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Intramolecular Cycloaddition of Azomethine Ylides in the Preparation of Pyrrolidino[2′,3′:3,4]pyrrolidino[1,2-*a*]benzimidazoles

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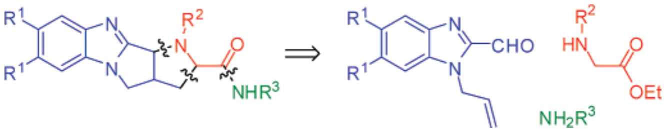
ABSTRACT



The parent pyrrolidino[2′,3′:3,4]pyrrolidino[1,2-*a*]benzimidazole heterocycle as well as a series of novel analogues have been synthesized utilizing a microwave-assisted intramolecular cycloaddition of azomethine ylides as the key transformation. A variety of diversity groups were added to explore the scope of this reaction and to provide a number of new compounds for biological screening.

Polycyclic nitrogen-containing heterocycles form the basic skeleton of numerous alkaloids and physiologically active compounds.[1] The pyrrolidine ring in particular is prominent in the structures of numerous bioactive molecules[2] and, as such, there is continued interest in the development of synthetic routes to pyrrolidine-containing heterocycles.

Recent reviews of the intramolecular azomethine ylide [3+2] cycloaddition[3] reveal the considerable versatility of this pericyclic reaction in the synthesis of pyrrolidines. For example, in previous work we developed a novel route to 1*H*-pyrrolidino[1,2-*c*]imidazole derivatives by intramolecular azomethine ylide cycloaddition and carbanilide cyclization chemistry.[4] In a continuation of our interest in the intramolecular azomethine ylide 1,3-dipolar cycloaddition and in compliance with our National Institutes of General Medical Sciences (NIGMS) collaboration, we have designed a pilot-scale library of polycyclic pyrrolidines (Figure 1) for high-throughput biological screening to identify potential drug candidates. Herein, we report a polycyclic pyrrolidine library, prepared by using solution-phase techniques, which exploits

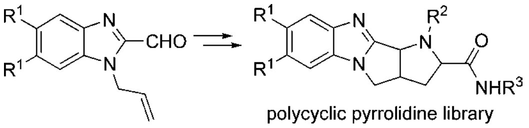


Figure 1. A three diversity point polycyclic pyrrolidine library.

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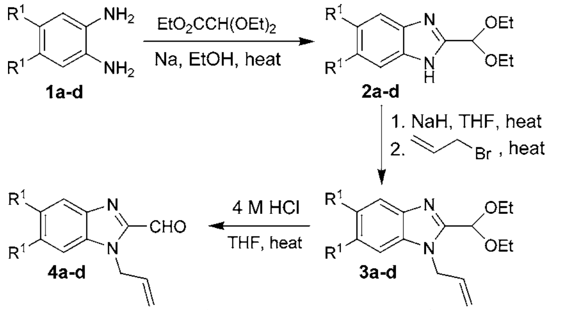
the pyrrolidine ring as an ideal template about which to deploy diverse pharmacophores. The key intramolecular cycloadditions, which employ azomethine ylides derived from *N*-allyl-2-carboxaldehyde benzimidazoles and secondary α-amino esters, were mediated by microwave irradiation and resulted in the diastereoselective preparation of structurally complex, fused pyrrolidine heterocycles.

The requisite 1-allyl-1*H*-benzo[*d*]imidazole-2-carbaldehydes **4a−d** were prepared from *o*-diaminoarenes in three steps as summarized in Scheme 1. Step one consisted of the condensation of *o*-diaminoarene **1** with ethyl diethoxyacetate under strongly basic conditions[5] to afford the 2-benzimidazole acetal **2** in moderate to good yields (40−82%). In step two, these 2-benzimidazoles were transformed into their *N*-allyl derivatives **3** by alkylation with sodium hydride/allyl bromide in refluxing tetrahydrofuran. Step three consisted of an acid-catalyzed acetal deprotection of **3** to give carbaldehyde **4**.

Scheme 1. Synthesis of Carbaldehydes **4a−d**



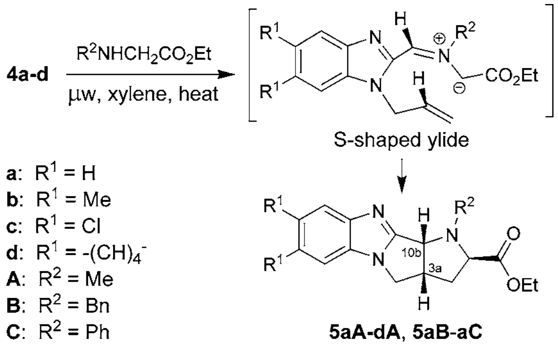
	R^1	Yield of **2**	Yield of **4**^{a}
a:	H	82%	92%
b:	CH_3	48%	99%
c:	Cl	74%	52%
d:	-(CH)$_4$-	40%	84%

[a] Isolated yields from **2** after chromatography on silica gel.

With **4a−d** in hand, attention was turned to construction of the polycyclic pyrrolidine ring systems employing the intramolecular cycloaddition of azomethine ylides—a powerful transformation for the synthesis of fused pyrrolidines. Azomethine ylide cycloadditions run under classical reaction conditions require longer reaction times and often afford products in lower yields and/or with lower diastereoselectivity than microwave-assisted variants.[6] Therefore, the condensation of carbaldehyde **4** with a secondary amino ester and the subsequent 1,3-dipolar cycloaddition of the S-shaped ylide[3b] depicted in Scheme 2 was mediated by microwave irradiation in xylene and delivered polycyclic pyrrolidine **5**.

Various reaction conditions for transformation **4** → **5**, initially with formyl derivative **4a** and ethyl 2-(benzylamino)-acetate, were explored (see entries 1−6, Table 1). The yield of this condensation−cycloaddition reaction improved with increasing substrate concentration; the better yield of **5aB** (54%) was obtained at a 1 M concentration of **4a** in xylene at 150 °C under microwave irradiation for 20 min. The nature of the secondary amine component was found to have a dramatic affect on the outcome of this reaction. As an example not listed in the table, the use of ethyl 2-(phenylamino)acetate and **4a** led to **5aC** but in only 10% yield, reflecting the fact that the nucleophilicity of the secondary amine is a critical determinant.[7]

Scheme 2. Synthesis of Pyrrolidino[2′,3′:3,4]pyrrolidino[1,2-*a*]benzimidazole-2-carboxylates



5aA-dA, 5aB-aC

Table 1. Azomethine Ylide Cycloadditions^a

entry	reactants	[**4**]^b	product. (%)^c	mixture^d
1	**4a** + *N*-Bn-Gly-OEt	0.05	**5aB** (16)	21:56:23
2	**4a** + *N*-Bn-Gly-OEt	0.1	**5aB** (22)	30:61:9
3	**4a** + *N*-Bn-Gly-OEt	0.2	**5aB** (33)	36:46:18
4	**4a** + *N*-Bn-Gly-OEt	1	**5aB** (43)	53:43:4
5^e	**4a** + *N*-Bn-Gly-OEt	1	**5aB** (14)	23:68:9
6^f	**4a** + *N*-Bn-Gly-OEt	1	**5aB** (54)	61:35:4
7	**4a** + *N*-Me-Gly-OEt	0.3	**5aA** (66)	93:7:0
8	**4a** + *N*-Me-Gly-OEt·HCl^g	0.3	**5aA** (59)	85:15:0
9	**4b** + *N*-Me-Gly-OEt·HCl^g	0.3	**5bA** (66)	98:2:0
10	**4c** + *N*-Me-Gly-OEt·HCl^g	0.3	**5cA** (93)	100:0:0
11	**4d** + *N*-Me-Gly-OEt·HCl^g	0.3	**5dA** (52)	100:0:0

[a] **4** (1 equiv) + 2-(alkylamino)acetate (2 equiv)/microwave at 130 °C for 20 min. [b] Molar concentration of **4** in xylene. [c] The number in parentheses is the yield of purified product. [d] A mixture of **5**:dimer: hemiaminal (see the Supporting Information) was obtained in these ratios as determined by analytical HPLC analysis. [e] **4** (1 equiv) + 2-(alkylamino)acetate (1 equiv)/microwave at 130 °C for 20 min. [f] **4** (1 equiv) + 2-(alkylamino)acetate (2 equiv)/ microwave at 150 °C for 20 min. [g] Et_3N (2 equiv) to neutralize HCl salt.

In addition to the desired product, analysis of the crude reaction mixture indicated that dimer and hemiaminal side products (see the Supporting Information) can make up a significant portion of the condensation/cycloaddition reaction mixture.[8] These side products are tied to what appear to be subtle but important conformational interactions of R^2 in the

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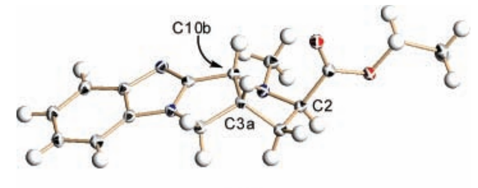
S-shaped ylide (see Scheme 2) such that a small R^2 (R^2 = Me; entries 7−11) accommodates the S-shaped ylide and efficiently leads to **5**. Changing R^2 from methyl to benzyl results in significantly lower yields of **5** (16−43%) and correspondingly higher production of dimer and hemiaminal.

The condensation/cycloaddition of **4a** with ethyl 2-(methylamino)acetate worked efficiently in xylene to afford **5aA** in good yield (66%, entry 7). When the hydrochloride salt of ethyl 2-(methylamino)acetate plus 2 equiv of triethylamine were applied to the cycloaddition of **4a** (0.3 M in xylene at 130 °C under microwave irradiation for 20 min), the yield of **5aA** was only slightly decreased (entry 8). Under these experimental conditions, 1-allyl-5,6-dimethyl-1*H*-benzimidazole-2-carbaldehyde (**4b**) delivered cycloadduct (**5bA**) in 66% yield (entry 9), 1-allyl-5,6-dichloro-1*H*-benzimidazole-2-carbaldehyde **4c** was transformed into **5cA** in excellent yield (93%, entry 10), and 1-allylnaphth[2,3-*d*]imidazole-2-carbaldehyde **4d** produced **5dA** in 52% yield (entry 11).

It is noteworthy that the azomethine ylide cycloadditions of **4a**−**d** with ethyl 2-(methylamino)acetate (as well as with *N*-Bn-Gly-OEt and *N*-Ph-Gly-OEt) are highly regio- and diastereoselective (**5aA**−**5dA** were the only intramolecular cycloadducts detected). The assignment of cis stereochemistry to the ring junctions of these cycloadducts was initially made by analogy with the stereochemistry observed for conventional azomethine ylide cycloadditions in similar systems[9] and further corroborated by the 7.8−8.4 Hz coupling constants between H_{3a} and H_{10b}, which are consistent with a cis ring fusion. The stereochemistry of the ester appendage was difficult to unambiguously determine spectroscopically, but was assigned on the basis of X-ray crystallographic analysis of compound **5aA** (Figure 2).[10] The stereochemistry observed can be explained by accepting that the cycloaddition proceeds through an ylide with S-shaped geometry (see Scheme 2).

With the pyrrolidino[2′,3′:3,4]pyrrolidino[1,2-*a*]benzimidazole-2-carboxylates in hand, attention was focused on building a library of carboxamide derivatives. Direct ester → amide conversion from **5aA** was tested with 2-(4-methoxyphenyl)ethanamine in EtOH at 60 °C overnight, but no reaction was observed. When 0.2 equiv of NaCN[11] was added to the reaction mixture and the reaction carried out under microwave irradiation at 160 °C for 40 min, the corresponding amide **7aA**{**1**} (note: *C*2 stereochemistry not determined for the product of this reaction) was obtained but in only 14% yield.

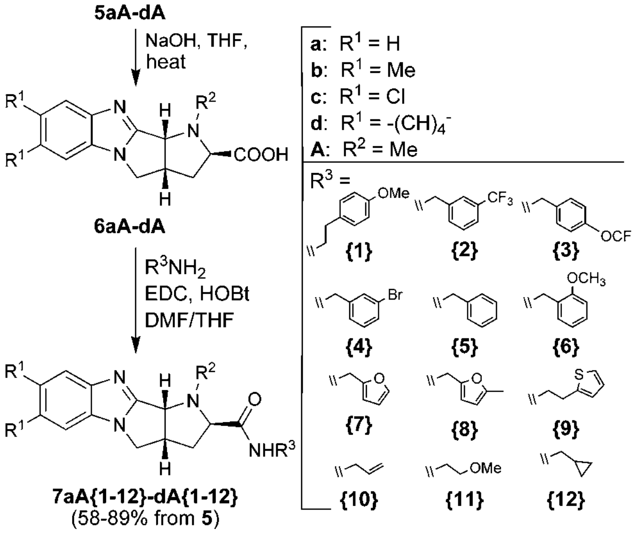


5aA

Figure 2. X-ray crystallographic structures of ester **5aA**.

As detailed in Scheme 3, a satisfactory yield of amide **7aA**{**1**} (78%) was achieved by EDC-mediated coupling of carboxylic acid **6aA**, which was quantitatively obtained by saponification of ester **5aA**. The solution phase array synthesis of pyrrolidino[2′,3′:3,4]pyrrolidino[1,2-*a*]benzimidazole-2-carboxamides by the EDC-mediated coupling of carboxylic acids **6aA**−**dA** with 12 commercially available amines gave 48 carboxamides (**7a**−**dA**{**1**−**12**}). The *C*2 amide stereochemistry was established by X-ray crystallographic analysis of **7aA**{**1**} (Figure 3),[10] which confirmed that the *C*2 stereochemistry was retained throughout the **5** → **6** → **7** sequence.

Scheme 3. Polycyclic Pyrrolidine Library Preparation



In summary, we have shown that the microwave-assisted intramolecular 1,3-dipolar cycloaddition of benzimidazole-tethered azomethine ylide and allyl reaction partners occurs

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(8) Dimer formation occurs when the azomethine ylide undergoes an intermolecular addition to its precursor aldehyde to form 3-(substituted)-oxazolidine-4-carboxylates as a complex mixture of regio- and stereoisomers. See: (a) Brome, V. A.; Harwood, L. M.; Osborn, H. M. I. *Can. J. Chem.* **2006**, *84*, 1448. (b) Aldous, D. J.; Drew, M. G. B.; Draffin, W. N.; Hamelin, E. M.-N.; Harwood, L. M.; Thurairatnam, S. *Synthesis* **2005**, 3271. (c) Travnicek, M.; Potacek, M. *ARKIVOC* (*Gainesville, FL, U.S.*) **2001**, 156. (d) Rudas, M.; Fejes, I.; Nyerges, M.; Szollosy, A.; Toke, L.; Groundwater, P. W. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1167. (e) Felluga, F.; Pitacco, G.; Visintin, C.; Valentin, E. *Helv. Chim. Acta* **1997**, *80*, 1457. (f) Kanemasa, S.; Sakamoto, K.; Tsuge, O. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1960.

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(10) Crystal structures have been deposited at the Cambridge Crystallographic Data Centre and allocated the following deposition numbers: CCDC 661436 for **5aA** and CCDC 661435 for **7aA**{**1**}.

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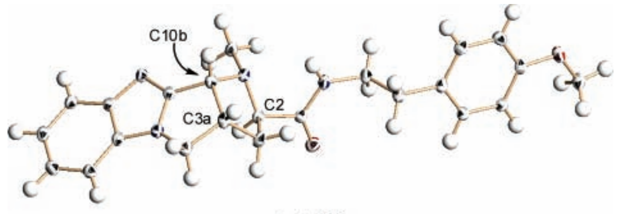

7aA{1}

Figure 3. X-ray crystallographic structures of amide **7aA**{**1**}.

via an S-shaped ylide with high regio- and stereoselectivity to provided an efficient synthesis of the diastereopure, fused pyrrolidine ring system **5**. In addition, a route to a pyrrolidino[2′,3′:3,4]pyrrolidino[1,2-*a*]benzimidazole-2-carboxamide library using a solution-phase array strategy has been developed. The resulting polycyclic pyrrolidine library, with its members containing diverse and medicinally relevant pharmacophores, will be available for academia to identify potential drug candidates through the NIGMS high-throughput biological screening program.

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Supporting Information Available: Experimental procedures and characterization data for all intermediates and selected library members. This material is available free of charge via the Internet at http://pubs.acs.org.

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