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Ionic Liquid Mediated Ugi/SN_2 Cyclization: Synthesis of 1,2,3-Triazole Containing Novel 2,5-Diketopiperazines †

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Abstract: The Ugi four-component reaction is versatile multicomponent reaction for generation of complex diversity, herein, we developed a novel methodology by using 4-((1-((tetrahydrofuran-2-yl)methyl)-1H-1,2,3-triazol-4-yl)methoxy)benzaldehyde as one of the components in Ugi 4CR that contains 1,2,3-triazole moiety which is a privileged molecule in medicinal chemistry to obtain Ugi adducts under room temperature ionic liquids as medium of solvent, then followed SN_2 pathway cyclization to get triazole containing 2,5-diketopiperazine derivatives in good yield using basic ionic liquids as a catalyst.

Keywords: Ugi multicomponent reaction; task specific ionic liquid; 1,2,3-triazole; 2,5-diketopiperazine

1. Introduction

In recent years, the rapid generation of complex molecules can be achieved by employing diversity-oriented synthetic strategies in combination with so-called complexity-generating reactions. In this context, MCR (multicomponent reactions) are of great interest in organic and medicinal chemistry because of high atom economy, versatility, and molecular complexity. [1–6] In this regard, Ugi four-component reaction is the cornerstone and has been explored to its potential transformation. By tuning the reactants used in the Ugi reaction, we can go for the post-transformation. Based on this, the molecule complexity has been generated. Herein we describe a novel ionic liquid mediated Ugi/SN_2 cyclization. Herein we report a Ugi 4CR with 4-((1-((tetrahydrofuran-2-yl)methyl)-1H-1,2,3-triazol-4-yl)methoxy)benzaldehyde Figure 1 as aldehyde component that contains triazole moiety.

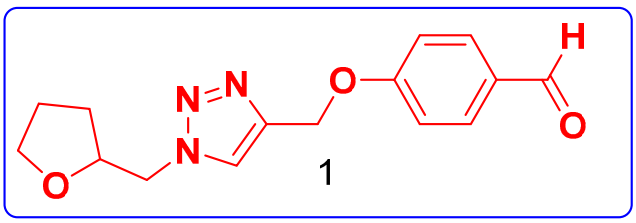
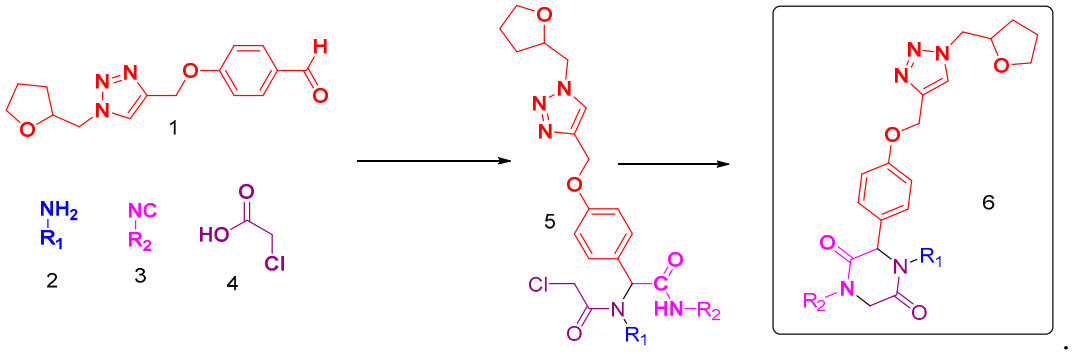


Figure 1. 1,2,3-Triazole Containing benzaldehyde used Ugi reaction.

Triazoles are an important class of heterocycles in the context of pharmacological properties, such as antifungal, [7] antibacterial [8,9], anticancer [10], and antimicrobial [11]. In our research investigation group, Erick Cuevas et al. have developed a functionalization and incorporation of triazole moiety to aromatic aldehydes. The present work involves the triazole containing aldehyde as a component in Ugi reaction followed by base catalyzed SN_2 intramolecular cyclization for obtaining 2,5-diketopiperazine derivatives (Scheme 1).



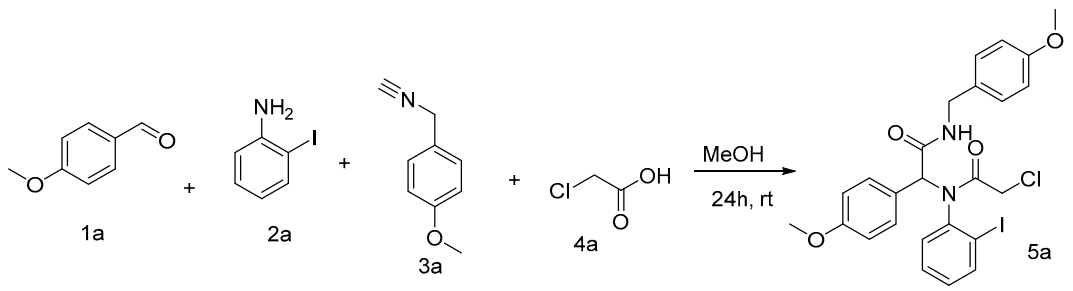
Scheme 1. Synthesis of synthesis of 1,2,3-triazole containing novel 2,5-diketopiperazines.

2,5-Diketopiperazine is a class of compounds that consists of a cyclic dipeptide, and these compounds are present in many natural products produced by bacteria, fungi, plants, and mammals [12,13]. As we mentioned that our strategy in synthesis of (**6**) via Ugi/SN_2 under ecofriendly conditions. In this context, we used ionic liquids as a solvent medium.

Eco-friendliness and sustainability has become a tremendously significant challenge nowadays, due to environmental safety control, health, and societal concerns. Within this context, there is demand for developing versatile greener and nonpolluting synthetic protocols that reduce the use of toxic reagents. In designing chemical products and processes that eliminate or reduce the use of hazardous substances, by-product formation is the most crucial challenge nowadays. Within this context, we choose ionic liquid as a green solvent medium in this reaction. Ionic liquids have unique characteristics, such as solvophobic, which can generate internal pressure in the reaction to promote the association between reactants, which accelerates the reaction. This characteristic feature is very efficient for MCR. We initially started optimization with symmetric imidazolium salts ([BBIM]Br, [BBIM]BF_4), these ionic liquids were selected according to literature reports [14–16].

2. Results and Discussion

The most common methods for the synthesis of 2,5-diketopiperazines were Ugi 4CC followed by base-catalyzed reaction [17,18]. Most of these reactions use strong bases, such as KOH and NaOH, for the SN_2 cyclization. Herein, we initially started optimizing our reaction with a simple aromatic aldehyde (e.g., anisaldehyde) and for the Ugi reaction. The Ugi reaction (Scheme 2) was conducted according to a literature procedure with anisaldehyde (**1a**), 2-iodo aniline (**2a**), 2-chloroacetic acid (**3a**), and 4-methoxybenzyl isocyanide (**4a**) under methanol for 24 h to obtain Ugi adduct (**5a**) in good yield.



Scheme 2. Synthesis of Ugi adduct.

Later, the same Ugi reaction was repeated with respective ionic liquids ([BBIM]Br, [BBIM]BF4), the difference between the reported procedure and our modified procedure is that we reduced the time of reaction to 8 h with excellent yield (95%) with easy workup of the reaction. The product obtained was confirmed by NMR (Figures S1 and S2). The resulting Ugi adduct was utilized for the base catalyzed SN_2 cyclization. Here, we selected base cesium carbonate under ionic liquid medium. A strong base, such as NaOH, under heating conditions would also give a secondary product, such as β-lactam, because we had two acidic protons in the Ugi adduct which are quarternary proton (A) and amide proton which is at isocyanide part. Therefore, there was a competition between two protons, and we selectively abstracted amide proton to obtain 2,5-diketopiperazine 6a instead of lactam under mild conditions using cesium carbonate and ionic liquid as a green solvent.

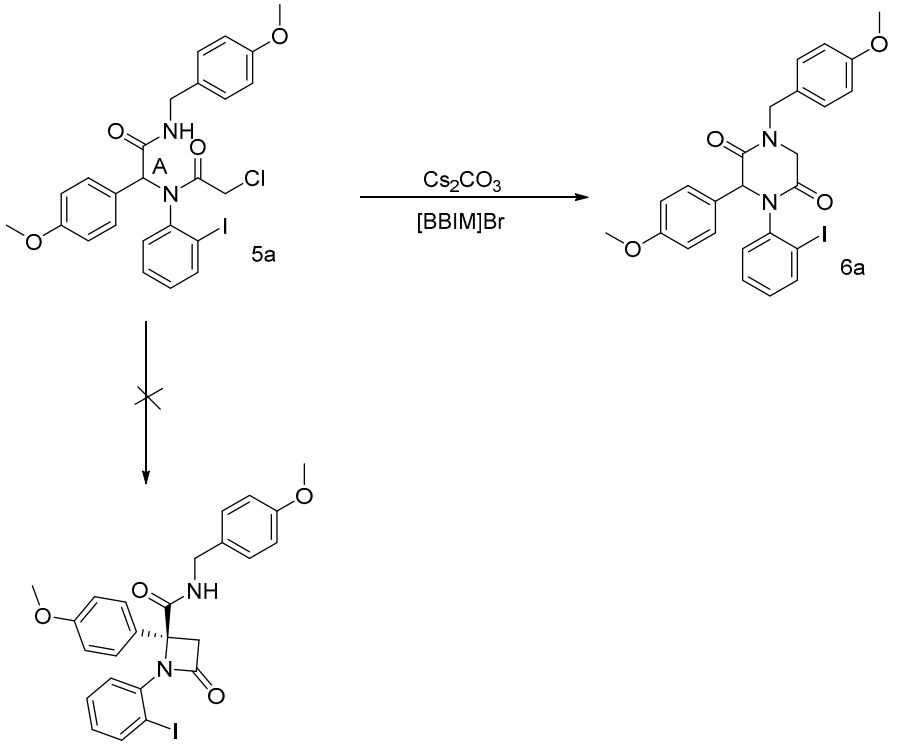


Figure 2. Synthesis of 2,5-diketopiperazines and their competive products via base catalyzed cyclization.

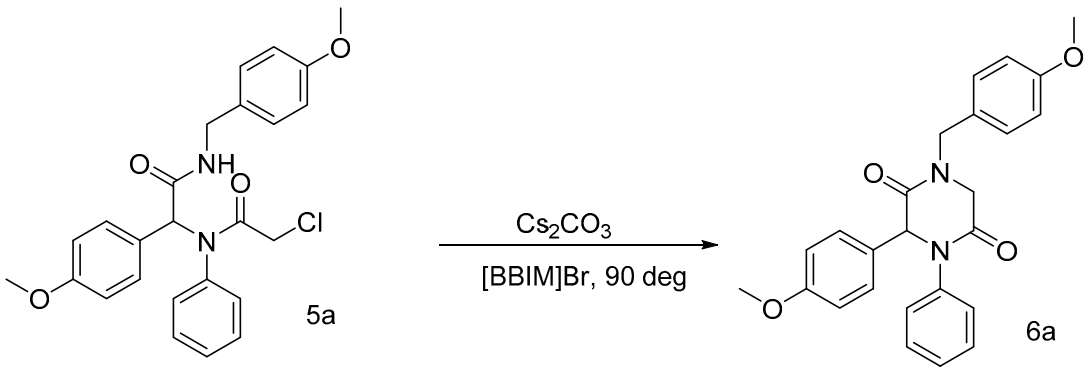


Figure 3. Synthesis of 2,5-diketopiperazines with Ugi adduct (**5a**).

Once we have optimized conditions we repeated the same with the 4-((1-((tetrahydrofuran-2-yl)methyl)-1H-1,2,3-triazol-4-yl)methoxy)benzaldehyde (**1**) to obtain Ugi adduct with aniline (**2**), N-propyl isocyanide (**3**), 2-chloacetic acid (**4**) Scheme 1 (5%–95%) followed by SN^2 cyclization product Scheme 1 (6%–90%) under mild efficient conditions. The confirmation of products was through NMR spectroscopy, where we can observe the absence of amide proton in the ^1H NMR at around 5.76 ppm.

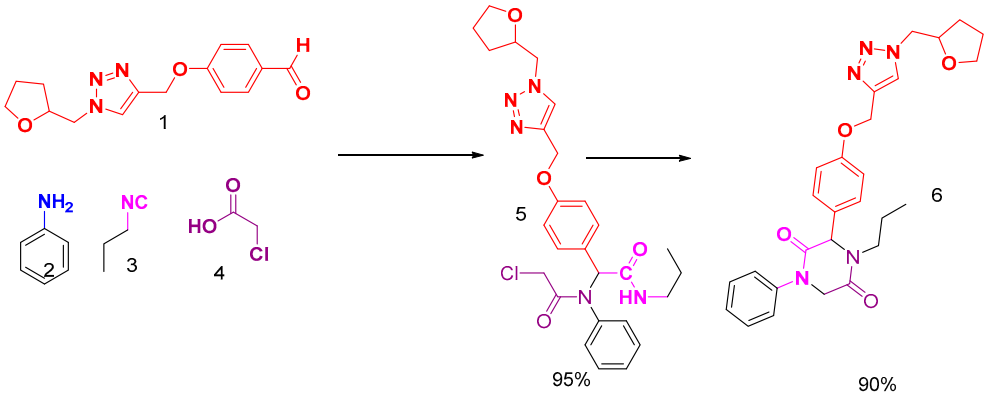


Figure 4. Synthesis of Novel 1,2,3-triazole containing 2,5-diketopiperazine moiety.

3. General Experimental Procedure

3.1. Synthesis of Ugi Adduct **5**

To the 10 mL vial equimolar quantities of aldehyde, amine, isocyanide, and 2-chloroacetic acid was added with a mixture of [BBIM]BF_4 at room temperature for 8 h. The reaction was monitored by TLC. After completion, the reaction mixture was poured into water to remove ionic liquid, and the crude mixture was extracted with ethyl acetate and purified by column chromatography. The isolated compound was characterized by NMR (Figures S5 and S6). The isolated yield was 95%.

3.2. Synthesis of 2,5-Diketopiperazine Derivative **6**

In a 25 mL round-bottomed flask, the obtained Ugi adduct (1 equivalent) and 1.5 equivalent Cs_2CO_3 were dissolved in [BBIM]Br and kept at 90 degrees heating for 8 h. The completion of the reaction was checked by TLC. After completion, the reaction mixture was poured into water to remove ionic liquid followed by extraction with ethyl acetate and finally purified by column chromatography and characterized by NMR (Figure S7). The isolated yield was 90%.

4. Conclusions

In this work we present a new way to develop 1,2,3-triazole containing Ugi adducts via Room Temperature Ionic liquids ([BBIM]Br) was employed as solvent yielding excellent yields and followed by base catalyzed cyclization to obtain corresponding 2,5-diketopiperazine derivative with good yield.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1, Figures S1–S7. ^{1}H NMR **5a**, **6a**, **5**, **6** & ^{13}C NMR of **5a**, **6a**, **5**.

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