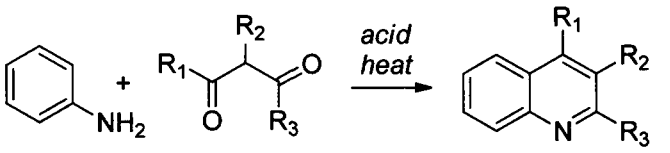
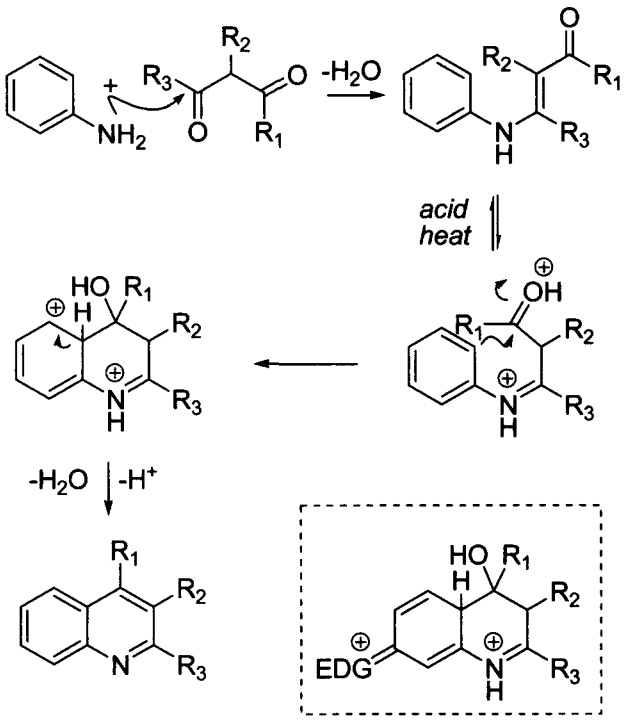


The initial condensation step proceeds usually well, even when sterically congested arylamines are used. On the other hand, the cyclization and dehydration step is affected by Friedel–Crafts-type directing substituents within the ring, following the proposed mechanism.[61] Strong electron-withdrawing groups on aromatic ring can completely prohibit the cyclodehydration step, producing only enamines.



Several conditions are used for the difficult cyclization step, avoiding the acidic hydrolytic conditions in the reaction mixture that can hydrolyze the initially formed enamine. Thus, use of concentrated inorganic acids is preferential (e.g., conc. sulfuric and hydrochloric acids), as well as chloroacetic acid, *p*-toluene sulfonic acid, etc.

Unsymmetrical diones have also been used as coupling partners for the Combes reaction, providing selectively, in some cases, otherwise difficult accessible quinoline compounds.[62,63]