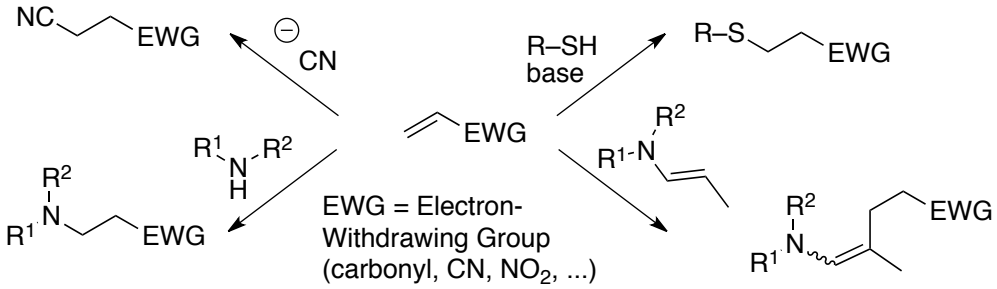
CHEM 330

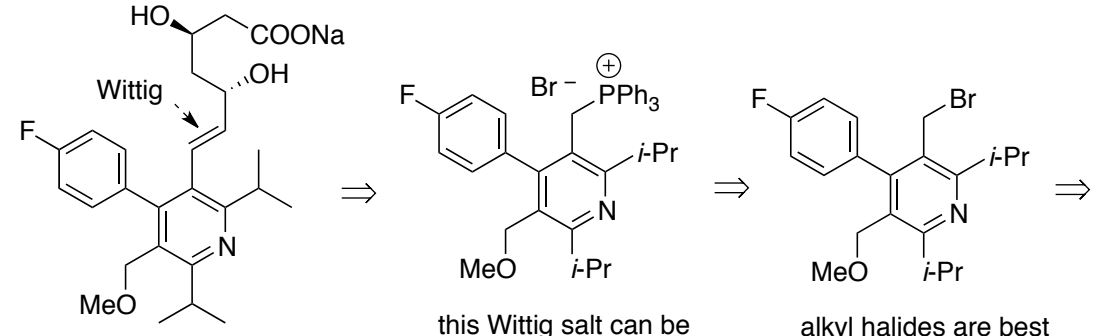
Topics Discussed on Oct. 28

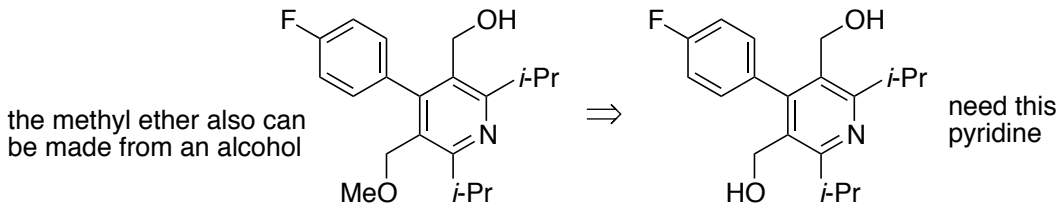
Facile 1,4-addition of weakly basic nucleophiles like cyanide ion (pKa ≈ 10), primary and secondary amines (pKa ≈ 10-12), enamines, sulfur nucleophiles (pKa ≈ 5-10) etc.:



Importance of aldol-dehydration and conjugate addition reactions in contemporary synthetic organic and heterocyclic chemistry

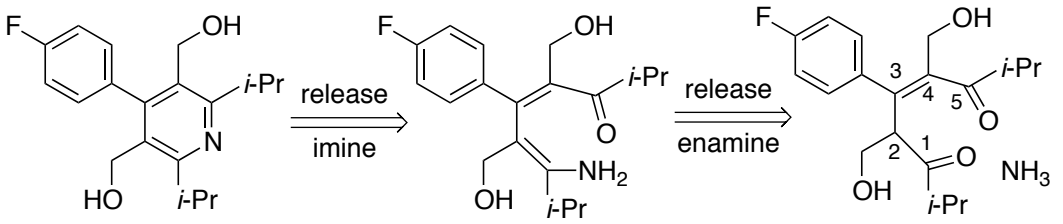
Application: industrial synthesis of cerivastatin (formerly used cholesterol-lowering drug)





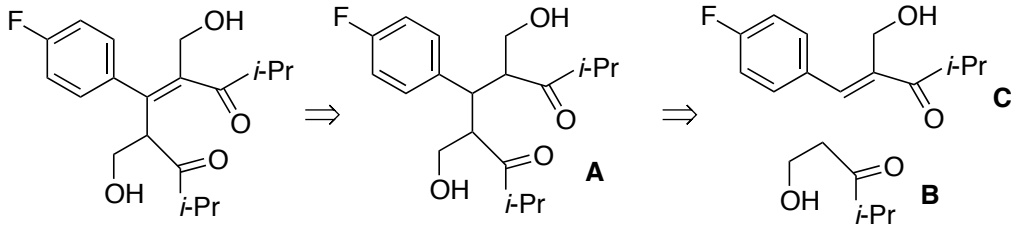
Retrosynthetic analysis of the pyridine required to make cerivastatin

> The logic presented on Sept 28 suggests that the requisite pyridine will be available from a precursor obtained by releasing the imino- and enamino-linkages:

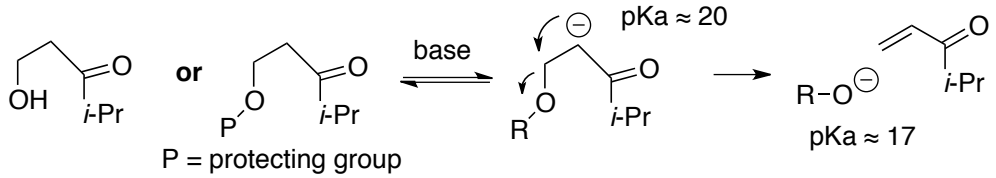


a 1,5-dicarbonyl compound . . .

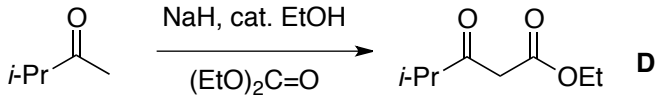
Whereas 1,5-dicarbonyl compounds are generally available by Michael chemistry, the one above is **not** directly accessible by such a method, because of the presence of a double bond between carbons 3 and 4. This double bond could be introduced *after* creating the molecular framework, using any of a number of methods. A reduced form of the above, compound **A**, is available by the Michael union of fragments **B** and **C:**



Problem: the conversion of ketone **B**, or an *O*-protected form thereof, into an enolate, would cause a thermodynamically favorable expulsion of the β-oxygen functionality:



Therefore, it is best to use a 1,3-dicarbonyl equivalent of **B**, for instance β-ketoester **D**, which is readily prepared from inexpensive methyl isopropyl ketone by cross-Claisen reaction with diethyl carbonate:

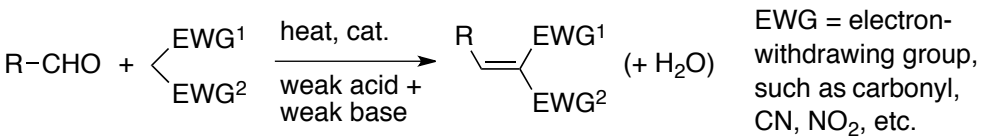


D

Compound **D** produces a stabilized enolate, which, relative to the enolate of an ordinary ketone: (i) can be prepared under milder conditions; (ii) does not require as stringent a control of reaction parameters (inert atmosphere, rigorously dry solvents, etc.); (iii) is quite competent as a Michael donor.

Problem: whereas in theory compound **C** could be made by an aldol-dehydration sequence from 4-fuorobenzaldehyde and ketone **B**, the latter cannot be converted into a well-behaved enolate. Solution: use active methylene compound **D** instead …

The **Knoevenagel reaction**: and aldol-dehydration sequence that involves the union of an aldehyde (sometimes a ketone) with an active methylene compound under simultaneous catalysis by a weak base and a weak acid; e.g. an amine + acetic acid (dual catalysis):

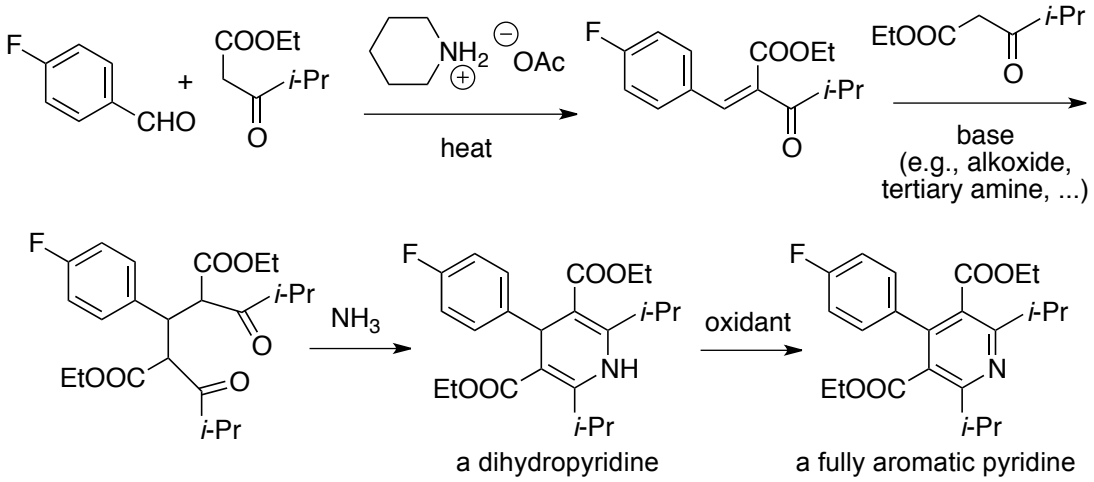


Knoevenagel products as powerful Michael acceptors, due to stabilization of incipient enolates by two EWG's

Widespread application of Knoevenagel products as building blocks for the synthesis of more complex carbon frameworks

Possible assembly of the pyridine fragment of cerivastatin:

Method 1: (1) Knoevenagel, (2) Michael, (3) NH_3, (4) oxidation:



Common presence of dihydropyridine of the above type in many heart drugs