

**Enabling Tools in Drug Discovery**  
**Microwave-Assisted Organic Synthesis**  
**&**  
**Automated Flash Chromatography**

*Shahnaz Ghassemi, Ph.D.*

*Boston, MA*

*05/26/05*



# Discovery in Chemistry



# MAOS as Enabling Tool in Drug Discovery

**Shortens  
Reaction Time**

**Increases Product  
Purity**

**Reproducible  
Results**

# MAOS Reaction Optimization

## Selecting Initial Time and Temperature



### Arrhenius Equation

$$K = A e^{-DG/RT}$$

- Increase ionic concentration
- Add polar co-solvent  
10luene, Dioxane, THF, DCM

# Presentation Overview

- **Microwave-Assisted Synthesis**

**Sulfamide**

- **Solid Phase Microwave Assisted Synthesis**

**1,3,5-Substituted triazine**

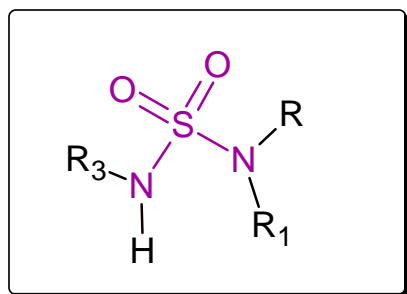
- **Rapid Purification of Compounds Synthesized by MAOS**

**Normal and reversed phase Flash Chromatography**

# Microwave-Assisted Sulfamide Synthesis

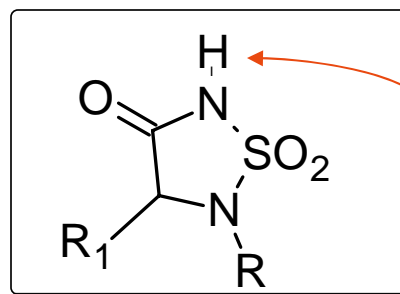
# Sulfamoyl Synthesis

- The sulfamide compounds are noted for their potent antibacterial activity



Anti-cancer

PTB-1b inhibitors may have role in controlling blood sugar in diabetes

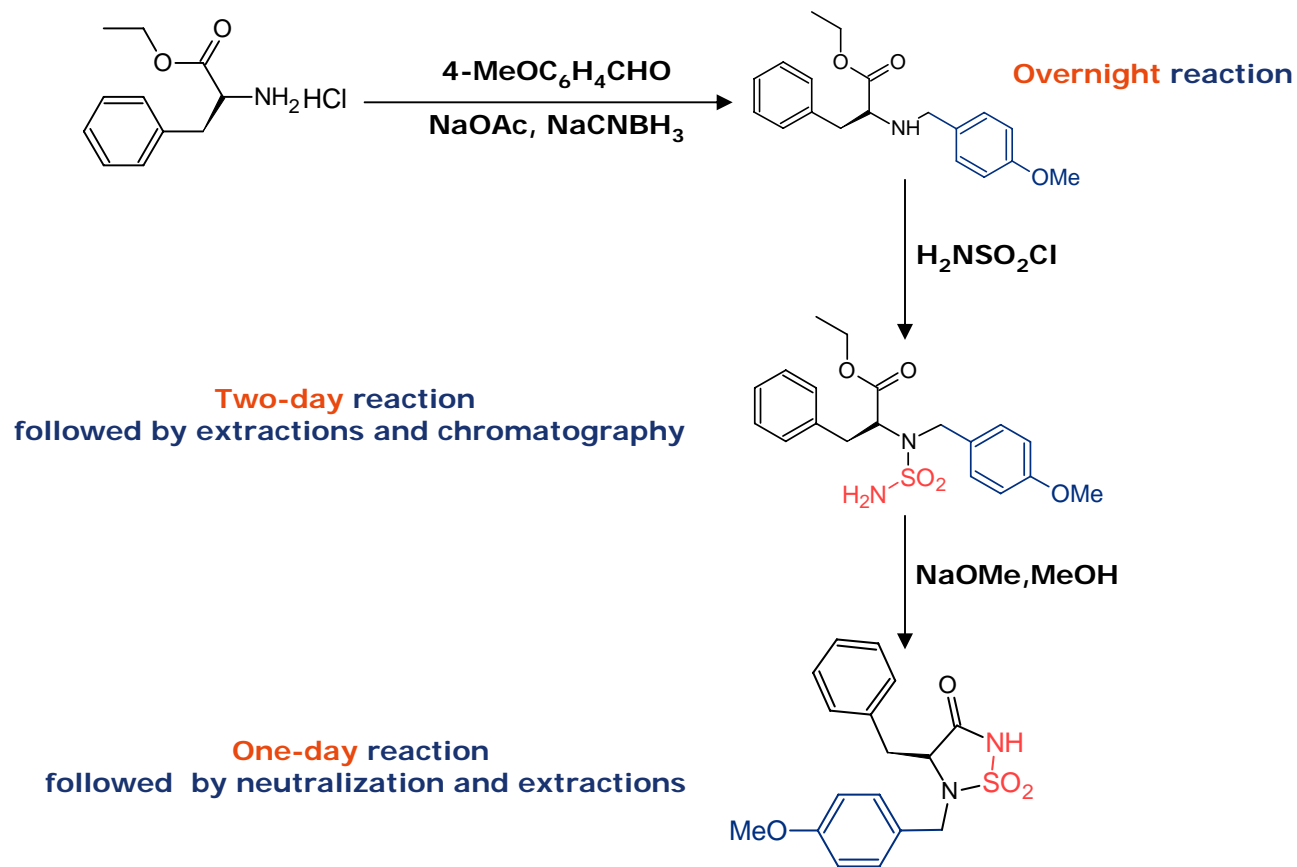


$Pk_a$  comparable to carboxylic acid ~ 4

Crop Protection Agents

Artificial sweeteners

# Literature Procedure of Sulfahydantion



**Total time for Conventional synthesis: 4 days**

Fernaando Albericio, Lois M. Bryman, Javier Garcia, Enrique I. Michelotti, Ernesto Nicolas, and Colin M. Tice, *J. comb. Chem.* 2001, 3, 290-300



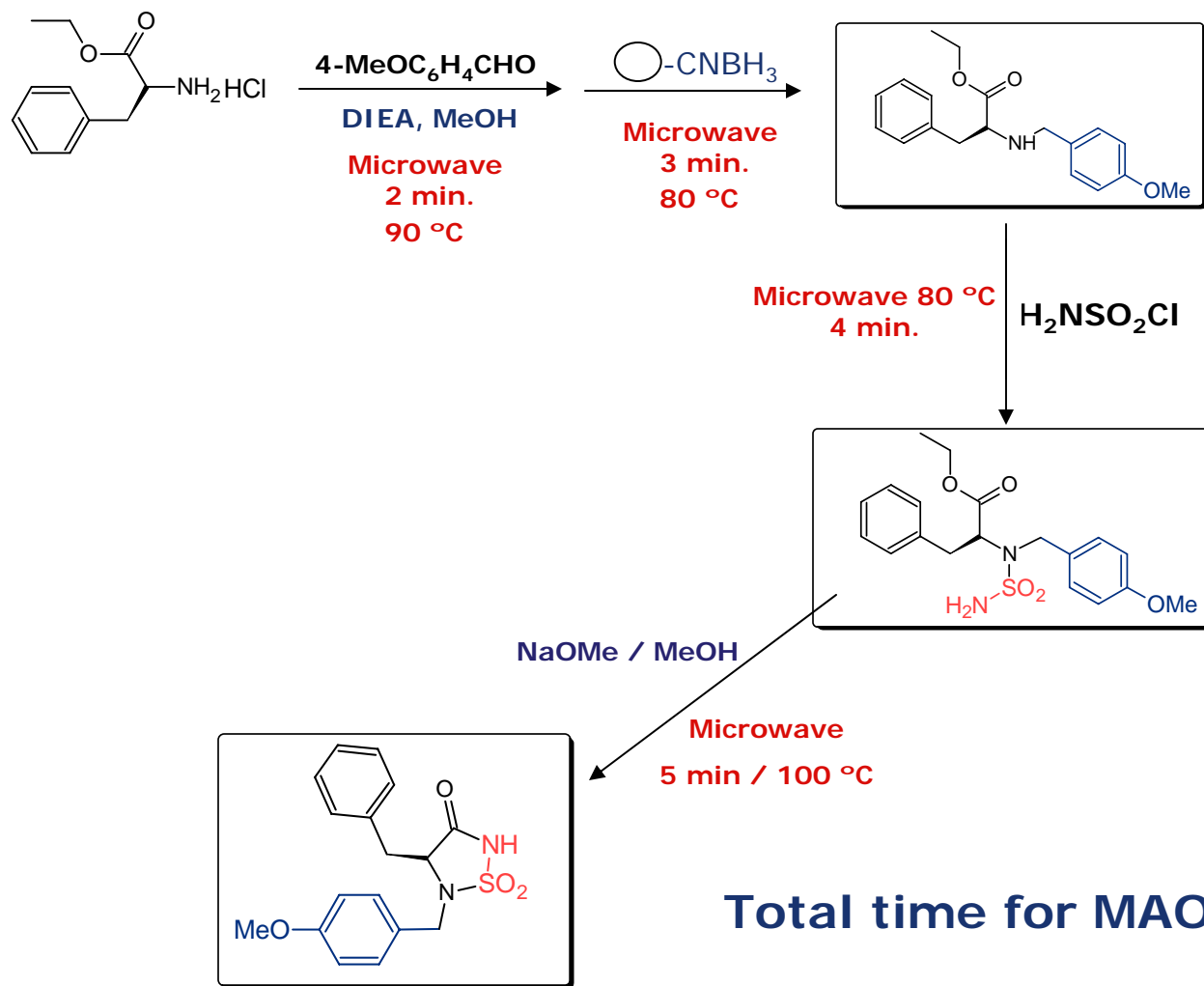
# Modifications in Sulfahydantion Synthesis Procedure

- **Microwave irradiation used to shorten reaction time**
- **Automated flash chromatography used for fast isolation of product**

# Instrumentation for MAOS

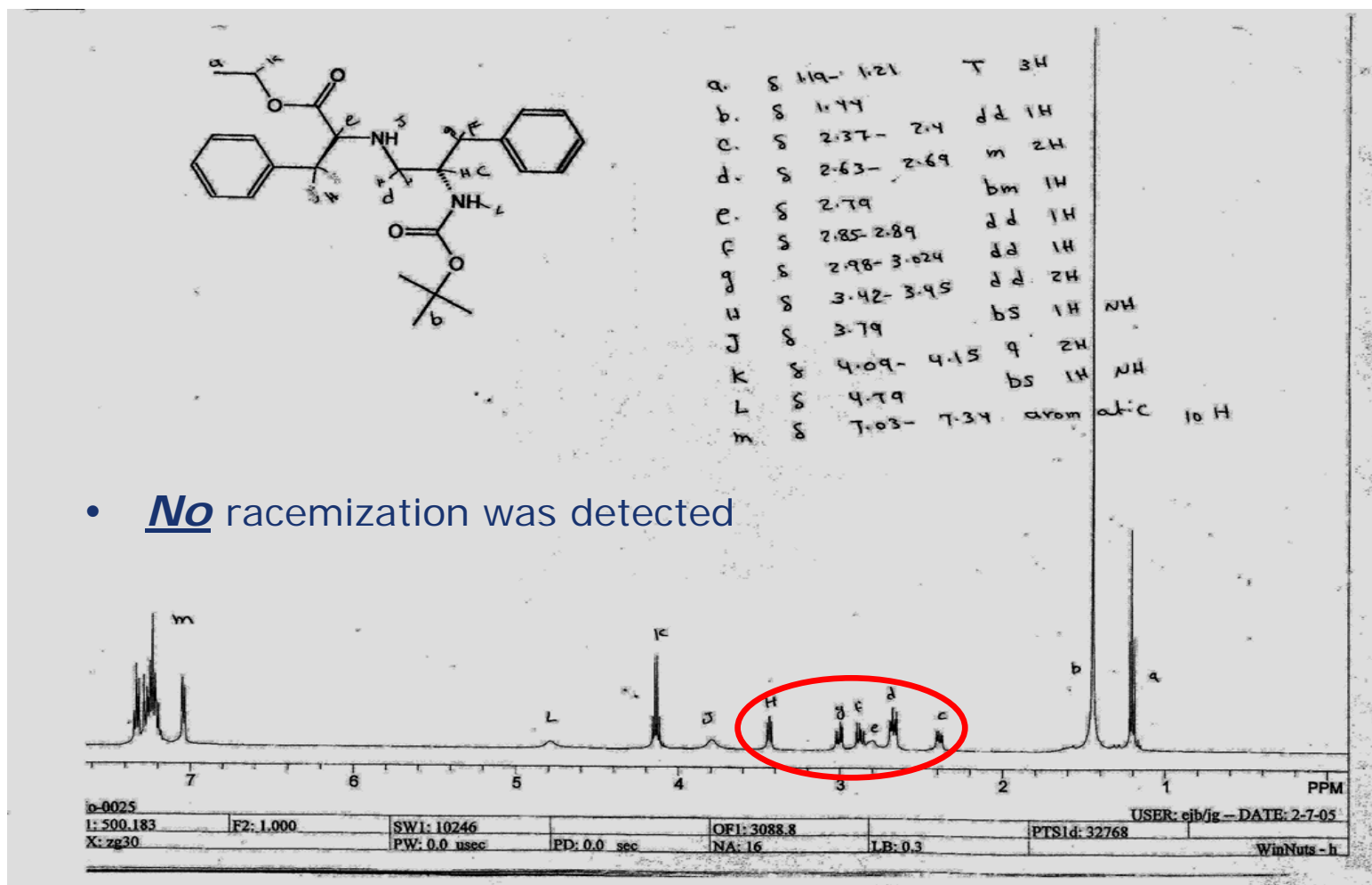


# Microwave-Assisted Sulfahydantion Synthesis



**Total time for MAOS: 15 min**

# Microwave-Assisted Reductive Amination Racemization Study

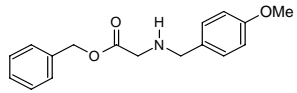
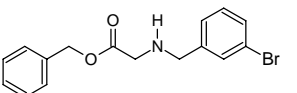
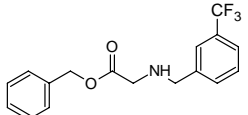
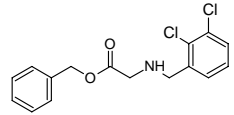
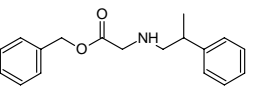
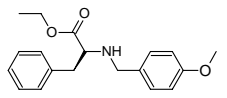
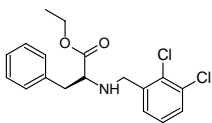
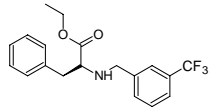
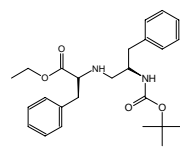


# Microwave-Assisted Amine Synthesis

Method A: 2 eq. 1 M NaCNBH<sub>4</sub>

Method B: 2 eq. Si-CN BH<sub>4</sub>

Method C: 2 eq. PS-CN BH<sub>4</sub>

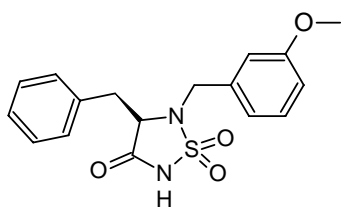
					
Method A	79%	83%	84%	68%	
Method B	74%	79%	85%	63%	
Method C	72%	80%	73%	59%	
					
Method A	85%	89%	88%	88%	75%
Method B	79%	84%	80%	78%	73%
Method C	80%	80%	77%	81%	65%

# Sulfahydantion Compounds

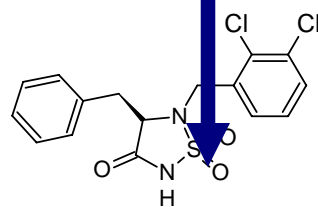
## Isolated yields

Conventional method of synthesis

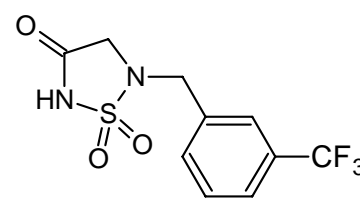
4 days



65%

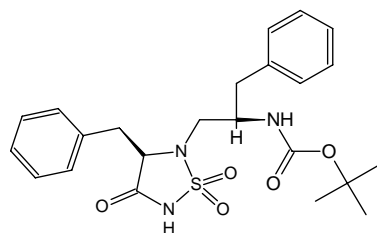


68%



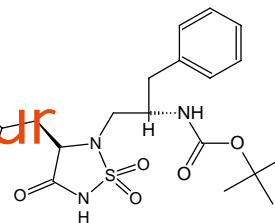
87%

Microwave-assisted organic synthesis



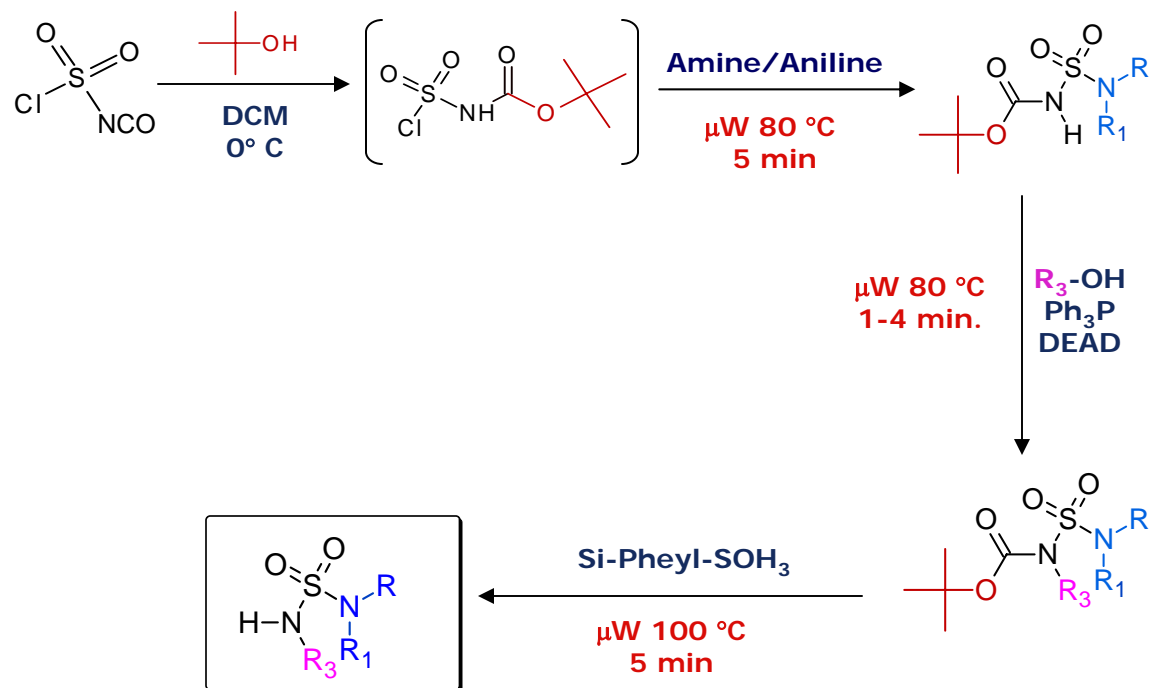
79%

1 hour



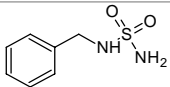
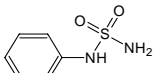
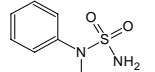

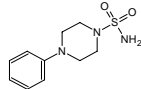
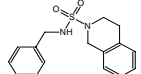
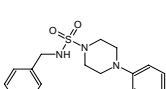
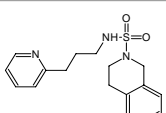
79%

# Microwave-Assisted Acyclic Unsymmetrical Sulfamides Synthesis



**Total time for MAOS: 15 min**

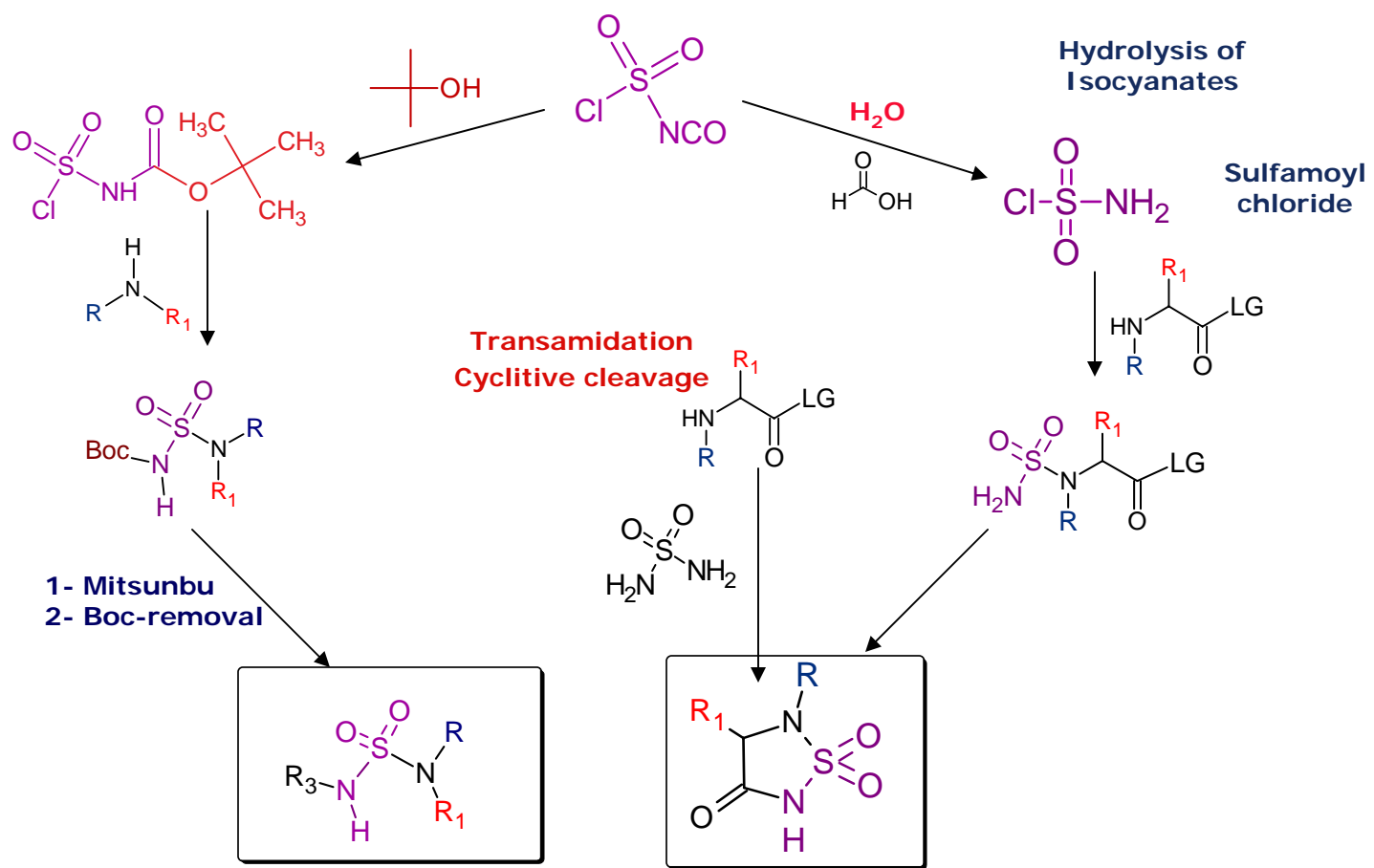
# Acyclic Unsymmetrical Sulfamides

#	Products	% Yield	M <sup>+</sup> + Na	<sup>1</sup> H NMR
15		90	209.11	4.19 (s, 2H), 4.2 (s, 2H), 7.257 (m, 6H)
16		75	195.03	2.48 (s, 2H), 6.93(t, 1H), 7.05 (m, 2H), 7.16 (m, 2H), 9.22 (s, 1H)
17		75	209.05	3.17 (s, 3H), 5.02 (s, 2H), 7.36 (m, 5H)
18		61	235.63	0.92 (t, 2H), 3.37 (t, 2H), 4.19 (s, 2H), 6.89 (s, 2H), 7.16 (m, 4H)
19		91	264.02	2.51 (bs, 2H), 3.11 (t, 4H), 3.21 (t, 4H), 6.83 (m, 1H), 6.98 (d, 2H), 7.389 (t, 2H)
20		71	325.38	2.52 (m, 1H), 2.79 (t, 2H), 3.44 (t, 2H), 4.20 (d, 2H) 4.29 (s, 2H), 7.33 (m, 9H)
21		92	353.99	3.12 (t, 4H), 3.06 (t, 4H), 4.19 (s, 2H), 4.68 (s, 1H), 6.832 (m, 3H), 7.22 (m, 7H)
22		89	354.42	1.92 (m, 2H), 2.68 (m, 4H), 3.23 (m, 2H), 3.49 (m, 2H), 4.54 (s, 2H), 5.68(bs, 1H), 7.1-7.5 (m, 8H)

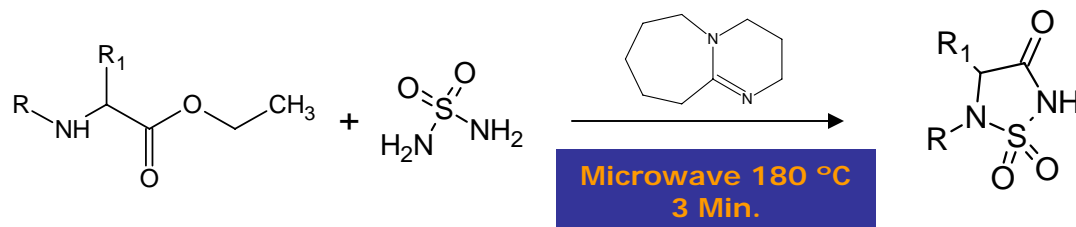
\* Shahnaz Ghassemi, Kristin Fuchs, *Molecular Diversity*, vol.9, issue 4, 2005



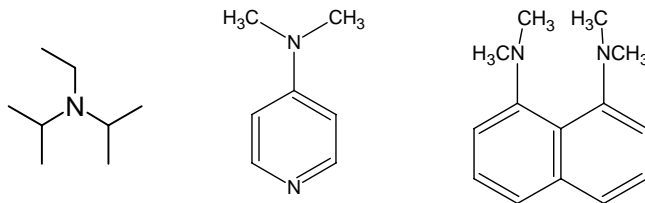
# Review in Literature Procedure



# One Step Sulfamoylation & Cyclization



- Alternative non-nucleophilic strong base have examined



# Microwave-Assisted Solid Phase Synthesis

# Growing Interest in Microwave-Assisted Solid Phase Synthesis

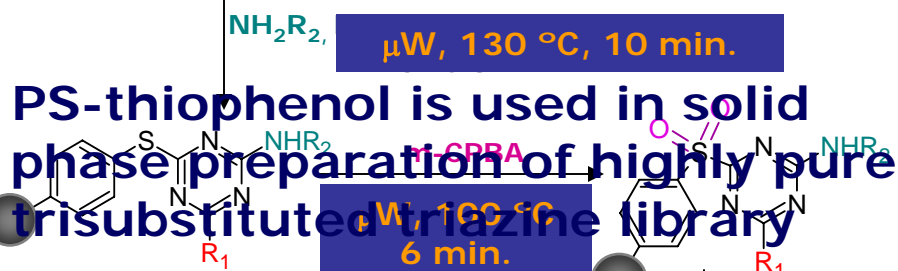
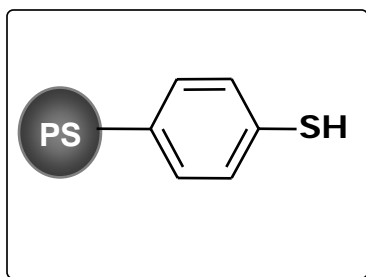
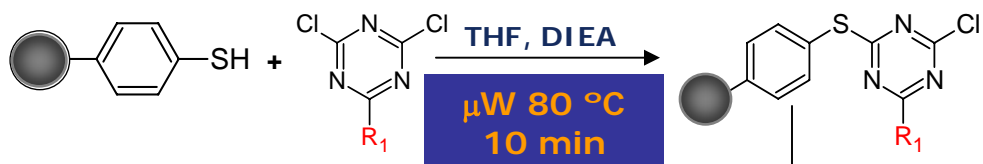
**significantly Shortens  
Reaction Time**

**Reduces Solvation  
Problem**

**Reduces Degradation  
of the Polymer Support**

Yu, H. M.; Chen, S. T.; Wang, K. T. *J. Org. Chem.*, **1992**, *57*, 4781  
Larhed, M.; Lindeberg, G.; Hallberg, A. *Tetrahedron Lett.*, **1996**, *37*, 8219  
Hoel A. M. L.; Nielsen, J. *Tetrahedron Lett.*, **1999**, *40*, 3941

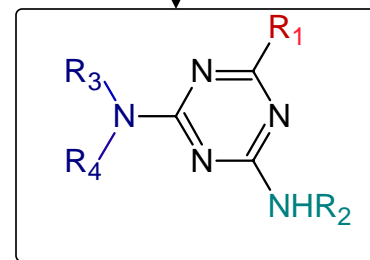
# Literature Reported Procedure 1,3,5-Substituted Triazine



PS-thiophenol is used in solid phase preparation of highly pure trisubstituted triazine library

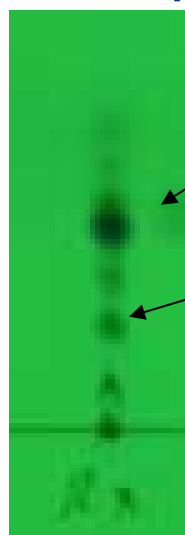
Total time: 18 hours

40 min



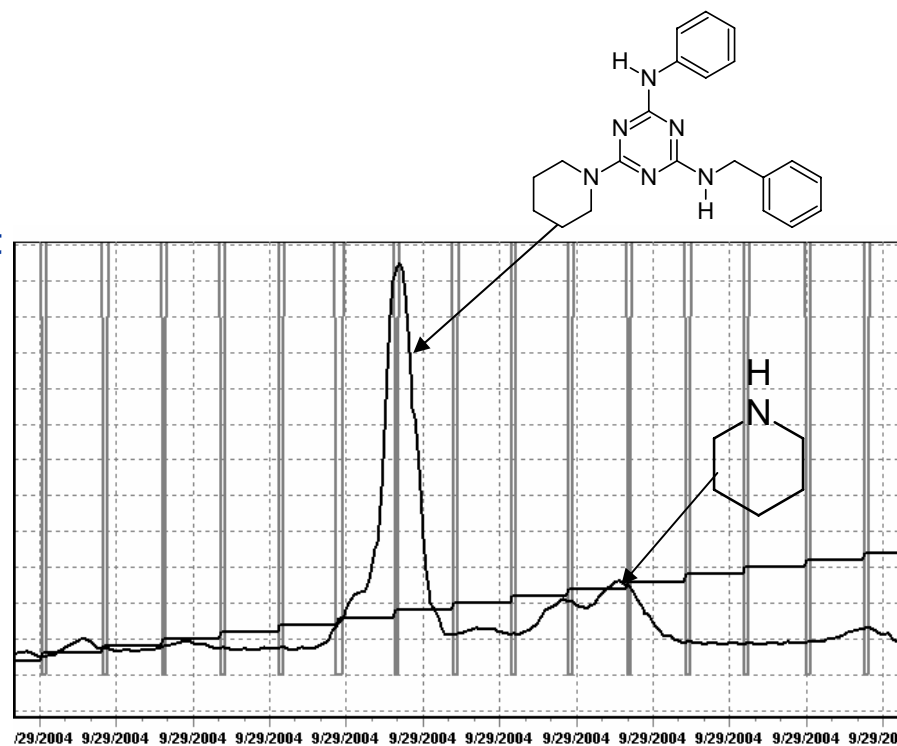
# Enhancing Triazine Purity

TLC: Crude product



Product

Piperidine



- MAOS+ Flash = Overall 1 hr.
- purity >99% isolated yield 64%



**Automated Flash Chromatography  
in Rapid Isolation of Organic  
Product**

# Conventional Workup & Purification Of Reductive Amination Product

1. Solvent is evaporated
2. The residue is suspended in 5% aq NaOH and extracted with EtOAc (x2)
3. Organic extract is dried over  $\text{MgSO}_4$
4. Concentrated under reduced pressure
5. Crude product is taken up in EtOAc and extracted with 5% HCl (x 2)
6. The combined aqueous extracts is neutralized with solid  $\text{K}_2\text{CO}_3$
7. Cooled to  $<5\text{ }^\circ\text{C}$  in an ice bath, and treated with 50% aq NaOH
8. The aqueous layer was extracted with EtOAc (x 3)
9. The EtOAc extracts is combined, dried over  $\text{MgSO}_4$  and concentrated



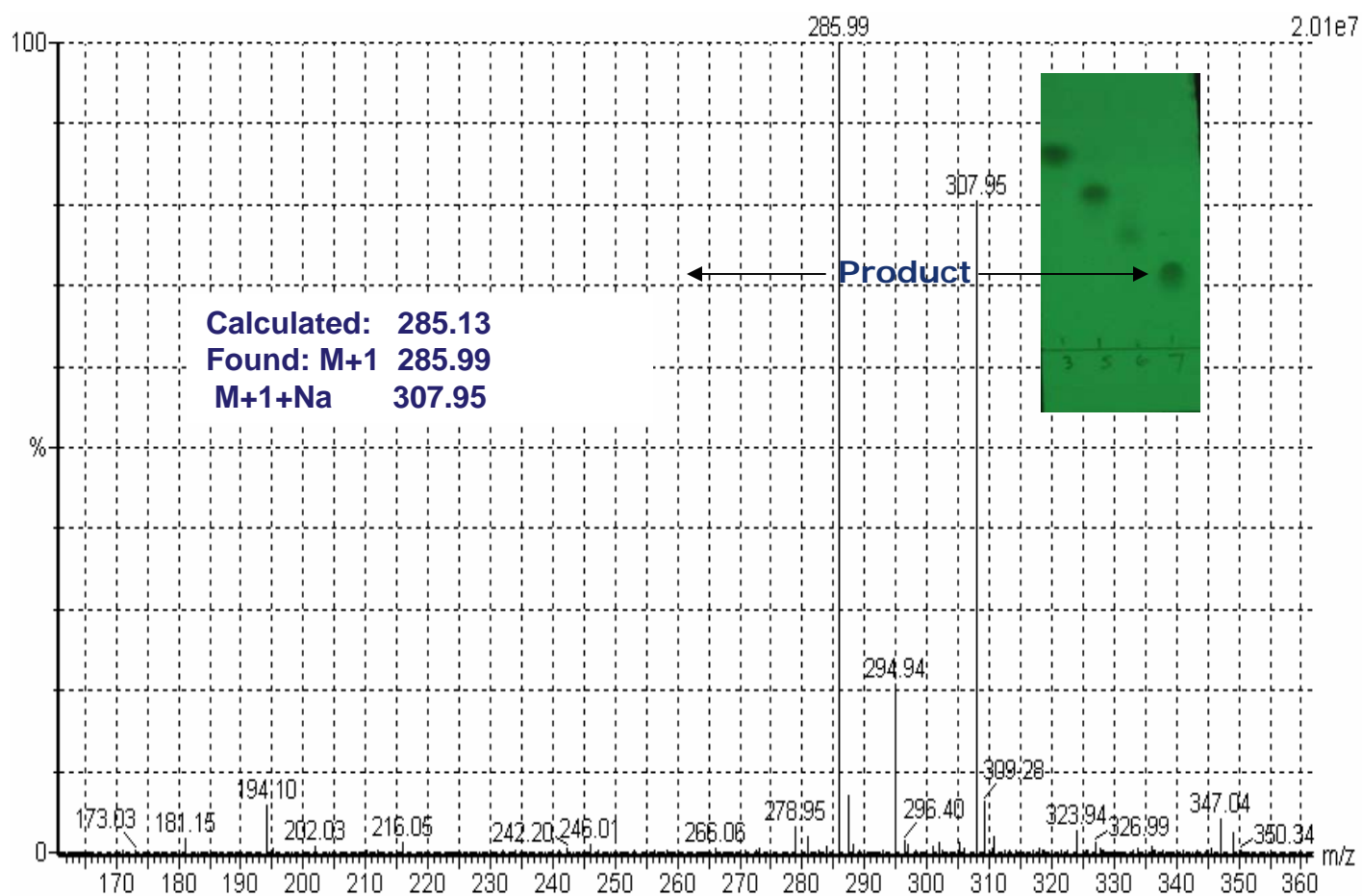
# Flash Workup & Purification

1. Reaction mixture transferred onto Samplet
2. Samplet inserted onto Flash cartridge
3. Cartridge loaded into barrel
4. *Automated Flash* chromatography was run

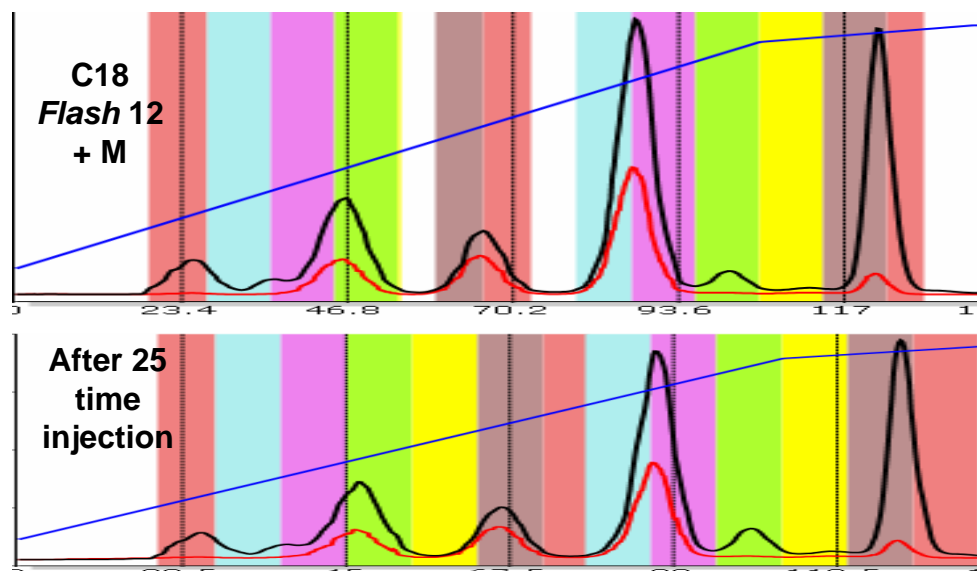
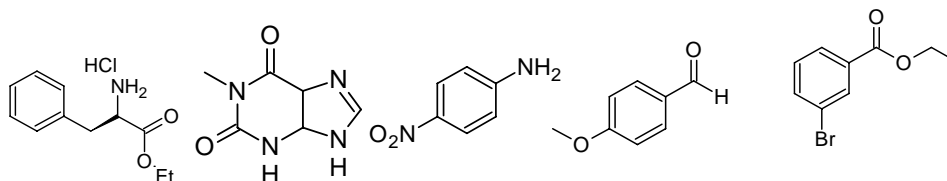


SP Automated Purification System

# Flash Purification of Amine



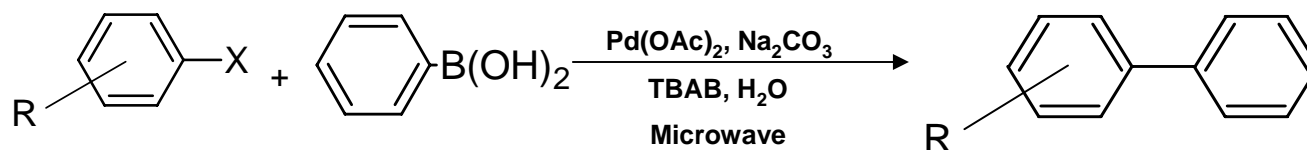
# C18 Flash Cartridge Performance



Consistent resolution, retention  
and same peak shape

# C18 Flash Purification in Suzuki Reaction

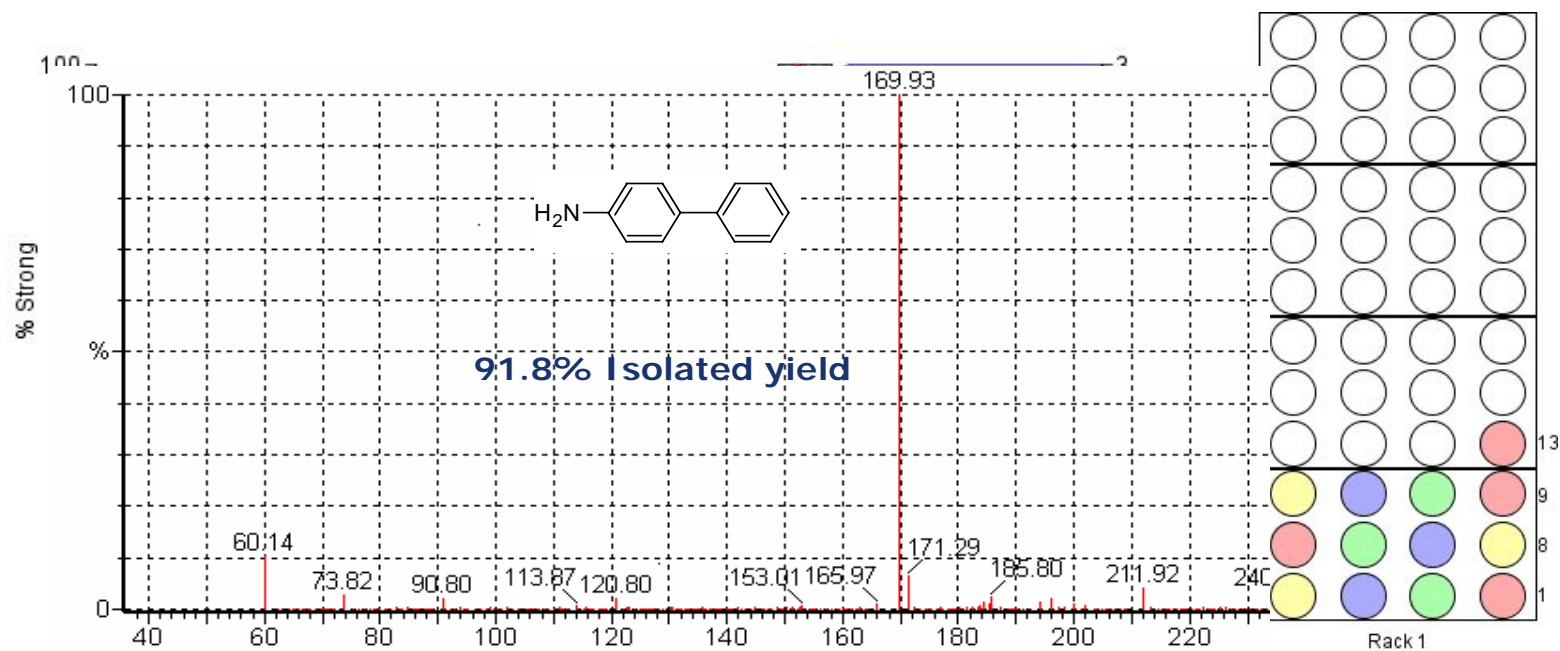
- Water can be used as solvent in microwave-assisted Suzuki reaction
  - Reaction is completed in minutes



- The product is isolated through extraction followed by chromatography

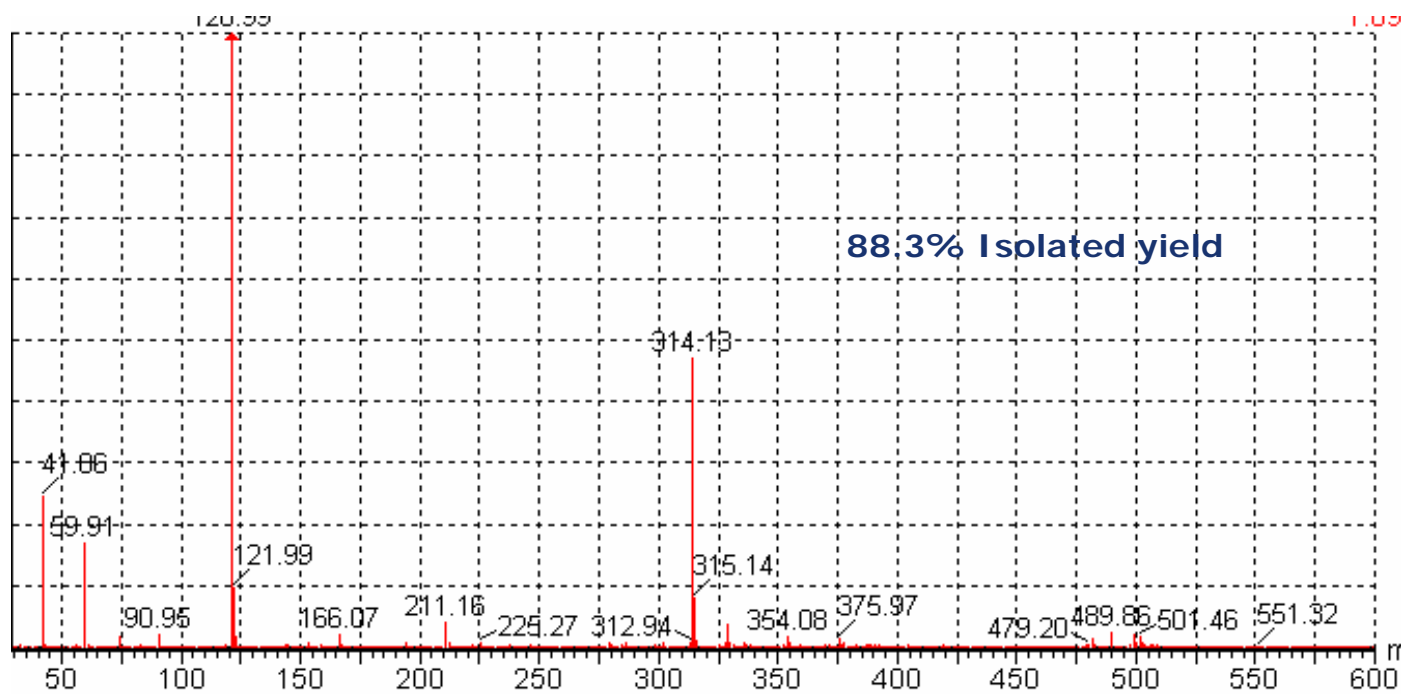
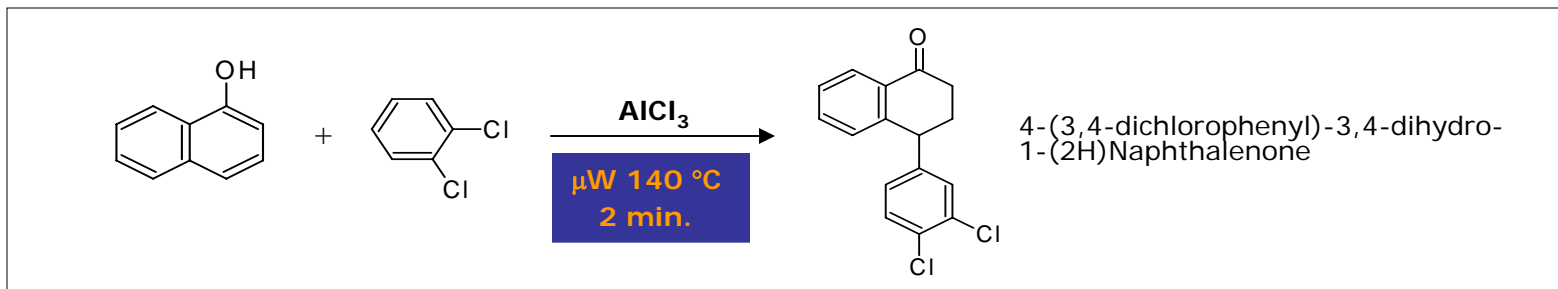
\* N. E. Leadbeater and M. Marco, *Org. Lett.*, 2002, 4, 2973

# C18 Flash Purification in Rapid Purification of Suzuki Reaction



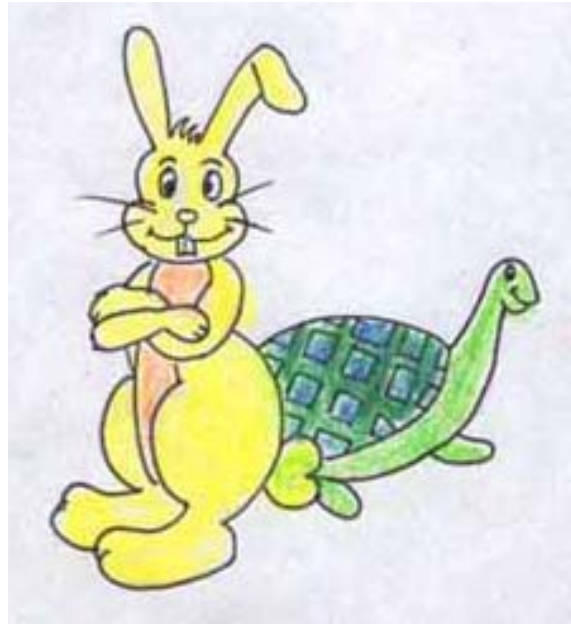
3	100%	100%	3 CV	uv microwave for 2.5
Method	C18 25 S	Weak Solvent	Water	
Sample	5 20 05 a	Strong Solvent	Methanol	
User	shahnaz	Cartridge	FLASH 25+S	
Project	suzuki	Flowrate	25mL/min	
Date	2005-May-20	UV Wavelength	Collection 254 nm	

# Microwave-Assisted Friedel-Crafts Alkylation



# Conclusion

# The Real Story of the Turtle and the Rabbit

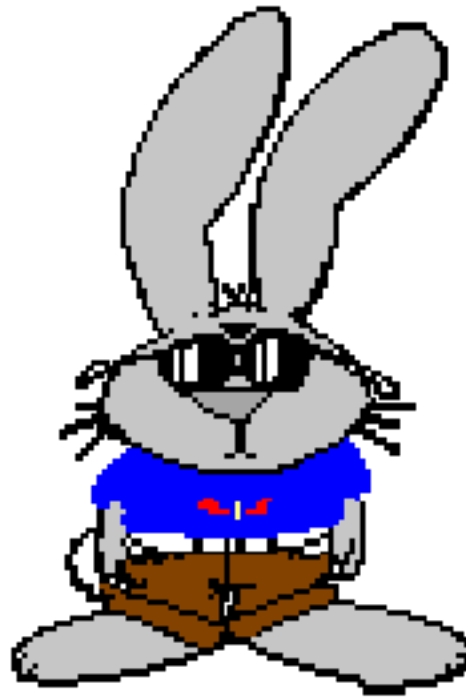




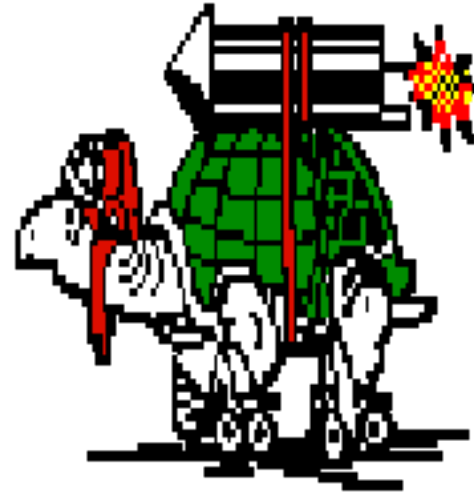
# The Real Story of the Turtle and the Rabbit



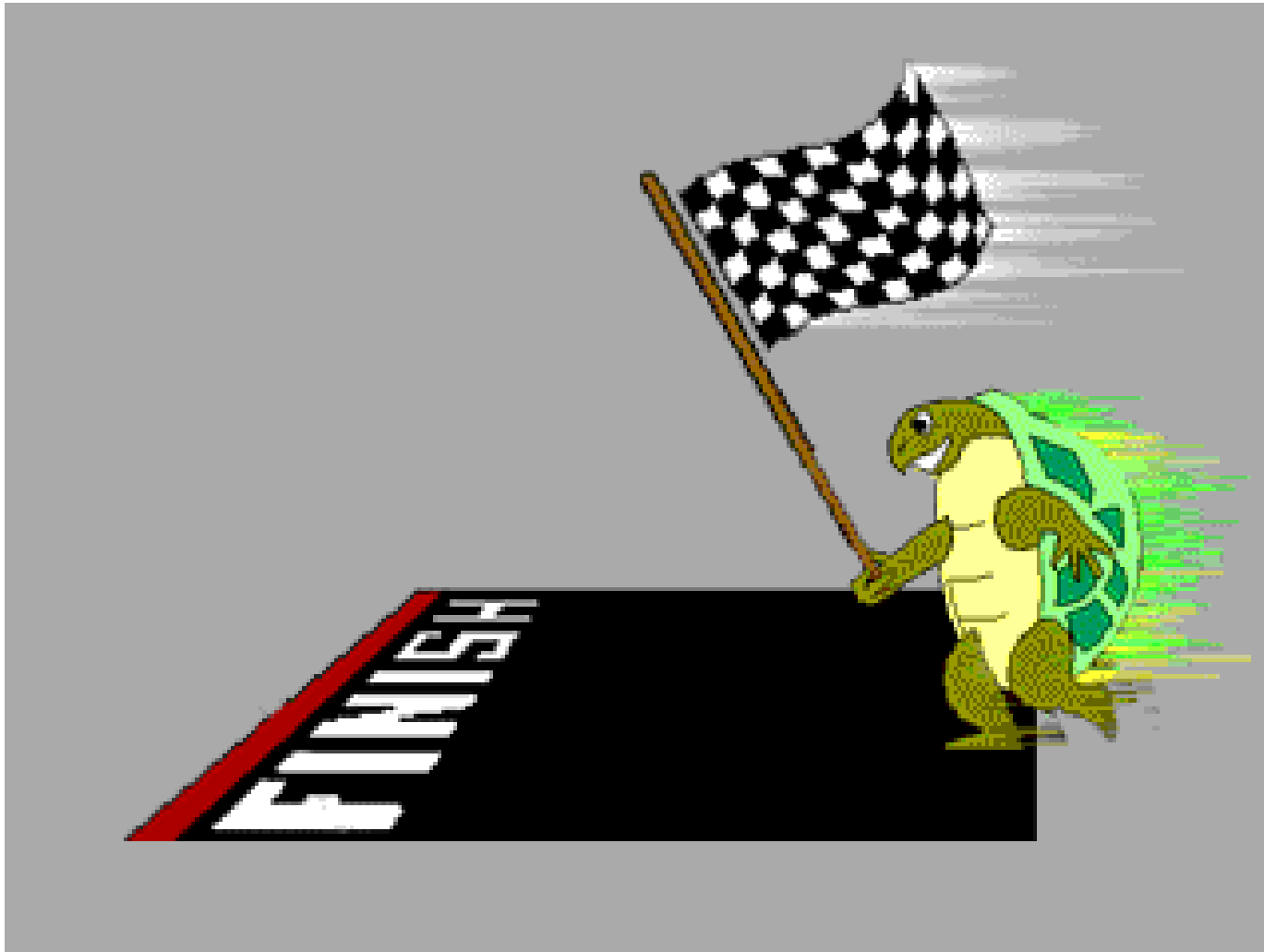
# The Real Story of the Turtle and the Rabbit



# Secret Weapon!



# The Real Story of the Turtle and the Rabbit



# SUMMARY

- **MAOS is a versatile tool that speeds up the chemistry development process**
  - Both in solution and solid phase organic synthesis
- **Automated Flash Chromatography can eliminates the workup and purification bottleneck**
- **Simplification and enhancement of drug discovery process**

## Discovery Chemistry Group in Charlottesville



Kristin Fuchs

Rebecca Previs

Dr. John Gupton (University of Richmond, VA)