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

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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, antibiotics, anti-ulcer, anxiety and anti-hypertensive agents, attributable to their mimetic cis amide of peptide bonds 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

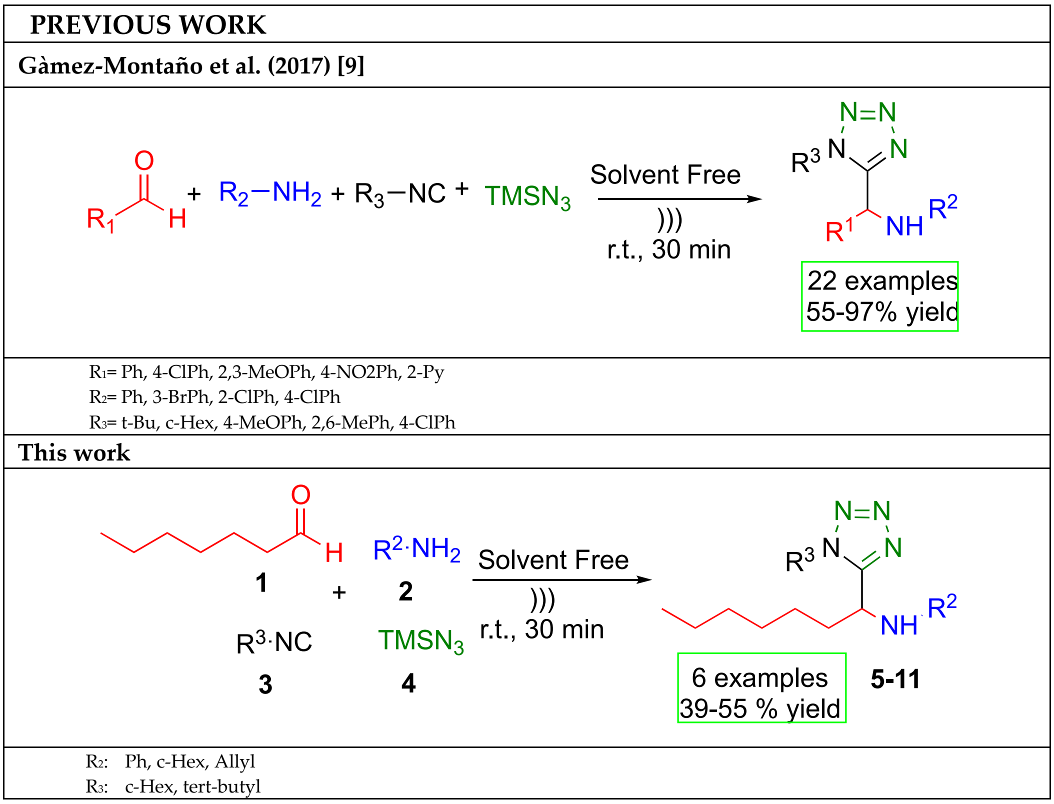
Isocyanide-based multicomponent reactions (IMCRs) stand out as highly effective synthetic tools for designing and developing sustainable strategies. IMCRs offer several advantages including high atomic economy, fast and straightforward methods, reduction in the number of workups, extraction and purification 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 synthesis of relatively complex molecules easy and 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 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 [10–16], In 2017, our research group reported the first ultrasound-assisted Ugi-azide reaction under solvent-free conditions using aromatic aldehydes and amines [9].

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 (Scheme 1).



**PREVIOUS WORK**

**Gàmez-Montaño et al. (2017) [9]**

$R_1$= Ph, 4-ClPh, 2,3-MeOPh, 4-NO2Ph, 2-Py
$R_2$= Ph, 3-BrPh, 2-ClPh, 4-ClPh
$R_3$= t-Bu, 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.

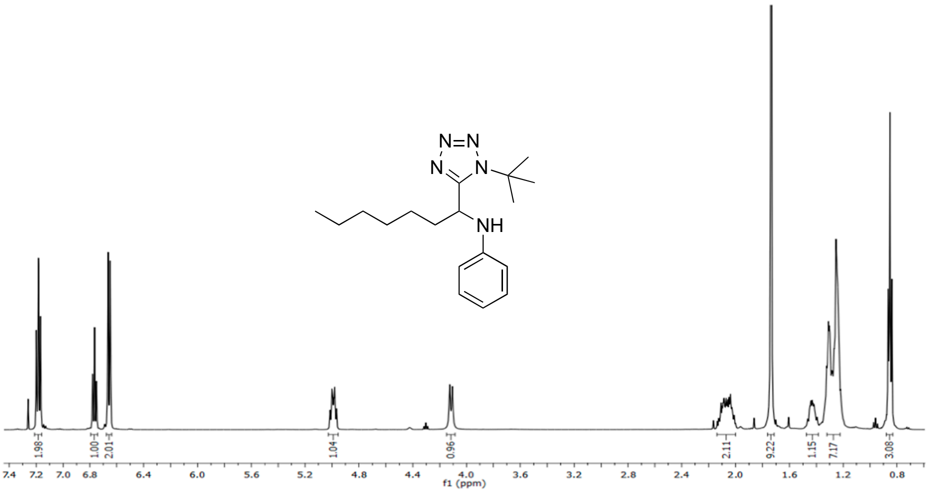
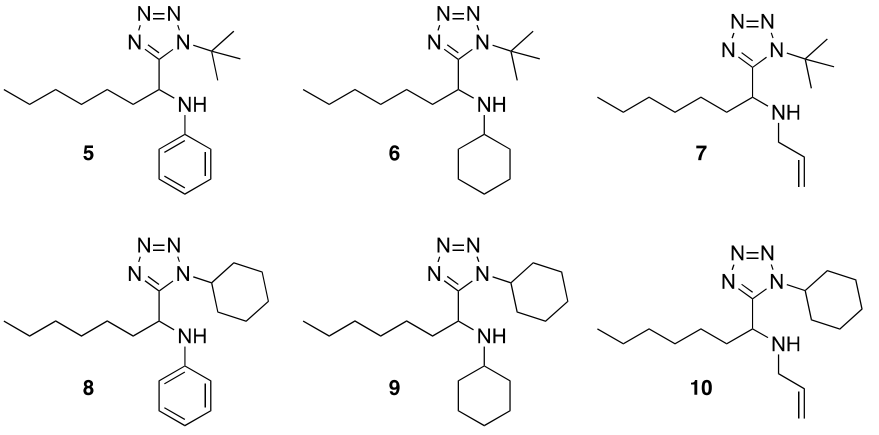


**Figure 1.** $^1H$ NMR spectrum of compound **5**.



**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 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 to 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, 0.031 mL 1-heptanal (0.219 mmol), 0.020 mL aniline (0.219 mmol), 0.027 mL tert-butyl isocyanide (0.241 mmol) and 0.032 mL $TMSN_3$ (0.241 mmol) were mixed together to afford 32 mg (44%) as 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, 0.031 mL 1-heptanal (0.219 mmol), 0.025 mL cyclohexyl amine (0.219 mmol), 0.027 mL tert-butyl isocyanide (0.241 mmol) and 0.032 mL $TMSN_3$ (0.241 mmol) were mixed together to afford 38 mg (52%) as 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, CDCl3) 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, 0.031 mL 1-heptanal (0.219 mmol), 0.016 mL allyl amine (0.219 mmol), 0.027 mL tert-butyl isocyanide (0.241 mmol) and 0.032 mL $TMSN_3$ (0.241 mmol) were mixed together to afford 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, 0.031 mL 1-heptanal (0.219 mmol), 0.020 mL aniline (0.219 mmol), 0.030 mL cyclohexyl isocyanide (0.241 mmol) and 0.032 mL $TMSN_3$ (0.241 mmol) were mixed together to afford 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, 0.031 mL 1-heptanal (0.219 mmol), 0.025 mL cyclohexyl amine (0.219 mmol), 0.030 mL cyclohexyl isocyanide (0.241 mmol) and 0.032 mL $TMSN_3$ (0.241 mmol) were mixed together to afford 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, 0.031 mL 1-heptanal (0.219 mmol), 0.016 mL allyl amine (0.219 mmol), 0.030 mL cyclohexyl isocyanide (0.241 mmol) and 0.032 mL $TMSN_3$ (0.241 mmol) were mixed together to afford 34 mg (49%) as 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, CDCl3) 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 less reported aliphatic aldehydes and amines, as demonstrated by 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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