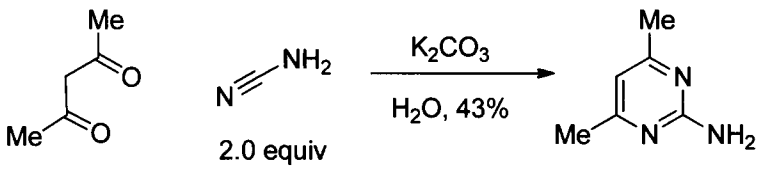
A convenient method for the synthesis of substituted pyrimidines involves the reaction of amidine or guanidine derivatives with a 1,3-dielectrophilic, three-carbon unit. Synthesis of 2,4,5-trisubstituted pyrimidines from Baylis–Hillman adducts and amidines is a good example.[14] The ester group in the reactant can be replaced with acetyl and cyano groups, and the corresponding products are isolated in moderate to excellent yields.

The reaction of α,α-dibromo-oxime ethers with a variety of Grignard reagents efficiently provides 2,4,6-trisubstituted pyrimidines.[15] α,α-Dibromo-oxime ethers are easily prepared from the corresponding α,α-dibromo-ketones upon treatment with *O*-methyl hydroxylamine hydrochloride in methanol. In addition to alkyl groups, both aryl and vinyl groups can also be introduced in this manner. This protocol enables the synthesis of heteroaromatic-substituted pyrimidines. A plausible mechanism for this transformation has been proposed to involve an azirine intermediate. Bromine–magnesium exchange affords magnesium carbenoid, which is then alkylated at the α-position with the Grignard reagent. α-Magnesiated oxime ethers undergo Neber-type cyclizations to provide highly reactive azirines. The reaction of an azirine with bromine–magnesium exchange affords an aziridine intermediate, which yields a diimine intermediate via ring opening. An electrocyclization of the diimine provides a heterocyclic ring system which is converted to the pyrimidine upon elimination of methanol.

13.2.2 Synthesis Involving Formation of Three or More Bonds



Another versatile approach to pyrimidine synthesis uses the N–C fragments. Nitriles are a common N–C source and have been used to form pyrimidines in many syntheses. Cyanamide is a particularly useful nitrile derivative in the synthesis of pyrimidines as illustrated.[16]

An improved and convenient preparation of pyrimidines and condensed pyrimidines from ketones and nitriles was reported.[17] In the presence of acetonitrile, the cation generated from methyl ethyl ketone with trifluoromethanesulfonic anhydride is trapped by the nucleophile, whereby a resonance-stabilized nitrilium species is formed. A second molecule of nitrile reacts with nitrilium intermediate, and after elimination of triflic acid, cyclization, and loss of a proton, the pyrimidine product was obtained in a useful yield. The formation of pyrimidines is accompanied by a minimum