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

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Abstract

An Ugi one-pot three-component 4-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

post-condensation; Ugi reaction; benzimidazole; lactams; one-pot

1. INTRODUCTION

The Ugi multi-component 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 features 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 post-condensations, 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 post-condensation 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

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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.

The Authors declare no competing financial interest.

surface areas (PSA) and clogP for all target molecules depicted in this article are as follows: [MW 255 to 399, av. 340], [PSA 40 to 63 $Å^2$, av. 47$Å^2$], [clogP 1.1 to 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 bi-functional 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 acid (TFA) in dichloroethane (DCE) and exposed to microwave irradiation at 120°C for 15 minutes. 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.

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 inhand, 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 formulae **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} to **1**{7}) and various amines (**2**{1} to **2**{6}) 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} (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 minutes. After cooling the reaction mixture to room temperature, it was directly loaded on a Combi*Flash* R_f system (silica gel) and using a gradient of ethyl acetate/ hexane (0 to 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 on a Combi*Flash* R_f system (silica gel) using a gradient of ethyl acetate/hexane (0 to 100%).

General Procedure for Compounds 12

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

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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ABBREVIATIONS

MCR	multi-component reaction
TFE	trifluoroethanol
TFA	trifluoroacetic acid
MLSMR	molecular libraries small molecule repository
BOC	tertiary butoxy carbonyl
DCE	dichloromethane.

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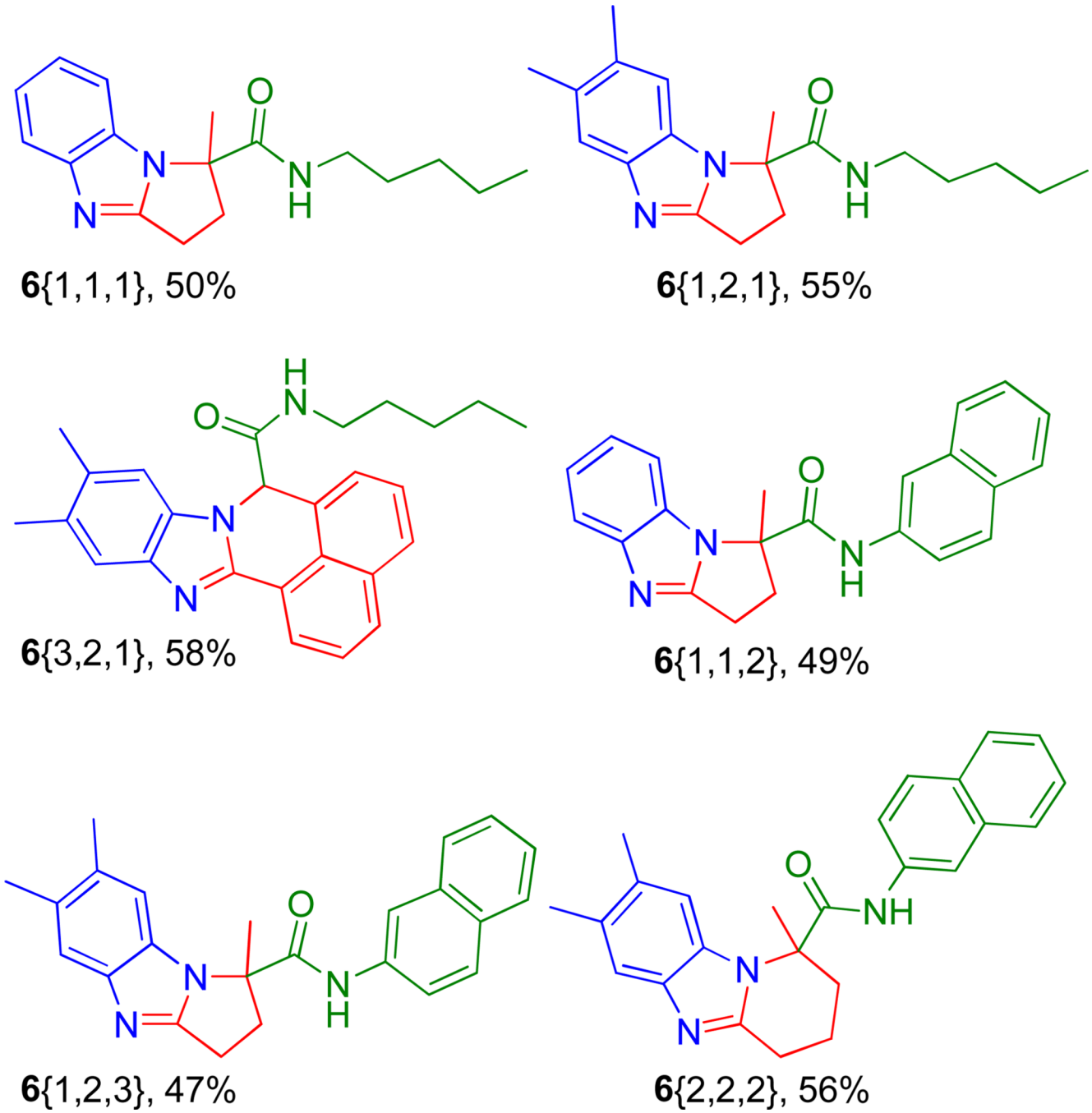


Figure 1.
Products **6**{1,1,1} through **6**{2,2,2}

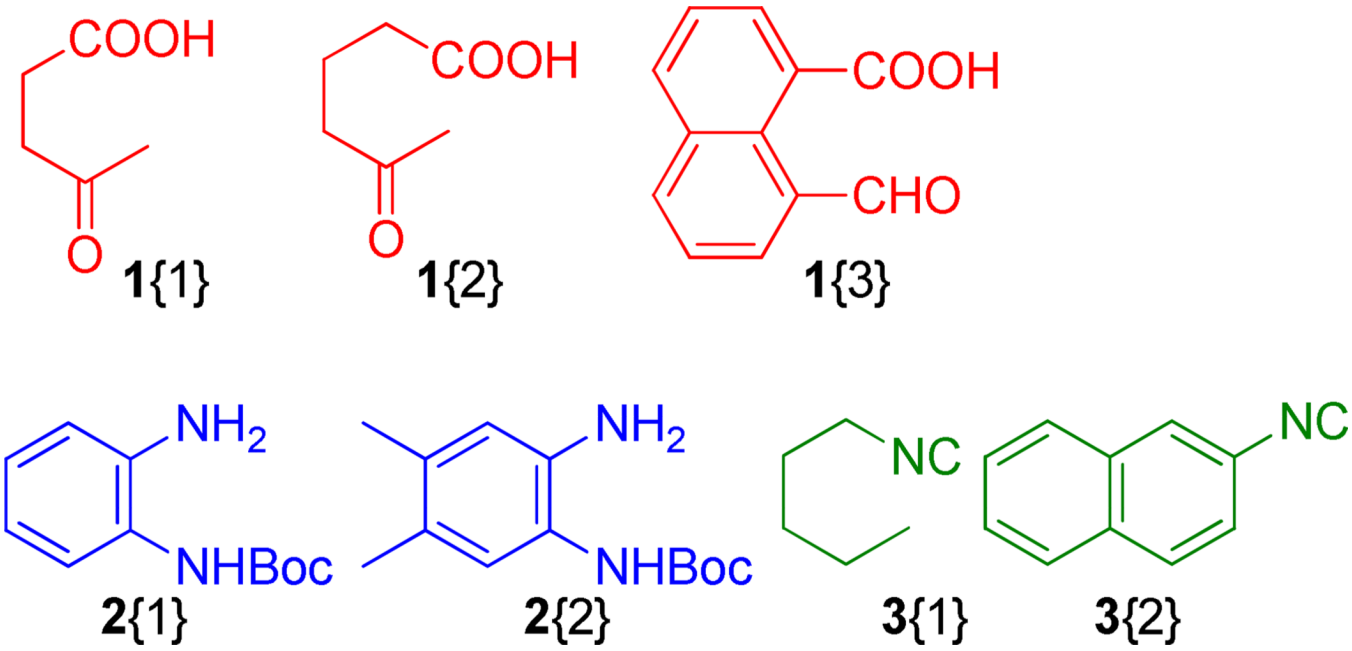


Figure 2.
Employed diversity reagents, **1, 2** and **3**.

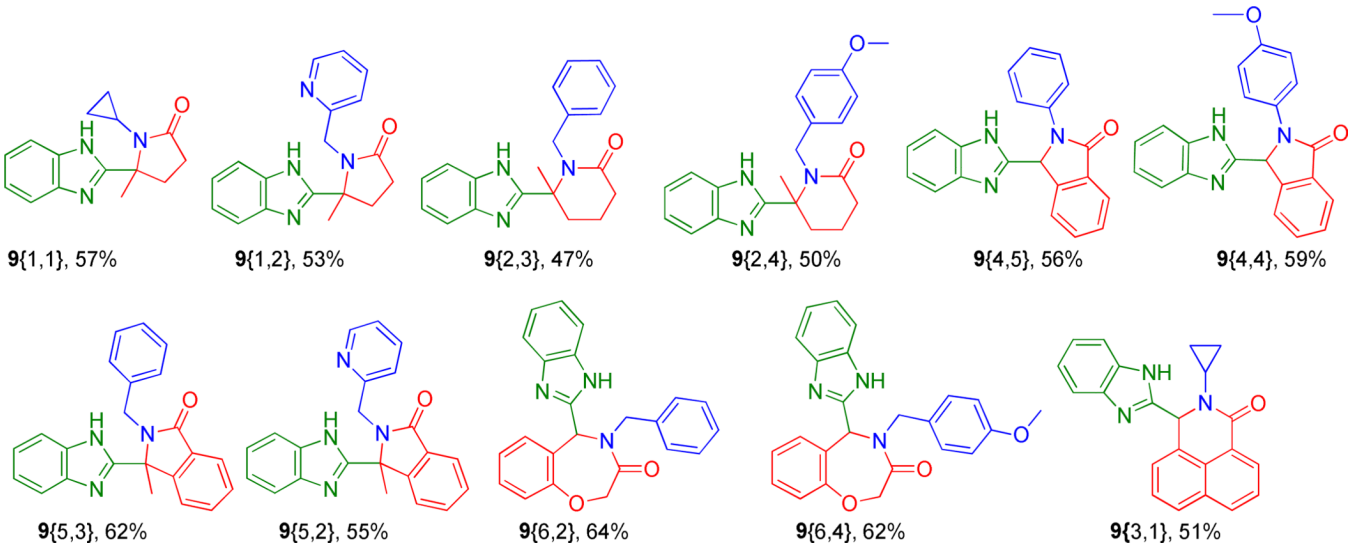


Figure 3.
Products **9**{1,1} through **9**{3,1}

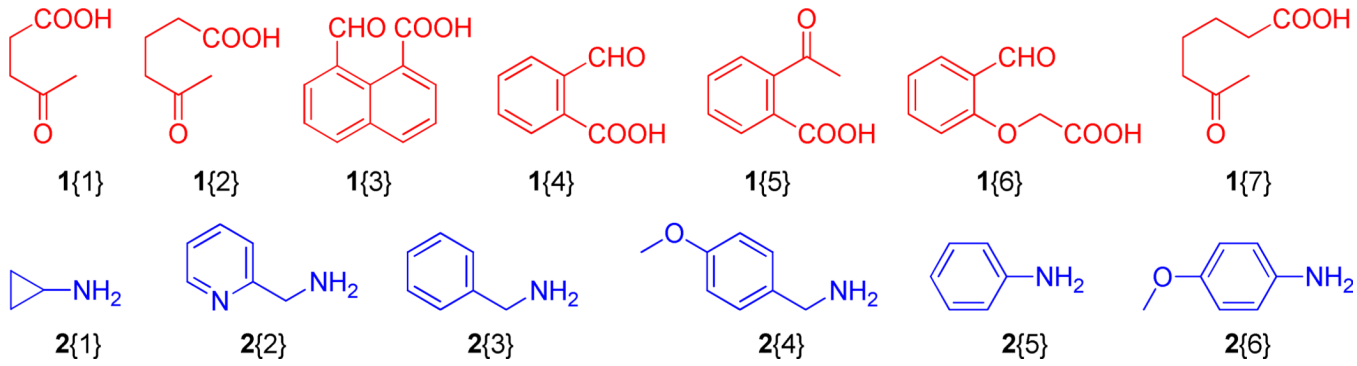


Figure 4.
Employed diversity reagents, **1** and **2**

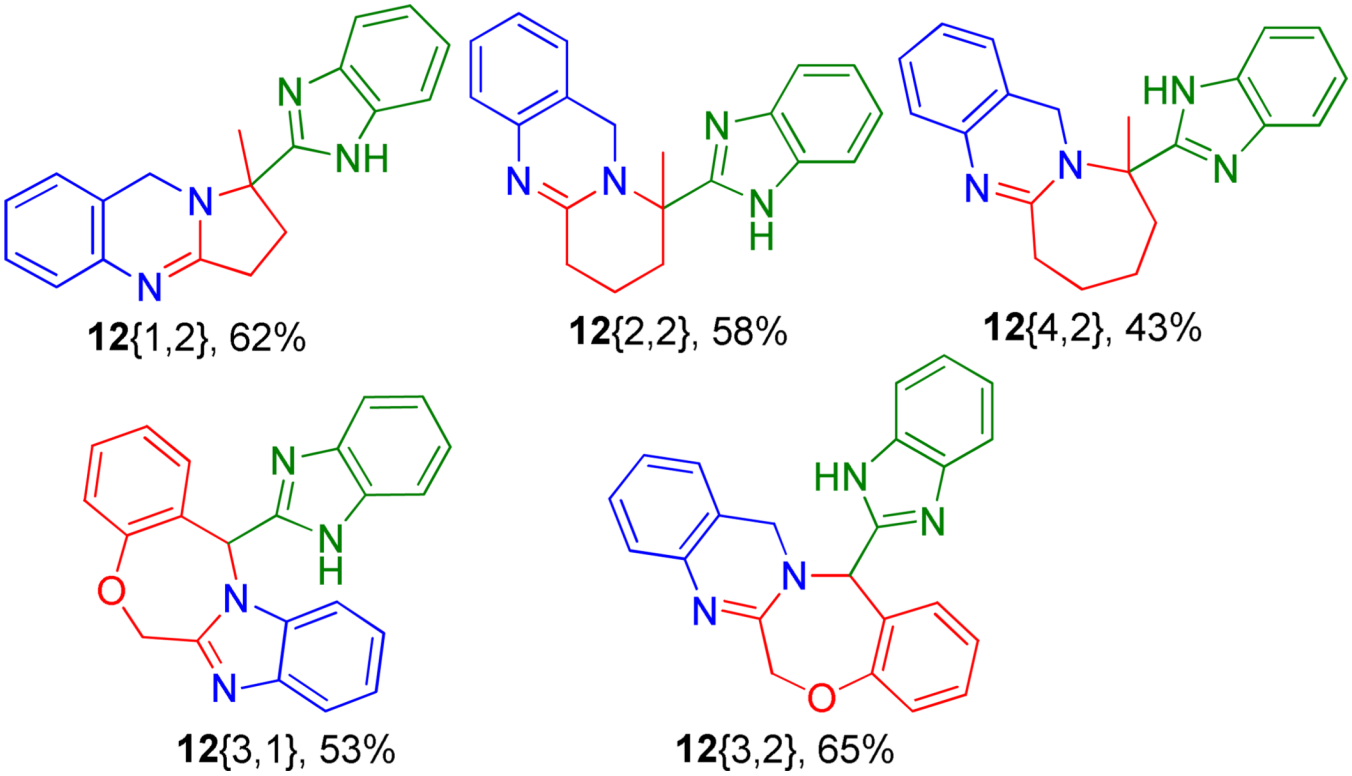


Figure 5.
Products **12**{1,2} through **12**{3,2}

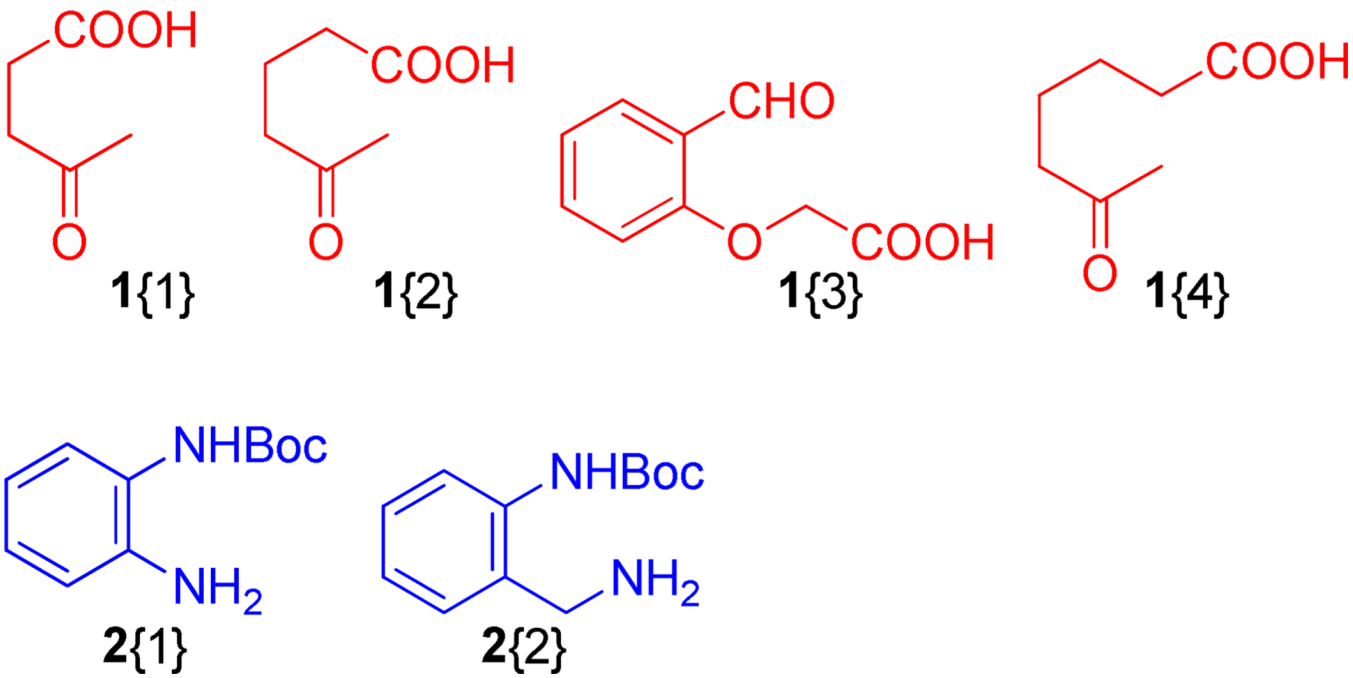


Figure 6.
Employed diversity reagents, **1** and **2**

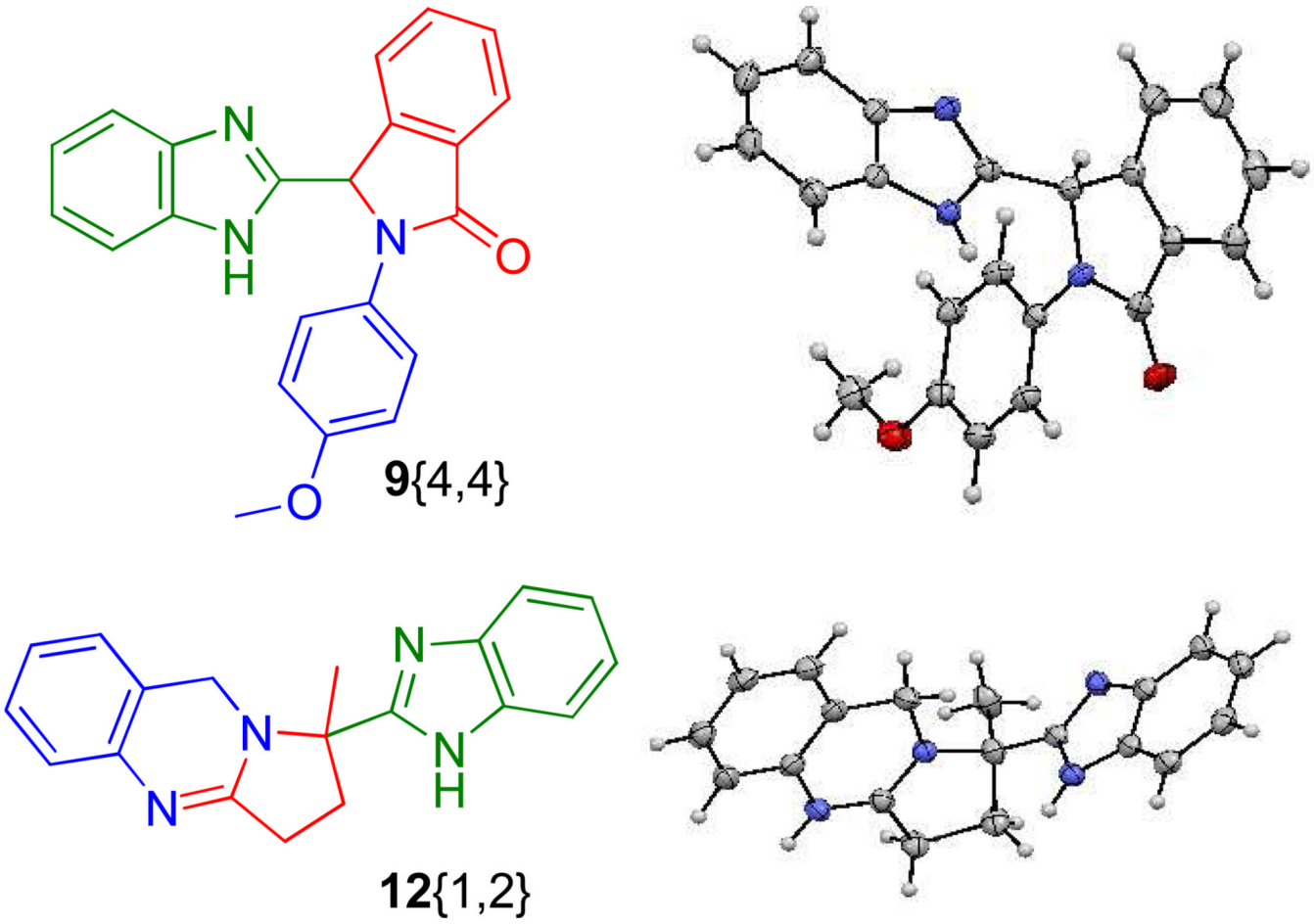
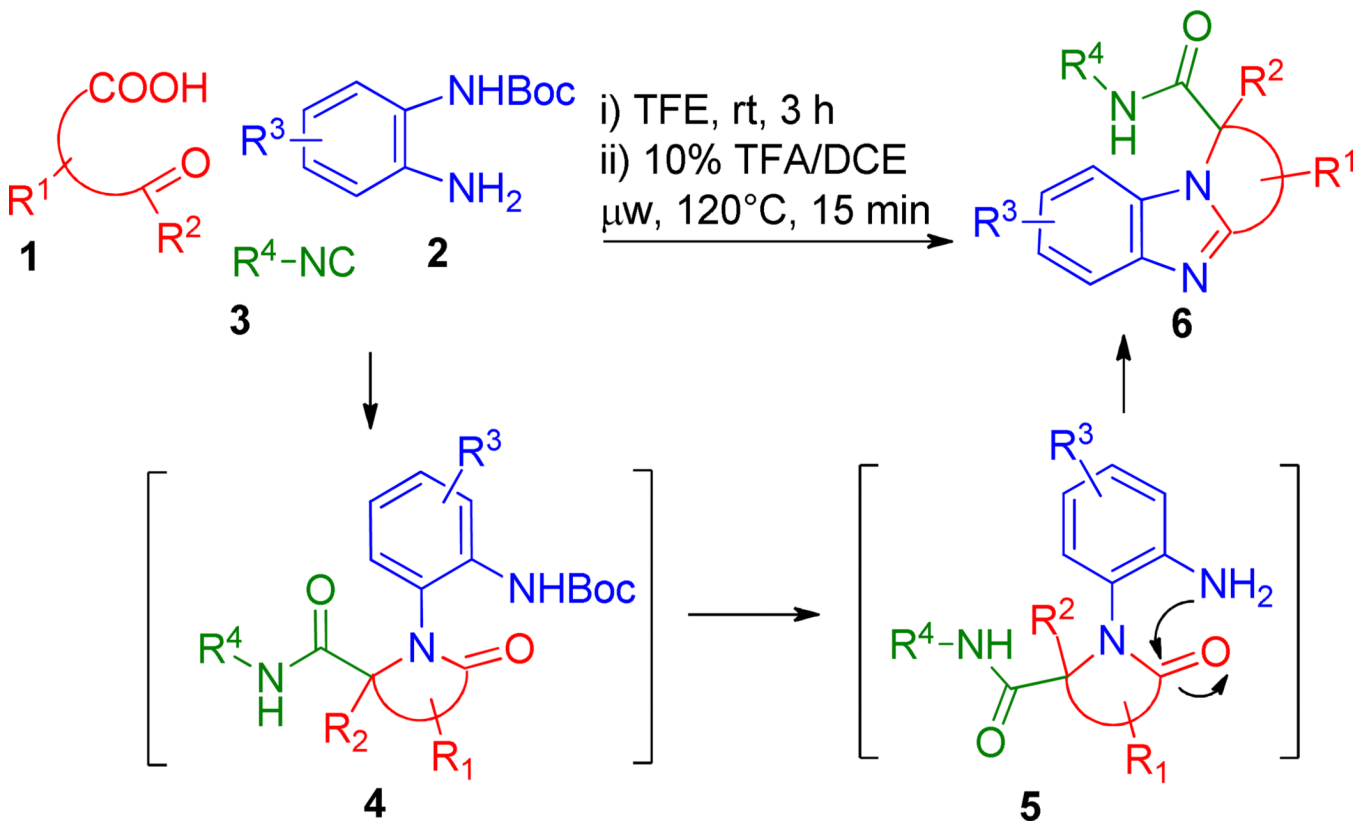
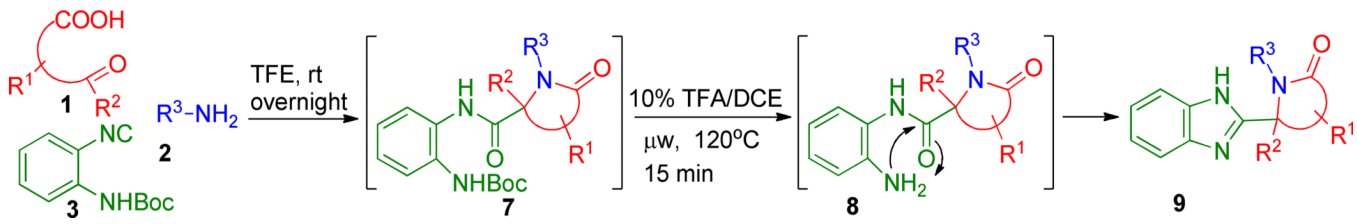


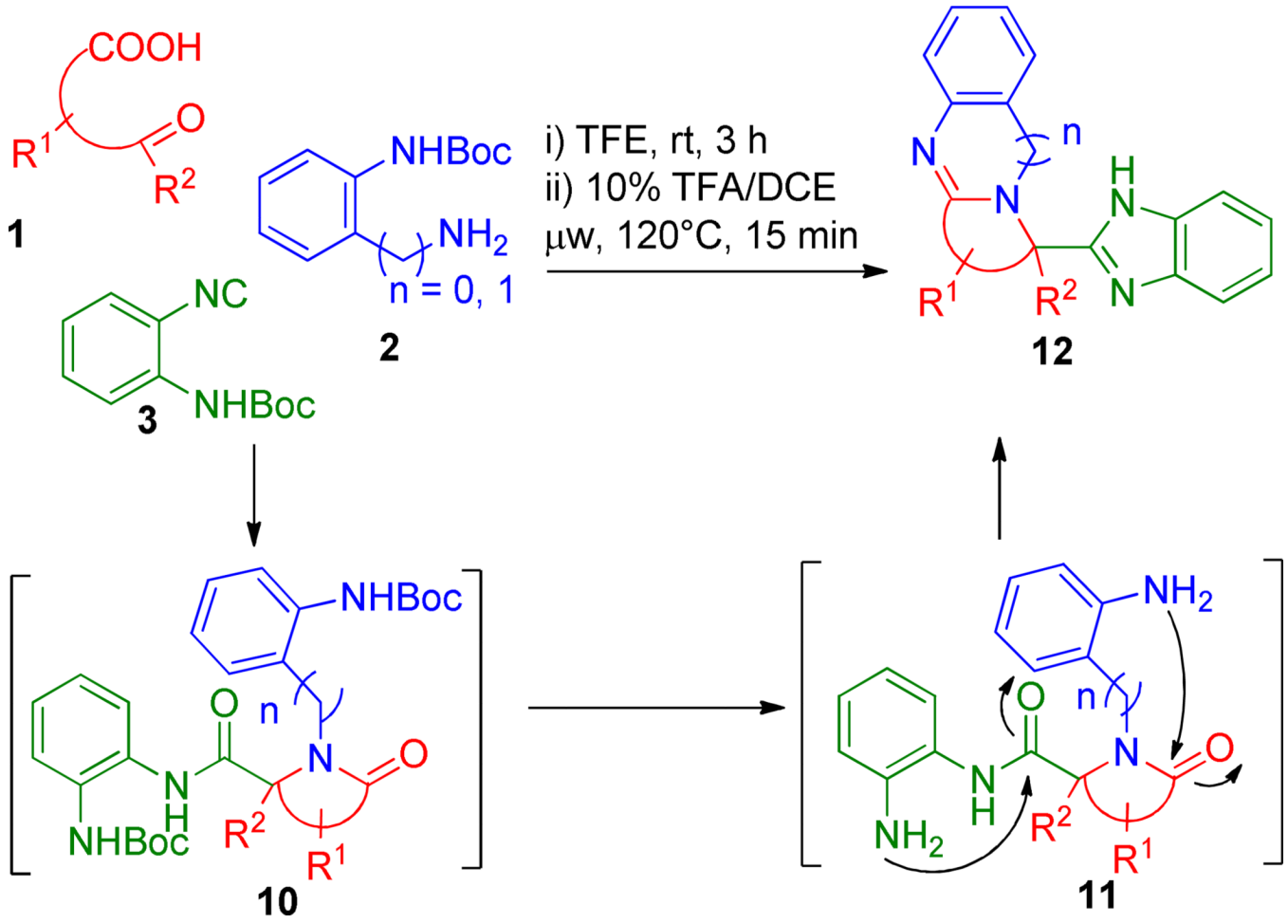
Figure 7.
X-rays structures of compound **9**{4,4} and **12**{1,2}



Scheme 1.
Synthesis of α-quaternized benzimidazole-carboxamides



Scheme 2.
Generic scheme for the synthesis of polycyclic scaffolds **9**



Scheme 3.
Synthesis of polycyclic scaffolds **12**