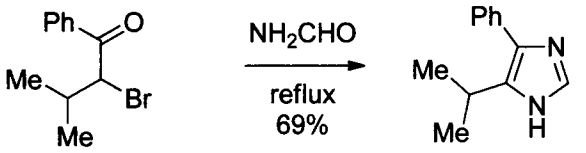
8.3.3 Bredereck

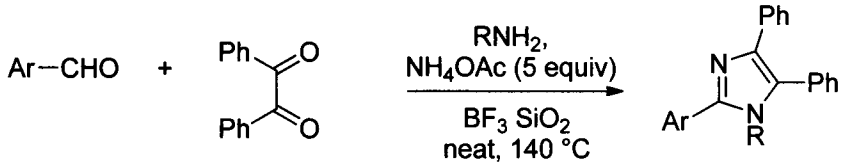
Bredereck reported the reaction of α-hydroxy, bromo, amino, or acetoxy-ketones with formamide to provide 4,5-di-substituted imidazoles. The formamide acts both as the N and C2 source.



If the substituents around the ketone are too large, then yields are low. Oxazoles can form during this reaction but can oftentimes be overcome by increasing the amount of formamide or nitrogen (N) source. Many other N sources can be used with these substrates. For example, acetimidates, KSCN, guanidines, amidines, and formimidamides have been used with many of these keto substrates to provide imidazoles.

8.3.4 Radiszewski

This reaction is a variation of the conditions reported by Debus in which a dicarbonyl is reacted with an amine salt and an aldehyde in the presence of an acid or Lewis acid. If an *N*-substituted imidazole is desired, then an amine can be used. Recent Lewis acids that have been used are $ZrCl_4$[21] or $InCl_3$.[22]



8.3.5 van Leusen

van Leusen and co-workers reported the cycloaddition of tosyl-methylisocyanide (TosMIC) with imines to afford 1, 5-di-substituted and 1, 4, 5-trisubstituted imidazoles. The procedure requires a base and the TosMIC reagent can be substituted but has limitations. Other than imines, the cycloaddition can also occur with acetimidates, nitriles, and iminoyl chlorides. Yields are moderate to good.[2,23] EWGs other than tosyl have been used for this transformation. For example, esters have been used.