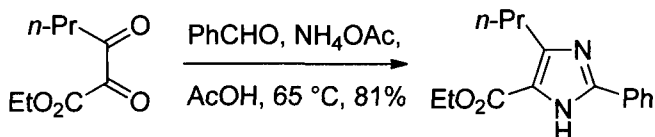


8.3.1 *Debus*

Debus is credited for first reporting the reaction of glyoxal, NH_3 , and formaldehyde to make imidazole.² It has been determined that primary amines and/or other salts of ammonia can be used. While it is best if a symmetrical dicarbonyl component is used or mixtures are likely to result, it was recently shown that polarizing the dicarbonyl can selectively provide one product.



A modification to this reaction can be seen in the reaction of a dicarbonyl equivalent, acyl-vinyl-phosphonium salt.¹⁸ Reaction of the phosphonium salt with an appropriately functionalized formamidine provides the imidazole phosphonium salt. The imidazole phosphonium salt can be further functionalized to an intermediate used to synthesize the cimetidine, an H_2 -receptor histamine antagonist used to treat ulcers.

A proposed mechanism for the condensation of formamidine sulfinic acid with the dicarbonyl equivalent involves attack of the amidine nitrogen atoms on both of the electrophilic centers with loss of water. The imidazole phosphonium salt does not react directly with sodium methoxide but instead generates the reactive methylene imidazole intermediate, which is trapped by MeOH. Reactivation can be promoted in protic solvents to elongate the chain to provide cimetidine.

