Convenient Preparation of Substituted 5-Amino oxazoles via a Microwave-Assisted Cornforth Rearrangement

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Trisubstituted 5-Aminooxazoles

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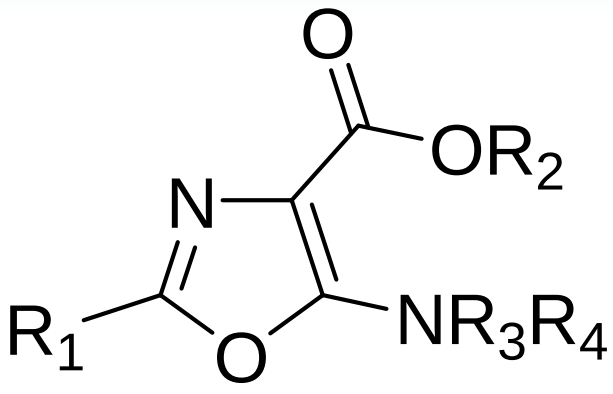
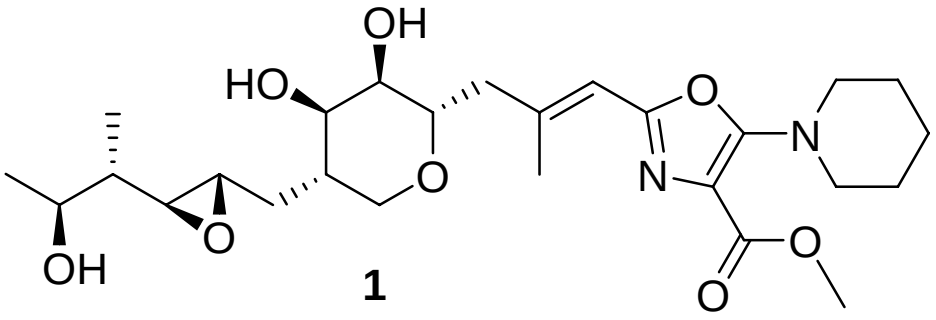


- Biologically active oxazole-containing compounds
- An established route involves a key thermal rearrangement and is conducive to microwave-assisted methodology
- Underrepresented in current literature

Biological Relevance

a

Antibiotics



1

	MIC (*u*g / mL)
Haemophilus influenzae Q1	2
Streptococcus pneumoniae PU7	32
Staphylococcus aureus	16

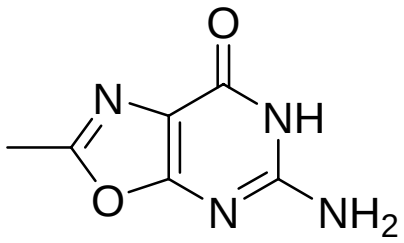
Psuedomonic acid derivative **1** has demonstrated growth inhibition of Gram-positive and -negative bacteria

Brown, P.; Davies, D. T.; O'Hanlon, P. J.; Wilson, J. M. *J. Med. Chem.* **1996**, *39*, 446.

Biological Relevance

a

Toxin Antidotes



2

	Stx1A1 IC_{50}	RTA IC_{50}
8-methyl-9-oxoguanine	1.0 mM	0.4 mM

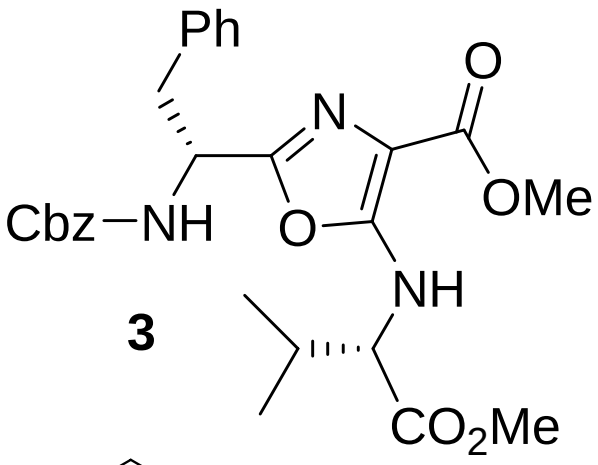
Bicyclic oxazole **2** is an inhibitor of the enzymatic A chain of ricin (RTA) and a Shiga-like toxin Stx1A1, produced from pathogenic *E. coli*.

Miller, D. J.; Ravikumar, K.; Shen, H.; Suh, J.-K.; Kerwin, S. M.; Robertus, J. D. *J. Med. Chem.* **2002**, *45*, 90.

Biological Relevance

a

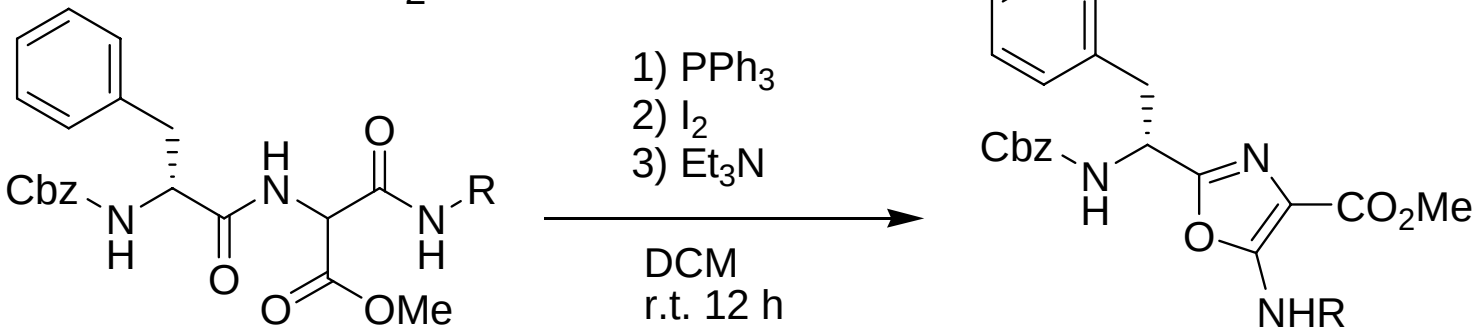
Protein Therapy



3

Oxazole **3** is based on the C-terminal hexapeptide His^{16}-Trp^{21} of the endothelin-1 receptor.

Peptidomimetics could attenuate specific protein binding pathogenic pathways



38%

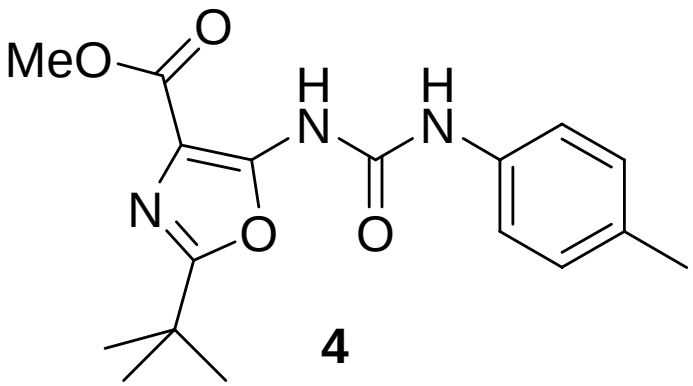
Falorni, M.; Giacomelli, G.; Porcheddu, A.; Dettori, G. *Eur. J. Org. Chem.* **2000**, 3217.

von Geldern, T. W.; Hutchens, C.; Kester, J. A.; Wu-Wong, J. R.; Chiou, W.; Dixon, D. B.; Opgenorth, T. J. *J. Med. Chem.* **1996**, *39*, 957.

Biological Relevance

a

Anti-neoplastic



4

Urea oxazole **4** has demonstrated Raf kinase inhibition and may be instrumental in limiting Ras oncogene activity

Smith, R. A.; Barbosa, J.; Blum, C. L.; Bobko, M. A.; Caringal, Y. V.; Dally, R.; Johnson, J. S.; Katz, M. E.; Kennure, N.; Kingery-Wood, J.; Lee, W.; Lowinger, T. B.; Lyons, J.; Marsh, V.; Rogers, D. H.; Swartz, S.; Walling, T.; Wild, H. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2775.

5-Aminooxazole Synthesis

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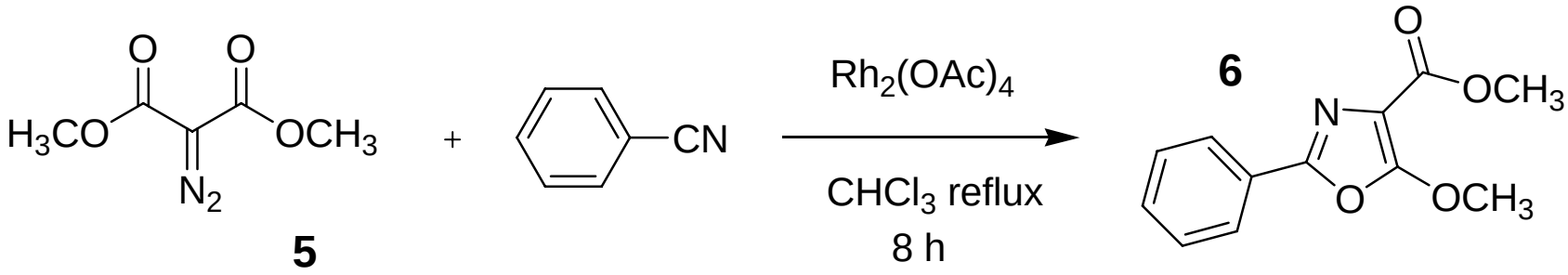
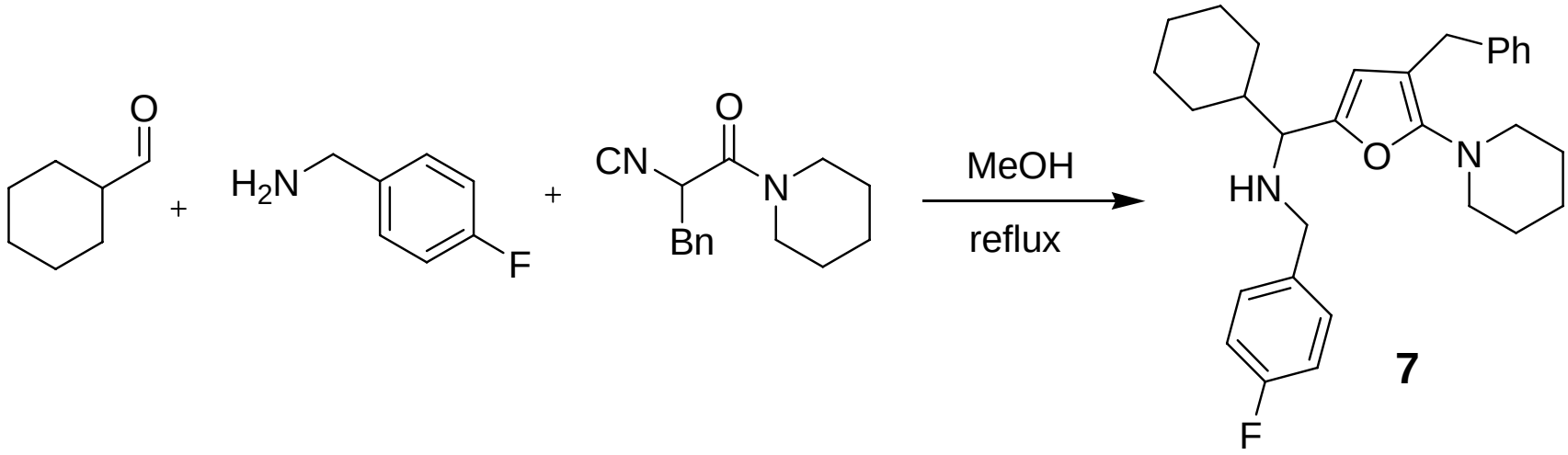


Connell, R.; Scavo, F.; Helquist, P.; Akermark, B. *Tetrahedron Lett*. **1986**, *27*, 5559.



Sun, X.; Janvier, P.; Zhao, G.; Bienaymé, H.; Zhu, J. *Org. Lett*. **2001**, *3*, 877.

5-Aminooxazole Synthesis

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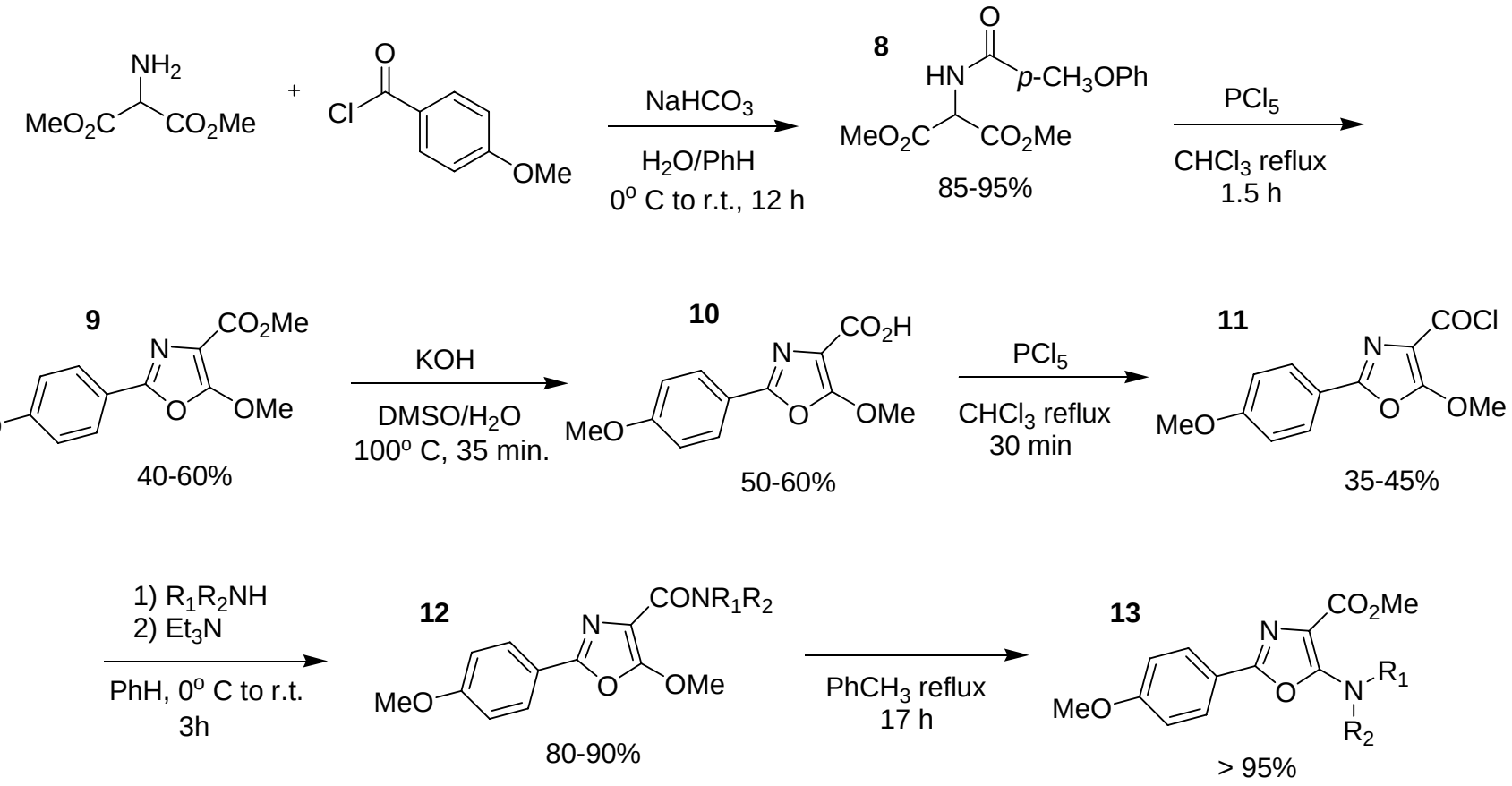

Dewar, M. J. S.; Turchi, I. J. *J. Am. Chem. Soc.* **1975**, *40*, 1521.
Dewar, M. J. S.; Turchi, I. J. *J. Am. Chem. Soc.* **1974**, *96*, 6148.
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5-Aminooxazole Synthesis

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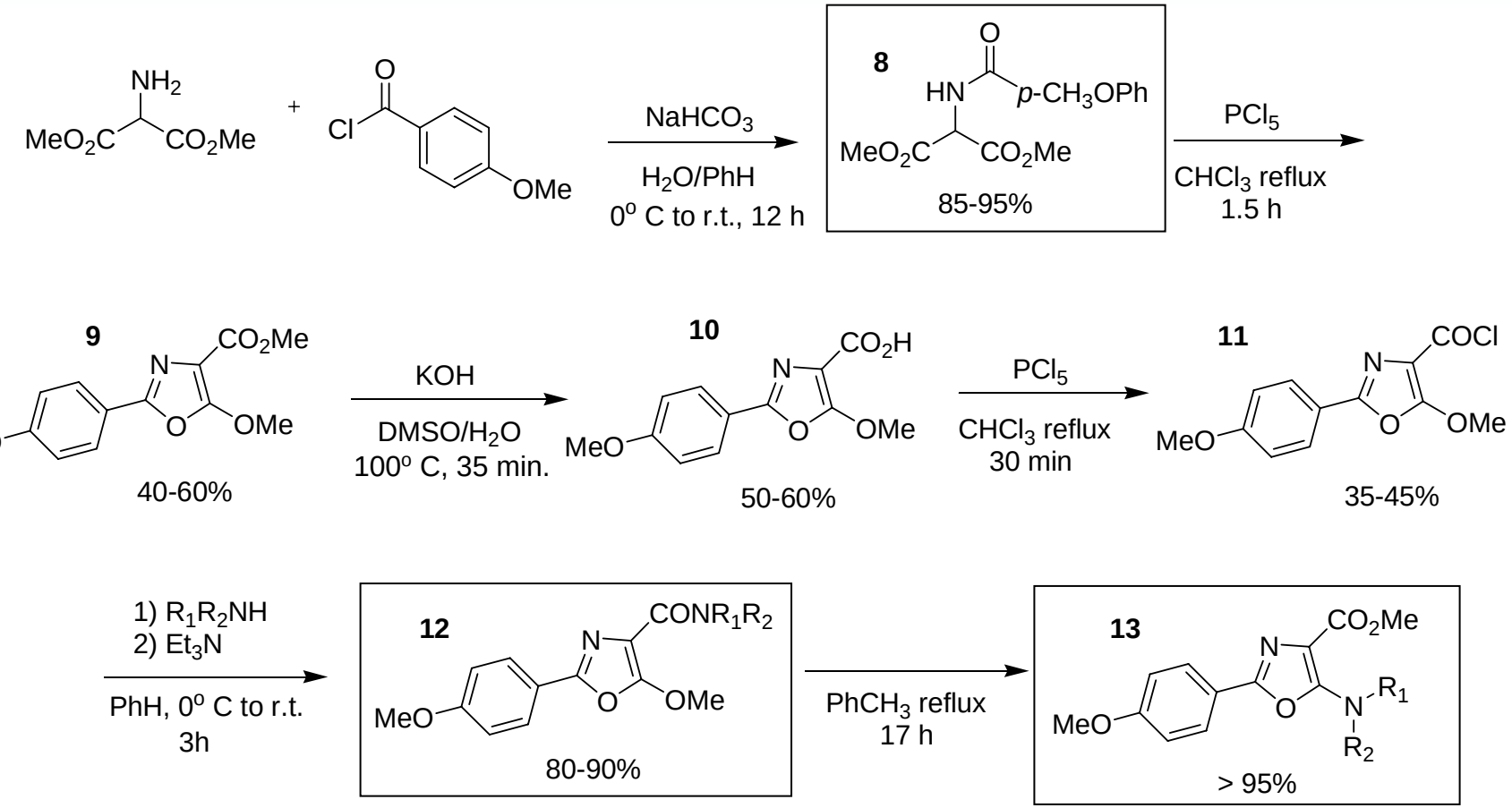

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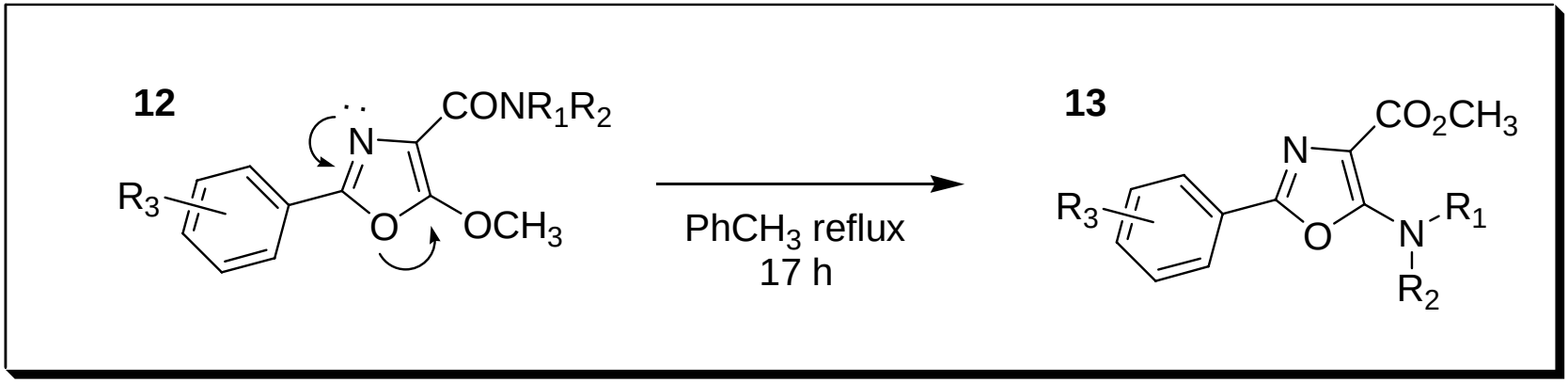
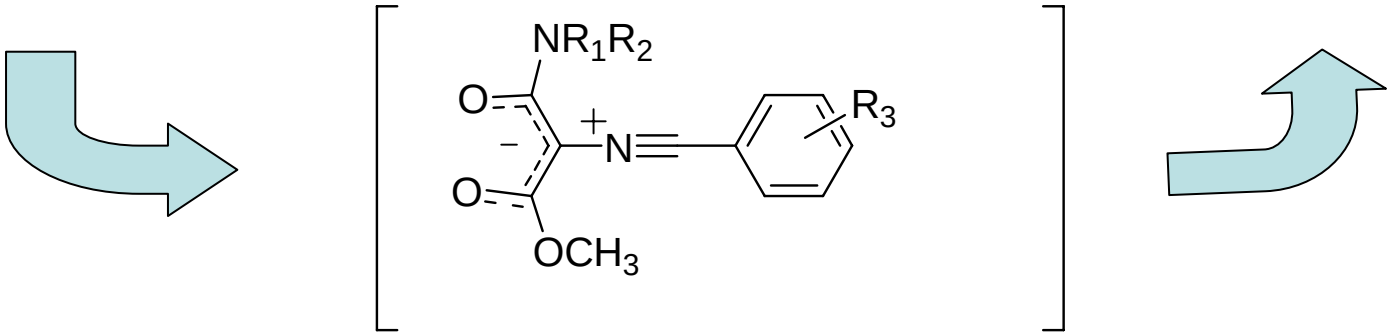
Cornforth Rearrangement

a





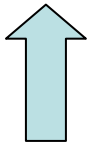
Dewar, M. J. S.; Turchi, I. J. *J. Am. Chem. Soc.* **1974**, *96*, 6148.
Dewar, M. J. S.; Spanninger, P. A.; Turchi, I. J. *J. Chem. Soc., Chem. Commun.* **1973**, 925.

2-Aminomalonate + Acid Chloride

Sequence

a

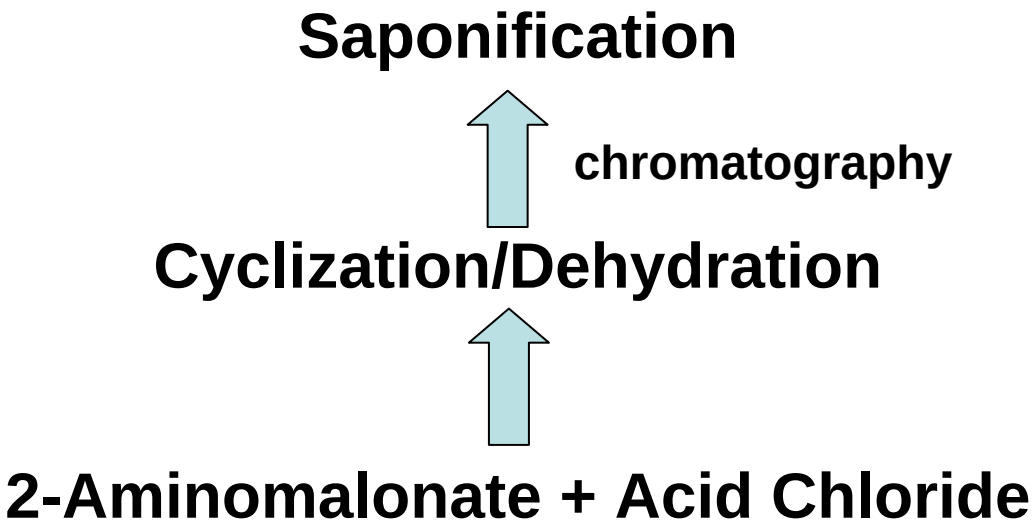
Cyclization/Dehydration



2-Aminomalonate + Acid Chloride

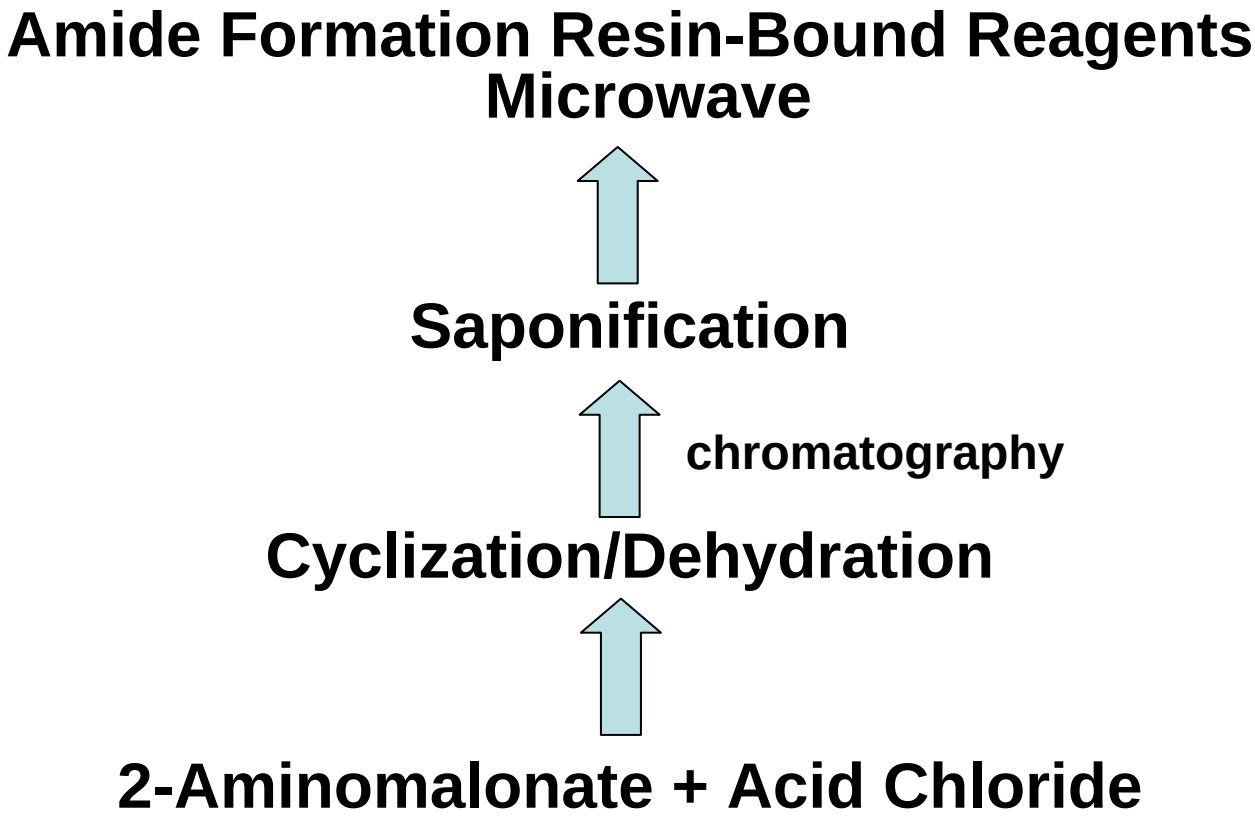
Sequence

a


Saponification
chromatography
Cyclization/Dehydration
2-Aminomalonate + Acid Chloride

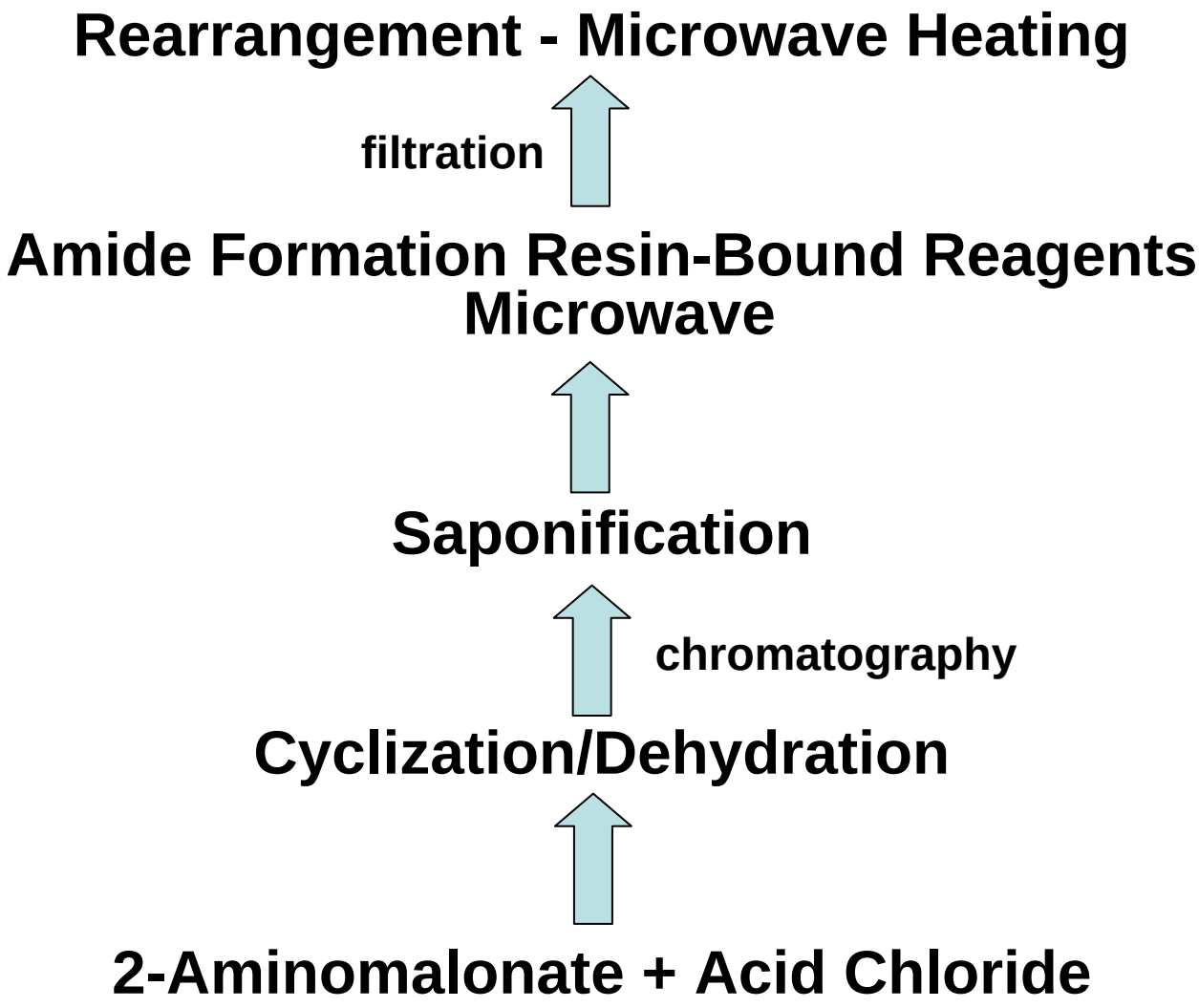
Sequence

a


Amide Formation Resin-Bound Reagents
Microwave
Saponification
chromatography
Cyclization/Dehydration
2-Aminomalonate + Acid Chloride

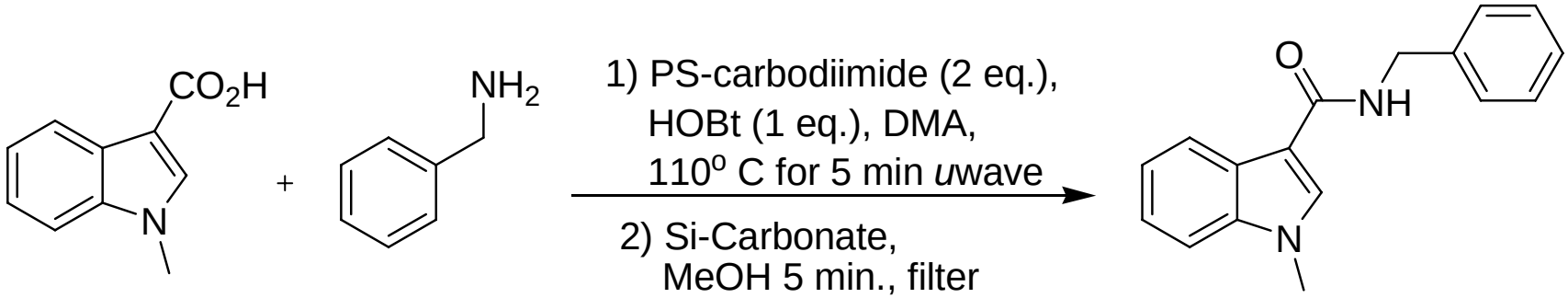
Sequence

a


Rearrangement - Microwave Heating
filtration
Amide Formation Resin-Bound Reagents
Microwave
Saponification
chromatography
Cyclization/Dehydration
2-Aminomalonate + Acid Chloride

Microwave-, Polymer-Assisted Amide Formation

a



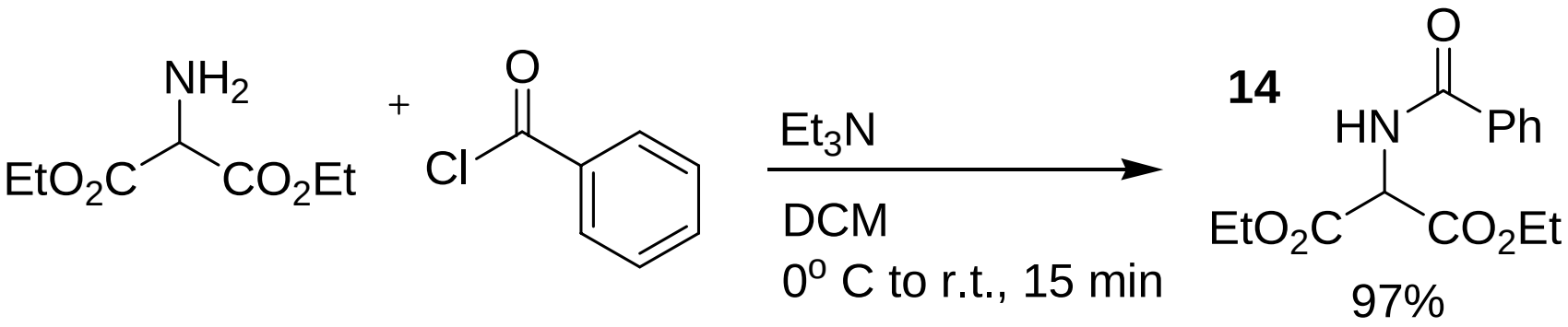
100% conversion
(LC/MS)

- Accelerated amide coupling (room temp. reaction times ~16 h)
- Complete conversion to product in excellent yield
- HOBt scavenging leaves material that is 98% pure

Sauer, D. R.; Kalvin, D.; Phelan, K. M. *Org. Lett.* **2003**, *5*, 4721.

Amide Formation - 1

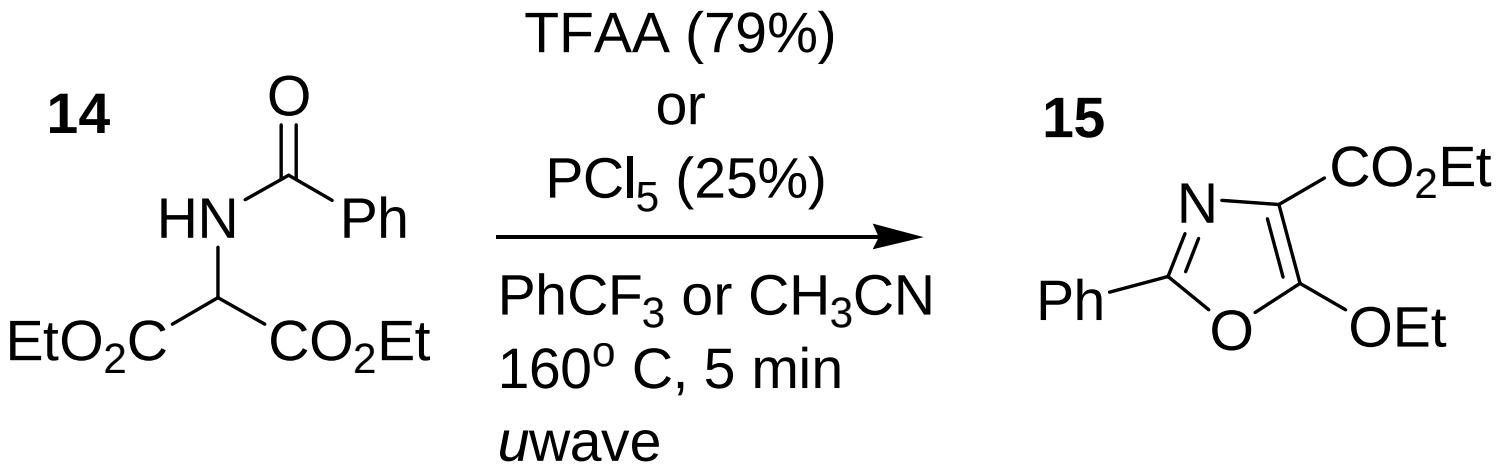
a



- Aqueous workup removes impurities
- High yields
- Amides from amines and acids

Cyclization/Dehydration

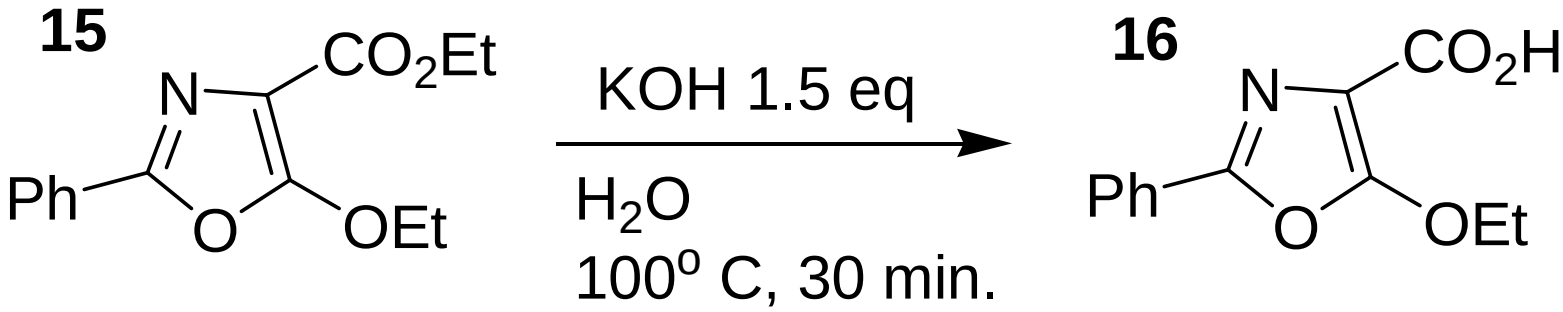
a



- Microwave heating decreases reaction time from ~1.5 h to 5 min
- Few byproducts by LC/MS
- Flash chromatography purification

Hydrolysis

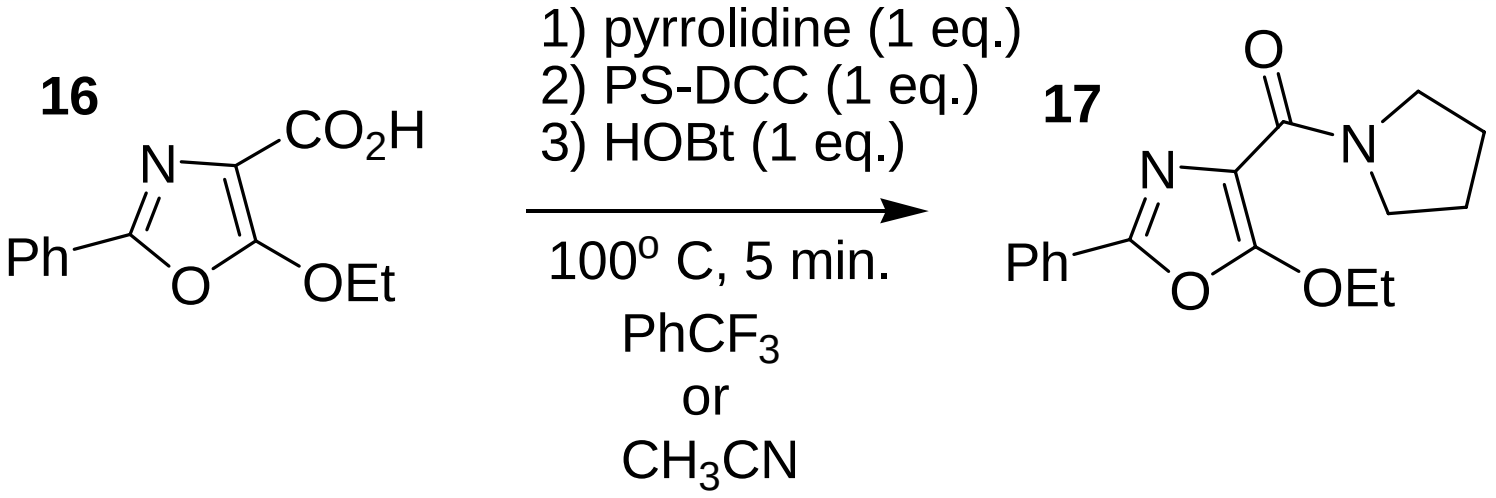
a



- Complete conversion to acid observed by LC/MS
- 48% yield of clean material by ^{1}H NMR
- Can be used without purification
- Possibility of microwave heating

Amide Formation - 2

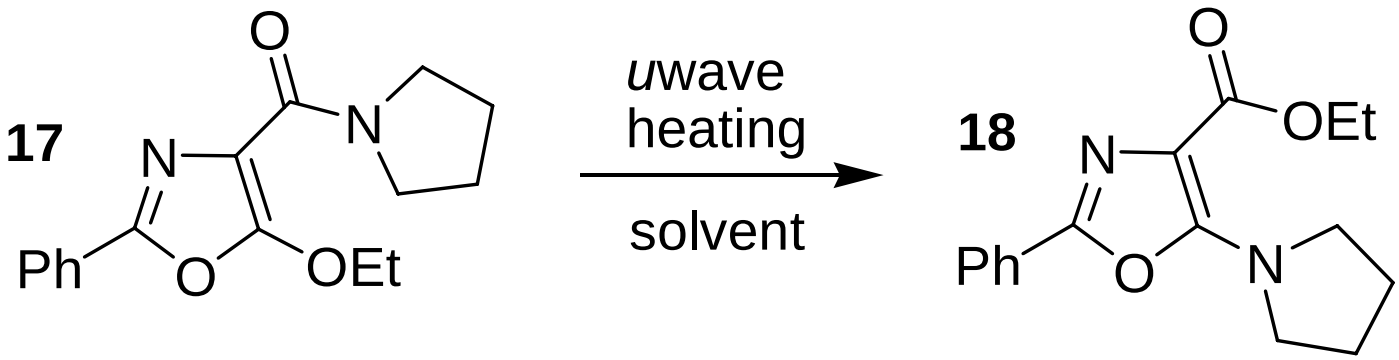
a



- Shortened reaction time, complete conversion to product
- No excess reagents required
- Simple filtration and optional wash with MP-carbonate removes HOBt

Microwave-Promoted Cornforth Rearrangement – Optimization Study

a

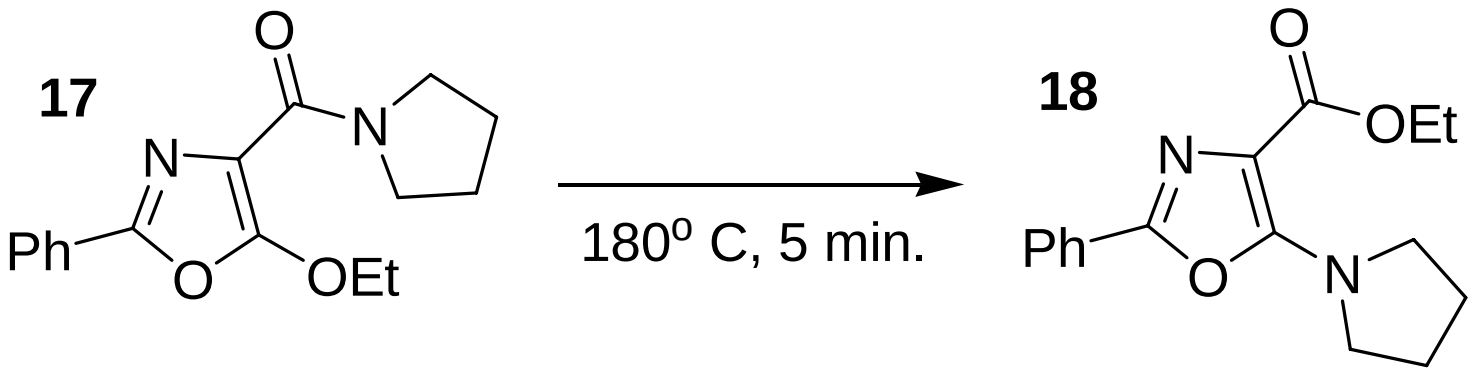


entry	solvent	rearrangement conditions	product/starting material[a]
1	acetonitrile	150° C, 10 min.	1:99
2	acetonitrile	160° C, 10 min.	1:2.2
3	acetonitrile	170° C, 10 min.	1:1.3
4	acetonitrile	180° C, 10 min.	99:1

a) determined by UV HPLC

Microwave-Promoted Cornforth Rearrangement

a

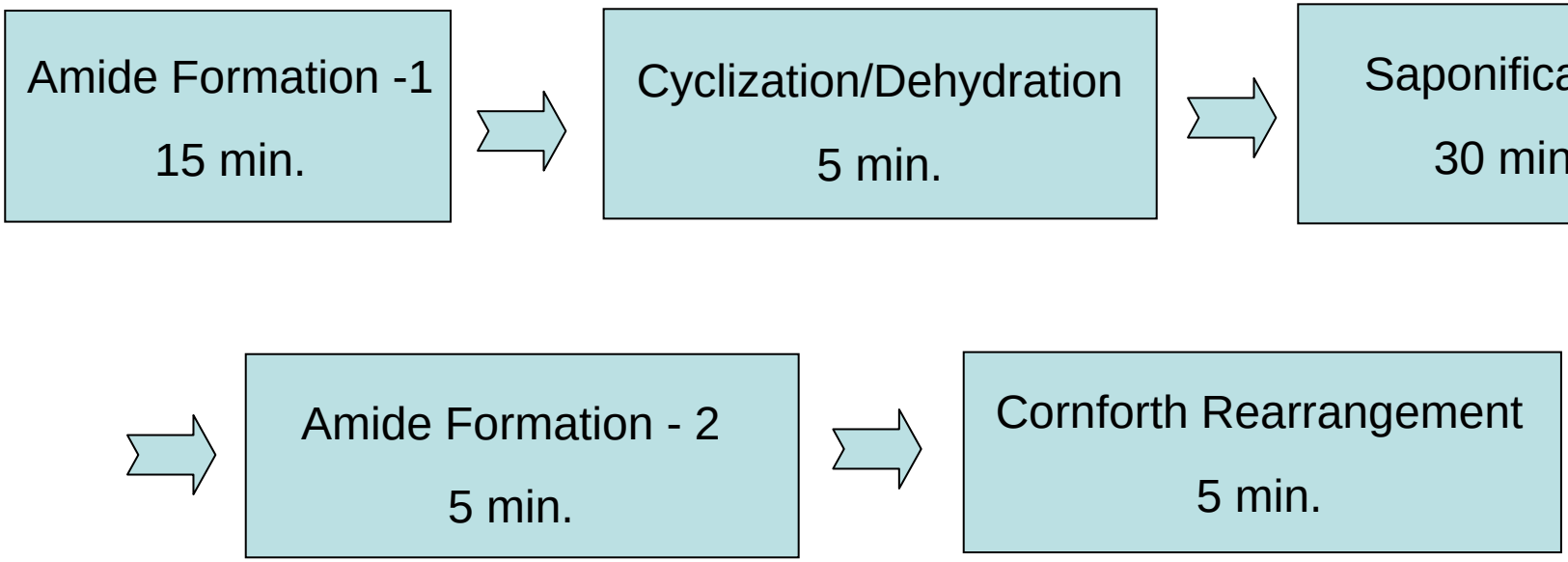


$PhCF_3$ 97%
CH_3CN 35%

- Dramatic decrease in reaction time - Microwave heating improves reaction time from 17 h to 5 min
- Good to excellent yields for two-step process
- Purity is typically > 93 % by ^1H NMR

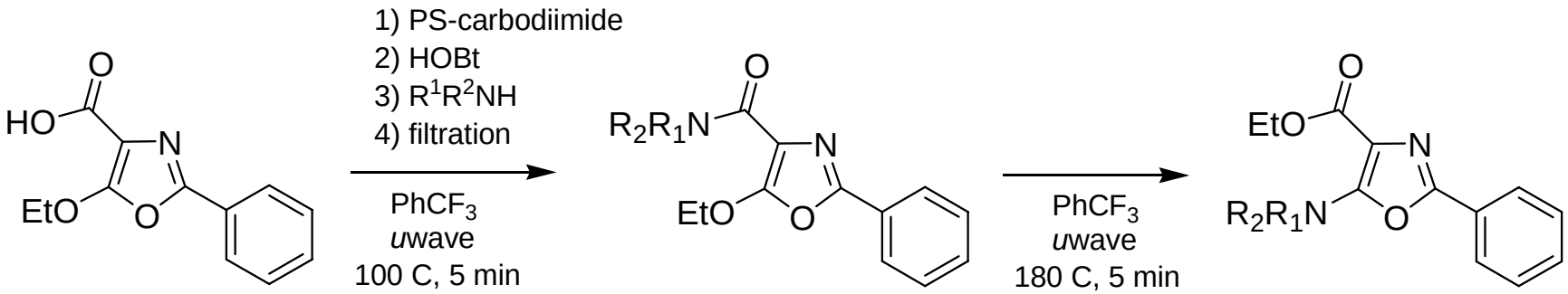
High-Speed Synthesis

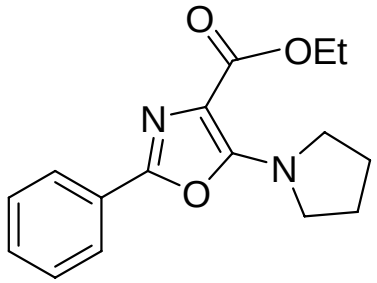
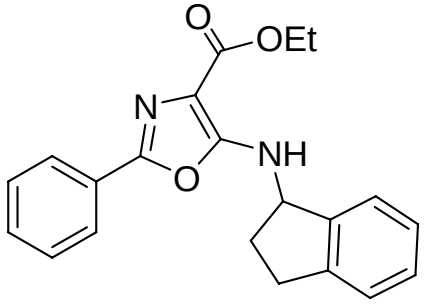
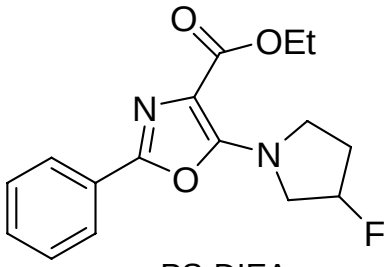
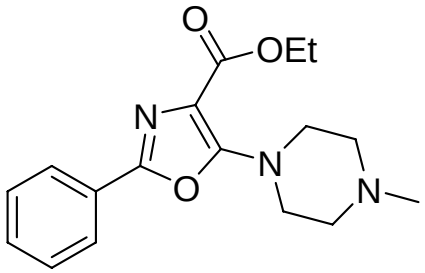
a



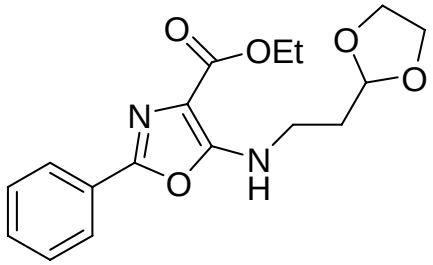
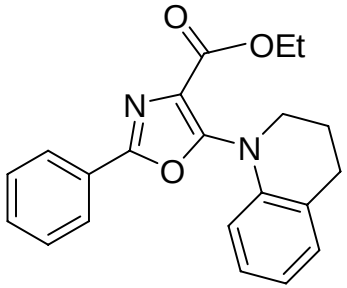
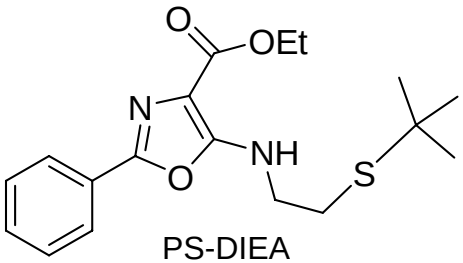
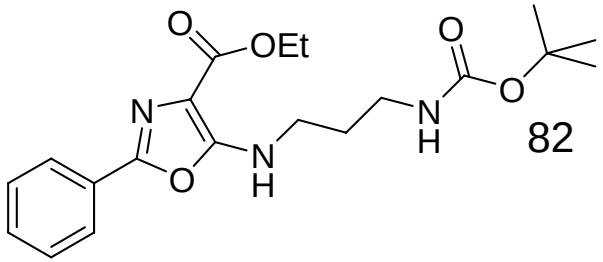
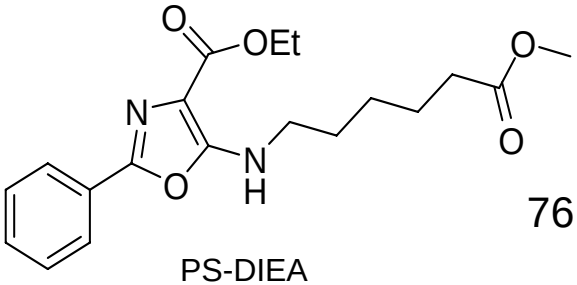
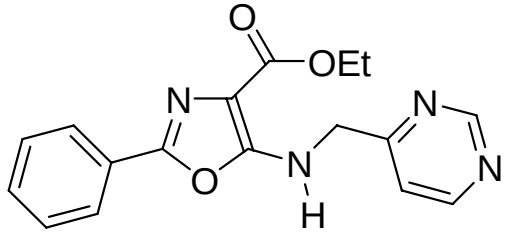
- Total reaction time approximately one hour
- More than 30-fold time reduction in comparison to original procedure

5-Aminooxazole-4-carboxylate Synthesis a

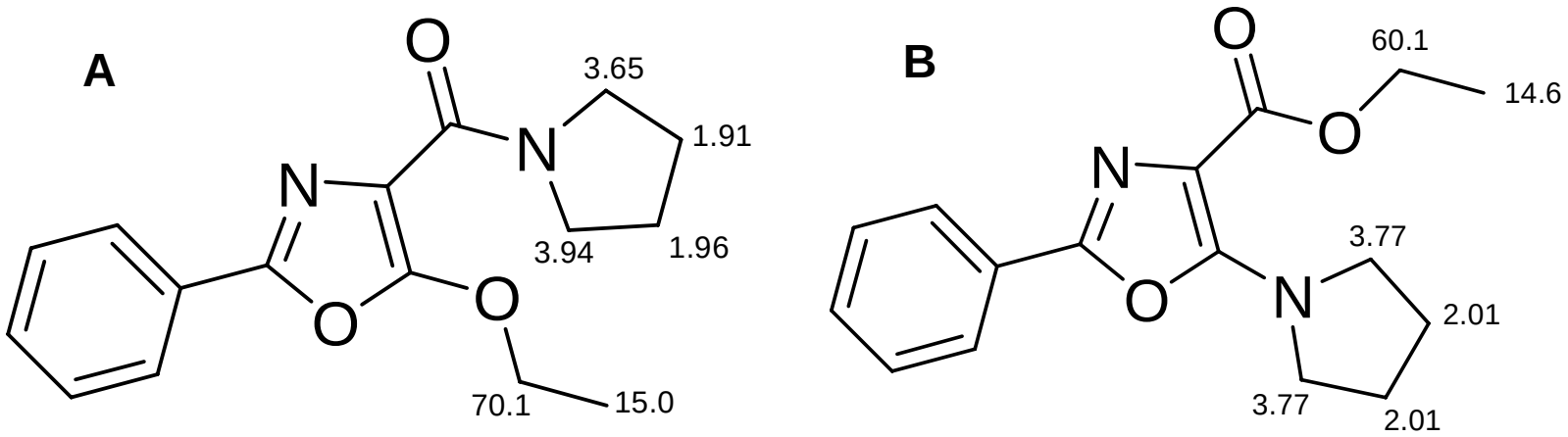


entry	product	yield (%)	entry	product	yield (%)
1		98	3		99
2	 PS-DIEA	47	4		99

5-Aminooxazole-4-carboxylate Synthesis a

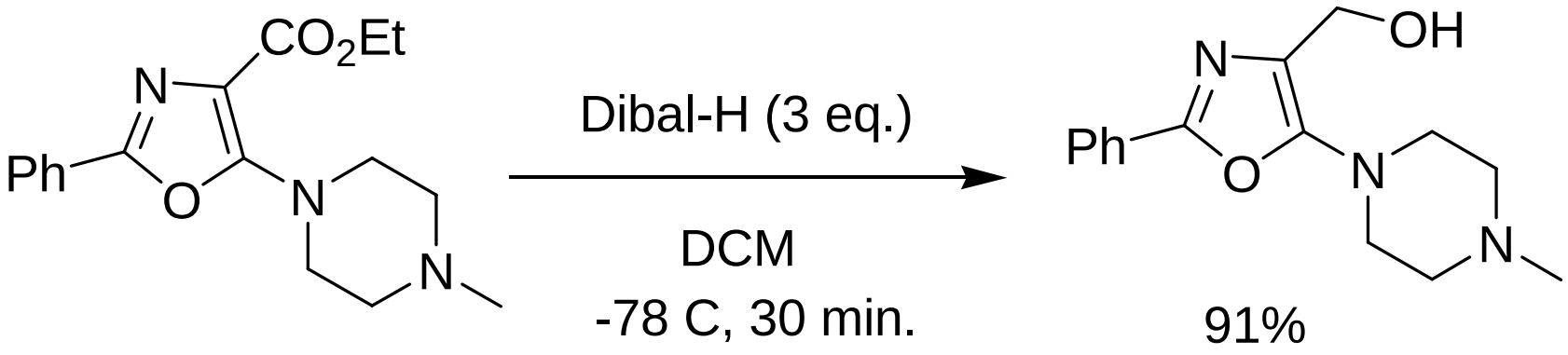
entry	product	yield (%)	entry	product	yield (%)
5		23	8		99
6	 PS-DIEA	51	9		82
7	 PS-DIEA	76	10		97

Cornforth Rearrangement Confirmation a



- HPLC Retention Times
- HMBC NMR Studies – Partial carbonyl shielding causes a difference in proton shifts on the pyrrolidine ring in the case of A, the rearranged product has equivalent methylene protons in the 2- and 5-positions of B

Cornforth Rearrangement Confirmation a



- The thermal rearrangement was unequivocally confirmed by the characterization of the reduced product

Retrosynthetic Strategy

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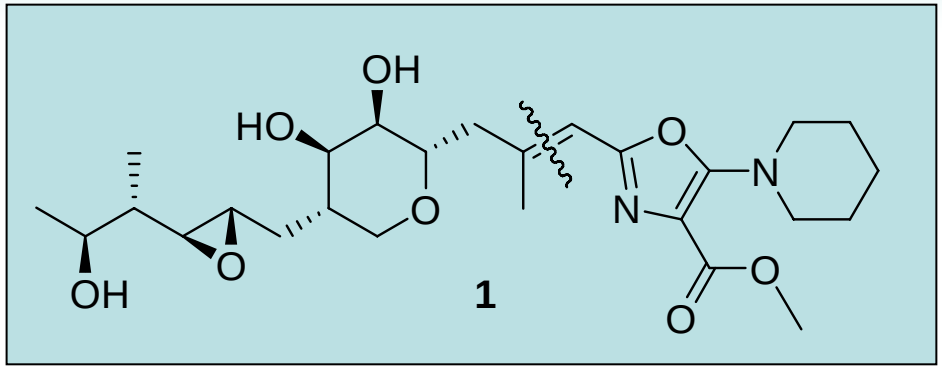
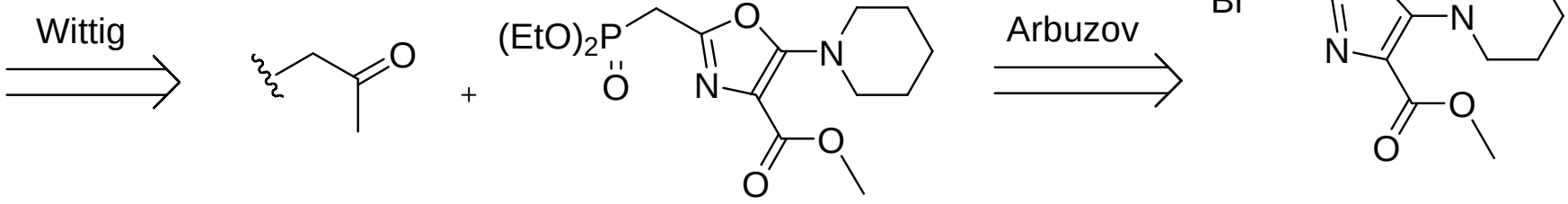
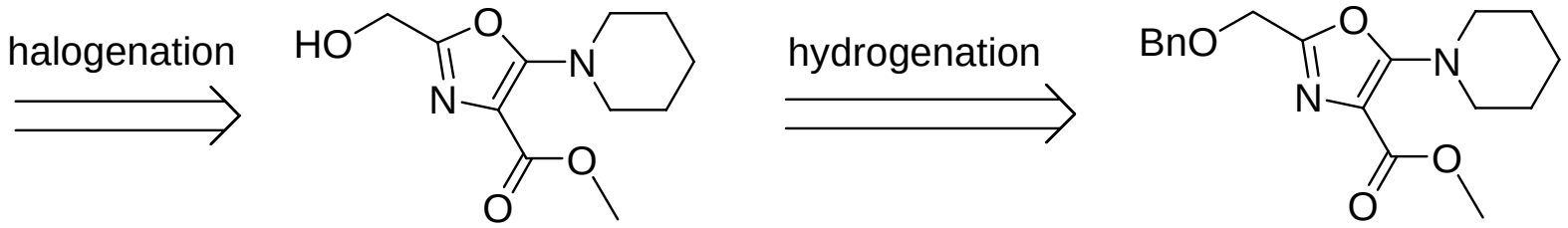
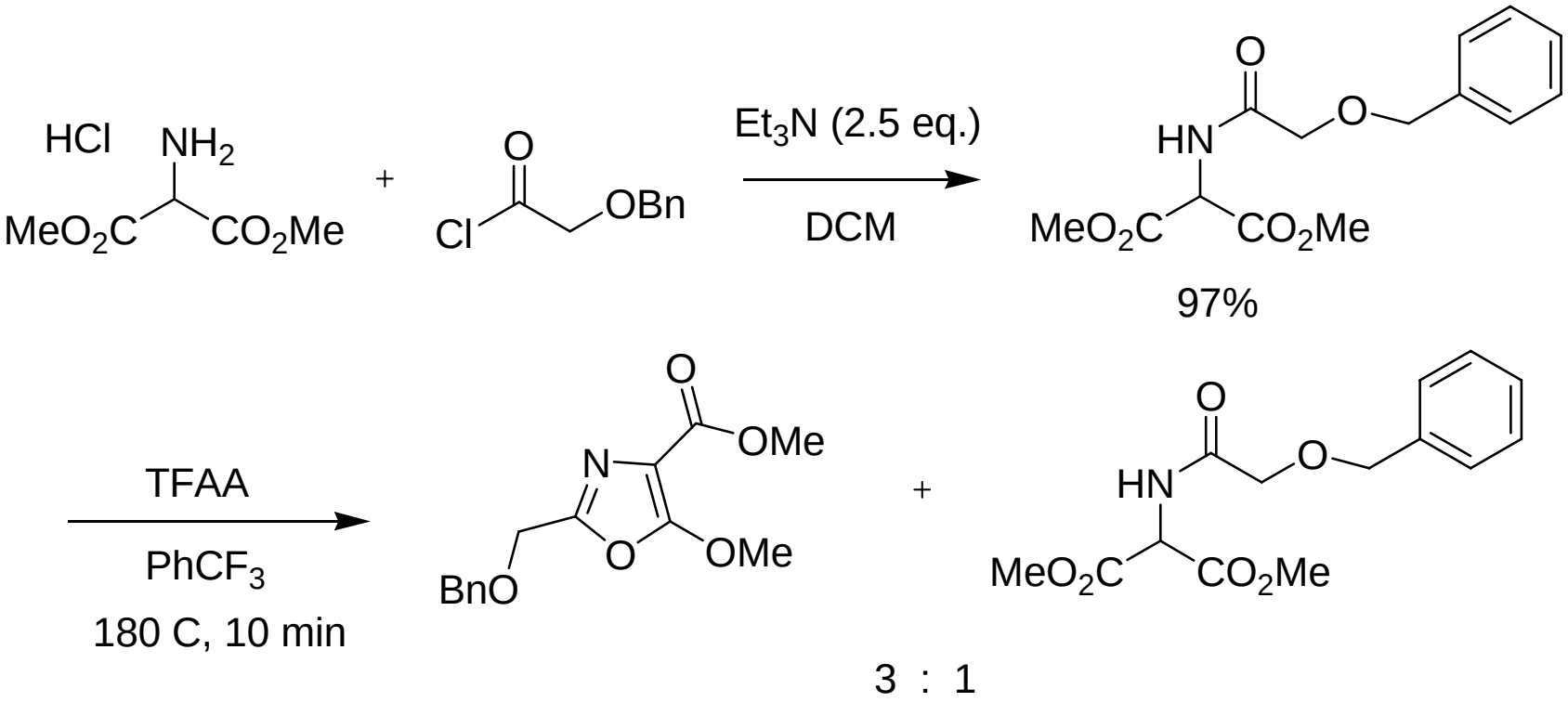






Synthesis

a



inseparable by flash/reverse phase chromatography

- Optimization studies are in progress

Conclusions

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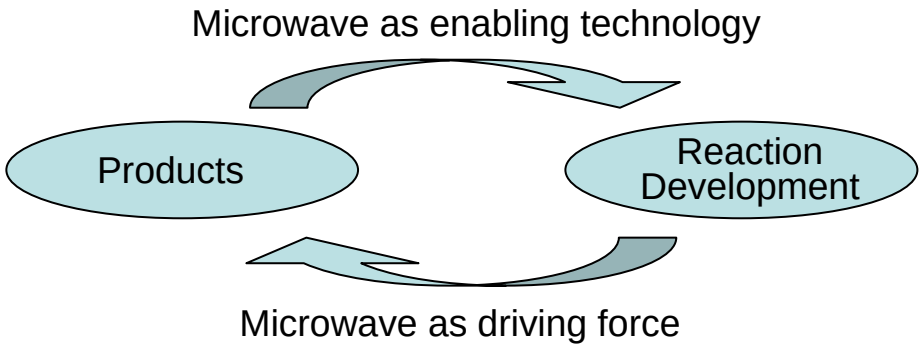
- Microwave heating can significantly shorten reaction times versus conventional thermal conditions
- Microwave-assisted synthesis can be used effectively in combination with solid-phase reagents
- Microwave reactors have become an integral part of method development in TES



Acknowledgments and Contributors

TES

Brian Eastman
Steve Sharik
Mark Smiley
William Shipe
Corey Theberge
David D. Wisnoski
F. Vivien Yang
Zhijian Zhao

Ray McClain
Todd Anderson

Scott Wolkenberg
Craig Lindsley

Research NMR

Sandor Varga

Medicinal Chemistry

George Hartman
Steve Young