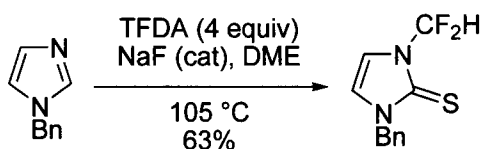


CYP oxidation, the imidazole structure may not be the only the structural moiety creating all of the inhibition. However, imidazoles can chelate to the heme Fe of the CYP450 enzyme complex and display slow dissociative kinetics. While reversible, this can disrupt the oxidation of another drug and greatly diminish the therapeutic window that was observed in animal studies.

As mentioned in the Introduction, imidazole is found in biologic systems and, as mentioned, is quite robust chemically. For example, the imidazole ring system is not readily oxidized; *N*-oxidation does not readily occur. Very powerful oxidizing agents are required to oxidize the imidazole ring. Chemically, this was recently reported by the use of trimethylsilyl fluorosulfonyldifluoroacetate (TFDA).³⁶ Mechanistically, this proceeds similar to the acyl transfer reaction described earlier.



8.6 Introduction to Benzimidazole



Benzimidazole Numbering and Tautomerism

The parent compound, benzimidazole, is a crystalline solid with a melting point of 169–171 °C. Benzimidazoles, like imidazoles, exist as a tautomeric pair of compounds. The tautomerism of 1*H*-benzimidazoles is sufficiently rapid that the compounds are observed as a single species on the NMR timescale at room temperature.³⁷ 1*H*-Benzimidazoles with substituents at the 4(7) or 5(6) positions appear to be a single compound rather than a tautomeric mixture; however, replacement of the NH proton with an alkyl group or other substituent results in formation of a pair of regioisomeric compounds. Thus, regioselectivity is a consideration in the synthesis of all *N*-substituted benzimidazoles that bear any substituents at the C4–C7 positions.

¹H-NMR and ¹³C-NMR spectra of the parent benzimidazole are a simple combination of the imidazole fragment and the benzene ring fragment. In the ¹H-NMR spectrum, the imidazole-H2 shows up as a singlet at 8.20 ppm, whereas the benzene-related H4+H7 and H5+H6 have chemical shifts at ~7.60 ppm and 7.20 ppm, respectively, both as multiplets. In the