in Taiwan. I thought that the same expressions would be used since the Chinese characters were the same as those used in Taiwan, but the signboard read “雜環化学”, which made me feel a sense of incongruity. This is because the character for “雜” is rarely used to mean something good, such as “雜誌 (magazine)”, “雜巾 (duster)”, “雜菌 (harmful germs)”, or “煩雜 (troublesome)”. However, after much deliberation, I have come to think that this expression is more appropriate for describing the miscellaneous nature of heterocyclic chemistry. Perhaps this field suited my “雜 (sloppy)” nature, and I have been involved in this field ever since.

### Dual Reactivity

As with the imprint of the baby bird, I still find myself drawn to papers that describe pyridine *N*-oxides, which I dealt with in my first topic. I am attracted to carbonyl and nitro groups due to their dual reactivity, but

their origin may lie in pyridine *N*-oxides.

As can be seen from the resonance structures, the ring carbon is electron-deficient due to the positive charge of the ring nitrogen. On the other hand, one can also draw



**Scheme 1.** Reactions of pyridine *N*-oxide with electrophiles and nucleophiles

resonance structures in which a negative charge appears on the ring carbon due to the back donation from oxygen (**Scheme 1**, eq. 1). In other words, pyridine *N*-oxides can react with both nucleophiles and electrophiles, changing their positions depending on the partner. The nitration of pyridine is very difficult and proceeds only in low yield

## Nucleophilic Ring Transformation

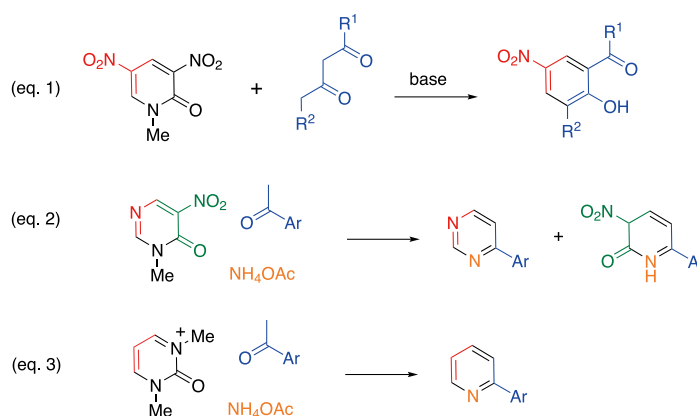
In the laboratory where I was first hired as an assistant professor, we traditionally developed nucleophilic ring transformation reactions (**Scheme 2**, eq. 1)<sup>2</sup> using dinitropyridones. The theme I received was a ring transformation reaction using its aza-analog, nitropyrimidinone. I had easily thought that the nitro group was simply replaced with a ring of nitrogen, but the difference was unexpectedly large, and I was unable to reach a favorable result. In searching for the causes, I discovered that the substrate was decomposed by ammonia, which was used as a nitrogen source. Then I used less nucleophilic ammonium acetate instead of ammonia, which led to a great improvement of the yield (eq. 2).<sup>3</sup> Additionally, a new ring transformation was also discovered that proceeds in a reaction mode not seen in

under severe conditions, whereas nitration easily proceeds even under mild conditions when it is converted to *N*-oxide because of the back donation (eq. 2). On the other hand, *O*-acylated *N*-oxide improves the electrophilicity of pyridines and readily react with nucleophiles accompanied by aromatization to afford substituted pyridines (eq. 3).<sup>1</sup>

the past.

When I established the ring transformation using nitropyrimidinone, I considered that a similar reaction could proceed by changing the ring nitrogen to onium without making the ring electron-deficient with a nitro group. However, I never told anyone about it, never actually tried it, and the time passed as it was. One day, a few years later, I was flipping through a magazine and saw an advertisement for a company with the exact reaction I was thinking of at the time. Although the idea was not stolen or anything, I vividly remember feeling regretful (with myself).

**Lesson learned, “It is better to act and have regrets than not to act and have regrets.”**



**Scheme 2.** Synthesis of heterocyclic compounds by ring transformation

## Pyridines Substituted with Five Aryl Groups

We were conducting a reaction with an unsaturated carbonyl compound using a push-pull alkene ( $\beta$ -methoxy acrylamide) with a biased electron density, which unexpectedly yielded pyridine. When I submitted a paper about finding the interesting reaction that nitrogen and oxygen were switched, one of the referees pointed out that the starting material was an enamino ester. Embarrassingly, I did not realize that the nitrogen and oxygen were switched during the synthesis of the starting material, not during the reaction (**Scheme 3**, eq. 1).<sup>4</sup> At the same time, I was relieved that the paper was not published in a journal.

We performed the same reaction using a pyridyl group instead of the ester functional group as an electron-withdrawing group and found that polysubstituted pyridines could be synthesized, although in some cases the substrates had to be activated by  $\text{FeCl}_3$ . The advantage of this reaction is that the pyridine ring can be easily modified by simply altering the enamine or unsaturated ketone. The conventional synthesis of pyridines with five different aryl groups requires a considerable number of steps,<sup>5</sup> but the new method successfully achieved only in three steps, including the synthesis of the starting materials (eq. 2).<sup>6</sup>

