

# NITROGEN ATOM INSERTION TO ACCESS DIVERSE MOLECULAR STRUCTURES

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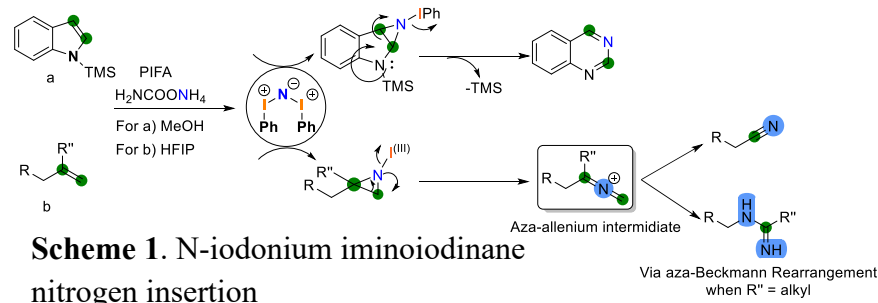
December 2, 2025

## INTRODUCTION

Nitrogen heterocycles are considered fundamental in the construction of medicinally active compounds. The formation of heterocyclic ring systems requires extensive *de novo* synthesis, which limits productivity. Therefore, reactions that can expand carbon skeletons, insert atoms, or delete atoms to form diverse scaffolds are highly sought after. Classical examples of reactions that can do similar chemistry include the Ciamician-Dennstedt rearrangement, which uses a halocarbene to insert a carbon atom into pyrroles to form pyridines, or the Schmidt reaction, which inserts nitrogen into carbonyl compounds to create amides. More recently, the insertion of nitrogen atoms into carbon skeletons or swapping an atom (C or O) for a nitrogen atom has emerged as a powerful tool to reach medicinally relevant compounds without requiring *de novo* syntheses.

## NITROGEN ATOM INSERTION VIA N-IODONIUM IMINOIODINANE SPECIES

Morandi and co-workers recently reported a method to generate 2-H quinazolines from indoles using [bis(trifluoroacetoxy)iodo]benzene (PIFA) as an oxidizing agent and ammonium carbamate as the

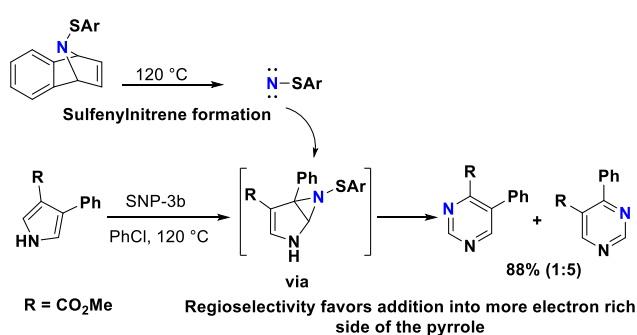


nitrogen source.<sup>1</sup> Subsequently, the same group discovered that by employing similar conditions, but changing the solvent to hexafluoroisopropyl alcohol (HFIP), a less nucleophilic solvent,

allows the amination of olefins into the corresponding nitriles or amidines (Scheme 1).<sup>2</sup> At the core of these methods is an *N*-iodonium iminoiodinane species that is proposed as the active nitrogen source.<sup>3</sup>

## NITROGEN ATOM INSERTION VIA SULFENYLNITRENE REAGENTS

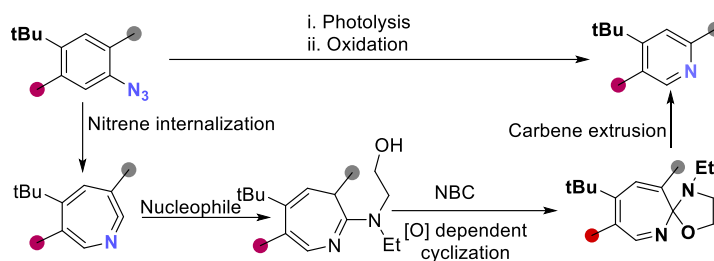
Sharma and co-workers recently introduced a new method that avoids using oxidizing agents by employing preoxidized sulfenylnitrene reagents. This sulfenylnitrene species, upon heating, decomposes to reveal the active nitrene species that can react with pyrroles, indoles, and imidazoles to produce the corresponding pyrimidines, quinazolines, or triazines (Scheme 2). It is postulated through DFT analysis that



the rate-limiting step is the formation of a singlet nitrene and that the reaction proceeds through the formation of an aziridine-like intermediate.<sup>4</sup>

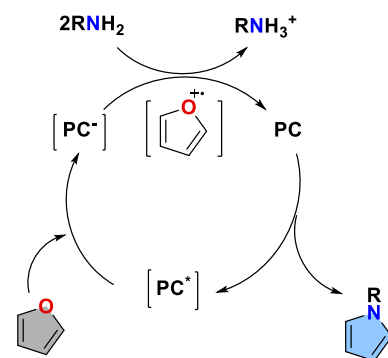
## CARBON TO NITROGEN AND OXYGEN TO NITROGEN TRANSMUTATION REACTIONS

Levin and coworkers reported a method to convert benzenes into pyridines (Scheme 3).<sup>5</sup> This method is a telescoped two-step process in which an aryl azide is irradiated and the intermediate ketenimine is trapped and then oxidized with *N*-bromocaprolactam to promote pyridine formation. Importantly, this method is selective for the ipso carbon and allows for fast generation of compound analogs.



**Scheme 3.** Arene nitrogen internalization

Park and coworkers reported a method for interchanging a furan oxygen atom with a nitrogen atom to form pyrroles (Figure 1).<sup>6</sup> This method avoids the necessity of multistep synthesis and streamlines the process to a one-step, radical, photochemical transformation. The key step in their transformation is leveraging photoredox catalysis to achieve a polarity inversion strategy on the furan ring, making it susceptible to redox-neutral addition of a simple amine.



**Figure 1.** Photochemical O to N transmutation

## OUTLOOK

Current efforts have demonstrated that N-atom insertion into carbon skeletons can be obtained through relatively mild conditions. Additionally, atom swapping is a promising area of research, and it certainly would be interesting to see the development of more photochemical methods that can swap other valuable atoms, such as (S, or Si), and methods that go beyond aromatic carbons.

## REFERENCES

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