"Ugi to the left, Ugi to the right. This is so fun, we're gonna Ugi all night."

OpenScience: A Vision for the Future:
The internet has not only provided college students with an opportunity to watch bootleg movies for free, but has spawned a plethora of opportunities for scientific data sharing and collaboration. Online collaboration and data sharing can take place in a number of different formats. Organic students and instructors have enjoyed the accessibility of online databases such as chemspider, emolecules, sigma-aldrich, chemfinder, and last but not least the omnipresent wikipedia that provide molecular information. There are also tutorials and online textbooks that offer resources for students and instructors who are looking for information or media on a particular topic that can supplement the course textbook. The most exciting online opportunity, however, is the possibility of creating online communities of instructors and students that will 1) distribute experimental findings to a wide audience, 2) allow for real-time feedback on issues and problems related to specific experimental protocols, and 3) create collaborations where several groups are working to solve a common problem or explore a common application of chemistry.

The UsefulChem Project:
This experiment represents the beginning of collaboration with the UsefulChem Bradley open notebook science group of graduate and undergraduate research at Drexel University.[1] The goal of the UsefulChem project is to use the Ugi 4 component reaction to synthesize possible anti-malarial compounds. Open notebook science allows immediate dissemination of experimental results that invites advice and suggestions as well as complementary experiments that enhance and advance the project. We are going to reproduce some of the Drexel results as well as perform three complementary reactions that have not been done at Drexel.

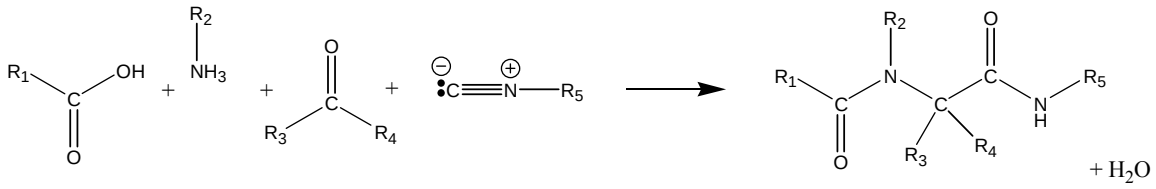
The Importance of Antimalarial Research:
According to the World Health Organization, "Malaria is caused by a parasite called *Plasmodium*, which is transmitted via the bites of infected mosquitoes. In the human body, the parasites multiply in the liver, and then infect red blood cells. Symptoms of malaria include fever, headache, and vomiting, and usually appear between 10 and 15 days after the mosquito bite. If not treated, malaria can quickly become life-threatening by disrupting the blood supply to vital organs. In many parts of the world, the parasites have developed resistance to a number of malaria medicines."[2]

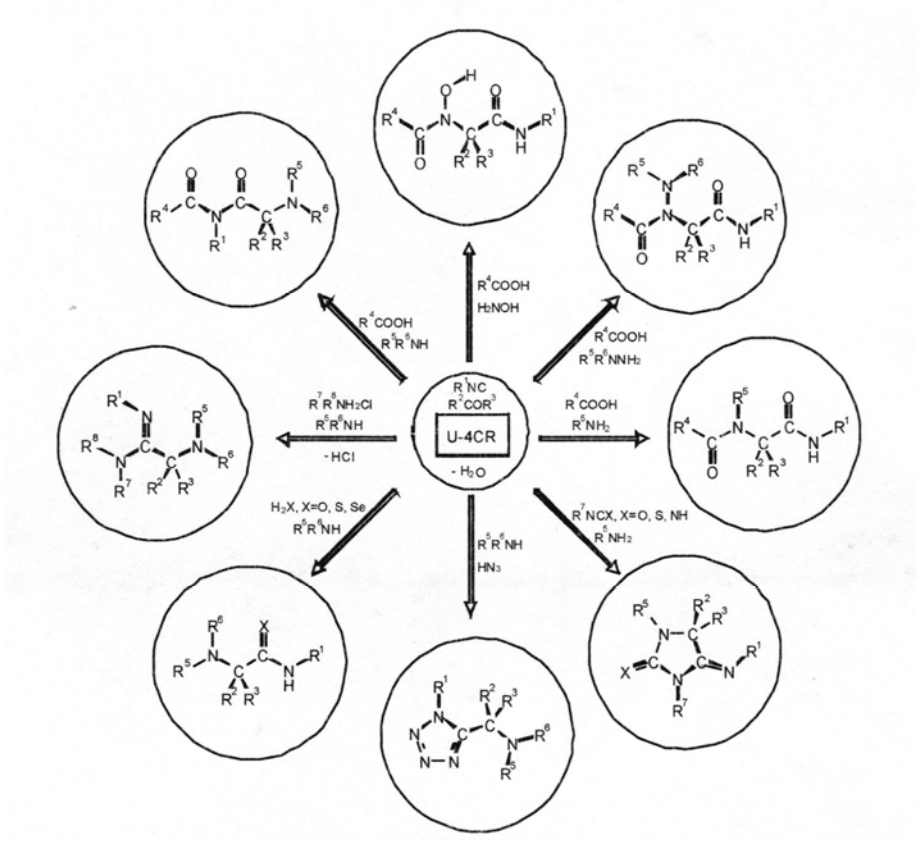
Most malaria medicines are taken as a prophylactic, which means that the medications are taken regularly to minimize the effects of an imminent infection. Since malaria is widespread in tropical countries where the majority of people are not wealthy, pharmaceutical companies have not worked very hard to produce compounds that can prevent, treat and cure malaria.

[1] http://usefulchem.wikispaces.com/
[2] World Health Organization, Malaria http://www.who.int/topics/malaria/en/
image: http://aenews.wsu.edu/Oct00AENews/Mosquito.gif

The Ugi Reaction:

The Ugi reaction was discovered by, you guessed it, Dr. Ivar Ugi, in 1959.[3] The Ugi reaction is a condensation between a carboxylic acid, an amine, an aldehyde, and an isonitrile. As you might imagine, there are a large number of combinations that can be attempted with such a reaction. As a result, the Ugi 4 component reaction has been an attractive reaction for combinatorial synthesis schemes that are used to build compound libraries. Compound libraries are simply large collections of compounds that can be catalogued and accessed by other chemists wishing to study their properties. In particular, compound libraries can be screened with various biological activity assays as part of drug discovery projects.





Scheme 4: The variability of U-4CR products.

[3] Ugi, I; Meyr, R.; Fetzer, U.; Steinbrückner, C. (1959). "Versuche mit Isonitrilen". *Angew. Chem.* **71**: 386. Scheme from Ugi, I.; Werner, B.: & Domling, A. "The Chemistry of Isocyanides, their multicomponent Reactions and their Libraries" Molecules, 2003, 8, 53-66

Procedure:

Part I.
Add 0.33 g of your aldehyde to 8 mL methanol in a 20 mL scintillation vial.

Screw on a Teflon (green) cap on the vial. Vortex to mix and dissolve the aldehyde.

Add 1 mL of methylamine solution to the vial.

Vortex to mix. Sing the "Ugi song" while vortexing.

Obtain 0.34 g of the carboxylic acid. Add the carboxylic acid to the vial.

Vortex to mix.

Obtain 0.39 g of tosylmethylisocyanide. Add the tosylmethylisocyanide to the vial.

Vortex to mix.

Take a photo of your reaction mixture.

Label the vial and let the reaction mixture sit in the sealed vial.

Part II.
Check the reaction after a couple of days. If a precipitate has formed, filter the precipitate.

You may wash the solid with a small amount of methanol.

Place the solid in a new 20mL vial and dry the solid in a vacuum chamber until the next laboratory period.

Save the filtrate in the original labeled 20 mL vial.

Part III.

- Obtain the mass of the dried product.
- Dissolve a small amount in methanol and obtain the UV-vis spectrum.
- Obtain an IR spectrum of your product. Prepare a KBr pellet for solid samples. (see photo)
- Do a melting point analysis of your product.
- Submit any remaining product in a properly labeled vial.

Image: http://www.chemistry.oregonstate.edu/courses/ch361-464/ch362/IR_NMRuse/IR4.htm

Checklist for completing the "Prelab" section:
(refer to Laboratory Syllabus for complete directions)

____ *Title and date*
____ *Purpose*.

____ *Physical constants*. Refer to the following table of physical constants and safety data for the chemical compounds referred to in the procedure:

Physical constants

Name	Formula	M.W. (g/mole)	m.p. (˚C)	b.p. (˚C)	Density (g/mL)
3,4-dimethoxybenzaldehyde	$C_9H_{10}O_3$	166.17	40-43	281	
3,5-dimethoxybenzaldehyde	$C_9H_{10}O_3$	166.17	45-48	151 at 16mmHg	
Methanol	CH_3OH	32.04	-98	64.6	0.791
Methylamine 2.0 M in MeOH	CH_5N	31.06		40	0.785
3,4,5-trihydroxybenzoic acid ●monohydrate	$C_7H_6O_5$	170.12 (anhydrous) 188.13 (monohydrate)	251		
2,4,6-trihydroxybenzoic acid ●monohydrate	$C_7H_6O_5$	170.12 (anhydrous) 188.13 (monohydrate)			
p-toluenesulfonylmethyl isocyanide (tosylmethyl isocyanide)	$C_9H_9NSO_2$	195.24	109-113		

Name	Solubility	Safety Information
dimethoxybenzaldehyde	somewhat soluble in water; soluble in alcohol and nonpolar solvents	Skin and eye irritant; flammable
Methanol	Miscible with water and most organic liquids including nonpolar liquids.	toxic and flammable
Methylamine 2.0 M in MeOH	insoluble in water; soluble in alcohol and nonpolar solvents	Skin and eye irritant; flammable
trihydroxybenzoic acid ●monohydrate	Soluble in water and alcohols. Insoluble in nonpolar solvents	Corrosive; toxic; skin, eye, and respiratory system irritant
p-toluenesulfonylmethyl isocyanide (tosylmethyl isocyanide)	Miscible with water and most organic liquids including nonpolar liquids.	Corrosive; toxic; skin, eye, and respiratory system irritant

Sources: 1) www.chemfinder.com
2) Sigma-Aldrich catalog online
3) www.wikipedia.com

___ *Flowchart.* Refer to "Procedure"

Structures and equations.

The following reacts will be used according to hood assignment:

Hoods	Aldehyde	Carboxylic Acid
1R, 8R, 4L, 5L	3,5-dimethoxybenzaldehyde	3,4,5-trihydroxybenzoic acid
2R, 7R, 3L, 6L	3,5-dimethoxybenzaldehyde	2,4,6-trihydroxybenzoic acid
3R, 6R, 2L, 7L	3,4-dimethoxybenzaldehyde	3,4,5-trihydroxybenzoic acid
4R, 5R, 1L, 8L	3,4-dimethoxybenzaldehyde	2,4,6-trihydroxybenzoic acid

___ Look up "tosylmethyl isocyanide" in chemspider. What is the InChI code? What is an InChI code?

___ What is the 6 letter synonym for tosylmethyl isocyanide?

___ Draw the structure of your Ugi product.

___ What could you do to isolate your product if after 7 days if there are no spontaneously formed crystals?

___ Refer to UsefulChem Experiment 171 <http://usefulchem.wikispaces.com/Exp171>. Which reaction most closely corresponds to our experiment? What were the results?

___ *Calculations.*

___ Determine the molecular formula and molecular weight of your Ugi product.
___ Calculate the amount of each reactant in moles.
___ Calculate the theoretical yield of your Ugi product.

___ *Safety Question*: What is the safest way to transfer 1 mL of 2.0 M methamine in methanol from the stock bottle to your reaction vial? Give a reasonable explanation of your choice.

Experimental Observations and Data:

Hand in a copy of your experimental observations and data before you leave lab.

Experimental Observations: Refer to Laboratory Syllabus for guidelines.

Raw Data: Refer to Laboratory Syllabus for guidelines.

Lab Report Checklist:

Presentation of Data.

____ Calculate percent yield of your Ugi product. Show calculations

____ Label the coordinates for all absorption maxima on your UV-vis spectrum.

____ Interpret the IR spectrum of your Ugi product.

Interpretation of Data.

_____ Consider the

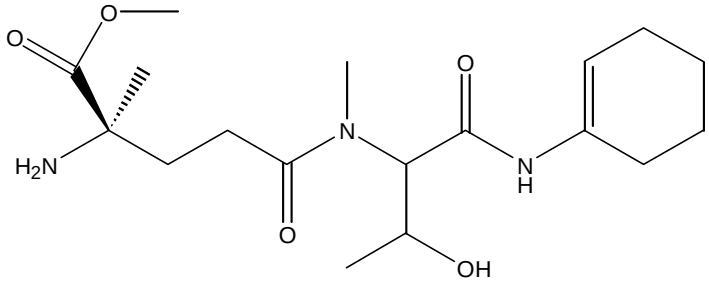
_____ The IR spectrum may reveal that there is unreacted isocyanide in your product mixture. Where does the isonitrile group appear in an IR spectrum? (Refer to appendix 2B in your textbook.)

_____ Consider the possible ^{1}H spectrum of your Ugi product. How many aromatic Hydrogens are there? How many methyl groups are there? Where would you expect to observe the methyl groups?

_____ Consider the possible ^{13}C spectrum of your Ugi product. How many aromatic Carbons are there? How many carbonyl carbons are there? How many methyl carbons are there? Where would you expect to observe the methyl carbons?

_____ If you were given four different compounds for each type of Ugi reactant (16 compounds in all), how many different Ugi products could you attempt to make?

_____ In 1999, S.M. Bauer and R.W. Armstrong reported the total synthesis of motuporin.[4] A key step in the synthesis was the formation of the following intermediate via an Ugi reaction. What were the four Ugi reactants for this reaction?



Green Question:

_____ Name two natural product malaria treatments.

[4] S.M. Bauer and R.W. Armstrong "Total Synthesis of Motuporin (Nodularin-V)" J. Am. Chem. Soc. 1999, 121, 6355