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Research Article

Scaffolding-Induced Property Modulation of Chemical Space

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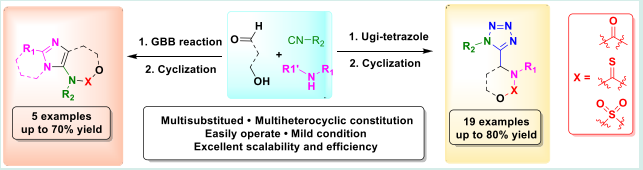
ABSTRACT: Physicochemical property switching of chemical space is of great importance for optimization of compounds, for example, for biological activity. Cyclization is a key method to control 3D and other properties. A two-step approach, which involves a multicomponent reaction followed by cyclization, is reported to achieve the transition from basic moieties to charge neutral cyclic derivatives. A series of multisubstituted oxazolidinones, oxazinanones, and oxazepanones as well as their thio and sulfur derivatives are synthesized from readily available building blocks with mild conditions and high yields. Like a few other methods, MCR and cyclization allow for the collective transformation of a large chemical space into a related one with different properties.



KEYWORDS: *multicomponent reaction, cyclic carbamate, Ugi reaction, cyclization, tetrazole, scaffold diversity*

INTRODUCTION

The property design of organic compounds is of uttermost importance during the process of optimization to obtain compounds with perfect performance. Properties such as charges or neutrality and 3D distribution of lipophilic or hydrogen donor/acceptor moieties are introduced into molecules by an often lengthy, stepwise, and sequential pathway. The principles of multicomponent reaction chemistry (MCR) allow for an orthogonally different approach.[1] In an intellectually and operationally easy building block approach, complex molecules are assembled in one step from a very large number of available building blocks.[2−5] Among, the most commonly used derivatizations are cyclizations, which often change the properties dramatically. In the context of medicinal chemistry, cyclizations are often introduced to rigidify and generate a conformation similar to the receptor-bound structure and also to modify druglike properties such as stability to metabolism or increasing permeability.[6] By overlapping the 3D structure of cyclic and noncyclic compounds, stabilization via cyclization and a shift of the terminal moiety were observed (Figure 1A). While the number of primary MCRs with useful synthetic properties such as great scope, ease of performance and large number of building blocks (and thus chemical space) is limited, the number of secondary transformations and especially cyclizations is infinite. Hulme and others introduced the very useful concept of UDC (Ugi-deprotection-cyclization) resulting in Epelsiban and Retosiban, which are currently being tested in advanced clinical trials.[7,8]

Carbamate containing heterocycles are abundantly present as dominant moieties in a number of valuable chemicals and therapeutic agents in modern drug discovery and material science development.[9] Cyclic carbamate moieties not only are

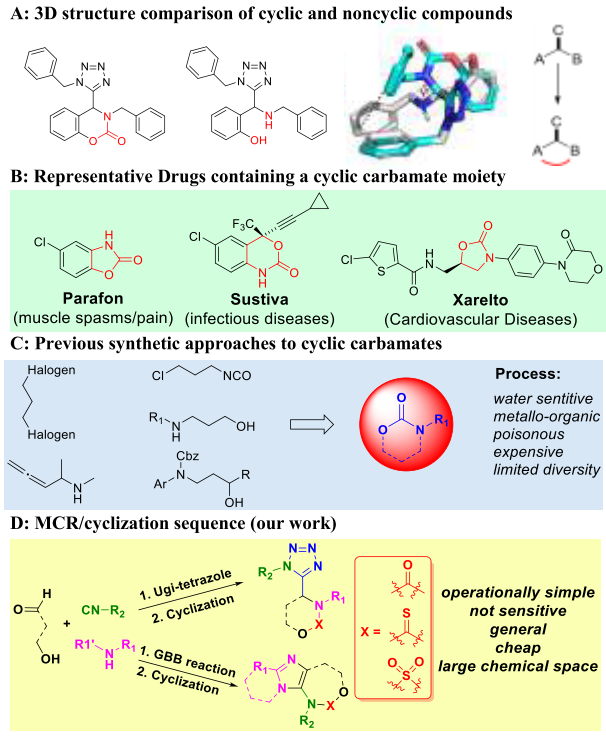


Figure 1. Cyclization strategies in chemistry.

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present in many drugs (Figure 1B) but also play important roles in several chemical processes such as chiral auxiliaries[10,11] and in the preparation of hyperbranched polymers.[12,13] In particular, 6-membered (2-oxazinanone) cyclic carbamates have cumulatively been regarded as privileged scaffolds in drug discovery due to excellent chemical stability and cell membrane permeability. Owing to the prominent medicinal and industrial applicability of cyclic carbamates, various synthetic routes have been exploited (Figure 1C).[14] The classical approaches generally involve either phosgene and its derivatives,[15,16] alkyl halide chemistry,[17] or sacrificial reagents,[18] such as urea and organic carbonates. Shortly afterward, several other synthetic approaches have been developed to supersede these dissipative, costly, and environmentally hazardous methods. Nevertheless, the following reactions confront various defects, for instance, harsh reaction conditions (0 °C or heating),[19] catalyst requirement,[20] difficult to access starting materials,[21,22] long reaction time,[23] multiple steps,[24] low yields,[25] and limited scope.[26]

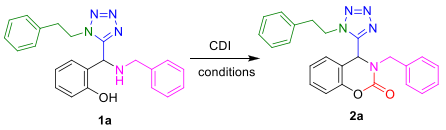
Our strategy for a cyclization-induced property change based on MCR chemistry was to use bifunctional orthogonal amino and hydroxyl aldehydes in specific variants of the Ugi reaction, GBB-3CR and UT-4CR, followed by a secondary cyclization on the intermediates to yield (thio) carbamates, ureas, and amino sulfonic acid esters of 6- and 7-membered ring size (Figure 1D).

RESULTS AND DISCUSSION

The azido-Ugi product **1a**, which features a secondary amine, was chosen as the model substrate to verify this hypothesis. Salicylaldehyde was selected in this azido-Ugi reaction as the supplier of the free hydroxyl group. 1,1′-Carbonyldiimidazole (CDI) is a coupling reagent mainly used for the synthesis of amides, peptides, and carbamates as well as ureas.[27,28] Therefore, we envisioned that CDI could enable the desired cyclic carbamate formation by affording the carbonyl group to the MCR product. Having synthesized the corresponding Ugi-tetrazole in hand, the optimization started with 1 equiv of CDI in DCM at room temperature, giving a moderate yield of 76% (Table 1, entry 1) after 3 h. Further optimization was conducted by increasing either temperature or the equivalent of CDI. As expected, both conditions performed better yields of 83% (Table 1, entry 2) and 93% (Table 1, entry 3), respectively. Several studies indicated that a catalytic amount of base in the CDI reaction will accelerate the formation of the corresponding product.[29] However, subsequent attempts have shown that the utilization of base (Table 1, entries 5 and 6) restricts the reaction process, even with a longer reaction time. To our delight, superior conditions were found with a shorter reaction time without heating. In the optimal protocol, 1.5 equiv of CDI was added to a solution of the azido-Ugi product in DCM at room temperature under air, and the corresponding oxazinanone was formed with nearly quantitative yield in a few hours (Table 1, entry 9).

Under optimized conditions, we next examined the substrate scope of cyclization with various amines, isocyanides, and salicylaldehydes with diverse substitutions (Scheme 1). The majority of the corresponding oxazinanones resulted in

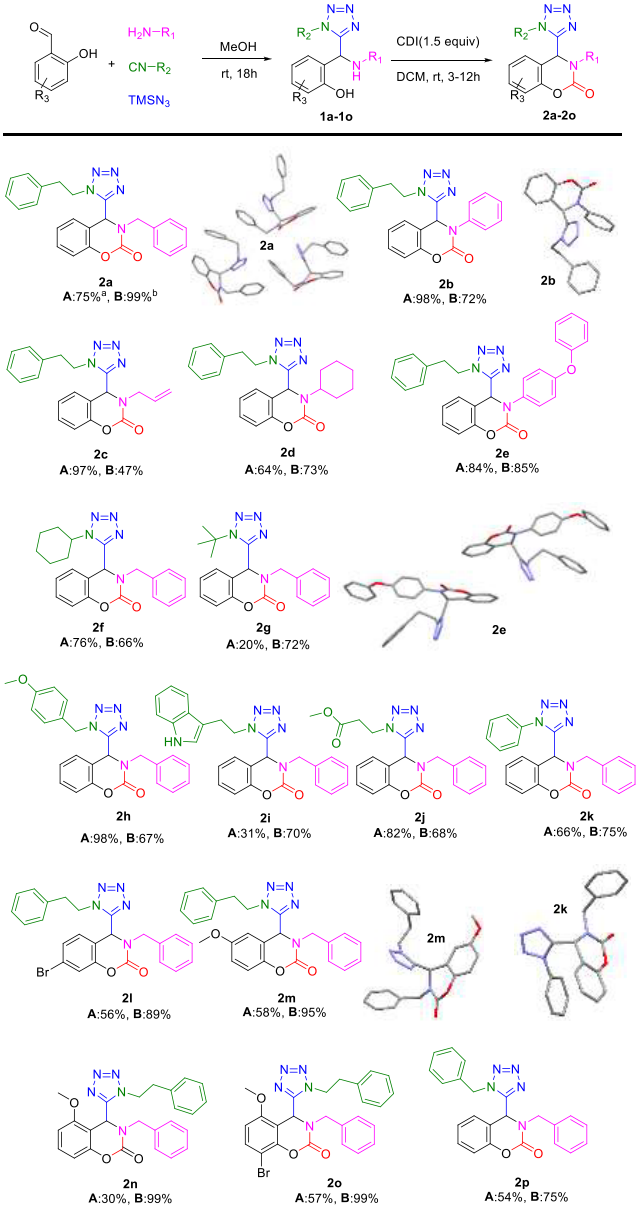
Table 1. Optimization of Reaction Conditions[a]



entry	equiv of CDI	base	time (h)	t (°C)	yield (%)[b]
1	1		3	rt	76
2	1		3	50	83
3	2		3	rt	93
4	2		3	50	88
5	2	TEA	12	rt	61
6	2	DIPEA	12	rt	71
7	2	$NaHCO_3$	12	rt	48
8	1.2		3	rt	85
9	**1.5**		**3**	**rt**	**99**

[a]The CDI conducted reaction was carried out in DCM with 1 M concentration. [b]Isolated yields.

Scheme 1. Yields of the Ugi Products (1) and Cyclized 1.3-Oxazinan-2-one (2)



[a]Isolated yield of **1**. [b]Isolated yield of **2**.

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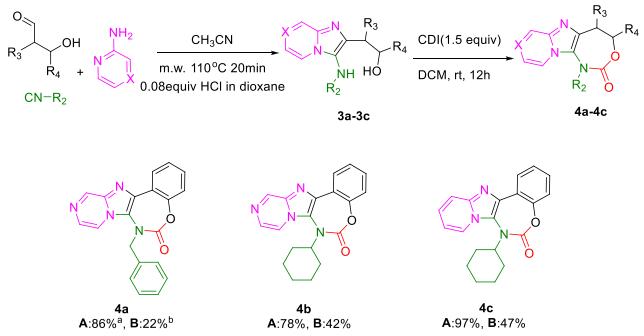
moderate to good yields over two steps. First of all, amino substituents have obvious influences on synthetic conversion. Compounds synthesized by aromatic amines exhibited excellent overall yields, including phenox phenyl substituted **2e** despite the possible steric hindrance. On the contrary, aliphatic amine substitutions reduced the yield of the cyclization. For instance, compound **2c** with allyl substitution affords only 47% yield. In addition, changes in the isocyanide components were well-tolerated. Most of the isolated products have approximately 70% yield. It is noteworthy that the desired compound **2i** was obtained in high yield in the presence of a competitive amino group in the indole ring. Furthermore, aldehydes with methoxyl and halogen substituents on ortho- or meta-positions were evaluated in the scope as well. Surprisingly, most of the cyclization products with either mono- or multisubstituents on the salicylaldehydes gave extraordinary quantitive yields.

Encouraged by the initial results, we investigated the potential of the cyclization strategy based on Groebke-Blackburn-Bienaymé reactions (GBB reactions) which could afford secondary amines on imidazole heterobicyclic rings (Scheme 2).[2−4] Equimolar amounts of aldehyde, amino amine,

Scheme 2. Yields of the GBB Products (3) and Cyclized Oxazepanones (4)

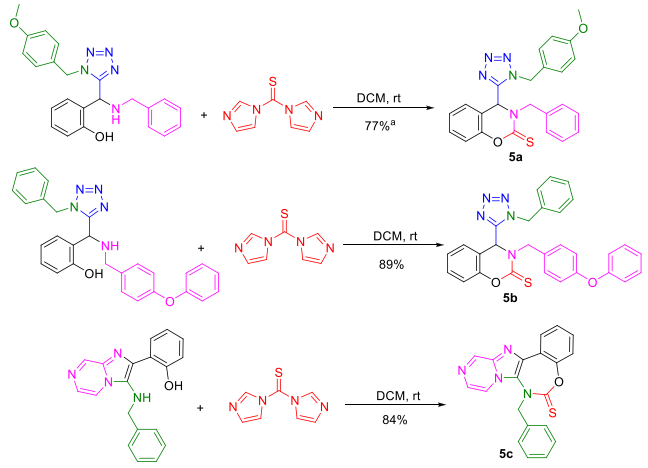


[a]Isolated yield of **3**. [b]Isolated yield of **4**.

and isocyanide, as well as 0.08 equiv of HCl in dioxane, were combined in CH_3CN (1 M) in a microwave at 110 °C for 20 min. The corresponding imidazole-heterobicyclic product **3** was isolated by column chromatography with excellent yields (for example, **3c**, 97%). The identical cyclization approach as above was employed. Not surprisingly, the carbamate formation of the 7-membered 1,3-oxazepan-2-one appeared more difficult than the 6-membered 1.3-oxazinan-2-one. The overall yields of the cyclized GBB products are below 50%. A large amount of imidazole-1-carboxylate intermediates were observed even with a longer reaction time.

In light of the aforementioned results, we next explored the synthesis of thiocarbamate derivatives (Scheme 3). 1,1′-Thiocarbonyldiimidazole (TCDI), the sulfur analog of CDI, was employed as the thiocarbonyl donor. Accordingly, the reaction was conducted with 2 equiv of TCDI in room temperature for 12 h in DCM. To our delight, the overall cyclization exhibited good to excellent yields. Positively, enhanced conversion to the thiocarbamate compounds was observed in the Ugi products, compared with the carbamate formation. Furthermore, it is noteworthy that the thiocarbamate GBB product (**5c**, 84%) went better than carbamate GBB

Scheme 3. Substrate Scope of Cyclized 1,3-Oxazinane-2-thiones and 1,3-Oxazepane-2-thiones (5)

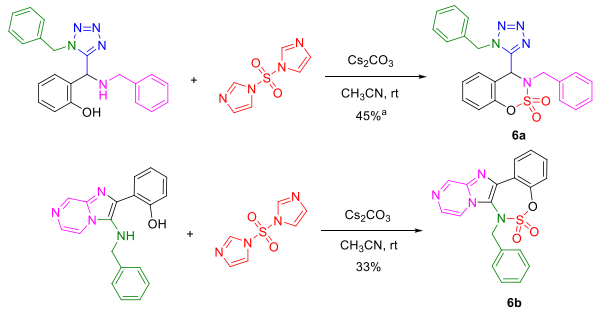


[a]Isolated yield of cyclic thiocarbamate **5**.

(**4a**, 22%), effectively comparable with the Ugi product yields (**5a**, 77%; **5b**, 89%).

Next, we attempted to use the uniform approach with the sulfonyl donor 1,1′-sulfonyldiimidazole (SDI), for the synthesis of sulfamate derivatives (Scheme 4). However, under the

Scheme 4. Substrate Scope of Cyclized 1,2,3-Oxathiazinane-2,2-dioxides and 1,2,3-Oxathiazepane-2,2-dioxides (6)



[a]Isolated yield of cyclic thiocarbamate **6**.

previous conditions, the reaction remained at the stage of the imidazole-1-sulfonyl intermediate instead of cyclization to the sulfamate product. In order to push the reaction to the desired cyclization, an excess amount of Cs_2CO_3 was added to the reaction solution. Under base catalysis, 6-membered and 7-membered cyclized sulfamate derivatives were then synthesized in 45% (**6a**) and 33% (**6b**) yields, respectively.

As an application of this methodology, we next investigated the scope of 5-membered carbamate cyclization and urea cyclization with CDI as the carbonyl donor (Scheme 5). The main innovation of 5-membered ring formation is the employment of various aldehydes. The glycolaldehyde dimer, providing a free hydroxyl group, was used in the azido-Ugi reaction. CDI afforded oxazolidin-2-one **8a** with 74% yield. Pyrrole-2-carboxaldehyde and 2-imidazolecarboxaldehyde, which provided secondary amines, were employed to the formation of heterobicyclic ureas with 99% (**8b**) and 60% (**8c**) yields, respectively. For better yields, a catalytic amount of DIPEA was added in the urea formation.

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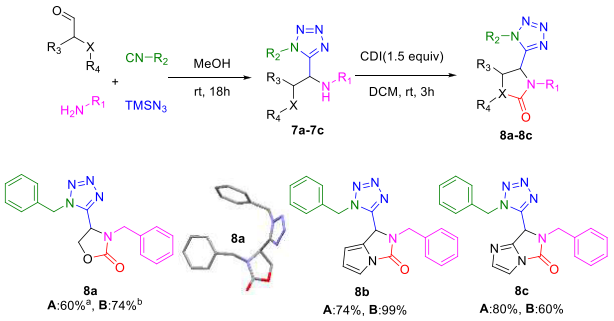
Scheme 5. Substrate Scope of 5-Membered CDI Cyclization of MCR Products (8)



[a]Isolated yield of **7**. [b]Isolated yield of **8**.

Additionally, five oxazinanone derivatives (**2a**, **2b**, **2e**, **2k**, **2m**) and one oxazolidinone derivative (**8a**) have been confirmed by X-ray single-crystal analysis (Scheme 1, Scheme 5, and Supporting Information).

To exemplify the scaffolding induced property modulation, we compared 14 physicochemical properties of each 1000 compound virtual libraries[30,31] of the cyclized and noncyclized structures (Figure 2 and Supporting Information). PCA of five

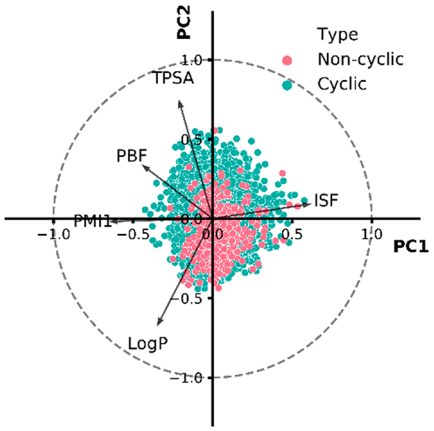


Figure 2. Normalized PC1 vs PC2 plot of cyclic and noncyclic molecules. Cyclic molecules (green) showed a different distribution against noncyclic molecules (pink).

nonredundant physicochemical properties included 3D descriptors allowing us to identify interesting differences between noncyclic and cyclic molecules. Topological polar surface area (TPSA) and logP, which are important values in medicinal chemistry, were identified as the most relevant descriptors (black arrows) to explain the variance among the cyclic and noncyclic molecules, indicating drug likeliness of all herein described cyclic scaffolds.

CONCLUSION

In summary, a MCR-based synthesis of 5-membered, 6-membered, and 7-membered cyclic carbamate derivatives with at least four substitutions has been developed with the purpose to modify physicochemical properties. Both the azido-Ugi reaction and the GBB reaction are instrumental in this approach, leading to potentially bioactive bis-heterocyclic or multiheterocyclic scaffold constructs. Furthermore, their thio and sulfur scaffolds are investigated along with the achievement of extraordinary scaffold diversity. The cheminformatics analysis clearly shows we are addressing a druglike chemical space. Our protocol, utilizing mild conditions and readily available building blocks, is of excellent maneuverability, scalability, and efficiency. It will add to a growing body in the development of material and organic synthesis, as well as medicinal chemistry.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscombsci.0c00072.

NMR spectra, crystal structure determinations, and chemical space exploration (PDF)

CIF 1 (CIF)

CIF 2 (CIF)

CIF 3 (CIF)

CIF 4 (CIF)

CIF 5 (CIF)

CIF 6 (CIF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

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