

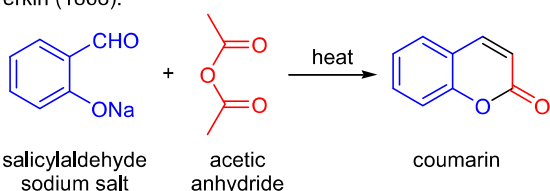
PERKIN REACTION

(References are on page 649)

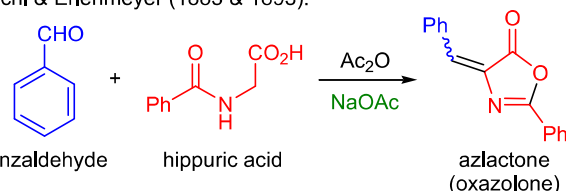
Importance:[Seminal Publications^{1,2}; Reviews^{3,4}; Modifications & Improvements⁵⁻²²]

In 1868, W.H. Perkin described the one-pot synthesis of coumarin by heating the sodium salt of salicylaldehyde in acetic anhydride.¹ After this initial report, Perkin investigated the scope and limitation of the process and found that it was well-suited for the efficient synthesis of cinnamic acids.² The condensation of aromatic aldehydes with the anhydrides of aliphatic carboxylic acids in the presence of a weak base to afford α,β -unsaturated carboxylic acids is known as the *Perkin reaction* (or *Perkin condensation*). The general features of the transformation are:^{3,4} 1) the aldehyde component is most often aromatic, but aliphatic aldehydes with no α -hydrogens as well as certain α,β -unsaturated aldehydes can also be used;¹⁷ 2) the reaction is more facile and gives higher yield of the product when the aromatic aldehyde has one or more electron-withdrawing substituents; 3) aliphatic aldehydes are not suitable for the reaction, since they often give enol acetates and diacetates when heated with acetic anhydride; 4) the anhydride should be derived from an aliphatic carboxylic acid, which has at least two hydrogen atoms at their α -position (if there is only one α -hydrogen atom, a β -hydroxy carboxylic acid is obtained); 5) the weak base is most often the alkali metal salt of the carboxylic acid corresponding to the applied anhydride or a tertiary amine (e.g., Et₃N); 6) the usual procedure requires heating of the aldehyde in the anhydride (often used as the solvent) at or above 150 °C; and 7) the stereochemistry of the newly formed double bond is typically (*E*). There are two important modifications of the *Perkin reaction*: 1) the condensation of an aromatic aldehyde or ketone with an *N*-acyl glycine in acetic anhydride in the presence of NaOAc to obtain azlactones (oxazolones), which are important intermediates for the synthesis of α -amino acids (*Erlenmeyer-Plöchl azlactone synthesis*);^{6-9,15,22} and 2) the condensation of aromatic aldehydes with α -arylacetic acids in acetic anhydride and in the presence of a weak base (proceeding *via* mixed anhydrides generated *in situ*) to obtain α -arylcinnamic acids (*Ogialoro modification*).⁵

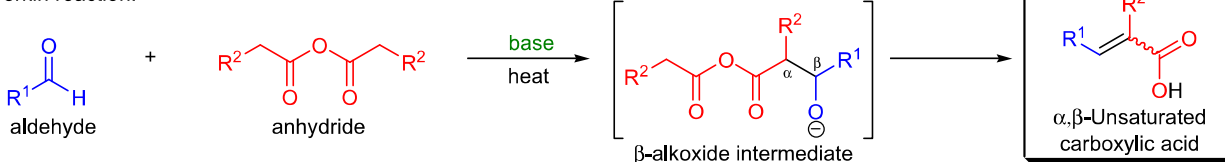
Perkin (1868):



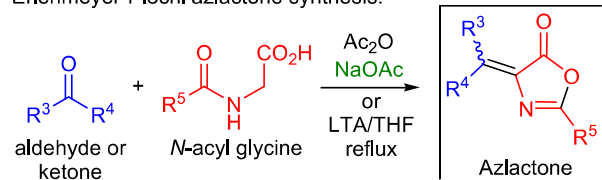
Plöchl & Erlenmeyer (1883 & 1893):



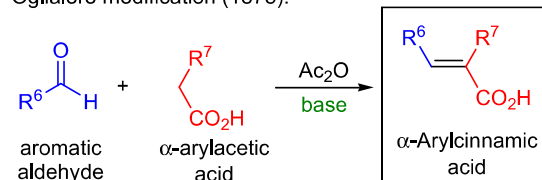
Perkin reaction:



Erlenmeyer-Plöchl azlactone synthesis:



Ogialoro modification (1878):



R^1 = aromatic, heteroaromatic, alkenyl, alkyl group with no α -hydrogen atom; R^2 = H, alkyl, aryl; R^{3-4} = H, alkyl, aryl; R^5 = alkyl, aryl; R^6 = aryl, heteroaryl; **base**: NaOAc, KOAc, CsOAc, Et₃N, pyridine, piperidine, K₂CO₃

Mechanism: 23,3,24-31,4,32-35