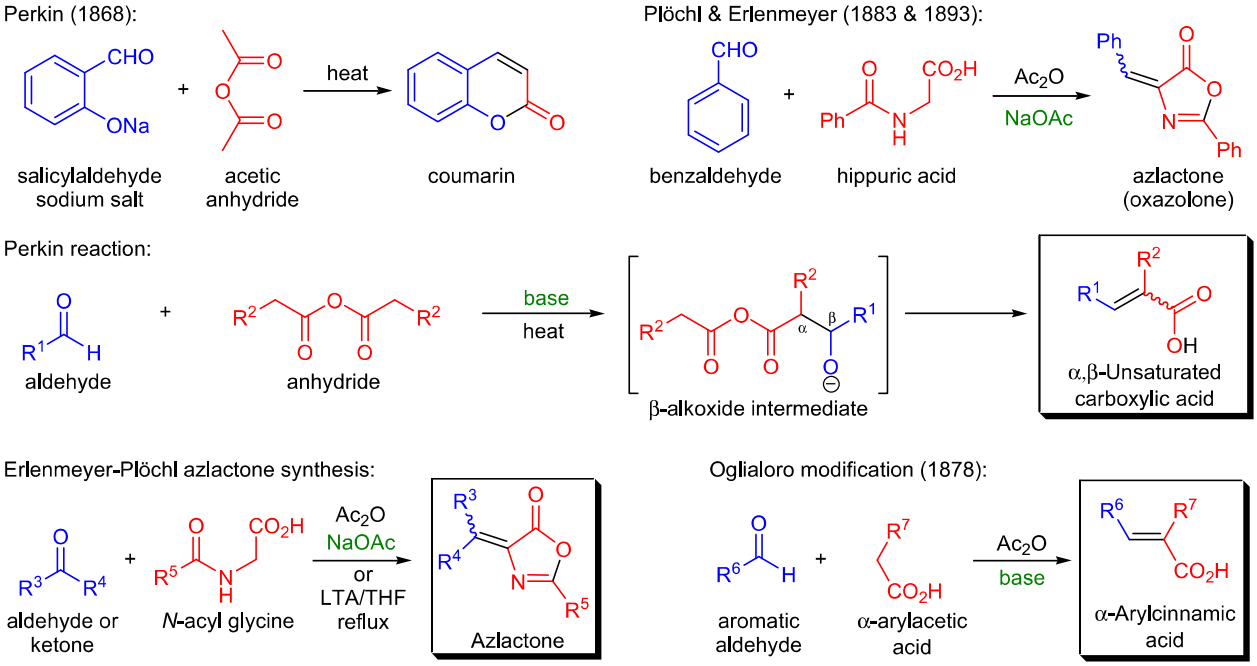
PERKIN REACTION

(References are on page 649)

Importance:

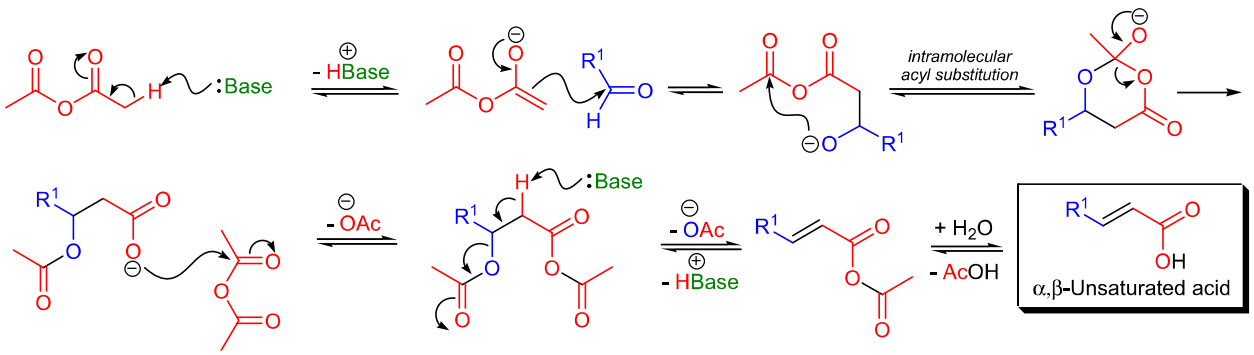
[*Seminal Publications*[1,2]; *Reviews*[3,4]; *Modifications & Improvements*[5-22]]

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., Et_3N); 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 (*Oglialoro modification*).[5]



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, Et_3N, pyridine, piperidine, K_2CO_3

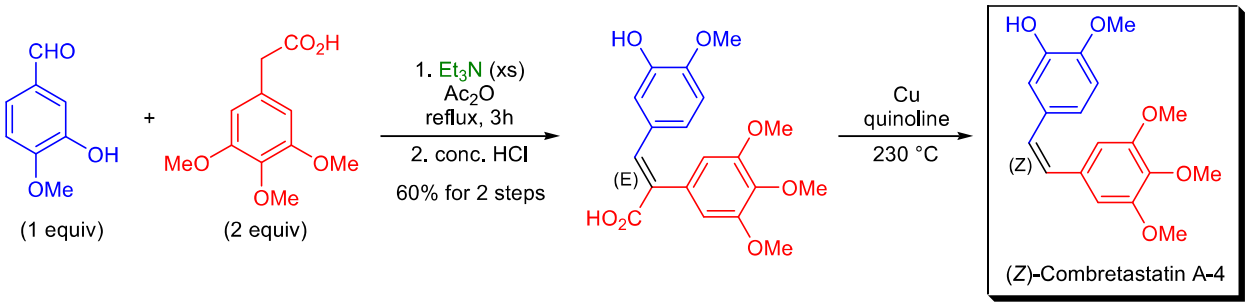
Mechanism:[23,3,24-31,4,32-35]



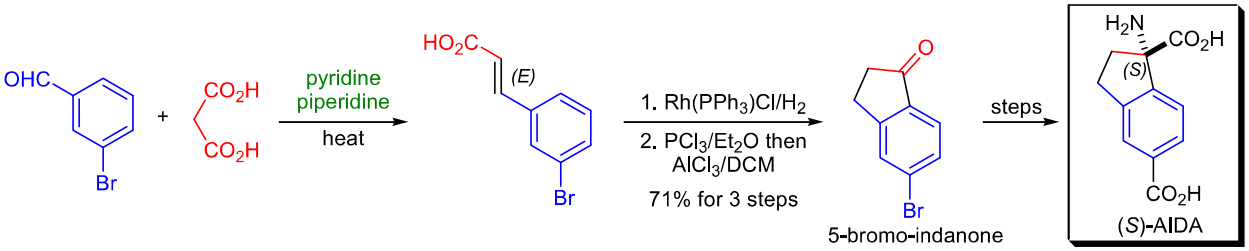
PERKIN REACTION

Synthetic Applications:

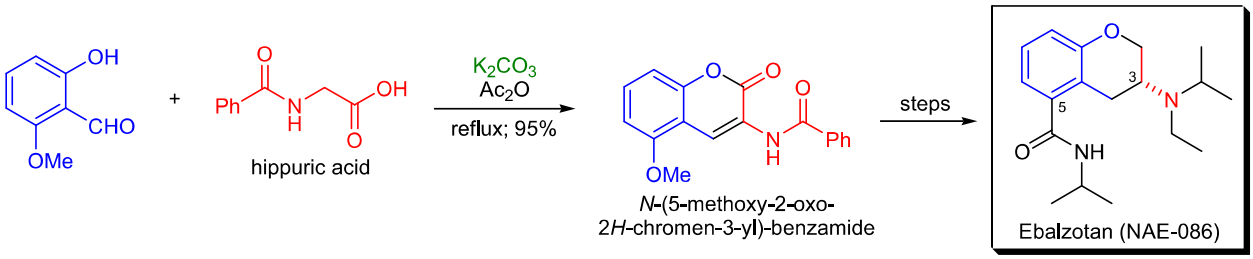
The combretastatins are a group of antimitotic agents isolated from the bark of the South African tree *Combretum caffrum*. A novel and highly stereoselective total synthesis of both the *cis* and *trans* isomers of combretastatin A-4 was developed by J.A. Hadfield and co-workers.[36] The (*Z*)-stereoisomer was prepared using the *Perkin reaction* as the key step in which 3,4,5-trimethoxyphenylacetic acid and 3-hydroxy-4-methoxbenzaldehyde was heated with triethylamine and acetic anhydride at reflux for several hours. The α,β-unsaturated acid was isolated in good yield after acidification and had the expected (*E*) stereochemistry. Decarboxylation of this acid was effected by heating it with copper powder in quinoline to afford the natural product (*Z*)-combretastatin A-4.



In the laboratory of D. Ma, the asymmetric synthesis of several metabotropic glutamate receptor antagonists derived from α-alkylated phenylglycines was undertaken.[37] The preparation of (*S*)-1-aminoindan-1,5-dicarboxylic acid (AIDA) started with the *Perkin reaction* of 3-bromobenzaldehyde and malonic acid. The resulting (*E*)-cinnamic acid derivative was hydrogenated and the following *intramolecular Friedel-Crafts acylation* afforded the corresponding indanone, which was then converted to (*S*)-AIDA.



The large-scale pilot plant preparation of the chiral aminochroman antidepressant ebalzotan (also known as NAE-086) was developed by H.J. Federsel and co-workers.[38] The structural features of the target included a disubstituted chroman skeleton, a stereocenter, as well as a non-symmetrical tertiary amine moiety at the C3 position and a secondary carboxamide group at C5. The backbone of the target molecule was constructed using the *Perkin condensation* of 2-hydroxy-6-methoxybenzaldehyde with hippuric acid under mild conditions.



Fluorinated analogs of naturally occurring biologically active compounds, such as amino acids, often exhibit unique physiological properties, and therefore there is substantial interest in their convenient and high-yielding preparation. The research team of K.L. Kirk synthesized 6-fluoro-*meta*-tyrosine and several of its metabolites employing the *Erlenmeyer-Plöchl azlactone synthesis*.[39] Hippuric acid and 2-benzyloxy-5-fluorobenzaldehyde were condensed in the presence of sodium acetate in acetic anhydride to isolate the corresponding azlactone, which was converted to the target fluorinated amino acid in three steps.