Letter

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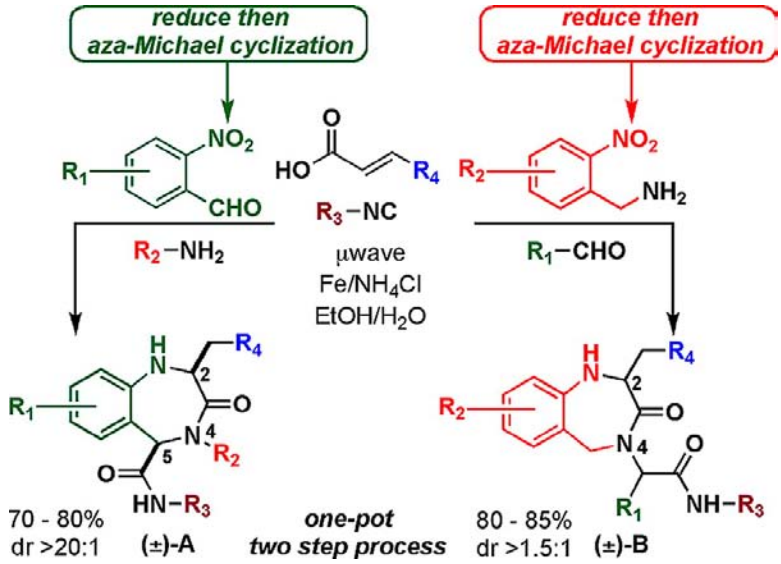

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A Tandem One-Pot, Microwave-Assisted Synthesis of Regiochemically Differentiated 1,2,4,5-Tetrahydro-1,4-benzodiazepin-3-ones

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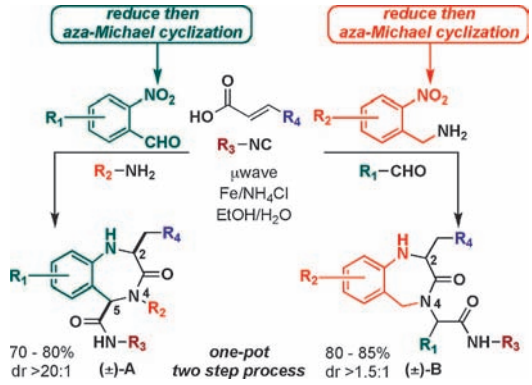
ABSTRACT



A one-pot, two-step synthesis of the title compounds employs a multicomponent Ugi condensation reaction, microwave irradiation, and Fe(0) as a reductant. Two pathways are accessible; both routes utilize bifunctional, *o*-nitro-substituted arenes leading to either C2, N4, C5 substitution (A) or C2, N4 substitution (B).

Tandem reactions allow for the generation of complex molecular scaffolds from simple precursors with, in most cases, the concominant formation of stereogenic centers.[1] Bifunctional substrates allow for progressional reactivity in tandem reactions leading to advantages such as intramolecular bond-forming processes,[2] with a high degree of atom economy[3] and the alleviation of workup and isolation of transient intermediates. One-pot tandem processes that generate biologically validated structural motifs will facilitate the development of new therapeutic agents.

For a number of years, scientists have been exploring the biological activities of benzodiazepine (BDZ) derivatives.[4−6] A number of synthetic approaches to 1,4-benzodiazepin-3-ones have been reported including a CuI-catalyzed Ullmann-type aryl amination,[7] addition/elimination nucleophilic aromatic substitution of primary or secondary amines,[4a,5b,8] a retro-Michael/amidation,[9] and an intramolecular 1,3-dipolar cycloaddition.[10] Of the aforementioned reaction types, none have been developed to access 1,4-benzodiazepin-3-ones in a single pot. Although substrate diversity can readily be accessible in all processes described, regiochemical substitution remains a challenge.

Our approach to synthesizing 1,4-benzodiazepin-3-ones involves the Ugi four-component coupling reaction (U-4CCR) in conjunction with microwave (μwave) irradiation to rapidly access differentially substituted motifs in a one-pot protocol utilizing environmentally benign reagents.[11] The

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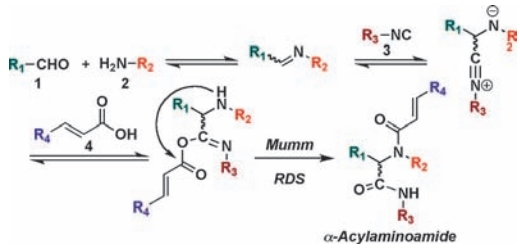
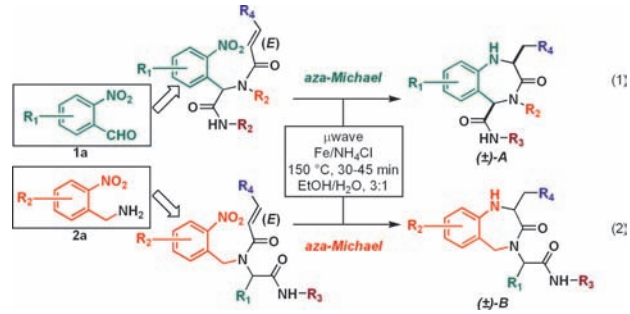
Ugi reaction is the condensation of an aldehyde or ketone (**1**), an amine (**2**), an isocyanide (**3**), and a carboxylic acid (**4**) yielding an α-acylaminoamide (Scheme 1). All steps are

Scheme 1. Mechanism of the Ugi Reaction Leading to an α-Acylaminoamide



reversible except for the proposed rate determining Mumm rearrangement.[12] Ultimately the reaction proceeds in the forward direction due to a more stable +4 oxidation state of carbon from its +2 state in the starting isonitrile.[13]

As a synthetic tool for creating diversity in compound libraries, the Ugi reaction readily accommodates a large number of potential inputs although a limited number of isocyanides are commercially available. However, by incorporating bifunctional substrates into the condensation reaction, one can readily achieve structural diversification through regioselective bond forming reactions in a one-pot protocol. Furthermore, μwave-based organic synthesis has underexplored potential for controlling pathway selectivity as we have recently illustrated.[14] In this paper, we describe use of microwaves to facilitate a 7-*exo* aza-Michael cyclization event which sets substitution patterns on BDZ arising from the bifunctional substrates *o*-nitrobenzaldehyde (**1a**) and *o*-nitrobenzylamine (**2a**).



We envisioned formation of a seven-membered diazepine through a post Ugi reductive aza-Michael reaction onto a doubly conjugated olefin obtained from (*E*)-fumaric acid monoethyl ester (**4a**) (eqs 1 and 2). Use of *o*-nitrobenzaldehyde (**1a**) gave a C2, N4, C5 substitution pattern (±**A**) while *o*-nitrobenzylamine (**2a**) provided a C2, N4 derivatized benzodiazepine product (±**B**). For the reduction, we elected to use the two electron reducing conditions of Fe(0)[15] and NH_4Cl in an aqueous media due to its mild nature and the fact that iron has a high functional group tolerance.[16] Benzyl-based substrates did not fair well under hydrogenolysis conditions with palladium or platinum and although tin(II) chloride worked reasonably well for the aryl nitro reduction, the combination of Fe(0) and NH_4Cl was most efficient and effective.

While optimizing the 7-*exo* aza-Michael cyclization something of particular interest was observed with substrates derived from *o*-nitrobenzaldehyde (**1a**). After the synthesis and purification of acyclic Ugi compound **5**, using Pirrung's method,[17] we assumed that a spontaneous cyclization would occur under Fe/NH_4Cl reduction conditions yielding benzodiazepine **6**. However, as noted in Table 1, entry 4, this cyclization event proceeded with μwave irradiation (300 W, 150 °C and 10 bar, 45 min). It is important to note that only C2, N4, C5 1,2,4,5-tetrahydro-1,4-benzodiazepin-3-one (mix of diastereomers) and acyclic aniline compound **7** could be isolated, inferring that substrate degradation did not occur. When the reaction was run in a sealed tube at temperatures exceeding 200 °C, less than 10% of **6** was observed after 45 min. In fact, reactions run at temperatures exceeding 200 °C for longer than 1 h (microwave and sealed tube) led to extensive decomposition.

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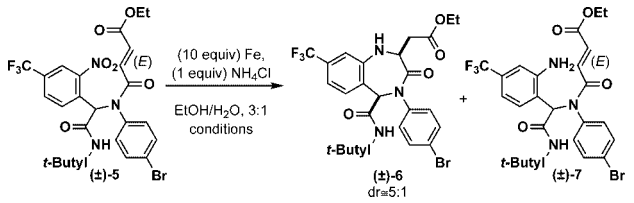
Table 1. Aza-Michael Cyclization Yielding C2, N4, C5 Substitution of 1,2,4,5-Tetrahydro-1,4-benzodiazepin-3-ones

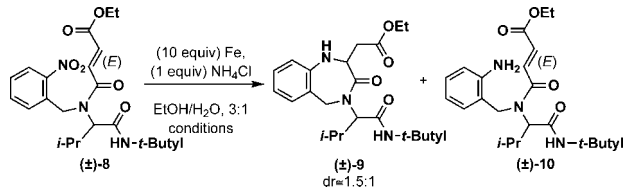


entry	conditions	% yield of **6**	% yield of **7**
1	140 °C[a], 5 h	<1[b]	>98[b]
2	140 °C[a], 24 h	<1[b]	>98[b]
3	sealed tube, 140 °C[a], 24 h	<1[b,c]	>98[b]
4	μwave for 45 min[d]	75[e]	25[e]

[a] Denotes oil bath temperature. [b] Determined by ^{1}H NMR. [c] At temperatures exceeding 200 °C, <10% was observed after 45 min. Extended reaction times led to extensive decomposition. [d] Microwave equilibrated to 300 W, 150 °C, and 10 bar. [e] Isolated.

A similar study was conducted to optimize a 7-*exo* aza-Michael cyclization for C2, N4 substituted 1,2,4,5-tetrahydro-1,4-benzodiazepin-3-ones. A purified acyclic Ugi product **8**, arising from isobutyraldehyde (**1d**), *o*-nitrobenzylamine (**2a**), *tert*-butyl isocyanide (**3a**), and fumaric acid monoethyl ester (**4a**), was used as the starting substrate. Traditional heating methods worked well in the cyclization process giving BDZ of type **B** (Table 2, entries 2−4) in 55−80% yield, however,

Table 2. Aza-Michael Cyclization Yielding C2, N4 Substitution of 1,2,4,5-Tetrahydro-1,4-benzodiazepin-3-ones



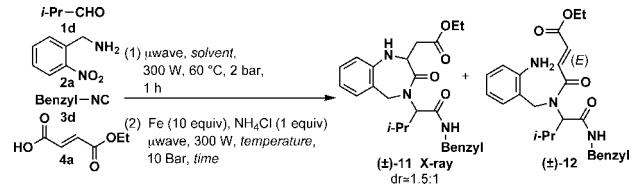
entry	conditions	% yield of **9**	% yield of **10**
1	rt for 48 h	NR	NR
2	140 °C[a]for 5 h	55[b]	40[b]
3	140 °C[a], 24 h	73[b]	22[b]
4	sealed tube, 140 °C[a], 24 h	80[b]	17[b]
5	μwave for 45 min[c]	90[d]	7[d]

[a] Denotes oil bath temperature. [b] Obtained via ^{1}H NMR. [c] Microwave equilibrated to 300 W, 150 °C, and 10 bar. [d] Isolated.

μwave irradiation (Table 2, entry 5) provided compound **9** in 90% yield with the greatest efficiency. It is important to note that the *o*-nitro group in compounds **5** and **8** was not reduced by Fe(0) and NH_4Cl at room temperature and **7** would not undergo an aza-Michael cyclization unless μwave irradiation was applied.

We were encouraged to attempt a one-pot two step protocol for the formation of 1,2,4,5-tetrahydro-1,4-benzodiazepin-3-ones based on our results with the 7-*exo* Michael additions described in Tables 1 and 2. We elected to use isobutyraldehyde (**1d**), 2-nitrobenzylamine (**2a**), benzyl isocyanide (**3d**), and fumaric acid monoethyl ester (**4a**) as our initial set of starting substrates leading to BDZ of type **B** (Table 3). Protic solvents such as aqueous methanol or

Table 3. One-Pot Protocol for BDZ Synthesis



entry	solvent	time (min)	T (°C)	% yield of **11**[a]	% yield of **12**[b]
1	EtOH	30	150	77	10
2	H_2O	30	150	73	5
3	EtOH/H_2O, 3:1	30	150	85	3
4	EtOH/H_2O, 3:1	15	180	71	7
5	EtOH/H_2O, 3:1	75	140	82	3
6	EtOH/H_2O, 3:1	100	120	80	3
7	EtOH/H_2O, 3:1	180	110	81	3

[a] Isolated. [b] Determined by ^{1}H NMR.

ethanol gave the desired Ugi product in high yields (>98%; denoted by ^{1}H NMR) after being subjected to μwave irradiation for 1 h at 60 °C. Fe(0) and NH_4Cl were then added to the reaction flask, and the mixture was further subjected to μwave irradiation until all starting materials were converted to **11** (X-ray) and **12**.

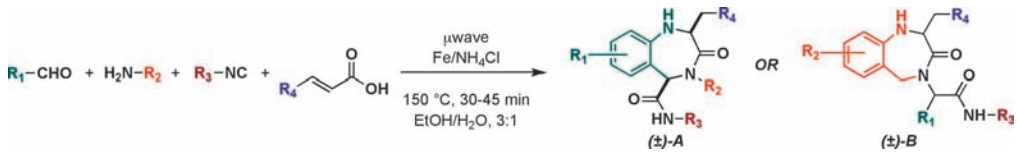
The reduction reaction worked best in the μwave at 150 °C for 30 min in a 3:1 ratio of EtOH/water. Important to note is that in the absence of μwave irradiation or other heat sources in the one-pot protocol, only the acyclic Ugi product could be isolated (approximately 80% yield in 18 h, refer to Table 2 for cyclization conditions) suggesting a high energy of activation for nitro reduction with Fe(0).

We next turned our attention to examining the scope of the one-pot protocol. As noted in Table 4, entries 1−5, BDZs of type **A** were formed in 70−80% yield with high diastereomeric ratios. In fact, compounds **15** and **16** (Table 4, entries 4 and 5) were obtained as single diastereomers determined by ^{1}H NMR. NOe data assisted in elucidating a 2,5-*cis* relationship between the acid and aldehyde components of the coupling product.

These data correspond nicely with literature precedent in which similar types of 1,2,4,5-tetrahydro-1,4-benzodiazepin-3-ones were synthesized.[8b] Diastereomers were rationalized to arise from the *E* olefin geometry of the fumaric acid component (**4a**/**4b**).

Using 2-nitrobenzylamine (**2a**) as a substrate in the U-4CCR gave benzodiazepines of type **B** following the one-pot protocol (Table 4, entries 6−7). Although we observed higher yields of C2, N4 substituted 1,2,4,5-tetrahydro-1,4-benzodiazepin-3-ones, diastereomeric ratios were determined

Table 4. Scope of the One-Pot Microwave-Assisted Synthesis of Regiochemically Differentiated 1,2,4,5-Tetrahydro-1,4-benzodiazepin-3-one



entry	R_1	R_2	R_3	R_4	compd. type[a]/ % yield[b]	dr[c]
1	2-nitro-4-(trifluoromethyl)phenyl (**1b**)	4-bromobenzyl (**2c**)	*tert*-butyl (**3a**)	ethoxycarbonyl (**4a**)	**A** (**6**)/75	5:1
2	2-nitrophenyl (**1a**)	benzyl (**2b**)	*tert*-butyl (**3a**)	ethoxycarbonyl (**4a**)	**A** (**13**)/75	20:1
3	4,5-dimethoxy-2-nitrophenyl (**1c**)	allyl (**2d**)	cyclohexyl (**3b**)	benzoyl (**4b**)	**A** (**14**)/70	20:1
4	2-nitrophenyl (**1a**)	piperonyl (**2e**)	*tert*-butyl (**3a**)	ethoxycarbonyl (**4a**)	**A** (**15**)/73	single
5	2-nitrophenyl (**1a**)	4-aminoacetophenone (**2f**)	cyclopentyl (**3c**)	4-methylbenzoyl (**4c**)	**A** (**16**)/78	single
6	isopropyl (**1d**)	2-nitrobenzyl (**2a**)	*tert*-butyl (**3a**)	ethoxycarbonyl (**4a**)	**B** (**9**)/90	1.5:1
7	isopropyl (**1d**)	2-nitrobenzyl (**2a**)	benzyl (**3d**)	ethoxycarbonyl (**4a**)	**B** (**11**[d,e])/85	1.5:1
8	isopropyl (**1d**)	2-nitrobenzyl (**2a**)	*tert*-butyl (**3a**)	H (**4d**)	acyclic (**17**[f])/100[d]	

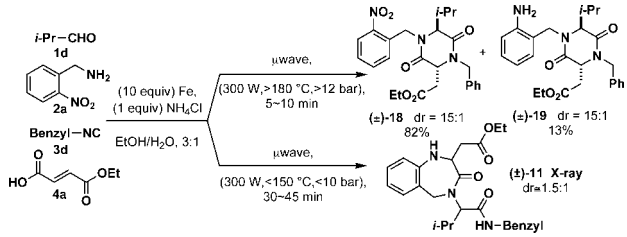
[a] Compound number denoted in parentheses. [b] Isolated. [c] Determined by using an unpurified sample with ^{1}H NMR. [d] See the Supporting Information for the X-ray structure. [e] At temperatures >180 °C the major product was 2,5-diketopiperazine. [f] Isolated the acyclic aniline Ugi product.

to be, at best, 1.5:1 (^{1}H NMR). The diastereomeric mixture proved difficult to separate and required a silica gel column of considerable length.

Interestingly, when acrylic acid (**4d**) was used as a coupling component and subjected to our one-pot cyclization conditions, an eight-membered ring was not observed and only the acyclic aniline U-4CC product **17** (X-ray) was isolated (Table 4, entry 8).

At high μwave intensity, a one-pot 6-*exo* aza-Michael cyclization occurred to form 2,5-diketopiperazines **18** and **19** as illustrated in Scheme 2.[13] This potentially competing

Scheme 2. Microwave Intensity Controls Pathway Selectivity



reaction pathway could readily be suppressed by reduction of μwave intensity to exclusively form BDZ **11**. This transformation indicates that a 6-*exo* aza-Michael cyclization, from an amide, occurs faster than the zerovalent iron metal reduction. Our results suggest that compound **19** resulted from the direct reduction of **18** and not from prior $-NO_2 \rightarrow -NH_2$ reduction.

In summary, we have developed a one-pot, two-step reaction protocol for the synthesis of regiochemically differentiated 1,2,4,5-tetrahydro-1,4-benzodiazepin-3-ones. Using protic solvents, controlled μwave irradiation and the two electron reducing agent Fe(0)/NH_4Cl, these biologically relevent small molecules can be prepared efficiently and are highly amenable to derivatization. We have shown that *o*-nitrobenzaldehyde (**1a**) and *o*-nitrobenyzlamine (**2a**) not only act as bifunctional substrates in the reaction protocol but establish a C2, N4, C5 substitution pattern for BDZ of type **A** and a C2, N4 substitution pattern for BDZ of type **B**. Our laboratory continues to explore the chemistry described herein and biological evaluation of the resulting products.

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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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