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Ultrasound-Assisted Ugi-Azide Multicomponent Reaction for the Synthesis of 1,5-Disubstituted Tetrazoles †

Alejandro Corona-Díaz, Sandra C. Ramírez-López, David Calderón-Rangel, Cristian Saldaña-Arredondo and Rocío Gámez-Montaño *

Departamento de Química, Universidad de Guanajuato, Noria Alta S/N, Col. Noria Alta, Guanajuato 36050, Mexico; alexcorona7@gmail.com (A.C.-D.); sandiiramirez22@hotmail.com (S.C.R.-L.); david.calderon@ugto.mx (D.C.-R.); c.saldanaarredondo@ugto.mx (C.S.-A.)

* Correspondence: rociogm@ugto.mx; Tel.:+52-473-732-0006 (ext. 8191)

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Abstract: The Ugi-azide MCR (UA) is one of the most efficient methods for the synthesis of 1,5-disubstituted-1H-tetrazoles (1,5-DS-T). Complex drug-like scaffolds incorporating tetrazoles have demonstrated a wide range of therapeutic benefits such as anti-inflammatory, antiviral, antibiotic, anti-ulcer, anti-anxiety and anti-hypertensive agents, attributable to their mimetic cis amide of peptide bonds that enhance metabolic stability, selectivity and other beneficial physicochemical properties, in addition to their applications in bioimaging, photoimaging and coordination chemistry. Herein, we present the ultrasound-assisted sustainable synthesis of six novel 1,5 DS-T under solvent-free conditions.

Keywords: Ugi-azide; isocyanide-based multicomponent reactions (IMCRs); 1,5-disubstituted tetrazoles (1,5-DS-T)

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1. Introduction

Isocyanide-based multicomponent reactions (IMCRs) stand out as highly effective synthetic tools for designing and developing sustainable strategies. IMCRs offer several advantages, including a high atomic economy, fast and straightforward methods, a reduction in the number of workups; extraction and purification processes, time and energy savings, aligning closely with the 12 principles of green chemistry [1–3]. Undoubtedly, IMCR-based strategies significantly contribute to the focus of organic synthesis in GC, allowing the easy synthesis of relatively complex molecules with high overall yields [4].

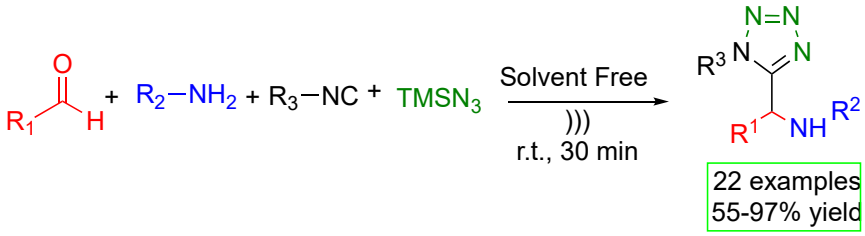
On the other hand, 1,5-disubstituted tetrazoles (1,5-DS-T) are heterocycles of high interest in medicinal chemistry; more complex drug-like scaffolds based on tetrazoles have demonstrated a wide range of therapeutic benefits attributable to their mimetic cis amide of peptide bonds, enhancing metabolic stability, selectivity and other beneficial physicochemical properties [5]. Several procedures have been reported for the synthesis of 1,5-disubstituted tetrazoles [6]. The traditional method for the synthesis of tetrazole derivatives involves the [2 + 3] azide–cyanide cycloaddition reactions [7]. However, the Ugi-azide MCR (UA) has become the main route for the synthesis of 1,5-DS-Ts, allowing access to highly functionalized derivatives under mild conditions [8].

2. Results and Discussion

Following our main research line focused on the design and development of efficient IMCR-based strategies to synthesize compounds of interest [9–15], in 2017, our research group reported the first ultrasound-assisted Ugi-azide reaction under solvent-free conditions using aromatic aldehydes and amines (Scheme 1) [16].

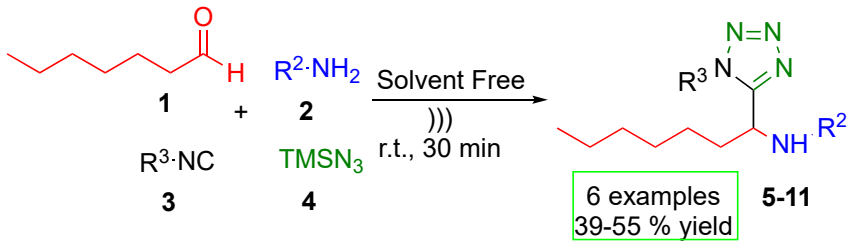
PREVIOUS WORK

Gàmez-Montaño et al. (2017)



R_1= Ph, 4-ClPh, 2,3-MeOPh, 4-NO_2Ph, 2-Py
R_2= Ph, 3-BrPh, 2-ClPh, 4-ClPh
R_3= *tert*-butyl, *c*-Hex, 4-MeOPh, 2,6-MePh, 4-ClPh

This work



R_2: Ph, *c*-Hex, allyl
R_3: *c*-Hex, *tert*-butyl

Scheme 1. Previous reports of 1,5-DS-T.

Here, we present the ultrasound-assisted synthesis of 1,5-DS-T using heptaldehyde as a reaction component. We demonstrate that this methodology is applicable to aliphatic aldehydes and aliphatic amines, as evidenced by the successful use of cyclohexylamine and allylamine (Figure 1) (Scheme 2).

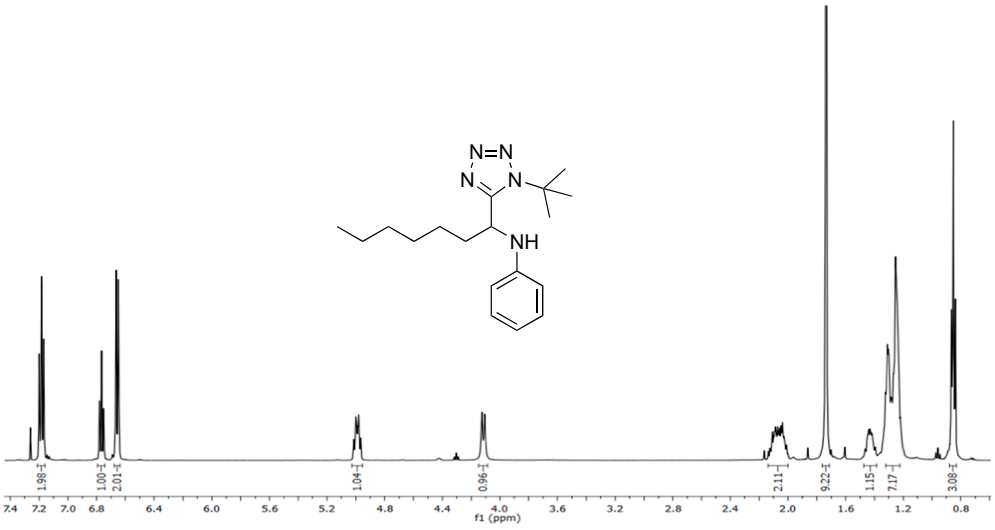
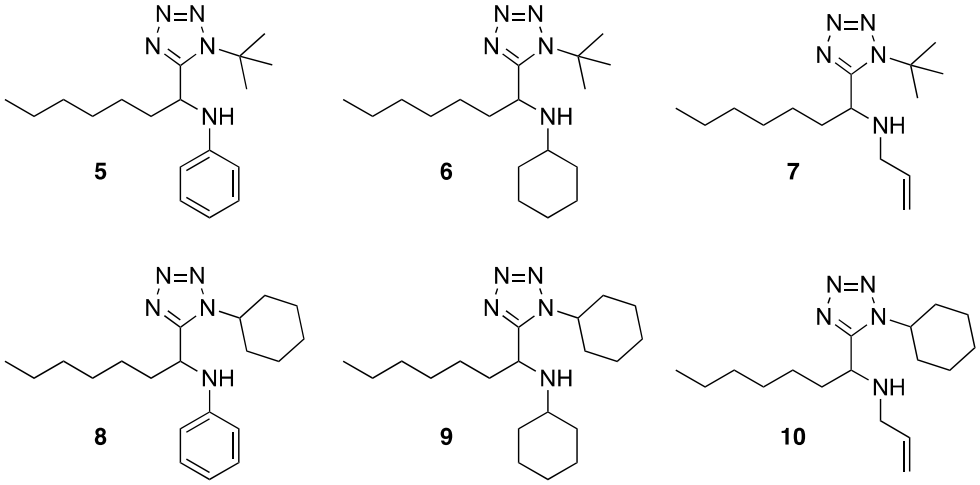


Figure 1. ^{1}H NMR spectrum of compound **5**.



Scheme 2. Substrate scope.

3. Experimental Section

3.1. General Information, Instrumentation and Chemicals

^{1}H and ^{13}C NMR spectra were acquired using a 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 was used as an 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). 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 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 (***5***–***10***)*

General procedure (GP): In a sealed CEM DiscoverTM microwave reaction tube with 10 mL capacity, heptaldehyde (1.0 equiv.), the respective amine (1.0 equiv., $TMSN_3$ (1.1 equiv.), and the correspondent isocyanide (1.1 equiv.) were combined. The reaction mixture was placed in the water bath in the sonicator. Subsequently, the mixture was US-irradiated at room temperature for 30 min. The crude product was purified by flash chromatography using mixtures of hexanes–EtOAc to afford the corresponding 1,5-DS-T.

3.3. Spectral Data

3.3.1. N-(1-(1-(tert-butyl)-1H-tetrazol-5-yl)heptyl)aniline (**5**)

Based on GP, 1-heptanal (0.031 mL, 0.219 mmol), aniline (0.020 mL, 0.219 mmol), tert-butyl isocyanide (0.027 mL, 0.241 mmol) and $TMSN_3$ (0.032 mL, 0.241 mmol) were mixed together to afford **5** (32 mg, 44%) of a yellow solid; mp 119–123 °C; Rf = 0.73 (Hex-AcOEt = 7:3; v/v); FT-IR (ATR) vmax 3287, 2923, 1603, 1500, 1369, 1319, 1208, 1128, 870, 755, 694 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (t, J = 7.9 Hz, 2H), 6.77 (t, J = 7.4 Hz, 1H), 6.66 (t, J = 7.9 Hz, 2H), 4.99 (m, 1H), 4.12 (d, J = 10.4 Hz, 1H), 2.06 (m, 2H), 1.74 (s, 9H), 1.43 (m, 1H), 1.27 (m, 7H), 0.85 (t, J = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.3, 146.2, 129.7, 119.2, 114.3, 61.5, 50.6, 35.2, 31.7, 30.3, 29.1, 26.3, 22.6, 14.1; HRMS calcd for $C_{18}H_{29}N_5$ [M + H]+ m/z 316.2496; found: 316.2554.

3.3.2. N-(1-(1-(tert-butyl)-1H-tetrazol-5-yl)heptyl)cyclohexanamine (**6**)

Based on GP, 1-heptanal (0.031 mL, 0.219 mmol), cyclohexyl amine (0.025 mL, 0.219 mmol), tert-butyl isocyanide (0.027 mL, 0.241 mmol) and $TMSN_3$ (0.032 mL, 0.241 mmol) were mixed together to afford **6** (38 mg, 52%) a yellow solid; mp 108–110 °C; Rf = 0.63 (Hex-AcOEt = 7:3; v/v); FT-IR (ATR) vmax 3327, 2925, 1686, 1451, 1373, 1234, 1103, 889, 814, 725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.21 (m, 1H), 2.15 (m, 1H), 1.77 (m, 2H), 1.73 (s, 9H), 1.65 (m, 4H), 1.53 (m, 2H), 1.24 (s, 8H), 1.10 (m, 5H), 0.84 (t, J = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1, 61.0, 54.3, 51.5, 36.6, 33.9, 33.4, 31.8, 30.4, 29.2, 26.4, 26.1, 24.9, 24.6, 22.7, 14.2; HRMS calcd for $C_{18}H_{35}N_5$ [M + H]+ m/z 322.2965; found: 322.2913.

3.3.3. N-allyl-1-(1-(tert-butyl)-1H-tetrazol-5-yl)heptan-1-amine (**7**)

Based on GP, 1-heptanal (0.031 mL, 0.219 mmol), allyl amine (0.016 mL, 0.219 mmol), tert-butyl isocyanide (0.027 mL, 0.241 mmol) and $TMSN_3$ (0.032 mL, 0.241 mmol) were mixed together to afford **7** (28 mg, 44%) as a yellow solid; mp 108–110 °C; Rf = 0.53 (Hex-AcOEt= 7:3; v/v); FT-IR (ATR) vmax 3324, 2927, 1727, 1456, 1375, 1236, 1105, 995, 918, 812, 725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.81 (ddt, J = 16.3, 10.9, 5.8 Hz, 1H), 5.14 (dd, J = 17.2, 1.5 Hz, 1H), 5.07 (dd, J = 10.3, 1.2 Hz, 1H), 4.15 (dd, J = 7.8, 5.4 Hz, 1H), 3.16 (dd, J = 14.1, 5.4 Hz, 1H), 3.00 (dd, J = 14.1, 6.1 Hz, 1H), 1.91 (br s, 1H), 1.79 (m, 2H), 1.72 (s, 9H), 1.55 (m, 1H), 1.28 (m, 7H), 0.86 (t, J = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.1, 136.5, 116.5, 61.2, 53.7, 49.9, 36.4, 31.8, 30.4, 29.3, 26.3, 22.7, 14.2; HRMS calcd for $C_{15}H_{29}N_5$ [M + H]+ m/z 280.2501; found: 280.2549.

3.3.4. N-(1-(1-cyclohexyl-1H-tetrazol-5-yl)heptyl)aniline (**8**)

Based on GP, 1-heptanal (0.031 mL, 0.219 mmol), aniline (0.020 mL, 0.219 mmol), cyclohexyl isocyanide (0.030 mL, 0.241 mmol) and $TMSN_3$ (0.032 mL, 0.241 mmol) were mixed together to afford **8** (43 mg, 55%) as a white solid; mp 112–114 °C; Rf = 0.83 (Hex-AcOEt= 7:3; v/v); FT-IR (ATR) vmax 3331, 2930, 1604, 1498, 1436, 1315, 1095, 895,750, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.14 (t, J = 7.8 Hz, 2H), 6.75 (t, J = 7.4 Hz, 1H), 6.61 (d, J = 8.2 Hz, 2H), 4.83 (q, J = 7.2 Hz, 1H), 4.38 (m, 1H), 4.06 (d, J = 7.4 Hz, 1H), 2.02 (m, 2H), 1.95 (m, 1H), 1.86 (m, 4H), 1.74 (m, 2H), 1.42 (m, 1H), 1.28 (m, 10H), 0.86 (t, J = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.4, 146.3, 129.6, 119.4, 114.0, 58.4, 49.9, 35.0, 33.3, 33.3, 31.6, 31.0, 29.0, 26.0, 25.5, 25.5, 24.9, 22.6, 14.1; HRMS calcd for $C_{20}H_{31}N_5$ [M + H]+ m/z 342.2658; found: 342.2712.

3.3.5. N-(1-(1-cyclohexyl-1H-tetrazol-5-yl)heptyl)cyclohexanamine (**9**)

Based on GP, 1-heptanal (0.031 mL, 0.219 mmol), cyclohexyl amine (0.025 mL, 0.219 mmol), cyclohexyl isocyanide (0.030 mL, 0.241 mmol) and 0.032 mL of $TMSN_3$ (0.241 mmol) were mixed together to afford **9** (31 mg, 39%) as a yellow solid; mp 108–110 °C; Rf = 0.67 (Hex-AcOEt = 7:3; v/v); FT-IR (ATR) vmax 3318, 2926, 1727, 1449, 1275, 1127, 893, 754 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.61 (m, 1H), 4.25 (t, J = 7.2 Hz, 1H), 2.14 (m, 1H), 2.04 (m, 2H), 1.94 (m, 5H), 1.77 (m, 3H), 1.62 (m, 4H), 1.39 (m, 3H), 1.25 (m, 8H), 1.12 (m, 4H), 1.01 (m, 2H), 0.85 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.2, 57.9, 54.7, 50.7, 35.5, 34.4, 33.6, 33.2, 33.1, 31.7, 29.1, 26.2, 26.1, 25.6, 25.0, 24.8, 22.6, 14.1; HRMS calcd for $C_{20}H_{37}N_5$ [M + H]+ m/z 348.3122; found: 348.3188.

3.3.6. N-allyl-1-(1-cyclohexyl-1H-tetrazol-5-yl)heptan-1-amine (**10**)

Based on GP, 1-heptanal (0.031 mL, 0.219 mmol), allyl amine (0.016 mL, 0.219 mmol), cyclohexyl isocyanide (0.030 mL, 0.241 mmol) and $TMSN_3$ (0.032 mL, 0.241 mmol) were mixed together to afford **10** (34 mg, 49%) of a yellow solid; mp 108–110 °C; Rf = 0.50 (Hex-AcOEt = 7:3; v/v); FT-IR (ATR) vmax 3320, 2929, 1672, 1451, 1275, 1096, 992, 918, 816, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.78 (ddt, J = 16.6, 11.1, 5.9 Hz, 1H), 5.11 (d, J = 17.2 Hz, 1H), 5.07 (d, J = 10.26 Hz, 1H), 4.51 (m, 1H), 4.09 (t, J = 7.2 Hz, 1H), 3.08 (dd, J = 14.2, 5.3 Hz, 1H), 3.01 (dd, J = 14.2, 6.3 Hz, 1H), 2.02 (m, 2H), 1.93 (m, 4H), 1.78 (m, 3H), 1.29 (m, 12H), 0.84 (t, J = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.6, 136.1, 116.6, 57.9,

52.8, 50.1, 35.1, 33.3, 31.6, 29.1, 26.0, 25.6, 25.5, 25.0, 22.6, 14.1; HRMS calcd for $C_{17}H_{31}N_5$ [M + H]+ m/z 306.2652; found: 306.2716.

4. Conclusions

A series of six 1,5-disubstituted-1H tetrazoles in moderate to good overall yields (39–55%) were synthesized via a one-pot Ugi-azide reaction under ultrasound irradiation, free of solvent and under mild conditions. Notably, this methodology allowed the use of fewer reported aliphatic aldehydes and amines, as demonstrated by the successful reactions employing heptaldehyde, cyclohexylamine, and allylamine as reactants.

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

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