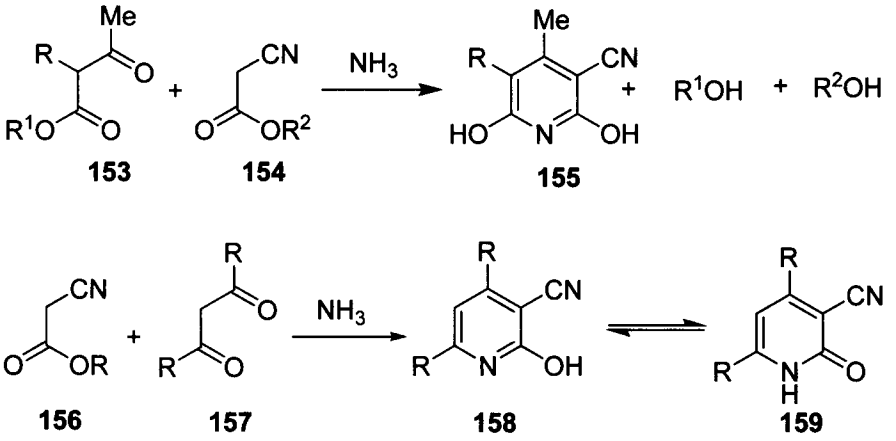
Guareschi–Thorpe pyridine synthesis

When using cyanoacetic esters instead of aldehydes, the Guareschi–Thorpe pyridine synthesis assembles pyridines **155** by the condensation of acetoacetic esters **153** with cyanoacetic esters **154** in the presence of ammonia.[109] A variation of this method involves the reaction of cyanoacetic ester **156** with β-diketone **157** in the presence of ammonia to generate 2-hydroxypyridine **158**.[110] The mechanism of this reaction has been studied, and it was initiated by an ester/amide exchange on cyanoacetic ester **156** with ammonia .[111]



Ethionamide (2-ethylthioisonicotinamide, Trecator SC, **8**) is an antibiotic prodrug used in the treatment of tuberculosis. One synthetic pathway involves the condensation of diketo-ester **160** with cyanoacetamide **161** followed by hydrolysis of the resulting pyridone **162** into give pyridone acid **163**. Treatment of **163** with $POCl_3$ converts the lactam to imine chloride and simultaneous ester formation in ethanol to give **164**. Hydrogenation of **164** to remove the chloride, amide formation, and sequential conversion to the thioamide provided **8**.[112]