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Proceeding Paper

One Pot Synthesis of Tetrahydro-*1H*-β-carbolines via Ugi-Azide/Pictet–Spengler Process †

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Abstract: Tetrahydro-β-carbolines (THβCs) are privileged heterocycles present in natural products and pharmaceutical compounds. On the other hand, 1,5-disubstituted-tetrazoles (1,5-DS-1H-T) are bioisosteres of *cis*-amide bond that improve the pharmacokinetic and pharmacodynamic properties in structural conformationally restricted peptidomimetics. Ugi-azide/post-transformation, as a multicomponent based one-pot synthesis, is a versatile and efficient strategy to achieve heterocycles of acquired value. Herein we developed the one-pot synthesis of tetrahydro-1*H*-β-carbolines via Ugi-azide/Pictet–Spengler strategy under mild conditions.

Keywords: tetrahydro- β-carboline; Ugi-azide; Pictet-Spengler

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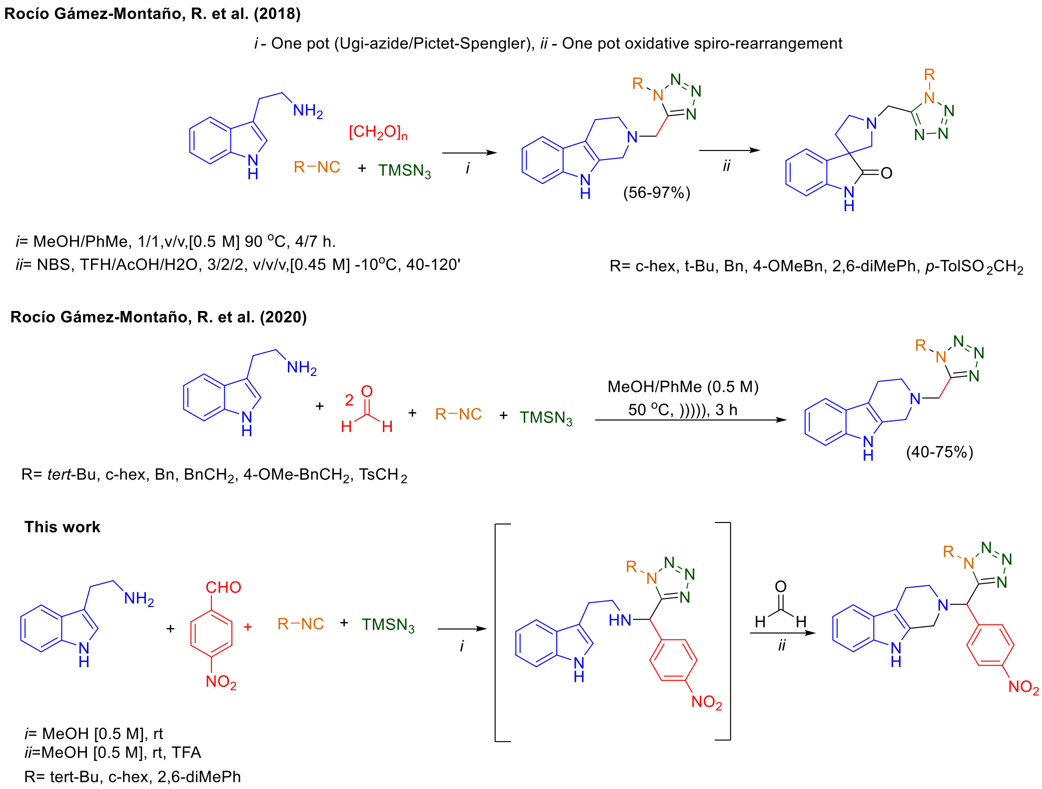
1. Introduction

The β-carboline alkaloids are a group of natural or synthetic indole alkaloids that contain a common tricyclic pyrido [3,4-b] indole ring in their structure [1–3]. The completely saturated members are known as tetrahydro-β-carboline (THβCs) which is one of the most interesting types of fused heterocycles. Natural or synthetic derivatives of THβCs are privileged molecules because they are present in a wide variety of bioactive compounds and commercial drugs [4]. On other hand, 1,5-disubstituted-tetrazoles (1,5-DS-1H-T) are a privileged class of heterocycles of high interest in medicinal chemistry, being bioisosteres of the *cis*-amide bond in peptides by mimicking their structure, polarity, and hydrogen donor/bond sites [5]. In this context, as a part of our ongoing research program to design and develop Ugi-azide reaction based synthetic strategies toward novel bis-heterocycles containing the 1,5-DS-T moiety connected with privileged heterocyclic scaffolds in medicinal chemistry. The objective compounds of our work have both the 1,5-DS-1H-T and THβCs scaffolds.

The synthesis of THβCs is traditionally achieved through the Pictet-Spengler reaction, which involves the condensation of tryptamines with aldehydes in the presence of protic or Lewis's acids [6]. In contrast, multi-component reactions (MCRs) are pivotal in generating combinatorial libraries of highly functionalized heterocycles for drug discovery. MCRs are notably convergent and efficient, enabling the creation of molecular complexity and diversity in a single step [7,8]. Furthermore, post-modification of MCRs allows for the straightforward production of fused heterocycles. Among these, three-component four-centered reactions are especially effective in creating diverse scaffolds, which are essential for advancing drug discovery [9–11]. In the group of MCRs, isocyanide-based multicomponent reaction (IMCR) is a powerful tool that plays a central role in the synthesis of heterocycles. The Ugi-azide reaction allow the convergent and efficient access to tetrazole scaffolds and is the most efficient methodologies to synthesize 1,5-DS-T. The combination with post-transformation processes allows increase molecular complexity [12].

We propose that the MCR process outlined here may be well-suited for the swift assembly of tetrahydro-β-carboline scaffolds, providing a complementary alternative to previously established methods. (Scheme 1). In this work a one-pot five-component two-step sequential synthesis are developed to afford more complex products.



Scheme 1. Previous work and this work.

2. Results and Discussion

After exploration of the reaction conditions tryptamine (1), 4-nitrobenzaldehyde (2), isocyanides (3), and azidotrimethylsilane (4) were reacted together in MeOH [0.5 M] at room temperature with stirring by 6–12 h. After completion of Ugi-azide adduct indicated by TLC, formaldehyde 37% solution (6) and catalyst were added and reacted by 8–11 h at the same conditions to afford the product (7 a–c) in moderate yields (48–53%).

We explored the versatility of this methodology employing isocyanides of different chemical nature.

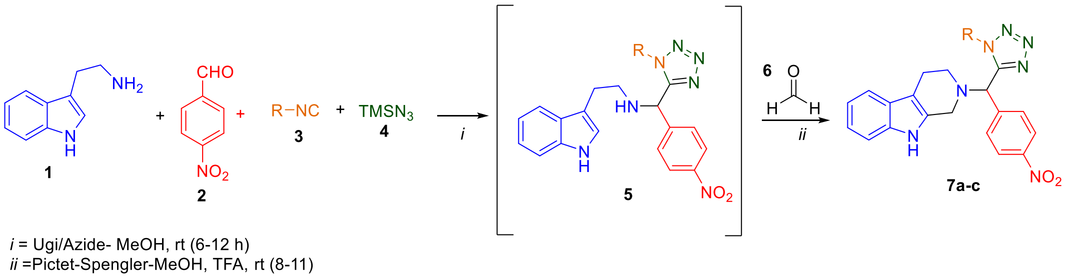
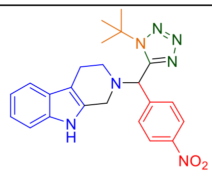
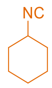
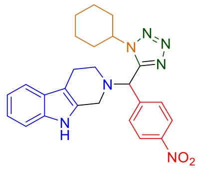
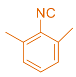
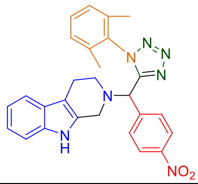


Table 1. This is a table. Tables should be placed in the main text near to the first time they are cited.

Entry	Isocyanide	Product	Time (h) [a]	Yield (%) [b]
7a			18	53
7b			14	48
7c			26	50

[a] One-pot time (UA/PS); [b] Isolated yield.

As seen, the product 7c was obtained in the highest time may be due to steric hindrance and the use of the less nucleophilic isocyanide.

One of the key advantages of these strategies is the relatively high complexity of the substituents at the C-5 position of the tetrazole ring. In this work, we employed two aldehydes in the methodology, which enhances the molecular complexity of the final products. Additionally, using methanol in both reactions facilitates a one-pot process through a domino reaction offering benefits that it is likely to result in greater product diversity and significantly reduce the effort required to synthesize the compounds.

As well, the products obtained may be used as synthetic platform for post-trasnformations, process that we report in previously reports [13].

3. Experimental Section

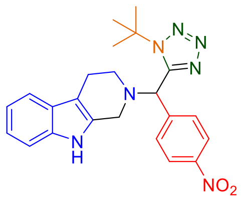
3.1. General Information

^{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 (δH = 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). The reaction progress was monitored by TLC and the spots were visualized under UV light (254–365 nm). NMR spectra were analyzed using MestreNova software version 12.0.0-20080. The products were isolated via flash column chromatography using silica gel (230–400 mesh) and eluents in different proportions. Commercially available reagents were used without further purification. Structures names and drawings were performed using the ChemBioDraw software (version 22.0.0).

3.2. Spectral Data

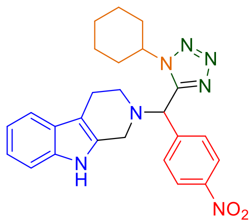
2-((1-(tert-butyl)-1H-tetrazol-5-yl)(4-nitrophenyl)methyl)-2,3,4,9-tetrahydro-1H-pyrido [3,4-b]indole (1a)

2-((1-(tert-butyl)-1H-tetrazol-5-yl)(4-nitrophenyl)methyl)-2,3,4,9-tetrahydro-1H-pyrido [3,4-b]indole (7a)



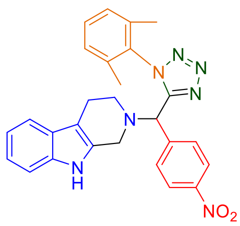
Yellow-pale oil after purification by silica gel column chromatography using a mixture of hexanes with ethyl acetate 7/3 to 3/2 (*v*/*v*) as eluent; Rf = 0.52 (hexanes–AcOEt, 1/1, *v*/*v*); 1H NMR (500 MHz, d6-DMSO, TMS): δ 8.21 (d, 2H), 7.82 (s, 1H), 7.70 (d, 2H), 7.42 (d,1H), 7.24 (d,1H), 7.05–7.12 (m, 2H), 5.77 (s, 1H), 4.0–4.15 (m, 2H), 3.60–3.80 (m, 2H), 2.91–3.01 (m, 2H), 1.72 (s, 9H).

2-((1-cyclohexyl-1H-tetrazol-5-yl)methyl)-2,3,4,9-tetrahydro-1H-pyrido [3,4-b]indole (7b)



Brow orange oil after purification by silica-gel column chromatography using a mixture of hexanes with ethyl acetate 7/3 to 3/2 (*v*/*v*) as eluent; Rf = 0.58 (hexanes–AcOEt, 1/1, *v*/*v*); ^{1}H NMR (500 MHz, d6-DMSO, TMS): δ 8.20–8.25 (m, 2H), 7.98 (s, 1H), 7.76–7.71 (m, 2H), 7.46 (d, J = 7.55, 1H), 7.28–7.25 (m, 2H), 7.15–7.25 (m, 2H), 7.15–7.07 (m, 1H), 5.49 (s, 1H), 4.53 (m, 1H), 3.85 (d, j = 14.47, 1H), 3.63 (d, J = 14.46, 1H), 3.03–2.96 (m, 2H), 2.90–2.77 (m, 2H), 2.05–1.95 (m, 2H), 1.92–1.80 (m, 2H), 1.72–1.69 (m, 2H), 1.61–1.56 (m,2H), 1.30–1.28 (m, 2H).

2-((1-(2,6-dimethylphenyl)-1H-tetrazol-5-yl)methyl)-2,3,4,9-tetrahydro-1H-pyrido [3,4-b] indole (7c)



Reddish oil after purification by silica- gel column chromatography using a mixture of hexanes with ethyl acetate 7/3 (*v*/*v*) as eluent Rf = 0.50 (hexanes–AcOEt, 3/2, *v*/*v*), ^{1}H NMR (500 MHz, CDCl3, TMS): δ 8.16–8.12 (m, 2H), 8.07–8.04 (m, 2H), 7.88 8 (s, 1H), 7.55–7.52 (m, 1H), 7.42–7.36 (m, 1H), 7.27–7.20 (m, 1H), 7.13–7.16 (m, 2H), 7.15–7.12 (m, 2H), 6.31 (s, 1H), 3.91 (d, J = 14.50, 1H), 3.77 (d, J = 14. 42, 1H), 3.69–3.64 (m, 2H), 3.30–3.20 (m, 2H), 1.98 (s, 6H).

4. Conclusions

This work contributes to the multicomponent one-pot synthesis of bis-heterocycles. The developed strategy include the sequence via Ugi-Azide/Pictet Spengler under room temperature. The synthesized heterocyclic molecules contain in their structure privileged drug-scaffolds such as 1,5-DS-T and βTHCs (), which are found in many bioactive compounds and pharmaceuticals.

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visualization, ; supervision, ; project administration; writing—original draft preparation, funding acquisition, . All authors have read and agreed to the published version of the manuscript.

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