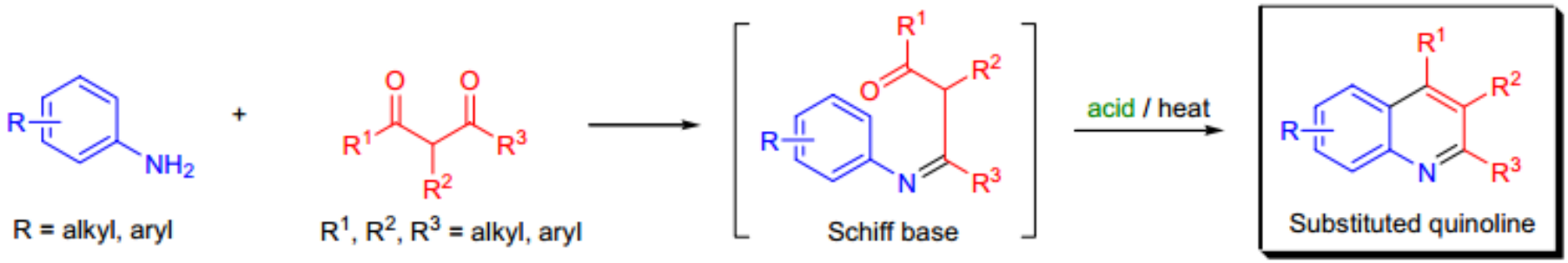
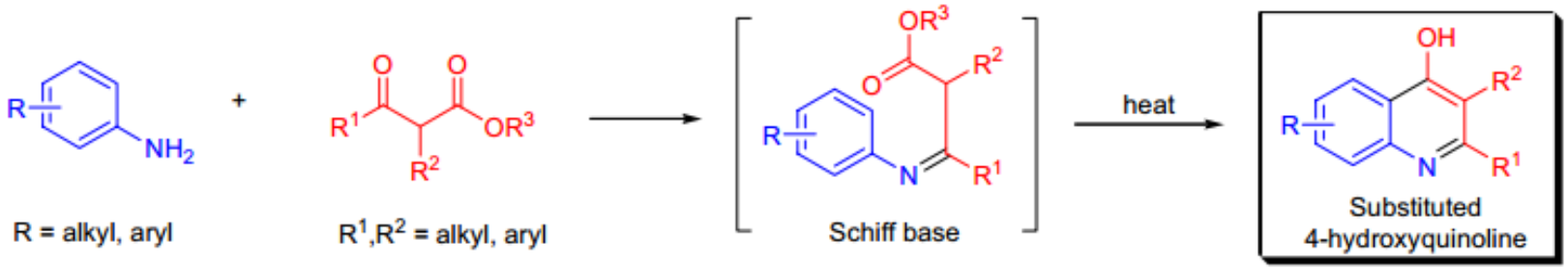
COMBES QUINOLINE SYNTHESIS

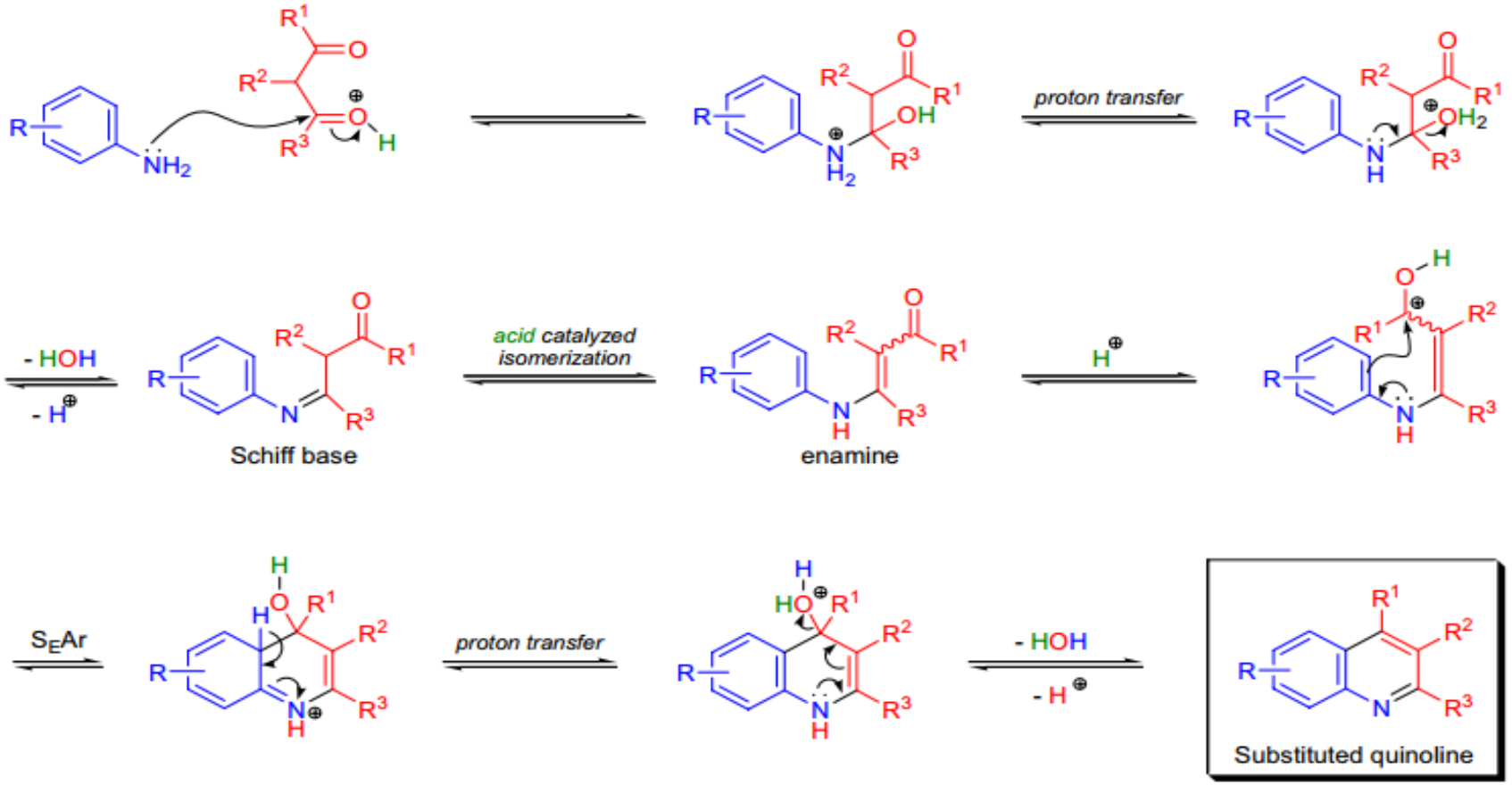
The formation of quinolines and benzoquinolines by the condensation of primary aryl amines with β-diketones followed by an acid catalyzed ring closure of the Schiff base intermediate is known as the Combes quinoline synthesis.



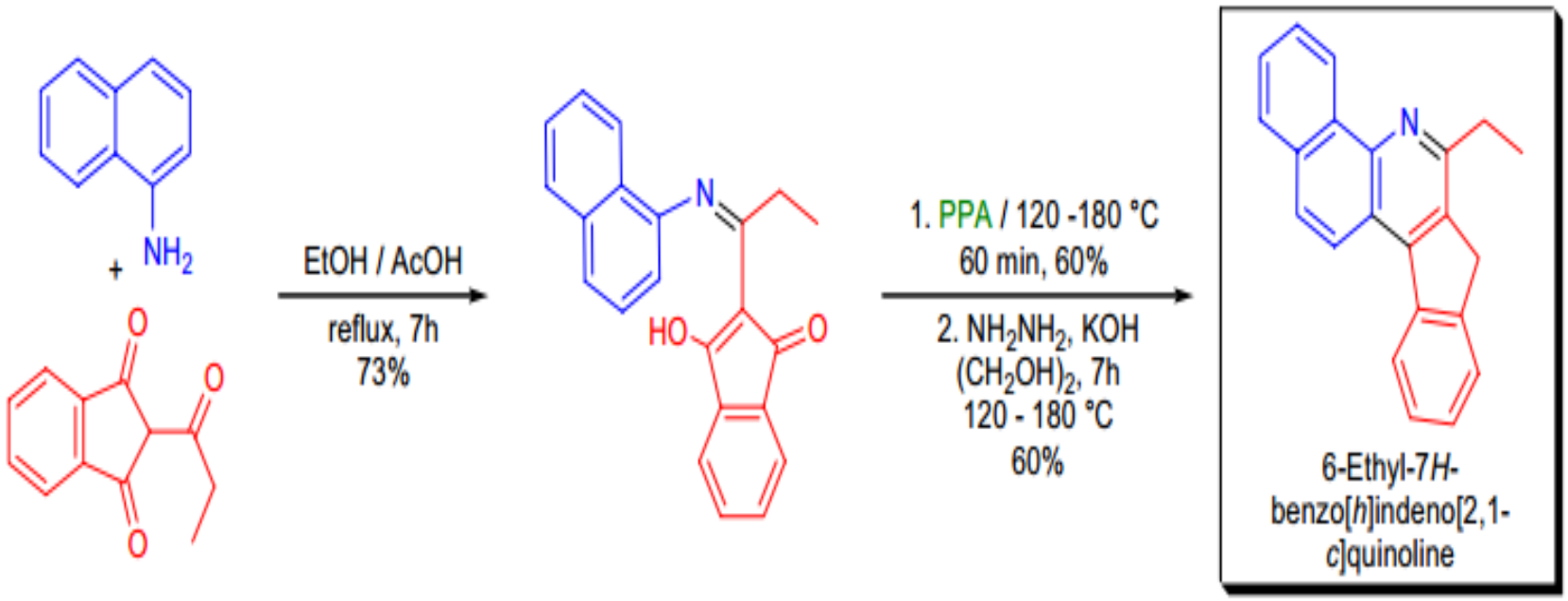
The closely related reaction of primary aryl amines with β-ketoesters followed by the cyclization of the Schiff base intermediate is called the Conrad-Limpach reactionand it gives 4-hydroxyquinolines as products.

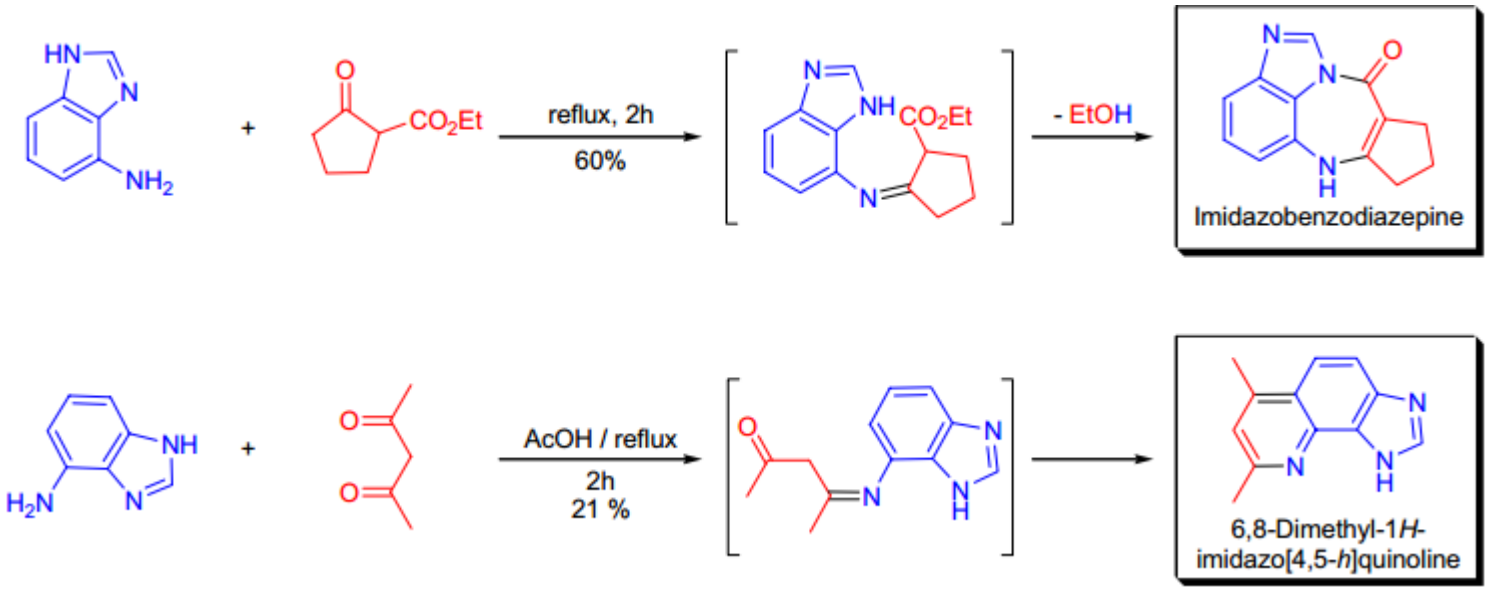


Mechanism:


proton transfer
- HOH
- H⊕
Schiff base
acid catalyzed isomerization
enamine
H⊕
SEAr
proton transfer
- HOH
- H⊕
Substituted quinoline

Synthetic Applications:




reflux, 2h
60%
- EtOH
Imidazobenzodiazepine
AcOH / reflux
2h
21 %
6,8-Dimethyl-1H-
imidazo[4,5-h]quinoline