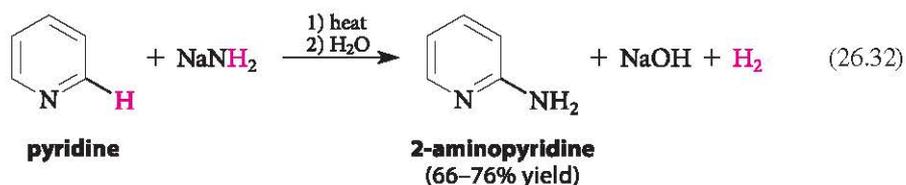


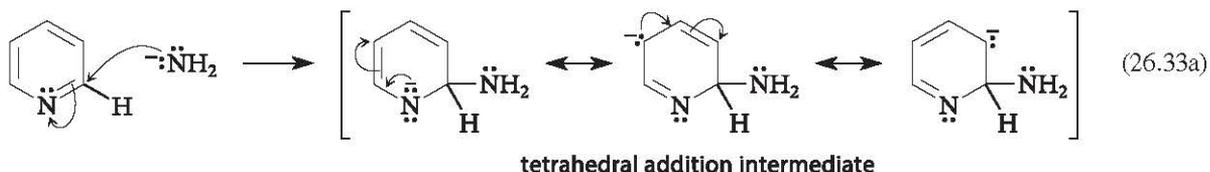
## B. Nucleophilic Aromatic Substitution

In contrast to its low reactivity in *electrophilic* aromatic substitution, the pyridine ring readily undergoes *nucleophilic* aromatic substitution. A rather unusual reaction of this type can be used to prepare 2-aminopyridine. In this reaction, called the **Chichibabin reaction**, treatment

of a pyridine derivative with the strong base sodium amide ( $\text{Na}^+ \text{NH}_2^-$ ; Eq. 14.21, p. 699) brings about the direct substitution of an amino group for a ring hydrogen.

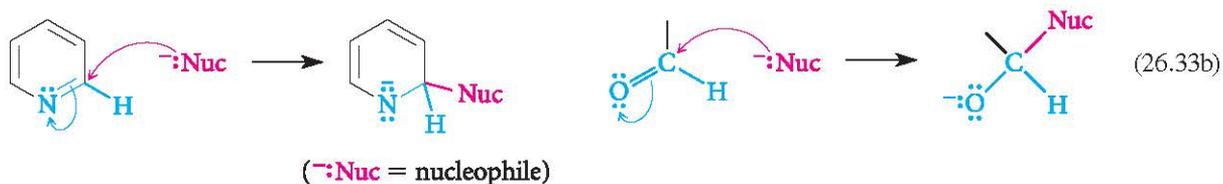


In the first step of the mechanism, the amide ion reacts as a nucleophile at the 2-position of the ring to form a *tetrahedral addition intermediate*.

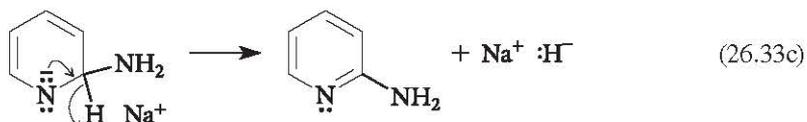


This step of the mechanism can be understood by recognizing that *the C=N linkage of the pyridine ring is somewhat analogous to a carbonyl group*; that is, carbon at the 2-position has some of the character of a carbonyl carbon and can react with nucleophiles. The C=N group of pyridine, though, is *much* less reactive than a carbonyl group because a nitrogen anion is considerably more basic than an oxygen anion and because it is part of an aromatic system.

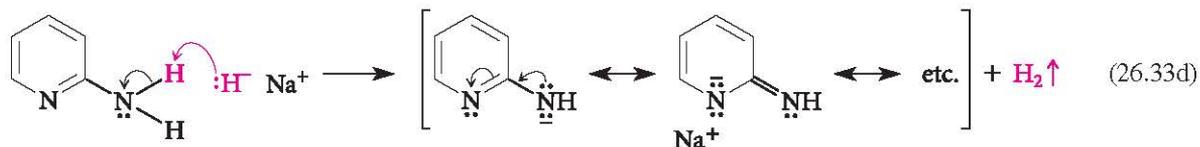
Compare:



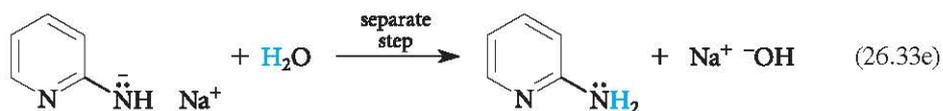
In the second step of the mechanism, the leaving group, a *hydride ion*, is lost.



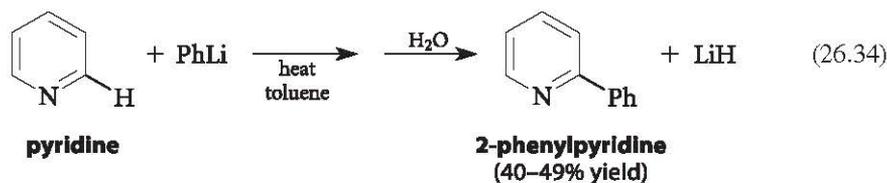
Hydride ion is a very poor, and thus very unusual, leaving group because it is very basic. This reaction occurs for two reasons. First, the aromatic pyridine ring is reformed; aromaticity lost in the formation of the tetrahedral addition intermediate is regained when the leaving group departs. Second, the basic hydride produced in the reaction reacts with the  $\text{—NH}_2$  group irreversibly to form dihydrogen (a gas) and the resonance-stabilized conjugate-base anion of 2-aminopyridine.



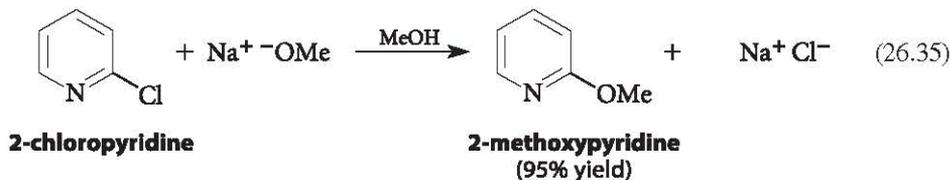
The neutral 2-aminopyridine is formed when water is added in a separate step.



A reaction similar to the Chichibabin reaction occurs with organolithium reagents.

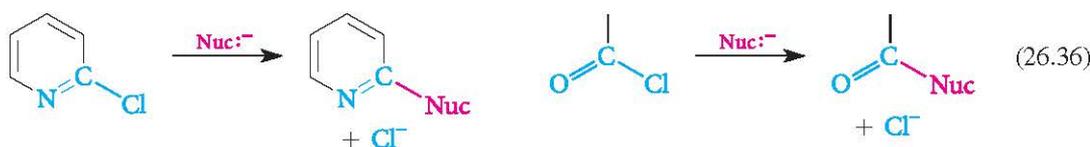


When pyridine is substituted with a much better leaving group than hydride at the 2-position, it reacts more rapidly with nucleophiles. The 2-halopyridines, for example, readily undergo substitution of the halogen by other nucleophiles under conditions that are much milder than those used in the Chichibabin reaction.



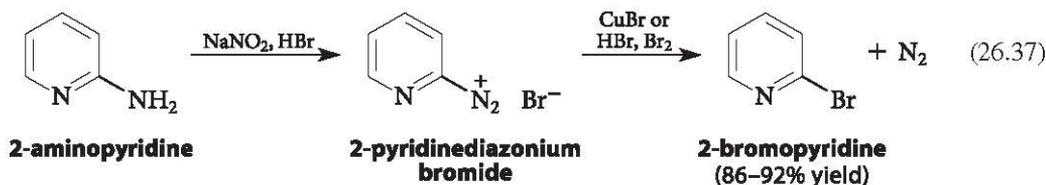
This nucleophilic substitution can also be related to the analogous reaction of a carbonyl compound. This reaction of a 2-chloropyridine resembles the nucleophilic acyl substitution reaction of an acid chloride—except that acid chlorides are *much* more reactive than 2-halopyridines.

Compare:



The nucleophilic substitution reactions of pyridines can be classified as *nucleophilic aromatic substitution* reactions. Recall that aryl halides undergo nucleophilic aromatic substitution when the benzene ring is substituted with electron-withdrawing groups (Sec. 18.4). The “electron-withdrawing group” in the reactions of pyridines is the pyridine nitrogen itself. The tetrahedral addition intermediate (Eq. 26.33a) is analogous to the Meisenheimer complex of nucleophilic aromatic substitution (Eqs. 18.15a–c, p. 886). Thus, there is a mechanistic parallel between three types of reactions: (1) nucleophilic acyl substitution, a typical reaction of carboxylic acid derivatives; (2) nucleophilic aromatic substitution; and (3) nucleophilic substitution on the pyridine ring.

The 2-aminopyridines formed in the Chichibabin reaction serve as starting materials for a variety of other 2-substituted pyridines. For example, diazotization of 2-aminopyridine gives a diazonium ion that can undergo substitution reactions (see Secs. 23.10A–B).



When the diazonium salt reacts with water, it is hydrolyzed to 2-hydroxypyridine, which in most solvents exists in its carbonyl form, 2-pyridone.

