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General One-pot, Two-Step Protocol Accessing a Range of Novel Polycyclic Heterocycles with High Skeletal Diversity

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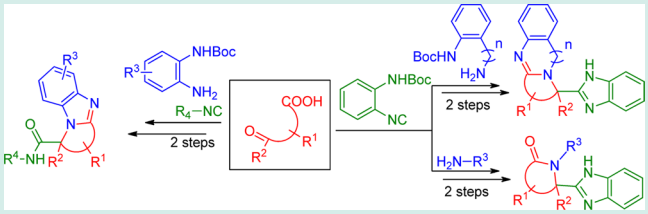
Supporting Information

ABSTRACT: An Ugi one-pot three-component four-center reaction was coupled with a subsequent acid mediated cyclodehydration step to furnish a multitude of unique scaffolds having in common an embedded or attached benzimidazole and often a ring system formed through lactamization. Using combinations of tethered Ugi inputs typically via tethered acid-ketone inputs and supporting reagents containing masked internal nucleophiles, such scaffolds were produced in good to excellent yields in an operationally friendly manner.



KEYWORDS: *postcondensation, Ugi reaction, benzimidazole, lactams, one-pot*

1. INTRODUCTION

The Ugi multicomponent reaction (MCR) and several closely related isocyanide based MCRs[1] are useful synthetic tools that are frequently applied in the drug design and development process.[2] The fact that the Ugi reaction utilizes four diversity reagents (acid, aldehyde, amine and isocyanide) in one-pot[3] makes it ideal for the high-throughput construction of chemical libraries.[4] Indeed, a key feature associated with such condensations is the process of tethering the diversity reagents in various combinations to generate new heterocyclic chemotypes.[5] In this context, the most commonly and successfully used tethered combination comprises an acid and ketone/aldehyde input[6] resulting in the formation of lactams of varying ring sizes which have widespread utility in disease modifying small molecules.[7] While exploring the potential of Ugi postcondensations, we have previously synthesized a number of novel scaffolds: benzodiazepines,[8] benzimidazoles,[9] ketopiperazines,[10] imidazoline-γ-lactams,[11] hydantoins[12] and quinazolines[13] to name a few.

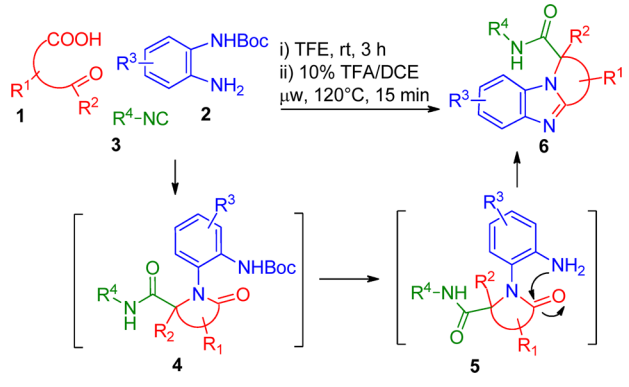
Herein, we report a postcondensation intramolecular-Ugi strategy that enables production of nitrogen-enriched polycyclic scaffolds endowed with benzimidazoles, lactams of various ring sizes, dihydroquinazolines and other moieties, coalesced within a single constrained molecular architecture. The range and average values of molecular weights (MW), polar surface areas (PSA) and clogP for all target molecules depicted in this article are as follows: [MW 255−399, av 340], [PSA 40−63 Å^2, av 47 Å^2], [clogP 1.1−5.1, av 4.0] and suggesting potential for high oral bioavailability and consequently interest from the file enhancement community. Indeed, there is a plethora of literature invoking the pharmacological relevance of benzimidazole scaffold.[14] Encouragingly, many of these compounds have been accepted by the Molecular Libraries Small Molecule Repository (MLSMR) for interrogation of targets of interest nation-wide.

2. RESULTS AND DISCUSSION

First studies were conducted employing the bifunctional reagent levulinic acid **1**{*1*} in combination with *N*-Boc-1,2-phenylenediamine **2**{*1*} and pentyl-isocyanide **3**{*1*} using trifluoroethanol (TFE) as solvent to enhance yields of the condensation product (Scheme 1).[15]

After monitoring the Ugi reaction by LCMS, the reaction was found to be complete in 3 h at room temperature affording **4**{*1,1,1*} (72% isolated yield). The Ugi product was subsequently dissolved in a 10% solution of trifluoroacetic

Scheme 1. Synthesis of α-Quaternized Benzimidazole-Carboxamides



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acid (TFA) in dichloroethane (DCE) and exposed to microwave irradiation at 120 °C for 15 min. As such, these conditions promoted an amino-cyclodehydration to render the tricyclic scaffold **6**{*1,1,1*} containing a valuable α-quaternary methyl group (70% isolated yield, 50% for two steps), Scheme 1.

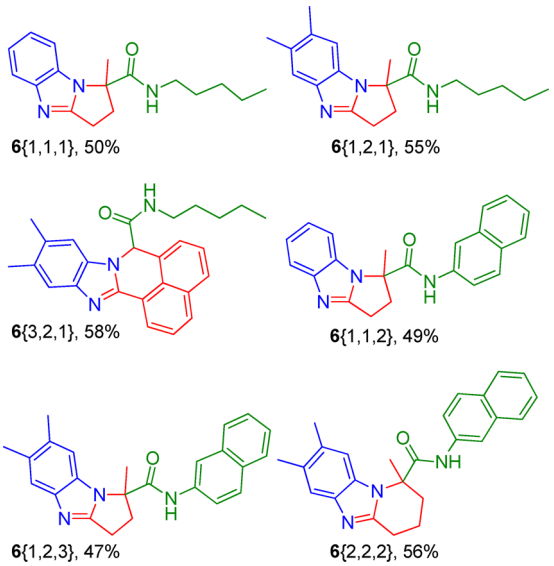


Figure 1. Products **6**{*1,1,1*} through **6**{*2,2,2*}.

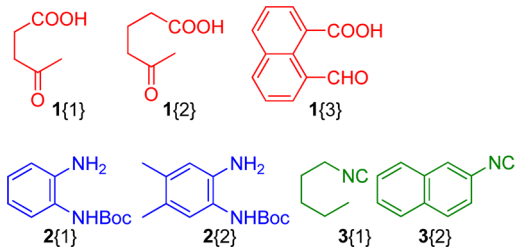


Figure 2. Employed diversity reagents, **1**, **2**, and **3**.

Heating the reaction mixture for shorter times or at lower temperatures resulted in only partial product formation with the amine **5**{*1,1,1*} being the major product. With this robust protocol in-hand, six congeners (**6**{*1,1,1*} through **6**{*2,2,2*}) were produced in up to 58% yields for the two overall steps, Figure 1. The comparable yields demonstrate the generic nature of the reaction with no apparent preference for aldehyde-acids over keto-acids or selected tethers under these expedited conditions. These findings prompted us to apply the procedure to aid formation of the chemically more complex scaffolds of generic formulas **9**, Scheme 2. Thus, isocyanide **3** (2-(*N*-Boc-amino)-phenyl-isocyanide) was prepared from *N*-Boc-1,2-phenylenediamine using standard methodology[16] and treated with tethered acids (**1**{*1*}−**1**{*7*}) and various amines (**2**{*1*}−**2**{*6*}) (Figure 4) to form the Ugi adducts of generic structure **7**. Exposure of the adducts **7** to the conditions used to promote cyclization in Scheme 2, successfully afforded a range of bis-heterocyclic scaffolds **9** in overall isolated yields of up to 64% (over two steps), Figure 3.

The developed process was then employed with amines carrying a second masked internal nucleophile (**2**{*1*} and **2**{*2*}), isocyanide **3** and tethered bifunctional reagents, **1**{*1*} through **1**{*4*} (Figure 6, Scheme 3). As expected, intramolecular Ugi reactions performed well and gratifyingly subsequent acid treatment of the Ugi adducts (**10**) and microwave irradiation afforded products **12** in excellent yields in a mere two synthetic operations, Figure 5.

Considering the medicinal potential of quinazolines embedded with benzimidazoles, scaffolds of generic structure **12** could be particularly interesting since the calculated values for bioavailabilty criteria fall well within the ideal ranges. Definitive structural elucidation of products **9**{*4,4*} and **12**{*1,2*} was confirmed by X-ray crystallographic analysis, Figure 7.

3. CONCLUSIONS

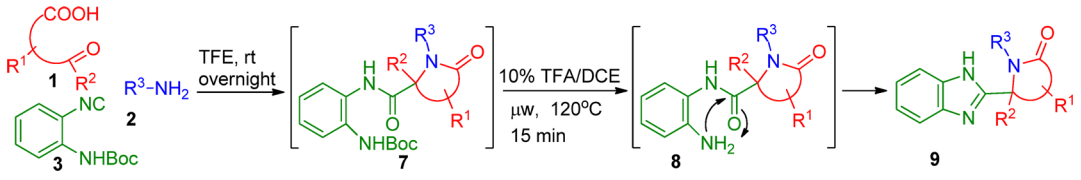
A range of tethered keto-acids or aldehyde acids were successfully employed in intramolecular ring forming Ugi reactions, followed by either one or two consecutive amino-cyclodehydrations to afford a range of unique scaffolds with excellent physicochemical properties in a general one pot, two step protocol. These concise routes coupled with attractive final products represent an excellent file enhancement opportunity delivering potential libraries of high "skeletal diversity" with "lead-like" properties.

4. EXPERIMENTAL PROCEDURES

General Procedure for the Preparation of Benzotetrazolodiazepinones 6. Using 8 mL microwave vial equipped with a magnetic stirring bar, a solution of 0.25 mmol of keto- or formyl acid (**1**) and 0.25 mmol of *N*-Boc-diamine (**2**) in 0.7 mL of trifluoroethanol (TFE) was stirred for a few minutes at room temperature followed by the addition of isocyanide (**3**) (0.25 mmol). The progress of the reaction was monitored using LCMS and completion of the Ugi reaction was observed after 3 h stirring. The reaction mixture was concentrated using a nitrogen flush and ∼2 mL of 10% (v/v) trifluoroacetic acid (TFA) in dichloroethane (DCE) were added. The reaction was heated in a CEM microwave at 120 °C for 15 min. After cooling the reaction mixture to room temperature, it was directly loaded on a CombiFlash R_f system (silica gel) and using a gradient of ethyl acetate/hexane (0−100%) followed by methanol/ethyl acetate (0 to 20%) the product **6** was purified.

General Procedure for Compounds 9. The same procedure as for compounds **6**, was used for this series of compounds with the following exceptions: reactions were conducted at 0.5 mmol scale in 3 mL of solvent (TFE) and after the deprotection/cyclization stage, purification was done

Scheme 2. Generic Scheme for the Synthesis of Polycyclic Scaffolds 9



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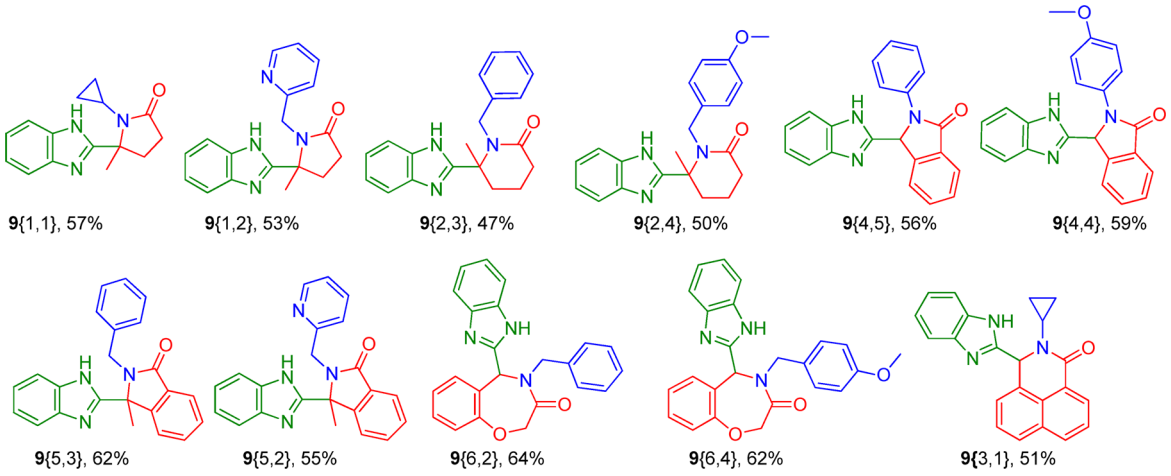


Figure 3. Products **9**{*1,1*} through **9**{*3,1*} derived from Scheme 2.

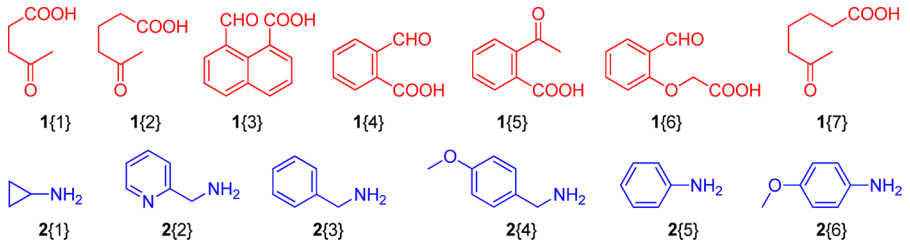
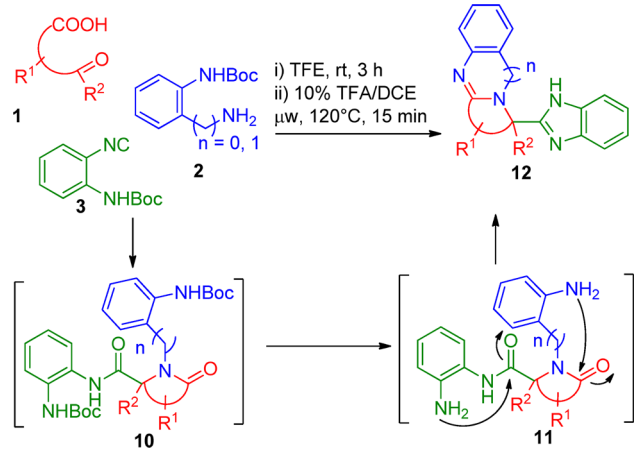


Figure 4. Employed diversity reagents, **1** and **2** in Scheme 2.

Scheme 3. Synthesis of Polycyclic Scaffolds 12



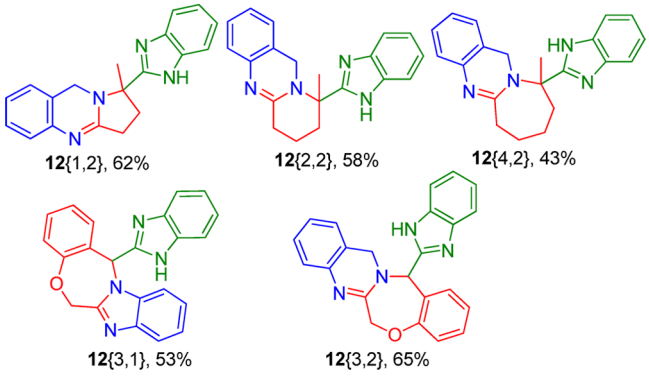


Figure 5. Products **12**{*1,2*} through **12**{*3,2*} derived from Scheme 3.

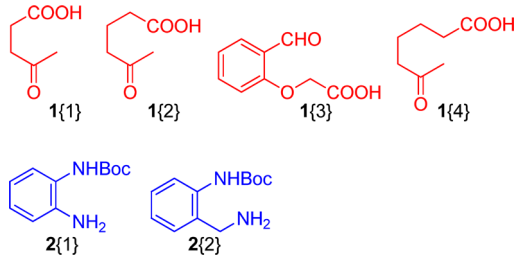


Figure 6. Employed diversity reagents, **1** and **2** in Scheme 3.

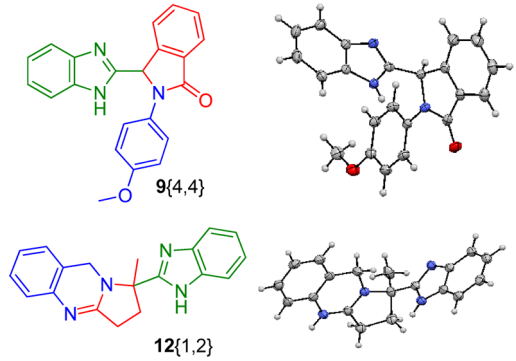


Figure 7. X-rays structures of compound **9**{*4,4*} and **12**{*1,2*}.

on a CombiFlash R_f system (silica gel) using a gradient of ethyl acetate/hexane (0−100%).

General Procedure for Compounds 12. Exactly the same procedure (as for **9**) was employed for the preparation and purification of compounds **12**.

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■ ASSOCIATED CONTENT

Supporting Information

Supporting Information including all experimental procedures, CIF files for compounds **9**{*4,4*} and **12**{*1,2*} and characterization data for all the compounds are available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

MCR, multicomponent reaction; TFE, trifluoroethanol; TFA, trifluoroacetic acid; MLSMR, molecular libraries small molecule repository; BOC, tertiary butoxy carbonyl; DCE, dichloromethane

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