chemistry proceedings

MDPI

Proceeding Paper

Multicomponent One-Pot Synthesis of 1,5-Disubstituted Tetrazoles Functionalized with Azides †

Diana García-García, Jorge Alejandro Tovar-Rosales, Manuel A. Rentería-Gómez and Rocío Gámez-Montaño *

Departamento de Química, Universidad de Guanajuato, Noria Alta S/N, Col. Noria Alta, Guanajuato 36050, Mexico; diana13g@hotmail.com (D.G.-G.); joralextovar@hotmail.com (J.A.T.-R.); vmx_rntclone@hotmail.com (M.A.R.-G.)

* Correspondence: rociogm@ugto.mx; Tel.: +52-473-732-006 (ext. 8191)

† Presented at the 28th International Electronic Conference on Synthetic Organic Chemistry (ECSOC 2024), 15–30 November 2024; Available online: https://sciforum.net/event/ecsoc-28.

Abstract: 1,5-disubstituted tetrazoles are valuable heterocyclic structures, present in many bioactive compounds and drugs. Additionally, organic azides are useful precursors for synthesizing of nitrogen-containing heterocycles. Isocyanide-based multicomponent reactions are efficient and versatile tools to synthesized heterocycles, in which orthogonal reagents can be included into components to increase its synthetic potential. We described a one-pot process to access 1,5-disubstituted tetrazoles functionalized with azides under mild conditions, which could be synthetic platforms for further post-transformations.

Keywords: 1,5-disubstituted tetrazoles (1,5-DS-1*H*-T); azides; IMCR; Ugi-azide; one-pot

Citation: García-García, D.; Tovar-Rosales, J.A.; Rentería-Gómez, M.A.; Gámez-Montaño, R. Multicomponent One-Pot Synthesis of 1,5-Disubstituted Tetrazoles Functionalized with Azides. *Chem. Proc.* **2024**, *6*, x. https://doi.org/10.3390/xxxxx

Academic Editor(s): Name

Published: 15 November 2024

1. Introduction

1,5-disubstituted tetrazoles (1,5-DS-1*H*-T) are bioisosteres of cis-amide bond which have contributed to decrease toxicity, increase potency, improve stability, selectivity, and pharmacokinetic properties in structural conformationally restricted peptidomimetics [1,2]. Additionally, they have been used as bident ligands, chelating agents, metal-organic framework precursors, bioimaging agents, energetic materials such as explosives, propellants and pyrotechnics [3,4].

On the other hand, organic azides are energy-rich molecules became valuable building blocks in organic synthesis for constructing diverse nitrogen-containing heterocycles via intra- or intermolecular C-N and N-N bond formation [5].

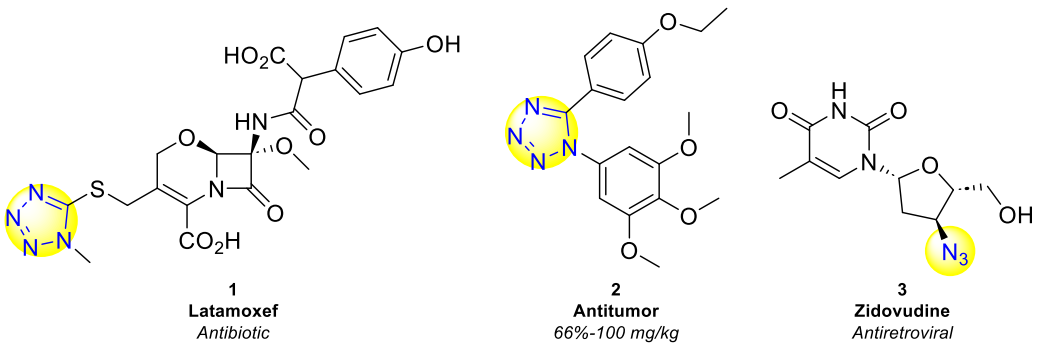
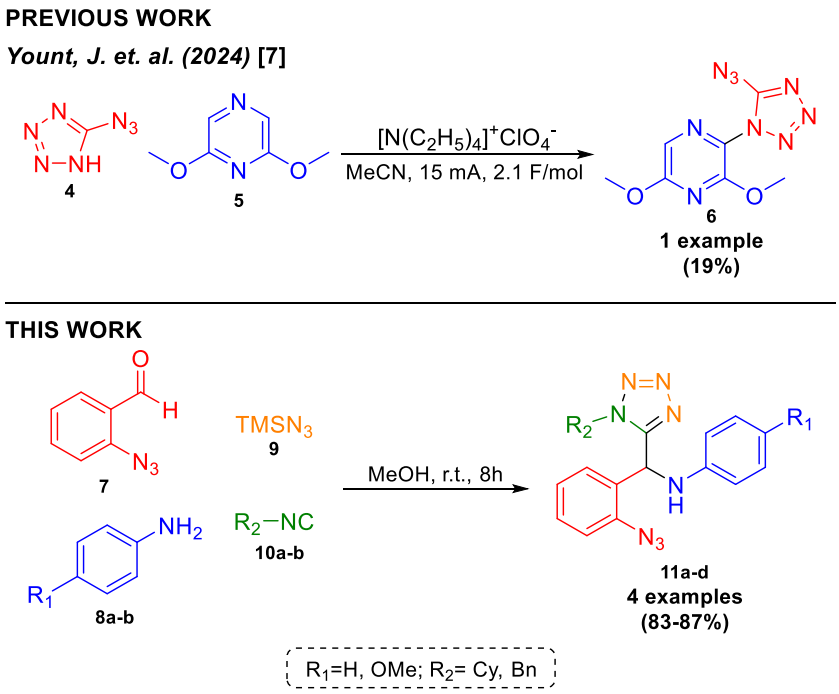


Figure 1. Bioactive molecules containing 1,5-DS-1H-T scaffold and azide group.

Isocyanide based multicomponent reactions have proven to be versatile synthetic tools for the synthesis of heterocycles, specifically the Ugi-azide reaction is the best tool

to access 1,5-DS-1*H*-T under mild conditions in which orthogonal reagents, such as 2-azidobenzaldehyde, can be included to increase its synthetic potential.

The Ugi-azide reaction involve and aldehyde or ketone, an amine, an isocyanide and replaced the carboxylic acid used in the classical Ugi reaction by hydrazoic acid. In that the imine is protonated by hydrazoic acid and the remaining azide anion captures the intermediate nitrilium ion, leading to the formation of the final 1,5-DS-T. In the past, Ugi was using isolated hydrazoic acid in a benzene stock solution. Nowadays, trimethylsilyl azide is often used as safer alternative to azide source, generating hydrazoic acid in situ in protic solvents [6].



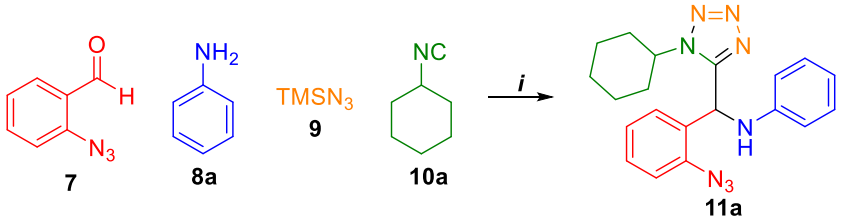
Scheme 1. Previous report of synthesis of 1,5-DS-1*H*-T functionalized with azides.

In the present work, we developed a one-pot synthesis under mild conditions to access functionalized 1,5-DS-1*H*-T which could be synthetic platforms for further post-transformations.

2. Results and Discussion

The synthesis of 1,5-DS-1*H*-T (**11a**) was made via Ugi-azide reaction between 2-azidobenzaldehyde (**7**), aniline (**8a**), trimethylsilylazide (**9**) and cyclohexyl isocyanide (**10a**). In 2017, Gámez-Montaño reported the solvent-free Ugi-azide reaction [8], however further model proposed here wasn't satisfactory. The reaction in MeOH at room temperature resulted in good yields (Table 1, **entries 1–2**).

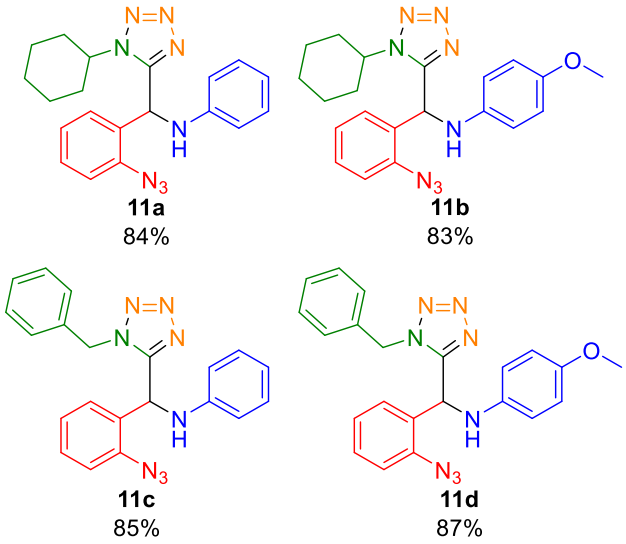
Table 1. Screening conditions for the synthesis of molecule 11**a**.



Entry	Solvent	Temperature	Time	Yield (%)

1	---	r.t.	12 h	Traces
2	**MeOH**	**r.t.**	**8 h**	**84**

In Scheme 2, a series of 1,5-DS-T (**11a–d**) is depicted, which was synthesized under the optimized conditions. The effect of electronic nature of the amine component was evaluated, employing aliphatic and aryl aliphatic isocyanides. Finally, products were obtained in good yields (**83–87%**).



Scheme 2. Synthesis of 1,5-DS-T scope.

3. Experimental Section

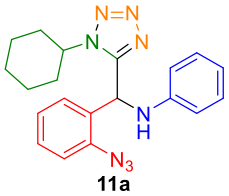
3.1. General Information, Intrumentation and Chemicals

^{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 (δ) 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 14.2.0-26256. 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 purification.

3.2. General Procedure

In a sealed vial, 2-azidobenzaldehyde (**7**, 1.0 equiv.), amine (**8a–b**, 1.0 equiv.), trimethylsilylazide (**9**, 1.0 equiv.) and isocyanide (**10a–b**, 1.0 equiv.) were dissolved in MeOH (1.0 M) and stirred at room temperature for 8 h. The solvent was removed, and the crude was purified by flash chromatography using silica gel and mixtures of ethyl acetate in hexanes as mobile phase and silica gel as stationary phase to afford the corresponding 1,5-disubstituted tetrazoles (**11a–d**).

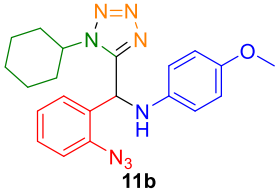
3.3. Spectral Data



11a

N((2-azidophenyl)(1-cyclohexyl-1H-tetrazol-5-yl)methyl)aniline (**11a**)

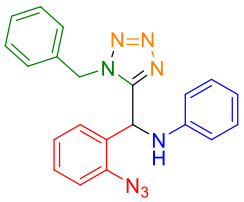
White solid, m.p. 163–165 °C, R_f = 0.58 (30% ethyl acetate in hexanes), ^{1}H (500 MHz, $CDCl_3$, 25 °C, TMS): δ 7.50 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.22–7.10 (m, 4H), 6.76 (t, *J* = 7.4 Hz, 1H), 6.68 (d, *J* = 7.9 Hz, 2H), 6.14 (d, *J* = 8.0 Hz, 1H), 5.05 (d, *J* = 8.0 Hz, 1H), 4.47–4.39 (m, 1H), 2.10–1.94 (m, 3H), 1.92–1.82 (m, 2H), 1.79–1.72 (m, 1H), 1.58–1.52 (m, 1H), 1.47–1.37 (m, 1H), 1.34–1.23 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 154.6, 145.4, 137.2, 130.2, 129.6, 129.1, 129.0, 126.1, 119.3, 118.2, 114.0, 58.4, 47.1, 33.0, 33.0, 25.6, 24.9.



11b

N((2-azidophenyl)(1-cyclohexyl-1H-tetrazol-5-yl)methyl)-4-methoxyaniline (**11b**)

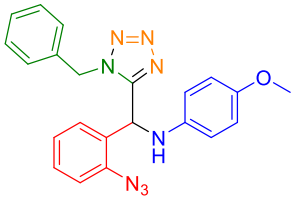
White solid, m.p. 153–155 °C, R_f = 0.50 (30% ethyl acetate in hexanes), ^{1}H (500 MHz, $CDCl_3$, 25 °C, TMS): δ 7.48 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 6.75 (d, *J* = 8.9 Hz, 2H), 6.66 (d, *J* = 8,9 Hz, 2H), 6.05 (d, *J* = 7.4 Hz, 1H), 4.72 (d, *J* = 8.3 Hz, 1H), 4.44–4.35 (m, 1H), 3.71 (s, 3H), 2.08–1.98 (m, 3H), 1.90–1.81 (m, 2H), 1.78–1.70 (m, 1H), 1.57–1.52 (m, 1H), 1.44–1.34 (m, 1H), 1.32–1.25 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 154.7, 153.5, 139.4, 137.3, 130.2, 129.3, 128.9, 126.1, 118.2, 116.0, 115.1, 58.3, 55.8, 48.4, 33.0, 33.0, 25.6, 24.9.



11c

N((2-azidophenyl)(1-benzyl-1H-tetrazol-5-yl)methyl)aniline (**11c**)

White solid, m.p. 139–141 °C, R_f = 0.50 (30% ethyl acetate in hexanes), ^{1}H (500 MHz, $CDCl_3$, 25 °C, TMS): δ 7.38 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.34–7.28 (m, 4H), 7.13–7.07 (m, 6H), 6.75 (t, *J* = 7.3 Hz, 1H), 6.48 (d, *J* = 7.7 Hz, 2H), 6.03 (d, *J* = 8.6 Hz, 1H), 5.64 (d, *J* = 15.4 Hz, 1H), 5.56 (d, *J* = 15.4 Hz, 1H), 4.67 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 155.4, 145.3, 137.6, 133.1, 130.2, 129.5, 129.2, 129.0, 128.8, 128.2, 127.6, 125.8, 119.4, 118.4, 113.9, 51.4, 27.4.



11d

N((2-azidophenyl)(1-benzyl-1H-tetrazol-5-yl)methyl)-4-methoxyaniline (**11d**)

White solid, m.p. 142–144 °C, R_f = 0.38 (30% ethyl acetate in hexanes), ^{1}H (500 MHz, $CDCl_3$, 25 °C, TMS): δ 7.39–7.27 (m, 5H), 7.15–7.04 (m, 4H), 6.68 (d, *J* = 8.9 Hz, 2H), 6.46 (d, *J* = 8.9 Hz, 2H), 5.93 (d, *J* = 7.2 Hz, 1H), 5.62 (d, *J* = 15.4 Hz, 1H), 5.54 (d, *J* = 15.4 Hz, 1H), 4.41 (d, *J* = 8.8 Hz, 1H), 3.71 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 155.5, 153.5, 139.3, 137.6, 133.2, 130.1, 129.2, 129.0, 128.8, 128.3, 127.6, 125.7, 118.4, 115.9, 115.0, 55.7, 51.3, 48.6.

4. Conclusions

The present work contributes a novel green multicomponent one-pot synthesis of a series of 1,5-disubstituted-1*H*-tetrazoles functionalized with azides using mild conditions, which were obtained good overall yields (83–87%).

The complex azides products have application as synthetic platforms to increase the synthetic potential of Ugi-azide strategy.

Author Contributions: Conceptualization, R.G.-M.; methodology, D.G.-G. and M.A.R.-G.; software, D.G.-G.; validation, R.G.-M.; formal analysis, R.G.-M.; investigation, D.G.-G. and M.A.R.-G.; resources, R.G.-M.; data curation, D.G.-G.; writing—original draft preparation, D.G.-G.; writing—review and editing, R.G.-M.; visualization, R.G.-M.; supervision, R.G.-M.; project administration, R.G.-M.; funding acquisition, R.G.-M. All authors have read and agreed to the published version of the manuscript.

Funding: D.G.-G. is grateful to CONAHCyT-Mexico for the scholarship (824233/1233507). R.G.-M. is grateful for the financial support from UG CIIC (066/2024).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

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

References

1. Kumari, S.; Carmona, A.V.; Tiwari, A.K.; Trippier, P.C. Amide Bond Bioisosteres: Strategies, Synthesis, and Successes. *J. Med. Chem.* **2020**, *63*, 12290–12358. https://doi.org/10.1021/acs.jmedchem.0c00530.
2. Wei, C.-X.; Bian, M.; Gong, G.-H. Tetrazolium Compounds: Synthesis and Applications in Medicine. *Molecules* **2015**, *20*, 5528–5553. https://doi.org/10.3390/molecules20045528.
3. Aromí, G.; Barrios, L.A.; Roubeau, O.; Gamez, P. Triazoles and Tetrazoles: Prime Ligands to Generate Remarkable Coordination Materials. *Coord. Chem. Rev.* **2011**, *255*, 485–546. https://doi.org/10.1016/j.ccr.2010.10.038.
4. Ponnuvel, K.; Padmini, V.; Sribalan, R. A New Tetrazole Based Turn-on Fluorescence Chemosensor for Zn^{2+} Ions and Its Application in Bioimaging. *Sens. Actuators B Chem.* **2016**, *222*, 605–611. https://doi.org/10.1016/j.snb.2015.08.096.
5. Haase, J. Large-Scale Preparation and Usage of Azides. In *Organic Azides*; Bräse, S., Banert, K., Eds.; Wiley: Hoboken, NJ, USA, 2009; pp. 29–51, ISBN 978-0-470-51998-1.
6. Neochoritis, C.G.; Zhao, T.; Dömling, A. Tetrazoles via Multicomponent Reactions. *Chem. Rev.* **2019**, *119*, 1970–2042. https://doi.org/10.1021/acs.chemrev.8b00564.
7. Yount, J.; Morris, M.; Henson, N.; Zeller, M.; Byrd, E.F.C.; Piercey, D.G. Sequential, electrochemical-photochemical synthesis of 1,2,4-triazolo-[4,3-a]pyrazines. *Chem. Eur. J.* **2024**, *30*, e202400661. https://doi.org/10.1002/chem.202400661.
8. 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 Chem.* **2017**, *19*, 1259–1262. https://doi.org/10.1039/C6GC03324E.