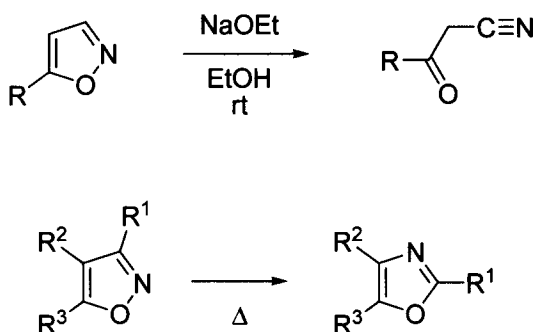


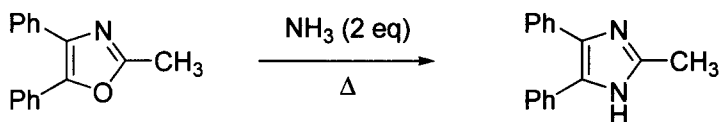
Other reagents such as reductants, strong bases, or thermal conditions cause cleavage of the isoxazole ring. For example, reaction with strong bases opens the ring to yield β-ketonitriles. Additionally, heating (or photochemical irradiation) of the isoxazole or benzisoxazole ring goes through diradical intermediates to yield oxazoles.⁹⁷



6.6 Possible Liabilities of Oxazole-Containing Drugs

As shown previously, C2-lithiated oxazoles are in equilibrium with their ring-opened counterpart. C2-unsubstituted oxazoles are therefore potentially unstable to strongly basic conditions.

Ammonia can react with the C2 position of oxazoles resulting in ring cleavage and formation of an imidazole ring. Ring cleavage by this mechanism occurs more frequently than S_NAr substitution.



Oxazoles with an acyl substituent at C4 can undergo a thermal rearrangement essentially exchanging the C4 and C5 substituents.⁹⁸ The facility of this rearrangement is improved when the C5 substituent is a heteroatom (–OR, –SR, –Cl). Dewar and Turchi observed deuterium scrambling of a labelled oxazole ester under thermal conditions. They propose a nitrile ylide intermediate in the rearrangement mechanism.⁹⁹ This