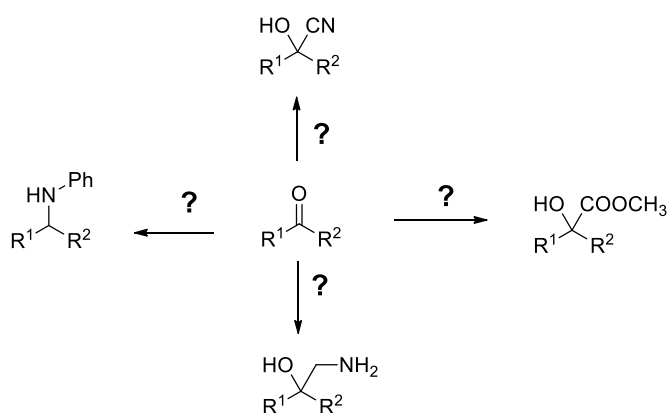
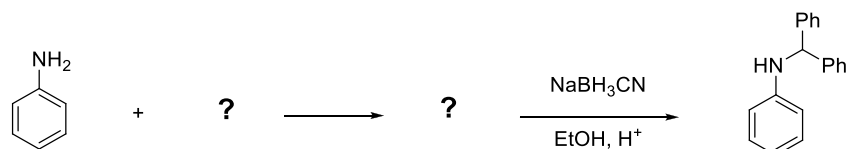


Solutions to Problems – Set 5 : Carbonyl compounds (part 2)

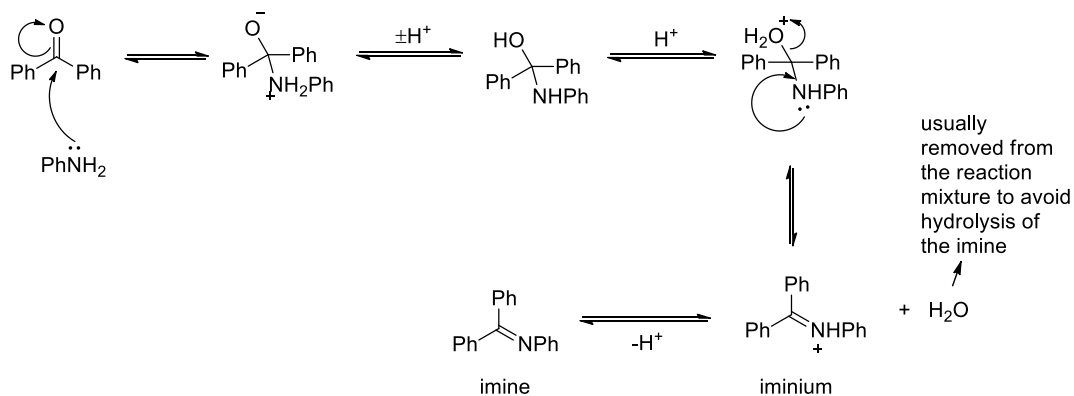
Problem 1

Find the missing compounds and conditions for the following transformations (may include more than one step) and provide the mechanism for each transformation.

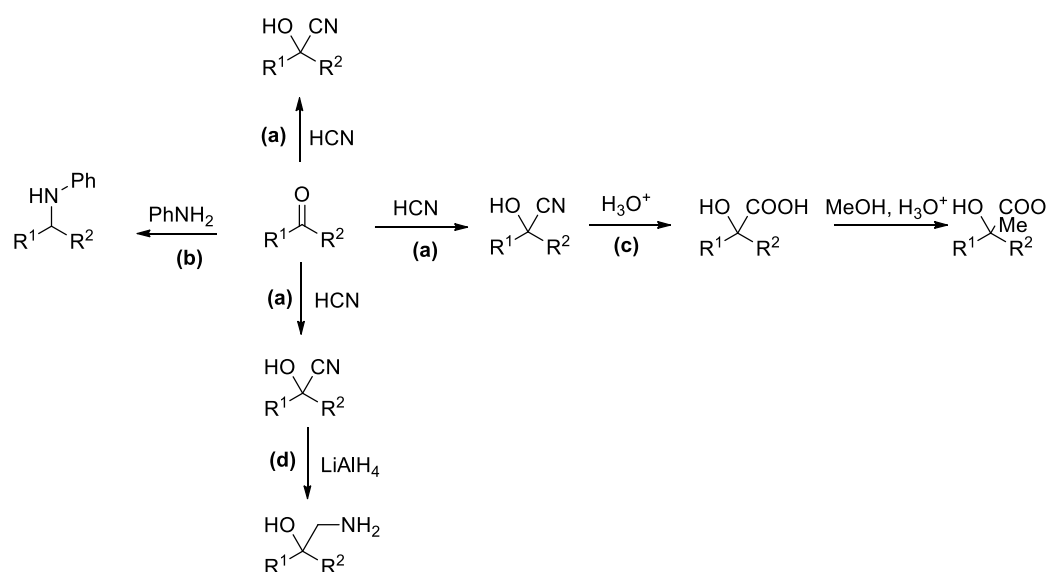


Solution

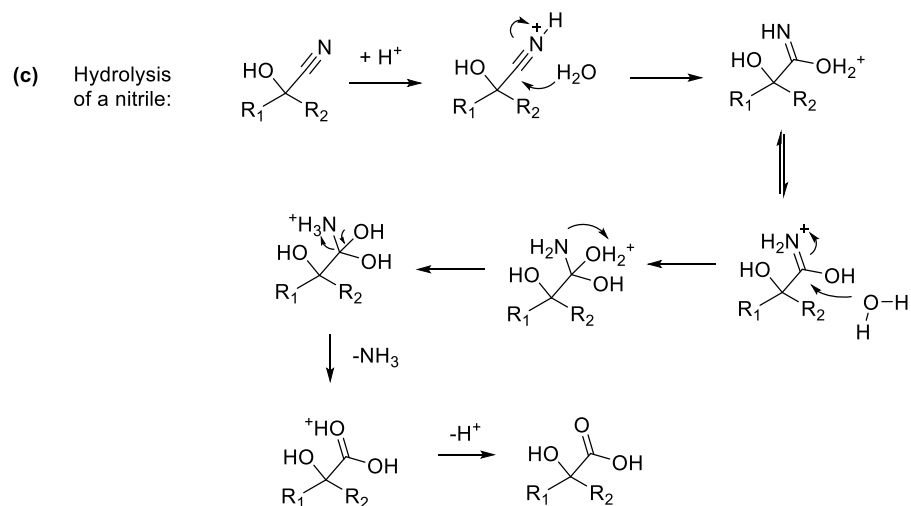
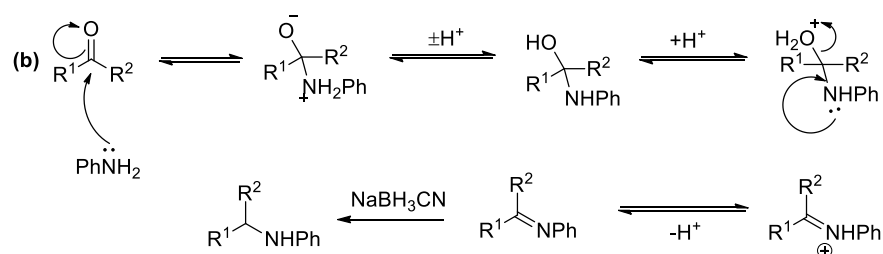
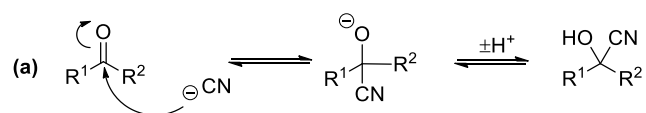
1) The proton required comes from the medium (for example from the iminium to imine step):

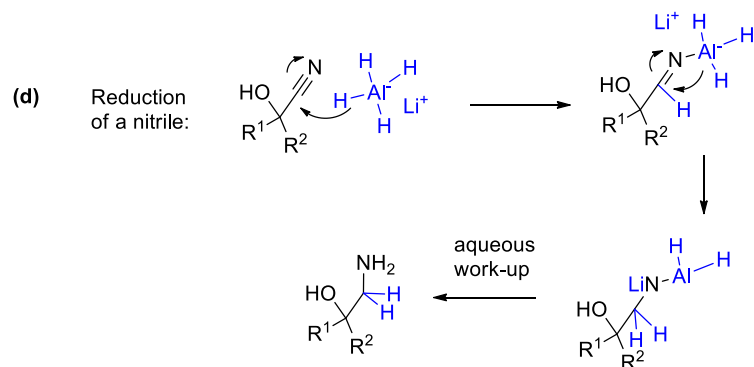


2) Transformations:



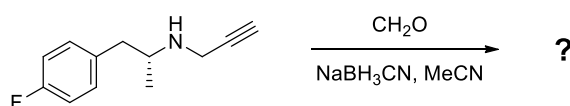
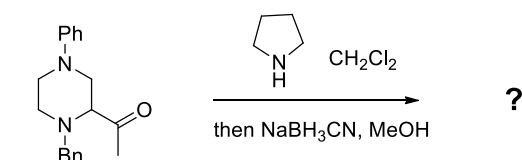
Mechanisms:



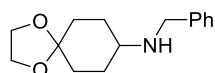


Problem 2

Find the products for the following reductive amination reactions and draw the mechanism for each:

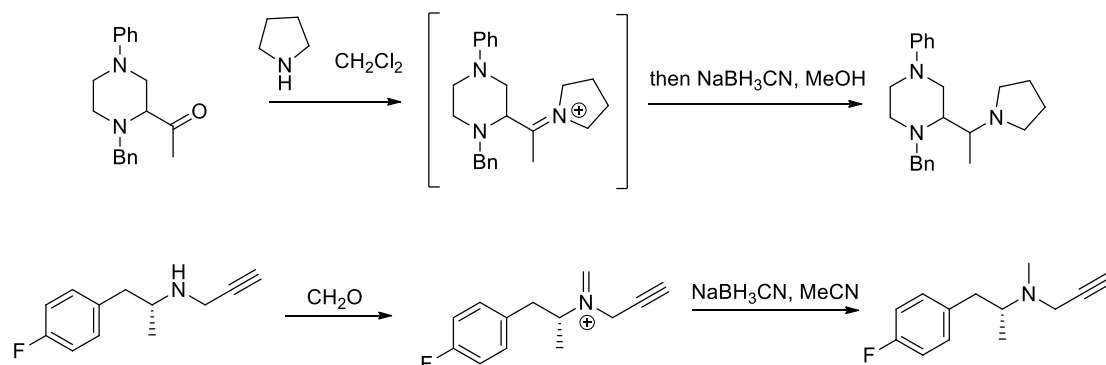


Suggest the transformations to synthesize the following compound from simple starting materials of your choice:

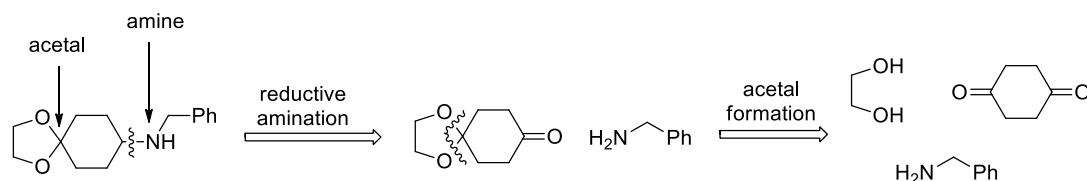


Solution

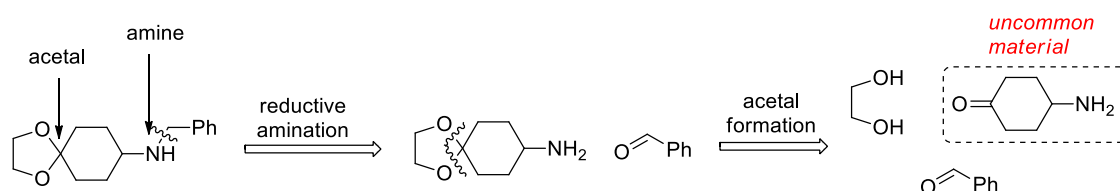
Amine reacts with ketone or aldehyde to form iminium intermediate which is readily reduced by NaBH_3CN to tertiary amine.



Retrosynthesis:

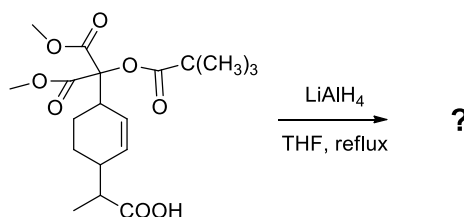
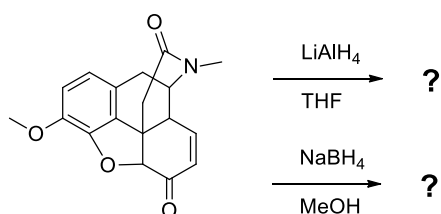


An alternative disconnection to form amine bond by reductive amination can be considered. However, this way requires 4-aminocyclohexanone which is uncommon and unstable (can self-condense) as a starting material. So this is not the best approach.



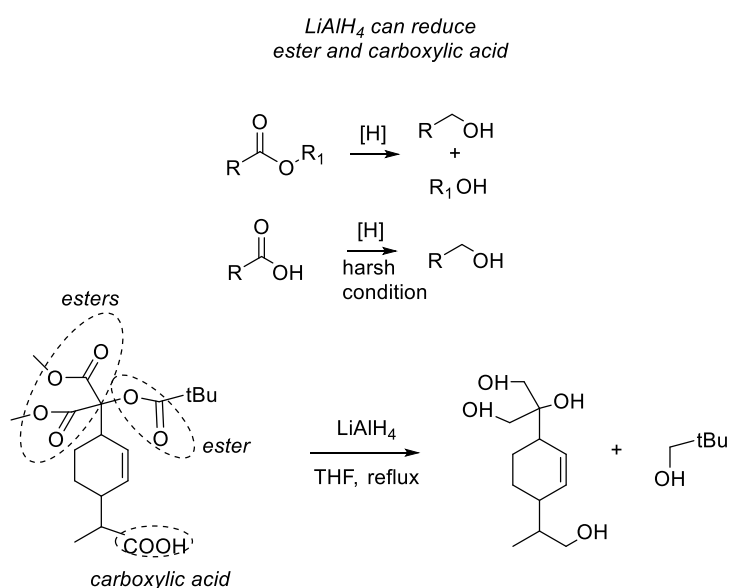
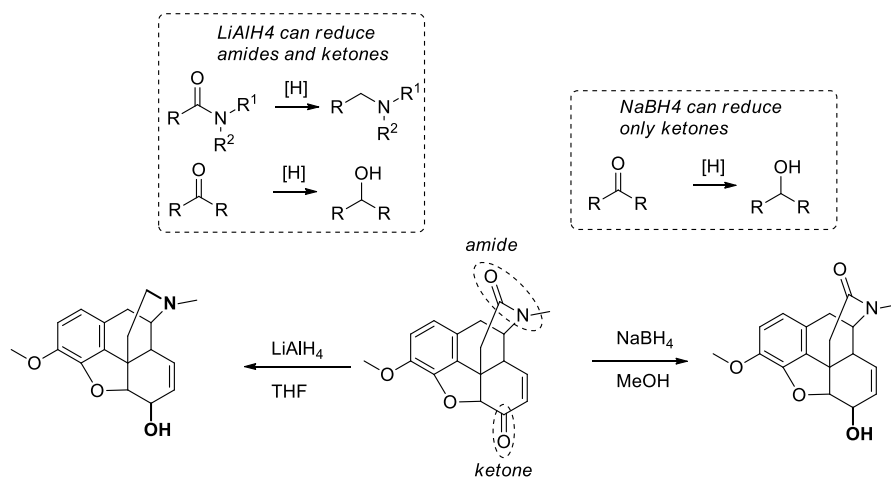
Problem 3

Find the structure of the products for the following reduction reactions:

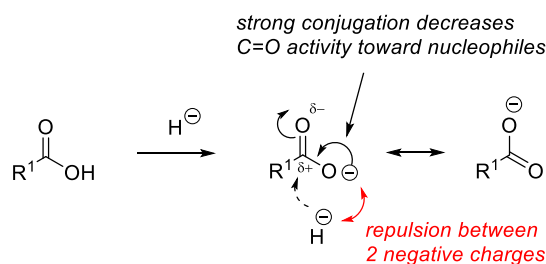


Solution

To do this type of exercises, need to identify the functional groups existing in the molecule.

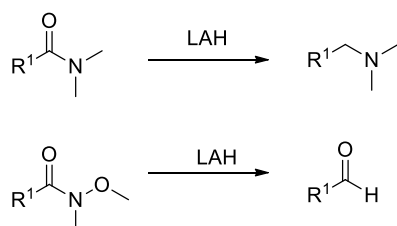


Notes: Reduction of carboxylic acids by LiAlH₄ is very difficult compared to esters, amides or aldehydes, ketones. It is because LiAlH₄ can instantly react with carboxylic acid to form carboxylate, of which carbonyl is by far less reactive than other carbonyl groups. Furthermore, negatively charged carboxylate is not favorable for approaching of other negatively-charged particles such as hydrides. Harsh conditions like high temperature is necessary to overcome this drawback.



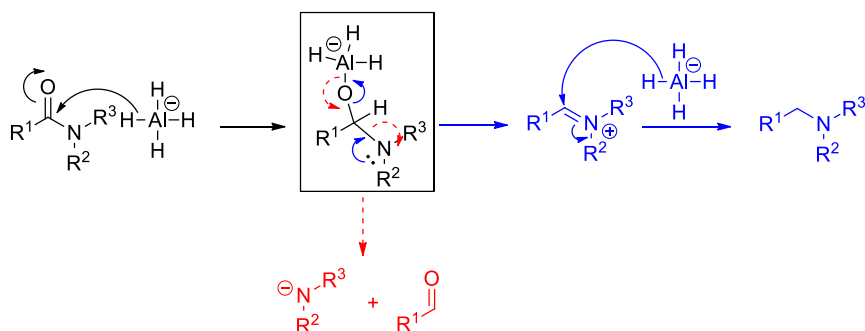
Problem 4

Based on the leaving group property, give an explanation for the reductions of these different amides:

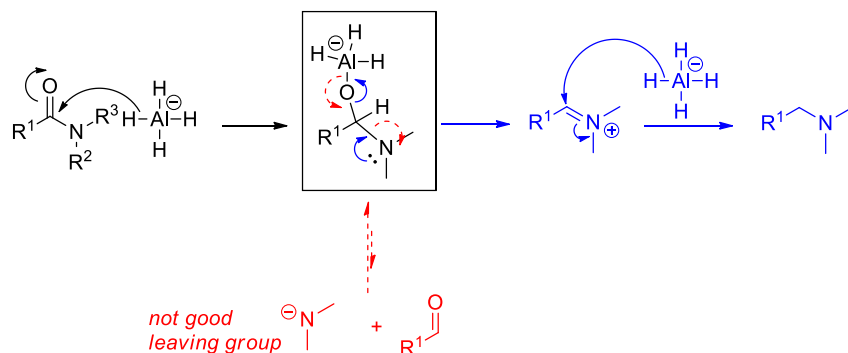


Solution

General mechanism of reduction amides is shown below. First step is hydride transfer from LAH to C=O to form an intermediate. In principle this intermediate can undergo 2 different fragmentations (demonstrated in blue and red pathways).



For normal amides, such as N,N-dimethyl amides, they can proceed through blue pathway. High electron-density on nitrogen atom due to inductive effects of alkyl groups favors electron migration from nitrogen to carbon, leading remove of OAlH_3 anion. In contrast, red fragmentation which eliminates amide anion – a highly active nucleophile (than hydride) is not favorable.



For N,N-methylmethoxyamides = Weinreb amides, oxygen atom decreases dramatically electro-density on nitrogen so that blue migration is not favorable. Also, both oxygen atoms coordinate the aluminium to make a complex that is stable in the reaction mixture. Once the reaction is complete, addition of water during the work-up process breaks the aluminium complex to release the unstable hemiaminal, which fragments to deliver the aldehyde as product.

