Scaling up Microwave Reactions

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Preparative Chemistry and Separations
Application of Modern Tools in Organic Synthesis
Biotage Summer Program
July 21 – 23, 2008
University of Richmond
Richmond, Virginia USA

Overview

- Introduction to MAOS
- MAOS at West Point
- Chemistry
- MAOS in prep of HIV Integrase Inhibitor
- MAOS in scaling up Rasta resins
- Conclusion

Early MAOS

Microwave Assisted Organic Synthesis (MAOS)

- **In 1986, Gedye and Giguere report first use of microwaves in organic chemical reactions**
- Late 1990's saw the arrival of single mode instruments with on-line monitoring of temperature and pressure.
- By end of 2005, estimated 3000 publications related to MAOS

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MAOS at West Point

Biotage Initiator Sixty

Reaction Vials

Advancer 350

- Batch Format
- 50 – 300 ml
- 60 – 250 degrees C
- 1 – 20 bar
- 1200 W magnetron
- Multi-tiered safety measures

Reaction Vessels

Chemistry

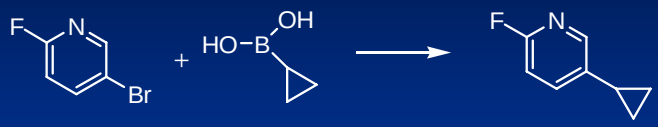
- Since May 2004, approx. 5.0 kgs of starting materials have been processed for various projects within Med Chem

- Largest run 100g

- Smallest run .625g

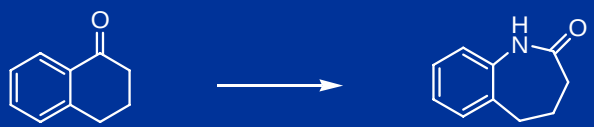
Examples

Suzuki

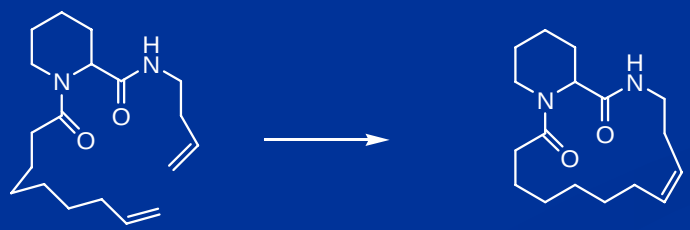


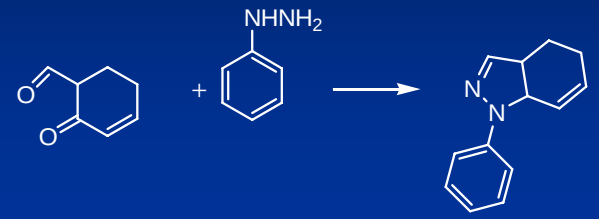
Amide

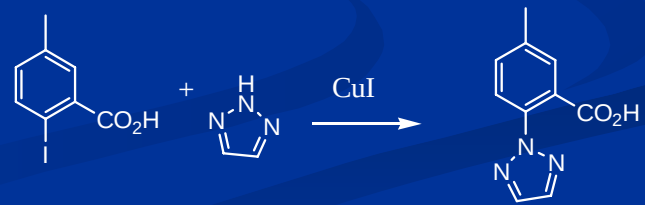
Beckmann Rearragement



Ring Closing Metathesis

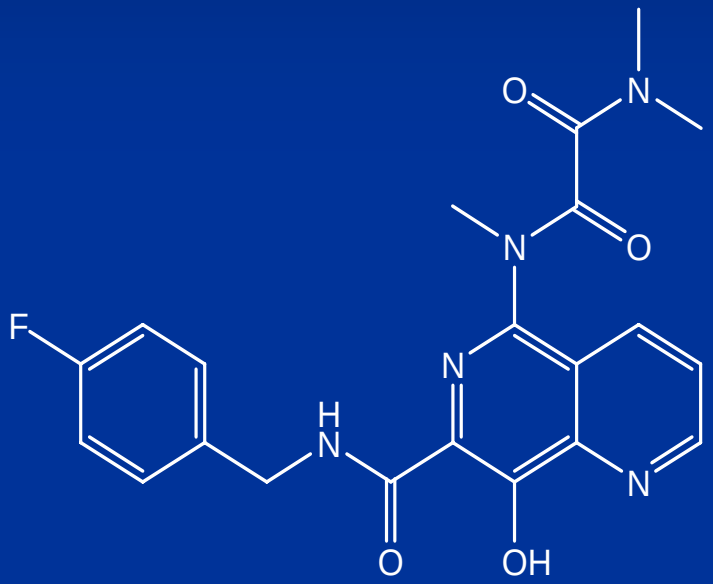






MAOS in synthesis of HIV Integrase Inhibitor

HIV Integrase Inhibitor



- Preclinical Proof of Concept for HIV therapy

Daria J. Hazuda, Steven D. Young et al. ***Science*** 23 July 2004, Volume 305, pp 528-532

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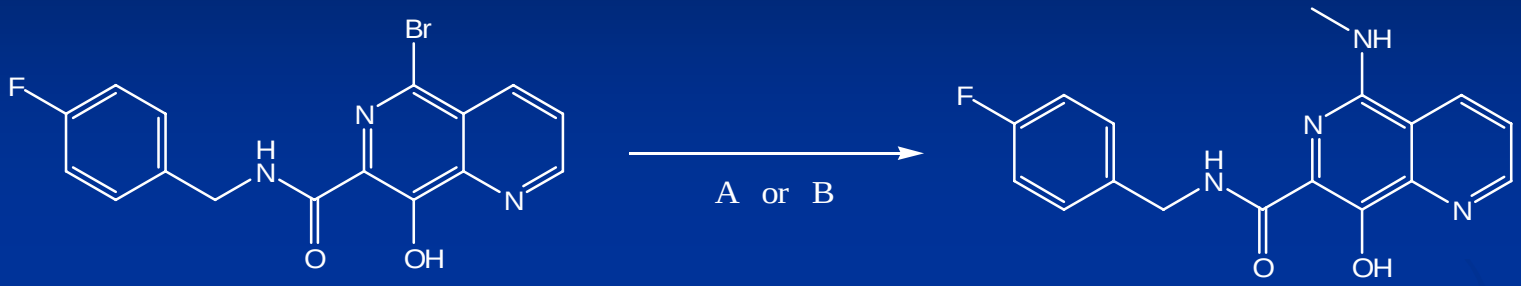
Bromide Displacement



The Challenge:

Process approximately 1200g of bromide.

Conditions:

A: $MeNH_2$ in THF, DIEA, DMSO, sealed vessel 140° C, 72 h 78% projected 120g/run

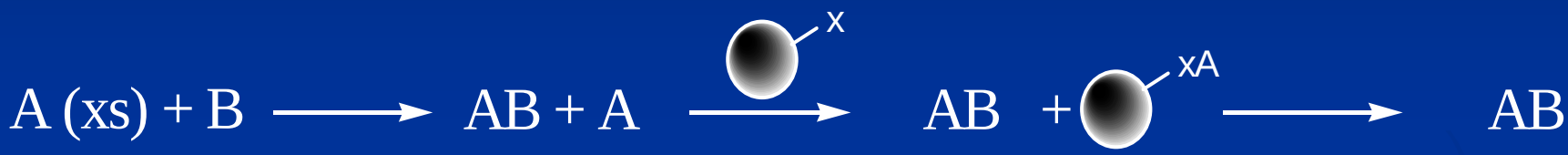
B: $MeNH_2$ in THF, DIEA, DMSO, microwave 170° C, 1 h 68% 35g/run

The Winner: MICROWAVES!

Microwaves: about 35 hours reaction time versus 30 days for conventional method.

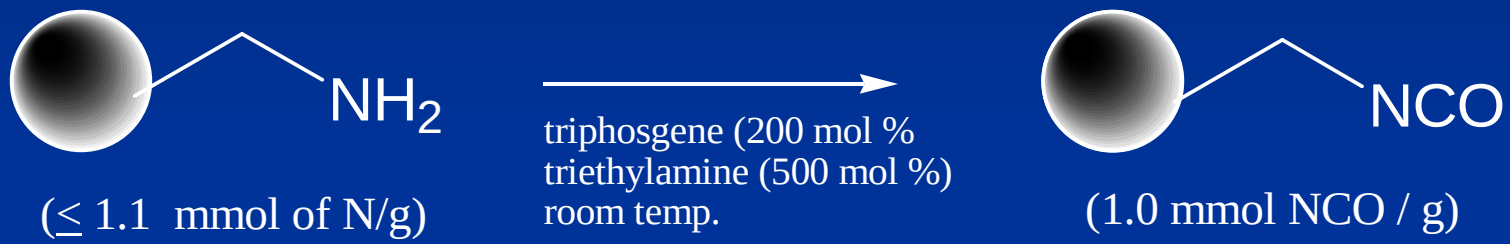
MAOS in preparation of Rasta Resins

Solid-Supported Scavengers



- solid-supported reagents to aid in purification
- published by Kaldor ***(Tet Lett Vol 37, No 4, pp7193-7196 (1996)***
- Hodges publishes paper on Polymer-Supported Quenching *(JACS **1997**, 119 4882-4886)*

Methylisocyanate for Amines



(≤ 1.1 mmol of N/g)

(1.0 mmol NCO / g)

- the highest loading possible with commercially available resin
- for scavenging, want highest loading of functionallity as possible
- maximal reproducible loading achieved was 1.5 mmol/g
- disadvantage: urea cross linking vs isocyanate formation at higher loading.

In Search of …

- Hodges et al *J. Comb. Chem. 2000, 2, 80-88*
- Begin investigating polymerization of isocyanate bearing monomers.
- Investigate living free radical polymerization.

Living Free-Radical Polymerization

- Defined in the 1950's as the process of chain polymerization that proceeds in the absence of irreversible chain-termination and chain-transfer steps.
- Realized by anionic polymerization (1950)
- Did not really emerge until the 1980's, the first successful form was nitroxide-mediated polymerization (NMP)

Living Free-Radical Polymerization

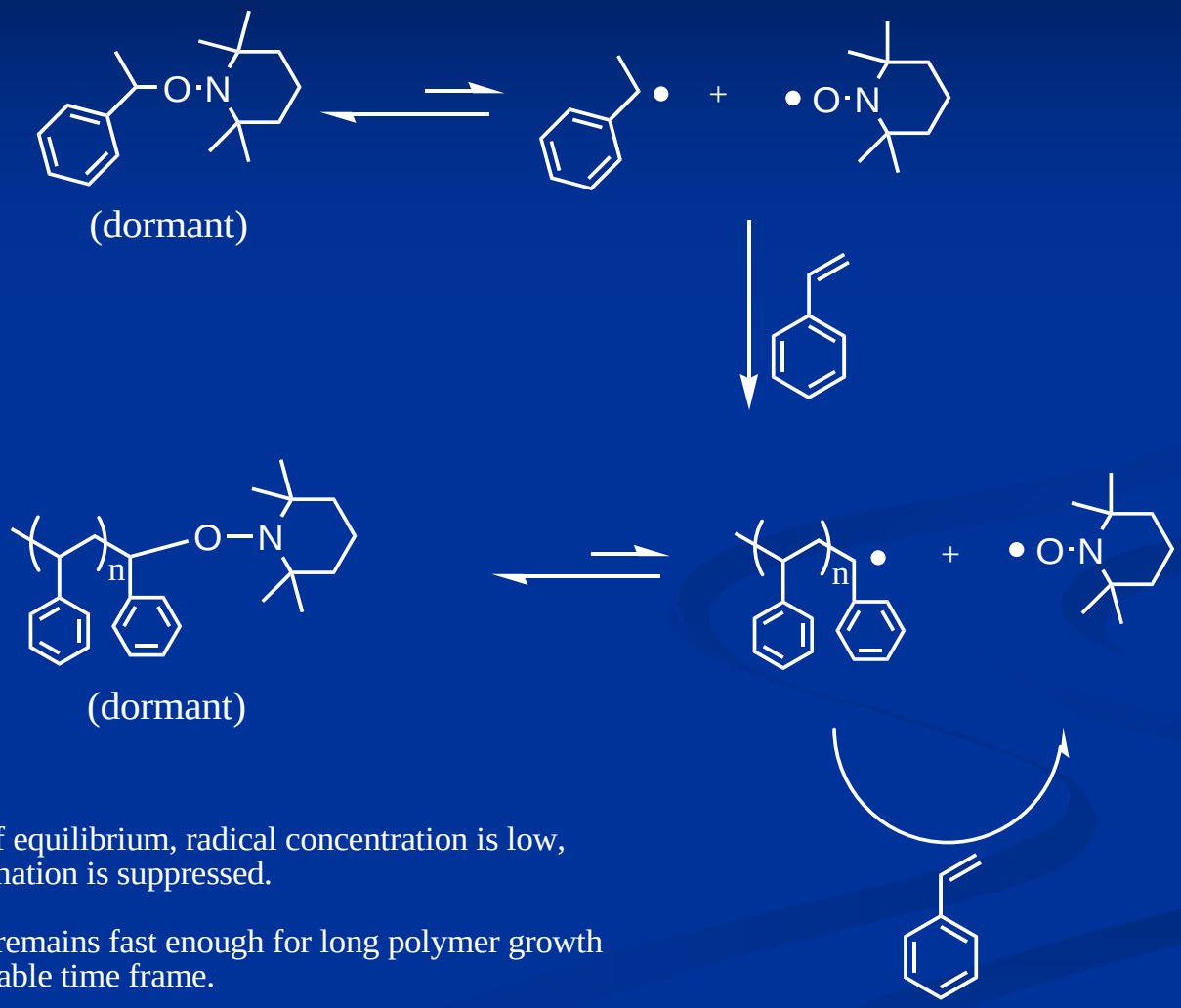
- polymer chain remains dormant until reactivated then a second monomer may be introduced. Equilibrium exists between dormant and active species.

- method provides end-group control and enables synthesis of macromolecules (ie block copolymers) by sequential addition of monomers.

- advantage: all chains are approximately the same if initiation is rapid on the time scale of monomer consumption.

Adash & Russell *Chemistry in New Zealand* 2004, *69*, 8-13

Nitroxide-mediated Polymerization



- because of equilibrium, radical concentration is low, thus termination is suppressed.

- activation remains fast enough for long polymer growth in a reasonable time frame.

Adash & Russell *Chemistry in New Zealand* 2004, *69*, 8-13

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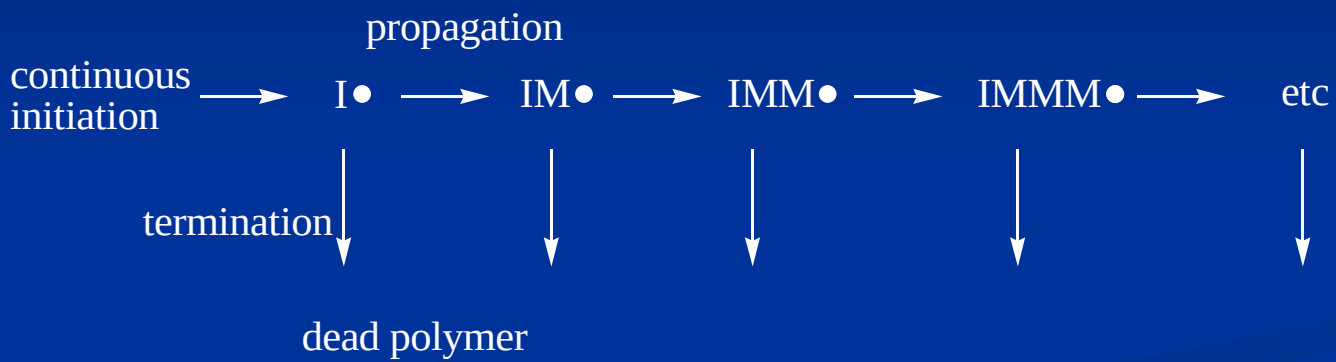
Conventional Free-Radical Polymerization



- many commercial polymers are prepared this way.
- allows for a wide range of monomers to be used under mild conditions
- disadvantage: polymer product is polydiverse

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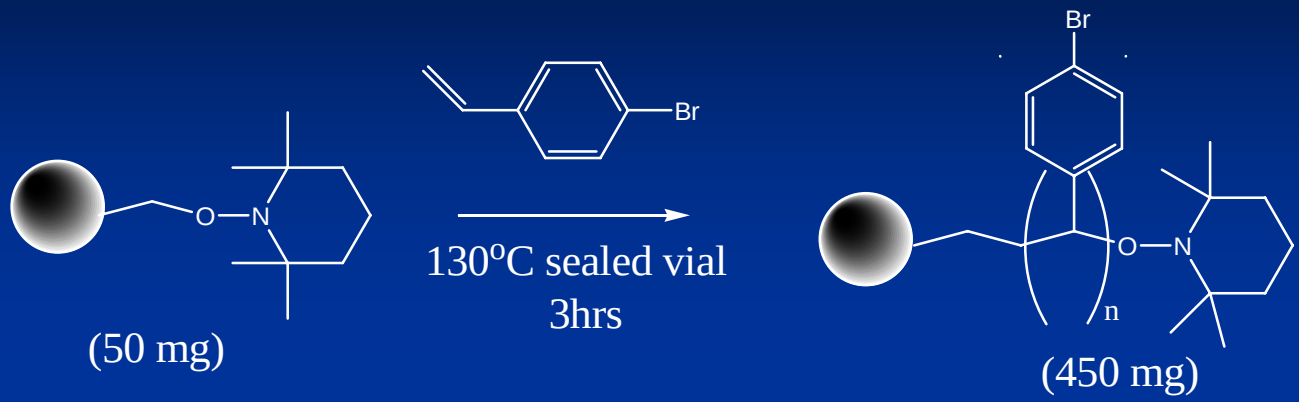
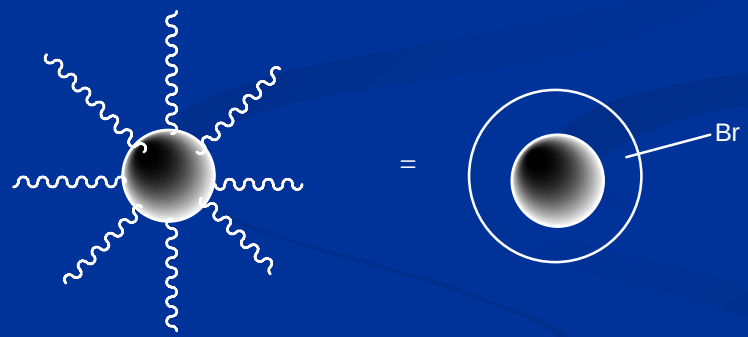
Proof of Concept



(50 mg)

(450 mg)

"Rasta resin"



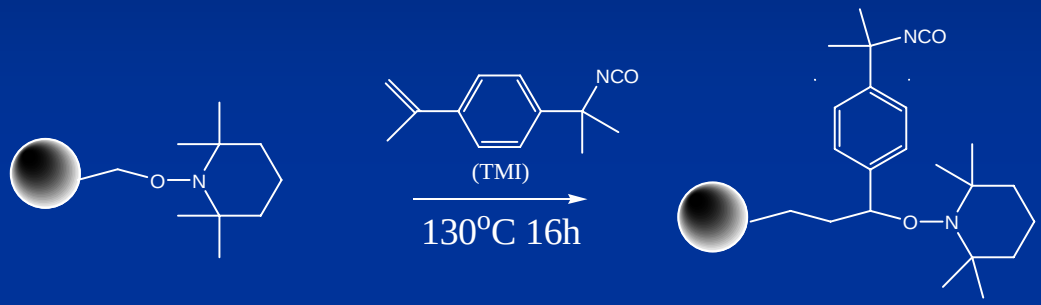
Results:

visibly larger bead with linear polymers

9- fold increase in mass

40.4% Br by elemental analysis (5.05 mmol/g loading)

Isocyanate Rasta Resin



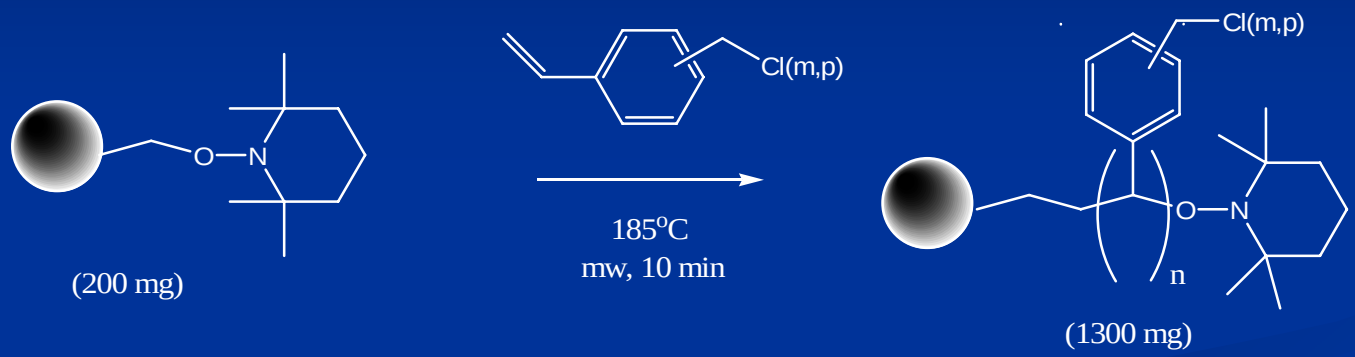
Results:

- workup of resin resulted in a disappointing 1.0 mmol NCO/g
- were able to achieve a Rasta resin through copolymerization with styrene (~2.5 mmol NCO/g)
- successful investigation as an amine scavenger

5 Rasta resins are commercially available through Aldrich !

Rasta Merrifield Resin

Wisnoski et al *Tetrahedron Letters* 44 (2003) 4321-4325

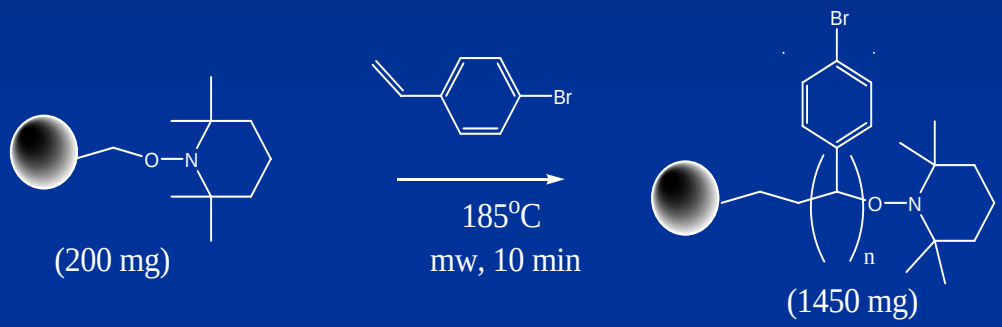


Initial run provided a 6.5 fold increase of mass and a loading level of 5.9 mmol/g (20.8% Cl)

Subsequent runs gave an average 6 fold increase of mass and ~5.8 mmol/g loading (23% Cl)

Microwave-initiated LFRP

Wisnoski et al *Tetrahedron Letters* 44 (2003) 4321-4325



(200 mg)

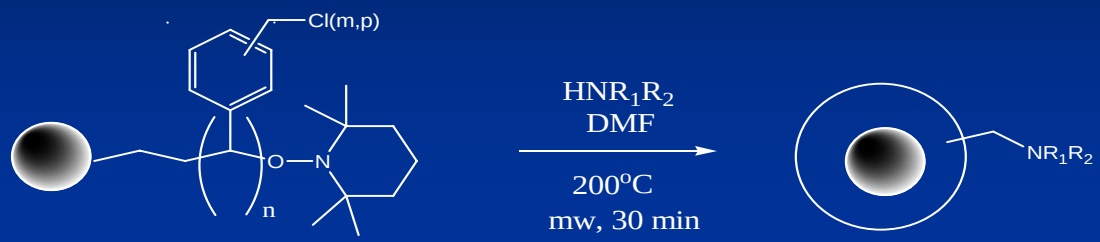
(1450 mg)

Results:

microwave preparation	**conventional preparation**
7.2 fold increase of mass	9 fold increase of mass
5.5 mmol/g loading (44% Br)	5.0g mmol/g (40.4% Br)
192um ⟶ ~ 550 um	75-150 um ⟶ 250um
spherical	spherical

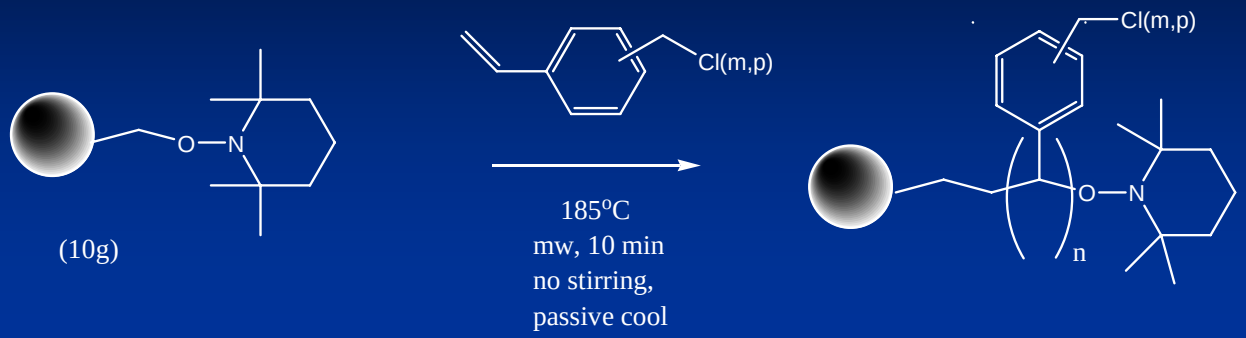
Rasta Amines

Wisnoski et al *Tetrahedron Letters* 44 (2003) 4321-4325



Amine	Loading
NEt	5.0 mmol/g
	4.5 mmol/g
	5.0 mmol/g
	4.2 mmol/g
	4.2 mmol/g

Scale-up of Merrifield Rasta resin



Results:

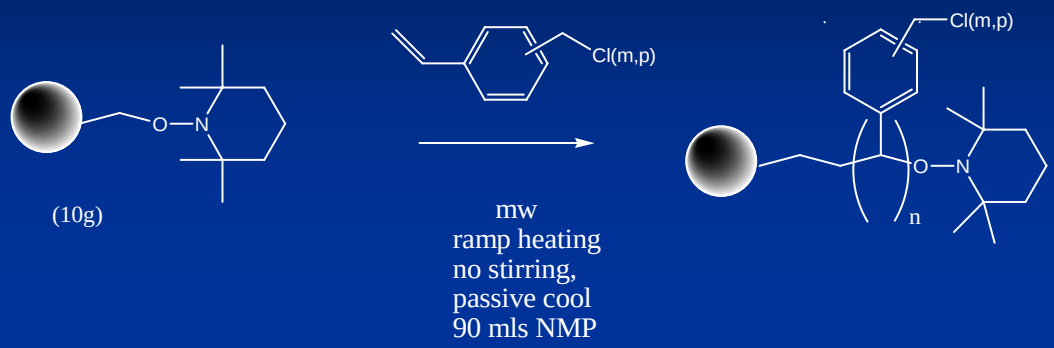
- initial run disappointing: reaction crashed cooled, internal temperature reached 225°C, fused polymeric mass

- repeat conditions, used ramp heating (.5°C/sec). Again crash cooled, temperature exceeded 200°C, polymeric mass

- repeat conditions, now add 90 mls NMP. Crashed cooled

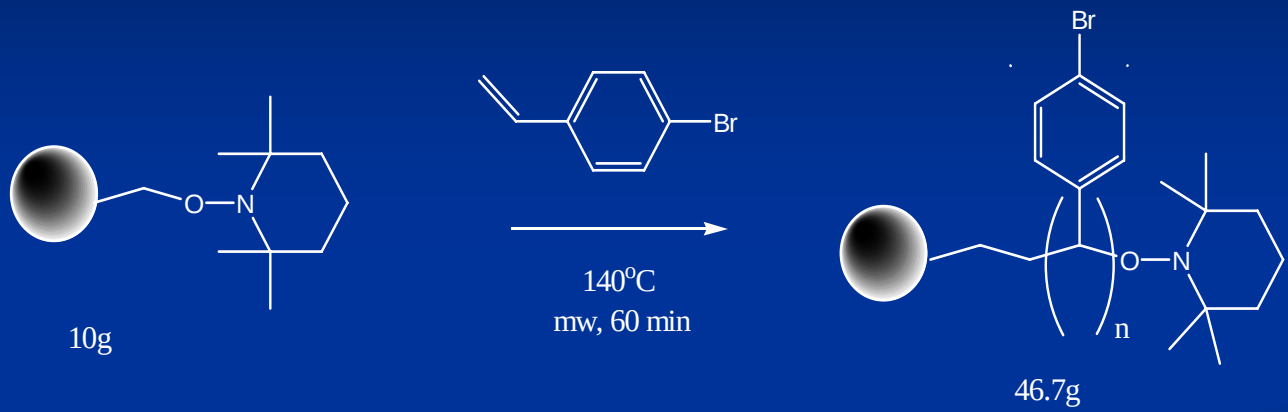
-reduced temperature to 140°C and increased time to 60 min
Recovered 50.55g of resin with a loading of 5.43mmol/g
(small scale produced a loading of 5.8 mmol/g)

Optimization of Temperature



Conditions	Results
15 min @ 170°C	crashed cooled (186°C)
30 min @ 160°C	41g resin 5.3 mmol/g
15 min @ 160°C	37.23g resin 5.45 mmol/g
10 min @ 160°C	32.20g resin 5.23mmol/g
5 min @ 160°C	28.96g resin 4.85 mmol/g

Microwave-initiated LFRP



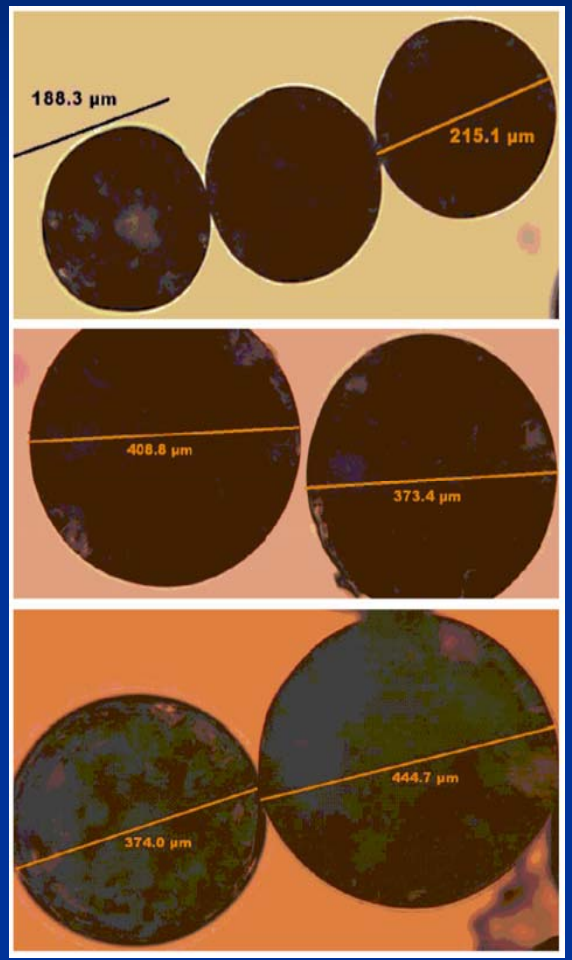
10g

46.7g

Results:

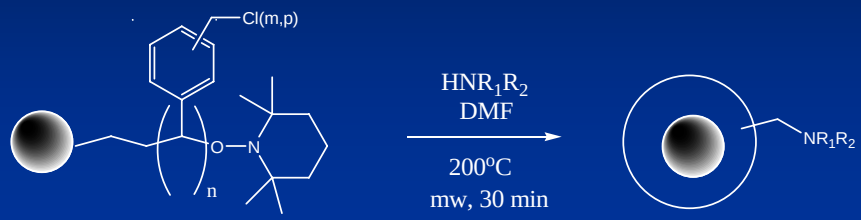
scale up	**microwave preparation**	**conventional preparation**
4.6 fold	7.2 fold increase of mass	9 fold increase of mass
3.85 mmol/g (30.45%)	5.5 mmol/g loading (44% Br)	5.0g mmol/g (40.4% Br)
370um to 450um	192um ⟶ ~ 550 um	75-150 um⟶250um
spherical	spherical	spherical

Rasta Resins

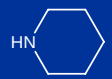
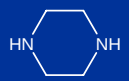


- PS – TEMPO resin
- Bromide
- Merrifield

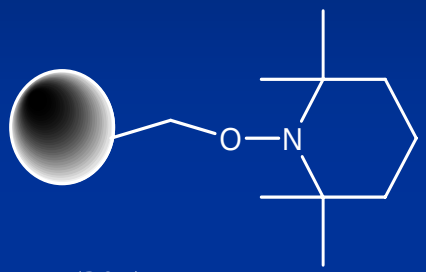
Rasta Amines



10g

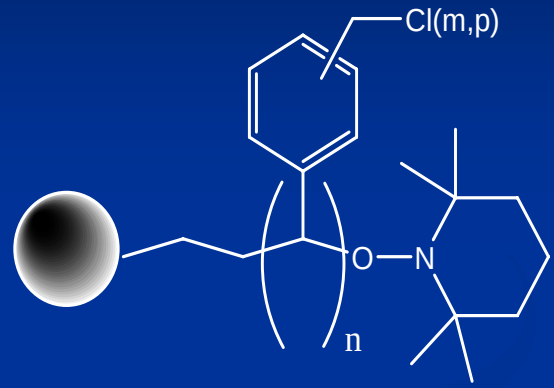
Amine	Small scale	Large scale
NEt_2	5.0 mmol/g	4.5 mmol/g
	4.5 mmol/g	3.28 mmol/g
	5.0 mmol/g	4.51 mmol/g
	4.2 mmol/g	4.44 mmol/g
	4.2 mmol/g	3.17 mmol/g

How Much ?



(30g)

mw
60 min@140°C
ramp heating
no stirring,
passive cool
100 mls NMP



116g

- unbreakable solid mass in core of rxn vessel

- 5.23 mmol/g loading

Conclusion

- Enhanced synthesis of intermediate to support further internal and external studies of HIV Integrase inhibitors.
- A new scalable protocol that affords multi-gram quantities of custom Rasta resins.

Tetrahedron Letters 48 (2007) 1497-1501

Acknowledgements

- Jim Guare

- Craig Lindsley
- Deanne Jackson Rudd
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