Microwave-Mediated Synthesis: A Green Chemistry Technology

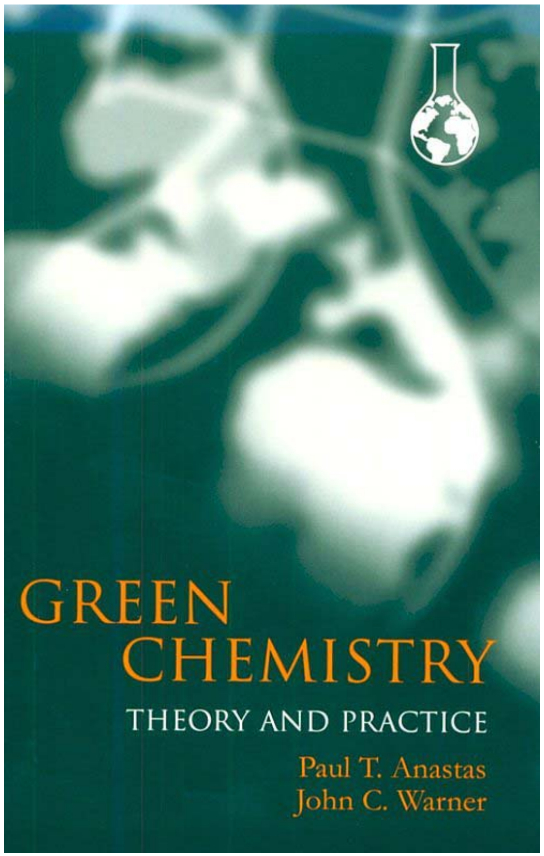
Michael Pollastri

Pfizer Global R&D – Cambridge Labs

Microwave Assisted Organic Synthesis Symposium

5 October 2004

What Is Green Chemistry?



"…the utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture and application of chemical products."

*Source: Paul T. Anastas and John C. Warner, *Green Chemistry: Theory and Practice* (New York, NY: Oxford University Press Inc., 1998). ISBN 0 19 850698 8

The 12 Principles of Green Chemistry

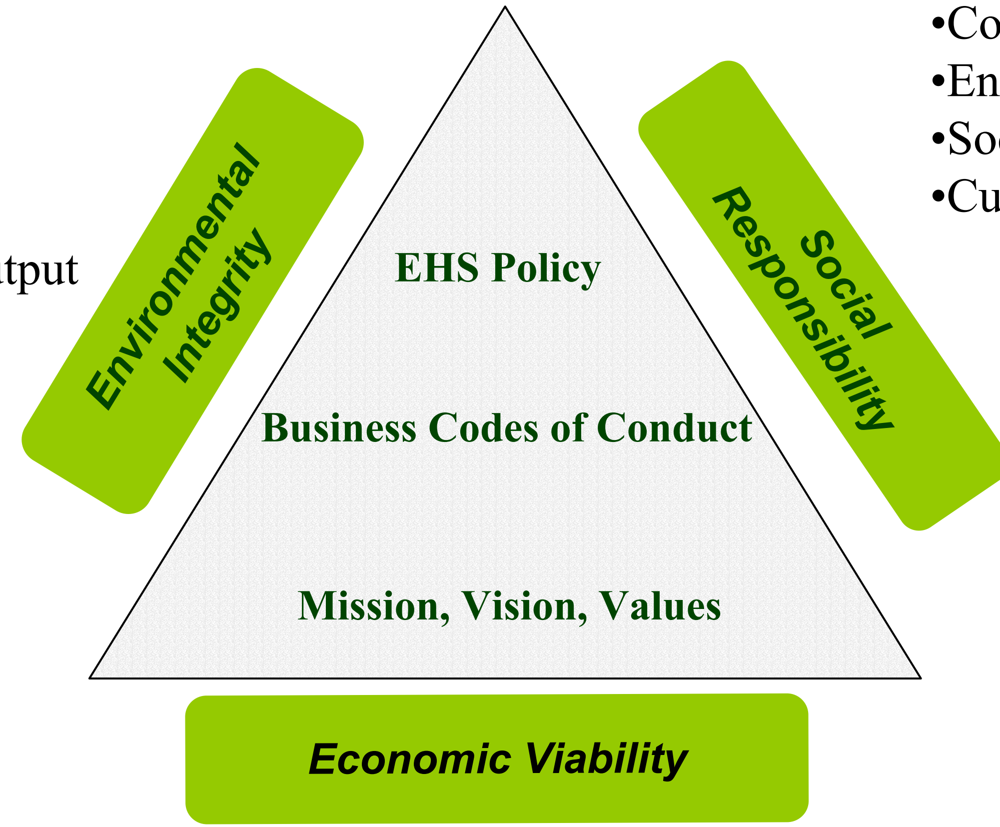
- Prevention of waste
- Atom Economy
- Less Hazardous Chemical Syntheses
- Design Safer Chemicals
- Safer Solvents and Auxiliaries
- Design for Energy Efficiency
- Use Renewable Feedstocks
- Reduce Derivatives
- Catalysis
- Design for Degradation
- Real-time Analysis for Pollution Prevention
- Inherently Safer Chemistry for Accident Prevention

Green Chemistry: Theory and Practice; Paul T. Anastas & John C. Warner: 1998

Sustainability

- Efficient use of natural resources
- Minimized harm
- Climate change
- Biodiversity
- Reduce byproduct output

- Protect employees
- Competitive benefits
- Engaging in comms.
- Social cohesion
- Cultural identity



- Dividends, share price
- Capital growth,

- Competitiveness
- Profitability

Green Chemistry – Seeking External Recognition

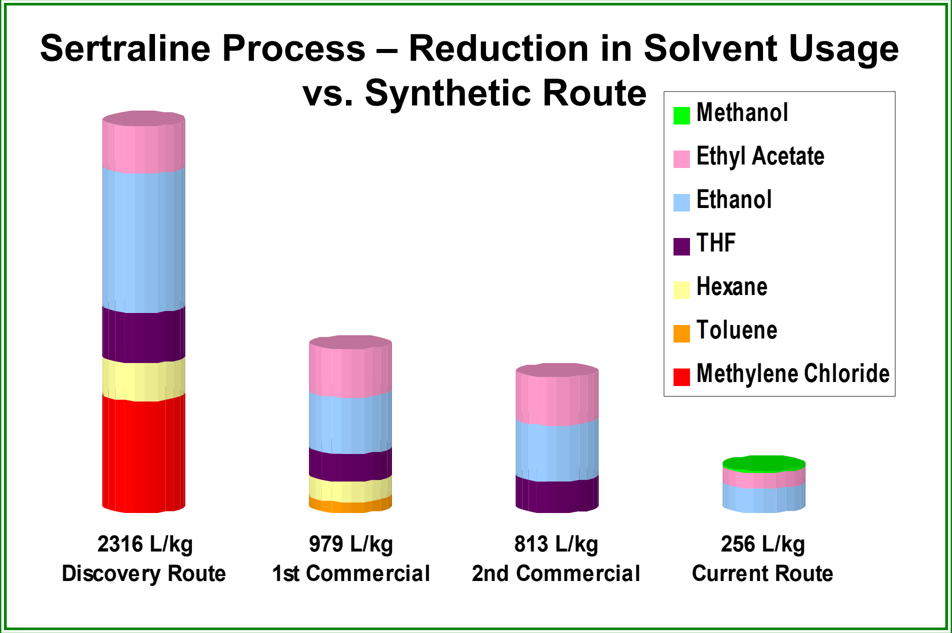
- To enhance our ability to attract and retain the best talent in the marketplace

- To assist in the communication to our external stakeholders that environmental responsibility is a key element of our R&D and manufacturing activities

- To contribute directly to our Corporate Citizenship initiatives:
    - US EPA's Climate Leaders Program
    - United Nations Global Compact
    - International Chamber of Commerce Business Charter for Sustainable Development
    - Global Sullivan Principles for Corporate Social Responsibility.

Sertraline – Presidential Green Chemistry Challenge Award 2002

Alternative Synthetic Pathway Category
for
Dramatic reduction in organic solvent usage

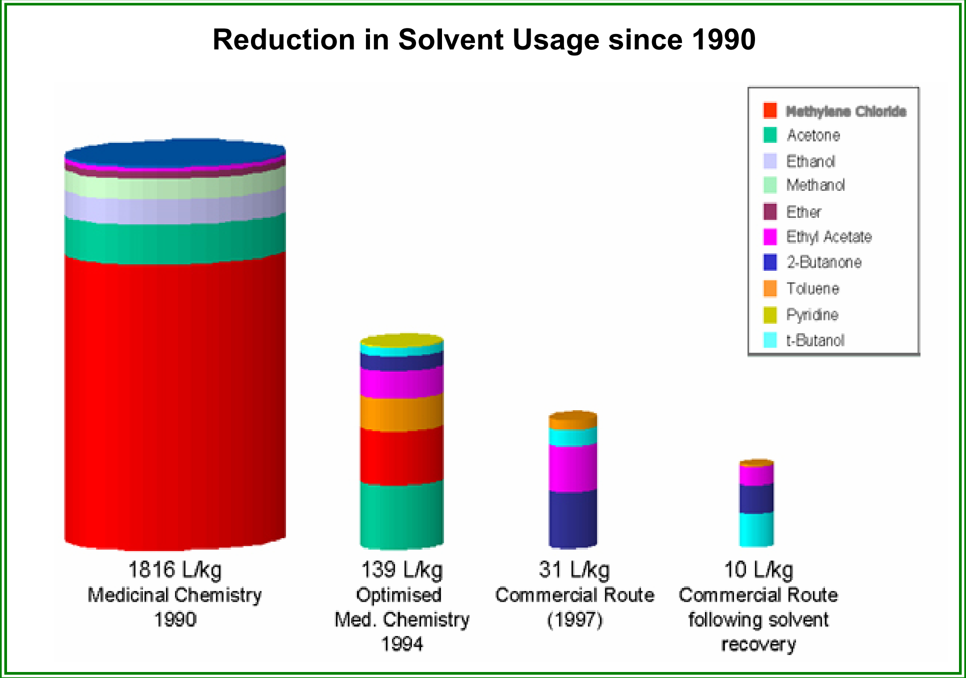


The Presidential Green Chemistry Challenge

The Presidential Green Chemistry Challenge promotes pollution prevention through an EPA Design for the Environment partnership with the chemistry community. Through high level recognition and support, the Challenge promotes innovative developments in and uses of green chemistry for pollution prevention. EPA's Office of Pollution Prevention and Toxics (OPPT) is leading this voluntary partnership program with other EPA offices, other federal agencies, members of the chemical industry, trade associations, scientific organizations, and academia.

Sildenafil – CRYSTAL Faraday Award 2003

For development of an environmentally-friendly method of manufacturing Sildenafil citrate, the active ingredient in Viagra.



The CRYSTAL Faraday Partnership is a virtual centre of excellence in green chemical technology accessing the considerable resources of its industrial and academic participants to promote lower-cost, sustainable manufacturing for the chemical industry. The chemical industry is facing increasing competition and pressure on costs from environmental legislation. CRYSTAL is helping industry to meet these challenges, and at the same time to build a research base of world-class quality in green technology.

For more information:

www.crystalfaraday.org

R&D Philosophy in Harmony With the Principles of Green Chemistry

	Environmentally Thinking	Economically Thinking
Atom Economy	Minimal by-product formation	More from less – incorporate total value of materials
Solvent Reduction	Less solvent waste	Higher throughput, less energy,
Reagent Optimization	Catalytic, low stoichiometry, recyclable reagents minimize usage	Higher efficiency - higher selectivities
Convergency	due to increased process efficiency	Higher efficiency – fewer operations
Energy Reduction	from power generation, transport, and use	Reduced energy reflects increased efficiency, shorter process, mild conditions
In-situ Analysis	Reduced possibility for exposure or release to the environment	Real-time data increases throughput and process efficiency, fewer reworks
Safety	Non-hazardous materials reduce risk of exposure, release, explosions and fires	Worker safety and reduced down time Reduced time on special control measures.

Microwaves: The Green Chemistry Perspective

- Rapid reactions = shorter reaction time
- Clean reactions = less purification & waste
- "Green solvents" (H_2O, EtOH, acetone) are excellent MW solvents
- Less solvent usage
  - 0.5-5mL per reaction
- Low energy input
  - (max=300w, typical rxn ~20w)

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Good solvents for MW heating

Solvent	BP	Temp Achieved	Pressure
N,N-Dimethylformamide (DMF)	153	250	5
Water	100	220	16
Ethanol	78	180	16
Methanol	65	160	17
N-Methylpyrrolidinone (NMP)	202	220	5
Ammonium hydroxide (28%)	-	150	19
Dimethylsulfoxide (DMSO)	189	250	5
Pyridine	115	220	8
1,2-Dimethoxyethane (DME)	85	200	6
Dichloromethane	40	140	15
Acetonitrile	86	200	10
o-Dichlorobenzene	190	250	2
1,4-Dioxane	101	200	4
Acetone	56	150	5
Tetrahydrofuran	65	180	12
Xylene	137	150	2
1,2-Dichloroethane	83	170	2
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Diethyl ether	35	135	4

Source: Personal Chemistry AB, Uppsala, Sweden

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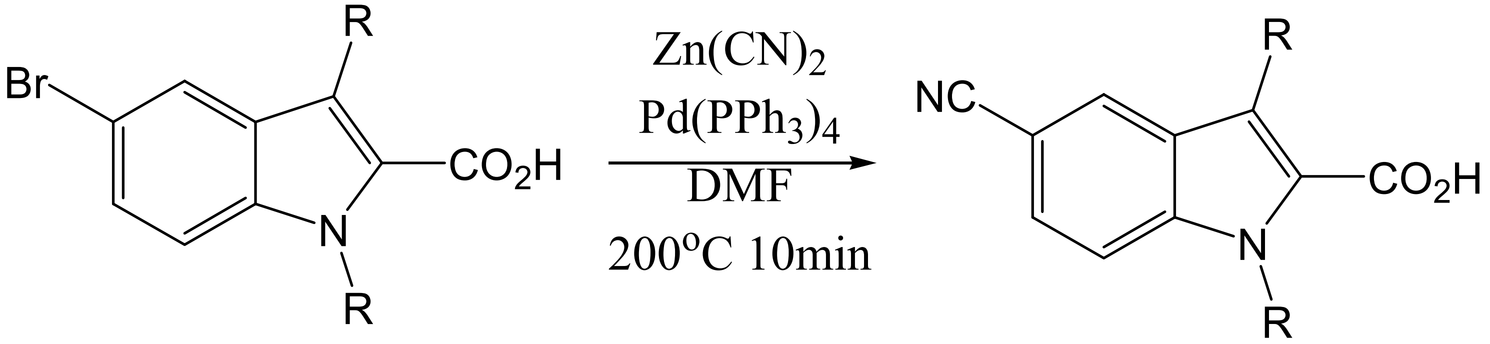
Open Access Microwave Units

- Emrys Optimizer units as walk-up instruments
- Growing enthusiasm for MW heating as a part of the organic chemist's toolbox
  - Periodic departmental training
  - Internal seminars and posters
  - Advice made readily available
  - Word of mouth of success stories
  - Ease of use – very shallow learning curve

Chemistry Examples

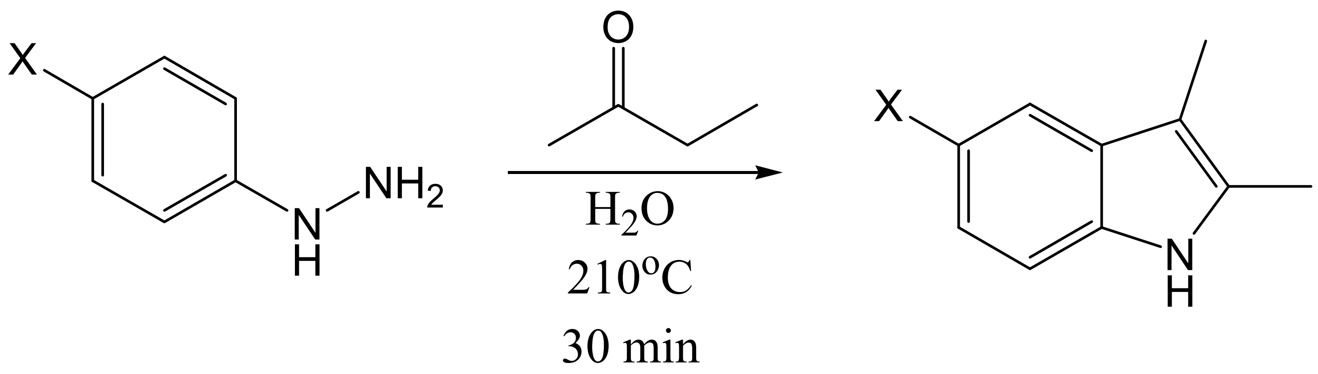
Striking rate enhancements



Conventional: 100^{o}C, 72h, ~75% conversion

MW Result: 100% conversion in 10min

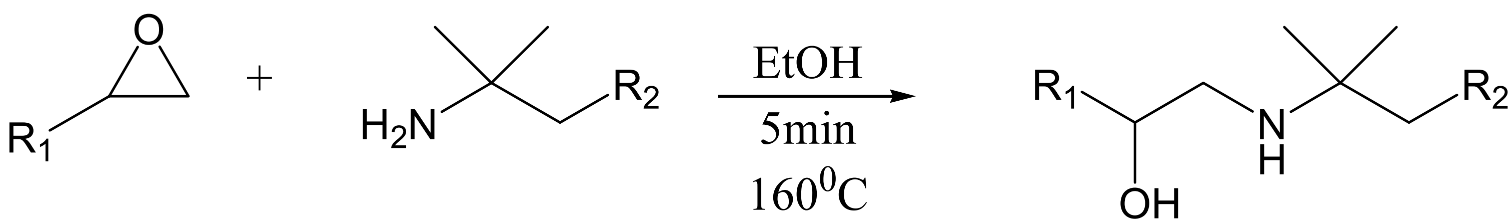
Clean Fischer indole syntheses



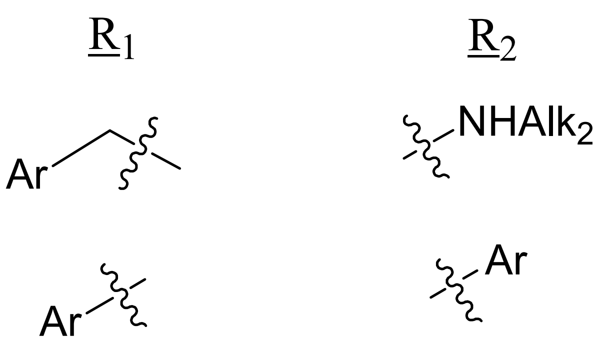
Quantitative yield, except where X=NO_2

Compare to 48h reflux in water, X=CN, 60% yield

Successes in Lewis acid-free epoxide opening

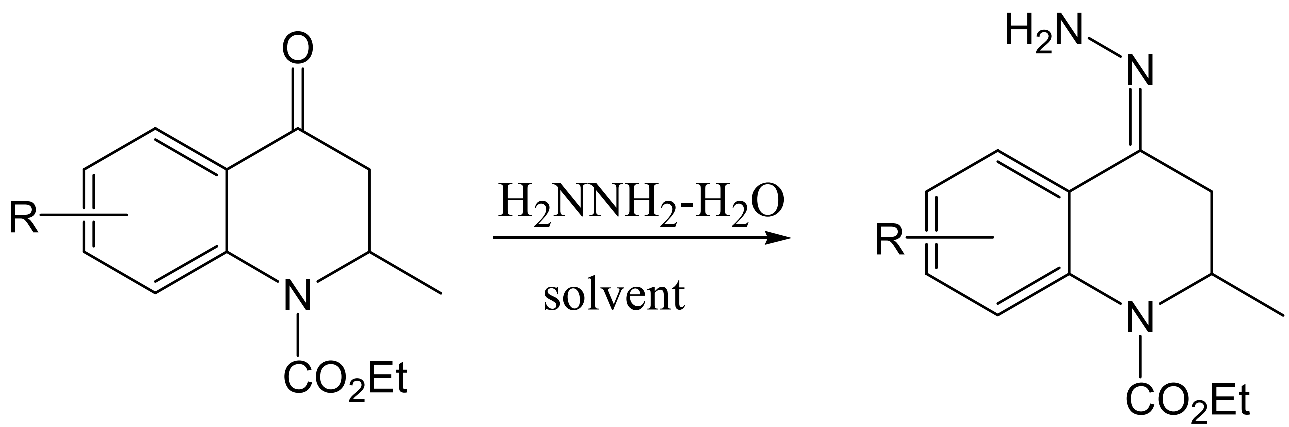


10-51% yields



Comparable yields if refluxed 2-3d in EtOH

Rapid method development



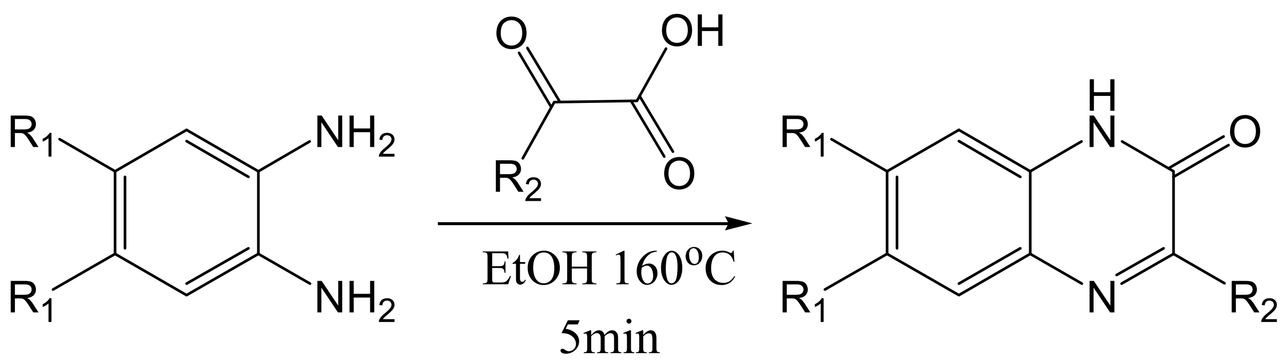
Conventional method:

- 48h, toluene, rt - ~25-50% conversion

Microwave method:

- 10min, toluene 175^oC - req. HPLC purification
- 30min, EtOH, 175^oC - 92% isol yield (aq. workup)
- 30min, EtOH, 150^oC - quant. yield (evap. workup)

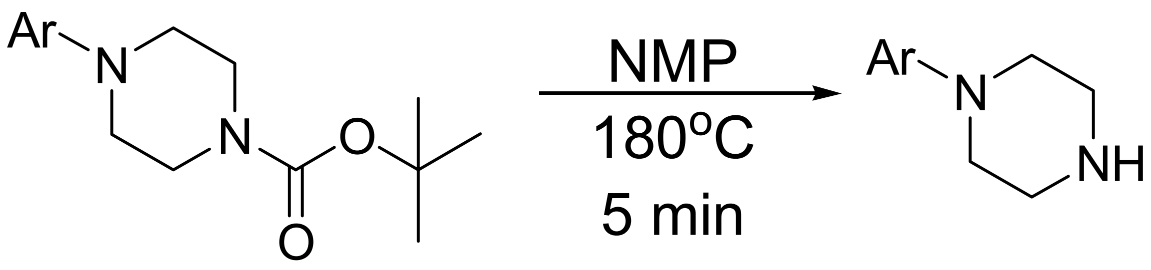
Synthesis of quinoxalinones



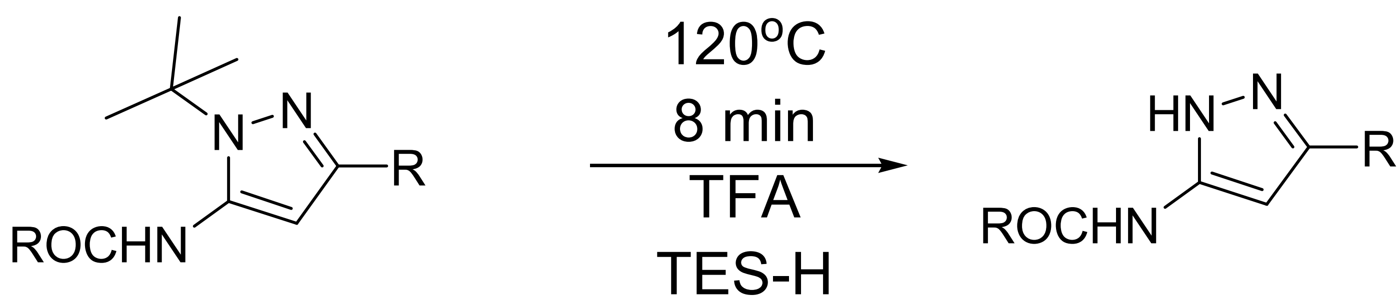
80-95% yields

Conventional: *Overnight reflux in EtOH, moderate yields, difficult to purify*
Microwave: *Reagent suspension irradiated, product suspension isolated.*

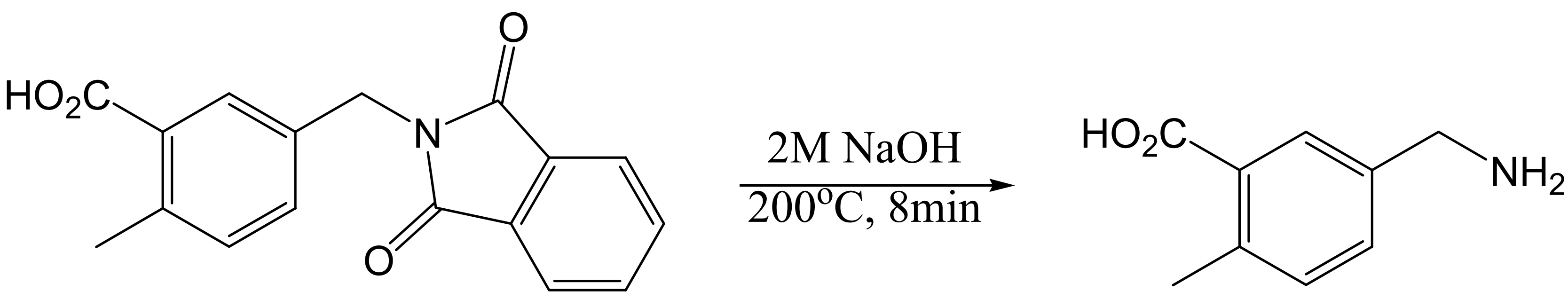
N-Deprotections



quant yield
monitor progress by
pressure increase



Milder phthalimide deprotection

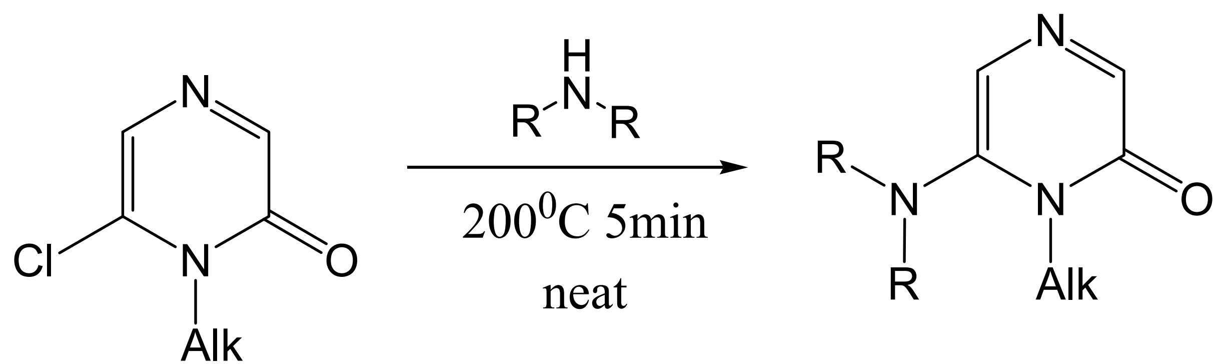


70%

Conventional conditions are harsh
- -refluxing with excess hydrazine
- -reflux 48h 6M NaOH

Microwave conditions faster and milder
- -able to achive some rxns with 2eq NaOH in water

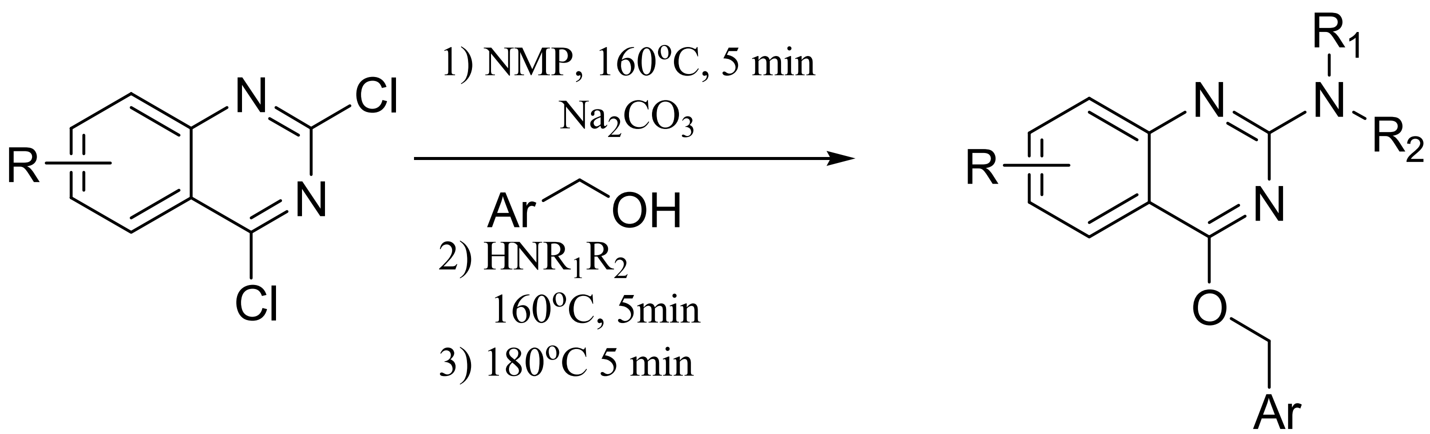
Solvent-free reactions



51-80%

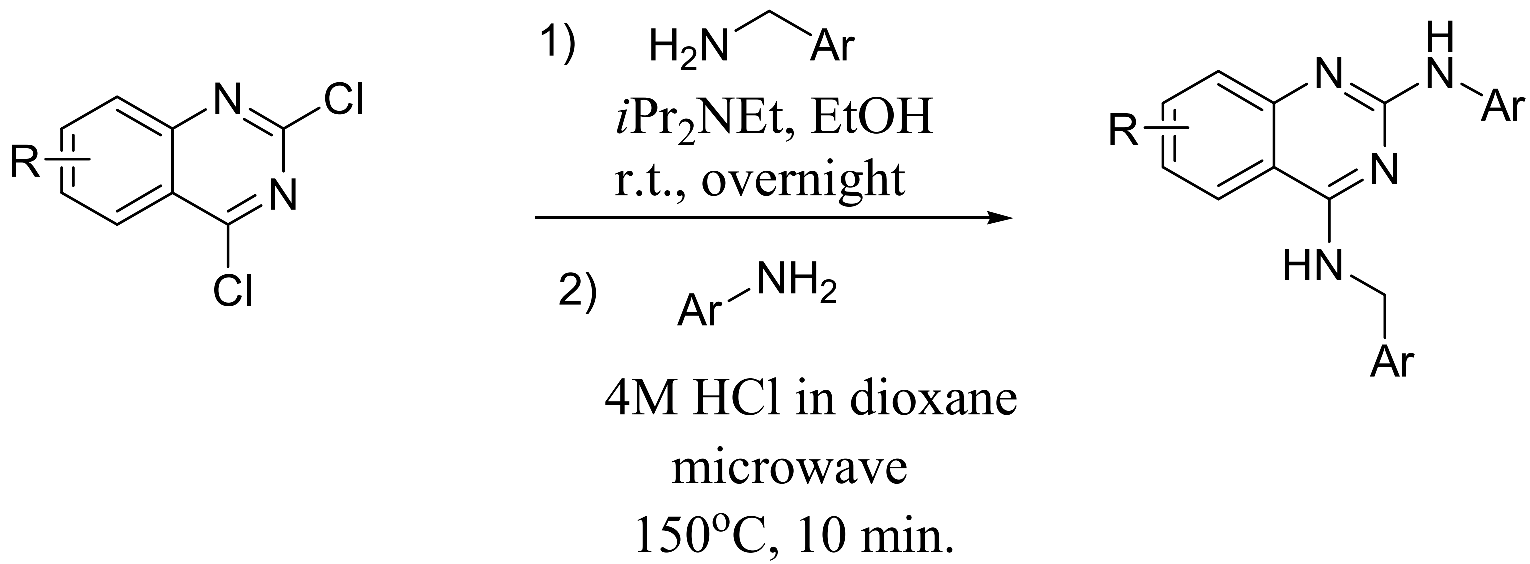
conventional method: 52% yield after heating o/n in methoxyethanol

Multistep/One pot sequences



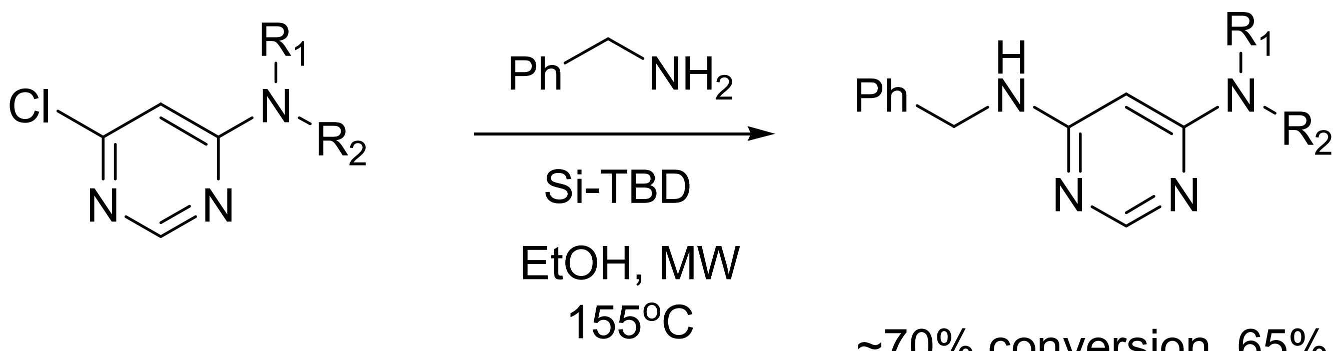
Three steps, one vial, one purification !

Multistep/One pot sequences



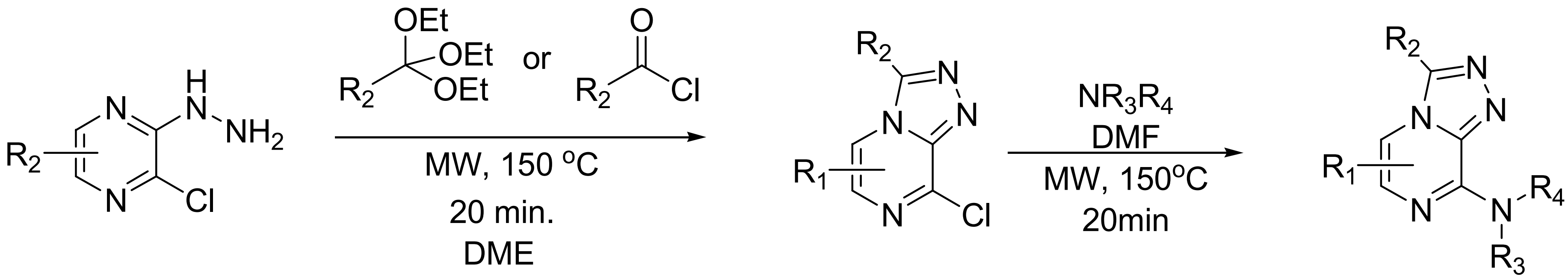
Purification consisted of filtration of reaction (>95% purity)

Stubborn aryl halide displacements

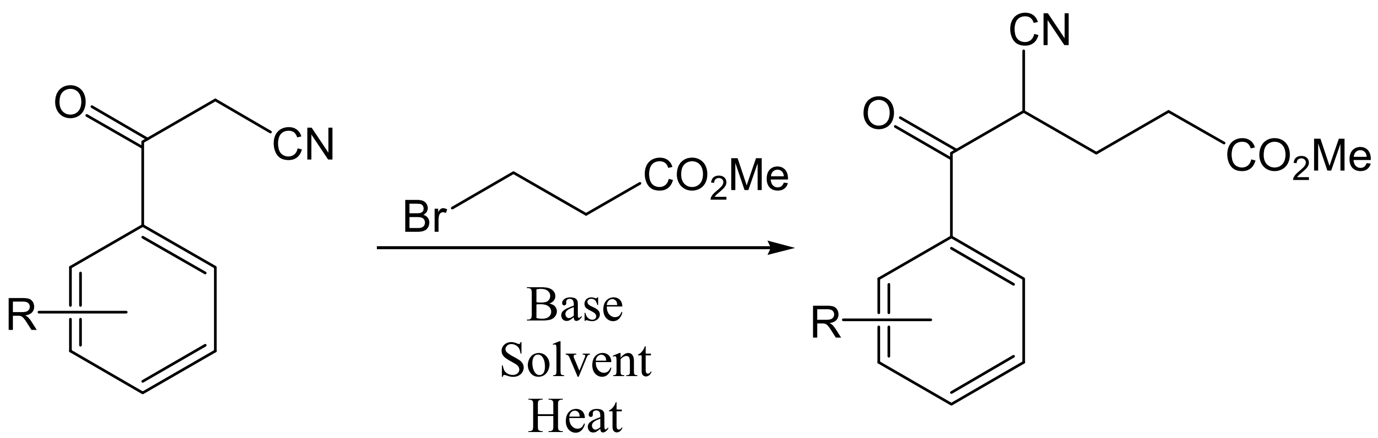


~70% conversion, 65% isolated yield
after 5 2-hour cycles

Preparation of fused triazoles



Alkylations



Conventional Conditions:

- iPr$_2$NEt, MgCl$_2$ (literature precedent) - no reaction
- DBU/DCE, 50^{o}C - 50% conversion

Microwave Conditions:

- DBU/DMSO, 150^{0}C, 5min, clean conversion

Summary
Microwave Heating and Green Chemistry

- Development and optimization of Pfizer processes is a continuum from the first gram to the last kilogram.

- Introduction of Green technology in discovery efforts can help streamline process improvements down the R&D road.

- Microwave technology has become easy for medicinal chemists to apply in a beneficial and reproducible manner, providing a Green technology that is widely embraced.

Acknowledgements

- Pfizer – Groton
  - Ravi Garigipati
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