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Synthesis of Peptidomimetics Via IMCR/Post-Transformation Strategy †

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Abstract: A series of three 2,5-Diketopiperazine (DKP's) were synthesized via one-pot process through the post-IMCR-transformation strategy. This strategy emphasizes the role of orthogonal bifunctional reagents in the IMCR process to increase their synthetic potential, allowing us accessing a synthetic platform from which it is possible to obtain privileged heterocyclic peptidomimetics via lactamization reaction.

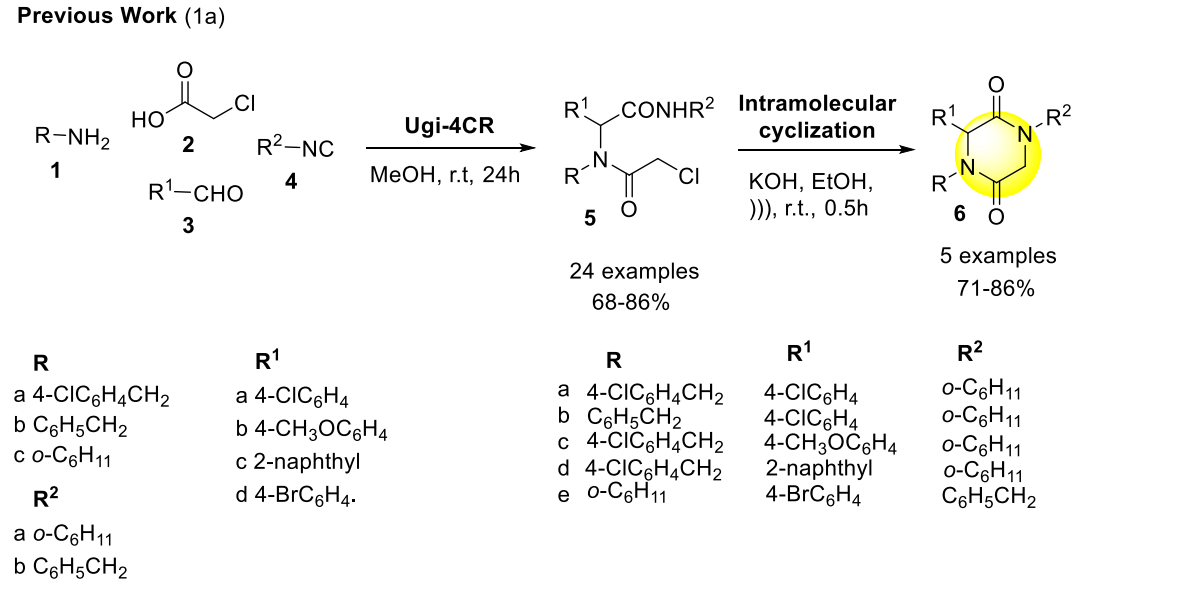
Keywords: 2,5-diketopiperazine (DKP's); Ugi-4CR/lactamization; peptidomimetics

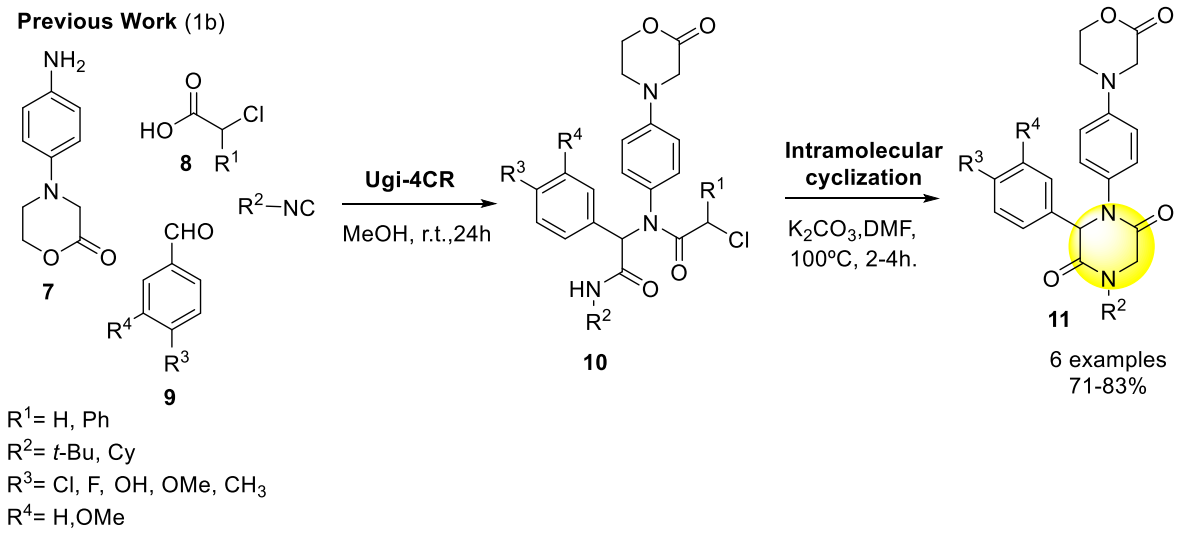
1. Introduction

The 2,5-Diketopiperazines (DKPs) are the smallest naturally occurring cyclic peptides, and this subunit is often found alone or embedded in more complex architectures in a variety of natural products (fungi, bacteria, the plant kingdom, and mammals). This privileged heterocycle-peptidomimetic (PHP) plays a vital role in drug discovery since it exhibits biological properties as anti-inflammatory, antitumor, neuroprotective, anxiolytic, and antiviral [1]. The common synthetic approaches to DKPs involve cyclization of a dipeptide ester, cleavage-induced cyclization, or intermolecular cyclization of α-haloacyl derivatives of amino acids. These methods generally employ non-eco-friendly reaction conditions such as high temperatures and toxic reagents.

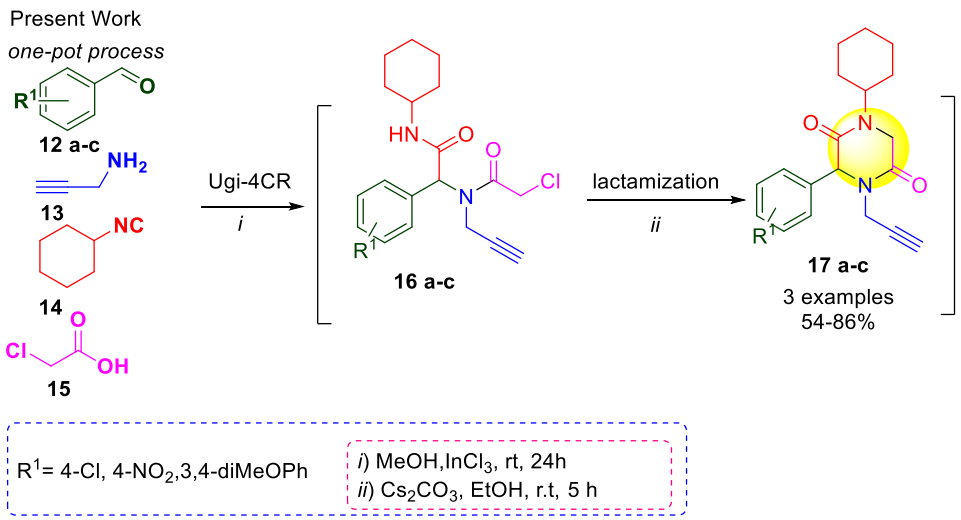
Multicomponent reactions (MCRs) have proven to be an efficient approach in organic synthesis. Particularly, the isocyanide-based multicomponent reactions (IMCRs), such as Ugi and Passerini reactions, are the most relevant for constructing peptidomimetics since they give access to linear peptides and depsipeptide-like structures. The post I-MCR-transformation strategy, via the Ugi-4CR followed by ciclization, is the most efficient alternative to produce cyclic peptidomimetics like DKPs [3]. The synthesis of 2,5-DKPs through post-I-MCRs-transformation strategy required additional processes like deprotection and activation- based cyclization under harsh acidic and/or basic conditions, using non-eco-friendly solvents [4–7].

Despite many efforts to efficient preparation of DKPs, the majority of the reported methods require long reaction times, high temperatures, and deprotection and activation-based cyclization. However, recently Marccacini et al. reported the ultrasound assisted synthesis in two steps of DKPs via Ugi-4CR followed by basic cyclization reaction under harsh basic conditions (Scheme 1a) [8]. In 2008 Naliapara et al. reported an efficient synthesis of DKPs using mild basic and catalysis-free conditions at 100 °C (Scheme 1b) [9]. Herein, we report a one-pot strategy for the synthesis of PHP like DKPs. The use of an orthogonal bifunctional amine and carboxylic acid resulted in a highly functionalized Ugi-adduct that enabled the subsequent post-transformation (lactamization) (Scheme 2).





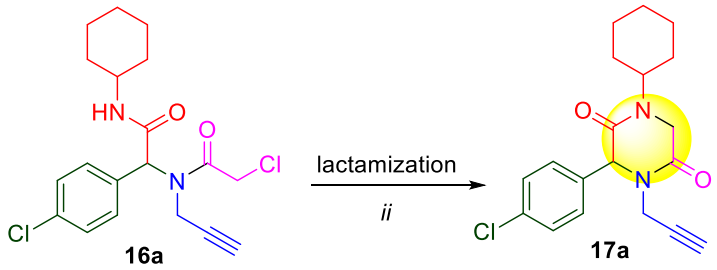
Scheme 1. Previous work on the synthesis of peptidomimetics via/post-IMCR-transformation strategy.



Scheme 2. Synthesis of bis-heterocycle peptidomimetics containing 2,5-DKPs via Ugi-4CR/lactamization.

2. Results and Discussion

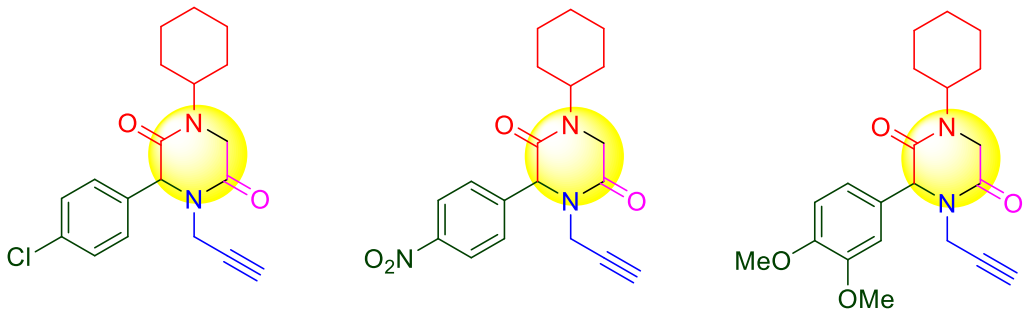
We began our preliminary experimental study by optimizing the Ugi 4-CR and lactamization reactions individually before proceeding to the one-pot synthesis. Firstly, we use the conditions for Ugi-4CR previously reported by us in 2018 [10]. The formation of Ugi-4CR product (16a) was made by the simple mixing of 4-chlorobenzaldehyde (12a), propargylamine (13), cyclohexyl isocyanide (14) and chloroacetic acid (15) using $InCl_3$ in MeOH at room temperature. Subsequent, the Ugi-adduct (16a) was initially subjected to lactamization without base but the target product was not obtained, then we used inorganic bases to promote the cyclization of the linear peptide-like Ugi-adduct into the DKP (17a). The use of strong, nucleophilic base resulted in decomposition of the reaction mixture. To our delight, using Cs_2CO_3 as base resulted in complete conversion of (16a).



Entry	Base	Solvent	Time (h)	Source Energy	Temperature (°C)	conversion
1	------	EtOH	3	r.t	25	n.c
2	------	EtOH	3	r.t	60	n.c
3	------	EtOH	1	Microwave	60	n.c
4	------	EtOH	1	Ultrasound	60	n.c
4	KOH	EtOH	1	r.t	25	Decomp
5	**$CsCO_3$**	**EtOH**	**5**	**r.t**	**25**	**77**

n.c = no conversion, decomp = decomposition.

The optimized conditions were utilized to synthesize a serie of three high functionalized DKPs (Scheme 3). The versatility of the developed methodology was examined using aldehydes containing electro-donating and withdrawing groups, and two orthogonal bifunctional reagents (amine and carboxylic acid). The products (**17a–c)** was obtained in moderate to good yields (54–86%). The products were purified by silica-gel column chromatography to afford the desired products, the structure of isolated product was confirmed by ^1H y ^{13}C NMR (Figure 1).



Scheme 3. Substrate scope.

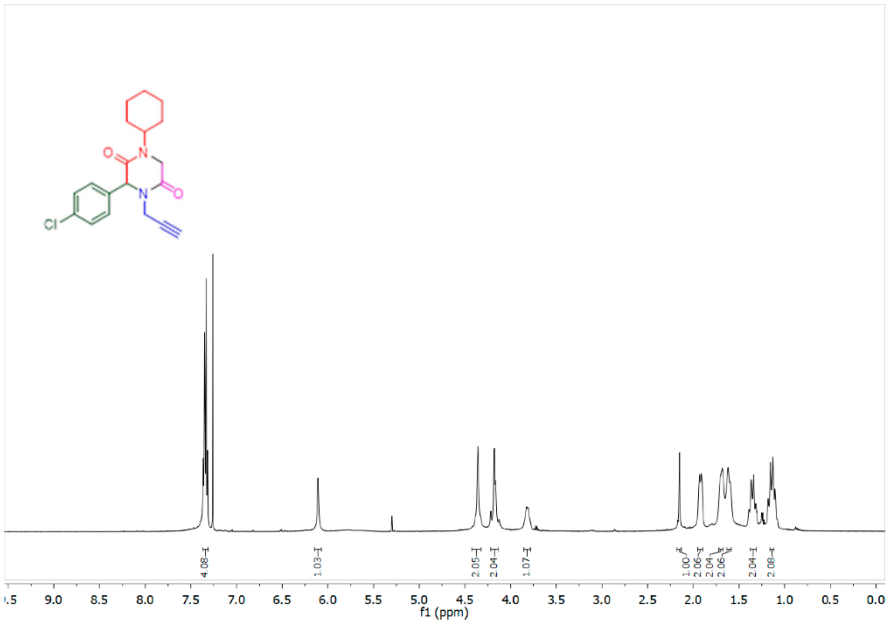


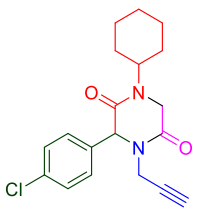
Figure 1. ^{1}H NMR spectrum of compound 17a.

3. Experimental Section

General Information: ^{1}H and ^{13}C NMR spectra were acquired on a 500 MHz spectrometer. The solvent for NMR samples was CDCl3. Chemical shifts are reported in parts per million (δ/ppm). Internal reference for NMR spectra is tetramethylsilane at 0.00 ppm. Coupling constants are reported in Hertz (J/Hz). Multiplicities of the signals are reported using the standard abbreviations: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). NMR spectra were analyzed using the MestreNova software version 10.0.1–14719. The reaction progress was monitored by TLC and the spots were visualized under UV light (254 or 365 nm). Flash column chromatography was performed using silica gel (230–400 mesh) and mixtures in different proportions of hexanes with ethyl acetate as mobile phase. Chemical names and drawings were obtained using the ChemBioDraw Ultra 13.0.2.3020 software package.

General method: To a solution of 0.5M anhydrous MeOH, 4-chloroaldehyde (50mg, 1mmol), propargylamine (1mmol) was added and stirred for 5 min followed by addition of $InCl_3$ (10 mol%), cyclohexyl isocyanide (1 mmol) and monochloro acetic acid (1 mmol) and stirred for 24 h at room temperature till completion of reaction was observed on TLC. Later, the solvent was evaporate in vacuo. Later, the same glass tube with dry product (Ugi adduct) was charged with EtOH (1M) and Cs_2CO_3 (1.5 equiv) and the reaction mixture was stirred for 5 h for base induced cyclization reaction was completed and monitored on TLC. Later, EtOH was evaporate in vacuo and the crude was purified by silica-gel column chromatography to afford the products **17 a–c**.

Spectral data



3-(4-chlorophenyl)-1-cyclohexyl-4-(prop-2-yn-1-yl)piperazine-2,5-dione (17a) brown soil (35 mg, 77%); Rf = 0.30 (Hexanes-EtOAc = 7/3 *v*/*v*); ^{1}H NMR (500 MHz, CDCl3) δ 7.37–7.31 (m, 4H), 6.10 (s, 1H), 4.36 (s, 2H), 4.23–4.13 (m, 2H), 3.85–3.79 (m, 1H), 2.15 (s, 1H), 1.95–1.89 (m, 2H), 1.73–1.67 (m, 2H), 1.64–1.58 (m, 2H), 1.40–1.30 (m, 2H), 1.20–1.08 (m, 2H). ^{13}C NMR (126 MHz, CDCl3) δ 167.7, 167.3, 134.9, 132.6, 130.7, 129.1, 72.9, 60.4, 48.8, 41.7, 35.2, 32.8, 25.4, 24.7(2).

4. Conclusions

A series of three new DKP's were synthesized via a one-pot process through the post-IMCR-transformation strategy in moderate to good yields (54–86%).The use of the bifunctional groups allows us to obtain highly functionalized molecules of interest in medicinal chemistry and with enormous potential for the generation of more complex molecules.

Author Contributions: All authors contributed equally to this work. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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