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A One Pot Synthesis of Diketopiperazines via Multicomponent Reactions Based on Isocyanides †

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Abstract: The 2,5-DKP are heterocyclic peptidomimetics, present in nature with high structural diversity, privileged in the design of new bioactive molecules with potential application in medicinal chemistry, exhibiting anticancer and antimicrobial properties, among others. Therefore, in the present work, we report the one-pot synthesis of 2,5-DKP and their linked to another heterocycle 1,4-disubstituted 1,2,3-triazole under mild reaction conditions by one-pot process via the sequence IMCR/postransformation/CuAAC with several advantages over previously reported conventional methods.

Keywords: 2,5-DKP; isocyanide-based multicomponent reactions (IMCR); CuAAC

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1. Introduction

During the last three decades there has been a considerable increase in reports on the synthesis, reactivity and biological properties of 2,5-diketopiperazines (2,5-DKPs) [1]. These compounds were discovered in 1880 and later studied by E. Fischer [2]. They occur in nature as the simplest cyclic forms of peptides, the 2,5-DKP core is made up of a six-membered bis-lactam ring, this core is widely distributed in natural molecules, with different complexity produced by biosynthetic modifications of cyclic dipeptides. Various derivatives of 2,5-DKP have been isolated, for example, from plants, fungi, bacteria, while a wide variety of these compounds have shown a variety of biological properties of interest, such as anticancer, antioxidant, antiviral, antibacterial, anti-inflammatory, among others [1,2]. Due to their rigid conformation, high resistance to enzymatic degradation, cell permeability, they have emerged in recent years as biologically validated platforms for drug discovery [1,2].

The synthesis by conventional multi-step methodology of 2,5-Diketopiperazines (2,5 DKP) has several disadvantages such as; limited structural diversification, drastic conditions, low global yields, use of a large number of reagents and solvents, among others. On the other hand, multicomponent reactions (MCRs) have attracted the interest of various researchers in organic synthesis [3–8], due to their efficiency in the formation of several bonds in a reaction step, considering that saving the number of steps is crucial. to achieve a reduction of the waste generated in the purification processes of the intermediates of the synthesis route, which contributes significantly to the development of friendly strategies with the environment.

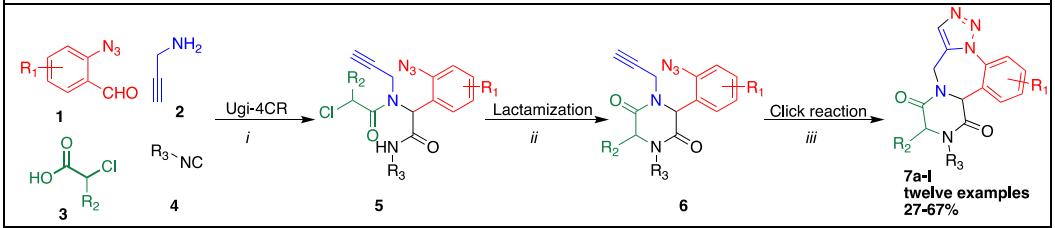
Vroemans R. in 2018 report a three-step protocol for the assembly of triazolobenzodiazepine-fused diketopiperazines [7].

The synthesis was initiated by the Ugi reaction, considering that the product contains orthogonal substituents for further post-transformations. The Ugi adducts were then subjected to a base-induced ring closing and an intramolecular azide–alkyne cycloaddition reaction (CuAAC) in succession to obtain highly fused benzodiazepine frameworks [7]. Recently our group reported the mechanochemical synthesis of DKPs via the four component Ugi reaction (MC-Ugi-4CR) with high yields, free of solvent, and catalyst, at room temperature [3].

Herein, we report, a one-pot synthesis of DKPs linked to another heterocycle 1,4-disubstituted 1,2,3-triazole in ecofriendly reaction conditions.

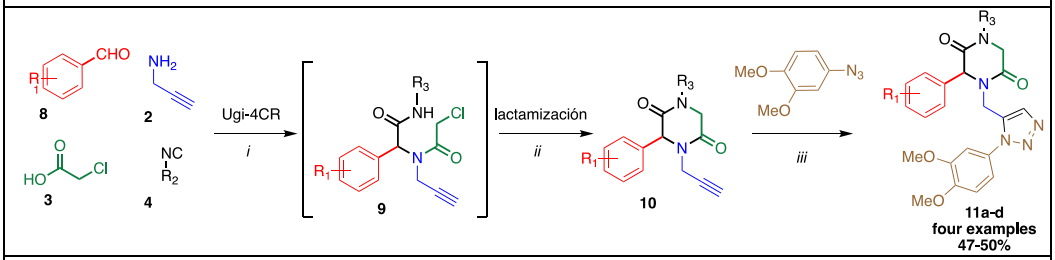
PREVIOUS WORK

Vroemans R. et. al. (2018) [8]



R^1: H, 4-Cl, 3,4-diOMe, 4-NO_2,
R_2: H, Me
R^3: c-Hex, tert-butyl, 4-MeO-Ph, -Bn
i) 4 A MS, MeOH, r.t., 24 h
ii) KOH, EtOH,))), r.t., 30 min
iii) EtO,H reflux, 3 h

This work



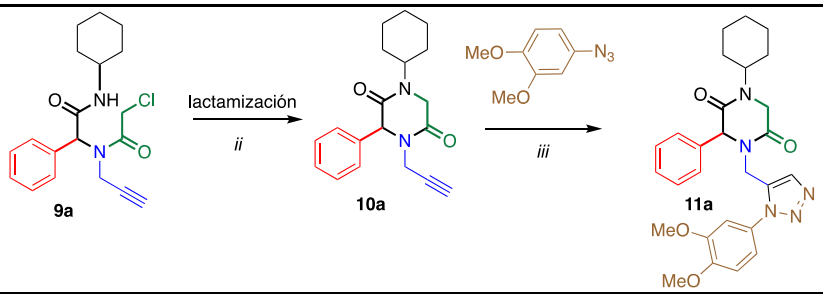
R^1: H, 4-NO_2,
R^3: c-Hex, tert-butyl,
i) $InCl_3$ (4), MeOH, r.t., 24 h
ii) $CsCO_3$ (4), EtOH, r.t., 5 h
iii) $CuCO_4$ (4), BuOH:H_2O, r.t., 2 h

Scheme 1. Previous reports of synthesis of peptidomimetics as 2,5-DKP linked to another heterocycle 1,4-disubstituted 1,2,3-triazole.

2. Results and Discussion

First, we use the conditions for Ugi-4CR previously reported by Us in 2018 [8]. The formation of Ugi-4CR product (**11a**) was made by the simple mixing of benzaldehyde (**8a**), propargylamine (**2**), cyclohexyl isocyanide (**4a**), and chloroacetic acid (**3a**) using $InCl_3$ in MeOH at room temperature. Subsequent, the Ugi-adduct (**9a**) was initially subjected to lactamization with an inorganic base (KOH) to cycle the linear peptide-like Ugi-adduct into the DKP (**10a**). Unfortunately, the resulted was the decomposition of the reaction crude. We tested Cs_2CO_3 as base resulted in complete conversion of (**9a**), these results are show in Table 1. Lately the cyclized product **11a** was subjected to the click reaction without purification. When the $Cu(OAc)_2$ (Table 1) was used as a catalyst, the product **11a** was obtained in 40%, but when we use as a catalytic $CuSO_4$ and sodium ascorbate as a reducing agent the yield was 50% (Table 1).

Table 1. Screening conditions for the synthesis of molecule **11a**.



(i)—Lactamization (entries 1–2)				
Entry	Solvent	Base	Time	Conversion
1	EtOH	KOH [a]	1 h	Decomp
2	EtOH	Cs_2CO_3 [a]	5 h	C
(ii)—Click reaction (entries 3–4)				
Entry	Solvent	Catalyst	Time	Yield **11a** (%)
3	$^tBuOH:H_2O$	$Cu(OAc)_2$ [a,b]	4 h	40
4	$^tBuOH:H_2O$	$CuSO_4$ [a,b]	2 h	50

a = stirring, b = with sodium ascorbate, C = conversion, decomp = decomposition.

The conditions showed in entry 2 and 4 were utilized to synthesize a series of four functionalized DKPs (Scheme 2). The versatility of the developed methodology was explored using different orthogonal bifunctional reagents. The products (**11a–d**) was obtained in moderate yields (47–50%). 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).

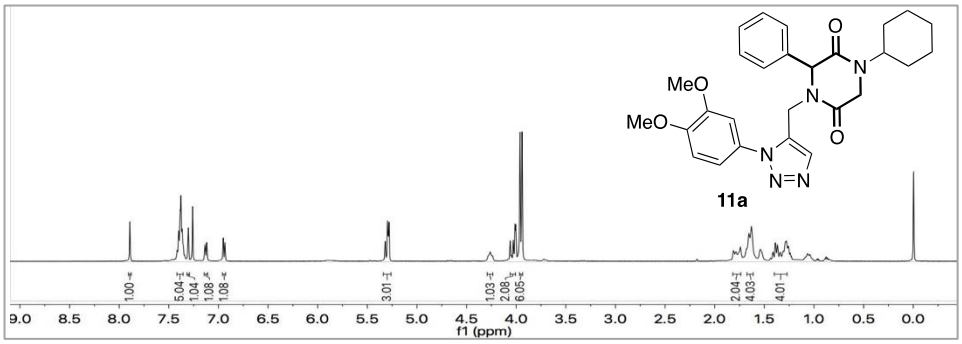
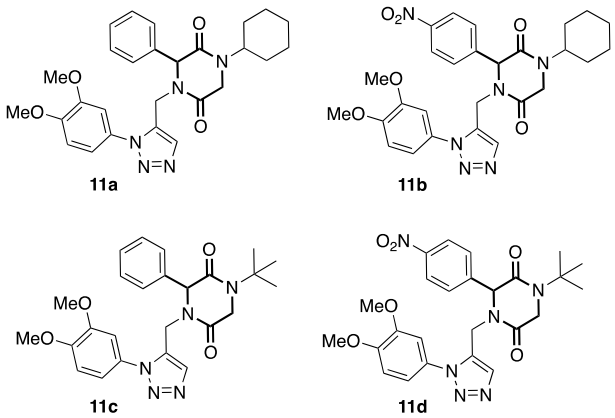


Figure 1. ^1H NMR spectrum of compound **11a**.



Scheme 2. Substrate Scope.

3. Experimental Section

3.1. General Information, Instrumentation and Chemicals

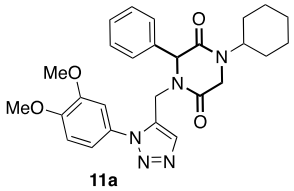
General Information: ^{1}H and ^{13}C NMR spectra were acquired on Bruker Advance III spectrometer (500 MHz). The solvent for NMR samples was $CDCl_3$. Chemical shifts are reported in parts per million (δ/ppm). Tetramethylsilane as internal reference for NMR ($\delta H = 0$ ppm). Coupling constants are reported in Hertz (J/Hz). Multiplicities of the signals are reported using the standard abbreviations: singlet (s), doublet (d), triplet (t), doublets of doublet and multiplet (m). HRMS spectra were acquired via electrospray ionization ESI (+) and recorded via the TOF method. The reaction progress was monitored by TLC and the spots were visualized under UV light (254–365 nm). The products were isolated via precipitation method using dichloromethane/hexane as solvent system or via flash column chromatography using silica gel (230–400 mesh) and eluents in different proportions. Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Commercially available reagents were used without further purification. Structures names and drawings were performed using the ChemBioDraw software (version 16.0.1.4(61)).

3.2. General Procedure (11 a–d)

To a solution of 0.5 M anhydrous MeOH, aldehyde 50 mg, propargylamine (1 eq) was added and stirred for 5 min followed by addition of $InCl_3$ (10 mol%), isocyanide (1 eq) and monochloro acetic acid (1 eq) and stirred for 24 h at room temperature till completion of reaction was observed on TLC. Later, the solvent was evaporated under reduced pressure. Next, the same flask with the dry product was charged with EtOH (1 M) and Cs_2CO_3 (1 eq) and was stirred and monitored by TLC for 5 h to induced cyclization, ones the reaction was completed, the EtOH was evaporate in vacuo, and 1 M solution of *t*-BuOH: H_2O (1:1) and 3,4 dimethoxy azide sodium ascorbate (40 mol%) and $CuSO_4.H_2O$ (10 mol%) were added and the reaction mixture was stirred for another 2 h to completion of click reaction. Subsequent, the crude of reaction was extracted with EtOAc and water (3 × 30 mL). Organic layer was dried with Na_2SO_4 and evaporated in vacuo. The product pure **11a–11b** was obtained by precipitation using dichloromethane/hexane, to obtain the product pure **11c–11d**. was performed a purification by flash column chromatography using silica gel (230–400 mesh), and Hexane/ EtOAc (3:7 *v*/*v*) as a mobile phase

3.3. Spectral Data

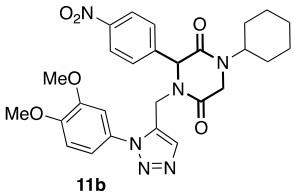
3.3.1. 1-cyclohexyl-4-((1-(3,4-dimethoxyphenyl)-1H-1,2,3-triazol-4-yl) methyl)-3-phenylpiperazine-2,5-dione (11a)



11a

According to *GP*, Benzaldehyde (50 mg, 0.47 mmol), propargylamine (0.03 mL, 0.47 mmol), $InCl_3$ (10 mol%), cyclohexyl isocyanide (0.06 mL, 0.47 mmol), 2-chloroacetic acid (44.52 mg, 0.47 mmol), gives as a product of synthesis a white solid (219.0 mg, 50%), mp = 182–183 °C, $R_f = 0.3$ (Hex/AcOEt = 2/8 *v*/*v*). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.43–7.35 (m, 5H), 7.30 (s, 1H), 7.15–7.11 (m, 1H), 6.96–6.92 (m, 1H), 5.34–5.27 (m, 3H), 4.30–4.22 (m, 1H), 4.07–3.99 (m, 2H), 3.98–3.92 (m, 6H), 1.82–1.73 (m, 2H), 1.69–1.54 (m, 4H), 1.42–1.24 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.7, 164.0, 149.7, 149.5, 142.9, 135.5, 130.5, 129.3, 128.8, 126.7, 121.6, 112.5, 111.1, 105.0, 64.1, 56.3, 56.2, 52.7, 44.7, 39.3, 29.4, 29.1, 25.4, 25.3 (2). **HRMS** (ESI+): *m*/*z* calcd. for $C_{27}H_{31}N_5O_4Na^+$ $[M+Na]^+$ 512.2274, found 512.2376.

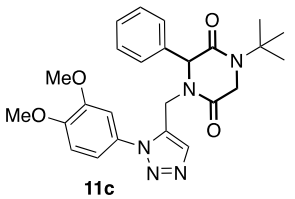
3.3.2. 1-cyclohexyl-4-((1-(3,4-dimethoxyphenyl)-1H-1,2,3-triazol-4-yl) methyl)-3-(4-nitrophenyl) piperazine-2,5-dione (11b)



11b

According to *GP*, 4-nitrobenzaldehyde (50 mg, 0.33 mmol), propargylamine (0.02 mL, 0.33 mmol), $InCl_3$ (10 mol%), cyclohexyl isocyanide (0.04 mL, 0.33 mmol), 2-chloroacetic acid (31.26 mg, 0.33 mmol) gives as a product of synthesis a white solid (168 mg, 50%), mp = 184–185 °C, R_f = 0.3 (Hex/AcOEt = 2/8 *v*/*v*). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.3 Hz, 2H), 8.09–8.05 (m, 1H), 7.92 (s, 1H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.21 (s, 1H), 7.09 (d, *J* = 8.8 Hz, 1H), 6.95 (d, *J* = 8.5 Hz, 1H), 4.62 (d, *J* = 15.5 Hz, 1H), 4.37 (d, *J* = 15.7 Hz, 1H), 3.94 (s, 6H), 3.86–3.81 (m, 1H), 3.23 (d, *J* = 15.3 Hz, 1H), 2.03–1.90 (m, 2H), 1.78–1.60 (m, 5H), 1.42–1.30 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.7, 167.3, 149.9, 147.7, 144.7, 130.0, 127.6, 123.9, 121.3, 112.8, 111.2, 105.0, 66.2, 56.3, 51.9, 49.7, 36.4, 32.7, 32.6, 25.4, 25.0. **HRMS** (ESI+): *m*/*z* calcd. for $C_{27}H_{31}N_6O_6Na^+$ $[M+Na]^+$ 557.2125, found 557.2114.

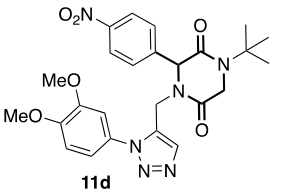
3.3.3. 1-(tert-butyl)-4-((1-(3,4-dimethoxyphenyl)-1H-1,2,3-triazol-4-yl) methyl)-3-phenylpiperazine-2,5-dione (11c)



11c

According to *GP*, Benzaldehyde (50 mg, 0.47 mmol), propargylamine (0.03 mL, 0.47 mmol), $InCl_3$ (10 mol%), tertbutyl isocyanide (0.05 mL, 0.47 mmol), 2-chloroacetic acid (39.17 mg, 0.47 mmol), gives as a product of synthesis a white solid (203 mg, 47%), mp = 176–177 °C, R_f = 0.3 (Hex/AcOEt = 2/8 *v*/*v*). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.42–7.33 (m, 5H), 7.31 (S, 1H), 7.14–7.11 (m, 1H), 6.96–6.93 (m, 1H), 5.30–5.25 (m, 1H), 5.15 (s, 1H), 4.17–4.01 (m, 3H), 3.97–3.92 (m, 6H), 1.37 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.2, 164.9, 149.8, 149.5, 142.8, 135.8, 130.5, 129.2, 128.7, 126.7, 121.7, 112.5, 111.2, 105.0, 65.1, 58.1, 56.3, 56.2, 46.9, 39.2, 27.7. **HRMS** (ESI+): *m*/*z* calcd. for $C_{25}H_{29}N_5O_4^+$ $[M+Na]^+$ 486.2117, found 486.2112.

3.3.4. 1-(tert-butyl)-4-((1-(3,4-dimethoxyphenyl)-1H-1,2,3-triazol-4-yl) methyl)-3-(4-nitrophenyl) piperazine-2,5-dione (11d)



11d

Based on *GP*, 4-nitrobenzaldehyde (50 mg, 0.33 mmol), propargylamine (0.02 mL, 0.30 mmol), $InCl_3$ (10 mol%), tertbutyl isocyanide (0.04 mL, 0.33 mmol), 2-chloroacetic acid (31.26 mg, 0.33 mmol), gives as a product of synthesis a white solid (156.4 mg, 47%), mp = 179–180 °C, R_f = 0.3 (Hex/AcOEt = 2/8 *v*/*v*) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16–8.12 (m, 2H), 7.92 (s, 1H), 7.64 (s, 1H), 7.50–7.46 (m, 2H), 7.18 (s, 1H), 7.09–7.05 (m, 1H), 6.95–6.91 (m, 1H), 4.62–4.57 (m, 1H), 4.49–4.43(m, 1H), 3.92 (s, 6H), 3.85–3.89 (m, 1H), 3.18–3.13 (m, 1H),

1.43 (s, 9H).^{13}C NMR (126 MHz, $CDCl_3$) δ 167.75, 167.47, 149.90, 149.83, 147.64, 145.03, 127.55, 123.91, 112.69, 111.26, 104.88, 66.69, 56.23, 52.90, 51.71, 36.19, 28.28. **HRMS** (ESI+): *m*/*z* calcd. for $C_{25}H_{28}N_6O_6^+$ 509.2070, found 509.2074.

4. Conclusions

This work contributes with a novel one-pot synthesis of peptidomimetics as 2,5-DKP linked to another heterocycle 1,4-disubstituted 1,2,3-triazole (**11a–d**), via an IMCR/post-transformation/CuAAC strategy in environmentally friendly conditions. The one-pot consecutive process was developed by combining two powerful tools (IMCR and click), resulting in a convergent alternative protocol towards the one-pot synthesis of peptidomimetics of interest in the design of new bioactive molecules. The final products were obtained in yields of 47–50%. This methodology is a contribution to the synthesis of bis-heterocycles of interest to medicinal chemistry.

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Conflicts of Interest: The authors declare no conflict of interest.

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