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Multicomponent Synthesis of Diverse 1,4-Benzodiazepine Scaffolds

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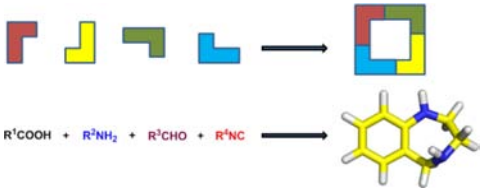
ABSTRACT



The 1,4-benzodiazepine (BDZ) scaffold is of particular interest in drug design due to a balanced ensemble of beneficial physicochemical properties including a semirigid and compact diazepine ring with spatial placements of several substituents, combined with low number of rotatable bonds, hydrogen bond donors and acceptors, and intermediate lipophilicity. As an alternative to traditional multistep sequential syntheses, we designed routes employing one-pot MCRs to accelerate access diverse BDZ scaffolds in two or three steps.

Library design and synthesis is becoming more and more important as the pharmaceutical industry is realizing that currently available compounds cover not even a glimpse of the chemical space of drug-like compounds. It is well documented that current screening libraries are made for historic targets and rather unsuitable for new target classes which emerged from the human genome project. Examples of such a difficult to target class are protein protein interactions or nuclear hormone receptors. Whereas many of these targets are cellular and biochemically validated, missing medicinal chemistry starting points make them useless for drug discovery. 1,4-Benzodiazepines are a family of drugs that are used to relieve insomnia and anxiety, as well as to treat muscles spasm and prevent seizures.[1] Over 40 medications highlight BDZ as a classic privileged structure with a broad range of therapeutic treatments, particularly for the central nervous system.[2] Since the BDZ scaffold is of particular interest for drug discovery, many synthetic derivatives with a wide pharmacological spectrum have been extensively developed.[3] However, the biological activity is highly dependent on the nature of the BDZ scaffold including the conformation of the 1,4-diazepine ring and its substituents, the propensity of hydrogen bond donor and acceptor, and the electrostatic profile.[4] Consequently, the development of expedient synthetic approaches to access new BDZ scaffolds have attracted considerable attention in the discovery of biologically active compounds.[5]

Multicomponent reaction (MCR) chemistry serves as a unique and versatile synthetic toolbox to access a range of highly substituted heterocyclic systems in a convergent manner.[6] Traditionally, substituted BDZs were often accessed by constitute linear syntheses, which limited the efficiency and diversity to build combinatorial libraries of varying sizes and properties.[7] In recent years, isocyanide-based

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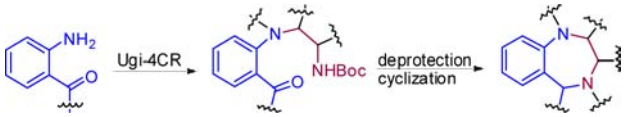
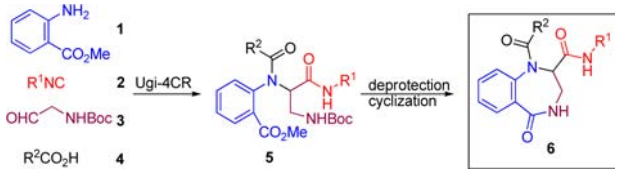
MCRs (IMCR) have been proven to be a promising strategy to access large chemical space of BDZs.[8] As part of our ongoing interest in the efficient discovery of biologically active compounds,[9] we herein report the design of diverse BDZ scaffolds via Ugi four-component reactions (Ugi-4CR) and postcondensation modifications (Scheme 1).

Scheme 1. General Strategy for the Design of Novel BDZ Scaffolds by Employing Bifunctional Orthogonal Starting Materials in the Ugi-4CR and Subsequent Intramolecular Cyclization



N-Boc-α-amino-aldehydes have been demonstrated to be suitable bifunctional starting materials for IMCR.[10] Hulme and others utilized the Ugi reaction with *N*-Boc-α-amino-aldehydes for a solution phase synthesis of an array of biologically relevant imidazolines and azepine-tetrazoles.[10,11] Thus, we envisioned novel applications of Boc-glycinal in the Ugi-4CR for the synthesis of BDZs utilizing the Ugi-deprotection-cyclization (UDC) strategy.[12] Taking advantages of the concise and powerful synthetic methodologies, this strategy is able to fulfill the drug discovery effort to access uncovered chemical space of BDZs. Anthranilic acid derivatives have been shown to react in the Ugi-4CR,[13] thus we proposed a synthetic route using methyl anthranilate **1** as the building block for the synthesis of the first of four 1,4-benzodiazepine scaffolds (Table 1). In the first step (Ugi), methyl anthranilate **1** serves as an amine component for the Ugi-4CR together with an isocyanide **2**, Boc-glycinal **3**, and a carboxylic acid **4**. The Boc protection group of **5** is cleaved in the second step (deprotection), and then the free amine group is condensed with the orthogonal ester group to form the 1,4-diazepine ring in the third step (cyclization) (Scheme 2). The UDC strategy allows the access of 1,4-benzodiazepine-6-ones **6a**–**f** with different substitutions derived from the isocyanide and carboxylic acid inputs (Table 1).

Table 1. Ugi-4CR Route to 1,4-Benzodiazepine-6-ones **6a**–**f**



ID	R^1	R^2	yields[a,b]
6a	^{t}Bu	Me	41%
6b	^{t}Bu	cyclohexyl	28%
6c	mesityl	Me	16%
6d	^{t}Bu	^{n}Pr	20%
6e	^{t}Bu	cyclopropenyl	38%
6f	^{t}Bu	*p*-F-C_6H_4	22%

[a] isolated yields (over three steps). [b] Method A: (i) MeOH, rt, 2 days; (ii) DCM (10% TFA), rt, 2 days; (iii) THF, Et_3N, triazabicyclodecene (TBD), 40 °C, overnight.

Aminophenylketones are commonly employed building blocks for the synthesis of BDZ scaffolds.[14] Since aminophenylketones have shown good reactivity in MCRs as an amine component,[15] we designed a new UDC strategy for the rapid access of the second 1,4-benzodiazepine scaffold starting from aminophenylketones. Initially, aminophenylketones **7** serve as an amine component for the Ugi-4CR with an isocyanide **2**, Boc-glycinal **3**, and a carboxylic acid **4**. Microwave irradiation was utilized for the Ugi-4CR to reduce the reaction time.[16] In most cases, microwave was applied when the Ugi product was not able to be isolated under the convential condition. In the second step, the deprotected amino group is immediately cyclized with the ketone functionality to form 1,4-diazepine ring. A small focused library of 1,4-benzodiazepines **9a**–**h** with four points of diversity was obtained using this convenient method (Table 2).

Encouraged by the previous results, the UDC strategy was further applied for the synthesis of the third 1,4-benzodiazepine scaffold. In the first step, aminophenylketones **7** serve as an amine component for the Ugi-4CR with an isocyanide **2**, Boc-glycinal **3**, and trimethyl azide **10**. Microwave assisted Ugi-4CRs proceeded in a reaction time of only 30 min compared to the conventional methodology which required up to 48 h. In the second step, the deprotected amino group immediately cyclizes with the ketone functionality to form a 1,4-diazepine ring. A group

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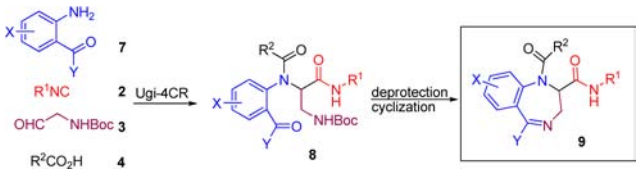
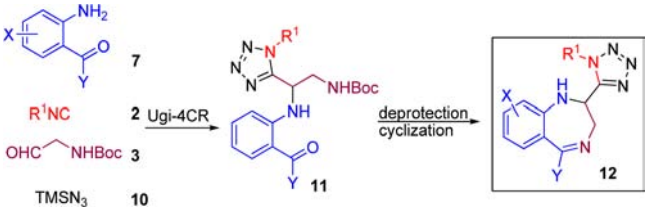
Table 2. Ugi-4CR Route to 1,4-Benzodiazepines **9a**–**h**



ID	X	Y	R^1	R^2	yields[a]
9a	H	Ph	^{t}Bu	Me	47%[b]
9b	H	Ph	cyclohexyl	Me	36%[b]
9c	H	Me	cyclohexyl	Me	43%[b]
9d	H	Ph	Benzyl	Me	40%[c]
9e	4-Cl	Ph	^{t}Bu	CH_2OH	22%[c]
9f	4-Cl	Ph	^{t}Bu	^{n}Pr	24%[c]
9g	4-Cl	Ph	^{t}Bu	cyclobutyl	25%[c]
9h	4-Cl	*o*–Cl-C_6H_4	benzyl	Me	13%[c]

[a] isolated yields (over two steps). [b] Method B: (i) MeOH, rt, 2 days; (ii) DCE (10% TFA), 40 °C, overnight. [c] Method C: (i) MeOH, microwave irradiation (100 °C, 30 min); (ii) DCE (10% TFA), 40 °C, overnight.

Table 3. Ugi-4CR Route to 2-Tetrazole Substituted 1,4-Benzodiazepines **12a**–**f**



ID	X	Y	R^1	yields[a]
12a	H	Ph	^{t}Bu	29%[b]
12b	H	Ph	cyclohexyl	35%[b]
12c	H	Me	cyclohexyl	49%[b]
12d	4-Cl	Ph	^{t}Bu	32%[c]
12e	4-Cl	*o*–F-C_6H_4	benzyl	12%[c]
12f	H	Ph	benzyl	26%[c]

[a] isolated yields (over two steps). [b] Method D: (i) MeOH, rt, 2 days; (ii) DCE (10% TFA), 40 °C, overnight. [c] Method E: (i) MeOH, microwave irradiation (100 °C, 30 min); (ii) DCE (10% TFA), 40 °C, overnight.

of 2-tetrazole substituted 1,4-benzodiazepines **12a**–**f** with three points of diversity were obtained (Table 3).

The above two scaffolds **9** and **12** are unprecedented in the chemical literature, and scaffold **6** is accessible in an unprecedented convenient way. Thus they nicely underscore the ability of the Ugi-4CR to address unexplored drug-like chemical space. Methyl anthranilate and aminophenylketones were for the first time used as the building block for the synthesis of 1,4-benzodiazepine scaffolds via UDC strategy. In the course of our efforts to discover inhibitors of protein–protein interactions (PPI), we aim to generate small molecules tailored "anchors" (amino acid motifs deeply buried in PPI interfaces).[17] On the basis of this concept, we have successfully identified several peptidomimetic scaffolds derived from Ugi-4CR as p53-Mdm2 inhibitors.[18] Although Boc-glycinal was employed to access 1,4-benzodiazepines, the commercial availability of substituted α-amino-aldehyde derivatives is rather limited. Therefore, we further developed an alternative approach for the synthesis of BDZ scaffold with an additional point of diversity, which would introduce an "anchor" fragment to the diazepine ring.

N-Boc-amino acid is an ideal building block to introduce "anchor" fragments, which can be incorporated into drug-like compounds via MCRs.[19] Hence, we employed the UDC strategy to assemble the orthogonal building block *N*-Boc-amino acid for the synthesis of a BDZ scaffold. First, we developed a synthetic method to allow rapid access to 1,4-benzodiazepines in just two steps from Boc glycine. In the first step, aminophenylketones **7** serve as an amine component for the Ugi-4CR with an isocyanide **2**, Boc glycine **13**, and an aldehyde **14**. The crude Ugi products **15** were not isolated but immediately treated with TFA in 1,2-dichloroethane (DCE) to produce 1,4-benzodiazepines in a one-pot procedure. To our delight, 1,4-benzodiazepines **16a**–**f** with four points of diversity were isolated in reasonable to good yields (Table 4).

Table 4. Ugi-4CR Route to 1,4-Benzodiazepines **16a**–**f**

ID	X	Y	R^1	R^2	yields[a,b]
16a	H	Ph	^{t}Bu	^{i}Pr	38%
16b	H	Ph	^{t}Bu	H	47%
16c	H	Me	^{t}Bu	^{i}Pr	53%
16d	H	Me	^{t}Bu	H	66%
16e	4-Cl	Ph	cyclohexyl	H	33%
16f	H	Ph	cyclohexyl	H	42%

[a] isolated yields (over two steps). [b] Method F: (i) MeOH, rt, 2 days; (ii) DCE (10% TFA), 40 °C, overnight.

Subsequently, we initiated to test the feasibility for the synthesis of "anchor" biased compound libraries using *N*-Boc-amino acid derivatives. Phenylalanine, leucine, tryptophan and tyrosine, which are abundant in the protein–protein interaction interface, were selected as examples.

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N-Boc-amino acids **17** were subjected to the same protocol for the synthesis of 1,4-benzodiazepines **16a**–**f** with variable aminophenylketones and isocyanides. Compounds **20a**–**m** with four points of diversity were isolated by chromatography in 22–69% yield over two steps (Table 5). These examples further demonstrate the ease of synthesis and the increase in molecular complexity during the two-step one-pot procedure, which is remarkable for the efficient synthesis of 1,4-benzodiazepines containing a variety of "anchor" residues.

It has to be noted that the same scaffold **16** synthesized here in 2 steps is also accessible by the Ellman's method via a versatile solid phase synthesis of 1,4-benzodiazepines over seven steps.[20] Thus we have significantly improved the efficiency and diversity for the synthesis of new BDZs using a convergent Ugi-4CR followed by deprotection and intramolecular cyclization. These scaffolds can serve as novel chemotypes for the drug design efforts especially on less tractable targets, since the pseudopeptidic backbone of the 1,4-benzodiazepine and its derivatives have shown the potential to develop PPI inhibitors.[18a,21]

Finally we have created virtual libraries based on the herein described BDZ scaffolds. These virtual libraries are now part of the ~25 million MCR compound comprising database of recently initiated pharmacophore-based virtual screening platform AnchorQuery (http://anchorquery.ccbb.pitt.edu) for the discovery of PPI inhibitors.[22] In addition, 1000 randomly selected compounds of each scaffold were analyzed for drug likeness (Supporting Information, Figures S1–S8). Around 75% of these compounds pass at least 3 criteria of Lipinski's rule of five. Although a majority of these compounds have a molecular weight above 500 Da (mean MW: **6** = 553 ± 85 Da, **9** = 578 ± 62 Da, **12** = 463 ± 56 Da, **16** = 601 ± 71 Da), it has to be mentioned that our AnchorQuery libraries are targeted specifically for PPIs. The molecular weight of potential inhibitors will most likely need to be larger than compounds targeting classical protein pockets.[23] Work is ongoing to profile the herein described scaffolds and its chemical space for small molecule inhibitors of protein–protein interactions.

Table 5. Synthesis of Anchor-directed 1,4-Benzodiazepines **20a**–**m**

ID	X	Y	R^1	anchor	yields[a,b]
20a	H	Ph	^{t}Bu	Phe	41%
20b	H	Ph	^{t}Bu	Leu	41%
20c	H	Ph	cyclohexyl	Phe	50%
20d	H	Ph	cyclohexyl	Leu	69%
20e	H	Me	^{t}Bu	Phe	44%
20f	H	Me	^{t}Bu	Leu	46%
20g	4-Cl	Ph	^{t}Bu	Phe	32%
20h	4-Cl	Ph	^{t}Bu	Leu	43%
20i	H	Ph	^{t}Bu	Trp	26%
20j	H	Ph	^{t}Bu	Tyr	29%
20k	H	Ph	cyclohexyl	Trp	65%
20l	H	Ph	cyclohexyl	Tyr	60%
20m	H	Me	benzyl	Trp	22%

[a] isolated yields (over two steps). [b] Method F: (i) MeOH, rt, 2 days; (ii) DCE (10% TFA), 40 °C, overnight.

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Supporting Information Available. Experimental procedures including the synthesis and characterizations of small molecules, as well as the analysis of virtual libraries are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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