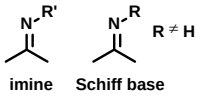
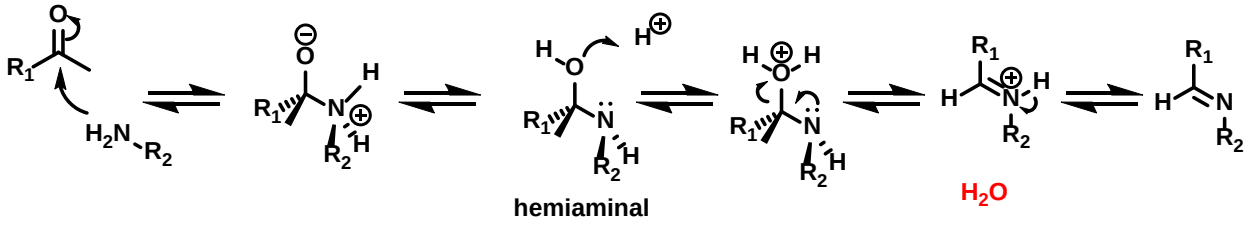
Microwave Assisted, Multi-component Synthesis of Lophine[1]

Introduction

The synthesis of imines is generally performed by the acid catalyzed condensation of a carbonyl with a primary amine. When performed using a **primary amine**, the product can also be referred to as a Schiff base.

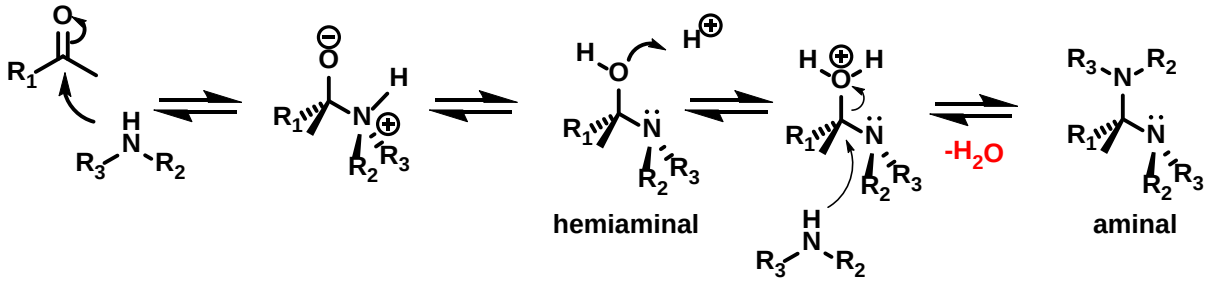


The synthesis of imines (or Schiff bases) is highly reversible, meaning reactions can be driven to completion by removal of the water by-product using methods such as azeotropic distillation or molecular sieves. The reaction involves nucleophilic attack of the primary amine on the carbonyl and proceeds through a hemiaminal intermediate before the loss of water and formation of the imine

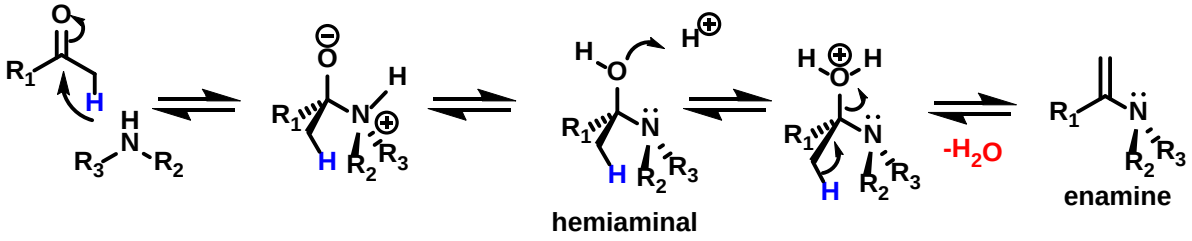


Scheme 1. Acid catalyzed imine formation

In the case of **secondary amines**, the imine product is disfavored and results in formation of an aminal or enamine. Initially, the same steps are followed to reach the hemiaminal, which is then protonated. In contrast to the case of primary amines, this protonated heminal is unable to lose an N-H proton and must follow a different reaction path. Nucleophilic attack of a second amine and loss water can result in formation of the aminal product (Scheme 2). Alternatively, when there is a proton α to the carbonyl, a simple elimination reaction can result in formation of the enamine (Scheme 3).

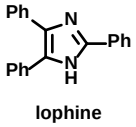


Scheme 2. Acid catalyzed aminal formation



Scheme 3. Acid catalyzed enamine formation

The synthesis of heterocyclic compounds often requires elevated temperatures and prolonged reaction times, making them well suited for microwave applications. The synthesis of the nitrogen heterocycle lophine (2,4,5-triphenylimidazole) from benzaldehyde, benzil and ammonium acetate can be performed rapidly using microwave irradiation.



[1]Experiment adapted from Crouch, R.D.; Howard, J.L.; Zile, J.L.; Barker, K.H. *J. Chem. Ed.* **2006**, *83*, 1658

Experimental

Draw the reaction scheme below and complete the following tables:

Reagent	CAS	MW (g/mol)	Density (g/mL)	Equivalents	mmol	Amount
Benzaldehyde	100-52-7	106.12	1.04	1	0.5	
Benzil	134-81-6	210.23	-	1		105 mg
Ammonium acetate	631-61-8	77.08	-	10		
Glacial acetic acid	64-19-7	-	-	-	-	5 mL
Ammonium hydroxide	1336-21-6	-	-	-	-	6 mL

Product	CAS	MW (g/mol)	Mmol	Theoretical yield
Lophine	484-47-9	296.37		

Required equipment: MARS™ Microwave Synthesizer
CEM GlassChem™ Vessel set
Small stir bar
2 small beakers
Ice bath
Vacuum filtration assembly

1) Add the appropriate amounts of benzaldehyde, benzil, ammonium acetate, glacial acetic acid, and a small stir bar to a GlassChem vessel.
2) Place the vent plug inside the top of the reaction vessel. Place the vessel top on the reaction vessel and finger tighten. Using the preset torqueing tool, tighten the top until you hear an audible click. For detailed instructions on vessel usage, please see the MARS™ 6 Synthesis Research Guide (PN 600432).
3) Insert the composite sleeves into the receptacles of the turntable and then insert each vessel inside a sleeve.

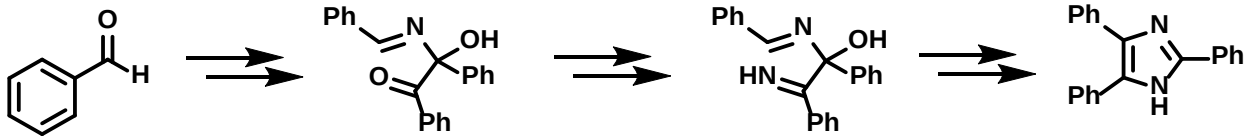
Note: Ensure that each vessel is properly positioned in the turntable. The outside of the cover must be below the top of the turntable as illustrated.
Note: Ensure the vessels are symmetrically distributed across the turntable if using fewer than 24 vessels and that the control vessel has been configured.

4) The microwave will run a ramp to temperature method which includes a 5 minute ramp to 125 °C followed by a hold time of 10 minutes. See the manuals for the appropriate wattage and method programming details.
5) After the vessels have cooled, pour the solution into a small beaker and place the beaker in an ice bath. Slowly add 6 mL of ammonium hydroxide solution to the beaker while gently swirling the solution.

6) Collect the precipitate on a Hirsch funnel. The product can be recrystallized by adding the product and 10 mL of ethanol to a beaker and mixing the solution while warming on a hotplate. Once the precipitate has dissolved completely, distilled water is added until the solution begins to turn cloudy. The beaker is then placed in an ice bath until cool and the recrystallized product collected on a Hirsch funnel.
7) Obtain the mass of product recovered and calculate a percent yield. Analyze the product using available instrumentation (melting point, NMR etc.)

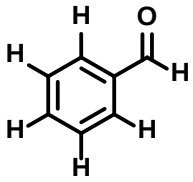
Results and Discussion

1) Using knowledge of the reactivity of amines and carbonyls and the structures below as a guide, draw the full mechanism for this transformation. (Hint: NH_4OAc will react as NH_3)



lophine

2) Predict the ^{1}H and ^{13}C spectrum of benzaldehyde, how many peaks do you expect?



3) Draw possible resonance structures of lophine.

4) Using Huckel's rule, determine if lophine is aromatic.