General Microwave-assisted Procedures for the Expedient Synthesis of Substituted Heterocycles

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Contents

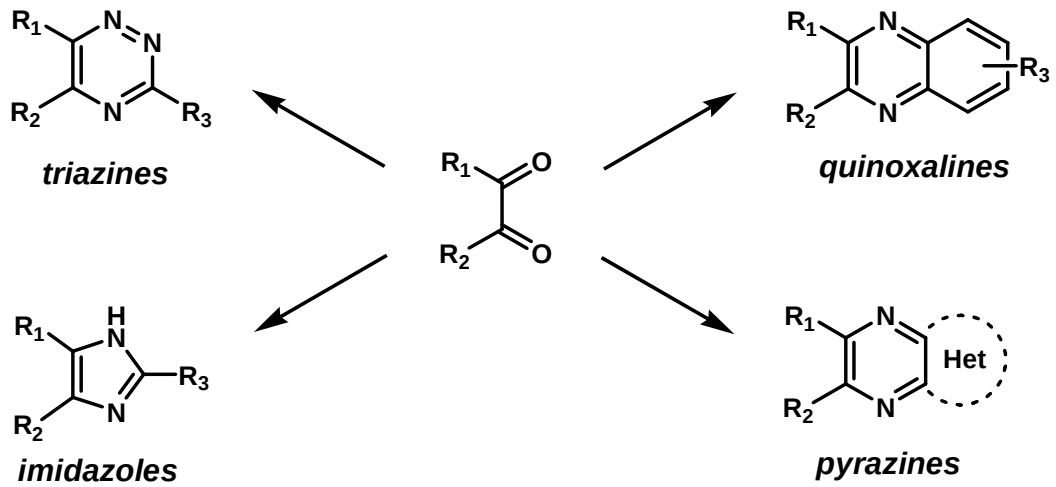
Technology Enabled Synthesis Group

- ***The TES group specializes in rapid lead discovery***
- ***Focus is on analog library synthesis***
- ***Rapidly developing programs and external competition are challenges that drive our efforts to maximize efficiency***
- ***Assisted by four single-mode microwave reactors and automated mass-guided purification***

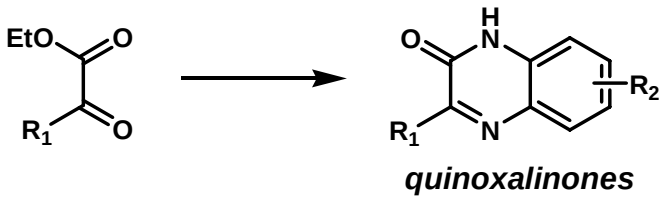
TES and Microwave Reactors

- ***Approximately 96% of all reactions requiring heating are conducted in the microwave reactor***
- ***Advantages of microwave heating are shorter reaction times, diminution of side products, and increased yields***
- ***Organic synthesis procedures using microwave heating are often scaleable***

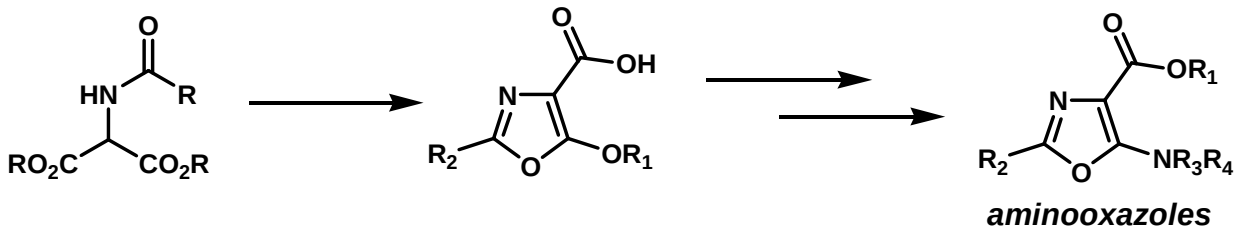
Heterocycle Formation



(1)



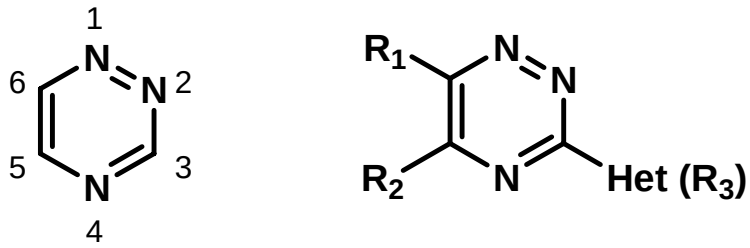
(2)



(3)

Triazines

- The triazine ring system is a key component in commercial dyes, herbicides, insecticides and pharmaceutical compositions
- The 1,2,4-triazine core structure is valuable for accessing a variety of ring systems via an intramolecular Diels-Alder reaction

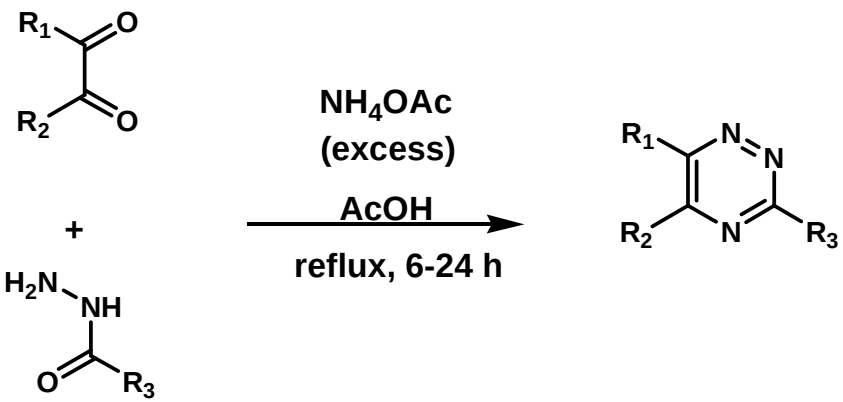


Generic and target 3-heterocyclic-1,2,4-triazines

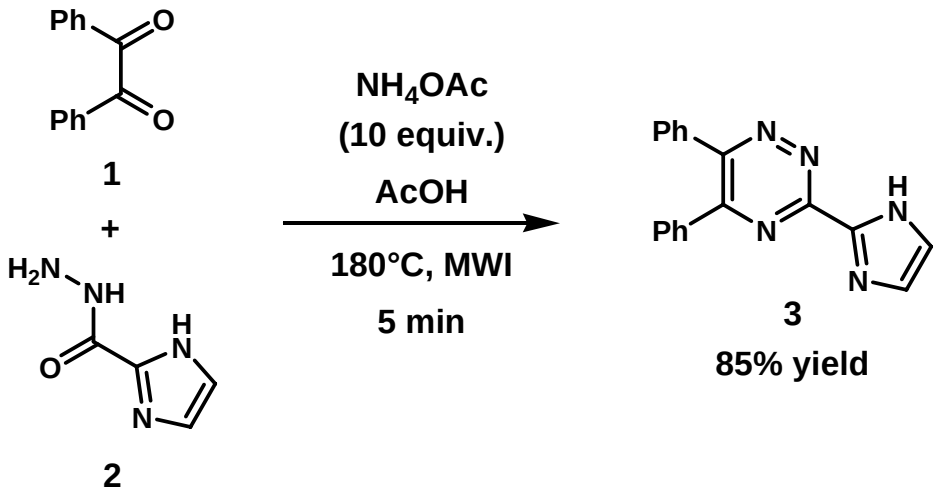
Shipe, W. D.; Yang, F.; Zhao, Z.; Wolkenberg, S. E.; Nolt, M. B.; Lindsley, C. W. *Heterocycles, in press*.

Triazine Synthesis

- Conventional heating with heterocyclic diketones or heterocyclic acyl hydrazides produced the target material in <30% yield with multiple side products
- Optimization of microwave heating conditions led to the synthesis of previously unknown **3**



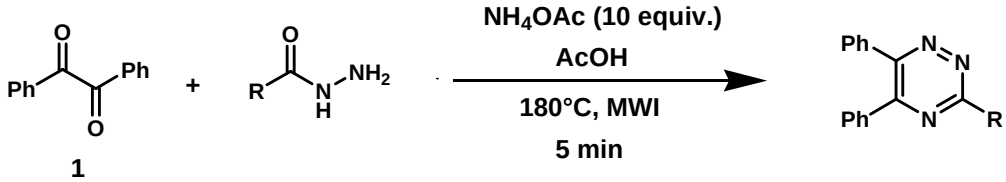
(1)

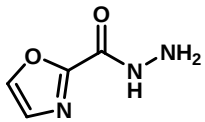
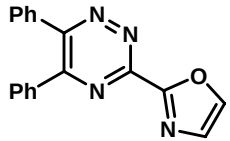
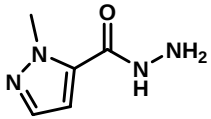
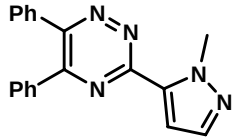
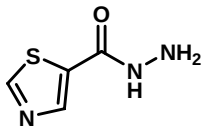
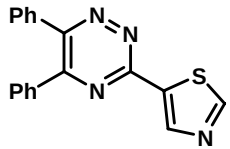
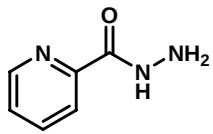
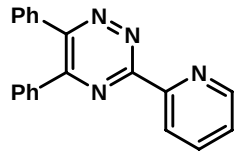
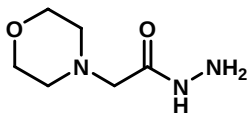
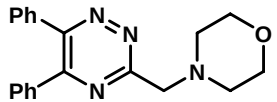


(2)

Zhao, Z.; Leister, W. H.; Strauss, K. A.; Wisnoski, D. D.; Lindsley, C. W. *Tetrahedron Lett*. **2003**, *44*, 1123-1127.

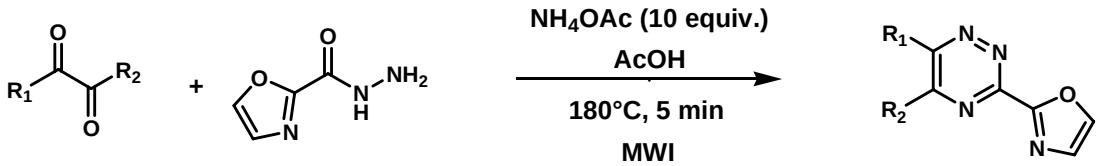
Triazine Synthesis – Scope of acyl hydrazides

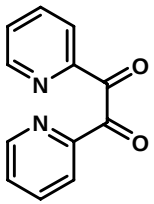
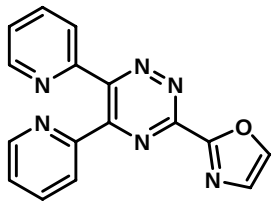
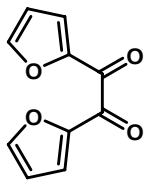
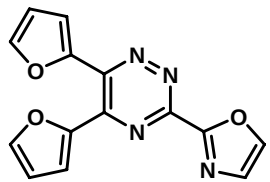
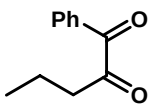
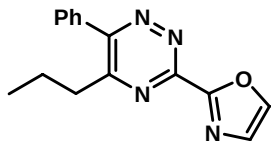
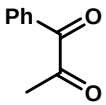
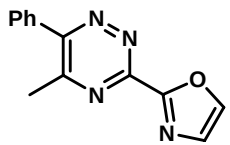


entry	$RCONHNH_2$	product	yield (%)[a]
1			84
2			80
3			92
4			90
5			81

[a]Yields for analytically pure compounds fully characterized by LCMS, NMR, and HRMS.

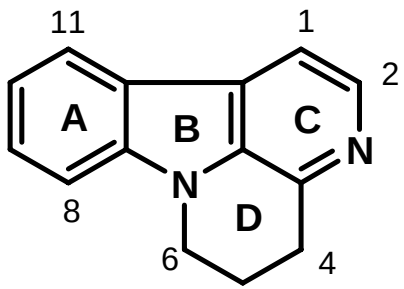
Triazines – Scope of diketones



entry	R_1COCOR_2	product	yield (%)[a]
1			92
2			90
3			64 (75)[b,c]
4			69 (80)[b,c]

[a]Yields for analytically pure compounds fully characterized by LCMS, NMR, and HRMS.
[b]Yields when reaction times extended to 10 min. [c]1:1 mixture of regioisomers

Canthines

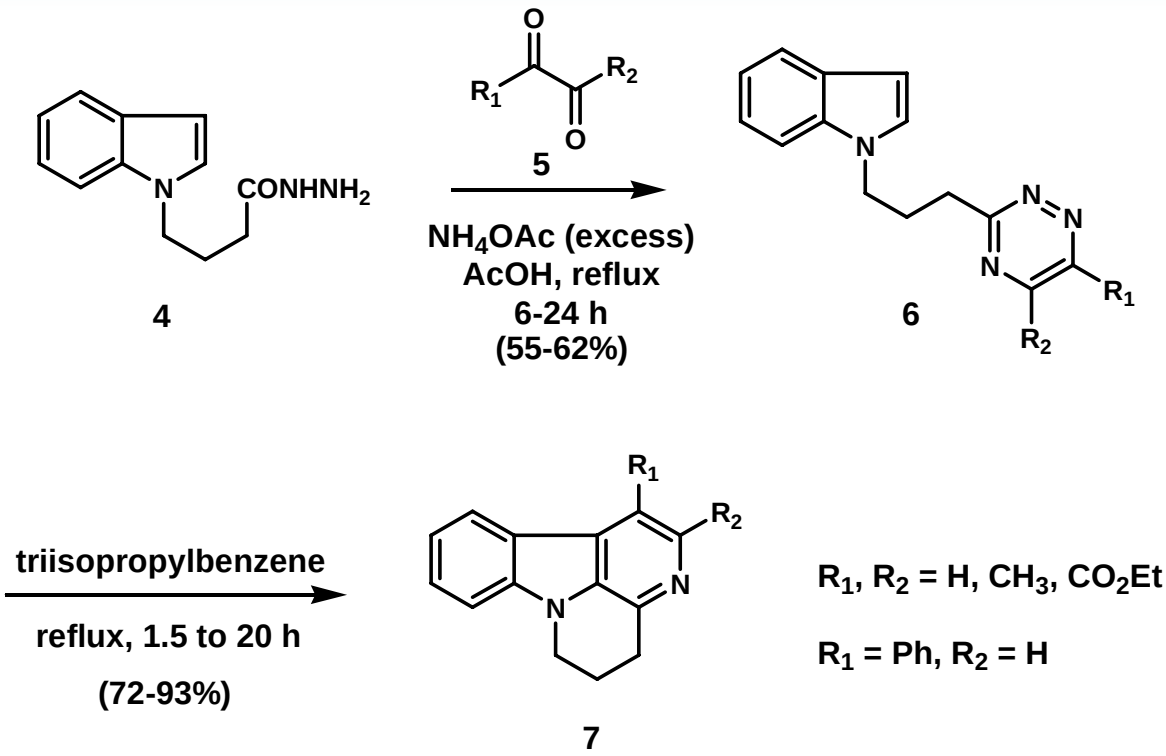


Canthine Tetracyclic Skeleton

- First isolated from *Pentaceras australis* in 1952
- Canthines are a tetracyclic subclass of β-carboline alkaloids that possess an additional D-ring
- Members of this family have exhibited a wide range of pharmacological activities including antifungal, antiviral, and antitumor properties

Ohmoto, T.; Koike, K. *The Alkaloids*; Brossi, A. Ed; Academic Press: New York, NY, 1989, Vol. 63, pp 135-170.

Conventional Canthine Preparation



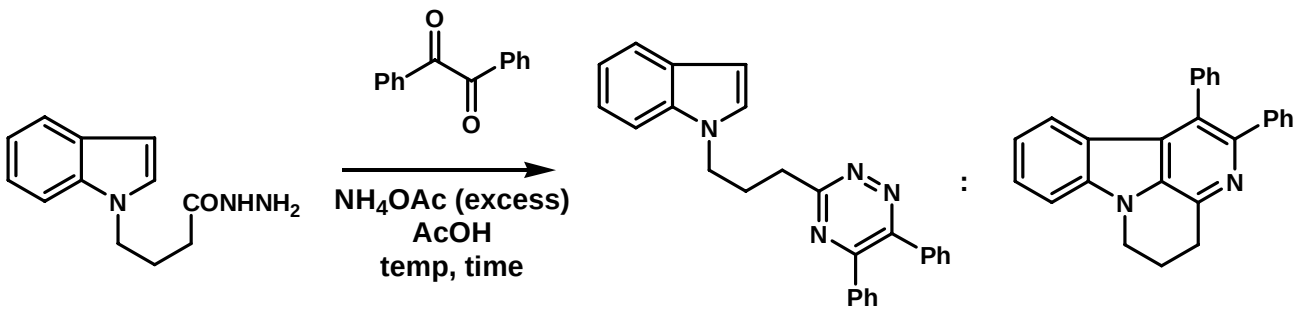
- Despite the development of this straightforward protocol, limited diversity has existed at the C1 and C2 positions of synthethetic canthines

Benson, S. C.; Li, J.-H.; Snyder, J. K. *J. Org. Chem.* **1992**, *57*, 5285-5287.

Microwave-assisted Canthine Synthesis

Optimization of Microwave Procedure

- 10 to 700-fold reduction in reaction times
- This procedure lead to the synthesis of unnatural canthines that inhibit Akt



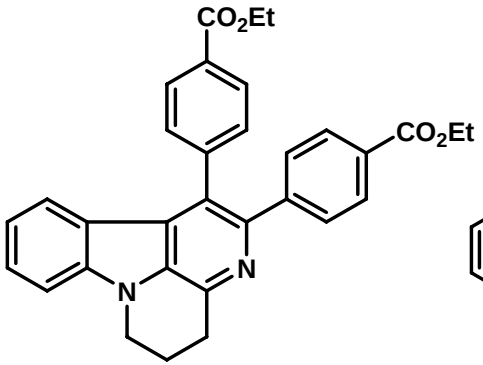
entry	time (min)	temp (°C)	6 : 7a
1	5	180	9 : 1
2	10	180	7 : 3
3	20	180	2 : 1
4	40	180	1 : 1
5	60	180	1 : 2
6	40	200	1 : 5
7	40	220	1 : 19

Ratios determined by analytical LCMS.

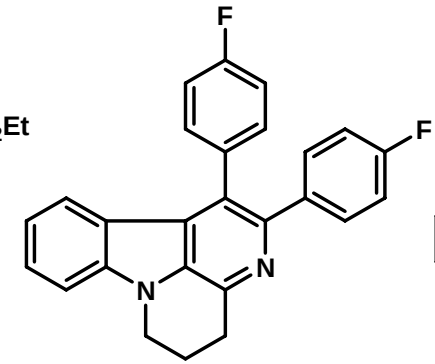
Lindsley, C. W.; Wisnoski, D. D.; Wang, Y.; Leister, W. H.; Zhao, Z. *Tetrahedron Lett.* **2003**, *44*, 4495-4498.

Lindsley, C. W.; Bogusky, M. J.; Leister, W. H.; McClain, R. T.; Robinson, R. G.; Barnett, S. F.; Defeo-Jones, D.; Ross, C. W.; Hartman, G. D. *Tetrahedron Lett.* **2005**, *46*, 2779-2782.

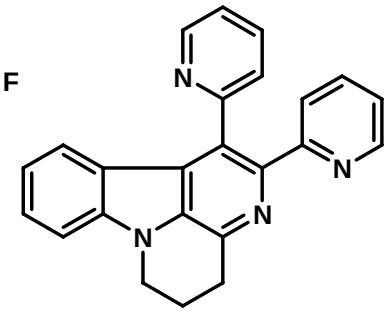
Canthines



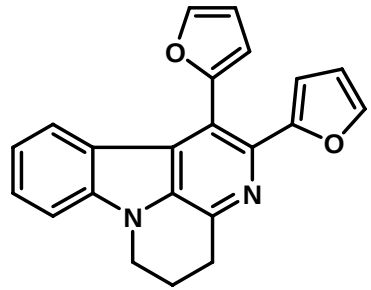
8 (81%)



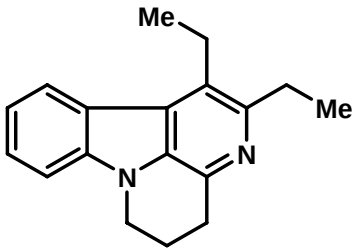
9 (83%)



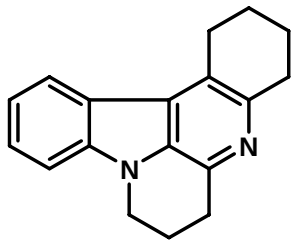
10 (59%)



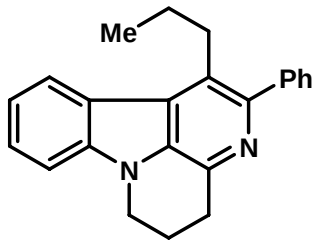
11 (62%)



12 (34%)



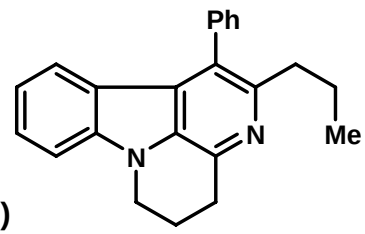
13 (26%)



14a

(1:1)

(62%)

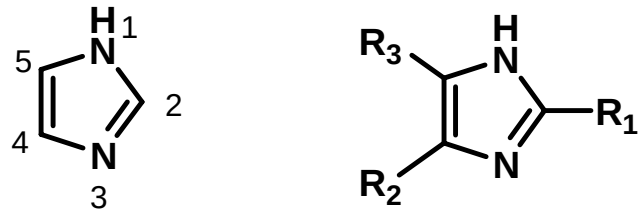


14b

Lindsley, C. W.; Wisnoski, D. D.; Wang, Y.; Leister, W. H.; Zhao, Z. *Tetrahedron Lett.* **2003**, *44*, 4495-4498.

Imidazoles

- Imidazoles are components of many natural products, dyes, herbicides, fungicides, catalysts, and pharmaceutical compounds
- Synthetic route via the formamide synthesis uses glyoxal, formaldehyde and ammonia, and heating for four to six hours



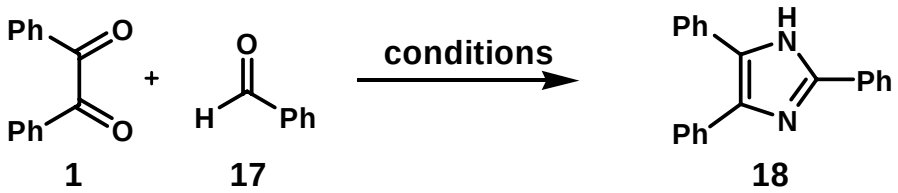
Generic and target imidazoles

(a) Grimmett, M. R. *Comprehensive Heterocyclic Chemistry*; Katrizky, A. R.; Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 5, pp 457-498. (b) Grimmett, M. R. *Comprehensive Heterocyclic Chemistry II*; Katrizky, A. R.; Rees, C. W.; Scriven , W. F. V., Eds.; Pergamon: New York, 1996; Vol. 3, p 77.

Imidazoles

Optimization of Microwave Procedure

- Ultimately, heating at 180°C for five minutes provided nearly complete conversion to **18**



1 **17** **18**

entry	temp (°C)	time (min)	conversion (%)[a]
1	60	5	24
2	80	5	51
3	100	5	61
4	120	5	68
5	140	5	87
6	160	5	98
7	160	0.5	71
8	160	1	82
9	160	3	95

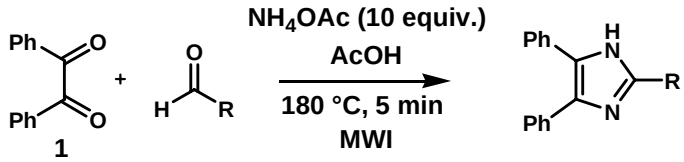
Reactions run in acetic acid with 0.2 mmol each of **1**, **17** and 10 equiv. of NH_4OAc.

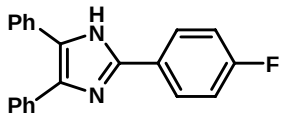
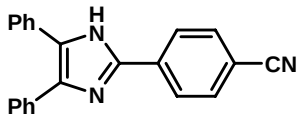
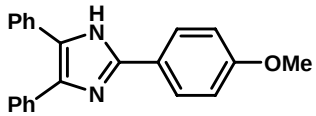
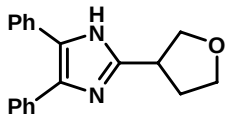
[a]Ratios determined by analytical LCMS, isolated yield for entry 6, 88%

Wolkenberg, S. E.; Wisnoski, D. D.; Leister, W. W.; Wang, Y.; Zhao, Z.; Lindsley, C. W. *Org. Lett.* **2004**, *6*, 1453-1456.

Imidazoles – aldehyde variations

- The procedure is successful with electron withdrawing and donating substitution on the aldehyde

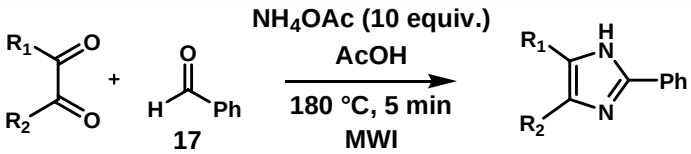


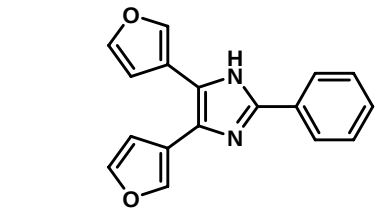
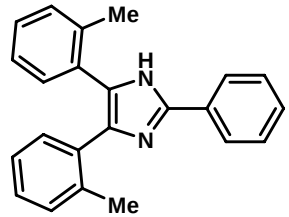
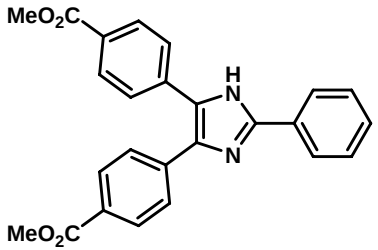
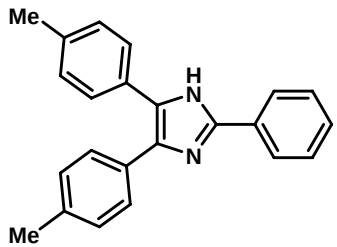
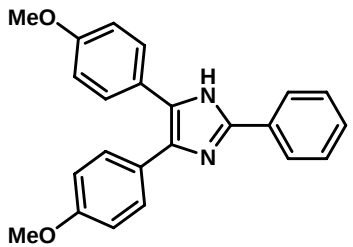
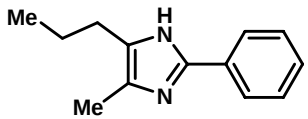
entry	product	yield (%)[a]
1		97
2		88
3		87
4		93

[a]Isolated yields for analytically pure compounds after neutralization and filtration

Wolkenberg, S. E.; Wisnoski, D. D.; Leister, W. W.; Wang, Y.; Zhao, Z.; Lindsley, C. W. *Org. Lett.* **2004**, *6*, 1453-1456.

Imidazoles – diketone variations

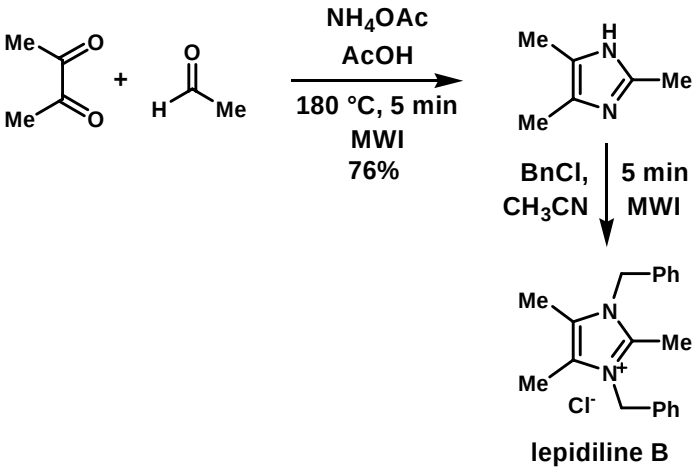


entry	product	yield (%)[a]	entry	product	yield (%)[a]
1		89	4		94
2		95	5		94
3		99	6		93

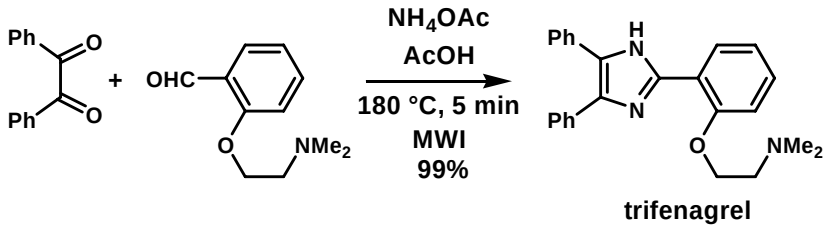
[a]Isolated yields for analytically pure compounds obtained after neutralization of the reaction mixture then filtration

Wolkenberg, S. E.; Wisnoski, D. D.; Leister, W. W.; Wang, Y.; Zhao, Z.; Lindsley, C. W. *Org. Lett.* **2004**, *6*, 1453-1456.

Imidazoles



lepidiline B



trifenagrel

- Natural product isolated from the roots of *L. meyenii*
- Micromolar cyctotoxicity against several human cancer cell lines

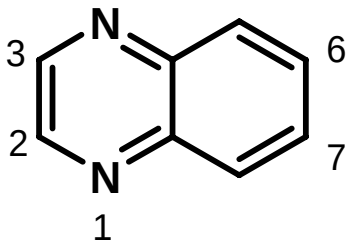
- Potent 2,4,5-triaryl imidazole arachidonate cyclooxygenase inhibitor
- Existing procedure requires two hours of reflux

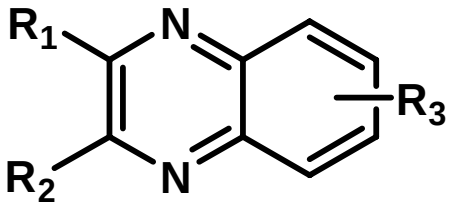
Wolkenberg, S. E.; Wisnoski, D. D.; Leister, W. W.; Wang, Y.; Zhao, Z.; Lindsley, C. W. *Org. Lett.* **2004**, *6*, 1453-1456.

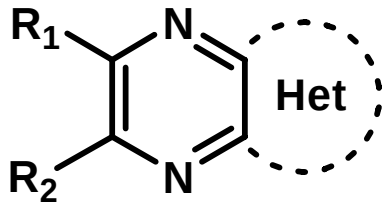
Cui, B.; Zheng, B. L.; He, K.; Zheng, Q. Y. *J. Nat. Prod.* **2003**, *66*, 1101.

Abrahams, S. L.; Hazen, R. J.; Batson, A. G.; Phillips, A. P. *J. Pharmacol. Exp. Ther.* **1989**, *249*, 359.

Quinoxaline and Fused Heterocyclic Pyrazines



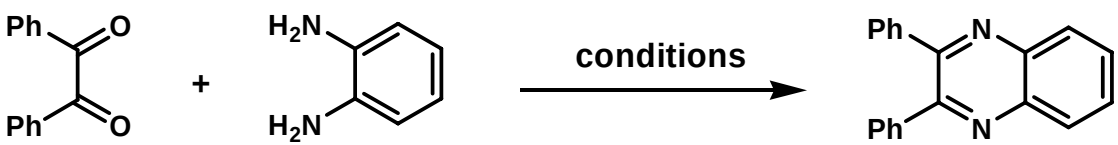




Generic and target quinoxaline and fused heterocyclic pyrazines

- Quinoxalines have demonstrated pharmaceutical value as antiviral agents, antibiotics, and kinase inhibitors
- The most common synthetic route requires the condensation of an aryl 1,2-diamine with a 1,2-dicarbonyl compound by refluxing in ethanol or acetic acid for two to 12 hours

Quinoxaline



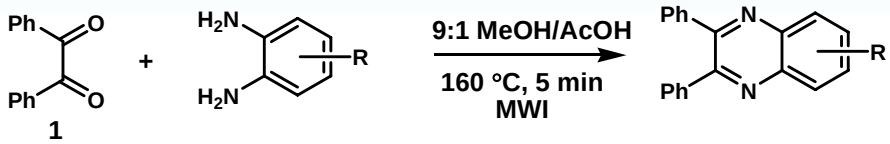
1 19 20

entry	conditions	yield
1	EtOH/AcOH, reflux, 2-12 hr	34-85
2	9:1 MeOH/AcOH, 160 °C (MWI), 5 min	99

- Optimal conditions give nearly complete conversion to product **20**
- This general procedure gives quinoxalines in high yields with tolerance for variations of the 1,2-diketone and 1,2-diamine

Zhao, Z.; Wisnoski, D. D.; Wolkenberg, S. E.; Leister, W. H.; Wang, Y.; Lindsley, C. W. *Tetrahedron Lett.* **2004**, *45*, 4873-4876.

Quinoxaline – 1,2-diamine variations



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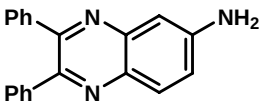
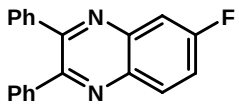
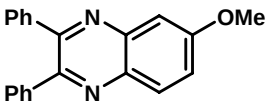
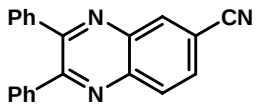
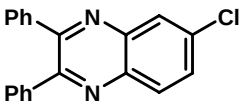
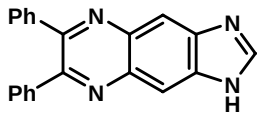
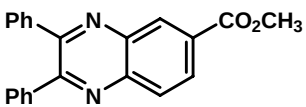
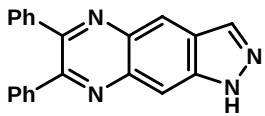
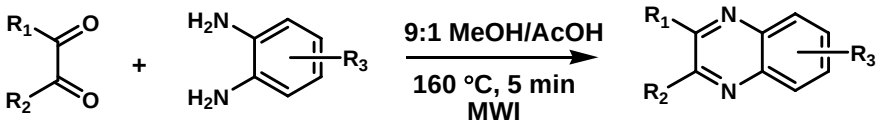
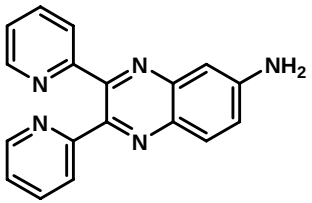
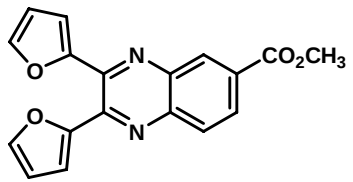
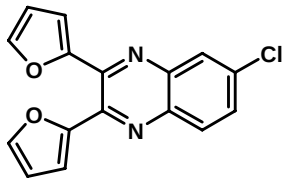
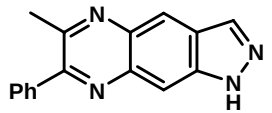
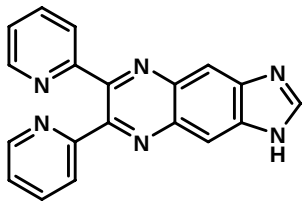
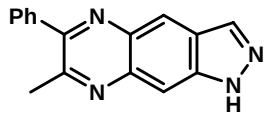
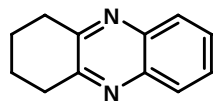
1		99	5		99
2		97	6		99
3		96	7		95
4		98	8		95

[a]Yields for analytically pure compounds fully characterized by LCMS, NMR, and HRMS.

Zhao, Z.; Wisnoski, D. D.; Wolkenberg, S. E.; Leister, W. H.; Wang, Y.; Lindsley, C. W. *Tetrahedron Lett.* **2004**, *45*, 4873-4876.

Quinoxaline – 1,2-diketone variations

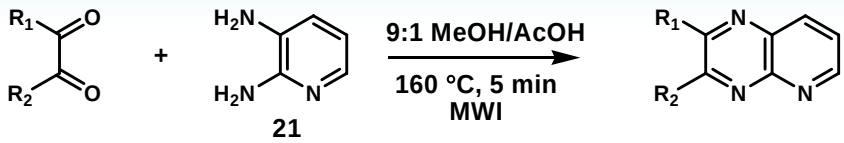


entry	product	yield (%)[a]	entry	product	yield (%)[a]
1		98	4		96
2		95	5		95
3		99			83
			6		

[a]Yields for analytically pure compounds fully characterized by LCMS, NMR, and HRMS.

Zhao, Z.; Wisnoski, D. D.; Wolkenberg, S. E.; Leister, W. H.; Wang, Y.; Lindsley, C. W. *Tetrahedron Lett.* **2004**, *45*, 4873-4876.

Pyrido[2,3-b]pyrazines



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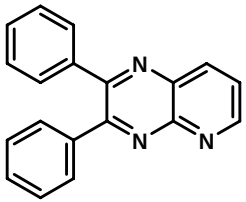
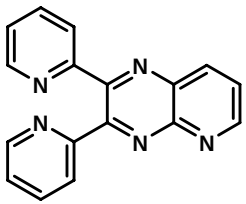
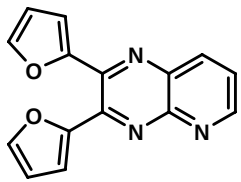
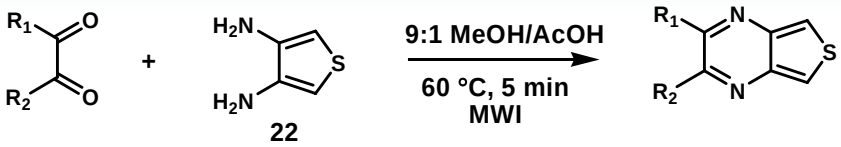
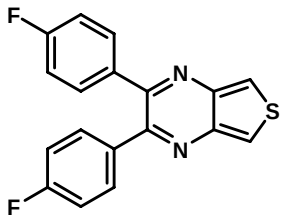
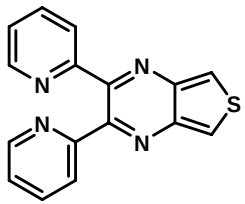
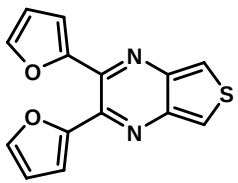
1		97
2		94
3		92

[a]Yields for analytically pure compounds fully characterized by LCMS, NMR, and HRMS.

Zhao, Z.; Wisnoski, D. D.; Wolkenberg, S. E.; Leister, W. H.; Wang, Y.; Lindsley, C. W. *Tetrahedron Lett.* **2004**, *45*, 4873-4876.

Thieno[3,4-b]pyrazines



entry	product	yield (%)[a]
1		74
2		77
3		69

[a]Yields for analytically pure compounds fully characterized by LCMS, NMR, and HRMS.

Zhao, Z.; Wisnoski, D. D.; Wolkenberg, S. E.; Leister, W. H.; Wang, Y.; Lindsley, C. W. *Tetrahedron Lett.* **2004**, *45*, 4873-4876.

Quinoxalinones

Generic and target quinoxalinones

- Although infrequently found in nature, the core structure of quinoxalinones is contained in biologically active structures with antifungal, antimicrobial, and analgesic activities

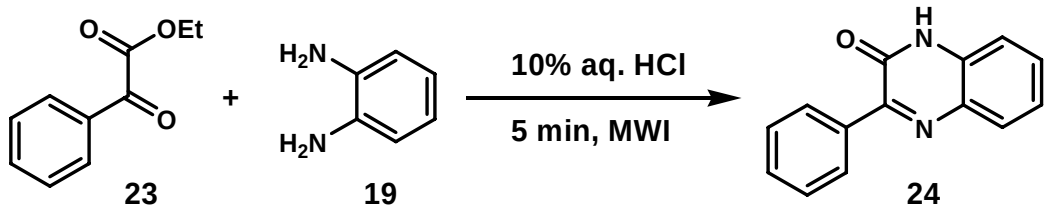
- Fernández et al. have carried out aqueous cyclocondensations of ethyl pyruvate and 1,2-diaminobenzene catalyzed by strong acids, classically called the Hinsberg reaction

Carta, A.; Sanna, P.; Loriga, M.; Setzu, M. G.; La Colla, P.; Savelli, F. *Farmaco* **2002**, *57*, 19-25.

Abasolo, M. I.; Gaozza, C. H.; Fernández, B. M. *J. Heterocyclic Chem.* **1987**, *29*, 129-133.

Quinoxalinones

Optimization of Microwave Procedure



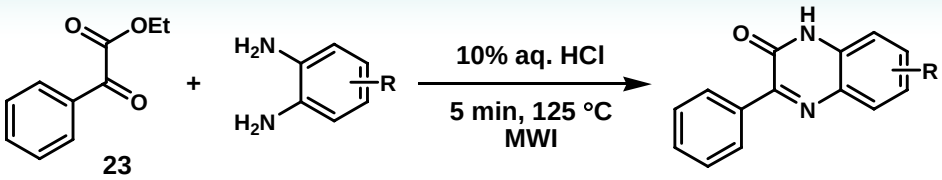
entry	temperature	conversion (%)[a]
1	60	84
2	100	90
3	125	97

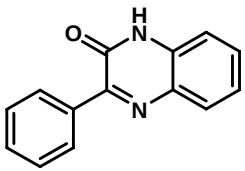
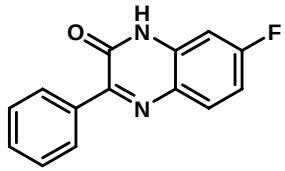
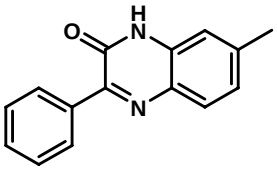
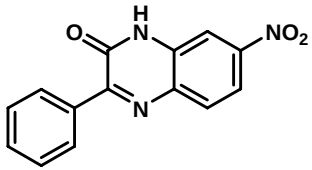
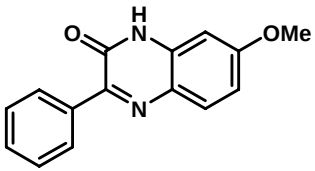
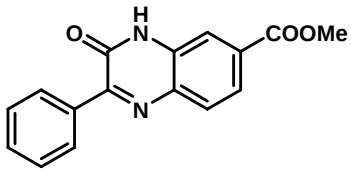
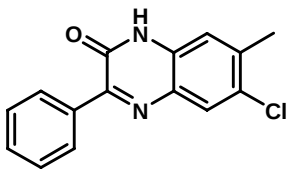
[a]Conversion determined by LCMS

- With prototypical substrate **23**, conversion to product was nearly quantitative with heating at 125°C for five minutes

Yang, F.; Shipe, W. D.; Lindsley, C. W. *previously unpublished work*

Quinoxalinones



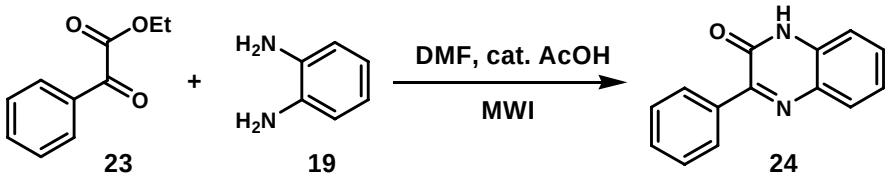
entry	product	conversion (%)[a]	entry	product	conversion (%)[a]
1		87	5		91
2		96	6		51[b]
3		100[b]	7		26
4		90			

[a]Determined by LCMS. [b]Isolated as a 3:1 mixture of regioisomers (major isomer shown)

Yang, F.; Shipe, W. D.; Lindsley, C. W. *previously unpublished work*

Quinoxalinones

Re-optimization of Microwave Procedure



23 19 24

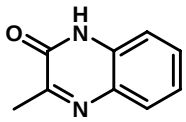
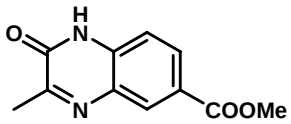
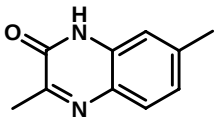
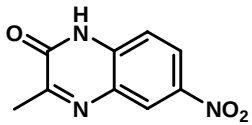
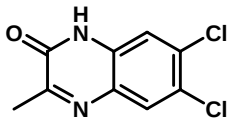
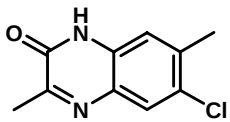
entry	time	temperature	conversion (%)[a]
1	5	160	1
2	10	160	2
3	20	160	2
4	5	170	100
5	5	180	100
6	15	180	100
7	5	190	100

[a]Conversion determined by LCMS

- The re-optimized procedure improved the conversion to target material and also proved to be general with electron-deficient aryl 1,2-diamines

Yang, F.; Shipe, W. D.; Lindsley, C. W. *previously unpublished work*

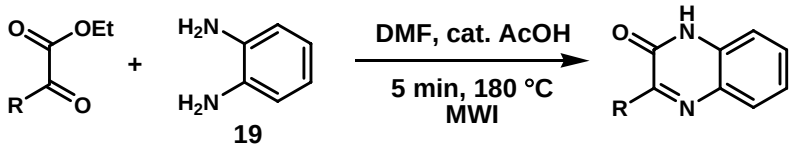
Quinoxalinones – scope of 1,2-diamine

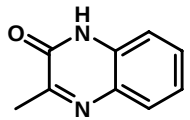
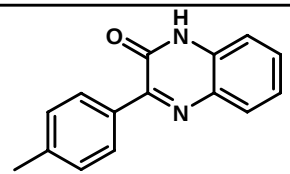
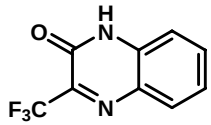
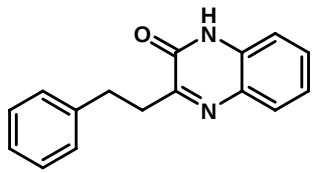
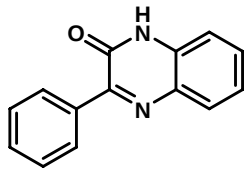
entry	product	conversion (%)[a]	entry	product	conversion (%)[a]
1		82	5		91
2		80	6		89
3		100			
4		89			

[a]Conversion determined by LCMS

Yang, F.; Shipe, W. D.; Lindsley, C. W. *previously unpublished work*

Quinoxalinones – scope of α-ketoester



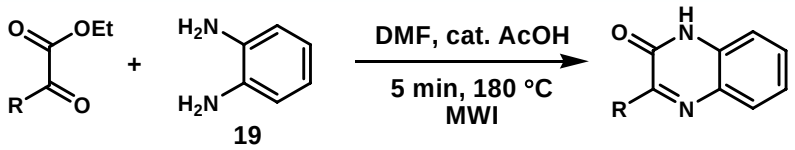
entry	product	conversion (%)[a]	entry	product	conversion (%)[a]
1		82	4		100
2		100	5		93
3		95			

[a]Determined by LCMS.

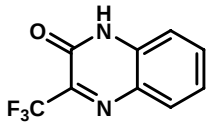
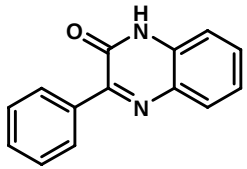
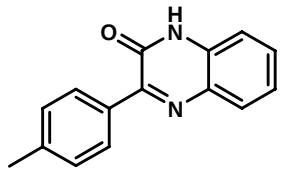
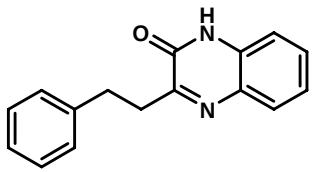
Yang, F.; Shipe, W. D.; Lindsley, C. W. *previously unpublished work*

Quinoxalinones

- Products are insoluble in solvents suitable for chromatographic separation
- Precipitation in methanol gives analytically pure quinoxzalinones



19

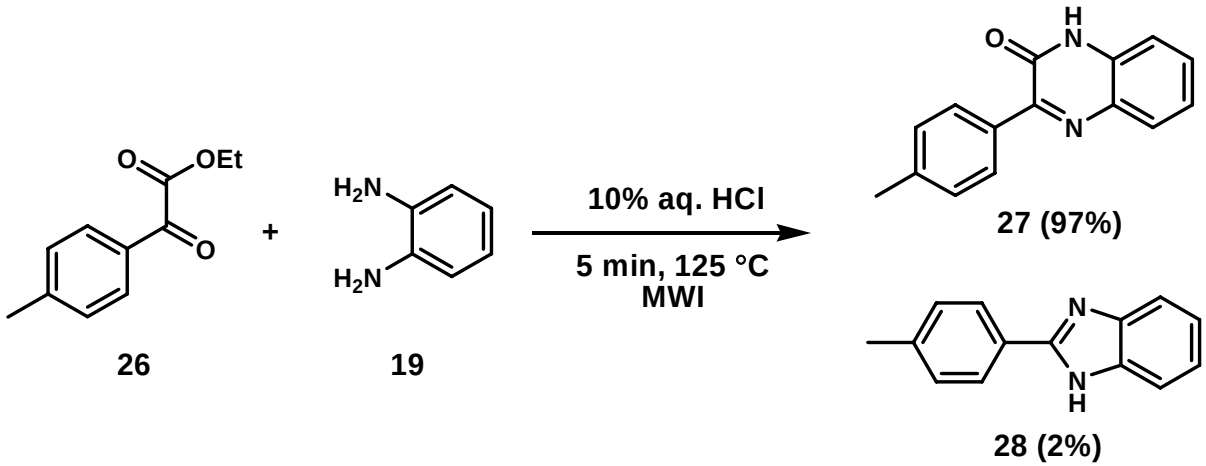
entry	product	isolated yield (%)[a]
1		69
2		74
3		60
4		59

[a]Yields for analytically pure compounds fully characterized by LCMS, NMR, and HRMS.

Yang, F.; Shipe, W. D.; Lindsley, C. W. *previously unpublished work*

Quinoxalinones

Unexpected side product



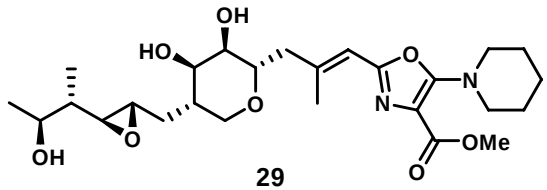
- While the appearance of side products was rare, **28** is presumable formed from the reaction with the carbonyl group of **26**, followed by oxidative decarboxylation

Yang, F.; Shipe, W. D.; Lindsley, C. W. *previously unpublished work*

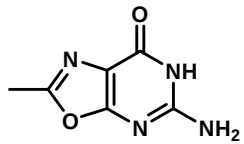
5-Aminooxazoles

Biologically active 5-aminooxazoles

- The 5-aminooxazole moiety exists in antibiotics, inhibitors of ricin and shiga toxins, peptidomimetics, and a Raf kinase inhibitor



29



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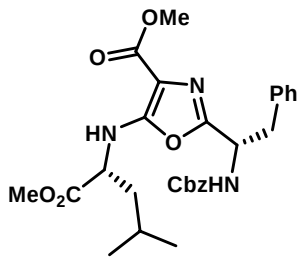
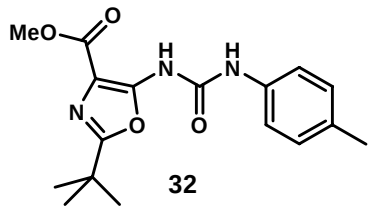


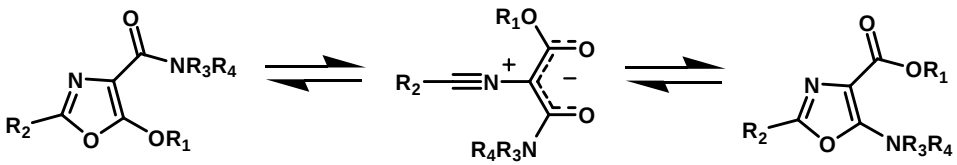
31



32

Cornforth rearrangement

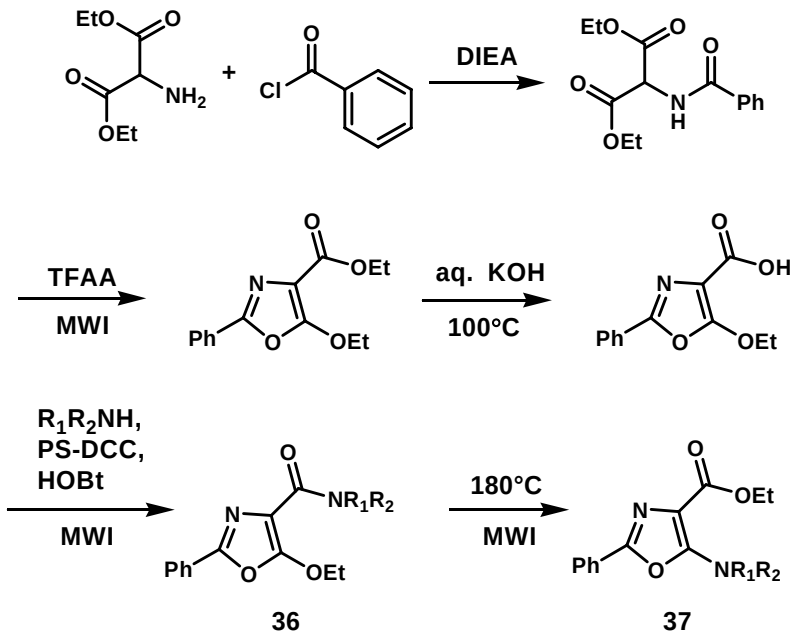
- We have accessed these structures via a microwave Cornforth rearrangement, to give the thermodynamically stable product **35**



33 34 35

5-Aminooxazoles

- Using a procedure borrowed from Dewar, we have incorporated microwave heating into a dramatically faster reaction sequence
- The result is a 200-fold reduction in reaction time while generating 5-aminooxazoles in good yield

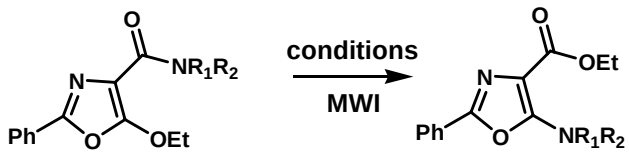


Nolt, M. B.; Smiley, M. A.; Varga, S. L.; McClain, R. T.; Wolkenberg, S. E.; Lindsley, C. W. *Tetrahedron* **2006**, *62*, 4698-4704.

5-Aminooxazoles

Optimization of Microwave-assisted Cornforth rearrangement

- We determined that microwave heating at 180°C for five minutes gave the most favorable results
- Trifluorotoluene is a high boiling solvent with sufficient dipole for rapid microwave heating



36 37

entry	solvent	temperature	time	product:starting material[a]
1	CH_3CN	150 °C	10 min	1:99
2	CH_3CN	160 °C	10 min	31:69
3	CH_3CN	170 °C	10 min	42:58
4	CH_3CN	180 °C	10 min	99:1
5	$PhCF_3$	180 °C	5 min	99:1

[a]Determined by LCMS. R_1R_2= piperidine

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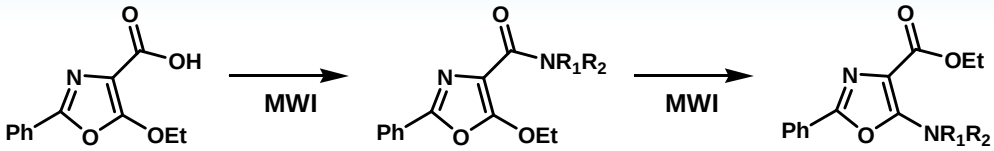
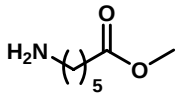
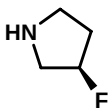
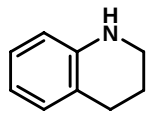
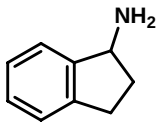
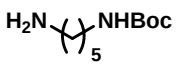
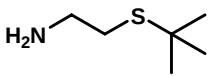
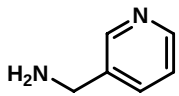
5-Aminooxazoles



36 37

entry	amine	coupling cond	rearrang cond	yield (%)	entry	amine	coupling cond	rearrang cond	yield (%)
1		100 °C, 5 min	180 °C, 5 min	98	5		100 °C, 5 min PS-DIEA (1 eq.)	180 °C, 5 min	76
2		100 °C, 5 min PS-DIEA (1 eq.)	180 °C, 5 min	47	6		100 °C, 5 min	180 °C, 5 min	85
3		100 °C, 5 min	180 °C, 5 min	99	7		100 °C, 5 min	180 °C, 5 min	99
4		100 °C, 5 min PS-DIEA (1 eq.)	180 °C, 5 min	51	8		100 °C, 5 min	180 °C, 5 min	82

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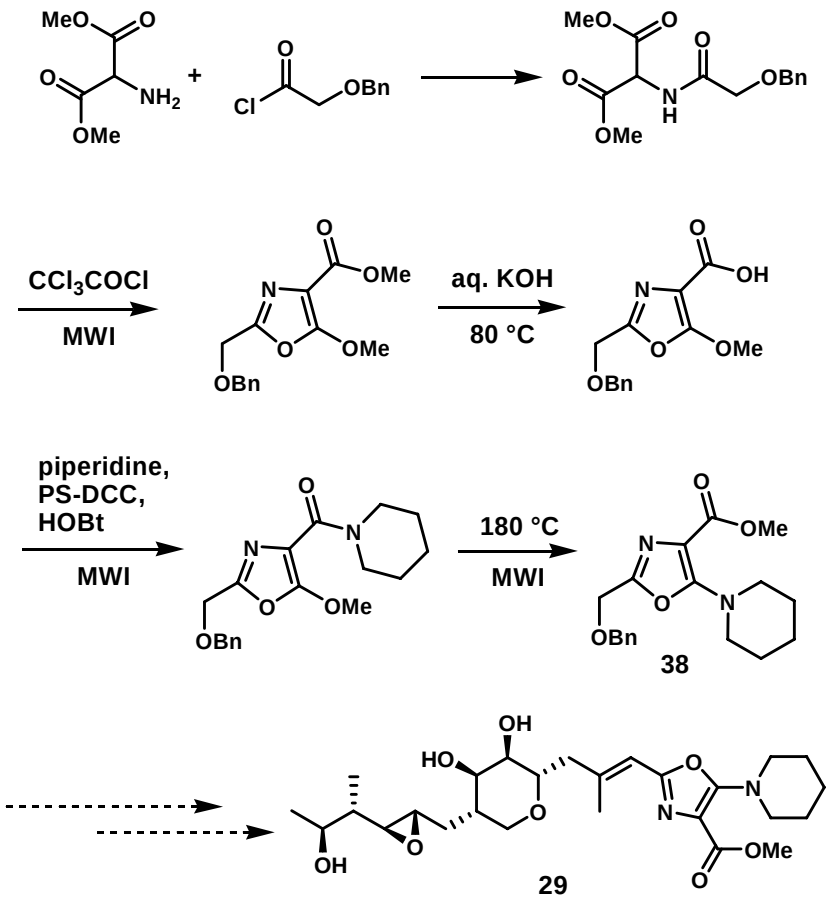
5-Aminooxazoles

- We have demonstrated the utility of this procedure in the formal synthesis of 4-(methoxycarbonyl)-2-(1-normon-2-yl)-5-piperidin-1-yloxazole (**29**)
- Intermediate **38** was obtained in 29% overall yield
- Deprotection followed by halogenation and olefination would provide **29**



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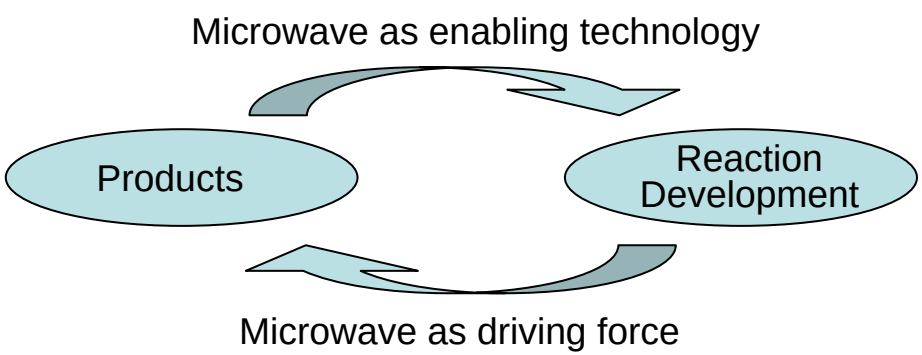
Conclusion

- Microwave heating can significantly shorten reaction times and increase efficiency
- We have demonstrated the effectiveness of microwave-assisted heating in the formation of heterocyclic targets
- Microwave reactors have become an integral part of method development in TES



Acknowledgements

Technology Enabled Synthesis Group	Former Members
James Barrow	Todd Anderson
Jaime Bunda	William Leister
April Cox	Craig Lindsley
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Ray McClain	
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Steven Sharik	
William Shipe	
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F. Vivien Yang	
Zhijian Zhao	