Isoquinolines Synthesis

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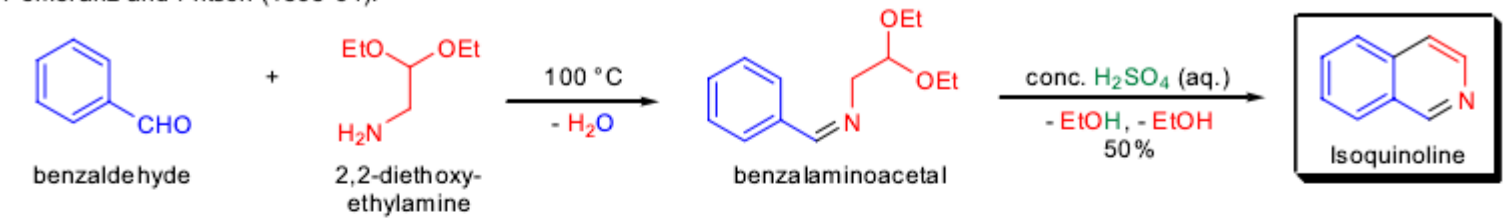
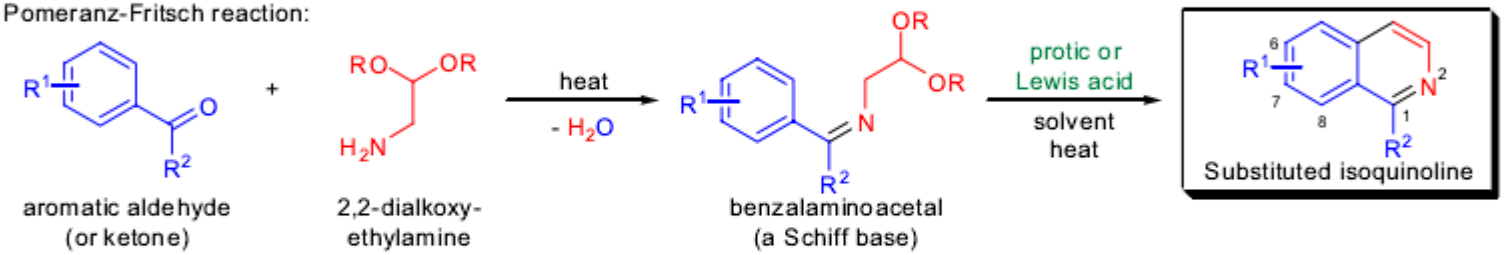
Pomeranz-Fritsch Isoquinoline Synthesis

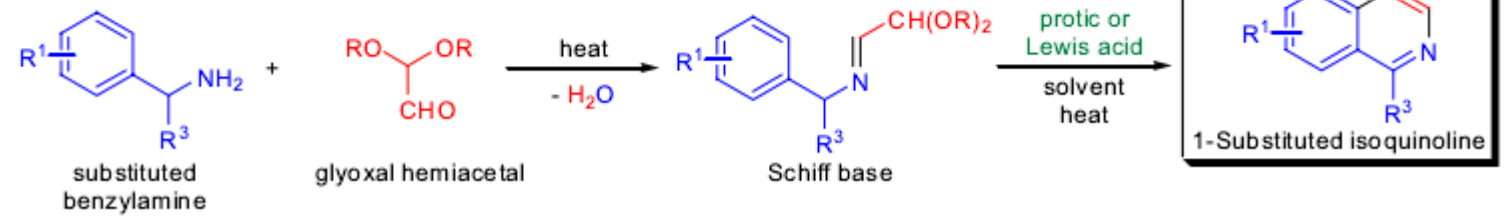
Pomeranz and Fritsch (1893-94):



Pomeranz-Fritsch reaction:

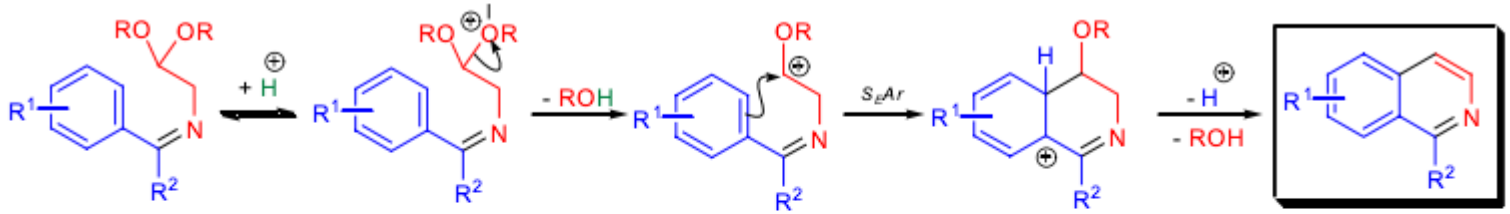


Schlittler-Müller modification (1948):

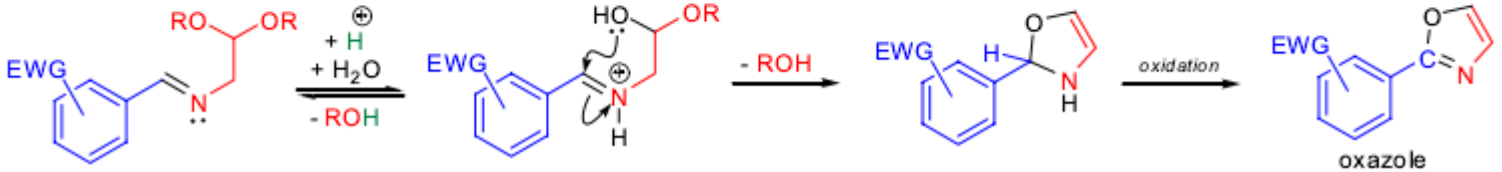


R^1 = usually an electron-donating group (EDG), H, alkyl, aryl, O-alkyl, Cl, Br; R^{2-3} = H, alkyl; R = Me, Et; protic acid: H_2SO_4, HCl, PPA; Lewis acid: $BF_3{\cdot}OEt_2$

Mechanism:



Formation of oxazole if R^1 = EWG (the oxidation is performed by the conc. H_2SO_4):

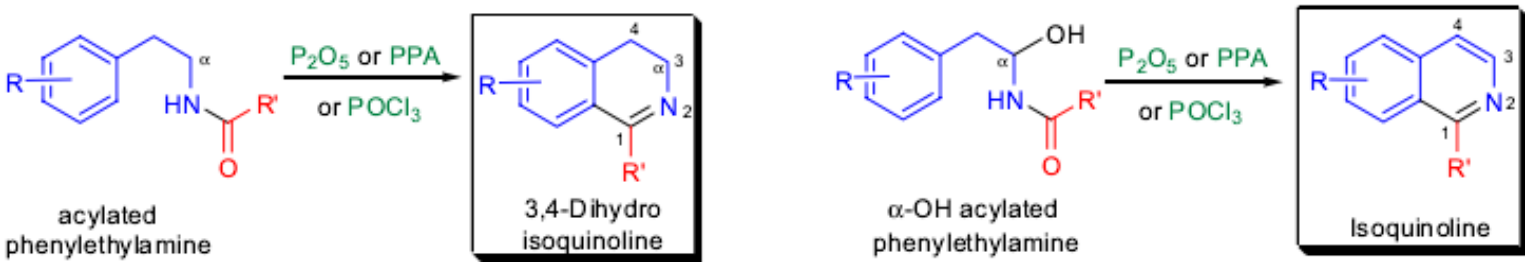


features : 1) the benzalaminoacetals are prepared by reacting 2,2-dialkoxyethylamines with substituted aromatic aldehydes or rarely with aromatic ketones;
2) the structural variation of the 2,2-dialkoxyethylamines is very restricted, and, in the overwhelming majority of the cases, the dimethyl or diethyl acetals are used without any substituents on the C1 carbon (C1-substituted analogues tend to fail to undergo the reaction);
3) aromatic aldehydes give rise to C1-unsubstituted isoquinolines, usually in good yield, while aromatic ketones afford C1-substituted isoquinolines albeit in low yield;
4) the highest yields are obtained when the substituents on the aromatic ring are electron-donating; 5) strongly electron-withdrawing substituents (e.g., NO2) on the aromatic ring prevent the formation of isoquinolines and the corresponding oxazoles are obtained instead;
6) when both of the ortho-positions (relative to the carbonyl group) are unoccupied, a regioisomeric mixture of isoquinolines is obtained;
7) the most commonly used protic acids are sulfuric acid and hydrochloric acid, but Lewis acids such as BF3·OEt2, trifluoroacetic anhydride and lanthanide triflates have been used occasionally;
8) unless the aromatic ring is highly electron-rich, heating of the reaction mixture is required in order to achieve cyclization.

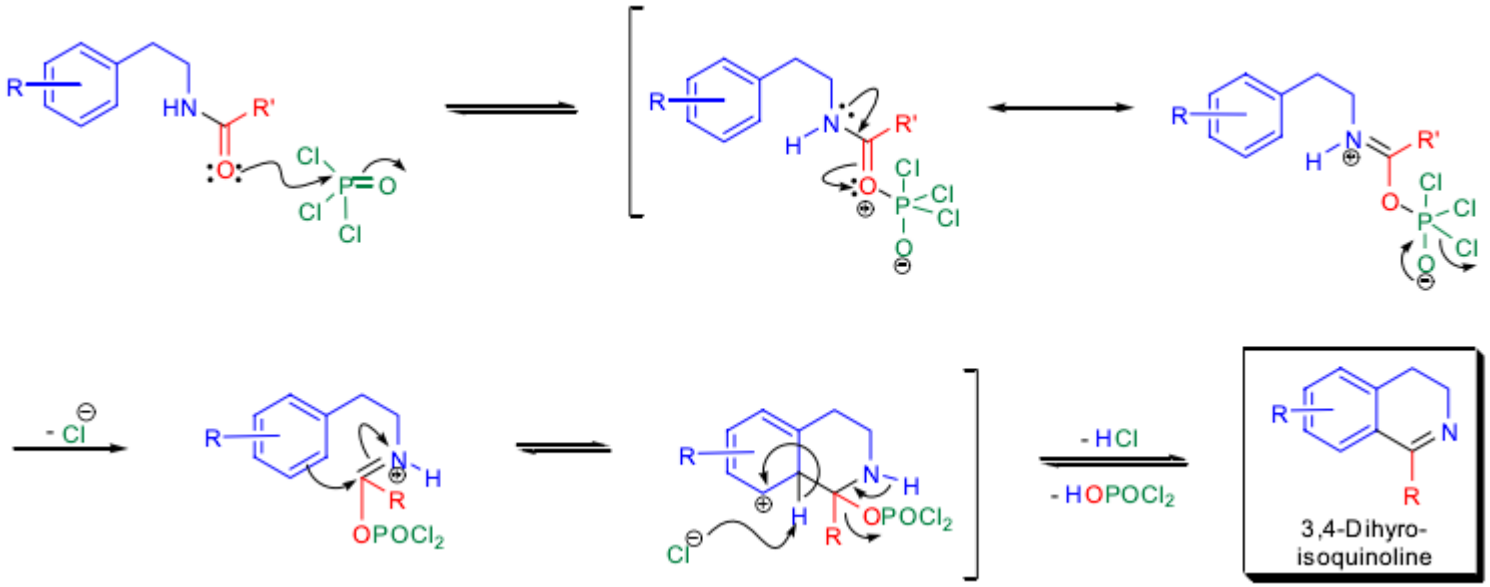
Two of the most important modifications are:
1) when a substituted benzylamine is condensed with glyoxal hemiacetal, the resulting Schiff base is efficiently cyclized to give the corresponding C1-substituted isoquinoline (Schlittler-Müller modification);
2) hydrogenation of the benzal-aminoacetal and the acid-catalyzed cyclization of the resulting amine gives rise to a tetrahydroisoquinoline (Bobbitt-modification).

Bischler-Napieralski Isoquinoline Synthesis

1893

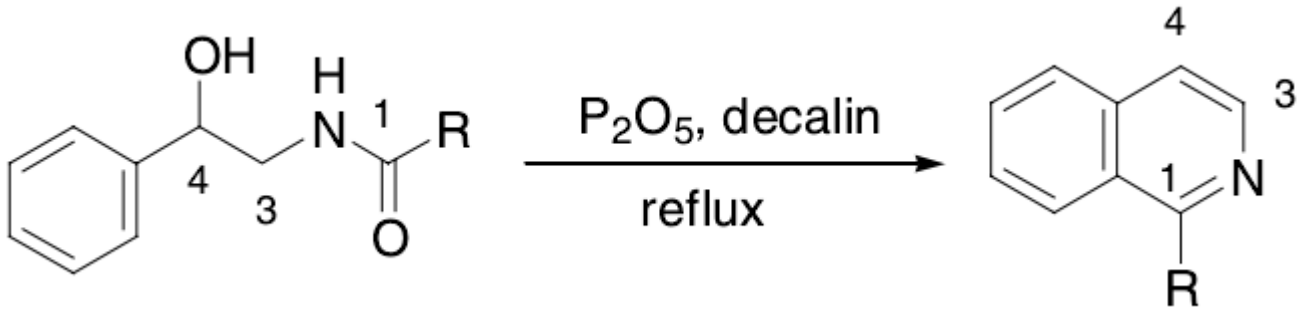


Mechanism:

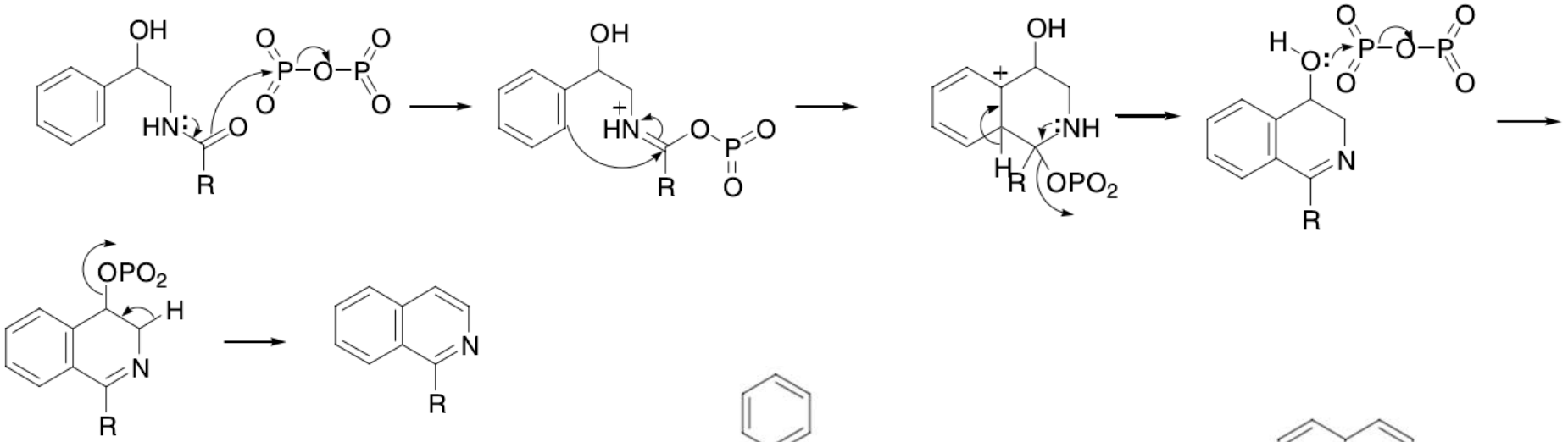


Pictet–Gams isoquinoline synthesis

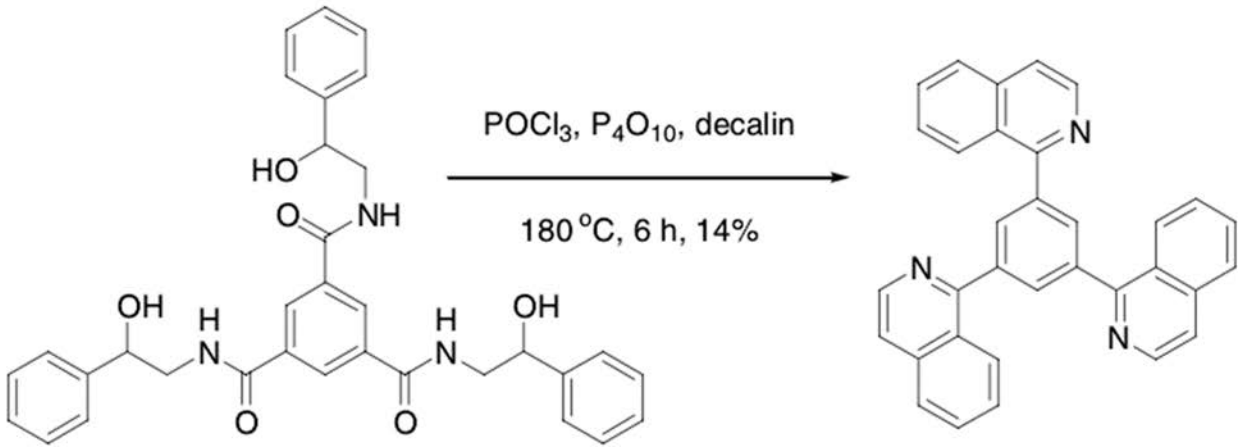
1909



Mechanism:

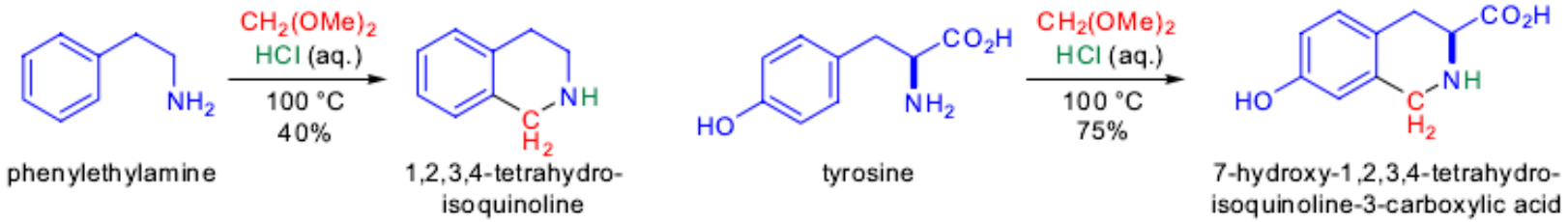


Synthetic Applications:



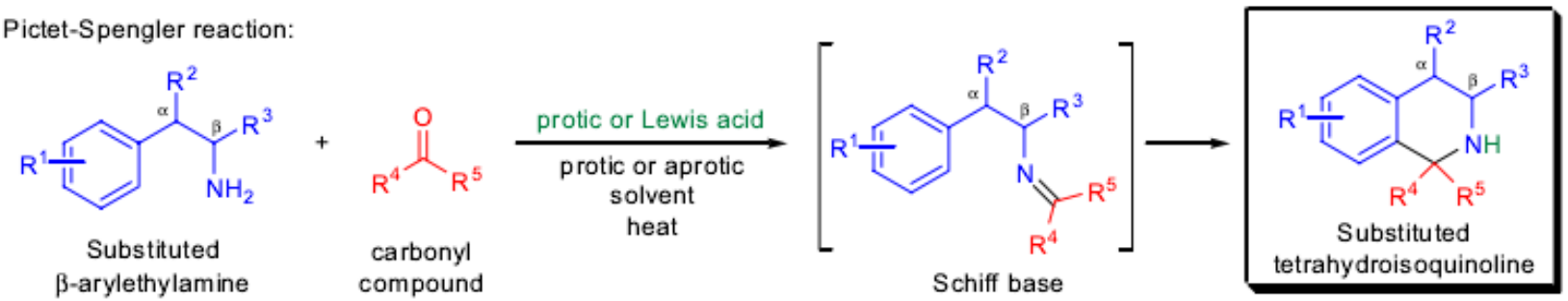
Pictet-spengler Tetrahydroisoquinoline Synthesis

Pictet & Spengler (1911):



phenylethylamine — 1,2,3,4-tetrahydro-isoquinoline — tyrosine — 7-hydroxy-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid

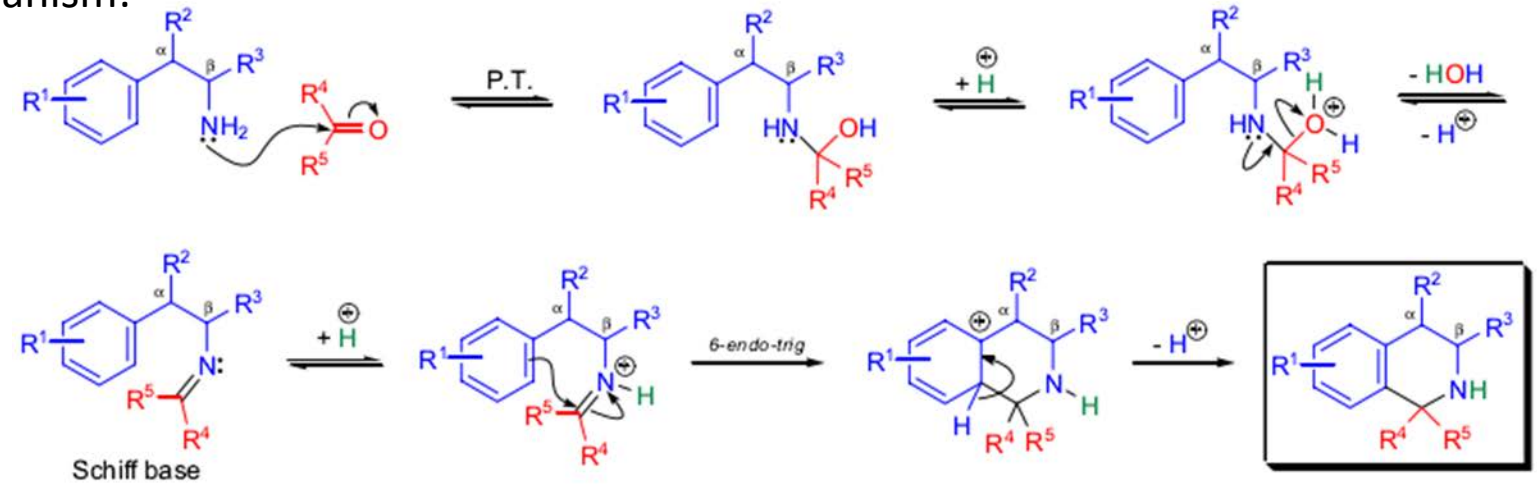
Pictet-Spengler reaction:



Substituted β-arylethylamine — carbonyl compound

R^1 = H, alkyl , aryl, *O*-alkyl, usually an electron-donating group (EDG); R^{2-3} = H, alkyl ,aryl; R^{4-5} = H, alkyl ,aryl; protic acid: HCl, H_2SO_4, TFA, silica gel; Lewis acid: $BF_3{\cdot}OEt_2$

Mechanism:



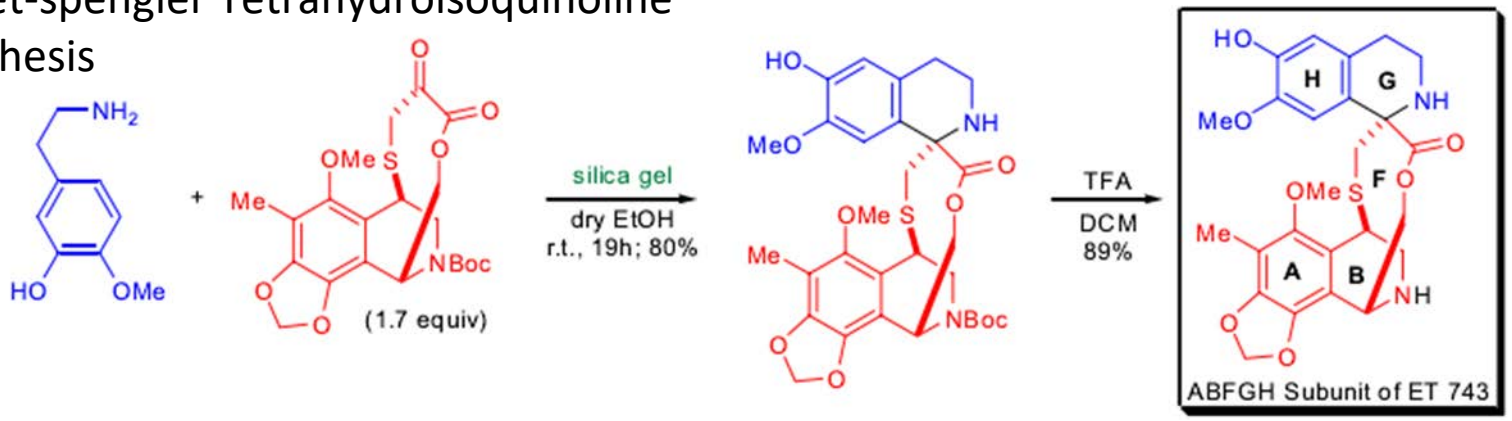
features:

1) only β-arylethylamines with electron-donating substituents afford high yields;
2) the carbonyl compound can be an aldehyde or a ketone or any acid-labile surrogate;
3) the most frequently used aldehyde is formaldehyde or its dimethyl acetal;
4) the number of electron-donating groups on the aromatic ring influences the ease of the reaction, and, for example, the presence of two alkoxy groups allows the Pictet-Spengler reaction to proceed under physiological conditions (this is important in the biosynthesis of alkaloids);
5) the reaction is usually carried out with a slight excess of the carbonyl compound (to ensure the complete consumption of the amine) in either protic or aprotic medium;

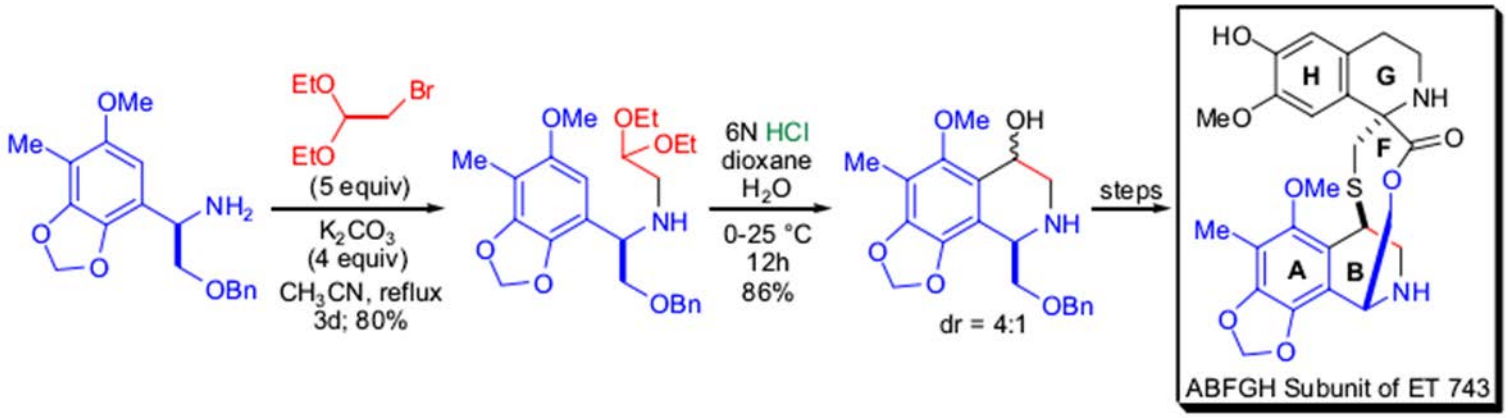
6) since the reaction goes through the intermediacy of a Schiff base, the Schiff base can be prepared separately and subjected to a protic or Lewis acid to afford the cyclized tetrahydroisoquinoline product.

Synthetic Applications:

Pictet-spengler Tetrahydroisoquinoline Synthesis

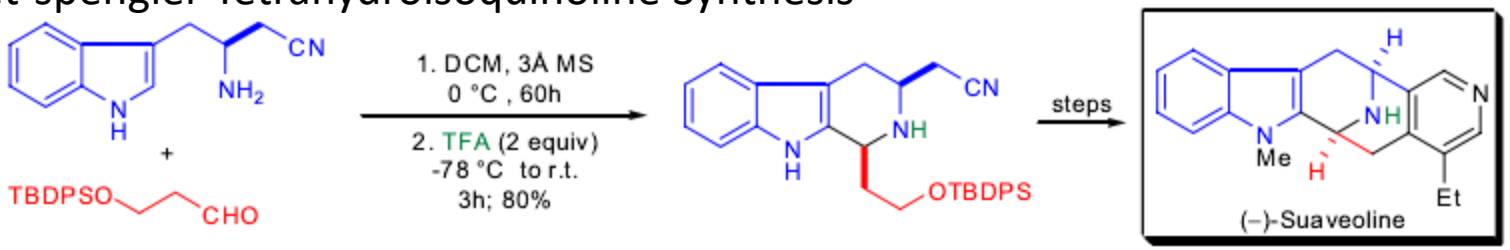


Bobbitt modified Pomeranz-Fritsch Isoquinoline Synthesis



Zhou, B., Guo, J., Danishefsky, S. J. Studies Directed to the Total Synthesis of ET 743 and Analogues Thereof: An Expeditious Route to the ABFGH Subunit. Org. Lett. 2002, 4, 43-46.

Pictet-spengler Tetrahydroisoquinoline Synthesis



Bischler-Napieralski Isoquinoline Synthesis