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A Rapid, One-Pot, Microwave-Influenced Synthesis of Spiro-2,5-diketopiperazines via a Cascade Ugi/6-*Exo-Trig* Aza-Michael Reaction

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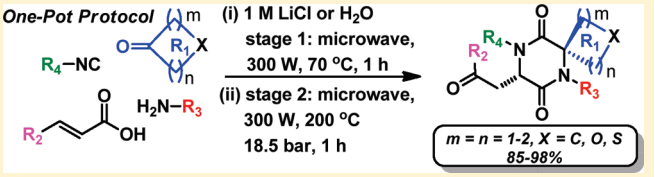
Supporting Information

ABSTRACT: A rapid, cascade reaction process has been developed to access biologically validated spiro-2,5-diketopiperazines. The facile and environmentally benign method capitalizes on commercially available starting reagents for a sequential Ugi/6-*exo-trig* aza-Michael reaction, water as a solvent, and microwave irradiation without any extraneous additives.



The vast majority of prescription drugs are small molecule natural products, derivatives thereof, or synthetically designed constructs aimed at a biological target possessing some specific function.[1] The involvement of heteroatoms for heterocyclic small molecule scaffolds has long been known to be a crucial component in the drug discovery process. Despite the tremendous advancements in the areas of synthetic and combinatorial chemistries, suitably functionalized heterocyclic "privileged" scaffolds are not easily or readily accessible. Consequently, the exponentially increased cost of lead generation and optimization has led to the introduction of far fewer drugs over the past decade.[2] Thus, a platform that allows rapid entry into new drug leads and expedites optimization is a necessary component to overcome these limitations. Concerted efforts among the scientific community to design and develop new reactions and strategies that rapidly access heterocyclic scaffolds are being pursued.[3]

As part of an ongoing research program aimed at developing a rapid drug discovery platform that includes the concepts of green chemistry, we became interested in spiro-2,5-diketopiperazines (spiro-DKPs) because of their known biological effects. Reports note similarities in effects to β-turn mimetics, and they have also been shown to be specific glycogen phosphorylase inhibitors (**A**)[4] as an emerging therapeutic approach to treat type 2 diabetes.[5] Moreover, they also possess antiproliferative effects (**B**), anti-inflammatory activity (**B**), and neuroprotective effects (**C**).[6] Recently, spiro-DKP **D** exhibited high potency against drug-resistant human tumor cell lines, as measured by IC_{50}.[7] Isolated spiro-DKP **E** from cosmopolitan fungus *Aspergillus versicolor* B-17 has also been shown to possess remarkable cytotoxicity against murine cancer cell line tsFT210 (Figure 1).[8] Aplaviroc (**F**), which was developed by GlaxoSmithKline, has potent anti-HIV activity as well as inhibitory effects against highly multidrug-resistant variants of HIV-1 through binding to the CCR5 coreceptor, which is crucial for entry of HIV type-1 into host cells.[9] Furthermore, spiro-DKPs are valuable synthetic precursors that can lead to α,α-disubstituted constrained amino acids, which have become important

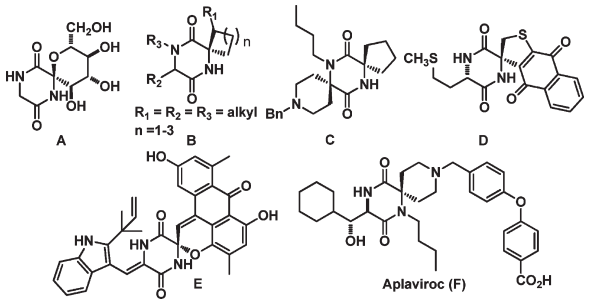


Figure 1. Biologically relevant spiro-DKPs.

small molecules used in proteomics-based approaches for new therapeutics.[10]

There are few literature reports describing the synthesis of spiro-DKPs. These include a ring-closing metathesis strategy,[11a] a post-Ugi cyclization,[11b] a Diels–Alder type reaction,[11c] an intramolecular aminolysis process,[11d,11e] as well as others.[11f–11i] Many of the reported methods are lengthy and employ harsh conditions including highly toxic reagents. Recently, however, we reported a facile, one-pot microwave influenced synthesis of DKPs via a multicomponent reaction cascade.[12] As an extension of this strategy and a means to overcome shortcomings with current methodology, we report on the synthesis of spiro-DKPs via a cascade Ugi four component coupling (U-4CC)/6-*exo-trig* aza-Michael reaction under microwave irradiation using water as the solvent.

We initially elected to use *p*-methoxybenzylamine (PMB-NH_2; **1a**), cyclopentanone (**2a**), fumaric acid monoethyl ester (**3a**), and *n*-butyl isocyanide (**4a**) in the U-4CC reaction (Scheme 1). Purified acyclic product **5a** was then subjected to microwave irradiation utilizing various temperatures, pressures,

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and times to find optimal conditions for the cyclization product **6a** (Table 1).

When the microwave was equilibrated to 300 W, 200 °C, and 18.5 bar for 1 h, spiro-DKP **6a** was obtained in 85% yield (Table 1). It must be noted that the aza-Michael reaction, for the acyclic Ugi product **5a** derived from a cyclic ketone,[13] took a substantially longer reaction time to complete as compared to the acyclic Ugi product derived from an aldehyde.[12] A likely explanation could be due to the ring strain of the resulting spiro-DKP. Extending the microwave irradiation time-course past 60 min only led to decomposition of starting material. We also noted that when purified **6a** alone was subjected to microwave irradiation for greater than a 60 min time frame, under the exact conditions as noted in Table 1, degradation was observed.

With conditions for the 6-*exo*-*trig* aza-Michael pathway in hand,[14] we re-examined the reaction for a potential one-pot protocol. Utilizing a two-stage microwave irradiation strategy: (i) stage 1, 1 M LiCl or H_2O, 300 W, 70 °C, 10 bar, 1 h, then (ii) stage 2, 300 W, 200 °C, 18.5 bar, 1 h; we attempted to obtain spiro-DKPs in a one-pot protocol for efficiency and minimization of chromatography. A two stage strategy was employed to ensure that the U-4CC reaction was not out competed by the Passarini three-component coupling (P-3CC) reaction. We further extended our studies to examine the substrate scope of this novel one-pot strategy.

Scheme 1. Two-Step Protocol for the Synthesis of Spiro-DKP 6a

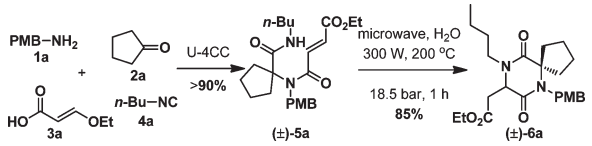


Table 1. Optimization of the Microwave Irradiation[a] Conditions for the 6-*Exo*-*Trig* Aza-Michael Cyclization

entry	solvent[b]	time (min)	power (W)	*T* (°C)	pressure (bar)	yield of **6a** (%)[c]
1	H_2O	20	300	200	18	50
2	H_2O	30	300	200	18	60
3	H_2O	30	300	200	18.5	65
4	H_2O	40	300	200	18.5	70
5	H_2O	50	300	200	18.5	80
6	H_2O	60	300	200	18.5	85

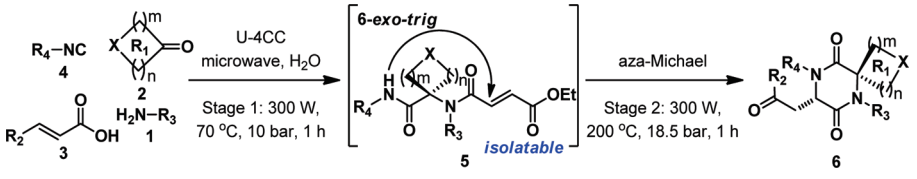
[a] CEM Discover Microwave. [b] 2.5 mL. [c] Isolated.

In general, the process is compatible with a range of cyclic ketones, amines, and isocyanides (Table 2). Although fumaric acid monoethyl ester (**3a**) has been utilized exclusively, other Michael acceptors can also be employed.[15] Despite scarce literature reports on the use of cyclobutanone (**2e**) in the U-4CC,[16] **2e** worked well with no unwanted side reactions or products. During the progress of this work, Pirrung and co-workers also reported that cyclobutanone (**2e**) reacted in the U-4CC and P-3CC reactions. They attributed the low LUMO energy and suitable hydrophobicity of cyclobutanone (**2e**) for the success of the coupling reaction and utilized this key component for the construction of dipeptides having identical physical properties to that of aspartame.[17] Furthermore, it must be noted that the cyclobutane ring, embedded in the spiro-DKP product **6e**, did not undergo ring opening under high temperature and pressure, contrary to literature reports.[18]

In order to understand the reactivity difference of acyclic Ugi product **5** derived from cyclic ketones over aldehydes in this cascade process, we replaced **1a** with *p*-hydroxybenzyl amine (PHB-NH_2; **1e**) while other coupling components were kept the same as noted in entry 2 (Table 1). Since *n*-butyl isocyanide (**4a**) is a less bulky isocyanide, formation of spiro-DKP **6f** was initially expected.[12] However, we were able to isolate biologically relevant 2-azaspiro[4.5]deca-6,9-diene-3,8-dione (**7a**, 85%) via a 5-*exo*-*trig* Michael pathway (Scheme 2). Replacement of **4a** with bulky *tert*-butyl isocyanide (**4c**) using the same reaction protocol afforded **7b** in 80% yield (Scheme 2).[12] Important to note is that **7a** and **7b** were obtained in a shorter time period (40 min vs 60 min) as compared to **6a**−**e**.

A proposed mechanism for the formation of spiro-DKPs is shown in Scheme 3. We argue that the acyclic Ugi product **5** can adopt either a *trans*-amide (**5″**) or *cis*-amide (**5‴**) conformation in equilibrium favoring **5″** at room temperature.[19] Due to the ring size of the spiro-DKPs, the acyclic Ugi product in the *cis*-amide conformation (**5‴**) can only undergo a 6-*exo*-*trig* aza-Michael reaction giving **6**.[20] Moreover, the *cis*-amide conformation brings the *N* lone pair (HOMO) and π^* of the Michael

Table 2. Substrate Scope of the Microwave-Influenced[a] One-Pot Synthesis of Spiro-DKPs



entry	R_1	R_2	R_3	R_4	compd/% yield[b]
1	cyclopentyl (**2a**)	ethoxycarbonyl (**3a**)	4-methoxybenzyl (**1a**)	*n*-butyl (**4a**)	**6a**/85
2	cyclohexyl (**2b**)	ethoxycarbonyl (**3a**)	4-methoxybenzyl (**1a**)	*n*-butyl (**4a**)	**6b**/80
3	4-thio-pyran (**2c**)	ethoxycarbonyl (**3a**)	3,4-dimethoxybenzyl (**1b**)	benzyl (**4b**)	**6c**/82
4	4-pyran (**2d**)	ethoxycarbonyl (**3a**)	3,4-methylenedioxybenzyl (**1c**)	benzyl (**4b**)	**6d**/83
5	cyclobutane (**2e**)	ethoxycarbonyl (**3a**)	benzyl (**1d**)	benzyl (**4b**)	**6e**/98

[a] CEM Discover Microwave. [b] Isolated.

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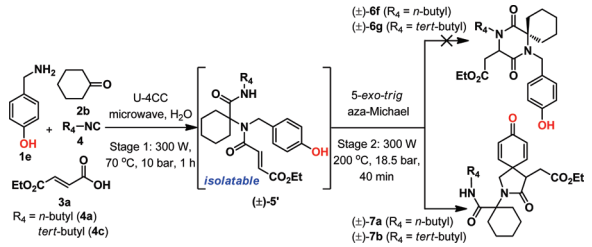
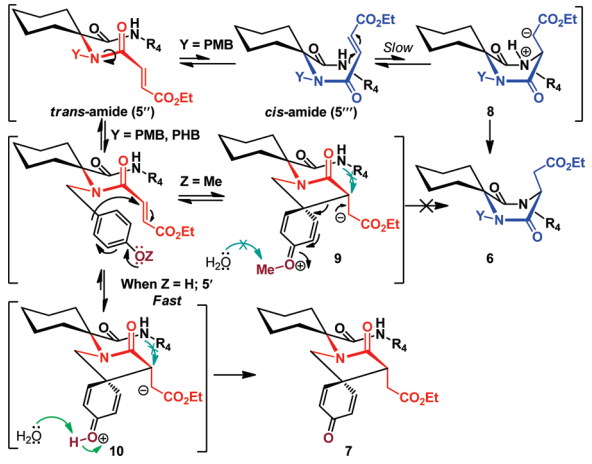
Scheme 2. Use of *p*-Hydroxybenzylamine Provides 2-Azaspiro[4.5]deca-6,9-diene-3,8-diones (7a and 7b)



Scheme 3. Proposed Mechanism for the Formation of Spiro-DKPs



acceptor (LUMO) in the same plane for optimum orbital overlap and therefore favors the Bürgi−Dünitz angle of attack.[21] Thus, in the first step, with microwave irradiation **5″** isomerizes to **5‴** due to a low energy barrier,[19] ultimately forming the zwitterionic boat intermediate **8**.[22] Intermediate **8** is believed to be stabilized by hydrogen bonding which assists in absorbing microwave energy.[23] Protonation−deprotonation provides the final product **6**. When an electron-donating group (Z = OMe) is present on the aryl-R_3 component, a 5-*exo-trig* Michael reaction can likely take place to form the unstable intermediate **9**, which in turn can rapidly reverse to form the *cis*-amide **5‴**. This is most likely due to the highly reversible oxocarbenium ion in **9**, which is not stable yet does not undergo Me-O bond cleavage under our reaction conditions.[12,24] When, Z = H, stable 2-azaspiro[4.5]deca-6,9-diene-3,8-dione zwitterionic intermediate (**10**) forms and deprotonation−protonation provides the final product **7** regardless of substituents on R_4. This is surprising since less bulky isocyanides (e.g., **4a**) were shown to provide DKPs via a 6-*exo-trig* aza-Michael pathway.[12] A likely explanation could be that the 5-*exo-trig* Michael pathway occurs at a faster rate due to a favorable *trans*-amide conformation. This further validates our hypothesis that the spiro-DKP formation occurs via a *cis*-amide conformation.

In summary, we have developed a rapid and efficient process for the synthesis of biologically relevant spiro-2,5-diketopiperazines from readily available starting materials. The reaction proceeds via a cascade U-4CC/6-*exo-trig* aza-Michael reaction in water under the influence of microwaves and generates four contiguous bonds, a tertiary spiro-carbon center, and one new stereogenic center. Further structural, functional, and substituent diversity can be achieved from these compounds through chemical manipulation. Future experiments will be aimed at evaluating antifungal, antileukemic, and anti-HIV properties of the spiro-DKPs via SAR studies. In addition, efforts are underway to extend the methodology to access other spiro compounds that will contribute to a small molecule focused library.

EXPERIMENTAL SECTION

General Procedure 1 for Spiro-DKPs (Commencing from the Acyclic Ugi Product). To a 10 mL vial equipped with a magnetic stirring bar was added 0.12 mmol (50 mg) of purified acyclic Ugi product (e.g., **5a**) and the mixture taken up in a mixture of 1.5 mL of 1 M LiCl and 1 mL of MeOH or 2.5 mL of distilled H_2O with a pH of 7.0. The vial was capped according to the manufacturer's suggestion and placed in the microwave cavity. The reaction ran for 1 h at 200 °C, 18.5 bar, and 300 W. After the vial was cooled to room temperature, ethyl acetate was added, and the mixture was shaken vigorously. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 2 mL). The organic layers were combined, dried over Na_2SO_4, and then filtered. The filtrate was dried under vacuum and purified by silica gel column chromatography using a 1:2 mixture of ethyl acetate and hexane as the eluent.

General Procedure 2 for the One-Pot Synthesis of Spiro-DKPs (Commencing from Four Starting Materials). To a 10 mL vial equipped with magnetic stirring bar, 4-methoxybenzylamine (**1a**, 15 mg, 0.11 mmol), cyclopentanone (**2a**, 9.3 mg, 0.11 mmol), furmaric acid monoethyl ester (**3a**, 16 mg, 0.11 mmol), and *n*-butyl isocyanide (**4a**, 9.3 μL, 0.11 mmol) were added to a mixture of 1.5 mL of 1 M LiCl and 1 mL of MeOH or 2.5 mL of distilled H_2O with a pH of 7.0. The vial was capped according to the manufacturer's suggestion and placed in the single-mode microwave cavity. The microwave was run at two separate stages: (1) 1 h at 70 °C, 10 bar, and 300 W; (2) 1 h, 200 °C, 18.5 bar, and 300 W. After the vial was cooled to room temperature, ethyl acetate was added, and the reaction mixture was shaken vigorously. The organic layer was separated, and the aqueous layer was extracted again with ethyl acetate (2 × 2 mL). The organic layers were combined and washed with $NaHCO_3$ (2 × 3 mL), 1 N HCl (2 × 3 mL), and finally with brine (2 × 3 mL). The organic layer was separated. All aqueous layers were combined and extracted with additional ethyl acetate (3 mL). The organic layers were then combined, dried over Na_2SO_4, and filtered. The filtrate was dried under vacuum and purified using silica gel column chromatography employing a 1:2 mixture of ethyl acetate and hexanes as the eluent.

Ethyl 2-(5,8-Dibenzyl-6,9-dioxo-5,8-diazaspiro[3.5]nonan-7-yl)acetate (6e). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21−7.37 (m, 8 H, Ph), 7.16−7.21 (m, 2 H, Ph), 5.17 (d, 1 H, J = 15.3 Hz, $-CH_2$Ph), 5.10 (d, 1 H, J = 15.9 Hz, $-CH_2$Ph), 4.70 (d, 1 H, J = 15.9 Hz, $-CH_2$Ph), 4.38 (t from dd overlap, 1 H, J = 5.5 Hz, H^c), 4.29 (d, 1 H, J = 15.3 Hz, $-CH_2$Ph), 4.10 (q, 2 H, J = 7.3 Hz, $-OCH_2CH_3$), 2.85 (dd, 1 H, J = 16.2, 5.5 Hz, H^d), 2.80−2.84 (m, 1 H, cyclobutane), 2.78 (dd, 1 H, J = 16.2, 5.5 Hz, H^d), 2.46−2.69 (m, 3 H, cyclobutane), 2.07−2.19 (m, 1 H, cyclobutane), 1.78−1.89 (m, 1 H, cyclobutane), 1.23 (t, 3 H, J = 7.3 Hz, $-OCH_2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 169.6, 166.5, 137.8, 136.1, 128.9, 128.7, 127.9, 127.2, 126.4, 63.1, 61.2, 56.2, 53.4, 48.0, 46.4, 37.1, 34.4, 31.2, 14.5, 14.1. HRMS (EIMS): calcd for $C_{25}H_{28}N_2O_4$ 420.2049, found 420.2051.

ASSOCIATED CONTENT

Supporting Information. Experimental details and characterization of new compounds **5a** and **6a−e** including ^{1}H, ^{13}C, and gDQFCOSY spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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