

# A One-Pot, Microwave-Influenced Synthesis of Diverse Small Molecules by Multicomponent Reaction Cascades

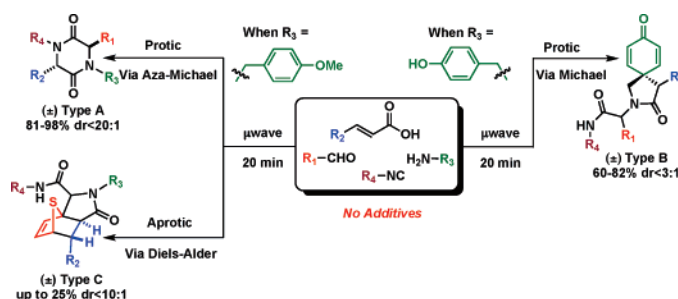
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## ABSTRACT



Small molecule diversity can be achieved in a single synthetic operation from bifunctional substrates in the absence of additives and under the influence of microwaves with complete control of pathway selectivity. The preliminary Ugi four-component coupling products give rise to three structurally distinct scaffolds that are dependent on solvent effects and sterics. 2,5-Diketopiperazines (Type A), 2-azaspiro[4.5]deca-6,9-diene-3,8-diones (Type B), and thiophene-derived Diels–Alder tricyclic lactams (Type C) predominate in this reaction cascade.

Multicomponent coupling reactions (MCRs) have been frequently used by synthetic chemists as a facile means to generate molecular diversity from bifunctional substrates that react sequentially in an intramolecular fashion.<sup>1</sup> Devising such types of MCRs that achieve the formation of multiple bonds in a single operation is one of the major challenges in modern organic synthesis.<sup>2</sup> As such processes avoid time-consuming and costly purification processes, as well as protection–deprotection steps, they are inherently more environmentally benign and atom economic.<sup>3</sup>

Microwave-assisted organic synthesis (MAOS), in multicomponent coupling reactions, has most commonly been

used to increase efficiency in a reaction timecourse.<sup>4</sup> There are two theories associated with microwave heating: ionic conduction and dipole rotation.<sup>5</sup> In ionic conduction, the electromagnetic radiation that is generated by a magnetron is thought to provide a significant amount of thermal energy to the reaction.<sup>6</sup> In dipole rotation, when a molecule is irradiated with microwaves, it will attempt to align itself with the electric field by rotation.<sup>7</sup> Although localized high temperature and pressure remains to be the favored argument for MAOS, some reports have emerged in the literature

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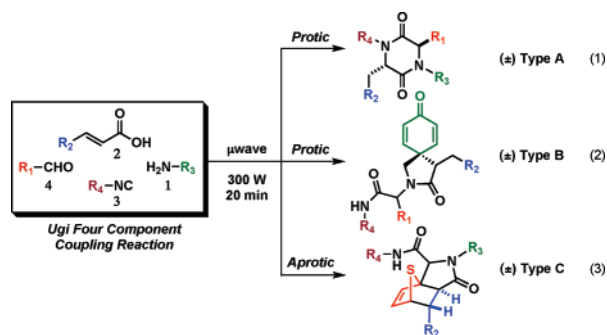
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detailing how microwaves influence rotational movement of bonds to directly influence new bond construction.<sup>8,9</sup>

Herein, we report on a one-pot synthesis of three very complex, yet structurally distinct scaffolds, in which microwaves, solvent effects, and bifunctional substrates mediate highly selective outcomes in the absence of any extraneous additives. The process described takes advantage of transition state stabilization by protic solvents, sterics of bifunctional substrates, and the influence of select electron-donating groups. The latter show unique potential for being influenced by microwaves to form new  $\sigma$ -bonds that cannot otherwise be accessed using other reagent-based protocols or other more conventional high temperature/pressure sealed glassware.



We demonstrate the ability to generate molecular diversity in the form of biologically validated 2,5-diketopiperazines from an aza-Michael reaction (eq 1), 2-azaspiro[4.5]deca-6,9-diene-3,8-diones (eq 2) from a 5-*exo* Michael cyclization, and unique intramolecular thiophene Diels–Alder-derived tricyclic lactams (eq 3).

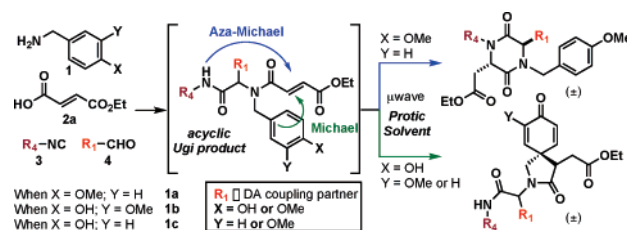
To the best of our knowledge, this report represents the first examples of how solvent effects influence bond formation solely under microwave irradiation to generate molecular diversity in a single operation arising from a multicomponent coupling reaction. Our interest in this methodology is twofold: molecular diversity from simple, readily available substrates in a one-pot protocol, without the use of reagent additives (environmentally benign), and the ability to generate biologically validated scaffolds such as 2,5-diketopiperazines<sup>10</sup> and 2-azaspiro[4.5]deca-6,9-diene-3,8-diones.<sup>11</sup>

A previous report of a tandem Ugi/intramolecular Diels–Alder reaction of *p*-methoxybenzylamine (**1a**), fumaric acid monoethyl ester (**2a**), furfural, and benzyl isocyanide (**3a**) forming a tricyclic lactam revealed that an acyclic Ugi product was not isolatable due to the rapid bond construction from the diene and dienophile.<sup>12</sup> We envisioned that the proposed olefinic acyclic intermediate could, however, be engineered to gain access to various other structural motifs (Figure 1).

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(9) Ultrasound-induced electrocyclic ring opening leading to products not otherwise obtainable from purely thermal or light-induced reactions: Hickenboth, C. R.; Moore, J. S.; White, S. R.; Sottos, N. R.; Baudry, J.; Wilson, S. R. *Nature* **2007**, *446*, 423–427.



**Figure 1.** Generating molecular diversity under the influence of microwaves, bifunctional substrates, and protic solvents.

Initial attempts to synthesize substituted 1,4-dihydroisoquinolinones from the acyclic Ugi product via a Friedel–Crafts alkylation using  $\text{AlCl}_3$  or  $\text{FeCl}_3$  resulted only in degradation or unreacted starting materials. Literature revealed that a number of rate accelerated Friedel–Crafts alkylation reactions had been accomplished using microwave irradiation and an appropriate additive.<sup>13</sup> Unfortunately, when prior protocols were employed in our system, the aforementioned problems were not negated. However, when the reactions were run in a protic solvent, such as water<sup>14</sup>/methanol (0.1 M), without any Lewis acid additives, under the influence of microwaves (300 W, 200 °C, and 18 bar) for 20 min, an intramolecular aza-Michael reaction (Figure 1) ensued to reveal 2,5-diketopiperazines in good to excellent yields with respectable diastereomeric ratios (Table 1, entries 1–11).<sup>11</sup> NOE data assisted in determining a 3,6-*trans* relationship between the acid and aldehyde components of the coupling product. Diastereomers were rationalized to arise from the *E* isomer of the fumaric acid component (**2a/b**).

With this result, we were encouraged to probe the mechanism for this unprecedented intramolecular aza-

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**Table 1.** Scope of the One-Pot Microwave-Influenced Synthesis of Diverse Small Molecules

entry	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	compound type/% yield <sup>a,b</sup>		
					H <sub>2</sub> O: <sup>d</sup>	CH <sub>2</sub> Cl <sub>2</sub> : <sup>d</sup>	dr <sup>e</sup>
1	<i>tert</i> -butyl ( <b>4a</b> )	ethoxycarbonyl ( <b>2a</b> )	4-methoxybenzyl ( <b>1a</b> )	benzyl ( <b>3a</b> )	<b>A</b> ( <b>5</b> )/91	acyclic ( <b>6</b> )/92	17:1
2	2-naphthyl ( <b>4b</b> )	ethoxycarbonyl ( <b>2a</b> )	4-methoxybenzyl ( <b>1a</b> )	benzyl ( <b>3a</b> )	<b>A</b> ( <b>7</b> )/88	acyclic ( <b>8</b> )/95	7:1
3	<i>tert</i> -butyl ( <b>4a</b> )	ethoxycarbonyl ( <b>2a</b> )	benzyl ( <b>1d</b> )	benzyl ( <b>3a</b> )	<b>A</b> ( <b>9</b> )/96	acyclic ( <b>10</b> )/97	11:1
4	<i>tert</i> -butyl ( <b>4a</b> )	ethoxycarbonyl ( <b>2a</b> )	cyclohexylmethyl ( <b>1e</b> )	benzyl ( <b>3a</b> )	<b>A</b> ( <b>11</b> )/88	acyclic ( <b>12</b> )/92	20:1
5	isopropyl ( <b>4c</b> )	ethoxycarbonyl ( <b>2a</b> )	benzyl ( <b>1d</b> )	4-methoxyphenyl ( <b>3b</b> )	<b>A</b> ( <b>13</b> )/85	acyclic ( <b>14</b> )/90	6:1
6	isopropyl ( <b>4c</b> )	ethoxycarbonyl ( <b>2a</b> )	4-methoxybenzyl ( <b>1a</b> )	4-methoxyphenyl ( <b>3b</b> )	<b>A</b> ( <b>15</b> )/81	acyclic ( <b>16</b> )/82	7:1
7	<i>tert</i> -butyl ( <b>4a</b> )	benzoyl ( <b>2b</b> )	benzyl ( <b>1d</b> )	benzyl ( <b>3a</b> )	<b>A</b> ( <b>17</b> )/98	acyclic ( <b>18</b> )/98	2:1
8	<i>tert</i> -butyl ( <b>4a</b> )	ethoxycarbonyl ( <b>2a</b> )	4-methoxybenzyl ( <b>1a</b> )	<i>n</i> -butyl ( <b>3f</b> )	<b>A</b> ( <b>19</b> )/92	acyclic ( <b>20</b> )/90	15:1
9	<i>tert</i> -butyl ( <b>4a</b> )	ethoxycarbonyl ( <b>2a</b> )	4-hydroxybenzyl ( <b>1c</b> )	benzyl ( <b>3a</b> )	<b>A</b> ( <b>21</b> )/83	acyclic ( <b>22</b> )/85	12:1
10	2-thienyl ( <b>4d</b> )	ethoxycarbonyl ( <b>2a</b> )	3,5-dimethoxybenzyl ( <b>1h</b> )	benzyl ( <b>3a</b> )	<b>A</b> ( <b>23</b> )/87	see entry 18	8:1
11	2-thienyl ( <b>4d</b> )	ethoxycarbonyl ( <b>2a</b> )	4-methoxybenzyl ( <b>1a</b> )	benzyl ( <b>3a</b> )	<b>A</b> ( <b>24</b> )/83	see entry 19	7:1
12	isopropyl ( <b>4c</b> )	ethoxycarbonyl ( <b>2a</b> )	4-hydroxybenzyl ( <b>1c</b> )	<i>tert</i> -butyl ( <b>3c</b> )	<b>B</b> ( <b>25</b> )/60	acyclic ( <b>26</b> )/75	3:1
13	<i>tert</i> -butyl ( <b>4a</b> )	ethoxycarbonyl ( <b>2a</b> )	4-hydroxybenzyl ( <b>1c</b> )	cyclohexyl ( <b>3g</b> )	<b>B</b> ( <b>27</b> )/82	acyclic ( <b>28</b> )/85	1:1
14	<i>tert</i> -butyl ( <b>4a</b> )	ethoxycarbonyl ( <b>2a</b> )	4-hydroxy-3-methoxybenzyl ( <b>1b</b> )	<i>tert</i> -butyl ( <b>3c</b> )	<b>B</b> ( <b>29</b> )/60	acyclic ( <b>30</b> )/80	3:1
15	<i>tert</i> -butyl ( <b>4a</b> )	ethoxycarbonyl ( <b>2a</b> )	4-hydroxybenzyl ( <b>1c</b> )	isopropyl ( <b>3d</b> )	<b>B</b> ( <b>31</b> )/80	acyclic ( <b>32</b> )/90	2:1
16	<i>tert</i> -butyl ( <b>4a</b> )	ethoxycarbonyl ( <b>2a</b> )	4-hydroxybenzylmethyl ( <b>1g</b> )	<i>tert</i> -butyl ( <b>3c</b> )	<b>B</b> ( <b>33</b> )/95	acyclic ( <b>34</b> )/96 <sup>g</sup>	ND
17	<i>tert</i> -butyl ( <b>4a</b> )	ethoxycarbonyl ( <b>2a</b> )	4-hydroxybenzyl ( <b>1c</b> )	cyclopentyl ( <b>3e</b> )	<b>B</b> ( <b>35</b> )/81	acyclic ( <b>36</b> )/90	2:1
18	2-thienyl ( <b>4d</b> )	ethoxycarbonyl ( <b>2a</b> )	3,5-dimethoxybenzyl ( <b>1h</b> )	benzyl ( <b>3a</b> )	see entry 10	<b>C</b> <sup>h</sup> ( <b>37</b> )/23	8:1
19	2-thienyl ( <b>4d</b> )	ethoxycarbonyl ( <b>2a</b> )	4-methoxybenzyl ( <b>1a</b> )	benzyl ( <b>3a</b> )	see entry 11	<b>C</b> <sup>h</sup> ( <b>38</b> )/25	10:1
20	<i>tert</i> -butyl ( <b>4a</b> )	ethoxycarbonyl ( <b>2a</b> )	4-methoxybenzyl ( <b>1a</b> )	<i>tert</i> -butyl ( <b>3c</b> )		acyclic ( <b>39</b> )/92	
21	isopropyl ( <b>4c</b> )	ethoxycarbonyl ( <b>2a</b> )	3,4-dimethoxybenzyl ( <b>1f</b> )	<i>tert</i> -butyl ( <b>3c</b> )		acyclic ( <b>40</b> )/91	
22	isopropyl ( <b>4c</b> )	ethoxycarbonyl ( <b>2a</b> )	benzyl ( <b>1d</b> )	<i>tert</i> -butyl ( <b>3c</b> )		acyclic ( <b>41</b> )/90	

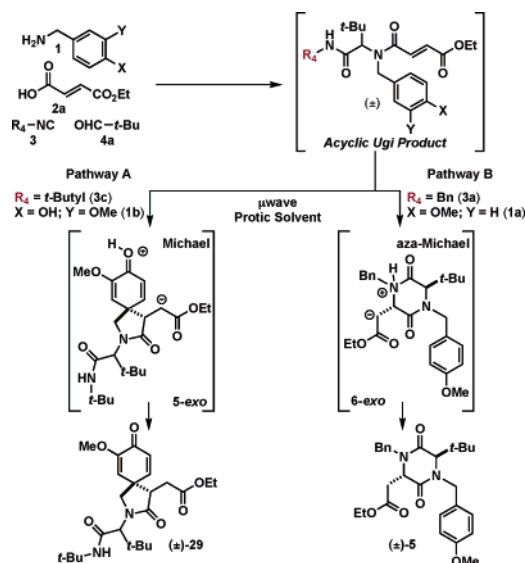
<sup>a</sup> Major product. <sup>b</sup> Isolated. <sup>c</sup> See Supporting Information for other aprotic and protic solvents used. <sup>d</sup> Compound number denoted in parentheses. <sup>e</sup> Determined by <sup>1</sup>H NMR. <sup>f</sup> See Supporting Information (S34) for X-ray structure. <sup>g</sup> Percent conversion based on starting substrates. <sup>h</sup> Only acyclic Ugi product remains. Also, a small amount (5–10%) of Type A could be isolated if reaction time exceeded 25 min. <sup>i</sup> See Supporting Information for detailed NMR characterization of tricyclic lactam. ND: not determined.

Michael transformation utilizing selective substrates with aprotic and protic solvents in the presence of microwaves.<sup>15</sup> When 4-hydroxyl-3-methoxybenzylamine **1b** (Figure 1) was employed under microwave irradiation (300 W, 200 °C, and 18 bar) for 20 min, with water as the solvent, 2-azaspiro[4.5]deca-6,9-diene-3,8-diones arose giving us our second unique molecular scaffold in good yields (Table 1, entries 12–17). It was rationalized that the electron-donating *p*-hydroxyl of **1b** (X = OH; Y = OMe) with the influence of microwave irradiation led to the formation of 2-azaspiro[4.5]deca-6,9-diene-3,8-dione product ((±)-**29**) through a

protic solvent-stabilized 5-*exo* Michael addition (Scheme 1, Pathway A). When *p*-methoxybenzylamine **1a** (X = OMe; Y = H) was used, the reaction yielded 2,5-diketopiperazines (±)-**5** (Scheme 1, Pathway B). Surprisingly, when methylene chloride was used with the same reaction conditions, only the Ugi acyclic product was observed and isolated (Table 1, entries 1–9, 12–17). With this result, we propose that protic solvents act to stabilize both the 5-*exo* and 6-*exo* zwitterionic intermediates through hydrogen bonding, leading to the observed products. It must be noted that bulky substituents at R<sub>4</sub> could influence the pathway outcome.

In comparison to entry 9 (where R<sub>4</sub> = benzyl), entries 13, 15, and 17 of Table 1 denote that a sterically encumbered isocyanide can direct the pathway selectivity toward the formation of 2-azaspiro[4.5]deca-6,9-diene-3,8-diones even when R<sub>3</sub> is 4-hydroxybenzyl (**1c**). It is important to note that, with the majority of substrates studied herein, no product overlap was observed, and the overall transformation was accomplished in one pot with readily available starting materials.

When thiophene-2-carboxaldehyde (**4d**) was employed (Table 1, entries 10 and 11) and water used as the solvent, compounds of the structural Type A were formed through an aza-Michael addition. Surprisingly, the hydrophobic effect of water on a possible 4π + 2π concerted reaction did not influence the formation of an intramolecular thiophene-based Diels–Alder tricyclic lactam in *either the presence or absence* of microwaves.<sup>16,17</sup> However, when the same starting

**Scheme 1.** Effects of Microwaves, Protic Solvent, and Bifunctional Substrates for Small Molecule Diversity

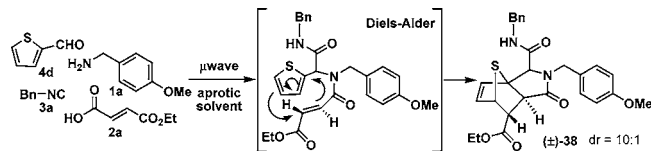
(15) For a recent microwave-assisted aza-Michael reaction employing a Ru catalyst, see: Fustero, S.; Jimenez, D.; Sanchez-Rosello, M.; del Pozo, C. *J. Am. Chem. Soc.* **2007**, *129*, 6700–6701.

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(17) For a review concerning microwave reactions in water as a solvent, see: Dallinger, D.; Kappe, C. O. *Chem. Rev.* **2007**, *107*, 2563–2591.

reagents were dissolved in methylene chloride, none of compound structures Type A, Type B, or the acyclic Ugi product formed. Instead an intramolecular thiophene-derived Diels–Alder tricyclic lactam emerged as illustrated in Scheme 2 (Table 1, entries 18 and 19) albeit in somewhat

**Scheme 2.** Thiophene-Derived Intramolecular Diels–Alder Reaction



low yield possibly due to reversibility.

This very unusual result added further evidence toward our proposed protic solvent stabilized mechanism leading to molecular diversity. Entries 10, 11, 18, and 19 from Table 1 illustrate this particular observation quite well, in fact entries 10, 11, 18, and 19, having identical starting substrates, produce Type A and Type C molecular scaffolds. It is important to note that the direct conversion of the four components to products of Type A, B, and C could not be achieved through conventional methods of heating/pressure.

Instances where Type A products might be expected—namely, having a sterically encumbered group at  $R_4$ , such as a *tert*-butyl (**3c**) and a 4-methoxybenzyl (**1a**) or 3,4-dimethoxybenzyl (**1f**) at position  $R_3$  (Table 1, entries 20–23)—led only to acyclic Ugi products under all conditions examined. In contrast, when  $R_3$  was substituted to contain a

4-hydroxybenzyl (**1c**, entries 12, 13, 15, and 17), 2-azaspiro[4.5]deca-6,9-diene-3,8-diones are formed.

In summary, we have developed a one-pot, additive-free method for constructing molecular diversity from a multi-component coupling reaction based on solvent effects and microwave irradiation. Using water as the solvent gives rise to 2,5-diketopiperazines from an aza-Michael reaction and 2-azaspiro[4.5]deca-6,9-diene-3,8-diones from a 5-*exo* Michael cyclization. An intramolecular thiophene Diels–Alder reaction was observed to proceed in the presence of methylene chloride and microwave irradiation, arguing against hydrophobic effects for rate acceleration in this intramolecular  $[4\pi + 2\pi]$  transformation. Our lab continues exploring the unusual chemistry described herein and biological evaluation of the resulting products.

**Acknowledgment.** This paper is dedicated to Prof. Carl R. Johnson on the occasion of his 70th birthday. S.S. and P.R.A. would like to thank Dr. Bashar Ksebati (Wayne State University) for NMR assistance, Dr. Lew Hryhorczuk (Wayne State University) for obtaining mass spectral data, and Dr. Mary Jane Heeg (Wayne State University) for X-ray data. The authors acknowledge a reviewer who provided helpful insights. P.R.A. also acknowledges WSU for start-up funds and a WSU Research Grant (145767).

**Supporting Information Available:** Experimental protocols and NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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