

Solid-Solid Synthesis of Imines: A Green Chemistry Experiment

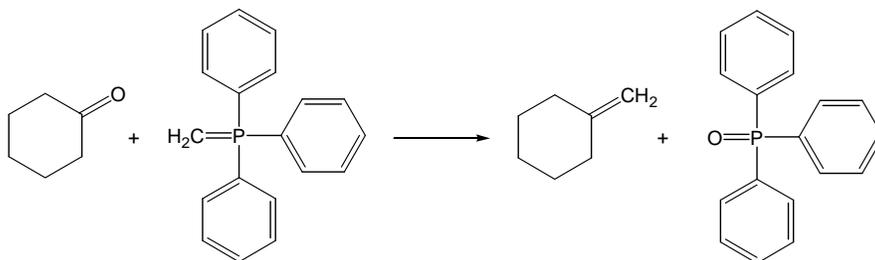
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The goal of green chemistry is to develop environmentally friendly synthetic reactions and industrial processes. Ways to accomplish that goal are to develop reactions and industrial processes that avoid use of reagents (reactions should be catalytic and the catalyst reusable), avoid use of solvents if possible, and minimize formation of byproducts.

Experimental Techniques:

- Determination of melting point

In 1979 H. G. Wittig received a Nobel Prize in chemistry for his work on organophosphorus chemistry. Reaction of organophosphorus ylides (now called Wittig reagents) with carbonyl compounds yields alkenes. While an extremely useful and versatile, a Wittig reaction requires use of a number of reagents (a base to generate the ylide, drying agent to dry the solvent), and as a byproduct of the reaction, a phosphine oxide is formed (which has to be disposed). For example, a Wittig reaction is one of the best methods for synthesis of methylenecyclohexane (recall that an elimination reaction of 1-methylcyclohexanol would yield 1-methylcyclohexene). However, in a reaction between cyclohexanone and methylene triphenylphosphine ylide, in addition to methylenecyclohexane (19 atoms), a molecule of triphenylphosphine oxide (35 atoms) is formed.



Witting reaction is only one of a number of reactions with poor “atom economy.” Some of the other examples include various hydroboraton – oxidation reactions, oxidation reactions involving metal ions, etc.

In this laboratory exercise, you will examine reactions that proceed without solvent and the only byproduct is water. Unless reaction is a rearrangement or an addition, it will always involve formation of byproducts. If our goal is green chemistry, when synthesizing a particular compound we should choose the reaction that produces environmentally friendly byproducts (for example water, lower alcohols, nitrogen, etc.).

Solid Phase vs. Solid-Solid Synthesis

Term solid phase synthesis can have different meanings. Often it refers to a reaction in which the substrate is attached to a solid support. It is commonly used in combinatorial synthesis. Alternatively the reagent may be adsorbed on or attached to a solid support (a polymer). In either case the reaction is done in a suitable solvent in which the reagent and/or the catalyst are dissolved. Thus, term solid phase synthesis does not usually mean that the reaction proceeds in a solid phase or without a solvent.

A solid-solid synthesis involves mixing of two solids without a solvent. Although solid-solid synthesis means that reaction proceeds without a solvent, the reaction does not necessarily proceed in the solid phase.

Solvents provide a medium for a chemical reaction. Before use a solvent has to be purified and in some cases dried. After the reaction solvent has to be removed and, in most cases, discarded. Thus, a reaction that proceeds without a solvent would have a number of advantages (lower cost as well as less labor intensive).

From the point of view of atom economy, the most efficient reactions are addition, dimerization (oligomerization in more general terms) and condensation reactions. The former does not produce any byproducts, while in the later only a small molecule (usually water) is the byproduct. A solid-solid synthesis, involving such reactions, is the ultimate in Green Chemistry and in "atom-economy."

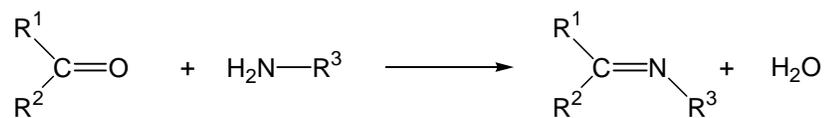
An important consideration in a solid-solid reaction is the reaction kinetics. While the concentration of the reagents is high, the mobility of their molecules is limited.

Depression of a Melting Point and Formation of a Melt

Mixing of two solids results in a melting point depression. Sometimes mixing of two solids will depress the melting point of the mixture so that it is below the room temperature. That will result in a formation of a liquid. Such liquid is called a melt. Note that formation of a melt does not necessarily involve a chemical reaction. An example is formation of a melt upon mixing water ice and sodium chloride. Recall the melting point lab and effect of impurities on the melting point of a compound.

Synthesis of Imines (Schiff Bases)

Imines are prepared in a reaction between a carbonyl compound and a primary amine.



$\text{R}^1, \text{R}^2, \text{R}^3 = \text{H}, \text{alkyl or aryl}$

If the imine contains a hydrogen atom ($R^3 = H$, therefore the starting material is ammonia), it is unstable and usually cannot be isolated. However, when the imine contains an aromatic (aryl) group on the nitrogen (than the starting amine is aromatic), the resulting imine is stable and can be isolated. The products are called Schiff bases. Carbonyl compounds differ in their reactivity towards amines. Some react in a short time to give imines in good to excellent yields (reaction equilibrium is to the right). Others react only after a prolonged time and the reaction equilibrium may not be favorable (it may be necessary to remove the formed water to shift the equilibrium towards the imine).

Orientation of the Reagents in the Course of the Reaction

For a number of reactions orientation of the reagent in the course of the reaction (pathway the reagent takes in approaching the substrate) is of crucial importance. Examples of such reactions include S_N2 reactions and some addition reactions. In other cases, usually when highly reactive intermediates are involved, approach of the reagent is less important. Examples of such reactions are S_N1 reactions and free radical reactions.

The mechanism of imine formation is shown in the Figure 1.

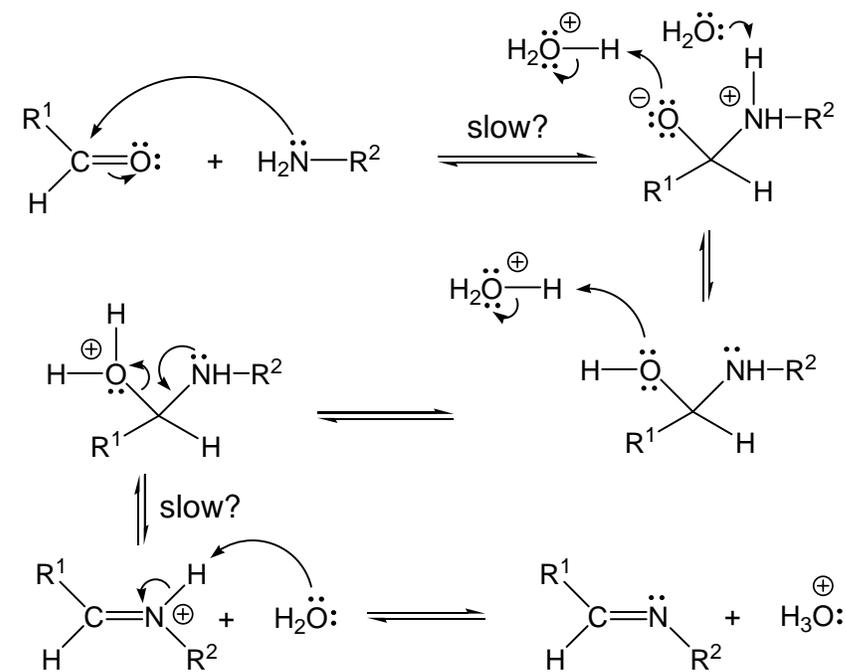
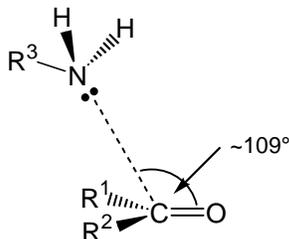


Figure 1. Formation of imines.

Note that in the reaction between a nucleophile and a carbonyl group the carbon atom changes hybridization from sp^2 (trigonal planar) to sp^3 (tetrahedral). That means that the attack of the nucleophile occurs at an angle of approximately 109° (tetrahedral angle) to the existing C=O bond.



In this laboratory exercise, your task will be to prepare mixtures of different carbonyl compounds (aldehydes or ketones) and aromatic amines, isolate the product(s), if any, and make conclusions about the effects of various factors (melting points of the starting materials, steric and electronic effects) on the outcome of the reaction (reaction rate and position of the reaction equilibrium).

Procedures

Caution: Substituted anilines used in this experiment are toxic. Wear nitrile gloves when handling them.

1. Weigh 1 mmol of an aromatic amine and 1 mmol of a carbonyl compound. Possible starting materials are shown in the Figure 2. You will be assigned a particular experiment involving one of the aldehydes and one of the amines.
2. Crush the crystals of each compound into a fine powder. You can use either a glass rod or the bottom of a test tube for it.
3. Mix the two powders in a beaker. Start timing the reaction.
4. Record any changes (melting, change in color) and the time they occur.
5. If the mixture melted, record the time at which the mixture become solid again. If it doesn't solidify within 30 minutes, you can assume that it won't solidify and stop timing.
6. Crush the crystals and take a melting point of them.

Exercise 1: Reactivity of Aldehydes and Ketones

Compare reactions of *o*-vanilline and benzophenone with *p*-anisidine.

- Which one reacts faster?
- Did you notice formation of a melt when *o*-vanilline and *p*-anisidine reacted?
- Did melt of benzophenone and *p*-anisidine solidify after 30 minutes?

Exercise 2: Reactivity of Anilines [p-Anisidine (+R), p-Toluidine (+I) and Nitroaniline (-R effect)]

React the above three with *o*-vanilline.

- Can you explain why reaction with *p*-Anisidine is so fast?
- Did nitroaniline react at all?

Exercise 3: Reactivity of Aldehydes

Compare reactivity of benzaldehyde, *o*-anisaldehyde, *o*-vanilline, vanilline (higher mp, no intramolecular hydrogen bonding) and *o*-nitrobenzaldehyde with anisidine.

- Why benzaldehyde reacts the fastest (hint: it is not because it is a liquid)?
- Why *m*-nitrobenzaldehyde (and *p*-nitrobenzaldehyde, too) reacts so slowly? Wouldn't you expect electron withdrawing group to increase reactivity? Hint: Consider the mechanism. Is the rate determining step the one you would expect? Could the second step (loss of water) be rate determining? If it is, how would -R (or -I) substituent affect the reaction rate?
- Can you now explain how is it possible that both electron withdrawing as well as electron donating substituents retard the reaction rate? Consider a possibility of a change in the reaction mechanism (different step may become rate determining).

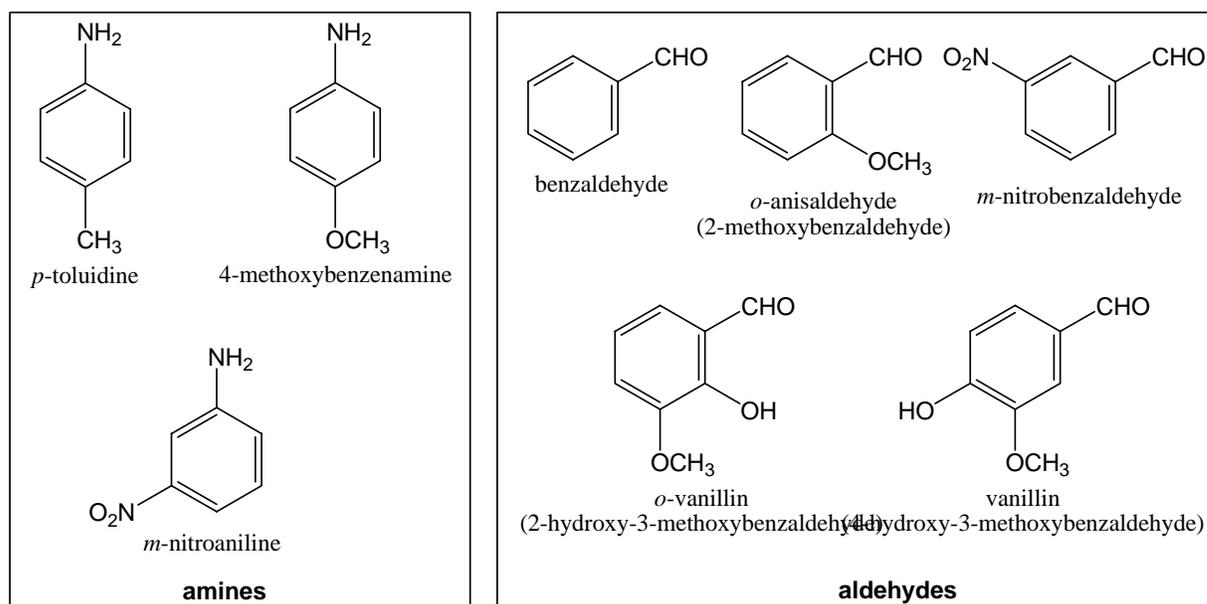


Figure 2. Some of the possible starting materials.

Questions

1. Consider the mechanism of a reaction between an imine and a carbonyl compound. Is the orientation of the molecules in the transition state important? If the mixture does not melt, is it likely that the reaction rate will be high? Explain your answer. Does the outcome of the experiment support your explanation?
2. Draw a figure representing an interaction between the free electron pair of the nucleophile and the π^* orbital of the carbonyl group in the transition state. How likely is that such reaction will proceed in a solid phase at a reasonable rate? Explain your answer.
3. Would you expect that the electronic effects would influence reactivity of the amine towards nucleophilic addition to the carbonyl group? How would substituents on the carbonyl group effect the reactivity of the carbonyl compound? Compare your experimental results to the expected outcome.
4. Would you expect that the steric effects would influence reactivity of the amine towards nucleophilic addition to the carbonyl group? Which of the amines may exhibit a steric effect?
5. Is the fact that the mixture melted always an indication of a chemical reaction?
6. If a solid mixture melted when placed in a heating bath and solidified when cooled down, how do you know whether a reaction happened, or you just recovered the original mixture?

Additional Reading

1. Toda, F.; Tanaka, K. *Chem. Rev.* **2000**, *100*, 1025-1074.
2. Rothenberg, G.; Downie, A.P.; Raston, C.L.; Scott, J.L. *J. Am. Chem. Soc.* **2001**, *123*, 8701-8708.

Pre-Lab Preparation**Synthesis of Imines**

Date: _____

Name: _____

Prelab Exercises

Look up the properties of the reactants (nature of substituents – whether they are electron-donating or electron-withdrawing, etc.). Examine the reaction mechanism. Would you expect that electronic and steric effects would have an effect on the reaction rate?

Would you expect that melting points of the starting materials would have an effect on the reaction rate?

Signature: _____

Results**Synthesis of Imines**

Date: _____

Name: _____

Exercise 1:

Exercise 2:

Exercise 3:

Signature: _____