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# Ugi-4CR/SN2-Cyclization Strategy for the One-Pot Synthesis of 2,5-Diketopiperazines †

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**Abstract:** 2,5-diketopiperazines (2,5-DKPs) are the smallest cyclic peptides in nature and display a variety of bioactivities including antibacterial, antifungal, and anticancer. The one-pot synthesis of 2,5-DKPs is few reported. Herein, we report a novel one-pot synthesis of 2,5-DKPs via Ugi-4CR/SN2-cyclization strategy, under mild conditions, ethanol was used as a solvent for both procedures.

**Keywords:** 2,5-DKPs; IMCR; Ugi-4CR; bis-amide

## 1. Introduction

2,5-diketopiperazines (2,5-DKPs) are the only cyclic peptides found in nature, composed of two a-amino acids cyclized by peptide bonds [1]. The 2,5-DKPs core exhibit several pharmacological properties (Figure 1). Therefore, 2,5-DKPs have attracted attention in the field of drug discovery as biologically validated platforms because of their rigid conformation, structural stability, high resistance to enzymatic degradation, and cell permeability [2,3].

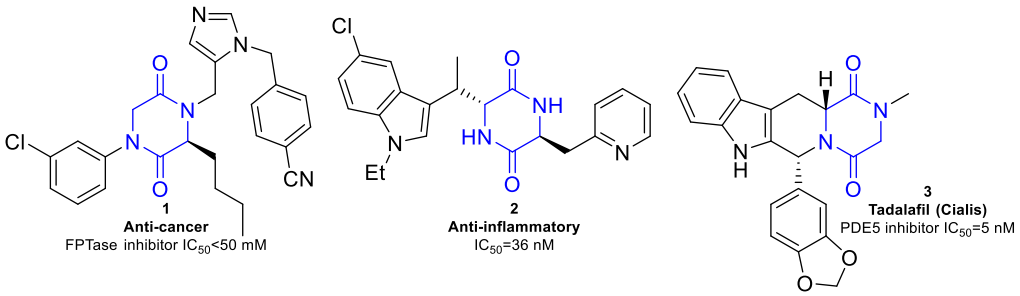


**Figure 1.** Bioactive molecules containing 2,5-DKP scaffold.

Conventional synthesis to 2,5-DKPs involve cyclization of a dipeptide ester, cleavage-induced cyclization, or intermolecular cyclization of a-haloacyl derivates of amino acids. These have several disadvantages, the use of drastic reaction conditions that include high temperatures, strong bases and/or toxic reagent (for deprotection-based cyclization) and low global yields [4]. In this context, isocyanide-based multicomponent reactions (IMCR) approach is advantageous in terms of facile reaction conditions, scope of the starting materials, broadness of synthetic variations and synthetic efficacy, which contributes significantly to the development of environmentally friendly strategies [5–8].

The Ugi reaction (Ugi-4CR) offers an alternative method to form an acyclic precursor which require post-transformation reactions like deprotection and activation-based

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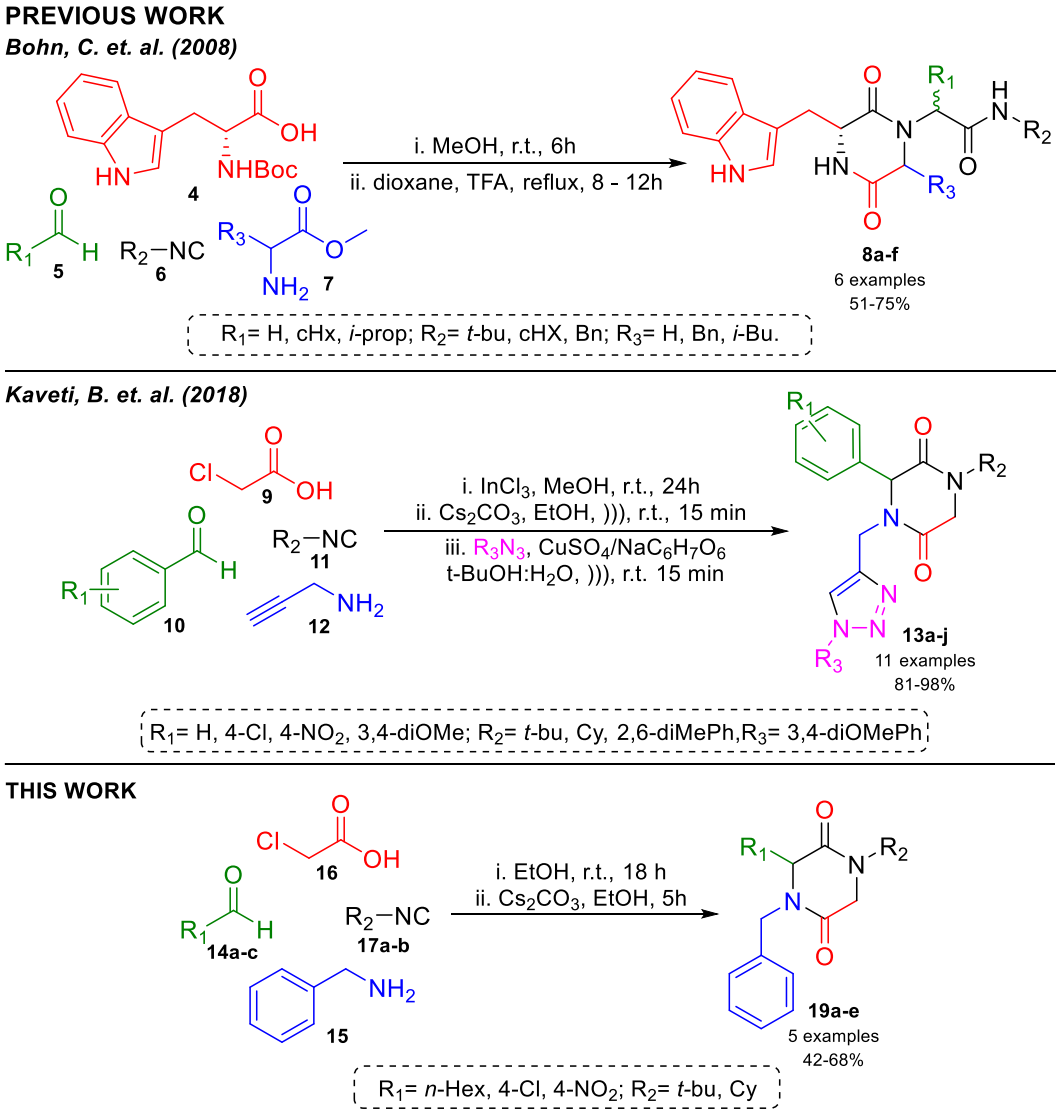
cyclization under basic and acid conditions, respectively to obtain 2,5-DKPs. In 2018 our research group reported a one-pot synthesis of 2,5-DKPs with other heterocyclic peptidomimetic under mild conditions (Scheme 1) [9,10].




**Scheme 1.** Previous reports of synthesis of 2,5-DKPs [9,10].

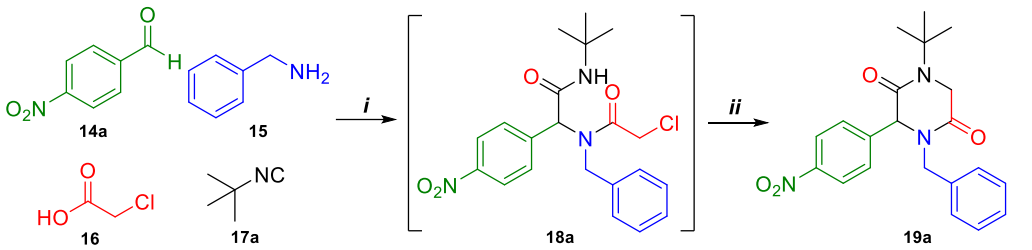
The one-pot synthesis of 2,5-DKPs via Ugi-4CR/ $S_N2$-cyclization strategy is reported. Herein we described the one-pot synthesis of 2,5-DKPs under mild conditions using ethanol as a solvent.

## 2. Results and Discussion

First, the synthesis of Ugi-4CR product (**18a**) was made by the mixing of 4-nitrobenzaldehyde (**14a**), benzylamine (**15**), monochloroacetic acid (**16**), and *tert*-butyl isocyanide (**17a**), using $InCl_3$ as a catalyst. The reaction in MeOH at room temperature resulted in good yields, changing to a greener and less toxic solvent, EtOH, obtained the desired products with similar yields to MeOH (Table 1, **entries 1–2**). Therefore, we opted to use EtOH for the synthesize Ugi adduct.

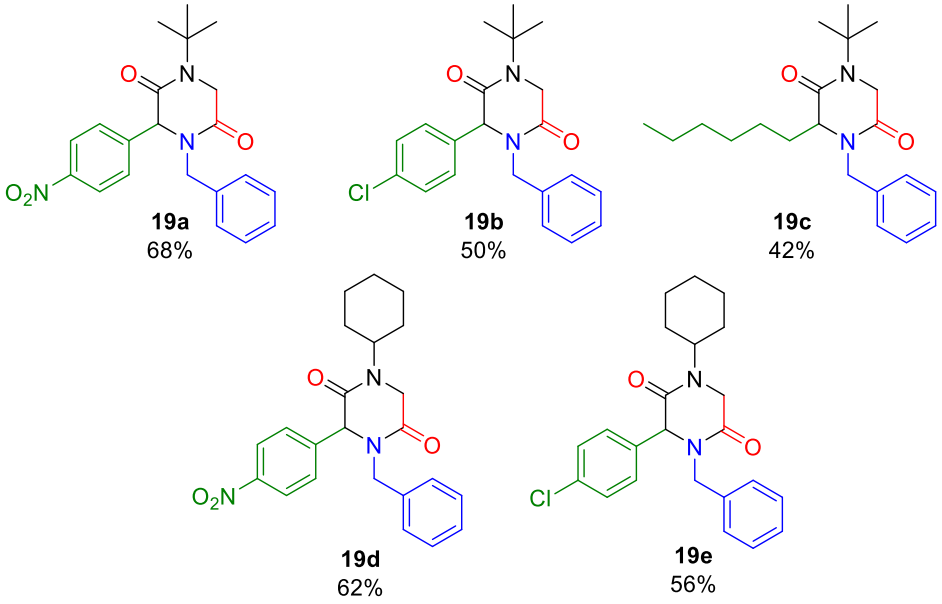
Subsequent, the Ugi-adduct was subjected to $S_N2$-cyclization with an inorganic strong base (KOH), the result was the decomposition of the reaction. However, with the use of $Cs_2CO_3$, a less strong base, the conversion of the Ugi-adduct into the 2,5-DKP (**19a**) was achieved (Table 1, **entries 3–4**).

**Table 1.** Screening conditions for the synthesis of molecule **19a**.




| *i. Ugi-4CR* | | | | | |
|---|---|---|---|---|---|
| **Entry** | **Solvent** | **Catalyst** | **Temperature** | **Time** | **Yield (%)** |
| 1 | MeOH | $InCl_3$ | r.t. | 24 h | 74 |
| **2** | **EtOH** | **$InCl_3$** | **r.t.** | **18 h** | **70** |
| *ii. $S_N2$-cyclization* | | | | | |
| **Entry** | **Solvent** | **Base** | **Temperature** | **Time** | **Yield** |
| 3 | EtOH | KOH | r.t. | 1 h | Decomp |
| **4** | **EtOH** | **$Cs_2CO_3$** | **r.t.** | **5 h** | **68** |

In Scheme 2, a series of 2,5-DKPs (**19a–e**) is depicted, which was synthesized under the optimized conditions (Table 1, **entry 2 and entry 4**). The effect of the stereo-electronic nature of the carbonyl component was evaluated, employing aromatic and aliphatic aldehydes. Finally, products were obtained in good yields (42–68%).




**Scheme 2.** Synthesis of 2,5-DKPs scope.

## 3. Experimental Section

### *3.1. General Information, Instrumentation and Chemicals*

$^{1}H$ and $^{13}C$ NMR spectra were acquired on Bruker Advance III spectrometer (500 MHz). The solvent used for NMR spectroscopy was deuterated chloroform ($CDCl_3$). Chemical shifts (d) are given in ppm relative to tetramethylsilane (TMS). Coupling constants are reported in Hertz (Hz). Multiplicities of the signals are reported using standard abbreviations: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). NMR spectra were analyzed using MestReNova software version 12.0.0-20080. Reaction progress was monitored by thin-layer chromatography (TLC) on pre-coated silica gel F254

aluminum sheets, and the spots were visualized under UV light at 254 nm. Column chromatography was performed using silica gel (230–400 mesh) as stationary phase. Mixtures of hexanes and ethyl acetate were used as mobile phase for column chromatography and in TLC for reaction progress monitoring and measuring retention factors ($R_f$). All reagents were purchased from Sigma Aldrich and were used without further purification.

### *3.2. General Procedure*

A solution of 1.0 M EtOH, aldehyde (**14a–c**, 0.13 mmol, 1.0 equiv.), benzylamine (15, 0.13 mmol, 1.0 equiv.), monochloro acetic acid (**16**, 0.13 mmol, 1.0 equiv.) and isocyanide (**17a–b**, 0.13 mmol, 1 equiv.) and stirred at room temperature for 18 h till. Then, $Cs_2CO_3$ (0.24 mmol, 1.5 equiv.) was added, and the reaction mixture was sonicated (45 KHz) for 15 min for base induced cyclization reaction was completed and monitored on TLC. The solvent was removed, and the crude was purified by column chromatography using silica gel and mixtures of ethyl acetate in hexanes, to afford the corresponding 2,5-DKPs (**19a–e**).

### *3.3. Spectral Data*

*j4-benzyl-1-(tert-butyl)-3-(4-nitrophenyl)piperazine-2,5-dione* (**19a**).

Yellow oil, $R_f$ = 0.32 (30% ethyl acetate in hexanes): $^1$H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): d 8.24 (d, *J* = 8,9 Hz, 2H), 7.54 (d, *J* = 8.9 Hz, 2H), 7.33 (m, 3H), 7.24 (m, 2H), 5.51 (s, 1H), 4.75 (d, *J* = 15.5 Hz, 1H), 3.73 (d, *J* = 15.5 Hz, 1H), 3.59 (d, *J* = 15.5 Hz, 1H), 3.46 (d, *J* = 15.4 Hz, 1H), 1.09 (s, 9H); $^{13}$C NMR (126 MHz, $CDCl_3$): d 168.4, 167.6, 147.9, 143.5, 135.9, 129.4, 128.8, 128.6, 128.3, 124.1, 66.0, 51.9, 51.8, 45.4, 28.1.

*4-benzyl-1-(tert-butyl)-3-(4-chlorophenyl)piperazine-2,5-dione* (**19b**).

Colorless oil, $R_f$ = 0.27 (30% ethyl acetate in hexanes): $^1$H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): d 7.42 (d, *J* = 8,5 Hz, 2H), 7.33 (m, 3H), 7.28 (d, *J* = 8.9 Hz, 2H), 7.24 (m, 2H), 5.54 (s, 1H), 4.45 (d, *J* = 15.6 Hz, 1H), 3.83 (d, *J* = 15.7 Hz, 1H), 3.77 (d, *J* = 15.5 Hz, 1H), 3.43 (d, *J* = 15.4 Hz, 1H), 1.19 (s, 9H); $^{13}$C NMR (126 MHz, $CDCl_3$): d 168.8, 165.3, 136.9, 135.9, 134.6, 129.4, 128.8, 128.6, 127.8, 127.1, 68.0, 63.3, 49.8, 42.5, 28.8.

*4-benzyl-1-(tert-butyl)-3-hexylpiperazine-2,5-dione* (**19c**).

Yellow oil, $R_f$ = 0.43 (10% ethyl acetate in hexanes): $^1$H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): d 7.30 (m, 3H), 7.19 (m, 2H), 5.43 (s, 1H), 4.70 (d, *J* = 15.6 Hz, 1H), 4.47 (d, *J* = 15.5 Hz, 1H), 3.64 (d, *J* = 15.5 Hz, 1H), 3.39 (d, *J* = 15.4 Hz, 1H), 1.76 (m, 2H), 1.31 (m, 2H), 1.29 (m, 2H), 1.26 (m, 2H), 1.24 (m,2H), 1.12 (s, 9H), 0.88 (t, *J* = 6.7 Hz, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$): d 166.8, 165.3, 136.9, 128.6, 127.8, 127.1, 70.6, 66.3, 49.6, 47.8, 31.4, 29.6, 28.8, 27.6, 24.7, 23.7, 18.3.

*4-benzyl-1-cyclohexyl-3-(4-nitrophenyl)piperazine-2,5-dione* (**19d**).

Yellow oil, $R_f$ = 0.38 (30% ethyl acetate in hexanes): $^1$H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): d 8.22 (d, *J* = 8.7 Hz, 2H), 7.53 (d, *J* = 8.8 Hz, 2H), 7.35 (m, 3H), 7.24 (m, 2H), 5.51 (d, *J* = 8.2 Hz, 1H), 4.77 (d, *J* = 15.5 Hz, 1H), 3.74 (d, *J* = 15.4 Hz, 1H), 3.65 (m, 1H), 3.60 (d, *J* = 15.4 Hz, 1H), 3.47 (d, *J* = 15.4 Hz, 1H), 1.62 (m, 4H), 1.25 (m, 3H), 1.02 (m, 1H), 0.61 (m, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$): d 168.2, 167.5, 147.9, 143.3, 135.9, 129.5, 128.8, 128.6, 128.3, 124.1, 65.9, 52.0, 48.7, 45.4, 32.6, 25.2, 24.8.

*4-benzyl-1-cyclohexyl-3-(4-chlorophenyl)piperazine-2,5-dione* (**19e**).

Yellow oil, $R_f$ = 0.30 (20% ethyl acetate in hexanes): $^1$H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): d 7.35 (m, 3H), 7.29 (d, *J* = 7.3 Hz, 2H), 7.23 (m, 2H), 6.99 (d, *J* = 7.1 Hz, 2H), 5.63 (s, 1H), 4.77 (d, *J* = 17.5 Hz, 1H), 4.59 (d, *J* = 17.8 Hz, 1H), 4.05 (d, *J* = 13.4 Hz, 1H), 3.97 (d, *J* = 13.4 Hz, 1H), 3.69–3.62 (m, 1H), 1.68–1.55 (m, 4H), 1.26 (m, 3H), 1.02 (m, 1H), 0.60 (m, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$): d 168.4, 167.8, 134.8, 133.2, 130.9, 129.0, 128.9, 128.8, 127.8. 127.6, 65.8, 51.9, 48.7, 45.3, 32.2, 25.1, 24.7.

## 4. Conclusions

The present work contributes a novel green one-pot synthesis of a series of 2,5-DKP, via Ugi-4CR/$S_N2$-cyclization strategy using mild conditions.

In the synthesized products were obtained good overall yields (42–68%) when aromatic and aliphatic aldehydes were employed, this is another example of the effect of the stereo-electronic nature of the components in the outcome of the IMCR/post-transformation strategy.

Finally, the methodology provides to the sustainable synthesis of peptidomimetic molecules of interest to medicinal chemistry that have been reported for their pharmacological and biological properties.

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