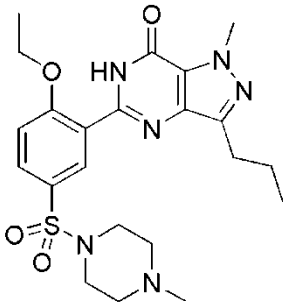
Name (Print)_____

ID#_____

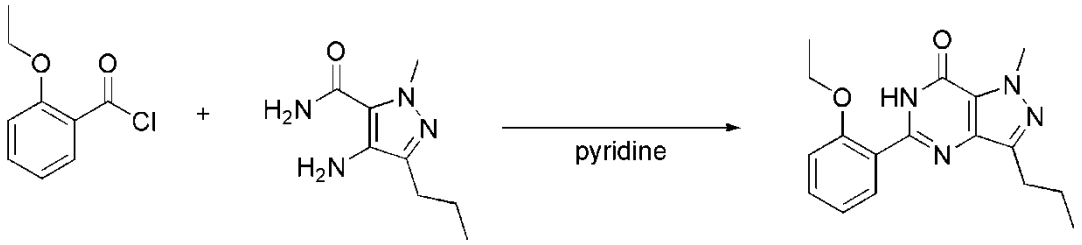
Group #_____

PS #8 – Condensation Chemistry for the Synthesis of Heterocycles

Part A) In 1998 Pfizer was searching for a heart medication and discovered Viagra, a potent PDE 5 inhibitor. The core of the drug contains a pyrazole fused to a pyrimidine ring which gives rise to a bicyclic aromatic **heterocycle**. Condensation of an acid chloride with an amide/amine bis-functionalized pyrazole ring generates the desired pyrimidine ring. Working together, propose a reasonable mechanism for this ring formation. *Note that nucleophilic attack of the nitrogen atom of one amide on the carbonyl of another amide would be unlikely to occur unless the product were thermodynamically favorable, ie. an aromatic heterocycle!*

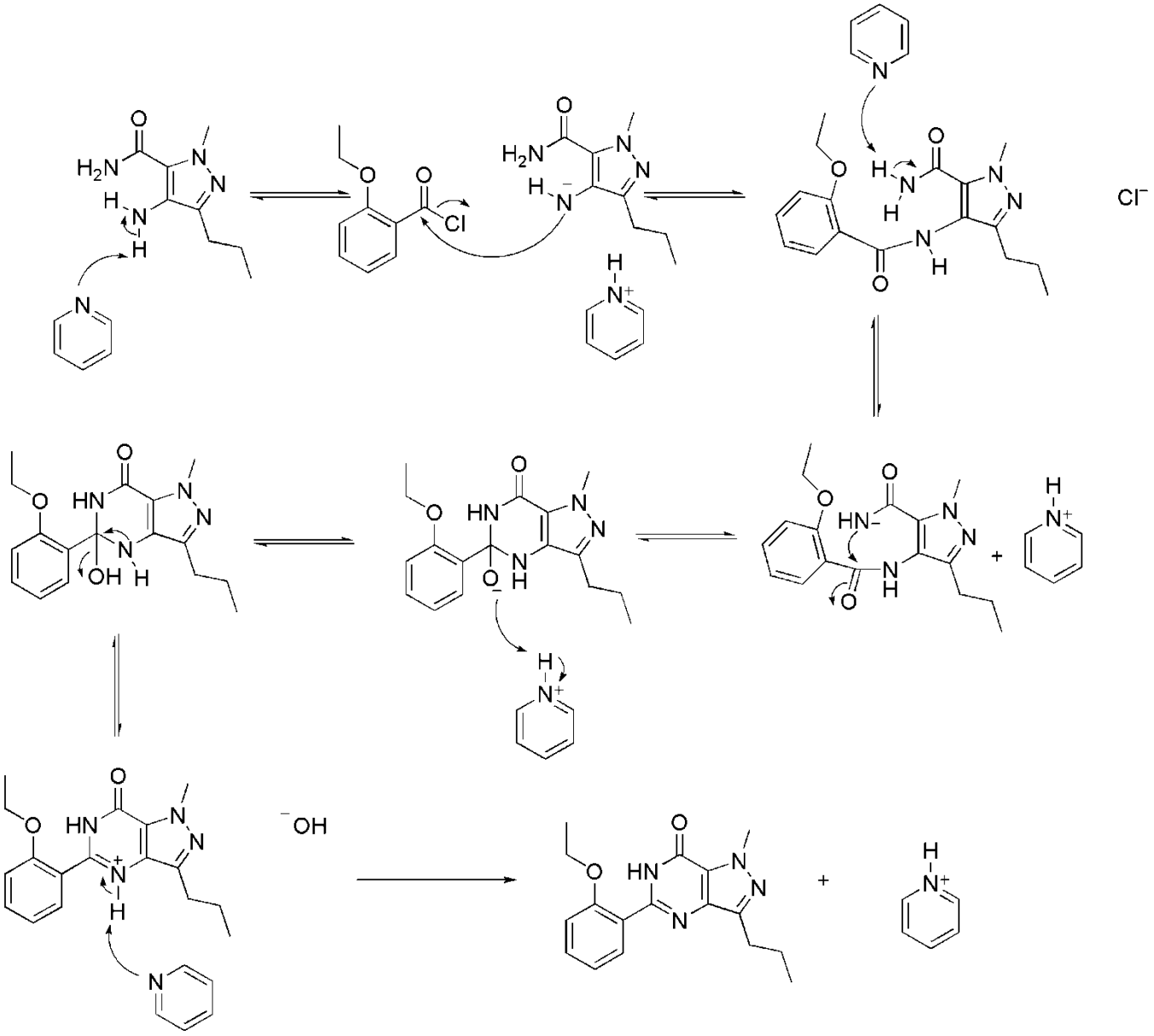


Viagra; Pfizer, 1998

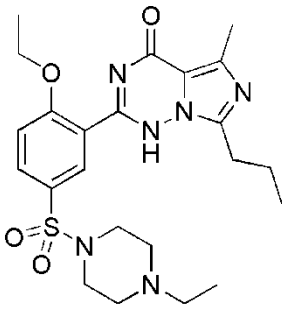


Note: The amine (and not the amide!) is the most nucleophilic NH_2.

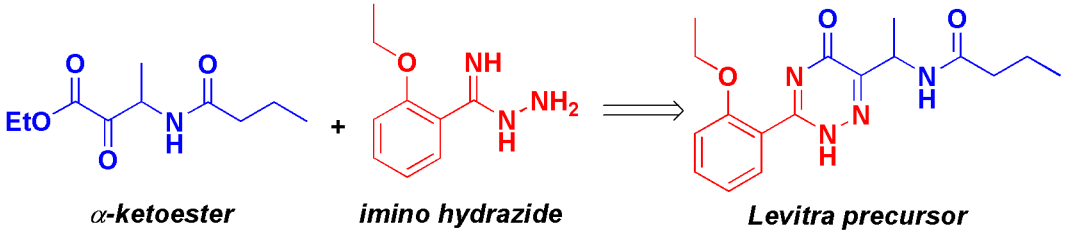
The amine is much more acidic than you might expect as its conjugate base is stabilized through resonance.

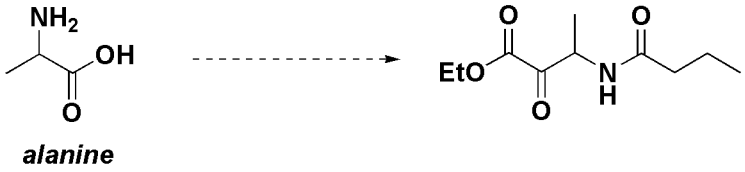


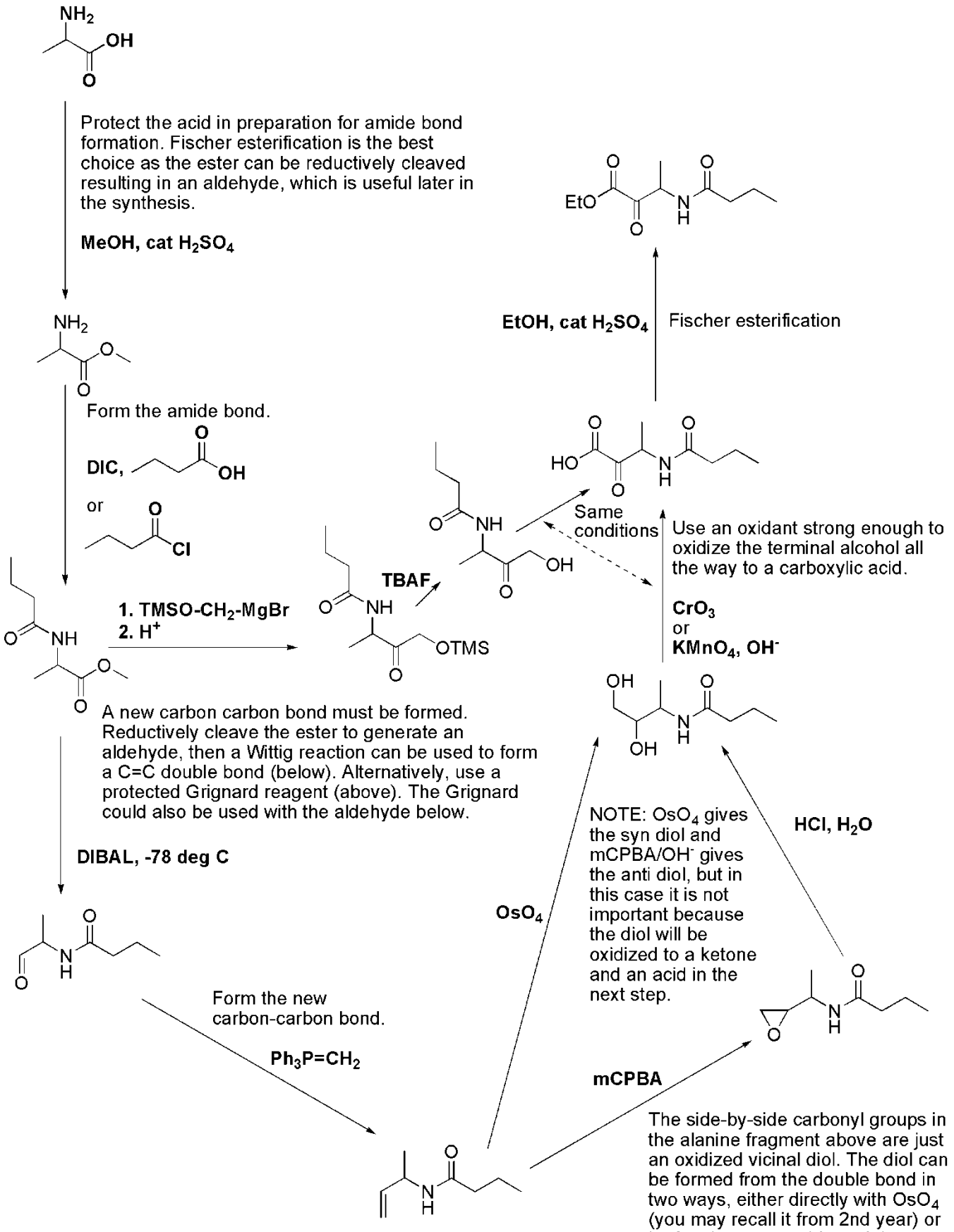
Part B) In 2001, Bayer (in competition with Pfizer) began clinical trials with Levitra (Vardenafil-hydrochloride). It is structurally very similar to Viagra, however, Bayer was clever and moved one of the nitrogen atoms in the heterocyclic core to get around the Viagra patent owned by Pfizer. Condensation of an imido hydrazide and an α–ketoester will form part of the heterocyclic core. As a group, come up with a reasonable synthesis of the **α–ketoester** starting from **alanine** using any additional reagents you require.



Levitra; Bayer, 2001






Protect the acid in preparation for amide bond formation. Fischer esterification is the best choice as the ester can be reductively cleaved resulting in an aldehyde, which is useful later in the synthesis.
MeOH, cat H2SO4
Form the amide bond.
DIC,
or
1. TMSO-CH2-MgBr
2. H+
TBAF
A new carbon carbon bond must be formed. Reductively cleave the ester to generate an aldehyde, then a Wittig reaction can be used to form a C=C double bond (below). Alternatively, use a protected Grignard reagent (above). The Grignard could also be used with the aldehyde below.
DIBAL, -78 deg C
Form the new carbon-carbon bond.
Ph3P=CH2
OsO4
NOTE: OsO4 gives the syn diol and mCPBA/OH- gives the anti diol, but in this case it is not important because the diol will be oxidized to a ketone and an acid in the next step.
mCPBA
HCl, H2O
Same conditions
CrO3
or
KMnO4, OH-
Use an oxidant strong enough to oxidize the terminal alcohol all the way to a carboxylic acid.
EtOH, cat H2SO4
Fischer esterification
The side-by-side carbonyl groups in the alanine fragment above are just an oxidized vicinal diol. The diol can be formed from the double bond in two ways, either directly with OsO4 (you may recall it from 2nd year) or by forming an epoxide and then cleaving it open with a hydroxyl nucleophile.