

Type of the Paper (Abstract, Meeting Report, Preface, Proceedings, etc.)

Synthesis of the 2-tetrazolylmethyl-2,3,4,9-tetrahydro-1*H*- β -carbolines via ultrasound-assisted one-pot Ugi-azide/Pictet–Spengler process [†]

Manuel A. Rentería Gómez ¹ Luis E. Cárdenas Galindo ² and Rocío Gámez-Montaña ^{1,*}

1 Departamento de Química, Universidad de Guanajuato, Noria Alta S/N, Col. Noria Alta, C.P. 36050 Guanajuato, Gto., Mexico; vmxrntclonealex@gmail.com (M.A.R.-G.)

2 Universidad Tecnológica de Salamanca. Área Química Industrial. Av. Universidad Tecnológica No. 200. Col. Ciudad Bajío. C.P. 36766, Salamanca, Guanajuato, México; lcardenas@utsalamanca.edu.mx (L.E.C.-G.)

* Correspondence: rociogm@ugto.mx (R.G.-M); Tel.: +52-473-73-20006 ext. 8191

[†] The 23rd International Electronic Conference on Synthetic Organic Chemistry, 15 November–15 December 2018; Available Online: <https://sciforum.net/conference/ecsoc-23>

Received: date; Accepted: date; Published: date

Abstract: A serie of 2-tetrazolylmethyl-2,3,4,9-tetrahydro-1*H*- β -carbolines were synthesized via a one pot Ugi-azide/Pictet–Spengler process under mild ultrasound-assisted conditions. The products containing two privileged heterocyclic frameworks: 1,5- disubstituted-1*H*-tetrazole and tetrahydro- β -carboline, which are present in a variety of bioactive compounds and commercial drugs.

Keywords: Ugi-azide/Pictet–Spengler; ultrasound-assisted; 1,5-disubstituted-tetrazole; β -carboline

1. Introduction

Tetrahydro-1*H*- β -carboline is one of the most interesting types of fused heterocycles. Natural or synthetic derivatives are privileged molecules because they are present in a wide variety of bioactive compounds and commercial drugs, including some alkaloids derivatives as nazlinine (1), trypargine (2), homotrypargine (3) and Neolamarckine (4). These heterocycles exhibit a broad spectrum of biological activities: antimalarial, neurotoxic, antihelminthic and serotonergic [1].

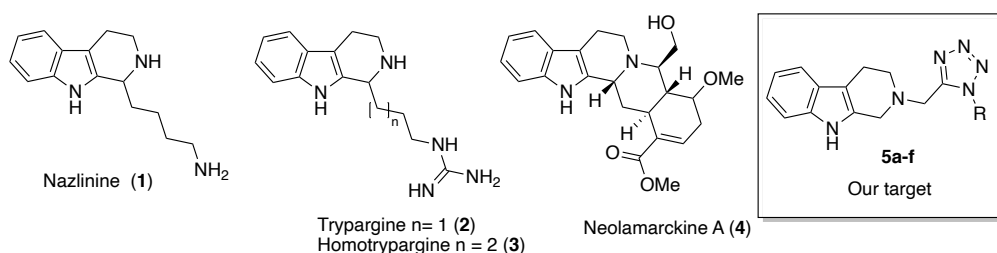


Figure 1. Some natural tetrahydro- β -carbolines

Additionally, 1,5-disubstituted-tetrazoles (1,5-DS-T) are a privileged class of heterocycles of high interest in medicinal chemistry because they are bioisosteres of the cis-amide bond of peptides by mimicking their bioactive conformations [2].

In this context, the interest in design and synthesis of bis-heterocycles containing 1,5-disubstituted-tetrazole moiety lies in their pharmacophoric features and abilities to improve

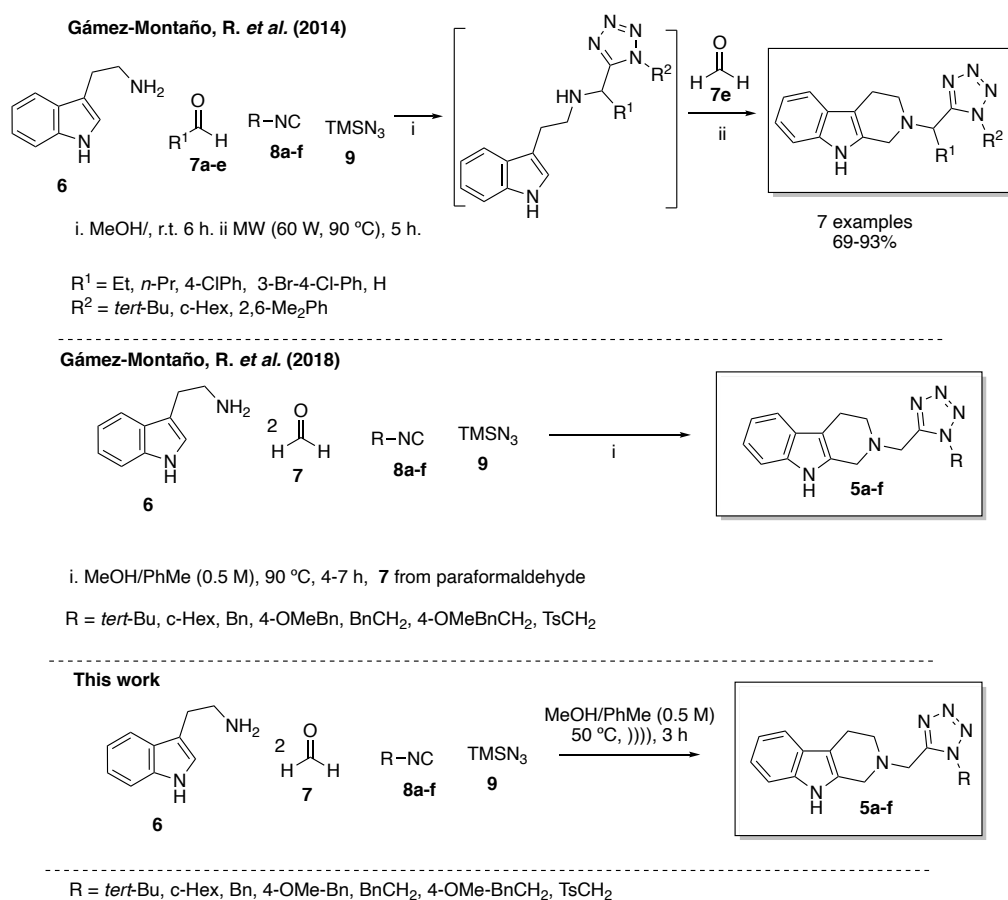
pharmacokinetic and pharmacodynamic properties like the increase of metabolic resistance and decrease of toxicity [3].

Several methods have been described for preparing of 1,5-DS-T, the most common methodologies for the synthesis of these are: (i) the [2 + 3] of azides with nitriles, which have limitations as high temperatures and long reaction times and ii) the Ugi-azide (UA) reaction, a variant of the Ugi multicomponent process, between an aldehyde, an amine, an isocyanide in which the carboxylic acid is replaced by hydrazoic acid [4]. On the other hand, the Pictet–Spengler (PS) reaction is the most popular approach to construct β -carboline derivatives from tryptamines [5-6].

The isocyanide-based multicomponent reaction (IMCR) is a powerful tool that plays a central role in the synthesis of heterocycles. UA 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 [4].

In recent years ultrasound irradiation (USI) has gained more attention in modern synthetic chemistry. The reactions assisted by USI accelerates the rate of reaction and reduce reaction times at ambient temperature. The use of USI in IMCR is little explored [7-14].

The methodology described here allows the one-pot synthesis of 2-tetrazolylmethyl-2,3,4,9-tetrahydro-1*H*- β -carbolines (**5a-f**) via ultrasound-assisted one-pot UA/PS process. The change of paraformaldehyde to formaldehyde is an alternative to carry out the reaction under milder conditions and shorter reaction times, compared to previous reports [15].

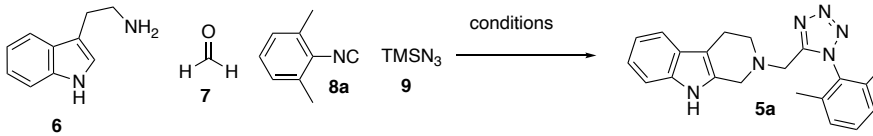


Scheme 1. Previous reports and our work.

2. Results and Discussion

In order to develop conditions for the UA/PS process, we started the synthesis of 2-tetrazolylmethyl-2,3,4,9-tetrahydro-1*H*- β -carbolines analogue **5a** by reacting triptamine (**6**), paraformaldehyde (**7**), 2,6-dimethylphenyl isocyanide (**8a**) and azidotrimethylsilane (**9**). Initially we performed the UA/PS process under USI conditions at room temperature, the **5a** product was generated in traces after 3 h (Entry 1, Table 1). When the reaction was performed at 60 °C (Entry 2), only traces of **5a** was detected. Changing the paraformaldehyde to formaldehyde solution in the next experiments better results were obtained. When the reaction was performance under room temperature after 12 h (Entry 3) the yield increased to 41%. The use of USI (Entries 4-5) resulted in better yields of 45% and 59%, after 1 and 2 h, respectively. Performing the reaction at 60 °C, the yield calculated was 65% (Entry 6). We then tested TFA as catalyst, the product yield increased to 72% at room temperature (Entry 7) [15]. And performing the TFA-catalyzed reaction at 60 °C the yield of product **5a** was 75% (Entry 8, Table 1).

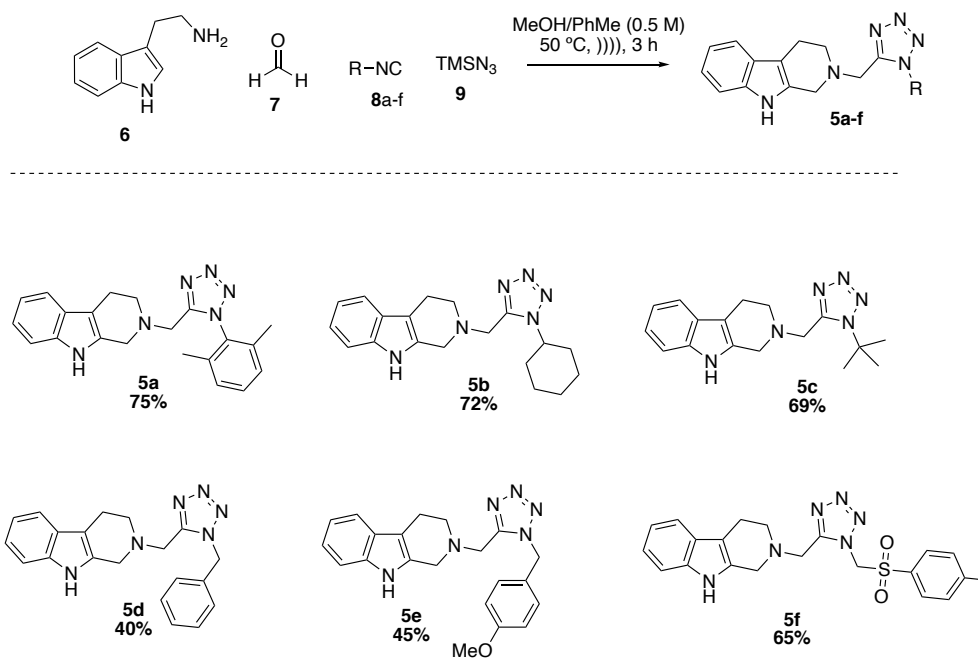
Table 1. Reaction optimizing conditions **5a**.



Entry ^a	Solvent ^b	Additive ^c	T (°C)	Time (h)	Yield (%) ^d
1 ^e	PhMe/MeOH	---	rt USI	3	traces
2 ^e	PhMe/MeOH	---	60 USI	3	traces
3 ^f	PhMe/MeOH	---	rt	12	41
4 ^f	PhMe/MeOH	---	rt USI	1	45
5 ^f	PhMe/MeOH	---	rt USI	2	59
6 ^f	PhMe/MeOH	---	60 USI	2	65
7 ^f	PhMe/MeOH	TFA	rt USI	2	70
8 ^f	PhMe/MeOH	TFA	60 USI	2	75

^a Reactions performed with 1.0 equiv. triptamine (**6**), 2.2 equiv. of paraformaldehyde (**7**) or 3.0 equiv. of formaldehyde (**7**), 1.0 equiv. of 2,6-dimethylphenyl isocyanide (**8**) and 1.0 equiv. of azidotrimethylsilane (**9**). ^b [0.5 M] ^c 5 % mol. ^d Isolated yield. r.t. = room temperature. ^e paraformaldehyde. ^f formaldehyde 37% solution.

Using optimized conditions, the series of 2-tetrazolylmethyl-2,3,4,9-tetrahydro-1*H*- β -carbolines (**5a–f**) shown in Scheme 2 were synthesized. The versatility of the developed methodology was examined using different isocyanides as aryl, alkyl, benzyl and tosyl (**8a–f**). The respective products **5a–f** were obtained in moderate to good yields (40–79%).



Scheme 2. Sustrate scope

Figures 2 and 3 show the ¹H and ¹³C NMR spectra for the representative 2-tetrazolylmethyl-2,3,4,9-tetrahydro-1H-β-carboline 5a.

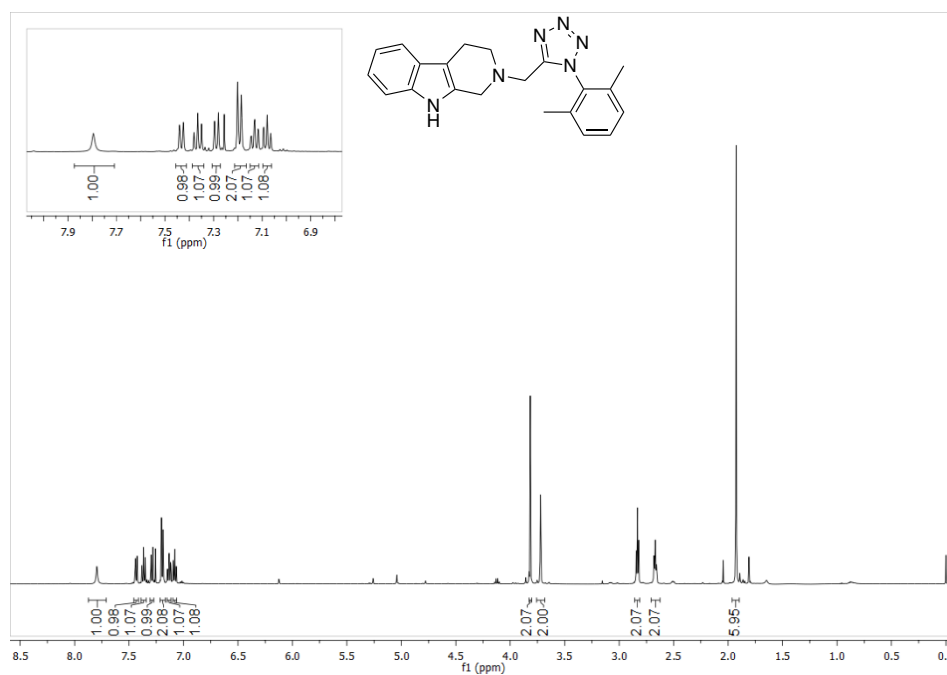


Figure 2. ¹H NMR spectrum of 2-tetrazolylmethyl-2,3,4,9-tetrahydro-1H-β-carboline 5a.

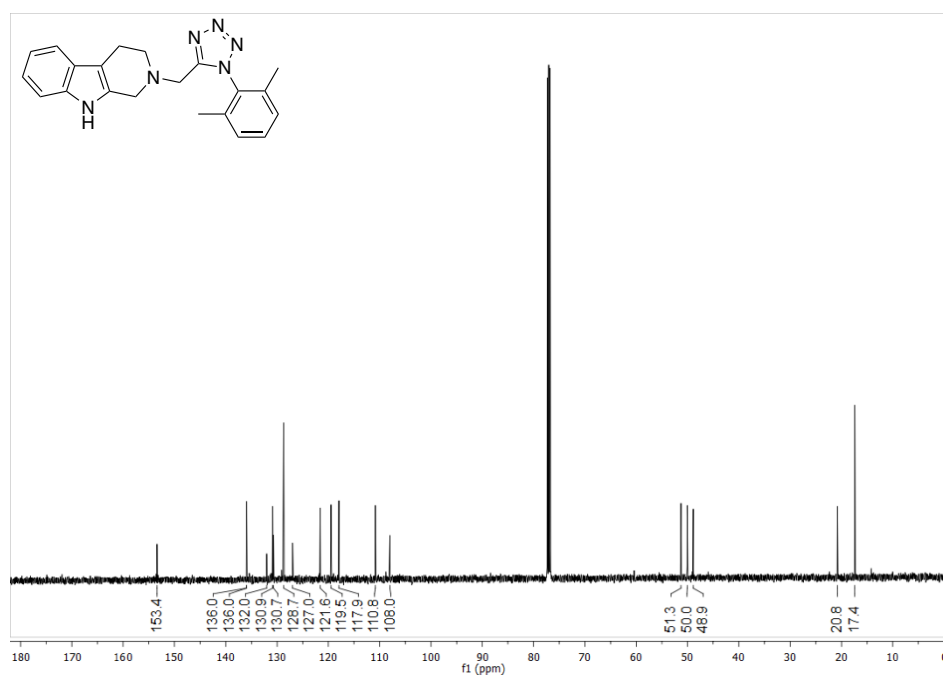


Figure 3. ¹³C NMR spectrum of 2-tetrazolylmethyl-2,3,4,9-tetrahydro-1H-β-carboline **5a**.

3. Experimental Section

3.1. General information, Instrumentation, and Chemicals

¹H and ¹³C NMR spectra were acquired on Bruker Avance III spectrometers (500 or 400 MHz). The solvent used was deuterated chloroform (CDCl₃). Chemical shifts are reported in parts per million (δ/ppm). The internal reference for ¹H NMR spectra is trimethylsilane at 0.0 ppm. The internal reference for ¹³C NMR spectra is CDCl₃ at 77.0 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), quartet (q), and multiplet (m). NMR spectra were analyzed using the MestreNova software version 10.0.1–14719. IR spectra were acquired on a Perkin Elmer 100 spectrometer using an Attenuated Total Reflectance (ATR) method with neat compounds. The absorbance peaks are reported in reciprocal centimeters (ν_{max}/cm⁻¹). Reaction progress was monitored by Thin-Layer Chromatography (TLC) on precoated silica-gel 60 F₂₅₄ plates and the spots were visualized under UV light at 254 or 365 nm. Mixtures of hexane with ethyl acetate (EtOAc) were used to run TLC and for measuring retention factors (*R_f*). Flash column chromatography was performed using silica gel (230–400 mesh) and mixtures of hexane with EtOAc in different proportions (v/v) as the mobile phase. All reagents were purchased from Sigma-Aldrich and were used without further purification. Chemical names and drawings were obtained using the ChemBioDraw Ultra 13.0.2.3020 software package. The purity for all the synthesized products (up to 99%) was assessed by NMR.

3.2. Synthesis and characterization of the 2-tetrazolylmethyl-2,3,4,9-tetrahydro-1H-β-carbolines **5a-f**

General procedure 1 (GP1): Tryptamine (**6**) (1.0 equiv.) in a mixture 1/1 (v/v) of MeOH and PhMe [0.5 M], formaldehyde (**7**) (3.0 equiv. of HCHO), the corresponding isocyanide (**8a**) (1.0 equiv.), and azidotrimethylsilane (**9**) (1.0 equiv.) were placed in a 10 mL sealed vial. The resulting mixture was sonicated at 60 °C (45 kHz) for 1 h and TFA (5% mol) was added. The mixture was again sonicated at 60 °C (45 kHz) for 1 h. Then, the solvent was removed to dryness and the crude was purified by silica-gel column chromatography to afford the products **5a-f**.

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

According to the GP1, tryptamine (**6**) (50.0 mg, 0.312 mmol), formaldehyde 37% solution (**7**) (70.0 μ L, 0.939 mmol of HCHO), 2,6-dimethylphenyl isocyanide (**8a**) (41.0 mg, 0.312 mmol), and azidotrimethylsilane (**9**) (41.0 μ L, 0.312 mmol) were reacted together during 3.0 h in a mixture of MeOH/PhMe [0.5 M] to afford the product **5a** (84 mg, 75%) as a white solid after purification by silica-gel column chromatography using a mixture of hexanes with ethyl acetate 7/3 (v/v) as eluent $r_f = 0.36$ (hexanes–AcOEt, 3/2, v/v); mp = 194–196 °C, FT-IR (ATR) $\nu_{\max}/\text{cm}^{-1}$ 1237 (N₃), 1451 (CN), 3200 (NH); ¹H NMR (500 MHz, CDCl₃, TMS): δ 1.93 (s, 6H), 2.66–2.68 (m, 2H), 2.81–2.83 (m, 2H), 3.71 (s, 2H), 3.81 (s, 2H), 7.07–7.09 (m, 1H), 7.11–7.14 (m, 1H), 7.20 (d, $J = 7.6$ Hz, 2H), 7.29 (d, $J = 8.0$ Hz, 1H), 7.37 (t, $J = 7.4$ Hz, 1H), 7.43 (d, $J = 7.7$ Hz, 1H); ¹³C NMR (126 MHz, CDCl₃, TMS): δ 17.4, 20.8, 48.9, 50.0, 51.3, 107.9, 110.9, 117.9, 119.4, 121.5, 127.0, 128.7, 130.8 (2), 130.9, 132.0, 135.9, 136.0, 153.4; HRMS (ESI⁺): m/z calcd for C₂₁H₂₂N₆⁺ [M+H]⁺ 359.1979, found 359.2000.

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

According to the GP1, tryptamine (**6**) (50.0 mg, 0.312 mmol), formaldehyde 37% solution (**7**) (70.0 μ L, 0.939 mmol of HCHO), cyclohexyl isocyanide (**8b**) (39.0 μ L, 0.312 mmol), and azidotrimethylsilane (**9**) (41.0 μ L, 0.312 mmol) were reacted together during 3 hours in a mixture of MeOH/PhMe [0.5 M] to afford the product **5b** (76.0 mg, 72%) as a pale-yellow solid after purification by silica-gel column chromatography using a mixture of hexanes with ethyl acetate 4/1 to 3/2 (v/v) as eluent; $r_f = 0.17$ (hexanes–AcOEt, 1/1, v/v); mp = 214–216 °C; FT-IR (ATR) $\nu_{\max}/\text{cm}^{-1}$ 1265 (N₃), 1443 (CN), 3206 (NH); ¹H and ¹³C NMR: All attempts to acquire NMR spectra were unsuccessful due to unexpected insolubility problems; HRMS (ESI⁺): m/z calcd for C₁₉H₂₄N₆⁺ [M+H]⁺ 337.2135, found 337.2141.

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

According to the GP1, tryptamine (**6**) (50.0 mg, 0.312 mmol), formaldehyde 37% solution (**7**) (70.0 μ L, 0.939 mmol of HCHO), *tert*-butyl isocyanide (**8c**) (35.0 μ L, 0.312 mmol), and azidotrimethylsilane (**9**) (41.0 μ L, 0.312 mmol) were reacted together during 3 h in a mixture of MeOH/PhMe [0.5 M] to afford the product **5c** (67.0 mg, 69%) as a white solid after purification by silica gel column chromatography using a mixture of hexanes with ethyl acetate 7/3 to 3/2 (v/v) as eluent; $R_f = 0.46$ (hexanes–AcOEt, 1/1, v/v); mp = 235–237 °C, FT-IR (ATR) $\nu_{\max}/\text{cm}^{-1}$ 1270 (N₃), 1451 (CN), 3200 (NH); ¹H NMR (500 MHz, d₆-DMSO, TMS): δ 1.69 (s, 9H), 2.66–2.69 (m, 2H), 2.80–2.83 (m, 2H), 3.61 (s, 2H), 4.14 (s, 2H), 6.91–6.95 (m, 1H), 6.98–7.02 (m, 1H), 7.25 (d, $J = 8.0$ Hz, 1H), 7.35 (d, $J = 7.7$ Hz, 1H), 10.68 (s, 1H); ¹³C NMR (126 MHz, CDCl₃, TMS): δ 21.1, 29.2, 50.0, 50.5, 50.9, 62.3, 106.7, 111.4, 117.9, 118.8, 121.0, 127.0, 132.3, 136.3, 152.1; HRMS (ESI⁺): m/z calcd for C₁₇H₂₂N₆⁺ [M+H]⁺ 311.1979, found 311.1984.

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

According to the GP1, tryptamine (**6**) (50.0 mg, 0.312 mmol), formaldehyde 37% solution (**7**) (70.0 μ L, 0.939 mmol of HCHO), benzyl isocyanide (**8d**) (42.0 μ L, 0.312 mmol), and azidotrimethylsilane (**9**) (41.0 μ L, 0.312 mmol) were reacted together during 3 h in a mixture of MeOH/PhMe [0.5 M] to afford the product **5d** (43.0 mg, 40%) as a white solid after purification by silica-gel column chromatography using a mixture of hexanes with ethyl acetate 7/3 to 3/2 (v/v) as eluent; $R_f = 0.40$ (hexanes–AcOEt, 1/1, v/v); mp = 165–167 °C; FT-IR (ATR) $\nu_{\max}/\text{cm}^{-1}$ 1239 (N₃), 1456 (CN), 3258 (NH); ¹H NMR (500 MHz, CDCl₃, TMS): δ 2.62–2.71 (m, 2H), 2.82–2.85 (m, 2H), 3.68 (s, 2H), 4.15 (s, 2H), 5.73 (s, 2H), 6.94–6.97 (m, 1H), 7.01–7.04 (m, 1H), 7.27–7.34 (m, 6H), 7.37 (d, $J = 7.6$ Hz, 1H), 10.69 (s, 1H); ¹³C NMR (126 MHz, d₆-DMSO, TMS): δ 21.1, 49.0, 50.1, 50.7, 50.8, 106.6, 111.4, 117.8, 118.8, 120.9, 127.1, 128.7 (2), 129.1, 132.3, 135.1, 136.3, 153.0; HRMS (ESI⁺): m/z calcd for C₂₀H₂₀N₆⁺ [M+H]⁺ 345.1822, found 345.1845.

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

According to the GP1, tryptamine (**6**) (50.0 mg, 0.312 mmol), formaldehyde 37% solution (**7**) (66.0 mg, 2.200 mmol of HCHO), 4-methoxybenzyl isocyanide (**8e**) (132.0 μ L, 1.000 mmol), and azidotrimethylsilane (**9**) (41.0 μ L, 0.312 mmol) were reacted together during 3 h in a mixture of MeOH/PhMe [0.5 M] to afford the product **5e** (53.0 mg, 45%) as a white solid 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 = 0.36 (hexanes–AcOEt, 1/1, v/v); mp = 142–144 °C; FT-IR (ATR) $\nu_{\max}/\text{cm}^{-1}$ 1246 (N3), 1453 (CN), 3200 (NH); ^1H NMR (500 MHz, CDCl_3 , TMS): δ 2.82–2.87 (m, 2H), 2.89–2.91 (m, 2H), 3.55 (s, 2H), 3.72 (s, 3H), 3.93 (s, 2H), 5.63 (s, 2H), 6.77 (d, J = 8.6 Hz, 2H), 7.09–7.12 (m, 1H), 7.14–7.16 (m, 1H), 7.18 (d, J = 8.7 Hz, 2H), 7.31 (d, J = 7.9 Hz, 1H), 7.48 (d, J = 7.7 Hz, 1H), 7.82–7.84 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3 , TMS): δ 21.2, 30.9, 50.0, 50.1, 51.1, 51.3, 55.3, 108.0, 110.9, 114.3, 118.0, 119.6, 121.7, 125.4, 126.9, 129.6, 130.5, 136.0, 151.8, 159.9, 207.0; HRMS (ESI+): m/z calcd for $\text{C}_{21}\text{H}_{22}\text{N}_6\text{O}^+$ [M+H]⁺ 375.1928, found 375.1927.

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

According to the GP1, tryptamine (**6**) (50.0 mg, 0.312 mmol), formaldehyde 37% solution (**7**) (66.0 mg, 2.200 mmol of HCHO), tosylmethyl isocyanide (**8f**) (199.0 μ L, 1.000 mmol), and azidotrimethylsilane (**9**) (41.0 μ L, 0.312 mmol) were reacted together during 3 h in a mixture of MeOH/PhMe [0.5 M] to afford the product **5f** (350.0 mg, 83%) as a white solid after purification by silica-gel column chromatography using a mixture of hexanes with ethyl acetate 1/1 (v/v) as eluent; Rf = 0.56 (hexanes–AcOEt, 1/1, v/v); mp = 149–151 °C, FT-IR (ATR) $\nu_{\max}/\text{cm}^{-1}$ 1057 (SO), 1267 (N3), 1456 (CN), 3229 (NH); ^1H and ^{13}C NMR: All attempts to acquire NMR spectra were unsuccessful due to unexpected insolubility problems; HRMS (ESI+): m/z calcd for $\text{C}_{21}\text{H}_{22}\text{N}_6\text{O}_2\text{S}^+$ [M+H]⁺ 423.1598, found 423.1609.

4. Conclusions

In conclusion, we have developed an efficient ultrasound-assisted one-pot Ugi-azide/Pictet–Spengler process, the use of formaldehyde solution allowed to obtain the products in short reactions time and under mild conditions. The main contribution of this work is the design and development of novel synthetic protocol based on the Ugi-azide reaction towards complex 1,5-DS-T under mild conditions. It is noteworthy that a tetrazole and a five-member ring were constructed in one-pot step.

Author Contributions: All authors contributed equally to this work.

Acknowledgments: M.A.R.G. thanks CONACYT for a scholarship (707974/585367). R.G.-M. thanks CONACYT-México (CB-2016-285622) and DAIP Universidad de Guanajuato ([CIIIC 154/2019](#)) for financial support, the Laboratorio Nacional de Caracterización de Propiedades Físicoquímicas y Estructura Molecular (CONACYT-México, Project: 123732) for the instrumentation time provided.

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.

1. Shmatova, O.I.; Khrustalev, V.N.; Nenajdenko, V.G. From Cyclic CF₃-ketimines to a Family of Trifluoromethylated Nazline and Trypargine Analogues. *Org. Lett.*, **2016**, *18*(18), 4494–4497. doi:10.1021/acs.orglett.6b02031.
2. Herr, R. J. 5-Substituted-1H-tetrazoles as carboxylic acid isosteres: medicinal chemistry and synthetic methods. *Bioorg. Med. Chem.*, **2002**, *10*(11), 3379–3393. doi:10.1016/s0968-0896(02)00239-0
3. Ostrovskii, V.A.; Trifonov, R.E.; Popova, E.A. Medicinal chemistry of tetrazoles. *Russ. Chem. Bull., Int. Ed.* **2012**, *61*(4), 768–780. doi:10.1007/s11172-012-0108-4.
4. Neochoritis, C.G.; Zhao, T.; Dömling, A. Tetrazoles via Multicomponent Reactions. *Chem. Rev.*, **2019**, *119*(3), 1970–2042. doi:10.1021/acs.chemrev.8b00564
5. Cox, E.D.; Cook, J.M. The Pictet–Spengler condensation: a new direction for an old reaction. *Chem. Rev.*, **1995**, *95*(6), 1797–1842. doi:10.1021/cr00038a004.

6. Stöckigt, J.; Antonchick, A.P.; Wu, F.; Waldmann, H. The Pictet-Spengler Reaction in Nature and in Organic Chemistry. *Angew. Chem. Int. Ed.*, 2011, 50(37), 8538–8564. doi:10.1002/anie.201008071.
7. Kurva, M.; Pharande, S.G.; Quezada-Soto, A.; Gámez-Montaño, R. Ultrasound assisted green synthesis of bound type bis-heterocyclic carbazolyl imidazo[1,2-*a*]pyridines via Groebke-Blackburn-Bienayme reaction. *Tetrahedron Lett.*, 2018, 59(16), 1596–1599. doi:10.1016/j.tetlet.2018.03.031.
8. Claudio-Catalán, M.Á.; Pharande, S. G.; Quezada-Soto, A.; Kishore, K. G.; Rentería-Gómez, A.; Padilla-Vaca, F.; Gámez-Montaño, R. Solvent- and Catalyst-Free One-Pot Green Bound-Type Fused Bis-Heterocycles Synthesis via Groebke–Blackburn–Bienaymé Reaction/SNAr/Ring-Chain Azido-Tautomerization Strategy. *ACS Omega*, 2018, 3(5), 5177–5186. doi:10.1021/acsomega.8b00170.
9. Kaveti, B.; Ramírez-López, S.C.; Gámez-Montaño, R. Ultrasound-assisted green one-pot synthesis of linked bis-heterocycle peptidomimetics via IMCR/post-transformation/tandem strategy. *Tetrahedron Lett.* 2018, 59(49), 4355–4358. doi:10.1016/j.tetlet.2018.10.062.
10. Shaabani, A.; Hooshmand, S.E. Diversity-oriented catalyst-free synthesis of pseudopeptides containing rhodanine scaffolds via a one-pot sequential isocyanide-based six-component reactions in water using ultrasound irradiation. *Ultrasonics Sonochemistry*, 2018, 40, 84–90. doi:10.1016/j.ultsonch.2017.06.030.
Pharande, S.G.; Corrales Escobosa, A.R.; Gámez-Montaño, R. Endogenous water-triggered and ultrasound accelerated synthesis of 1,5-disubstituted tetrazoles via a solvent and catalyst-free Ugi-azide reaction. *Green Chemistry*, 2017, 19(5), 1259–1262. doi:10.1039/c6gc03324e.
11. Chandgude, A.L.; Narducci, D.; Kurpiewska, K.; Kalinowska-Tłuścik, J.; Dömling, A. Diastereoselective one pot five-component reaction toward 4-(tetrazole)-1,3-oxazinanes. *RSC Adv.*, 2017, 7(79), 49995–49998. doi:10.1039/c7ra07392e.
12. Unnamatla, M.V B.; Islas-Jácome, A.; Quezada-Soto, A.; Ramírez-López, S. C.; Flores-Álamo, M.; Gámez-Montaño, R. Multicomponent One-Pot Synthesis of 3-Tetrazolyl and 3-Imidazo[1,2-*a*]pyridin Tetrazolo[1,5-*a*]quinolines. *J. Org. Chem.*, 2016, 81(21), 10576–10583. doi:10.1021/acs.joc.6b01576.
13. Chandgude, A.L.; Dömling, A. An efficient Passerini tetrazole reaction (PT-3CR). *Green Chemistry*, 2016, 18(13), 3718–3721. doi:10.1039/c6gc00910g.
14. Mamaghani, M.; Mahmoodi, N.O.; Shirini, F.; Azimi-Roshan, A.; Monfared, A. “On Water” Sonochemical Multicomponent Synthesis of Novel Bioactive 1,1'-(Aryl)bis(2-(cyclohexylamino)-2-oxoethane-1,1-diyl) Di(alkanoates and benzoates). *Journal of Chemistry*, 2013, 1–8. doi:10.1155/2013/125959.
15. Alvarez-Rodríguez, N.V.; Islas-Jácome, A.; Rentería-Gómez, A.; Cárdenas-Galindo, L.E.; Unnamatla, M.V.B.; Gámez-Montaño, R. Synthesis of 1'-tetrazolylmethyl-spiro[pyrrolidine-3,3'-oxindoles] via two coupled one-pot processes Ugi-azide/Pictet–Spengler and oxidative spiro-rearrangement. *New J. Chem.*, 2018, 42(3), 1600–1603. doi:10.1039/c7nj03829a.
16. Gholamzadeh, P. The Pictet–Spengler Reaction: A Powerful Strategy for the Synthesis of Heterocycles. *Advances in Heterocyclic Chemistry*. 2019, 153-226. doi:10.1016/bs.aihch.2018.09.002.

