

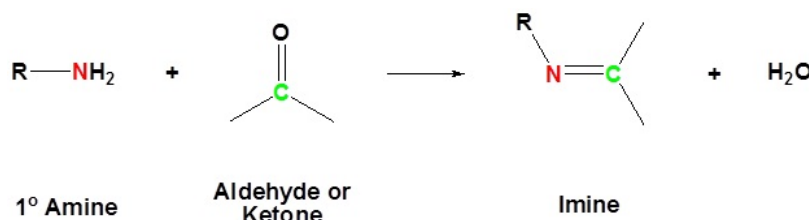
20.6: REACTIONS OF AMINES

AMINES AS NUCLEOPHILES

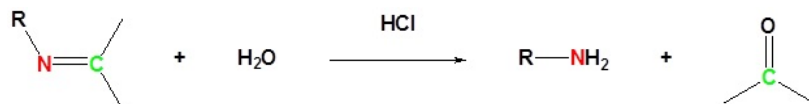
Amines seldom serve as leaving groups in nucleophilic substitution or base-catalyzed elimination reactions. Indeed, they are even less effective in this role than are hydroxyl and alkoxy groups. While we will see another section that it is possible to coax the amine to serve as a leaving group. As weak bases, amines are good nucleophiles.

AMINES AND CARBONYLS

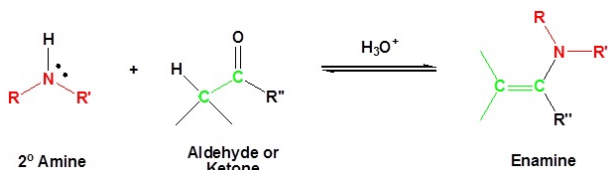
The reaction of aldehydes and ketones with ammonia or 1°-amines forms imine derivatives, also known as Schiff bases (compounds having a C=N function). Water is eliminated in the reaction, which is acid-catalyzed and reversible in the same sense as acetal formation. The pH for reactions which form imine compounds must be carefully controlled. The rate at which these imine compounds are formed is generally greatest near a pH of 5, and drops at higher and lower pH's. At high pH there will not be enough acid to protonate the OH in the intermediate to allow for removal as H₂O. At low pH most of the amine reactant will be tied up as its ammonium conjugate acid and will become non-nucleophilic.



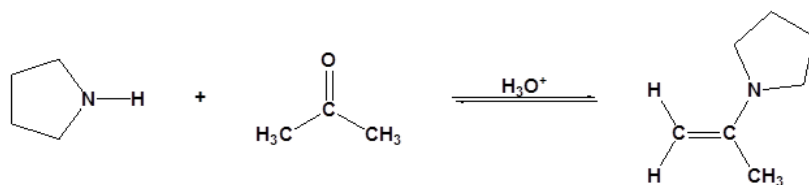
Imine formation is reversible. Imines can be hydrolyzed back to the corresponding primary amine under acidic aqueous conditions.



Most aldehydes and ketones react with 2°-amines to give products known as **enamines**.

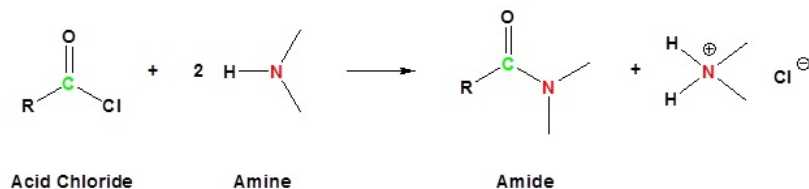


It should be noted that, like acetal and imine formation, these are acid-catalyzed reversible reactions in which water is lost. Consequently, enamines are easily converted back to their carbonyl precursors by acid-catalyzed hydrolysis.

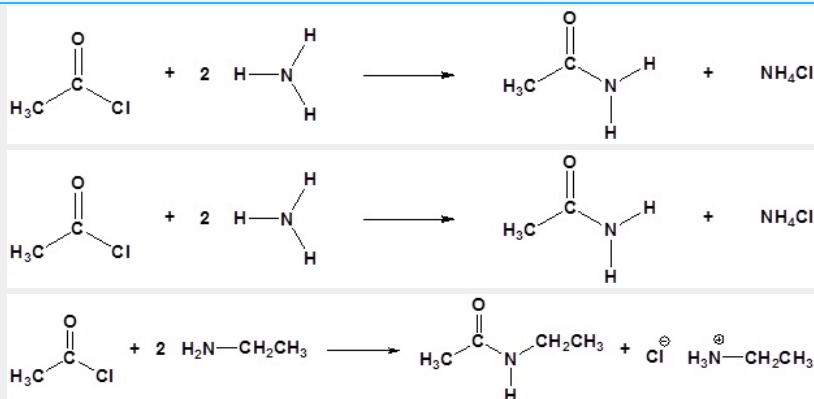


AMINES AND ACID CHLORIDES

Acid chlorides react with ammonia, 1° amines and 2° amines to form amides.

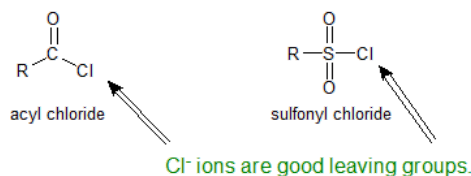


Examples:

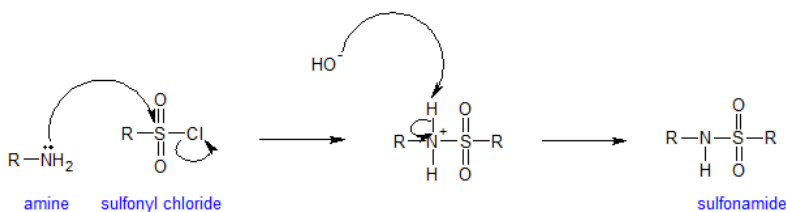


AMINES AND SULFONYL CHLORIDE

The sulfonyl group is the sulfur-analog to the carbonyl group. Both groups contain an electrophilic carbonyl carbon with chloride as an excellent leaving group. Because sulfur is a third shell element it can form "expanded octets".



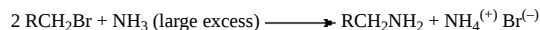
Amines react with sulfonyl groups to form sulfonamides. Sulfonamides are used as antimicrobial agents therapeutically and called sulfa drugs. The reaction to form sulfonamides occurs under alkaline conditions to keep the amine nucleophilic. Any time amines are present in an aqueous solution, measurable hydroxide is present. The mechanism for the sulfonation reaction is analogous to the acylation mechanism as is shown below.



The end of this chapter includes some additional information on sulfonamides.

ALKYLATIONS

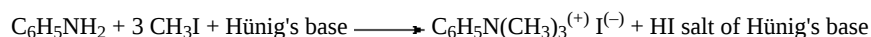
IT IS INSTRUCTIVE TO EXAMINE NITROGEN SUBSTITUTION REACTIONS USING COMMON ALKYL HALIDES AS THE ELECTROPHILES. THUS, REACTION OF A PRIMARY ALKYL BROMIDE WITH A LARGE EXCESS OF AMMONIA YIELDS THE CORRESPONDING 1°-AMINE, PRESUMABLY BY AN S_N2 MECHANISM. THE HYDROGEN BROMIDE PRODUCED IN THE REACTION COMBINES WITH SOME OF THE EXCESS AMMONIA, GIVING AMMONIUM BROMIDE AS A BY-PRODUCT. WATER DOES NOT NORMALLY REACT WITH 1°-ALKYL HALIDES TO GIVE ALCOHOLS, SO THE ENHANCED NUCLEOPHILICITY OF NITROGEN RELATIVE TO OXYGEN IS CLEARLY DEMONSTRATED.



It follows that simple amines should also be more nucleophilic than their alcohol or ether equivalents. If, for example, we wish to carry out an S_N2 reaction of an alcohol with an alkyl halide to produce an ether (the Williamson synthesis), it is necessary to convert the weakly nucleophilic alcohol to its more nucleophilic conjugate base for the reaction to occur. In contrast, amines react with alkyl halides directly to give N-alkylated products. Since this reaction produces HBr as a co-product, hydrobromide salts of the alkylated amine or unreacted starting amine (in equilibrium) will also be formed.



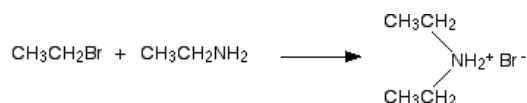
Unfortunately, the direct alkylation of 1° or 2°-amines to give a more substituted product does not proceed cleanly. If a 1:1 ratio of amine to alkyl halide is used, only 50% of the amine will react because the remaining amine will be tied up as an ammonium halide salt (remember that one equivalent of the strong acid HX is produced). If a 2:1 ratio of amine to alkylating agent is used, as in the above equation, the HX issue is solved, but another problem arises. Both the starting amine and the product amine are nucleophiles. Consequently, once the reaction has started, the product amine competes with the starting material in the later stages of alkylation, and some higher alkylated products are also formed. Even 3°-amines may be alkylated to form quaternary (4°) ammonium salts. When tetraalkyl ammonium salts are desired, as shown in the following example, Hünig's base may be used to scavenge the HI produced in the three S_N2 reactions. Steric hindrance prevents this 3°-amine (Hünig's base) from being methylated.



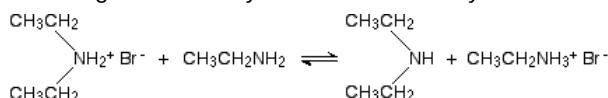
You get a complicated series of reactions on heating primary amines with halogenoalkanes to give a mixture of products - probably one of the most confusing sets of reactions you will meet at this level. The products of the reactions include secondary and tertiary amines and their salts, and quaternary ammonium salts.

MAKING SECONDARY AMINES AND THEIR SALTS

In the first stage of the reaction, you get the salt of a secondary amine formed. For example if you started with ethylamine and bromoethane, you would get diethylammonium bromide



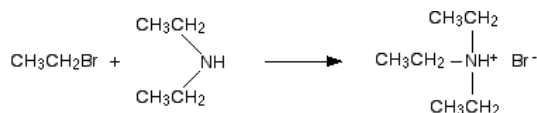
In the presence of excess ethylamine in the mixture, there is the possibility of a reversible reaction. The ethylamine removes a hydrogen from the diethylammonium ion to give free diethylamine - a secondary amine.



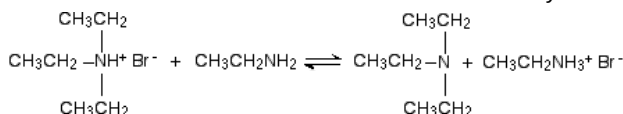
MAKING TERTIARY AMINES AND THEIR SALTS

But it doesn't stop here! The diethylamine also reacts with bromoethane - in the same two stages as before. This is where the reaction would start if you reacted a secondary amine with a halogenoalkane.

In the first stage, you get triethylammonium bromide.



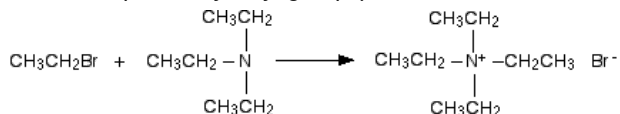
There is again the possibility of a reversible reaction between this salt and excess ethylamine in the mixture.



The ethylamine removes a hydrogen ion from the triethylammonium ion to leave a tertiary amine - triethylamine.

MAKING A QUATERNARY AMMONIUM SALT

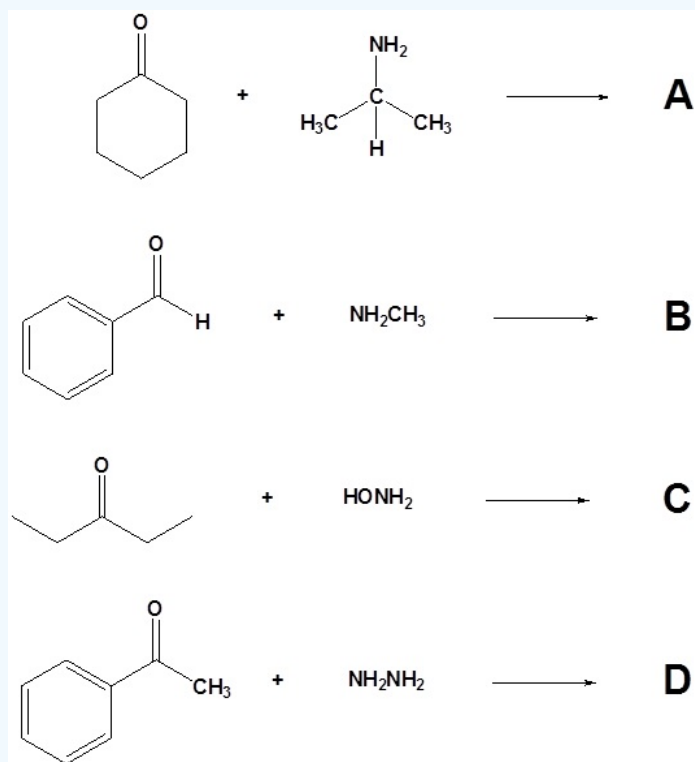
The final stage! The triethylamine reacts with bromoethane to give tetraethylammonium bromide - a quaternary ammonium salt (one in which all four hydrogens have been replaced by alkyl groups).



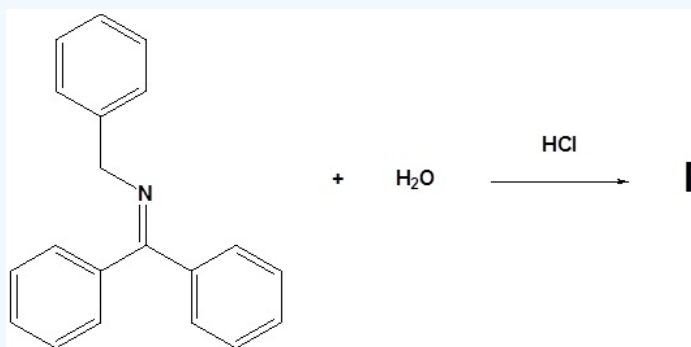
This time there isn't any hydrogen left on the nitrogen to be removed. The reaction stops here.

EXERCISE

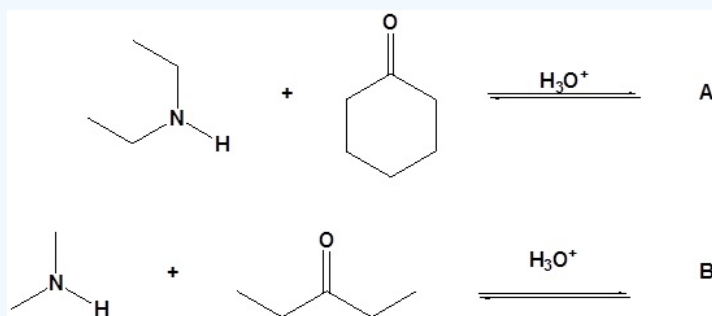
10. Draw the products of the following reactions.



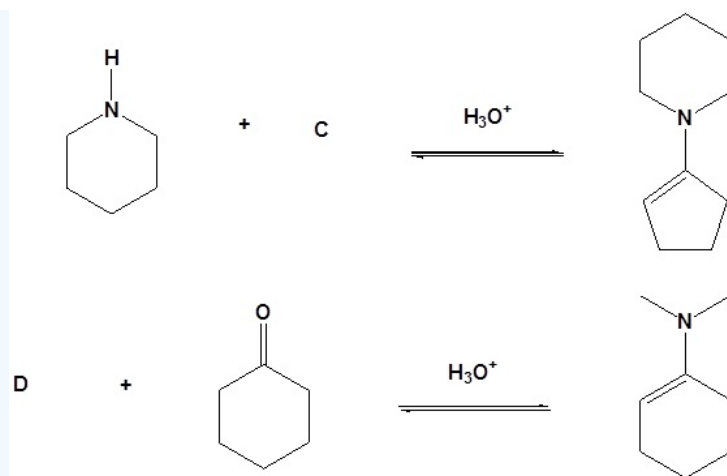
11. Draw the structure of the reactant needed to produce the indicated product.



12. Draw the products for the following reactions.

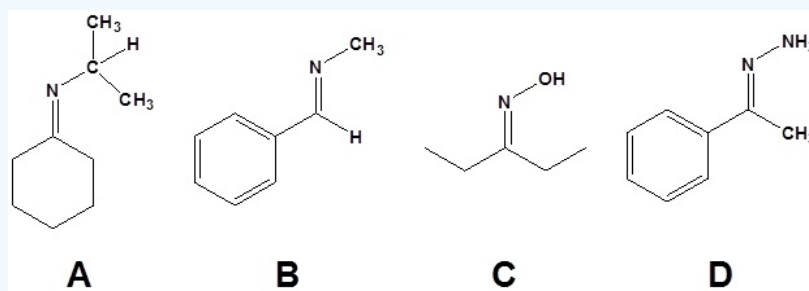


13. Draw the missing reactant to complete each reaction below.

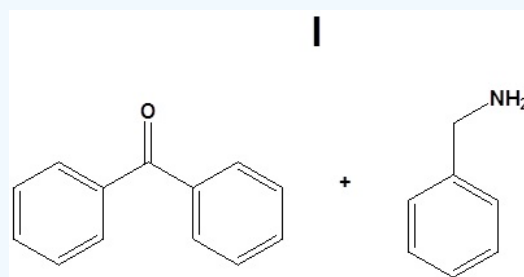


Answer

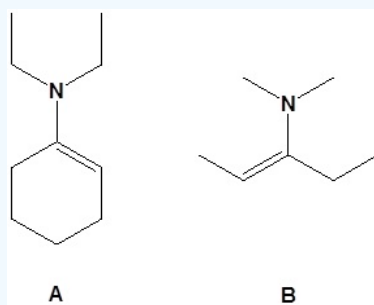
10.



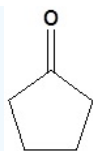
11.



12.



13.



C



D

CONTRIBUTORS AND ATTRIBUTIONS

- [Dr. Dietmar Kennepohl](#) FCIC (Professor of Chemistry, [Athabasca University](#))
- Prof. Steven Farmer ([Sonoma State University](#))
- William Reusch, Professor Emeritus ([Michigan State U.](#)), [Virtual Textbook of Organic Chemistry](#)

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