MIT Organic Chemistry 5.13
Drill Problems – Organic Structure Elucidation & Review *(Solutions)*

BDC

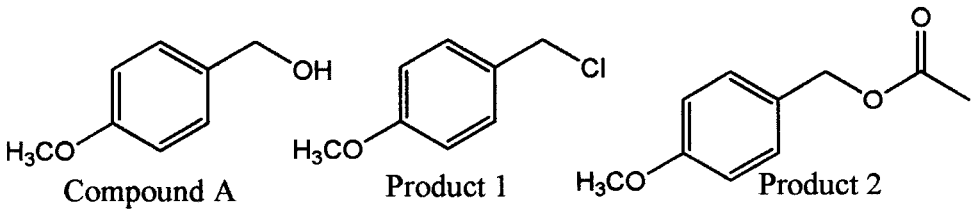
1a. The original sample IR shows most clearly the H-bonded alcohol O-H stretching band centered at ~3350 cm^{-1}. Also visible are key structural elements such as the presence of both sp^2 and sp^3 carbons as revealed by the C-H stretching bands centered at ~3000 cm^{-1}, the "C=C" stretching of an aromatic ring at ~1600 cm^{-1}, and strong C-O stretching bands ranging from 1000 to 1300 cm^{-1}. It might also be noted that the aromatic substitution pattern is *para*, both from careful observation of the overtone/combination bands ranging from 2100 to 1650 cm^{-1} and of the characteristic band at ~815 cm^{-1}. The pair of bands at ~1040 and ~1250 cm^{-1} in particular signify that the C-O stretching band mentioned above results from the alkyl aryl ether functionality.

b. The first experiment performed is an S_N1 reaction between the starting material (an alcohol) and hydrochloric acid, catalyzed by the Lewis acidic zinc chloride. The fact that reaction occurs very slowly at room temperature but proceeds after heating and agitation is evidence that the alcohol is very unlikely to be tertiary or allylic (unless very insoluble in the reagent), but could be secondary or benzylic (the latter due to the decreased solubility in the reagent displayed by even the simplest of these alcohols).

c. Product 1's IR spectrum shows that the compound has lost its alcoholic O-H group, as an alcohol would in such a reaction. No other functional group transformations have occurred. Evidence of the new C-Cl bond of product 1 is not so straightforwardly obtained from an IR spectrum, but C-Cl stretching bands can appear in the fingerprint region ranging from 850 to 650 cm^{-1}. Elemental analysis, on the other hand, cannot provide enough information for determination of a molecular formula at this point, since no definitive information has been given about any heteroatoms already present in the structure.

d. Product 2's IR spectrum shows the absence of the starting material's alcoholic O-H stretching band, and instead we see a strong peak centered at ~1730 cm^{-1} that represents the newly formed C=O bond of the ester. This is in addition to the new strong, relatively broad band centered at ~1240 cm^{-1}, which represents the C-O stretching of the ester functionality. The weak peaks in the hydroxyl/amino region are actually overtone/combination bands of the ester carbonyl group and should **not** be identified as peaks from O-H or N-H vibrations of any kind.

e. Analysis of the mass spectrum should furnish enough information to propose a molecular formula. The molecular ion peak is apparent at m/z 180, which primarily allows the assumption of zero or an even number of nitrogen atoms; zero is a safe assumption at this point since there is no evidence for the presence of any nitrogenous functional group. Also important is the lack of heavy isotope (M+2, M+4, etc.) peaks, allowing the assumption that neither chlorine nor bromine is present. Using the carbon-13 isotope peak (M+1) intensity to calculate roughly the number of carbons present gives 9.3, which will be discover upon calculation to be one too few for the formula to work out nicely, so this will lead to the correct answer of 10 carbons by logical "experimentation." The knowledge that an ester is present in the product as well as the prior discovery of an ether linkage in the structure (which would be carried through the esterification undisturbed) allows an assumption of 3 oxygen atoms, and the formula that gives the best fit for the data is $C_{10}H_{12}O_3$. Calculated IHD is 5, which allows one for the pi bond of the ester and four for the aryl ring. More structural information can be gained by MS fragmentation analysis: elimination of ketene ($H_2C{=}C{=}O$, m/z 42) from the ester leaves the radical cation of *p*-anisyl alcohol at m/z 138; loss of the entire acetyl group gives rise to the base peak at m/z 121; and the prominent series of peaks at m/z 91, 77/78, 65, and 51 belies the presence of a benzylic aromatic system. Mass spectra will not necessarily indicate the correct aromatic substitution pattern, but based on the information given, proposing ortho or meta isomers cannot be ruled out with certainty. The unknown compound A is ***p*-anisyl alcohol** (4-methoxybenzyl alcohol). Product 1 is ***p*-anisyl chloride** (4-methoxybenzyl chloride). Product 2 is ***p*-anisyl acetate** (4-methoxybenzyl acetate). Structures for each are found below.



Compound A Product 1 Product 2

f. Pyridine is added to the reaction mixture in order to trap the HCl that is eliminated from the esterification reaction between the acyl chloride and the alcohol. Were the pyridine absent, the HCl would easily be able to protonate the alcohol and induce the S_N1 pathway discussed above. This would logically result in a mixture of the ester and benzylic chloride products.

2a. The IR spectrum of Compound B shows a prominent carbonyl C=O stretching band at roughly 1680-1690 cm^{-1}; this shifted range allows consideration only of conjugated aldehydes and ketones with any certainty, and given the lack of prominent aldehydic C-H stretching bands from 2900-2680 cm^{-1}, it can be concluded that this compound is indeed a conjugated ketone. The carbonyl combination/overtone bands at >3300 cm^{-1} further justify this decision. Again we see the presence of both sp^2 and sp^3 carbons from the C-H stretching bands centered at ~3000 cm^{-1}. The strong band at ~1600 cm^{-1} represents aromatic ring "C=C" stretching, and the band at ~815 cm^{-1} also hints at *para* substitution on the ring. Overall, it could be concluded that the compound is a ketone whose carbonyl is probably conjugated with an aryl ring (a "phenone"), with saturated carbons also included in the structure.

b. The reaction with 2,4-dinitrophenylhydrazine should confirm that the compound is indeed a ketone of some sort, so one might conclude that reaction with the organomagnesium reagent prepared in the second experiment would both convert the ketone to an alcohol and alkylate it. The IR spectrum validates this proposal, as we now see an unmistakably broad H-bonded alcoholic O-H stretching band centered at ~3350 cm^{-1}, the loss of the carbonyl band, and increased complexity in the range from 1050 cm^{-1} to 1175 cm^{-1} that alludes to formation of a new C-O bond. As there is no reason to consider the presence of other heteroatomic functionality in this product, it is valid to assume only presence of C, H, and O in the structure, with one oxygen likely present. Evaluation of the molecular formula from the given elemental analysis should provide the formula $C_{10}H_{14}O$, which in turn should yield an IHD value of 4, corresponding perfectly with a phenyl ring. Working backward from this product should allow removal of a methyl group (added by the methylmagnesium bromide) and reversion of the alcohol to its original ketone state. Unless the aromatic substitution pattern as revealed by the original IR spectrum is recognized, answers might vary. Nevertheless, the correct compound B is **4'-methylacetophenone**, whose IHD would be 5, as follows from the additional pi bond of the ketone (which the alcohol lacks). The structure can be found in **Solutions Fig. 1**.

c. Everyone may not necessarily recognize a ketone's reaction with 2,4-dinitrophenylhydrazine as a classical derivatization, but it should be recognizable as a carbonyl addition analogous to imine formation. The weakly acidic conditions are necessary because protonation of the carbinolamine (α-amino alcohol) is necessary to effect dehydration and imine formation, but too much acidity results in protonation of the amine (or hydrazine in this case) and negation of its nucleophilicity, stopping the reaction before it starts! The equation and mechanism

can be found on **Solutions Fig. 1**. Looking at the IR spectrum, we can verify that the expected hydrazone product was indeed formed; the absence of the prominent ketone C=O stretching band and overtone/combination bands is supplemented by the new presence of a hydrazone (2° amine) N-H stretching band at ~3300 cm^{-1}, as well as the nitro ($-NO_2$) group stretching bands around 1550 cm^{-1} and 1350 cm^{-1} and the hydrazone (imine) C=N stretching band from ~1620 cm^{-1} to 1635 cm^{-1}.

d. The second experiment is the familiar Grignard reaction, in which (for this instance) a ketone reacts with an alkylmagnesium reagent to produce an alkylated tertiary alcohol. Here we see that methylmagnesium bromide reacts with 4'-methylacetophenone to produce α,α,4-trimethylbenzylalcohol. See **Solutions Fig. 2** for the equation and mechanism. We have already discussed how the IR spectrum verifies formation of the appropriate product in part **b** above. Grignard reagents must be prepared and utilized under absolutely anhydrous conditions due to their powerfully basic character – water alone is sufficiently acidic to protonate an alkylmagnesium reagent, forming the corresponding alkane along with a magnesium salt. Needless to say, there are more straightforward (and less frustrating) methods for deliberately reducing alkyl halides to their parent alkanes.

3a. Perhaps the most egregious feature of Compound C's IR spectrum is the strong, sharp band at ~2200 cm^{-1}, corresponding most closely to the C≡N bond of a nitrile. Additionally, the pair of bands at approximately 3350 cm^{-1} and 3450 cm^{-1} seems to hint at the presence of a primary amine ($-NH_2$); primary amides also give rise to bands in this region, so it is prudent to check the carbonyl region for C=O bands. There is indeed a strong absorption at ~1620 cm^{-1}, but even given the characteristically low frequency of amide C=O vibration (typically from 1700 cm^{-1} to 1630 cm^{-1} at the least), assigning this as a definitive C=O band cannot be done in good conscience; more evidence should be gathered first. Finally, the lack of C-H stretching bands <3000 cm^{-1} leads to the conclusion that this compound lacks sp^3-hybridized carbons, and the fairly strong peak at ~750 cm^{-1} could indicate an *ortho*-substituted aromatic ring. Now, the knowledge that the compound contains nitrile functionality helps us understand the point of hydrolysis. Recall that hydrolysis of nitriles under harsh, strongly basic or acidic conditions leads to the corresponding carboxylate salt or carboxylic acid (respectively). Aqueous workup should then yield the isolable organic acid. Also recall that under milder conditions, nitriles can be hydrolyzed only as far as the primary amide. In fact, the IR spectrum of the hydrolysis product, while showing only minor changes in the N-H stretching region, tells the most important story by

completely lacking a C≡N stretching band! To further confirm our suspicions, the spectrum also now shows what could pass for a strong carbonyl peak at ~1660 cm^{-1}, a prime location for an amide C=O band. So in summary, the IR confirms that the starting material nitrile has been hydrolyzed under the milder conditions to yield an amide. The mass spectrum might give further hints as to the structure of the product. The molecular ion (M^+) peak is seen at 136 m/z; this is assumed to be the molecular weight of the compound, and also indicates that since we know the compound must contain at least one nitrogen (the amide group), an even number is likely present. Calculation of the approximate number of carbons yields 7.37, which can be rationalized as 7 for our purposes. Neither chlorine nor bromine is present. Putting the information together, 7 carbons plus the –NH2 and carbonyl O of a primary amide have a total mass of 116 amu. This leaves only 20 amu left for consideration, and if we try the potential primary amine group hinted at by the IR spectrum of Compound C itself, we can arrive at the formula $C_7H_8N_2O$, and thus an IHD of 5. This would work well for an aromatic ring and the amide carbonyl. Indeed, Compound C is **anthranilonitrile** (aka *o*-aminobenzonitrile). The structure can be found on **Solutions Fig. 3**. This would also explain the murky purple color of the compound – aromatic amines (anilines) tend to be very susceptible to air oxidation and become contaminated with dark-colored impurities over time.

b. See **Solutions Fig. 3** for the mechanism and all related equations. When the initial basic hydrolysis mixture is acidified during the workup step, no product can be isolated. Whereas a primary amide would also be hydrolyzed to the acid product and thus become isolable upon workup, the amine would be protonated during acidic workup, and thus become soluble in the aqueous medium! A similar result is seen for the initial acidic hydrolysis. Whereas in the acidic medium, the isolable acid would separate upon aqueous workup, the protonated amine group facilitates dissolution in the aqueous medium. Furthermore, Sachiko's basic workup, although well-intentioned, is one of many classic examples of overcompensation in chem lab; instead of slowly neutralizing the acid, she chose to make the mixture completely basic during workup, which would deprotonate the amine as desired, but would also deprotonate the carboxylic acid group, rendering it soluble in the aqueous medium again! Thus it cannot be said in truth that her first two hydrolysis procedures "didn't work."

4a. Looking at the IR spectrum of Compound D, all that can be deduced above the fingerprint region is that the compound seems to contain only sp^2-hybridized carbons, and the sharp peak at ~1600 cm^{-1} would suggest that this is a result of aromaticity rather than olefinic

structure. The fingerprint region is of little assistance, offering only the unmistakable signature of the nitro ($-NO_2$) group, a pair of strong, sharp peaks at ~1550 cm^{-1} and ~1350 cm^{-1}. In contrast, we can usually extract quite a bit of information from mass spectra, and this is certainly no exception. Compound D's mass spectrum shows a molecular ion (M^+) peak at 186 m/z, implying a molecular weight of 186 amu. This indicates also that, given the presence of the nitro group on the IR spectrum, the compound should contain an even number of nitrogen atoms. While tertiary amines might be a valid possibility since they show no particularly diagnostic IR bands, it will soon be clear that the formula would not permit such a compound. It is also clear that neither chlorine nor bromine is present in the compound by the absence of heavy isotope peaks. The number of carbon atoms calculated from the spectrum turns out to be 6.73, which could logically turn out to be 6 or 7, so some experimentation with potential formulas is in order. We can check our theory concerning the nitrogenous functional groups by noticing the loss of a nitro group (46 amu) from our molecular ion, leaving a fragment of m/z 140. This fragment then proceeds to lose another nitro group, leaving the prominent peak at m/z 94. Knowing that we have two nitro groups allows preliminary conception of a molecular formula. Choosing 7 as the number of carbons leads to the only possible formula, $C_7H_{10}N_2O_4$. This gives an IHD of 4 – but that matches a phenyl ring exactly, leaving no more hydrogen deficiency for the nitro groups! Trying 6 as the number of carbons seems equally futile at first, since a formula of $C_6H_{22}N_2O_4$ makes little sense. But try sketching a structure. Draw the phenyl ring with its two nitro groups attached, leaving 4 positions open on the ring. Is there any substituent that would pick up the leftover mass but would not show an obvious functional group peak on the IR? Checking a periodic table might lead us to a fluorine substituent, which would be absolutely right! (Remember that fluorine and iodine do NOT show isotope peaks on mass spectra.) The compound is **2,4-dinitrofluorobenzene**. The structure can be found in **Solutions Fig. 4**.

b. Knowing the course of this reaction is much more important at this point than attempting to read the spectra and generate a structure "from scratch." It can be done perfectly well, but might be unnecessary work. Recall that there exists a mechanism by which extraordinarily electron-deficient aromatic rings, when substituted with a sufficiently activated leaving group, can undergo substitution reactions with good nucleophiles in what is often referred to as the S_NAr reaction, a nucleophilic aromatic substitution. 2,4-Dinitrofluorobenzene fits all the above criteria, and turns out to be among the most reactive of known candidate compounds! Conversely to what we know about S_N1 and S_N2 reactions, fluoride (F^-) is by far the BEST leaving group in these reactions, and aniline is a perfect candidate for the nucleophile. The

mechanism is most helpful in determining product structure, and can be found in **Solutions Fig. 4**. The product, 2,4-dinitrodiphenylamine, shows all expected peaks in its IR spectrum: the secondary amine N-H stretching band at ~3300 cm^{-1}, the sp^2 aromatic C-H stretching bands >3000 cm^{-1}, and the aromatic and nitro bands that were previously discussed. Furthermore, the mass spectrum does indeed show the expected molecular ion at m/z 259. Further analysis of the mass spectrum would be encouraged for the sake of practice. Note in the mechanism that our leaving group in fact leaves not as F^-, but will abstract a proton from the intermediate to form hydrogen fluoride, HF. Since this compound is relatively insoluble in the reaction solvent (dichloromethane, a nonpolar organic solvent), it will bubble out of the reaction mixture. One of the most important lessons to learn when carrying out reactions involving many reactive fluorine compounds is that the strength of the silicon-fluorine bond is ~580 kcal/mol, and is among the strongest bonds we're likely to encounter! This is vastly favored over the common silicon-oxygen bonds found in glass, and as such, a great many fluorine reagents have a nasty habit of eating reaction vessels. Not to mention the other habit of eating bones…

c. This method of determining the N-terminal amino acid residue of a polypeptide was developed by Frederick Sanger at Cambridge in 1945, and thus the method is referred to as the Sanger method, and 2,4-dinitrofluorobenzene is commonly called "Sanger's reagent." By analogy with the reaction discussed above, this method involves a nucleophilic aromatic substitution between "Sanger's reagent" and the N-terminal amino group of the polypeptide; the solution is maintained at a weakly basic pH to ensure that the amino group is deprotonated and therefore sufficiently nucleophilic to participate in the reaction. The added bonus of the basic solution is that the HF by-product is trapped as an F^- salt rather than dissolving as an acid in the aqueous solution and doing all sorts of nasty things to the peptide. After the polypeptide is hydrolyzed, it is a relatively simple matter to isolate and characterize the now **labeled** amino acid. (As an added challenge, how is the labeled amino acid easily separated from the other amino acid residues?)

5. Here are the matched pairs for this problem:

Spectra 15 & 16: **Cmpd. 5H**; Spectra 17 & 18: **Cmpd. 5B**;

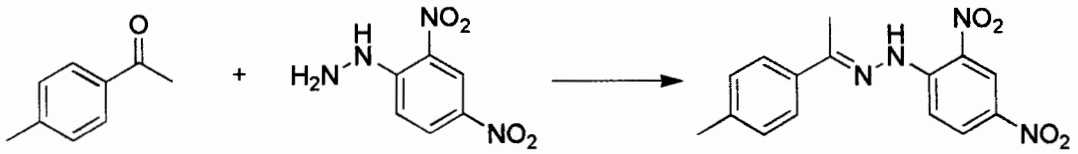
Spectra 19 & 20: **Cmpd. 5C**; Spectra 21 & 22: **Cmpd. 5A**.

6. Here are the matched pairs for this problem:

Spectra 23 & 24: **Cmpd. 6B**; Spectra 25 & 26: **Cmpd. 6G**;

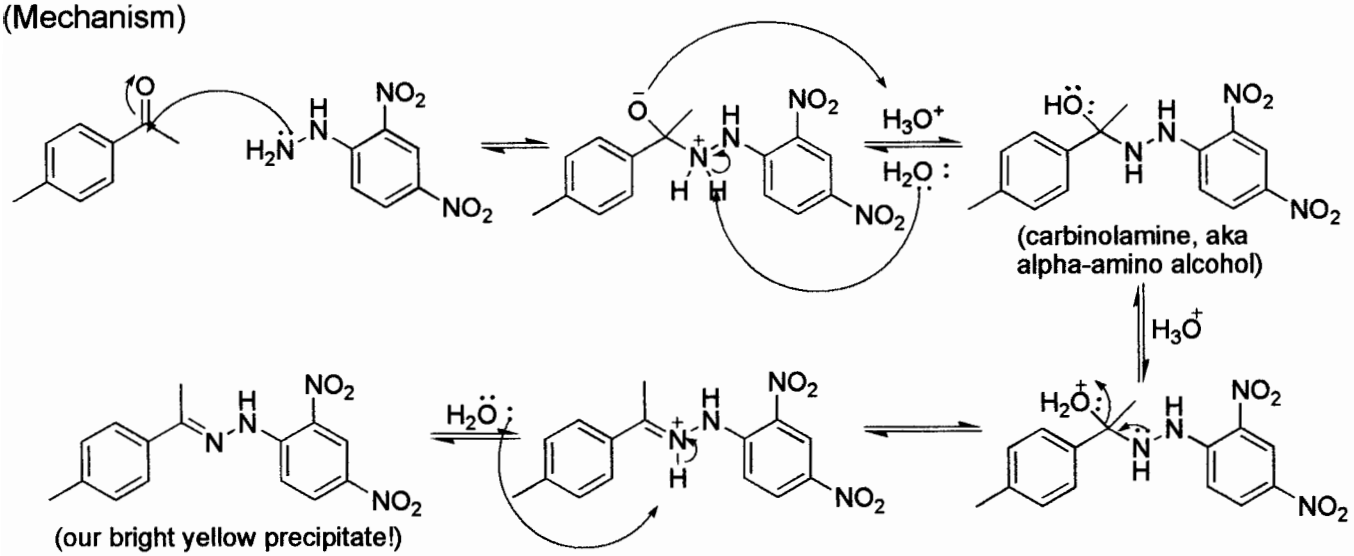
Spectra 27 & 28: **Cmpd. 6F**; Spectra 29 & 30: **Cmpd. 6C**.

Solutions Fig. 1



4'-methylacetophenone 2,4-dinitrophenylhydrazine a 2,4-dinitrophenylhydrazone (like an imine)

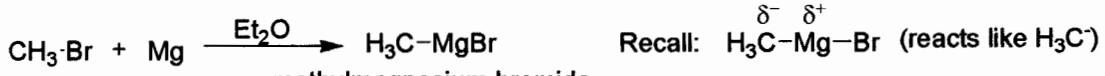
(Mechanism)



(carbinolamine, aka alpha-amino alcohol)

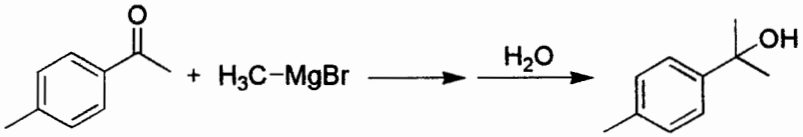
(our bright yellow precipitate!)

Solutions Fig. 2



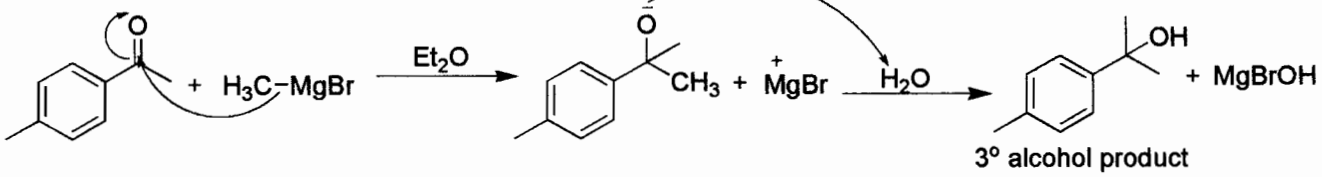
methylmagnesium bromide, our Grignard reagent

Recall: $H_3C^{\delta-}-Mg^{\delta+}-Br$ (reacts like H_3C^-)



4'-methylacetophenone α,α,4-trimethylbenzyl alcohol

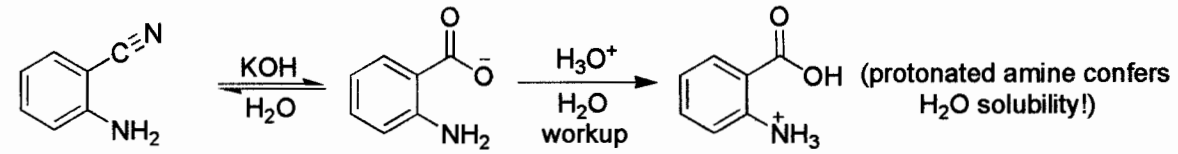
(Mechanism)



3° alcohol product

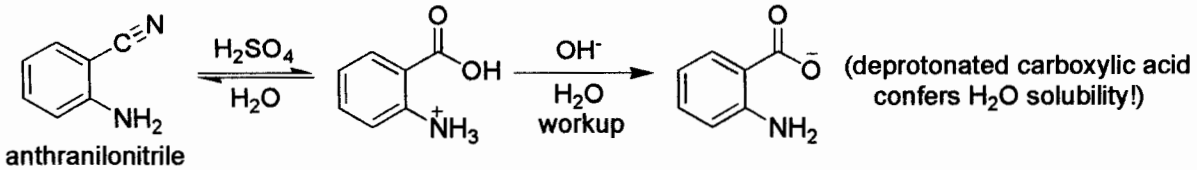
Solutions Fig. 3

(Sachiko's First Hydrolysis)



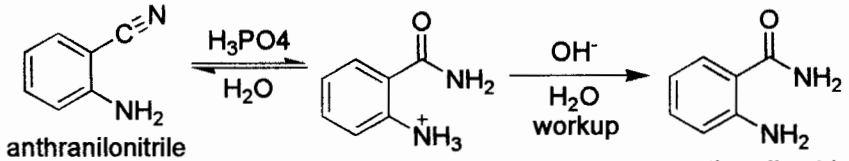
anthranilonitrile

(Sachiko's Second Hydrolysis)



anthranilonitrile

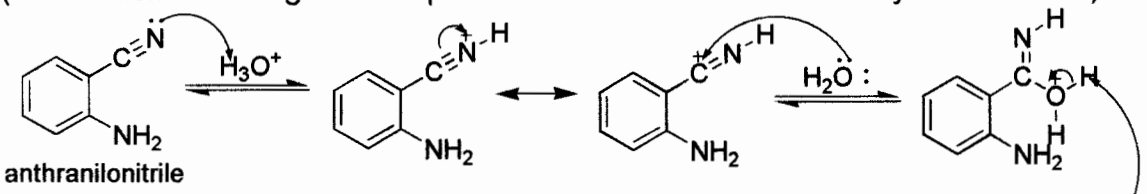
(Sachiko's Third Hydrolysis -- the charm)



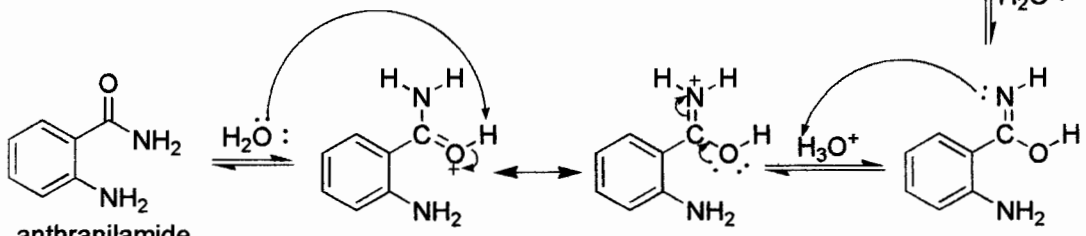
anthranilonitrile

anthranilamide

(Mechanism -- let's ignore the protonation of the amine for clarity until the end)



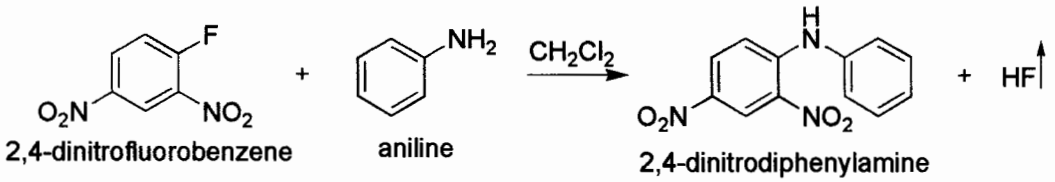
anthranilonitrile



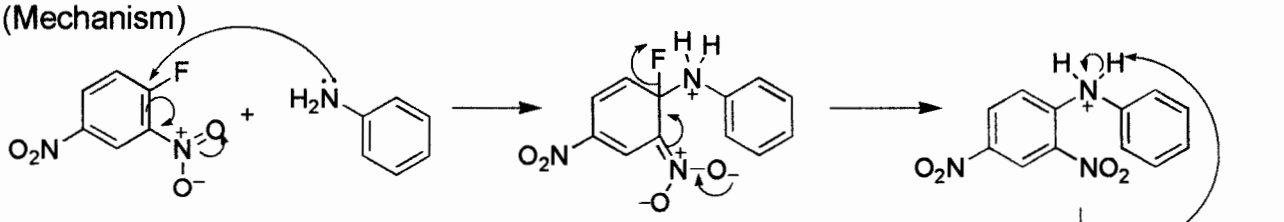
anthranilamide
(this would be after workup)

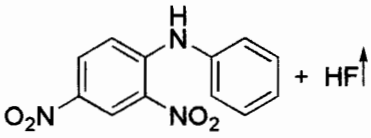
(think about keto-enol tautomers!)

Solutions Fig. 4



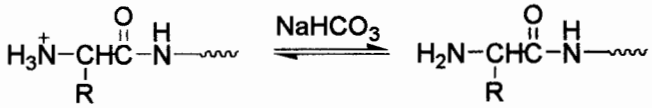
(Mechanism)





Solutions Fig. 5

(using a generic amino acid as an example)



(refer to fig. 4 for the mechanism)