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General microwave-assisted protocols for the expedient synthesis of quinoxalines and heterocyclic pyrazines

Zhijian Zhao, David D. Wisnoski, Scott E. Wolkenberg, William H. Leister, Yi Wang and Craig W. Lindsley*

Department of Medicinal Chemistry, Technology Enabled Synthesis Group, Merck Research Laboratories, PO Box 4, West Point, PA 19486, USA

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Abstract—Functionalized quinoxalines and heterocyclic pyrazines are expediently prepared in excellent yields (69–99%) from common 1,2-diketone intermediates under microwave irradiation. In addition to being general for a variety of aryl/heteroaryl 1,2-diamines and 1,2-diketones, this protocol suppresses the formation of polymeric species, characteristic of traditional thermal conditions.

Microwave-assisted organic synthesis (MAOS), fuelled by the development and availability of precision controlled, single-mode microwave reactors, has had a profound impact on the way chemists approach organic and parallel synthesis. Clearly, reductions in reaction times, improved yields and suppression of side products, relative to traditional thermal heating, are benefits of this emerging technology.[1] Recently, the literature has seen a plethora of MAOS protocols for various chemical transformations; however, the application of MAOS as a diversity engine for parallel synthesis has only begun to accrue.

With the competitive nature of the pharmaceutical landscape, lead discovery groups are challenged to rapidly develop nascent programs and secure strong intellectual property (IP) position early on.[2] As many of the leads identified from high-throughput screens are small heterocyclic compounds, our laboratory has devoted a significant effort to develop efficient protocols for the preparation of a diverse collection of substituted heterocyclic scaffolds from common intermediates. In recent Letters, we have reported on simple, high-yielding MAOS protocols (5 min, 80–99%) for the preparation of 1,2,4-triazines **2**[3] and imidazoles **3**[4] from common 1,2-diketone **1** intermediates (Fig. 1). In addition to providing a dramatic rate acceleration versus classical thermal heating (8–24 h, 30–65%), 1,2-diketones serve as diversification elements en route to biologically active heterocycles.[3,4] When incorporated into an iterative analogue library synthesis paradigm, a single 'library' will contain multiple heterocyclic scaffolds to rapidly justify a broader generic scope in support of IP position. While possessing similar topology, libraries of this type vary in terms of the electron deficiency and basicity of the core heterocycle. This diversity-oriented strategy is in sharp contrast to the typical library design wherein a single heterocyclic template is 'decorated' with various monomer units. In this Letter, we report on a further extension of this methodology to include quinoxalines **4** and heterocyclic pyrazines **5**.

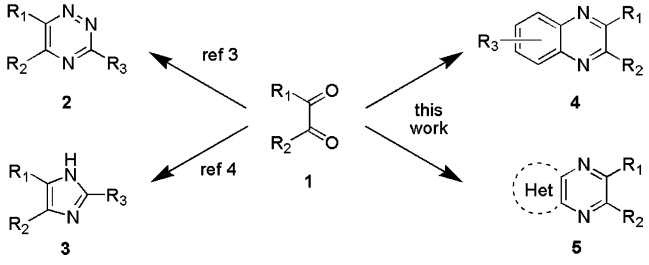

Figure 1. MAOS with 1,2-diketones to furnish diverse heterocycles.

Keywords: Microwave; Quinoxaline; Pyrazine.
* Corresponding author. Tel.: +1-215-652-2265; fax: +1-215-652-6345; e-mail: craig_lindsley@merck.com

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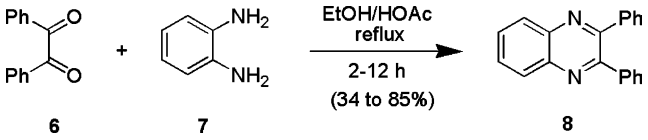
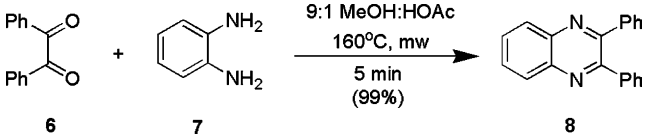


6 7 8

Scheme 1.

Functionalized quinoxalines represent an important class of nitrogen-containing heterocycle. While rarely described in nature, synthetic quinoxalines are well known in the pharmaceutical industry and have been shown to possess a broad spectrum of biological activities including antiviral, antibacterial and as kinase inhibitors.[5] A number of synthetic strategies have been developed for the preparation of substituted quinoxalines.[6] By far, 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 2–12 h. For example, the condensation of 1,2-diaminobenzene **6** with benzil **7** provides quinoxaline **8** in literature yields ranging from 34–85% depending on the reaction conditions (Scheme 1).[7] In our hands, similar results are achieved for the synthesis of **8**; 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.

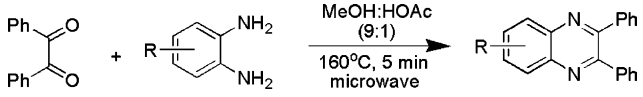
Conventional thermal conditions were quickly adapted and optimized on a single-mode microwave synthesizer.[8] Optimized reaction conditions required heating a 1:1 ratio of **6**:**7** under microwave irradiation for 5 min at 160 °C in 9:1 MeOH–HOAc to deliver quinoxaline **8** in quantitative yield (Scheme 2). Unlike traditional thermal heating, this MAOS protocol proved to be general with respect to both the aryl 1,2-diamine and the 1,2-dicarbonyl component (Table 1) providing functionalized quinoxalines in 95–99% yield in only 5 min.[9] For instance, high yields of quinoxaline were obtained for either electron-donating 1,2-diamines (Table 1, entries 1 and 2) or electron-withdrawing 1,2-diamines (Table 1, entries 3–5, and 8). Tricyclic derivatives such as 6,7-diphenyl-1*H*-pyrazolo[4,5-*g*]quinoxaline (entry 6) and 6,7-diphenyl-1*H*-imidazolo[3,4-*g*]quinoxaline (entry 7) were also readily prepared in 95% yield. In addition to benzil, **6**, heterocyclic 1,2-diketones and aliphatic 1,2-diketones also afforded excellent isolated yields (83–99%) of the desired quinoxalines (Table 2). Both 2-pyridyl (Table 2, entries 1 and 3) and 2-furyl (Table 2, entries 2 and 4) 1,2-diketone congeners delivered the desired quinoxalines in near quantitative yield. Application of an unsymmetrical diketone, 1-phenylpropane-1,2-dione delivered a 1:1

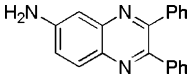
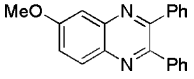
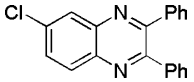
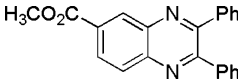
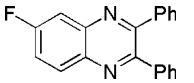
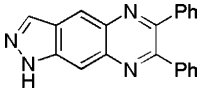
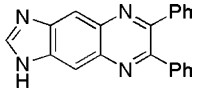
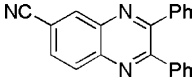


6 7 8

Scheme 2.

Table 1. Representative functionalized quinoxalines



Entry	Product	Yield (%)[a]
1		99
2		97
3		96
4		98
5		99
6		95
7		95
8		99

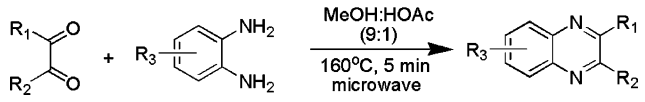
[a] Yields for analytically pure compounds fully characterized by LCMS, NMR and HRMS.

ratio of regiosiomers in 95% yield (Table 2, entry 5) and the cyclic cyclohexane-1,2-dione provided the tricyclic congener (Table 2, entry 6) in 83% yield.

Heteroaryl pyrazines, also referred to as heterocyclic quinoxalines, such as thieno [3,4-*b*]pyrazine **10** and pyrido[2,3-*b*]pyrazine **11** (Fig. 2) represent a related class of nitrogen-containing heterocycles that attracted our attention. Unlike standard quinoxalines, heterocyclic variants **10** and **11** are prone to follow unwanted polymerization pathways during their preparation under conventional thermal heating that result in diminished yields.[6,10] In our hands, pyrido[2,3-*b*]pyrazines **11** were readily prepared according to our optimized protocol employing 2,3-diaminopyridine and a variety of 1,2-diketones (Table 3) in excellent isolated yields;[11] however, the corresponding thieno[3,4-*b*]pyrazines **10**, under the same reaction conditions primarily provided polymeric material.[10] Notably, Rasmussen and co-workers reported that significant polymerization was observed when heating 3,4-diamino thiophene **12** with various 1,2-diketones, including benzil **6**, at 50–70 °C for 15 min to produce **13** (Scheme 3).[12]

However, unwanted polymerization reactions were reduced by conducting the reaction at room temperature for ~3 h, providing 2,3-diphenylthieno[3,4-*b*]pyrazine **13**

Table 2. Representative functionalized quinoxalines



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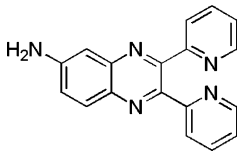
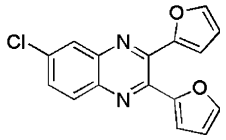
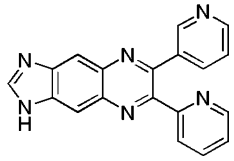
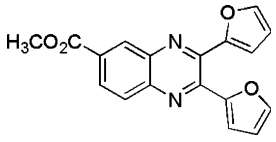
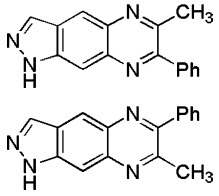
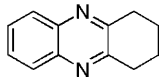
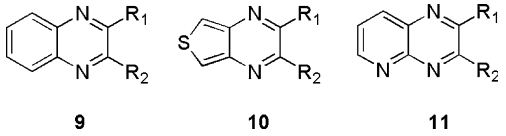
1		98
2		95
3		99
4		96
5		95
6		83

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



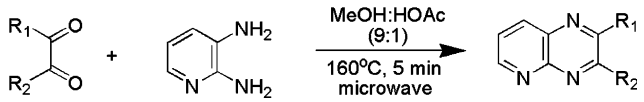
9 **10** **11**

Figure 2. Generic quinoxaline and heterocyclic pyrazines.

in 37% yield. Other congeners of **10** were prepared with yields ranging from 42–76%, and without any observed polymerization side products.[12]

Once again, while an acceptable route to access a single thieno[3,4-*b*]pyrazine, a general, high-yielding protocol is required for an iterative library approach. 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, as a result, fewer side products.[1,13] In light of this, examination of the preparation of **10** by a MAOS protocol, at lower temperatures, seemed warranted.

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



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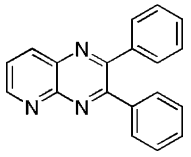
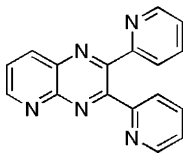
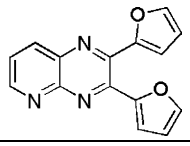
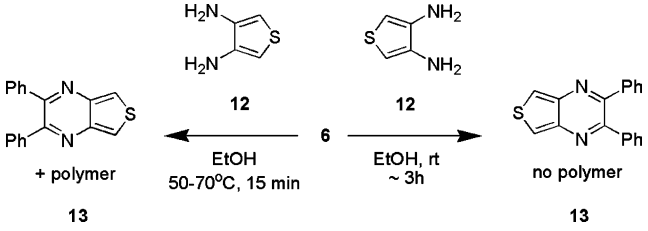
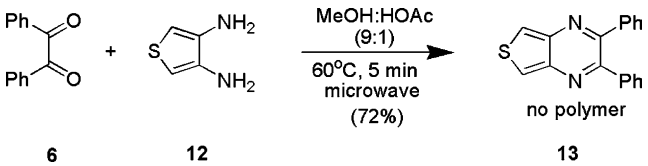
1		97
2		94
3		92

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



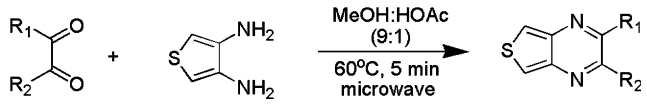
Scheme 3.

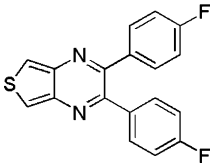
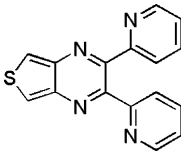
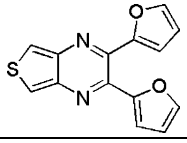
In the event, heating a 1:1 ratio of **6**:**12** under microwave irradiation at 60 °C for 5 min afforded **13** in 72% isolated yield with no detectable polymerization side products (Scheme 4).[14] This is in sharp contrast, in terms of both yield and purity, to the results obtained with either conventional thermal heating (50–70 °C) or reactions run for extended periods at room temperature. The generality of this procedure for the synthesis of a diverse set of thieno[3,4-*b*]pyrazines **10** is highlighted in Table 4. Various 1,2-diketones react smoothly with **12** to deliver congers of **10** in yields ranging from 69–77%.[14] More importantly, polymerization side products were not



Scheme 4.

Table 4. 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.

observed. Therefore, this MAOS protocol represents the best method reported to date for the synthesis of thieno[3,4-*b*]pyrazines **10**.

In summary, microwave-assisted protocols for the *general* synthesis of functionalized quinoxalines and heterocyclic pyrazines have been developed. In addition to providing rapid, high-yielding access to a variety of quinoxalines and heterocyclic pyrazines, microwave irradiation suppressed undesired polymerization pathways, characteristic of 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. Additional examples of microwave technology for diversity-oriented library synthesis are in progress and will be reported in due course.

Acknowledgements

The authors thank Joan S. Murphy for HRMS data.

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8. The single-mode microwave synthesizer employed for this work was an Emrys Liberator™ by Personal Chemistry. For more information, see: www.personalchemistry.com.
9. Typical experimental (Table 1, entry 4): methyl 2,3-diphenylquinoxaline-6-carboxylate: To a 5 mL reaction vial (part# 351521) was added benzil (38 mg, 0.2 mmol) and methyl 3,4-diaminobenzoate (34 mg, 0.2 mmol), followed by 3 mL of 9:1 MeOH–HOAc. The vessel was heated in Emrys Liberator™ reaction cavity for 5 min at 160 °C. After 5 min, the reaction vessel was rapidly cooled to 40 °C. Upon cooling, a white precipitate formed. The precipitate was collected and dried to afford 66 mg of the title compound. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (d, J = 1.8 Hz, 1H), 8.37 (dd, J = 8.7, 1.8 Hz, 1H), 8.21 (d, J = 8.7 Hz, 1H), 7.52–7.56 (m, 4H), 7.33–7.37 (m, 6H), s, 3H); HRMS: calcd for $C_{22}H_{16}N_2O_2$ (M+H); found: 341.1295.
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11. Typical experimental (Table 3, entry 3): 2,3-di-2-furylpyrido[2,3-*b*]pyrazine: To a 5 mL reaction was added 1,2-di-2-furylethane-1,2-dione (38 mg, 0.2 mmol) and pyrdine-2,3-diamine (22 mg, 0.2 mmol), followed by 3 mL of 9:1 MeOH–HOAc. The vessel was heated for 5 min at 160 °C. Analysis of the crude reaction mixture by LCMS indicated a purity of 90%. The product was purified by preparative LCMS to afford 69 mg (92%, mono-TFA salt) of the title compound as a brown solid. ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm): 9.12 (dd, J = 4.2, 1.9 Hz, 1H), 8.47 (dd, J = 8.4, 1.9 Hz, 1H), 7.68 (dd, J = 8.4, 4.2 Hz, 1H), 7.66 (dd, J = 1.8, 0.5 Hz, 1H), 7.60 (dd, J = 1.8, 0.5 Hz, 1H); 7.07 (dd, J = 3.6, 0.5 Hz, 1H); 6.74 (dd, J = 3.5, 0.5 Hz, 1H); 6.61 (dd, J = 3.5, 1.8 Hz, 1H); 6.59 (dd, J = 3.5, 1.8 Hz, 1H); HRMS: calcd for $C_{15}H_9N_3O_2$ (M+H); 264.0768, found: 264.0767.
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14. Typical experimental (Table 4, entry 2): 2,3-di-pyridin-2-ylthieno[3,4-*b*]pyrazine: To a 5 mL reaction vial was added 1,2-dipyridin-2-ylethane-1,2-dione (42 mg, 0.2 mmol) and thiophene-3,4-diamine (38 mg, 0.2 mmol), followed by 3 mL of 9:1 MeOH–HOAc. The vessel was heated for 5 min at 60 °C. Analysis of the crude reaction mixture by LCMS indicated a purity of 93%. Note, no polymer was observed or detected. The product was purified by preparative LCMS to afford 79 mg (92%, bis-TFA salt) of the title compound as a brown solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm): 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: calcd for $C_{16}H_{11}N_4S$ (M+H); 291.0626; found 291.0630.