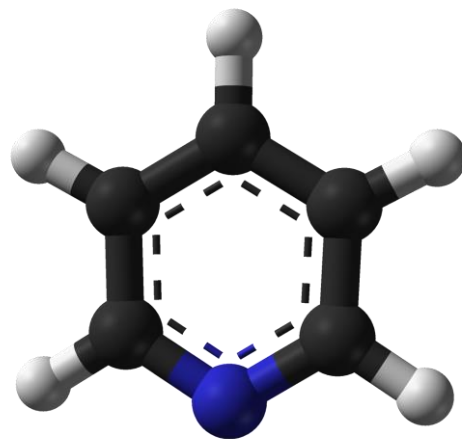


Reactivities of Heteroaromatics – Radical Substitution



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Recommended Textbook:

Heterocyclic Chemistry, 5th Edition, J. A. Joule, K. Mills, **2010**, Wiley

Substitution Reactions – Radical

Types of Radicals

- Although electrically neutral, radicals exhibit varying degrees of **nucleophilic** or **electrophilic** character and this has a very significant effect on their **reactivity towards different heterocyclic types**
- These electronic properties are a consequence of the interaction between the **SOMO** (**S**ingly **O**ccupied **M**olecular **O**rbital) of the **radical** and either the **HOMO**, or the **LUMO**, of the **substrate**, depending on their relative energies

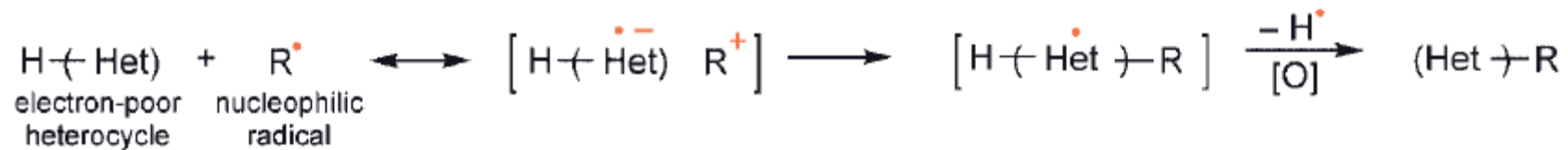
4) Substitution Reactions – Radical

- Nucleophilic Radicals:**

Carry **electron-donating groups** on the radical carbon

They react only with **electron-poor heterocycles**

Examples: $\cdot\text{CH}_2\text{OH}$, alkyl \cdot and acyl \cdot + (aryl \cdot)

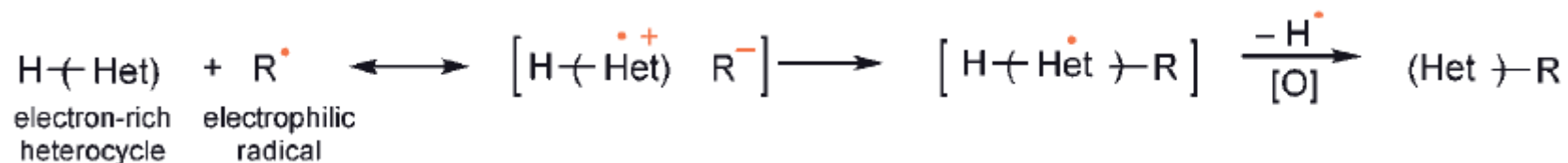


- Electrophilic Radicals:**

Carry **electron-withdrawing groups** on the radical carbon

They react only with **electron-rich heterocycles**

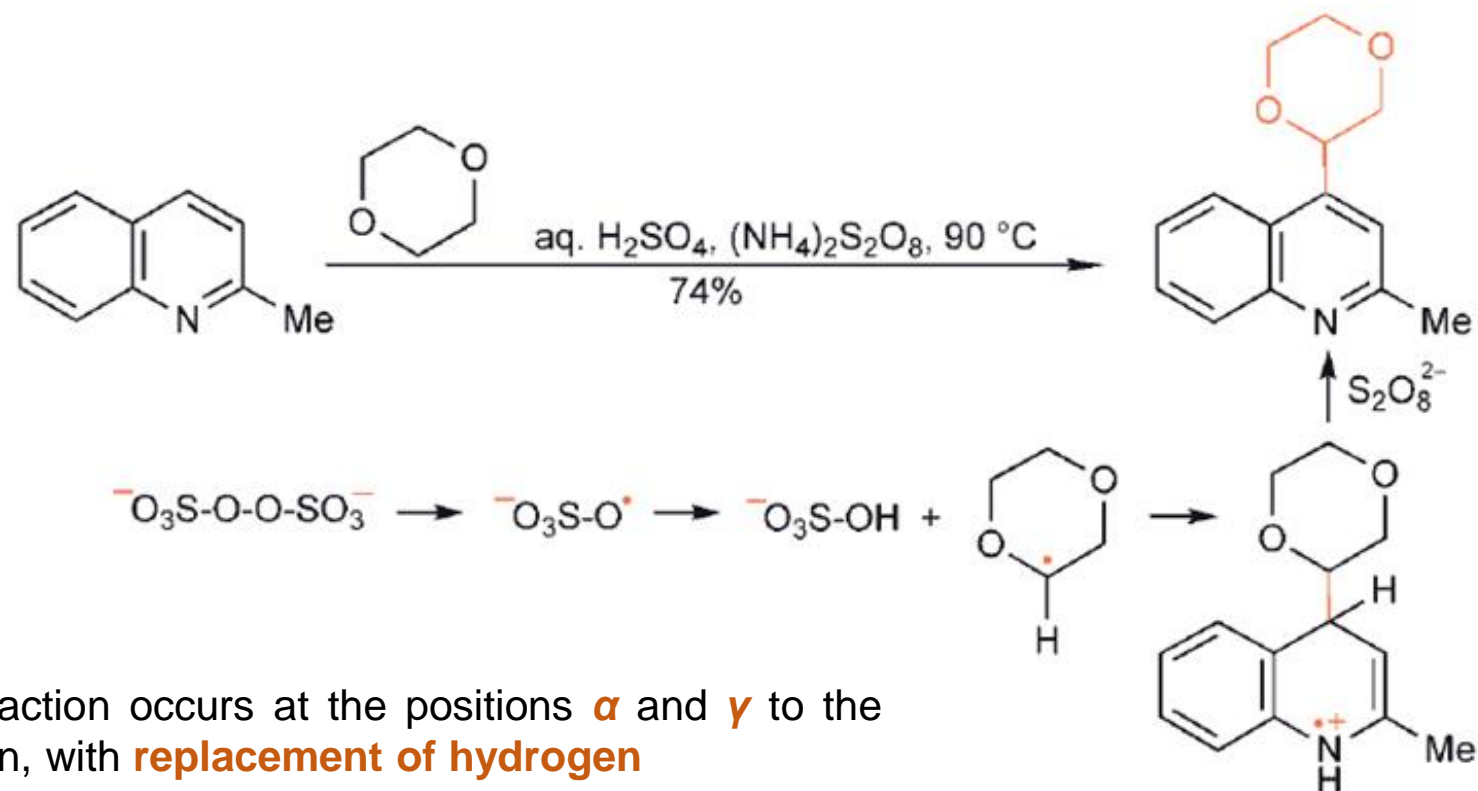
Examples: $\cdot\text{CF}_3$ and $\cdot\text{CH}(\text{CO}_2\text{Et})_2$ + (aryl \cdot)



4) Substitution Reactions – Radical

The Minisci Reaction (by far the most important and synthetically useful radical substitution of heterocyclic compounds!)

- Reaction of **nucleophilic radicals**, under **acidic conditions**, with **heterocycles containing an imine unit** (pyridines, quinolines, diazines, imidazoles, benzothiazoles and purines)

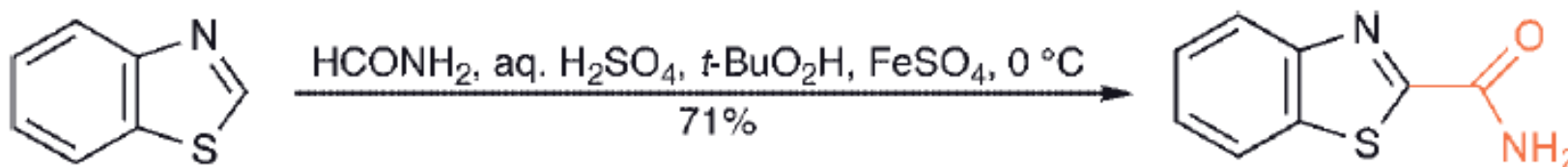


The reaction occurs at the positions α and γ to the nitrogen, with **replacement of hydrogen**

4) Substitution Reactions – Radical

The Minisci Reaction

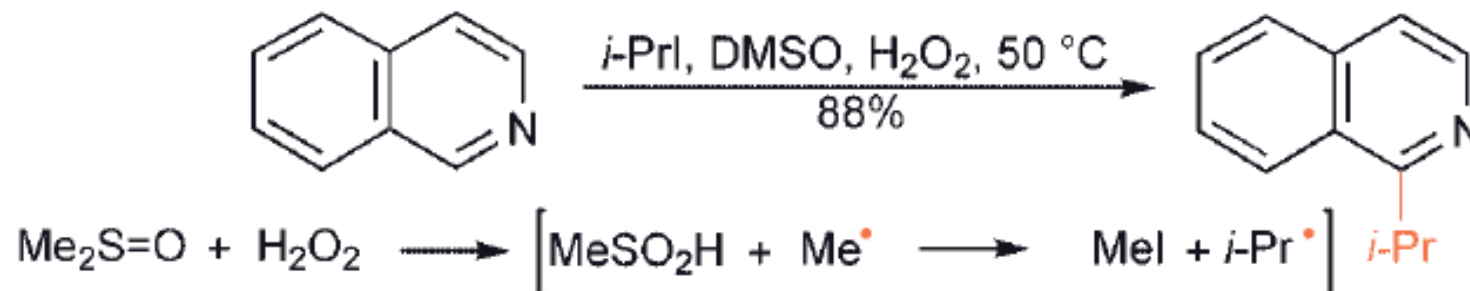
- Acidic conditions are essential because **N-protonation** of the heterocycle both greatly increases its **reactivity** and promotes **regioselectivity** towards a nucleophilic radical (*most of which hardly react at all with the neutral base*)
- A particularly useful feature of the process is that it can be used to introduce **acyl groups** directly



4) Substitution Reactions – Radical

The Minisci Reaction

- Tertiary (and secondary) radicals are **more stable**, but also **more nucleophilic** and therefore more reactive than methyl radicals in Minisci reactions



- The majority of Minisci substitutions have been carried out in **aqueous**, or at least partially aqueous, media, making isolation of organic products particularly convenient

4) Substitution Reactions – Radical

The Minisci Reaction

- **Carboxylic acids** (α -keto acids) are useful precursors for alkyl (or acyl) radicals via **silver-catalysed peroxide oxidation**, or from their **1-hydroxypyridine-2-thione derivatives**

