



## The Toad Suck Institute for Green Organic Chemistry



### Development of a Green Organic Chemistry Laboratory at Hendrix College, Conway, Arkansas

We began microscale labs around 1988, for green reasons.

We began “green chemistry” in 2001, as follows.

- “The unexamined reaction is not worth running.”
- Does the experiment teach something that is indispensable?
- Is there a greener way to do it?
- University of Oregon, Green Chem. in Educ. Workshop

### “An Asymptotic Approach to the Development of a Green Organic Chemistry Laboratory”\*

“...the goal of making a chemical product or process ‘environmentally benign’ is a mere statement of the ethic of continuous improvement more than it is a metric by which to measure improvement.”

“Green Chemistry, Theory and Practice”, P.T. Anastas and J. C. Warner, Oxford University Press, 1998.)

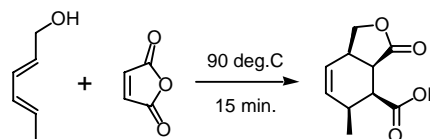
\**J. Chem. Educ.* **2004**, *81*, 1187-1190 (August)

### The Ideal Synthesis-P. Wender

“The ideal synthesis may be defined as one in which the target molecule is prepared from readily available starting materials in one simple, safe, environmentally-acceptable, and resource-effective operation that proceeds quickly and in quantitative yield.”

P.A. Wender & B. L. Miller, in “Organic Synthesis: Theory and Applications”, T. Hudlicky, Ed., *Greenwich: JAI Press*, **1993**, *2*, 27-66.

### Diels-Alder/Nucl. Acyl Subst.

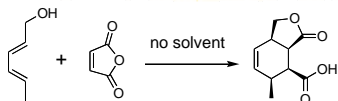


McDaniel, K.F.; Weekly, R. M. *J. Chem. Educ.* **1997**, *74*, 1465.

- original procedure calls for reflux in toluene
- all protons visible in 300 MHz NMR in acetone-d<sub>6</sub>
- proton NMR assignments by COSY
- diastereotopic hydrogens

## Solventless Green Evolution

K. Tanaka, *Solvent-free Organic Synthesis*; Wiley-VCH: Weinheim, 2003



### Three variations :

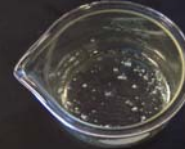
1. 90 °C, 15 min, no solvent;
2. microwave, reduced power, 30 sec., no solvent;
3. manual mixing, RT, no solvent, 11 min.

**Mechanistic study:** M. N. Paddon-Row, M. S. Sherburn *et al.*, *Org. Biomol. Chem.* 2005, 3, 1302-1307.

0.5 Minutes



4.0 Minutes



5.0 Minutes



10.5 Minutes



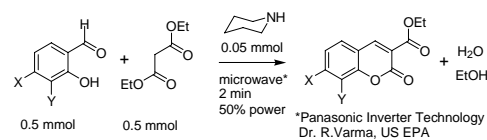
## Intramolecular Reactions

"We all know that enforced propinquity often leads on to greater intimacy." (The closer we hold reagents together, the more likely they are to react.)

--R. B. Woodward

(Quoted in K. B. Sharpless, *Chem. Brit.* **1986**, 22, 38-44)

## Solventless Microwave-Assisted Coumarin Synthesis



0.5 mmol  
a. X=Y=H  
b. X=OMe, Y=H  
c. X=H, Y=OMe  
[Heinrich  
Emil  
Albert  
Knoevenagel  
(1865-1921)]

1. Grind at RT, no solvent; T. Sugino, K. Tanaka *Chemistry Lett.* **2001**, 30, 110-111.
2. Meldrum's acid, 10 hr reflux in H<sub>2</sub>O, no catalyst; R. Maggi *et al.* *Green Chem.* **2001**, 3, 173-174.
3. Microwave, no solvent; D. Bogdal Politechnika Krakowska, Poland (Google)

## A Truly Green Starting Material

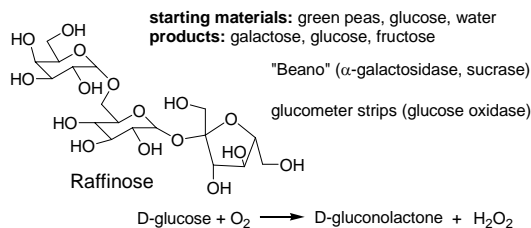


## A Green Tale of Three Enzymes

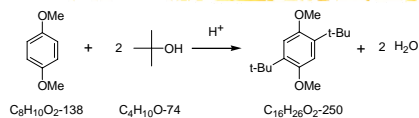


## "Chemistry and Flatulence: An Introductory Enzyme Experiment"

J. R. Hardee et al. *J. Chem. Educ.* **2000**, *77*, 498-500.



## Green Metrics: "Atom Economy" is not the Whole Story



1. % atom economy =  $(250 / (138 + 74 + 74)) \times 100 = 87.4\%$
2. Suppose the purified yield is 50%:  
% atom efficiency =  $87.4\% \times 50 = 43.7\%$
3. 120 mg 1,4-dimethoxybenzene; 155 mg t-BuOH; 920 mg H<sub>2</sub>SO<sub>4</sub>;  
recrystallization solvent (70% i-PrOH/H<sub>2</sub>O), 1.5 mL = 1.287 g  
Effective mass yield =  $\frac{\text{mass of desired product}}{\text{mass of all reactants, solvents etc.} + \text{mass of prod.}}$  X 100  
=  $\frac{109 \text{ mg}}{2897.5 \text{ mg}} \times 100 = 3.76\%$

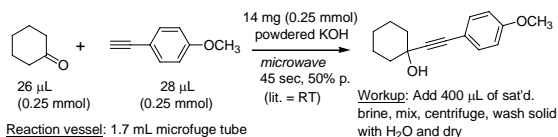
## Microwave in a Microfuge

VWR SuperClear polypropylene Micro-centrifuge Tubes, vol. 1.7 mL (cat.no. 20170-355), in a 10 mL Pyrex beaker

**WARNING:**  
DON'T OVERHEAT!  
(~30 sec, 50% power)

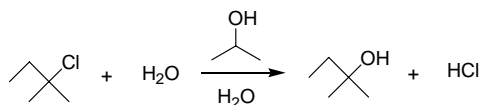


## Microwave-assisted, Solvent-free Addition of 4-Ethynylanisole to Cyclohexanone



Reference: Adapted from H. Miyamoto, S. Yasaka, and K. Tanaka, *Bull. Chem. Soc. Jpn.* **2001**, *74*, 185-186. (See also: K. Tanaka *Solvent-free Organic Synthesis*; Wiley-VCH: Weinheim, 2003; p 43.)

## Chemical Kinetics: Evidence for the S<sub>N</sub>1 Mechanism; Green Solvent Effect on Rate

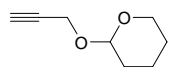
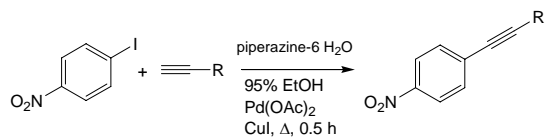


- Determination of rate constants for different solvent mixes;
- Titration using microburets; 118  $\mu$ L of t-pentyl chloride, 10 mL of solvent.

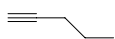
Adapted from: a. *Modern Experimental Organic Chemistry*, Roberts et al., 4<sup>th</sup> Ed., Saunders, NY, 1985; b. *Chemistry in the Laboratory*, Postma et al., 5<sup>th</sup> Ed., Freeman, NY, 2000.



## Sonogashira Coupling



T. E. Goodwin, E. M. Hurst, A. S. Ross  
*J. Chem. Educ.* **1999**, 76, 74-75.

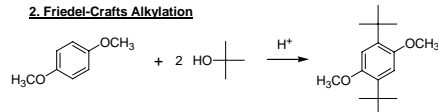


G. M. Lampman, Western Washington Univ.  
2005.

## Molecular Modeling (Spartan)

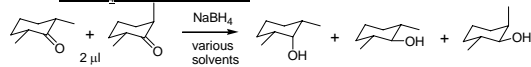
1. Solventless, RT Diels-Alder reaction, Hendrix College

2. Friedel-Crafts Alkylation



J. R. Mohrig et al., "Experimental Organic Chemistry", Freeman, NY, 1998.

3.  $\text{NaBH}_4$  reduction: COSY nmr



a. C.M. Gamer, *J. Chem. Educ.* **1993**, 70, A310; b. B.A. Hathaway, *J. Chem. Educ.* **1998**, 75, 1623; c. T.E. Goodwin, J. M. Meacham, M.E. Smith, *Can J. Chem.* **1998**, 76, 1308

## Acknowledgements

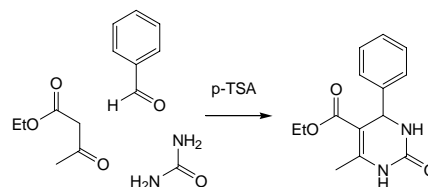
- Hendrix College organic chem. students (Courtney Rogers, Cortney Higgins)
- Shelly Bradley, Hendrix Lab Manager
- Linda Desrochers, Asst. Lab Manager
- Elephant research \$: NSF CRUI #0217068
- Research Corporation (\$)
- ACS-PRF (\$)
- Anonymous Hendrix alumnus (\$)
- Riddle's Elephant Sanctuary ([www.elephantsanctuary.org](http://www.elephantsanctuary.org))



## The End

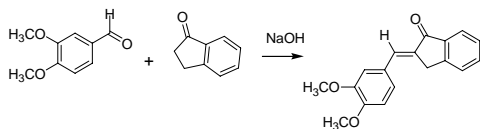


## Grindstone Chemistry-Ajay Bose



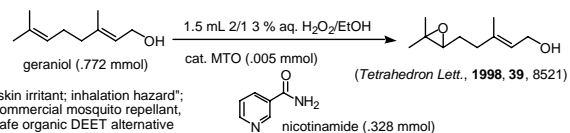
(Biginelli three component condensation  
--grind 10 min with no solvent, room temp.)

## Solventless Aldol Condensation

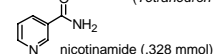


1. K. M. Doxsee, J. E. Hutchison, "Green Organic Chemistry", Thomson-Brooks/Cole, 2004.
2. G. Rothenberg, A. P. Downie, C.L. Raston, J. L. Scott, *J. Am. Chem. Soc.* **2001**, 123, 8701.

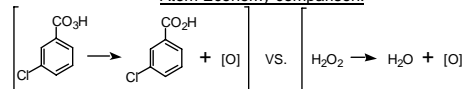
## A Green Epoxidation



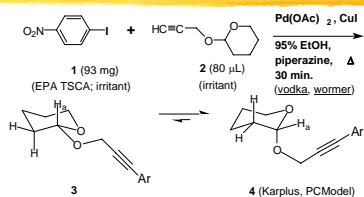
"skin irritant; inhalation hazard";  
commercial mosquito repellent,  
safe organic DEET alternative



Atom Economy comparison:



## Palladium-catalyzed coupling



Goodwin, T. E.; Hurst\*, E. M.; Ross\*, A. S.  
*J. Chem. Educ.* **1999**, 76, 14-75.  
(\*undergraduates)

## The Ideal Synthesis-P. Wender

"Progress in the advancement of synthesis can be measured by parameters such as the step count, overall yield, selectivity, cost, scale, **resource requirements**, **waste stream**, development time, execution time and personnel."

P.A. Wender et al., *Chemistry & Industry* 1997, 19, 765-769.

## Green Organic Chemistry: An Elephantine Task



## Temporal Gland Secretion



## GREEN EDUCATION: Discuss experiments with students

- Explain experiment choices and rejections
- MSDS discussions (**caffeine**: “toxic if swallowed; irritating to eyes, respiratory system, and skin; target organs: central nervous system, heart”)-**risk assessment**
- use natural products and familiar chemicals (vodka, rubbing alcohol)

## Why Green Chemistry?

- **It’s the right thing to do**, for the environment, for our students, for ourselves.
- **It makes you feel good** about being a chemist.
- **It’s great p.r.** Students like it, as do administrators, public officials, the media, and (we hope) granting agencies.

## Two Simple Questions and a Warning

- What’s **green** about it?
- What’s not **green** about it?
- Pasteur pipets, disposable gloves, etc.