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CONVENIENT AND GENERAL MICROWAVE-ASSISTED PROTOCOLS FOR THE EXPEDIENT SYNTHESIS OF HETEROCYCLES

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Abstract – We have developed convenient and general MAOS protocols for the synthesis of functionalized 1,2,4-triazines, canthines, imidazoles, quinoxalines, pyrazines, quinoxalinones, and 5-aminooxazoles. The methodology described herein makes use of readily available building blocks, facilitating the generation of structurally diverse analog libraries to support nascent medicinal chemistry programs. Other advantages over classical heating conditions include shortened reaction times, increased yields, and the suppression of side product formation.

INTRODUCTION

With the increased availability of precision controlled, single-mode microwave reactors, microwave-assisted organic synthesis (MAOS) has had a significant impact on the fields of organic and parallel synthesis.[1] Such benefits over conventional thermal conditions as shortened reaction times, increased yields, and the suppression of side product formation have been demonstrated for a wide variety of transformations with MAOS. Much of the power of MAOS for accelerating lead development also derives from the fact that the technology has been coupled with automated samplers that permit reactions to be run in an unattended and parallel fashion, saving the researcher time.

Today, lead discovery groups are presented with the challenge of rapidly developing emerging programs and securing intellectual property position. Since many leads identified by high-throughput screening are small heterocyclic compounds, methods for their expedient synthesis are highly valued. Our continued interest in applying MAOS as a diversity engine for parallel synthesis drives us to develop efficient protocols for the preparation of heterocycles. In this Review, we will survey our group's recent studies

This paper is dedicated to Professor Steven M. Weinreb on the occasion of his 65th birthday.

on the microwave-assisted synthesis of substituted triazines,[2] canthines,[3] imidazoles,[4] quinoxalines,[5] fused heterocyclic pyrazines,[5] quinoxalinones,[6] and aminooxazoles.[7]

In particular, 1,2-diketones have shown great utility in the majority of these applications (Figure 1, eq. 1). As an extension of our methodology in these systems, α-ketoesters were used for the preparation of diverse quinoxalinones (eq. 2). Employing fundamentally different chemistry, a family of 5-aminooxazoles was prepared by the microwave-assisted Cornforth rearrangement of 5-alkoxyoxazoles (eq. 3).

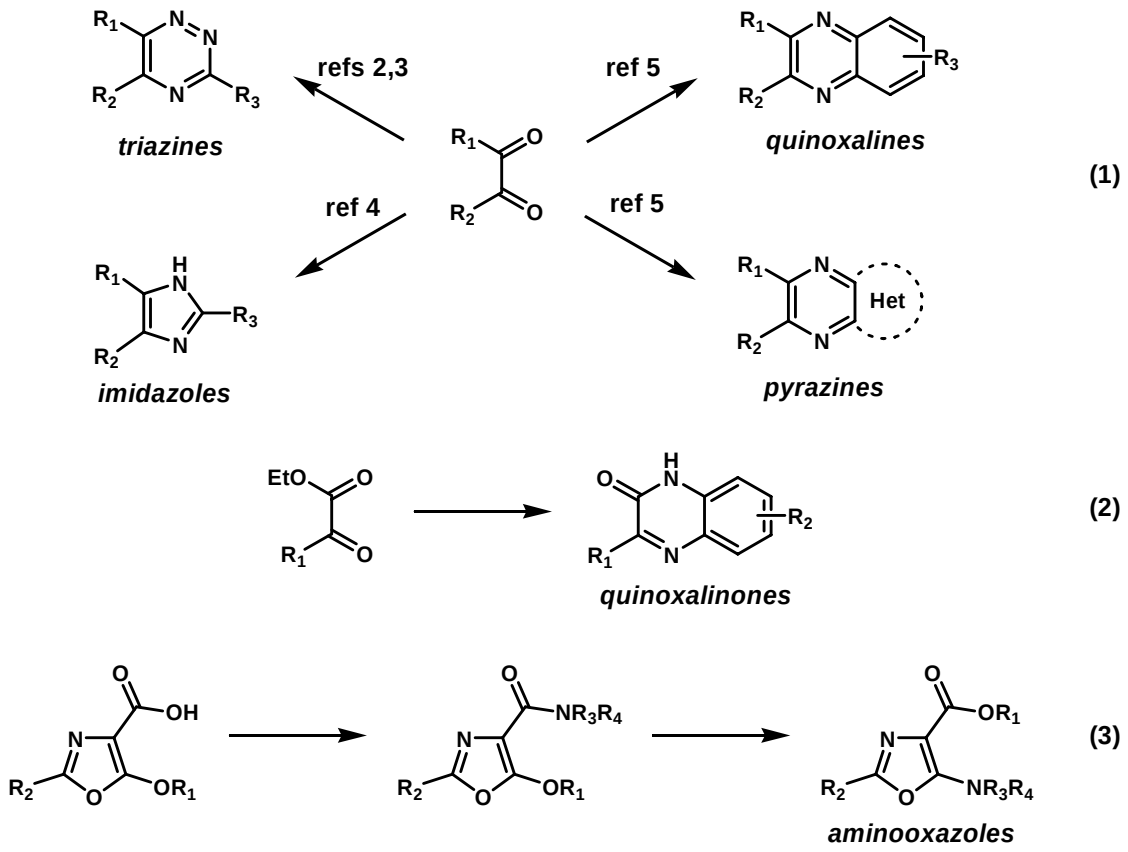


Figure 1. MAOS for the synthesis of diverse substituted heterocycles.

1,2,4-TRIAZINES[2]

Substituted triazines are an important class of nitrogen-containing heterocycles. The 1,2,4-triazine core is a useful synthetic platform for access to various ring systems via intramolecular Diels-Alder reactions with a vast array of dienophiles.[8] Additionally, the triazine ring system is a key component of commercial dyes, herbicides, insecticides, and more recently, pharmaceutical compositions.[9] While developing structure-activity relationships (SAR) for a small heterocyclic lead compound in support of a medicinal chemistry program, the need arose for a general protocol to synthesize 3-heterocyclic-1,2,4-triazines, preferably in a manner amenable to analog library synthesis (Figure 2).

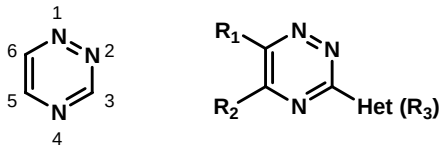
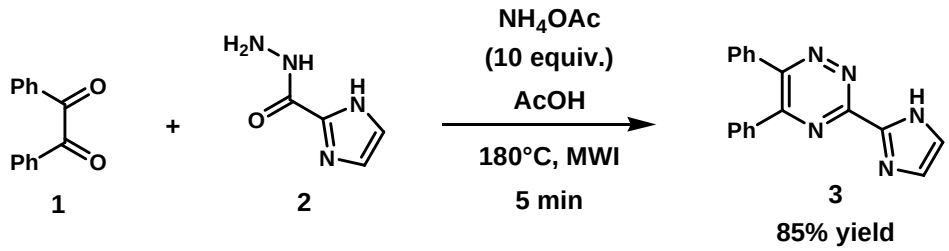


Figure 2. Generic and target 3-heterocyclic-1,2,4-triazines.

Numerous methods for the synthetic preparation of triazines exist in the literature.[10] However, the examples highlighted by these protocols typically focus on simple aliphatic, phenyl, and ester substituents at R_1-R_3.[8-11] Owing to our in-house reagent library of structurally diverse acyl hydrazides, our efforts centered on exploring a synthetic route involving the condensation of 1,2-diketones with acyl hydrazides and ammonium acetate. The traditional thermal conditions entail heating a 1:1 ratio of a 1,2-diketone and an acyl hydrazide with excess ammonium acetate in refluxing acetic acid for 6-24 hours. In our hands, these conditions with either a heterocyclic acyl hydrazide or heterocycle-containing 1,2-diketone gave low yields (<30%), required extended heating to consume starting materials (10-24 h), and resulted in numerous side products. With non-heterocyclic starting materials, these conditions yielded the desired triazines in under 8 hours and in >65% isolated yields, in accord with literature precedent.[8,11]

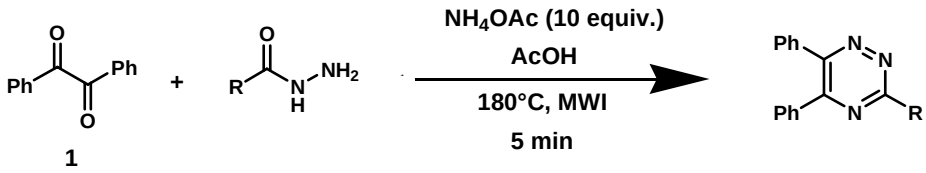
Conventional thermal conditions were quickly adapted and optimized under microwave irradiation (MWI) on the Smithsynthesizer™ (Scheme 1) to deliver the previously unknown 3-imidazoly-1,2,4-triazine (**3**) in 85% isolated yield.[12] The optimized conditions involved reacting a 1:1 ratio of benzil (**1**) and an imidazoyl acyl hydrazide (**2**) with 10 equivalents of ammonium acetate in 1 mL of acetic acid for 5 minutes at 180 ˚C, 60 ˚C above the boiling point of acetic acid.



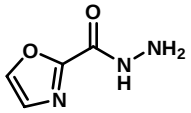
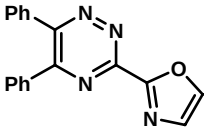
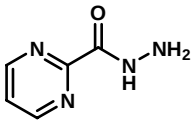
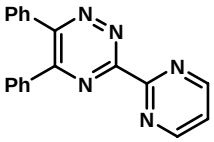
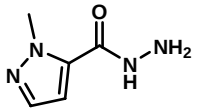
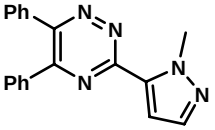
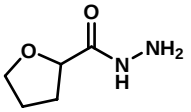
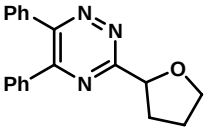
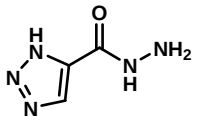
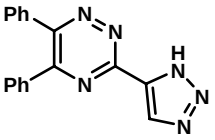
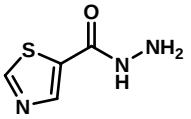
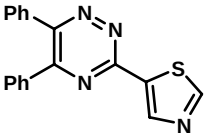
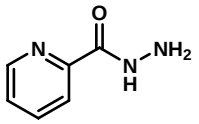
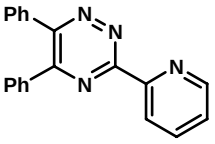
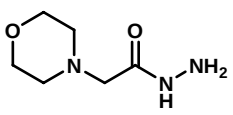
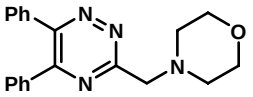
Scheme 1. Synthesis of **3**.

With this result in hand, a 48-membered library was synthesized employing a diverse set of acyl hydrazides using **1** as the 1,2-diketone component. The desired product was obtained in every instance, with crude LCMS purity > 75% and isolated yields > 79%. Representative library members are depicted in Table 1. This new protocol allowed for the synthesis of various heteroaromatic (entries 1-3, 5-7) and saturated heterocyclic congeners (entry 4) as well as other aminoalkyl derivatives (entry 8) demonstrating the generality of this methodology for analog library synthesis.

Table 1. Scope of the acyl hydrazide in the MAOS of triazines.



1

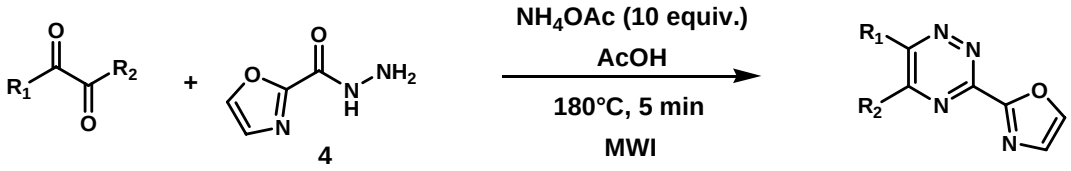
entry	$RCONHNH_2$	product	yield (%)[a]
1			84
2			83
3			80
4			79
5			89
6			92
7			90
8			81

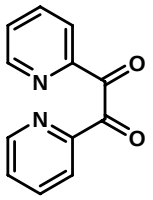
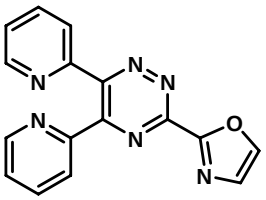
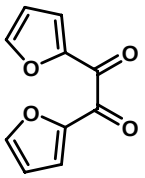
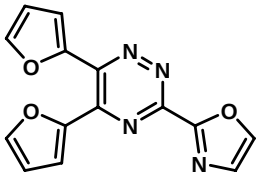
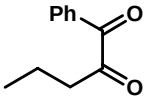
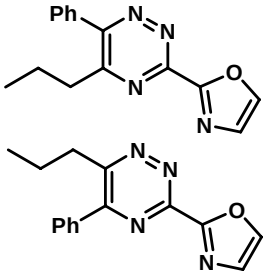
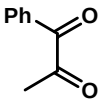
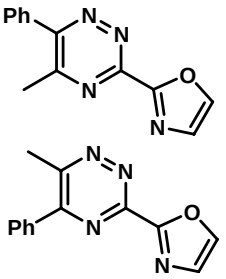
[a] Yields for analytically pure compounds fully characterized by LCMS, NMR, and HRMS.

This methodology appears to be general for the 1,2-diketone component (Table 2) as well as the acyl hydrazide component. Again, excellent crude LCMS purities (>70%) and isolated yields were attained

under standard reaction conditions with acyl hydrazide (**4**) for heterocyclic (entries 1-2), and 1-alkyl-2-phenyl-3,4-diketones (entries 3-4). As entries 3 and 4 involved unsymmetrical 1,2-diketones, a 1:1 ratio of regioisomers was obtained; moreover, extending the reaction time from 5 to 10 minutes increased the yields by ~10% for these entries.

Table 2. Scope of the 1,2-diketone in the MAOS of triazines.



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

[a] Yields for analytically pure compounds fully characterized by LCMS, NMR, and HRMS. [b] Yields when reaction time extended to 10 minutes.

In addition to providing high yielding access to a number of previously unknown 3-heterocyclic-1,2,4-triazines, overall reaction times have been reduced 60 to 300-fold over conventional thermal conditions using this MAOS protocol.

CANTHINES[3]

The canthines are a tetracyclic subclass of β-carboline alkaloids that possess an additional D-ring (Figure 3).[13] Since the isolation of the parent canthine in 1952 from *Pentaceras australis*, over forty members of this alkaloid class have been isolated and characterized.[14] Members of the canthine family exhibit a wide range of pharmacological activities including antifungal, antiviral, and antitumor properties.[13-15]

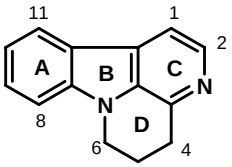
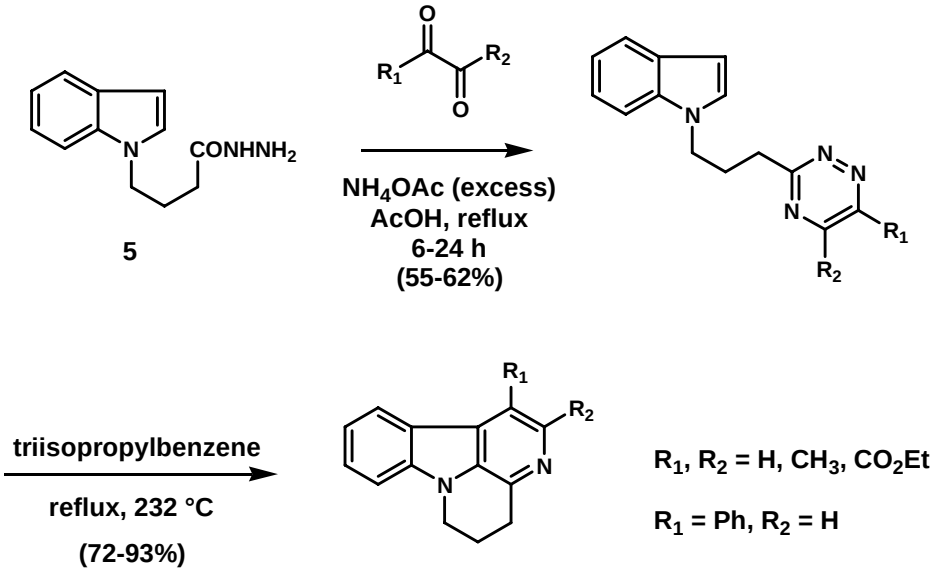


Figure 3. Canthine alkaloid tetracyclic skeleton.

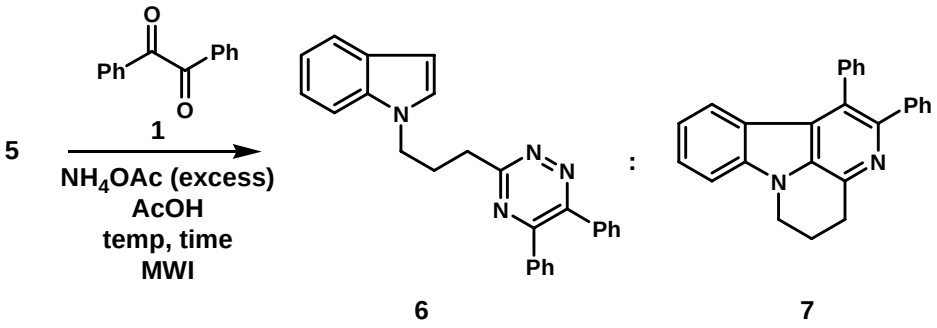
The canthine skeleton has frequently been accessed using Pictet-Spengler or Bischler-Napieralski synthetic strategies.[16] In 1992, the Snyder group disclosed an elegant entry to the canthine skeleton utilizing indole as a dienophile in an intramolecular inverse electron demand Diels-Alder reaction (Scheme 2).[17] Treatment of acyl hydrazide-tethered indole (**5**) with 1,2-diketones and excess ammonium acetate in refluxing acetic acid for several hours provided triazine-tethered indoles. After purification, these intermediates were refluxed in triisopropylbenzene (232 ˚C) for 1.5 to 20 hours to provide the canthine skeleton in 45-56% overall yield. Despite this notable synthetic advance, limited diversity exists at the C1 and C2 positions of natural and unnatural canthine alkaloids reported to date.[13-17]



Scheme 2. Synthesis of the canthine skeleton by an intramolecular Diels-Alder strategy.

In prior work, we reported on a new microwave-mediated protocol for the rapid synthesis of diverse 3,5,6-trisubstituted-1,2,4-triazines (*vida supra*).[2] During the course of this work, acyl hydrazide (**5**)[17] was subjected to our standard microwave conditions (AcOH, 180 ˚C, 5 min) in the presence of benzil (**1**) and 10 equiv. of ammonium acetate, producing not only 1,2,4-triazine (**6**) in 83% yield, but also the 1,2-diphenyl-canthine derivative (**7**) in 6% yield (Table 3). LCMS and NMR analysis indicated a 9:1 ratio of **6**:**7**. Thus, in a single synthetic operation, **5** underwent a three component condensation to generate triazine (**6**), followed by an intramolecular Diels-Alder reaction and subsequent cheletropic extrusion of N_2 to provide the previously unknown 1,2-diphenyl canthine (**7**). With this result in hand, our efforts centered on the optimization of this "one pot" reaction to deliver **7** exclusively. Reaction parameters were quickly evaluated in an automated fashion on a single-mode microwave (Table 3), leading to the optimal conditions of 220 ˚C for 40 minutes (entry 7), which delivered a 1:19 ratio of **6**:**7**.

Table 3. Optimization of "one pot" synthesis of **7**.



entry	time (min)	temp (°C)	6 : 7
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

[a] Ratios determined by analytical LCMS.

On a 0.5 mmol scale reaction, running this reaction under the optimal conditions (entry 7) delivered **7** in 80% isolated yield with no detectable trace of triazine (**6**).[18] With a reliable "one pot" protocol for the

expedient synthesis of the basic canthine skeleton, we turned our attention toward the generality of this reaction with respect to other 1,2-diketones.

A variety of 1,2-diketones and **5** were reacted using our standard "one pot" protocol to deliver unnatural canthine alkaloids in moderate to excellent isolated yields (Figure 4). Functionalized aryl analogs such as **8** and **9** provided the best yields (>80%), while heteroaryl congeners, exemplified by **10** and **11** afforded reasonable yields (~60%). Dialkyl derivatives generally afforded lower overall yields (~30%) under this protocol, as illustrated by **12** and the novel pentacyclic congener (**13**). However, replacement of one alkyl group with a phenyl substituent increased the yield to 62%, though a 1:1 mixture **14a**:**14b** of regioisomers resulted. Preparative mass-guided HPLC on a custom Agilent 1100 instrument smoothly separated the regioisomers.[19]

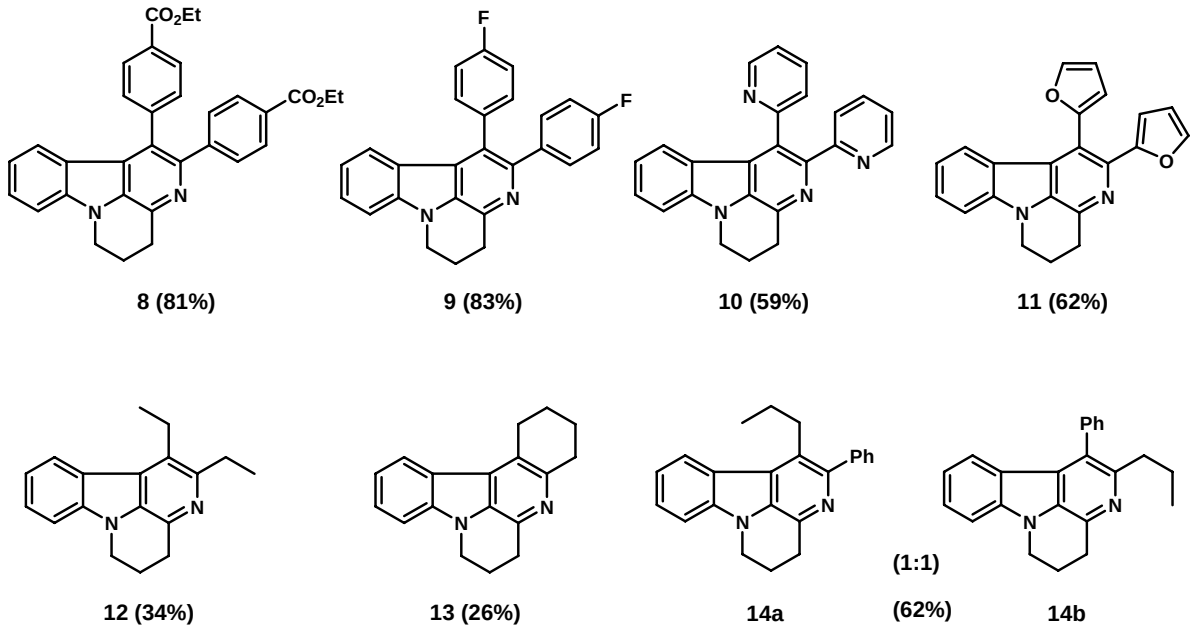
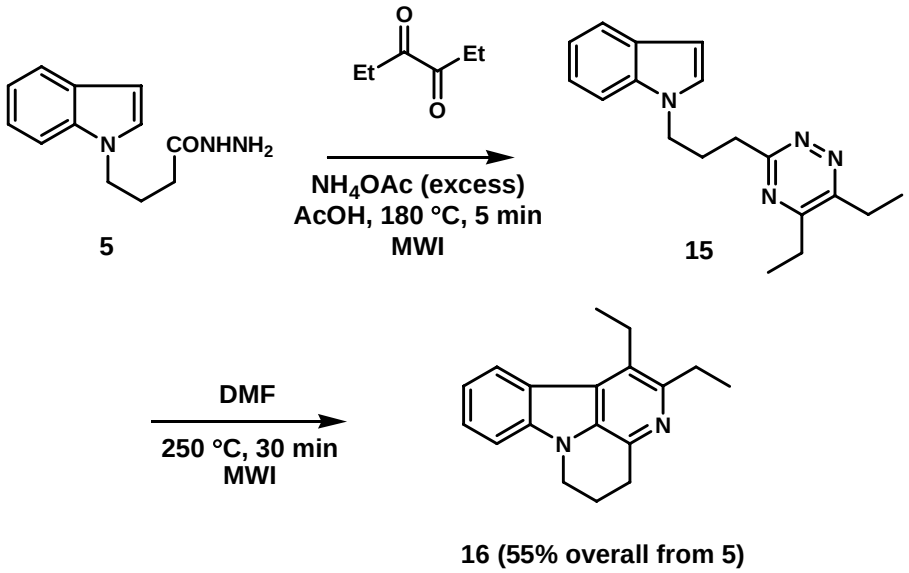


Figure 4. Representative unnatural canthine alkaloids.

Attempts to modify the reaction parameters to increase the "one pot" yields of C1/C2 dialkyl analogs failed. Ultimately, improved yields were achieved by a "two pot" microwave-accelerated procedure that required only 35 minutes of total reaction time (Scheme 3). Our standard condensative triazine protocol was employed to deliver **15**. After isolation, **15** was dissolved in dry DMF and heated at 250˚C, 100˚C above the boiling point of DMF, for 30 minutes in a single-mode microwave to provide **16** in 55% overall yield from **5**.[20]



Scheme 3. Synthesis of **16**.

Recently, diversity-oriented synthesis has attracted much attention as unnatural analogs of natural products have been shown to possess novel biological activity.[21] Relatively few canthine alkaloids have been investigated, yet the class possesses a wide range of biological activities. Using the described "one pot" protocol, the preparation of a library of unnatural canthine alkaloids coupled with biological screening was undertaken, leading to the discovery of compounds with biological activities beyond those of the natural products.[22]

In addition to providing high yielding access to a number of previously unknown canthine alkaloids, overall reaction times have been reduced 10 to 700-fold over conventional thermal conditions with this MAOS protocol.

IMIDAZOLES[4]

The imidazole system is contained in many natural products with biological significance, such as histidine, histamine, and the purines as obvious examples. As such, numerous synthetic imidazoles have been prepared for evaluation as pharmacological agents. Additionally, imidazoles find many other applications as components of commercial dyes, herbicides, fungicides, catalysts, and polymerization agents.[23]

The original synthesis of the parent imidazole employed glyoxal, formaldehyde, and ammonia, and established that the condensative formation of four C–N bonds was a viable route to this heterocyclic nucleus.[23-24] Although classical methods followed from this early success, the reaction suffered low yields, mixtures of products (including reversed aldol condensations and oxazole formation), and lack of generality. Many synthetic methodology alternatives exist, but resort to harsh conditions (e.g., the

formamide synthesis, which requires excess reagents, sulfuric acid as a condensing agent, 150–200 °C, 4–6 h, 40–90%).[23,25] Additionally, reagents for these procedures are not readily or commercially available, a key limitation when developing conditions for library synthesis. As an extension of the microwave-assisted methodology developed for the synthesis of 1,2,4-triazines from 1,2-diketones,[2] we examined the application of microwave conditions to a system that would produce substituted imidazoles (Figure 5).

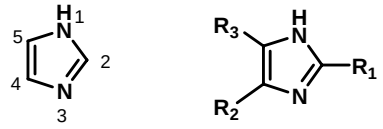
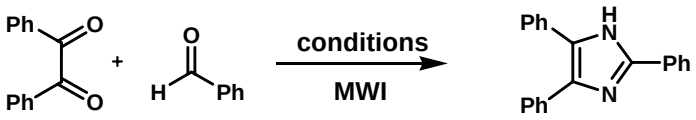


Figure 5. Generic and target imidazoles.

Initial efforts focused on optimizing microwave conditions for the formation of 2,4,5-triphenylimidazole (**18**) using ammonium acetate in acetic acid, based on prior investigations of conventional thermal conditions (Table 4).[26] The optimal conditions with respect to time and temperature were found to be 180 ˚C for 5 min. Isolation of the product from this and subsequent reactions simply required neutralization of the reaction mixture (typically achieved with concentrated NH_4OH) and filtration to furnish solid substituted imidazoles of analytical purity.[27]

Table 4. Optimization of the synthesis of imidazole (**18**).



1 **17** **18**

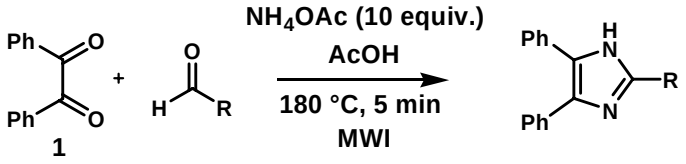
entry	temp (°C)	time (min)	conversion (%)[a]
1	60	5	24
2	80	5	51
3	100	5	61
4	120	5	68
5	140	5	87
6	160	5	98
7	160	0.5	71
8	160	1	82
9	160	3	95

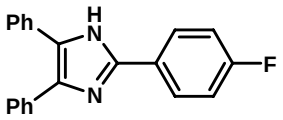
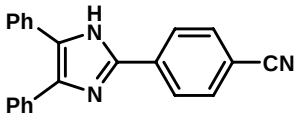
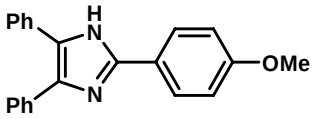
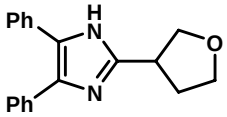
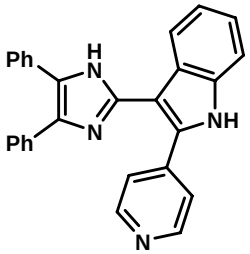
[a] Reactions run in AcOH with 0.2 mmol each of **1**, **17**, and 10 equiv. of NH_4OAc. Conversion determined by LCMS; isolated yield for entry 6, 88%.

These conditions were general for the reacting aldehyde, as demonstrated in Table 5. Aldehydes bearing either electron-withdrawing (entries 1 and 2) or electron-donating groups (entry 3) perform equally well

in the reaction. Additionally, aliphatic (see entry 4 and Scheme 6 below) and heterocyclic aldehydes (entry 5) deliver the corresponding imidazoles in high yield.

Table 5. Scope of the aldehyde in the MAOS of imidazoles.

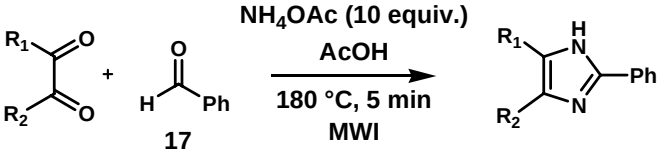


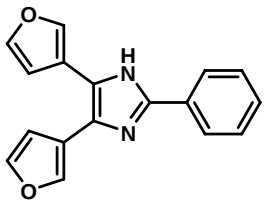
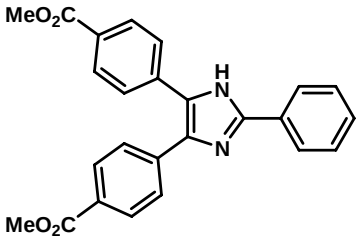
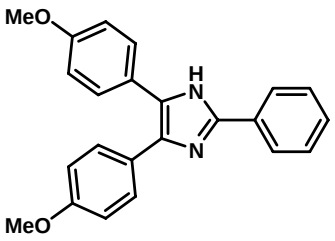
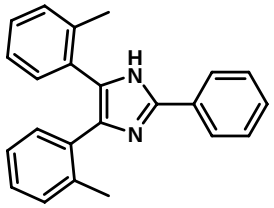
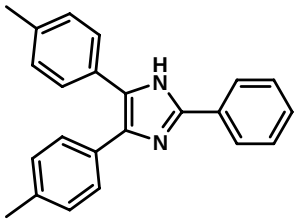
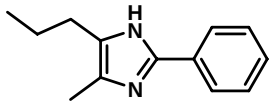
entry	product	yield (%)[a]
1		97
2		88
3		87
4		93
5		90

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

With the ultimate goal of applying this reaction in a diversity-generating strategy, we examined these conditions for their generality with respect to the 1,2-diketone substrate (Table 6). Heteroaromatic, aryl, and aliphatic 1,2-diketones provide uniformly excellent yields of the corresponding imidazoles. This includes both electron-deficient (entry 2) and electron-rich (entry 3) 1,2-diketones, as well as sterically hindered systems (entry 4).

Table 6. Scope of the 1,2-diketone in the MAOS of imidazoles.

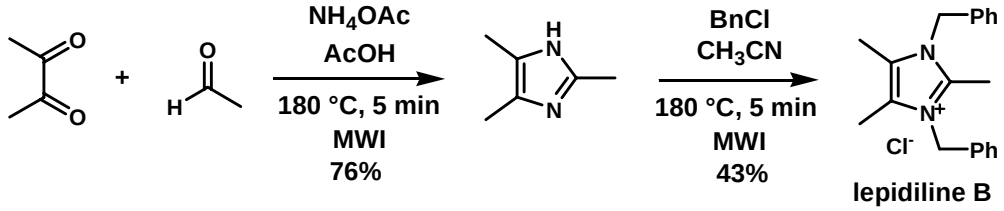


entry	product	yield (%)[a]
1		89
2		95
3		99
4		94
5		94
6		93

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

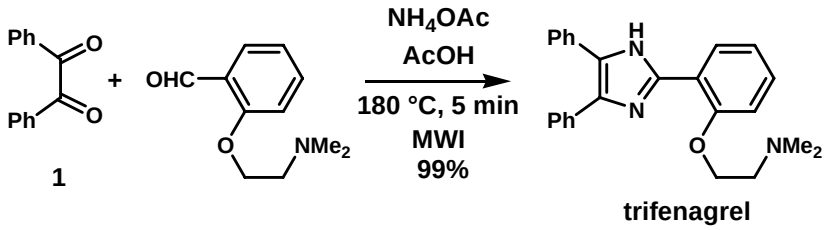
Part of the motivation for pursuing libraries of imidazoles is their prevalence among naturally occurring and synthetic biologically active compounds. As an exercise aimed at determining the utility of the conditions described here, two biologically active imidazole targets were prepared.

Lepidiline B[28] is a symmetrical imidazolium structure that exhibits micromolar cytotoxicity against several human cancer cell lines. Employing the developed methodology, we prepared the natural product in two microwave-assisted steps from 2,3-butanedione and acetaldehyde (Scheme 4) with an overall yield of 33%. Evaluation of the route[29] and completion of the synthesis was possible in less than 2 hours. This preparation, which delivered 25 mg of the natural product in one day, compares favorably with the reported isolation, which yielded 10 mg of lepidiline B from 10 kg of *L. meyenii* roots after multiple chromatographic separations.[28]



Scheme 4. Synthesis of lepidiline B.

Trifenagrel[26] is a potent 2,4,5-triaryl imidazole arachidonate cyclooxygenase inhibitor that reduces platelet aggregation in several animal species and humans. Indeed, it inhibits both arachidonate and collagen-induced aggregation with equal or greater potency (5–21 fold) than indomethacin and aspirin without exhibiting the gastric damage associated with these typical cyclooxygenase inhibitors. Preparation of the drug (Scheme 5) using the microwave-assisted aldehyde–1,2-diketone condensation reaction proceeded smoothly and in high yield. This example highlights the speed of the method: whereas the existing optimized procedure for its preparation furnishes product after 2 hours at reflux, the MAOS protocol delivers pure trifenagrel in 99% yield after 5 minutes.



Scheme 5. Synthesis of trifenagrel.

This general microwave-assisted synthesis of 2,4,5-trisubstituted imidazoles offers as its advantages a simple setup, short reaction times, and high yields for a variety of substrates, emphasizing its utility for library synthesis.

QUINOXALINES AND FUSED HETEROCYCLIC PYRAZINES[5]

In our iterative analog library synthesis paradigm, when possible, we wish to incorporate multiple heterocyclic scaffolds to rapidly justify a broader generic scope in support of intellectual property position. Libraries of this type vary in terms of the electron deficiency and basicity of the core

heterocycle while possessing a similar overall topology. The quinoxalinones and heteroaryl pyrazines (also referred to as heterocyclic quinoxalinones) provide an example of the execution of this strategy (Figure 6).

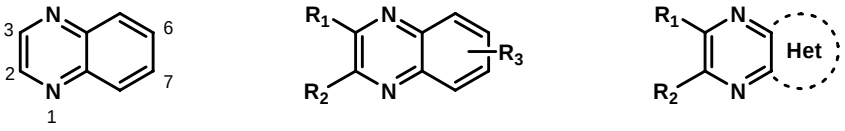
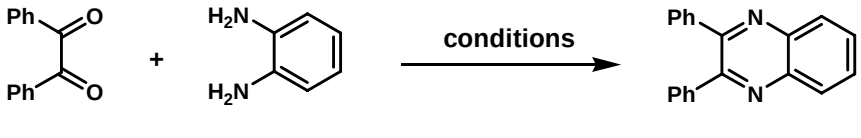


Figure 6. Generic and target quinoxalines and heterocyclic pyrazines.

While infrequently found in nature, quinoxalines are often described in the pharmaceutical industry and have been shown to possess antiviral, antibacterial, and kinase inhibitory biological activities.[30] A number of synthetic strategies have been developed for the preparation of substituted quinoxalines.[31] The most common method relies on the condensation of an aryl 1,2-diamine with a 1,2-dicarbonyl compound in refluxing ethanol or acetic acid for 2 to 12 hours. For example, the condensation of 1,2-diaminobenzene (**19**) with benzil (**1**) provides quinoxaline (**20**) in literature yields ranging from 34-85% depending on the reaction conditions (Table 7, entry 1).[32] In our hands, similar results are achieved for the synthesis of **20**; however, incorporation of functionality to either reaction partner leads to dramatic variations in reaction time and yield. While an acceptable route to access a single quinoxaline, a general, high-yielding variant is required for an iterative library approach wherein structural diversity is maximized.

Table 7. Classical thermal and optimized microwave conditions for the synthesis of quinoxaline (**20**).

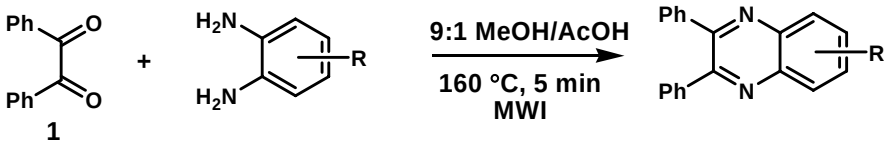


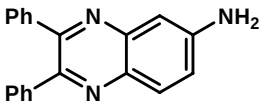
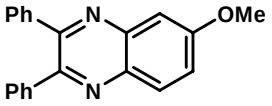
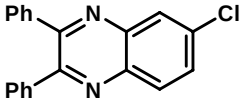
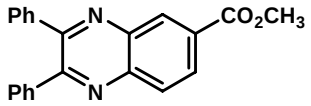
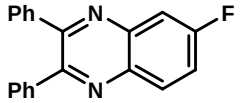
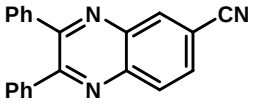
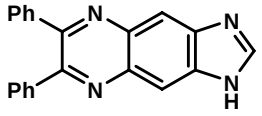
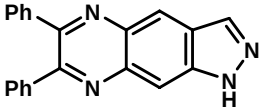
1 **19** **20**

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

Conventional thermal conditions were quickly adapted and optimized on a single-mode microwave synthesizer. Optimized reaction conditions required heating a 1:1 ratio of **1**:**19** under microwave irradiation for 5 minutes at 160 ˚C in 9:1 MeOH/AcOH to deliver quinoxaline (**20**) in 99% yield (entry 2). In contrast to results seen with traditional thermal heating, this MAOS protocol proved to be general with respect to both the aryl 1,2-diamine (Table 8)[33] and the 1,2-dicarbonyl component (Table 9), typically providing functionalized quinoxalines in 95-99% yield in only 5 minutes. High yields of quinoxaline were obtained regardless of the electronic nature of the 1,2-diamines (Table 8, entries 1-6). Tricyclic derivatives were also readily prepared in 95% yield (Table 8, entries 7-8).

Table 8. Scope of the aryl 1,2-diamine in the MAOS of quinoxalines.

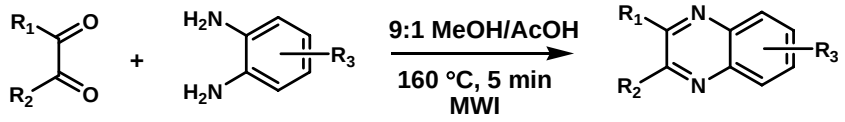


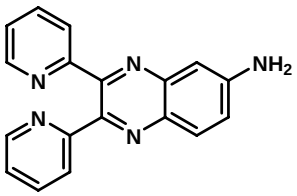
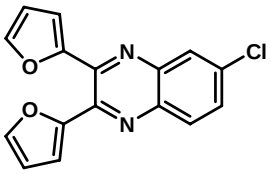
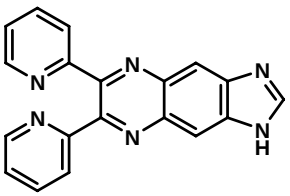
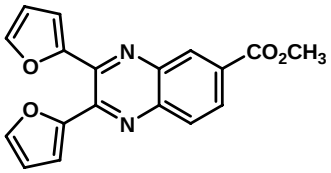
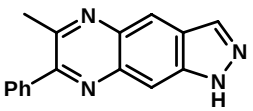
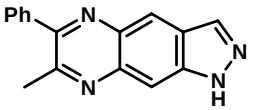
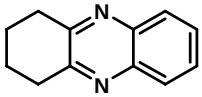
entry	product	yield (%)[a]
1		99
2		97
3		96
4		98
5		99
6		99
7		95
8		95

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

In addition to benzil (**1**), heterocyclic 1,2-diketones and aliphatic 1,2-diketones also afforded excellent isolated yields (83-99%) of the desired quinoxalines (Table 9). An asymmetrical diketone, 1-phenylpropane-1,2-dione, delivered a 1:1 mixture of regioisomers in 95% yield (entry 5).

Table 9. Scope of the 1,2-diketone in the MAOS of quinoxalines.

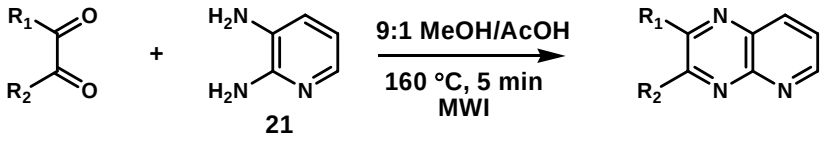


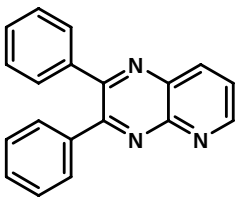
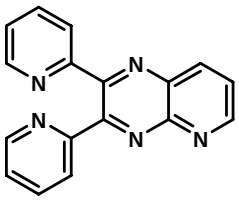
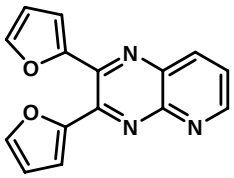
entry	product	yield (%)[a]
1		98
2		95
3		99
4		96
5	 	95
6		83

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

Unlike standard quinoxalines, heterocyclic variants are prone to follow undesired polymerization pathways on heating that result in diminished yields.[31,34] In our hands, pyrido[2,3-*b*]pyrazines were readily prepared according to our optimized protocol employing 2,3-diaminopyridine (**21**) and a variety of 1,2-diketones in excellent isolated yields (Table 10).

Table 10. Representative pyrido[2,3-*b*]pyrazines.

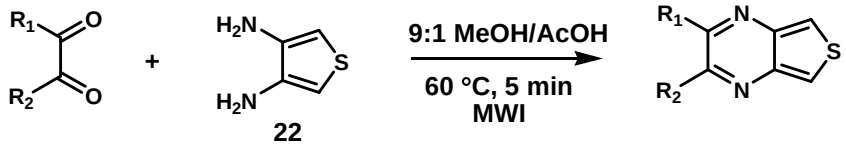


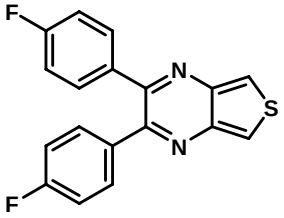
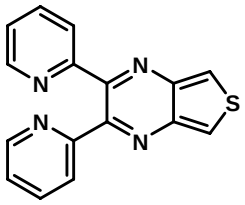
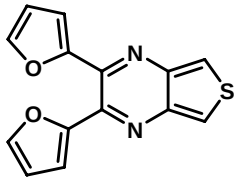
entry	product	yield (%)[a]
1		97
2		94
3		92

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

However, under the same reaction conditions the corresponding thieno[3,4-*b*]pyrazines yielded primarily polymeric material.[34] Notably, Rasmussen reported that significant polymerization was observed when heating 3,4-diaminothiophene with various 1,2-diketones, including benzil (**1**), at 50-70 ˚C for 15 minutes.[35] The polymerization pathway could be avoided by conducting the reaction at room temperature for 3 hours, providing 2,3-diphenylthieno[3,4-*b*]pyrazine in 37% yield. Similarly, other thieno[3,4-*b*]pyrazine congeners were prepared with yields ranging from 42-76%, and without any observed polymerization side products. Despite the data indicating that even mild conventional heating (50-70 ˚C) can lead to undesirable polymerization reactions, MAOS provides a fundamentally different method of heating than a conventional oil bath. Based on the generation of heat by molecular friction of dipolar molecules (or solvents), the reactants experience fewer hot spots under microwave irradiation, and accordingly fewer side products.[1,36] In light of this, and with the need for a general, high-yielding protocol for an iterative library approach, we further investigated the reaction with a MAOS protocol, at lower temperatures. In the event, heating a 1:1 ratio of 1,2-diketone and 2,3-diaminothiophene (**22**) under microwave irradiation at 60 ˚C for 5 minutes afforded diverse product thieno[3,4-*b*]pyrazines in 69-77% yield without any polymerization side products (Table 11).[37] This MAOS protocol represents the best method reported to date for the synthesis of thieno[3,4-*b*]pyrazines.[34]

Table 11. Representative 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.

In addition to providing rapid, high-yielding access to a variety of quinoxalines and heterocyclic pyrazines, microwave irradiation suppressed the undesired polymerization pathways seen with conventional thermal heating. The efficiency of these protocols enables facile library synthesis and further extends the application of MAOS as a diversity engine, employing common 1,2-diketone intermediates for solution phase parallel synthesis.

QUINOXALINONES[6]

As we have already described, 1,2-diketones found beneficial use as diversity points in the synthesis of libraries of triazines,[2] imidazoles,[4] quinoxalines,[5] and pyrazines.[5] Quinoxalinones are another class of heterocycles that can be formed by cyclocondensation with a 1,2-dicarbonyl compound. Further extending our published efforts in this area, we sought to develop a MAOS protocol that would facilitate the parallel synthesis of quinoxalinones analogs to aid in drug discovery (Figure 7).[38] While infrequently found in nature, quinoxalinones exhibit a core structure contained in biologically active compounds that have shown antifungal, antimicrobial, and analgesic activities.[39]

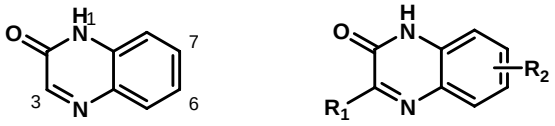
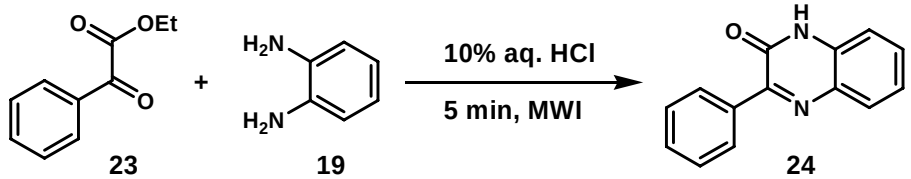


Figure 7. Generic and target substituted quinoxalinones.

Classically, quinoxalin-2[*1H*]-ones are synthesized by the cyclocondensation of aryl 1,2-diamines with an α-ketoester (the Hinsberg reaction).[40,41] A method that would efficiently deliver the product quinoxalinones in pure form would be valuable, since complex mixtures are often observed and their purification is difficult.[33,42]

As our starting point, we noted the conditions of Fernández et al.,[41] who had carried out aqueous cyclocondensations of ethyl pyruvate and 1,2-diaminobenzene (**19**) catalyzed by HCl or H_2SO_4 at room temperature. They reported typical yields of 70-80% for this reaction, and as high as 95% by catalysis with 10% H_2SO_4. Equipped with a microwave reactor, we sought conditions that would retain the high yields and allow us to screen a variety of substrates in a minimal amount of time (Table 12). With ethyl oxo(phenyl)acetate (**23**) and **19** as our prototypical substrates and a reaction time of 5 min, we determined that for this short reaction time, 125 ˚C was the optimal temperature (entry 3).

Table 12. Optimization of reaction temperature in the synthesis of quinoxalinone (**24**).



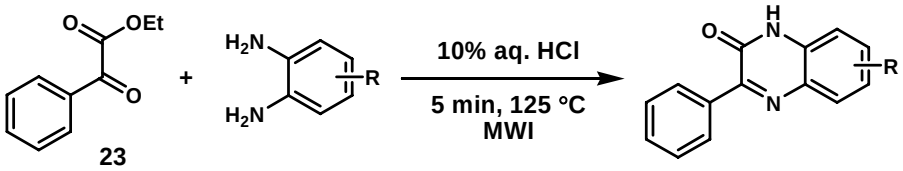
23 **19** **24**

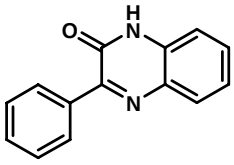
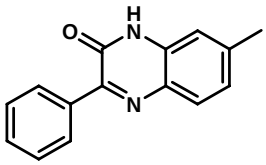
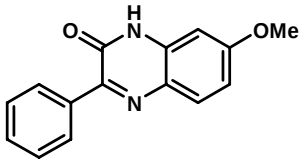
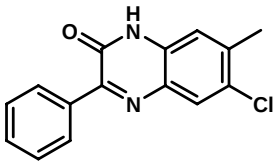
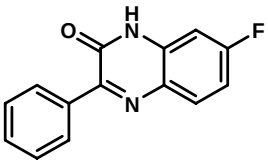
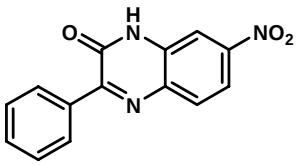
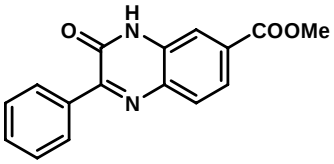
entry	temperature	conversion (%)[a]
1	60	84
2	100	90
3	125	97

[a] Conversion determined by LCMS.

We then sought to test the scope of the reaction with respect to the aryl 1,2-diamine partner (Table 13). In accord with literature precedent, we observed improved yields with electron-rich diamines (entries 2-3), and diminished yields with electron-poor ones (entries 6-7).[43] Considering the literature precedent,[44] we expected to see little regioselectivity in entry 2. Since we observed a single product peak by HPLC for most reactions where regioselectivity was an issue, we wished to discern if the reactions were truly regioselective or the product regioisomers simply co-eluted. Probing this matter, we examined two reaction products by NMR (entries 3 and 6) and found that the reaction gave rise to a mixture of regioisomers with modest selectivity (3-3.6:1).

Table 13. Scope of the aryl 1,2-diamine in the MAOS of quinoxalinones.



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

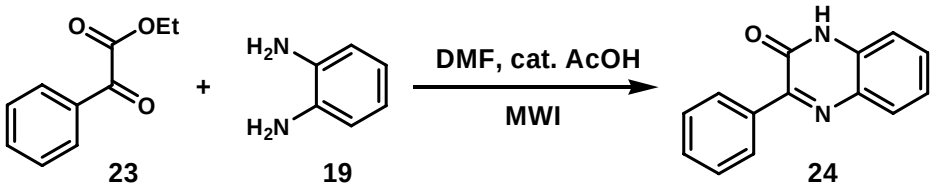
[a] Conversion determined by LCMS.

[b] The product was isolated as a 3.6:1 mixture of regioisomers (major isomer depicted).

[c] The product was isolated as a 3:1 mixture of regioisomers (major isomer depicted).

Though the aqueous conditions were convenient, we were dissatisfied with the poor yields for electron-poor 1,2-diamine substrates. To improve the generality of our method, we explored several organic solvent systems, including EtOH, DMF/EtOH, and DMF/DMSO. We found the use of DMF and a catalytic amount of acetic acid to be quite advantageous in this application, and sought to optimize the reaction in this solvent (Table 14). Unexpectedly, 170 ˚C seemed to be a threshold temperature required for good conversion. Based on these results, we chose irradiation for 5 minutes at 180 ˚C (entry 5) as our preferred reaction conditions.

Table 14. Optimization of reaction time and temperature in the synthesis of quinoxalinone (**24**).



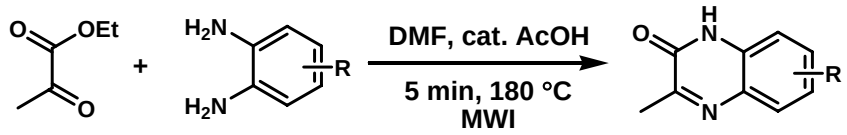
23 **19** **24**

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

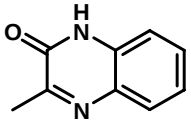
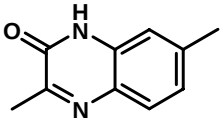
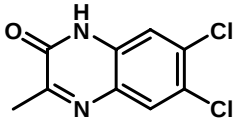
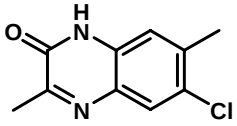
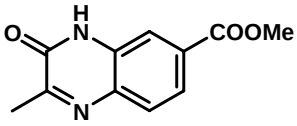
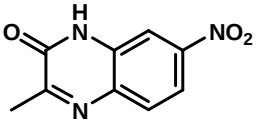
[a] Conversion determined by LCMS.

With these standard conditions, we explored the reaction of various 1,2-diaminobenzenes with ethyl pyruvate (**25**) (Table 15). We observed very clean reactions and uniformly high yields. Significantly, the reaction of **25** with electron-deficient aryl 1,2-diamines (entries 5-6) proceeded under these conditions in high yield. The conditions also proved to be general with respect to the α-ketoester used (Table 16).

Table 15. Scope of the aryl 1,2-diamine in the MAOS of quinoxalinones.



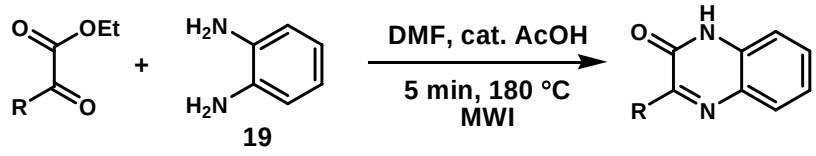
25

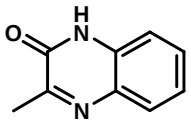
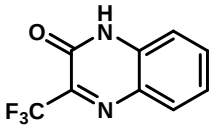
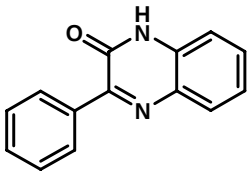
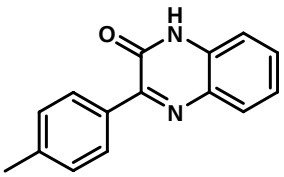
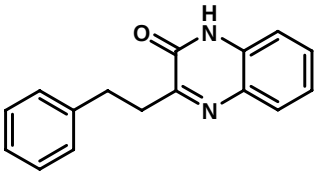
entry	product[a]	conversion (%)[b]
1		82
2		80
3		100
4		89
5		91
6		89

[a] The products of entries 2, 4, 5, and 6 were formed as a mixture of regioisomers. For clarity, a single isomer is depicted.

[b] Conversion determined by LCMS.

Table 16. Scope of the α-ketoester in the MAOS of quinoxalinones.

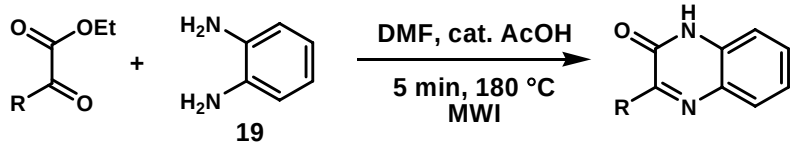


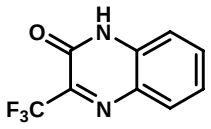
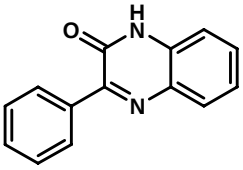
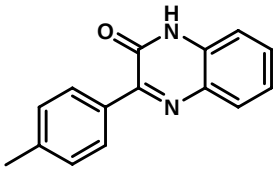
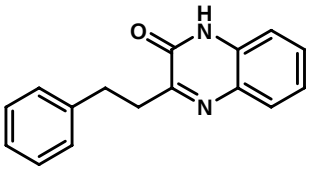
entry	product	conversion (%)[a]
1		82
2		100
3		95
4		100
5		93

[a] Conversion determined by LCMS.

To explore the preparative utility of this reaction, it was incumbent on us to purify and isolate the product quinoxalinones, a notably difficult task with these substrates.[38,42] Our attempts to purify the compounds by preparative HPLC were confounded by the insolubility of the compounds in any acceptable solvent. Solubility also stymied attempts to purify the products by silica gel flash column chromatography (normal and reverse phase) and by preparative thin layer chromatography (normal and reverse phase); low isolated yields (<40%) generally resulted from these efforts. We found that the best means of obtaining analytically pure compounds in acceptable yields (59-74%) was by simply precipitating the products in methanol (Table 17).[45]

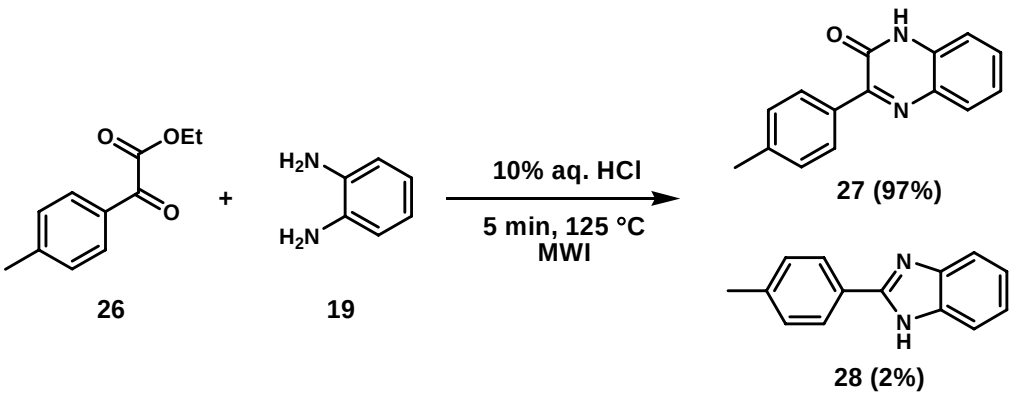
Table 17. Isolation of analytically pure quinoxalinones.



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

[a] Isolated yields for analytically pure compounds characterized by LCMS, NMR, and HRMS.

While the appearance of side products in the course of this investigation was rare, we did make note of one in the condensation of **19** with ethyl (4-methylphenyl)(oxo)acetate (**26**) (Scheme 6). The expected quinoxalinone (**27**) was formed as the major product, but characterization of the minor product showed it to be benzimidazole (**28**). This likely formed as a result of the reaction of the 1- and 2-amino groups of **19** with the ketone carbonyl group of **26**, followed by oxidative decarboxylation.[46]



26 19 27 (97%) 28 (2%)

Scheme 6. Products of the condensation of **26** and **19**.

We have developed general MAOS conditions employing catalytic acetic acid and DMF as solvent that efficiently yield functionalized quinoxalinones by the cyclocondensation of α-ketoesters with both electron-rich and electron-deficient aryl 1,2-diamines, facilitating the synthesis of this class of heterocycle in a library format. The advantages of this protocol include its substrate generality with respect to both the α-ketoester and diamine components, short reaction times, high purities, and the suppression of side product formation.

5-AMINOOXAZOLES[7]

The final microwave-assisted heterocycle synthesis we have explored to date is a Cornforth rearrangement approach to 5-aminooxazoles. The biological activity and therapeutic potential of 5-aminooxazole containing structures is demonstrated in the pseudomonic acid derived antibiotic (**29**),[47] oxazolo[5,4-*d*]pyrimidine (**30**), an inhibitor of ricin and shiga toxins,[47] and peptidomimetics with oxazole-incorporated amino acids, such as **31**.[47] Additionally, 5-(*p*-tolyl)urea-oxazole (**32**) is shown to have *in vitro* activity as a Raf kinase inhibitor with the possibility of use as a treatment for cancers (Figure 8).[47]

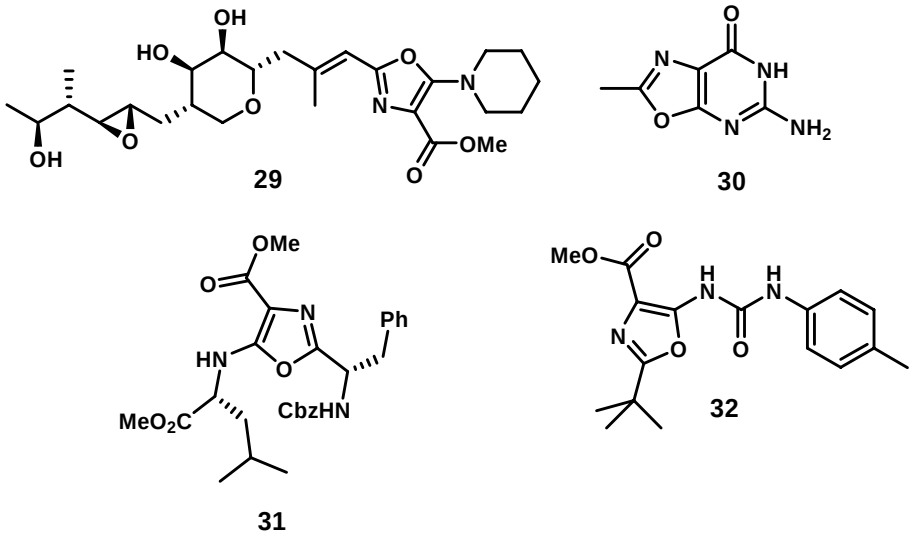
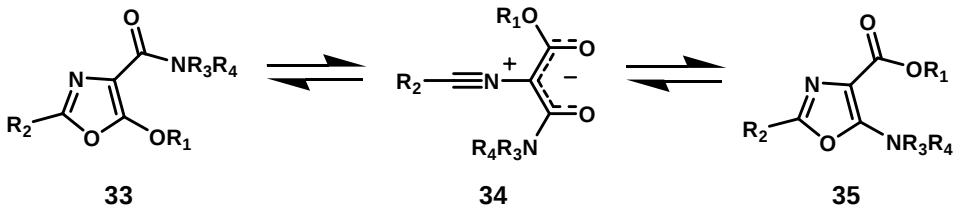


Figure 8. Biologically active 5-aminooxazoles.

A number of synthetic routes have been described for the preparation of 5-aminooxazoles.[48,49] While suitable for the generation of individual compounds, the typical procedures are not readily amenable to the rapid generation of diverse libraries. Furthermore, these protocols do not make use of readily available starting materials and hence, are not easily applied in a parallel format. The Cornforth rearrangement presents a particularly attractive solution to this problem (Scheme 7). This formal rearrangement occurs on heating 5-alkoxyoxazole-4-carboxamides (**33**) at ≥ 100 ˚C for 17 h and is

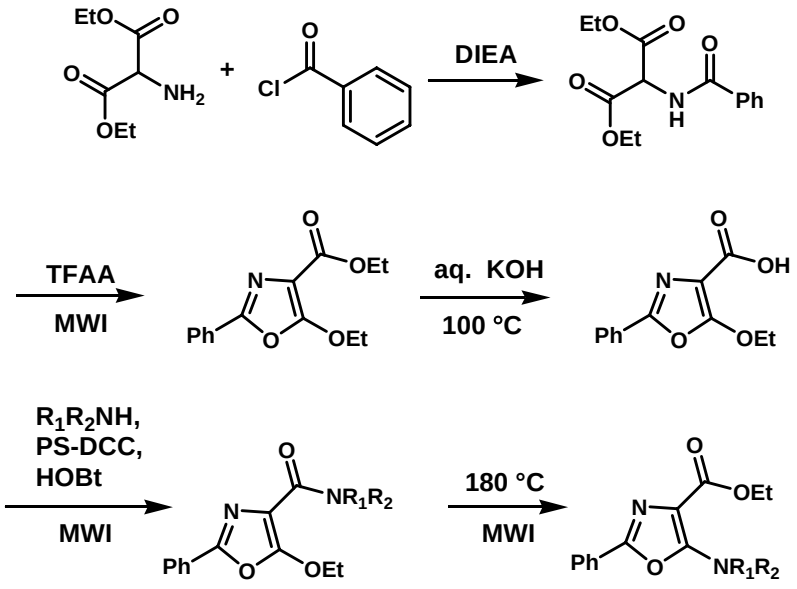
believed to proceed via an intermediate nitrile ylide (**34**). Originally discovered by Cornforth during studies related to penicillin, the reaction was studied in detail by Dewar, et al.,[49] whose mechanistic and computational work defined the intermediate as a delocalized zwitterion.[50] Intermediate (**34**) is a pseudosymmetrical dicarbonyl which can cyclize either to reform **33** or proceed to **35**. Since the formation of **34** is reversible, the final product distribution (**33**:**35**) is entirely determined by the relative thermodynamic stabilities of the 5-alkoxyoxazole-4-carboxamide and 5-aminooxazole-4-carboxylate. Despite its intriguing mechanism and synthetic potential, the reaction has received relatively little attention since these pioneering studies.



33 **34** **35**

Scheme 7. Cornforth rearrangement.

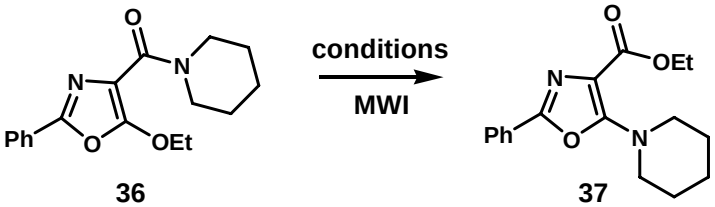
Based on literature precedent, the synthesis we envisioned is shown in Scheme 8.[48] This route permits the incorporation of diverse substituents at all positions of the oxazole and importantly does so via the use of readily available acid chloride and amine building blocks, providing the opportunity to generate fully substituted oxazoles with a diverse array of functionality. A secondary goal was to generate these structures rapidly and therefore microwave-assisted conditions were investigated.



Scheme 8. General synthesis of 5-aminooxazole-4-carboxylates.

Cornforth rearrangement products were produced by heating 5-alkoxyoxazole-4-carboxamide (**36**) under microwave irradiation (Table 18). The reaction requires temperatures of >170 ˚C for complete conversion to the thermodynamically favored products (**37**). While excellent conversions were realized in acetonitrile and trifluorotoluene, isolated yields were much higher in the latter solvent. The solvent trifluorotoluene could be used in the amide coupling as well; only filtration of the reaction mixture was required after amide coupling, resulting in a convenient two-step sequence. Using the optimized conditions of 180 ˚C for 5 min, a range of 5-aminooxazoles was prepared (Table 19).[51] Diverse functional groups are tolerated in the reaction including acetals, thioethers, sulfonamides and Boc-protected amines. Primary and secondary amines perform equally well in this amide formation-rearrangement sequence.

Table 18. Optimization of Cornforth rearrangement.

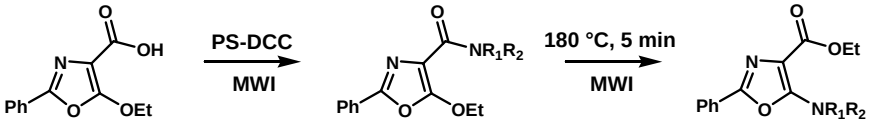


36 **37**

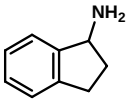
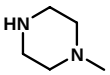
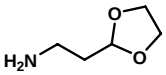
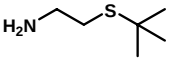
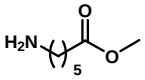
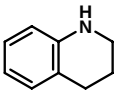
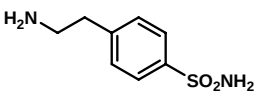
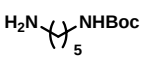
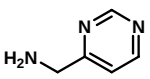
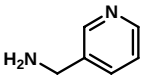
entry	solvent	temperature	time	product:starting material[a]
1	CH_3CN	150 °C	10 min	1:99
2	CH_3CN	160 °C	10 min	31:69
3	CH_3CN	170 °C	10 min	42:58
4	CH_3CN	180 °C	10 min	99:1
5	$PhCF_3$	180 °C	5 min	99:1

[a] Determined by UV HPLC.

Table 19. Microwave-assisted amide formation and Cornforth rearrangement.



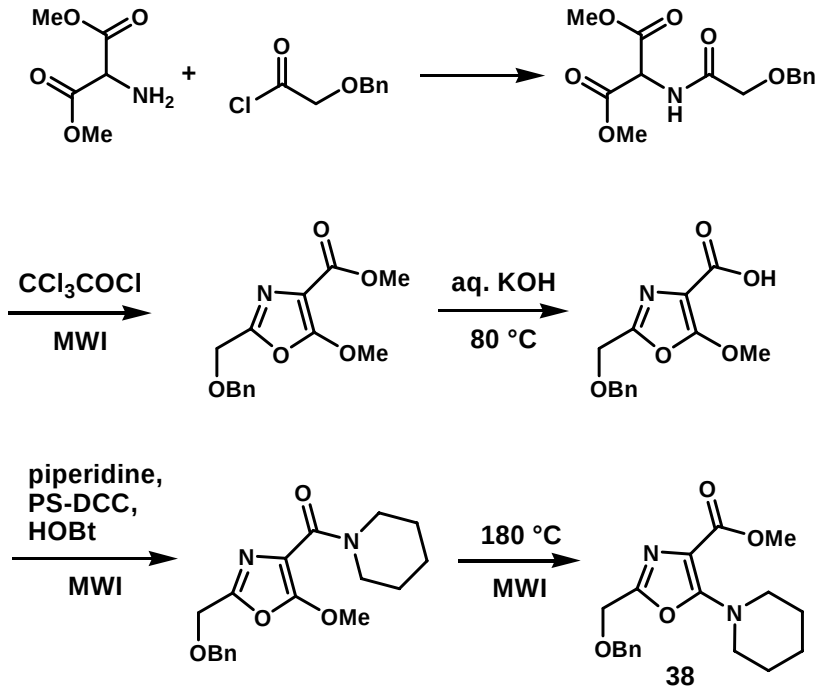
36 37

entry	amine	coupling conditions	yield (%)[a]
1		100 °C, 5 min	76
2		100 °C, 5 min	98
3		100 °C, 5 min PS-DIEA (1 eq.)	47
4		100 °C, 5 min	99
5		100 °C, 5 min	99
6		100 °C, 5 min	23
7		100 °C, 5 min PS-DIEA (1 eq.)	51
8		100 °C, 5 min PS-DIEA (1 eq.)	76
9		100 °C, 5 min	85
10		100 °C, 5 min	19
11		100 °C, 5 min	99
12		100 °C, 5 min PS-DIEA (1 eq.)	23[b]
13		100 °C, 5 min	82
14		100 °C, 5 min	97

[a] Isolated yield of crude product (≥ 93% pure by ^{1}H NMR analysis).

[b] Isolated yield after flash column chromatography.

To demonstrate the utility of this methodology, we conducted efforts toward a formal synthesis of pseudomonic acid derivative (**29**) (Scheme 9). The thermal Cornforth rearrangement proceeded in 99% yield under the optimized conditions to give the benzyl protected compound (**38**), which would constitute a formal synthesis of **29** after debenzylation and conversion of the resulting primary alcohol to a halide.[47,52]



Scheme 9. Efforts toward a formal synthesis of pseudomonic acid derivative (**29**).

The synthesis of 5-aminooxazoles via a Cornforth rearrangement has been achieved employing readily available starting materials. By providing a 200-fold improvement in reaction time, this microwave-assisted protocol is clearly amenable to the rapid generation of diverse libraries.

CONCLUSION

The methods showcased in this Review serve to highlight the power of MAOS as a tool for organic and parallel synthesis. We have developed convenient protocols for the rapid synthesis of diverse triazines, canthines, imidazoles, quinoxalines, pyrazines, quinoxalinones, and aminooxazoles, which should benefit iterative analog library efforts in the drug discovery field.

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ammonium acetate (154 mg, 2.0 mmol), and 1 mL of glacial AcOH. The reaction vessel was heated in the Smithsynthesizer™ reactor cavity for 5 min at 180 ˚C. After 5 min, the vessel was rapidly cooled to 40 ˚C by the unit. After removal from the reactor cavity, a bright yellow precipitate was collected by filtration from the reaction vessel. The solid was washed with water and dried in a vacuum oven overnight at 50 ˚C to afford 51 mg (85%) of **3** as a bright yellow solid. Analytical LCMS indicated a single peak (2.190 min, CH_3CN/H_2O/0.1%TFA, 4 min gradient) >98% pure by UV (214 nm) and 100% pure by ELSD. ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.3 (bs, 1H), 7.83 (d, J = 3 Hz, 2H), 7.76 (d, J = 9 Hz, 2H), 7.54 (m, 2H), 7.48 (m, 6H); HRMS m/z 300.1248 ($C_{18}H_{13}N_5$ + H^+ requires 300.1244).

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(m, 9H), 7.16 (m, 1H), 4.42 (t, *J* = 5.7 Hz, 2H), 3.71 (t, *J* = 5.7 Hz, 2H), 2.61 (t, *J* = 5.7 Hz, 2H); HRMS m/z 361.1705 ($C_{26}H_{20}N_2 + H^+$ requires 361.1699).

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solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.32 (ddd, *J* = 6.7, 1.7, 0.9 Hz, 2H), 8.12 (s, 2H), 7.91 (dt, *J* = 7.9, 1.1 Hz, 2H), 7.80 (ddd, *J* = 7.8, 6.7, 1.8 Hz, 2H), 7.21 (ddd, *J* = 7.8, 6.7, 1.1 Hz, 2H); HRMS: m/z 291.0630 ($C_{16}H_{10}N_4S + H^+$ requires 291.0626).

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44. On the reaction of ethyl pyruvate with 1,2-diamino-4-methoxybenzene, Fernández et al[41] observed a >50 to 1 ratio of 7-methoxy-3-methylquinoxalinone to 6-methoxy-3-methylquinoxalinone. However, reacting 1,2-diamino-4-methylbenzene with ethyl pyruvate afforded no regioselectivity.
45. Typical experimental procedure for the preparation of quinoxalinones: **3-(trifluoromethyl)-quinoxalin-2(*1H*)-one** (Table 17, entry 1): 1,2-diaminobenzene (**19**) (109 mg, 1.0 mmol), ethyl 3,3,3-trifluoro-2-oxopropanoate (190 mg, 1.1 mmol), 1 drop of AcOH, and 1.0 mL of DMF were combined in a 2 mL microwave reaction vial. The reaction vessel was heated for 5 min at 180 ˚C using a Biotage Initiator™, after which time the vessel was rapidly cooled to 40 ˚C by the unit. Analysis of the crude mixture by LCMS indicated a purity of 100% (by ELSD). The reaction mixture was concentrated to dryness to give a dark brown semisolid. Methanol was added and the precipitate was collected by filtration. After two washes with cold methanol, the resulting light purple solid was dried *in vacuo* to give 147.5 mg (69%) of 3-(trifluoromethyl)quinoxalin-2(1*H*)-one. ^{1}H NMR (600

MHz, DMSO-d_6) δ 13.06 (s, 1H), 7.92 (dd, J = 1.4, 8.2 Hz, 1H), 7.72 (ddd, J = 1.4, 7.2, 8.3 Hz, 1H), 7.42 (ddd, J = 1.3, 7.2, 8.2 Hz, 1H), 7.41 (dd, J = 1.3, 8.3 Hz, 1H); HRMS m/z 215.0441 ($C_9H_5F_3N_2O + H^+$ requires 215.0432).

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[44] On the reaction of ethyl pyruvate with 1,2-diamino-4-methoxybenzene, Fernández et al[41] observed a >50 to 1 ratio of 7-methoxy-3-methylquinoxalinone to 6-methoxy-3-methylquinoxalinone. However, reacting 1,2-diamino-4-methylbenzene with ethyl pyruvate afforded no regioselectivity.
[45] Typical experimental procedure for the preparation of quinoxalinones: **3-(trifluoromethyl)quinoxalin-2(*1H*)-one** (Table 17, entry 1): 1,2-diaminobenzene (**19**) (109 mg, 1.0 mmol), ethyl 3,3,3-trifluoro-2-oxopropanoate (190 mg, 1.1 mmol), 1 drop of AcOH, and 1.0 mL of DMF were combined in a 2 mL microwave reaction vial. The reaction vessel was heated for 5 min at 180 ˚C using a Biotage Initiator™, after which time the vessel was rapidly cooled to 40 ˚C by the unit. Analysis of the crude mixture by LCMS indicated a purity of 100% (by ELSD). The reaction mixture was concentrated to dryness to give a dark brown semisolid. Methanol was added and the precipitate was collected by filtration. After two washes with cold methanol, the resulting light purple solid was dried *in vacuo* to give 147.5 mg (69%) of 3-(trifluoromethyl)quinoxalin-2(1H)-one. ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.06 (s, 1H), 7.92 (dd, J = 1.4, 8.2 Hz, 1H), 7.72 (ddd, J = 1.4, 7.2, 8.3 Hz, 1H), 7.42 (ddd, J = 1.3, 7.2, 8.2 Hz, 1H), 7.41 (dd, J = 1.3, 8.3 Hz, 1H); HRMS m/z 215.0441 ($C_9H_5F_3N_2O + H^+$ requires 215.0432).
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