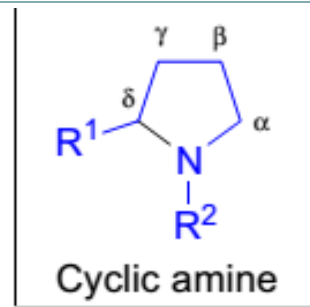
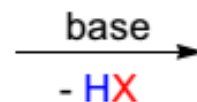
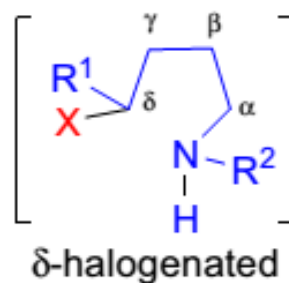
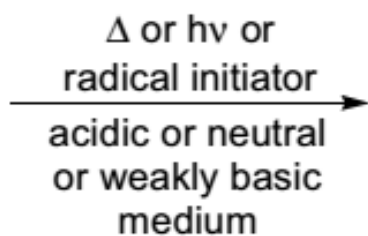
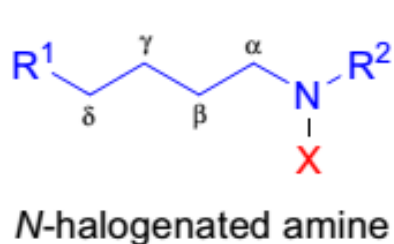


Hofmann Löffler-Freytag reaction (HLF reaction)



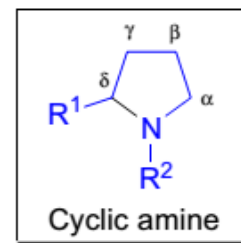
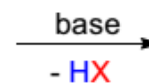
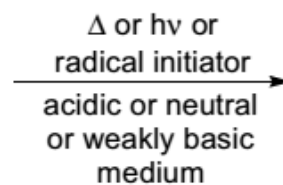
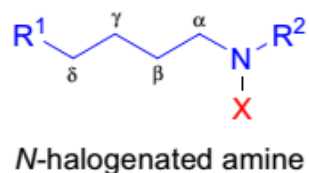
Origin

In the early 1880s, A.W. Hofmann was trying to determine if piperidine, whose structure was unknown at the time, was unsaturated by exposing it to hydrohalic acids or bromine, the treatment of 1-bromo-2-propylpiperidine with hot sulfuric acid, followed by basic work-up, yielded octahydroindolizine, a bicyclic tertiary amine.

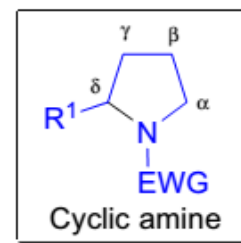
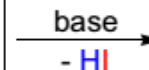
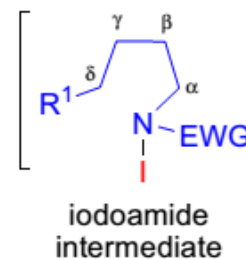
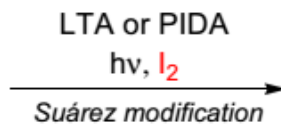
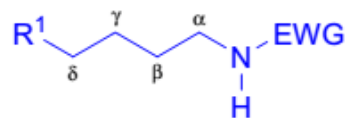
In 1909, K. Löffler and C. Freytag applied this transformation to simple secondary amines and realized that it was a general method for the preparation of pyrrolidines.⁴ The formation of cyclic amines from N-halogenated amines via an intramolecular 1,5-hydrogen atom transfer to a nitrogen radical is known as the HofmannLöffler-Freytag reaction (HLF reaction)

Importance

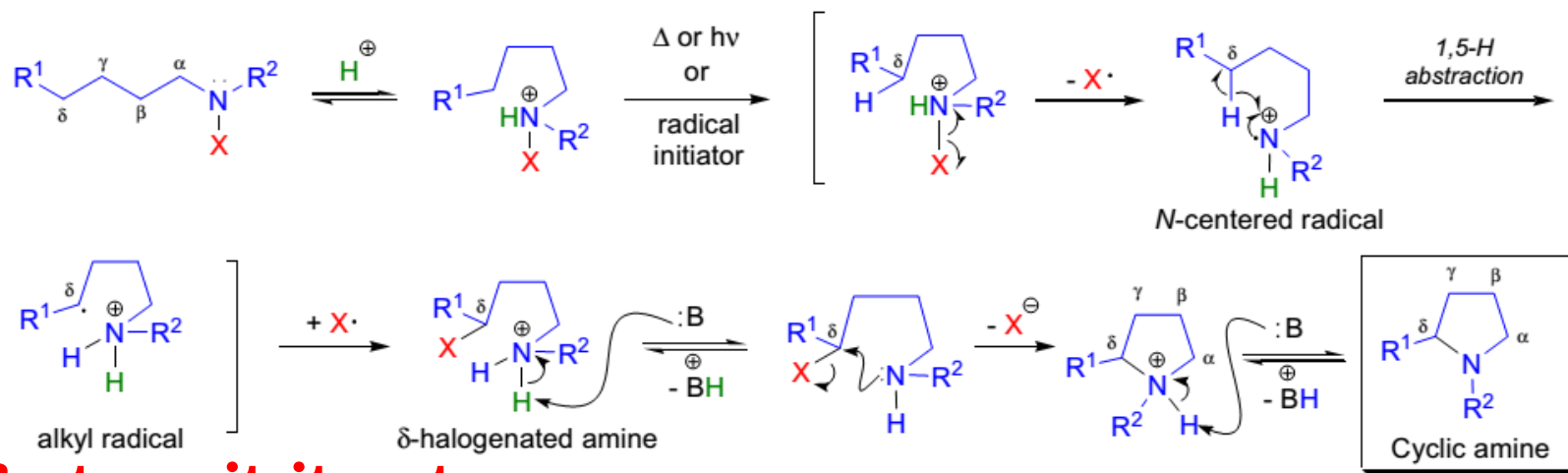
R^1 = alkyl, aryl, H
 R^2 = alkyl, acyl, H
 X = Cl, Br, I



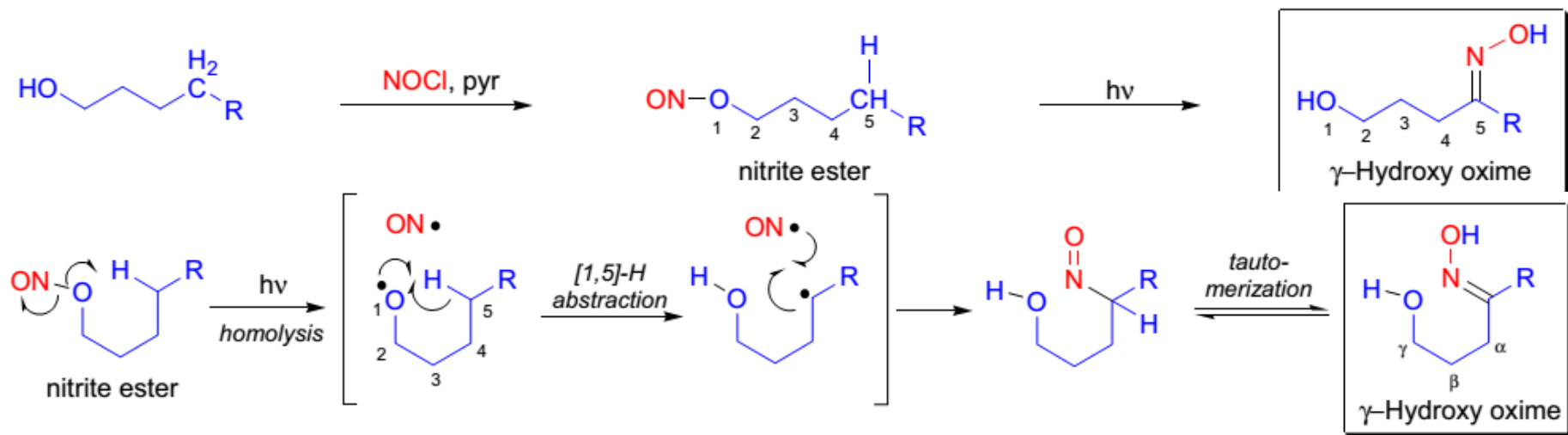
EWG = NO_2
EWG = CN
EWG = $P(O)(OR)_2$



Mechanism

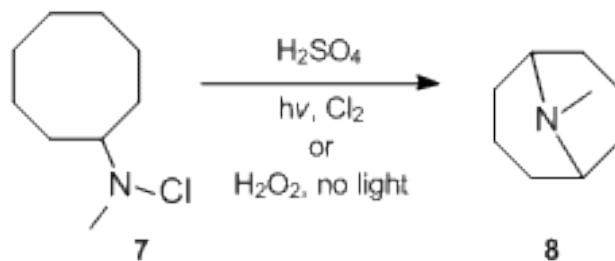


Barton nitrite ester reaction



Features

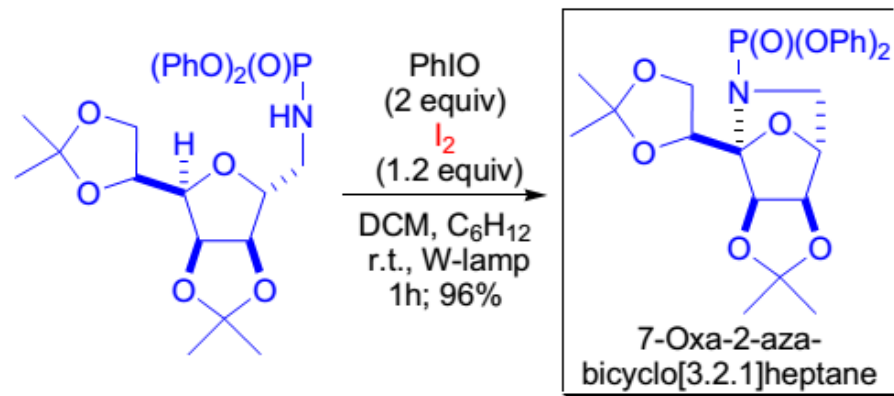
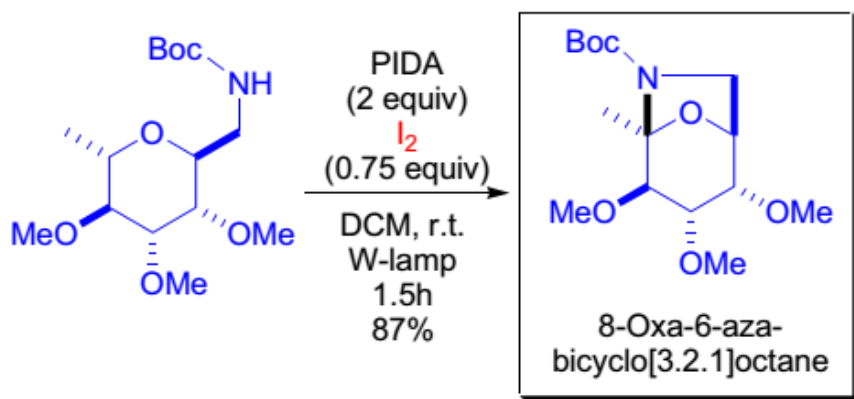
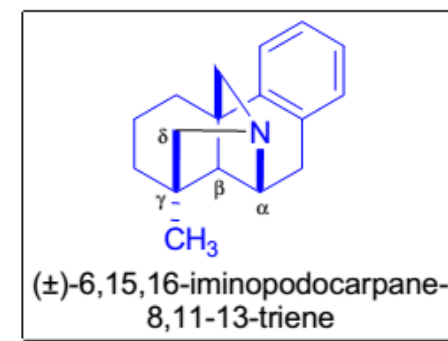
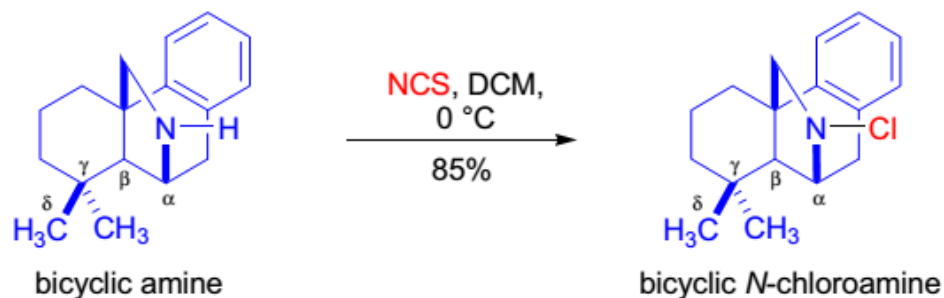
- It may be carried out in acidic solutions, but neutral and even weakly basic reaction conditions have been applied successfully.
- It can be conducted under milder conditions if the intermediate alkyl radical is stabilized by a heteroatom.
- Initiation of the radical process can be done by heating, irradiation with light or with radical initiators .
- The initially formed nitrogen-centered radical abstracts a H-atom mostly from the δ -position (or 5-position) and predominantly 5-membered rings are formed.
- Rarely, in rigid cyclic systems, the formation of 6-membered rings is possible.



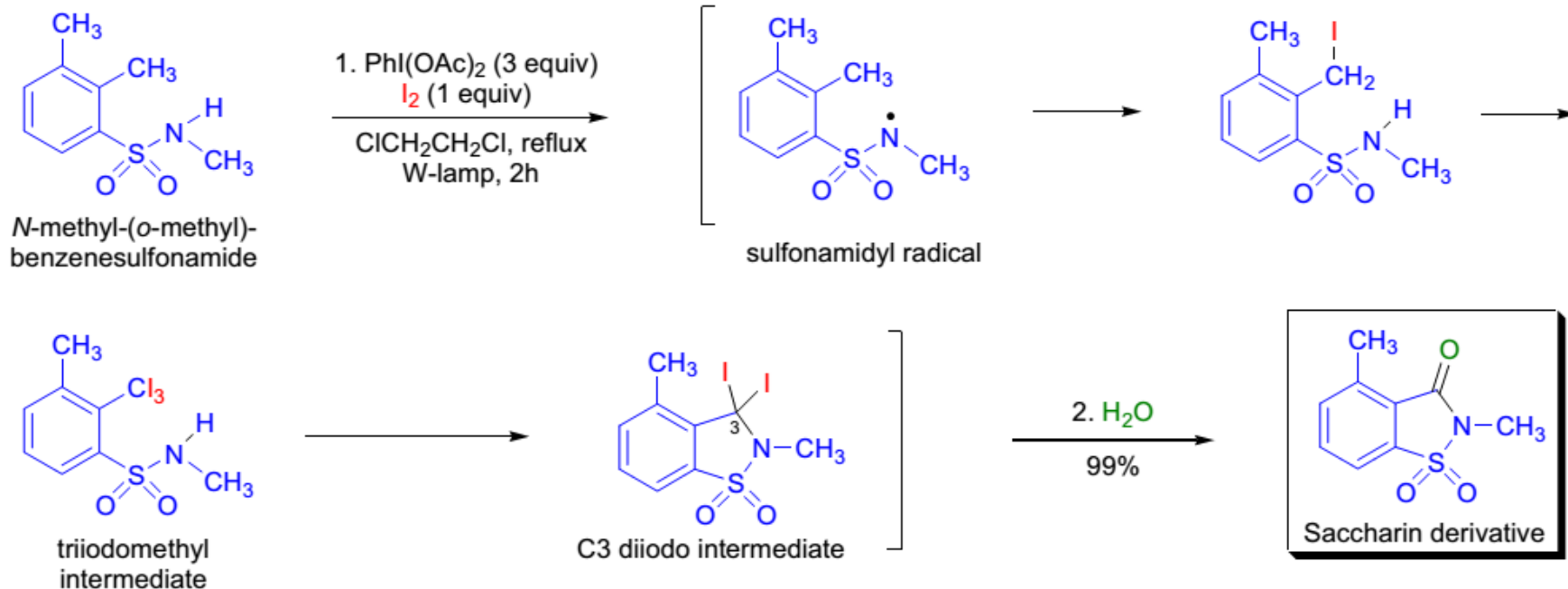
Modification

- **Photolysis of N-bromoamides proceeds under neutral conditions.**
- **The most important variant of this reaction is the Suárez modification.**

Synthetic Applications



Suárez modification





Thanks