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A Green Isocyanide-Based Multicomponent Click Reaction for the Synthesis of 1-Substituted 1H-1,2,3,4-Tetrazoles †

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Abstract: A series of five 1-substituted-1H-1,2,3,4-tetrazoles were synthesized via a novel isocyanide based multicomponent click reaction (IMCCR) under solvent, catalyst, and column-free conditions at room temperature. This novel IMCCR methodology resulted in good overall yields (46–63%). All the compounds are characterized using ^{1}H and ^{13}C, FT-IR and HRMS.

Keywords: green synthesis; 1-substituted 1H-1,2,3,4-tetrazoles; isocyanide-based multicomponent reactions (I-MCR).

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1. Introduction

Green chemistry is an important and crucial concept to develop novel methodologies that allow synthetize complex molecules with the minimum impact to the environment, in this way Isocyanide based multicomponent reactions (IMCRs) and click reactions share various common features and often considered as ideal reactions, therefore they have become some of the most efficient synthetic tools. Click Chemistry is a term to describe that are high yielding, wide scope, create only byproducts that can be removed without chromatography, and are simple to perform. [1] In this context, one-pot process like IMCRs are simple, convergent, ecofriendly, that allows the synthesis of molecules reducing the environmental impact that would be caused with old synthetic methodologies. [2]

On the other hand, tetrazole derivatives are a very important class of heterocycles to medicinal chemistry and drug design due to not only their bioisosterism to -COOH group and amide moieties but also their metabolic stability and other beneficial physicochemical properties. [3]

A considerable number of drugs approved by the Food and Drug Administration (FDA) which are medicinally important possess tetrazole moieties in their structures. [4] It has been reported that the lipophilic nature of tetrazole moieties in a drug improves its oral bioavailability and cell penetration. In this regard, tetrazole chemistry has gained so much interest due to its potential therapeutic profile. The tetrazole moiety is an important synthetic scaffold that found broad applications in numerous fields such as in medicine, biochemistry, pharmacology, and in industry as materials, e.g., in photography, imaging chemicals, and military.[5] However, the most important and fruitful application of tetrazoles are a widely range of biological properties, such as antifungal, [6] anti-inflammatory, [7] antitubercular, [8] and anticancer activities [9] (Figure 1).

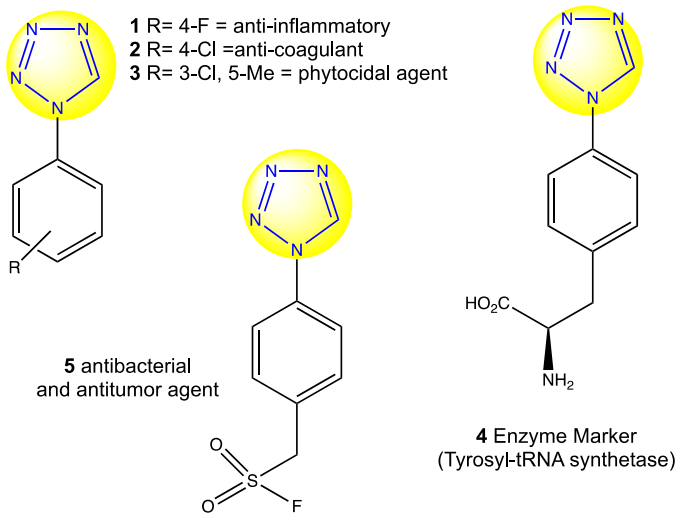


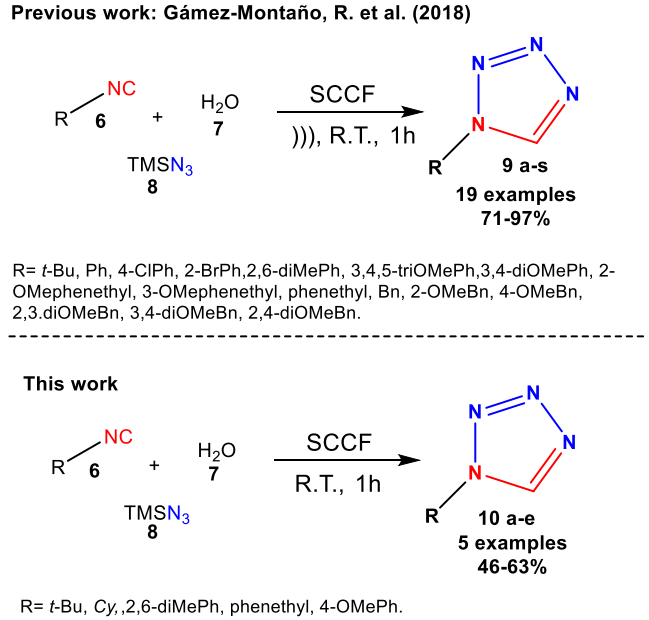
Figure 1. Applications of 1-ST molecules.

In this context, multicomponent reaction (MCR) in a convergent process permits access to multiple tetrazole scaffolds providing the three important elements of novelty, diversity, and complexity, yet MCR pathways to tetrazoles are far from completely explored.[10] Nevertheless, the most common strategy for the synthesis of 1-substituted tetrazoles (1-STs) is the multicomponent reaction (MCR) of primary amines, triethyl orthoformate and sodium azide, always achieved by using a catalyst, [11] which suffers from various disadvantages such as high temperature, non-green solvents, long reaction times, expensive reagents, use of hazardous NaN_3 and toxic catalysts, which make this method non-green and limited.

Accordingly, it is essential to develop new and more efficient IMCR methodology to improve the synthesis of 1-STs. From the green chemistry point of view, the development of green solvent, catalyst-free IMCRs under mild conditions is a hot topic in organic synthesis. In this context, the application of ultrasound, and microwave technology are in extensive use at present-time due these techniques were used as a greener heating tool and substitutes of conventional heating. However, the most effective way-out to save energy is to develop strategies/protocols that are capable enough to carry out the transformations at room temperature (RT).[12]

2. Results and Discussion

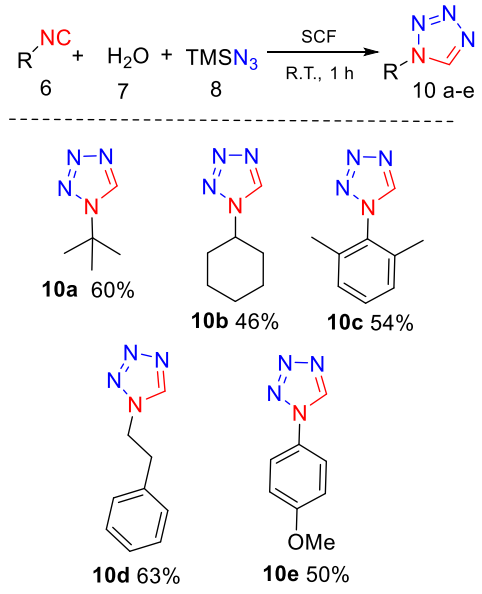
As part of our ongoing research program towards green strategies based on IMCRs to synthesize tetrazole [13–17], we recently reported the first ultrasound-assisted, under solvent, catalyst, and column-free (SCCF), mild and green IMCR/Click reaction (IMCCR) strategy via 3 + 2 cycloaddition using water as a component towards 1-substituted-1H-1,2,3,4-tetrazoles (1-STs) in yields (71–97%). [18] Herein, we describe the one-pot synthesis of 1-STs carrying out under milder conditions (Scheme 1).



Scheme 1. Previous work and this work.

In our previous work [18] we obtained the 1-STs in excellent yields under catalyst and solvent-free USI conditions. Encouraged by our previous work, we decided to work in the synthesis of 1-STs at room temperature due there is nothing greener that developed strategies/protocols that are capable to carry out the transformations at RT.

Using solvent-free (SF) conditions at RT for one hour, we explored the scope of the reaction with isocyanides of different stereoelectronic nature were tested to synthetize 1-STs analogues **10a-e** (Scheme 2). The yield obtained with the unstable phenethyl isocyanide rarely was the best yield (10d, 63%). Interestingly, sterically hindered and with low-nucleophilic ortho dimethyl-substituted phenyl isocyanide, also afforded good yields (54%, **10c**), gratifyingly aliphatic isocyanides worked well, leading to the expected 1-ST in excellent yields (46 and 60%, 10a-b), demonstrating the versatility and the wide scope of the developed novel strategy.



Scheme 2. Synthesis of 1-STs **10 a-e**.

The structures of all the newly synthesized compounds were established by ^{1}H and ^{13}C NMR, FT-IR, and the molecular weight of all the compounds was confirmed by HRMS. It is important to mention that all the compounds are free column. Figures 2 and 3 show the ^{1}H and ^{13}C NMR spectra of the 1-ST 10e.

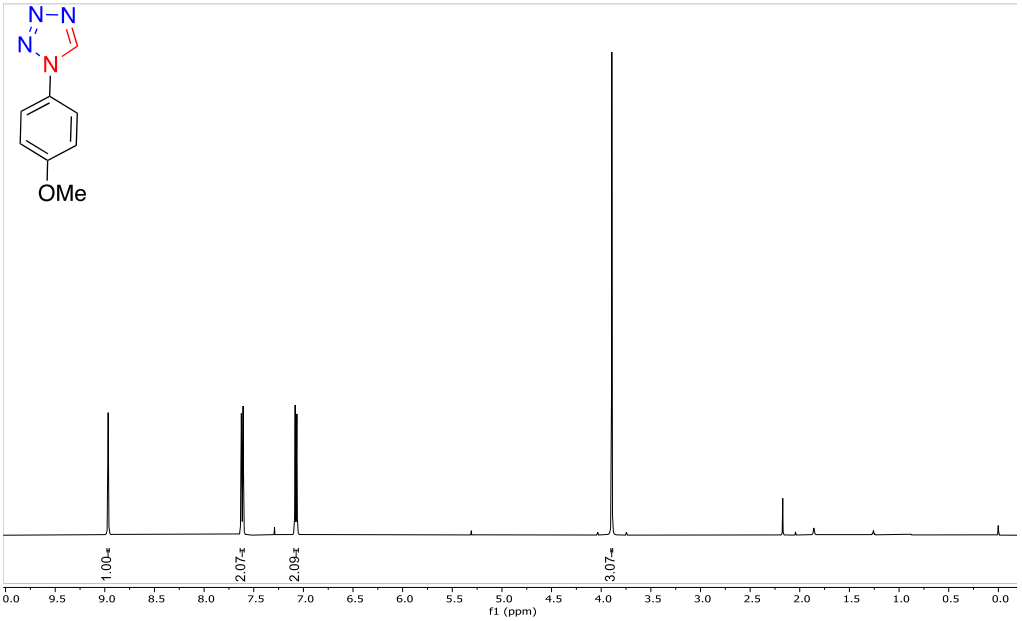


Figure 2. ^{1}H NMR spectrum of 1-ST **10e.**

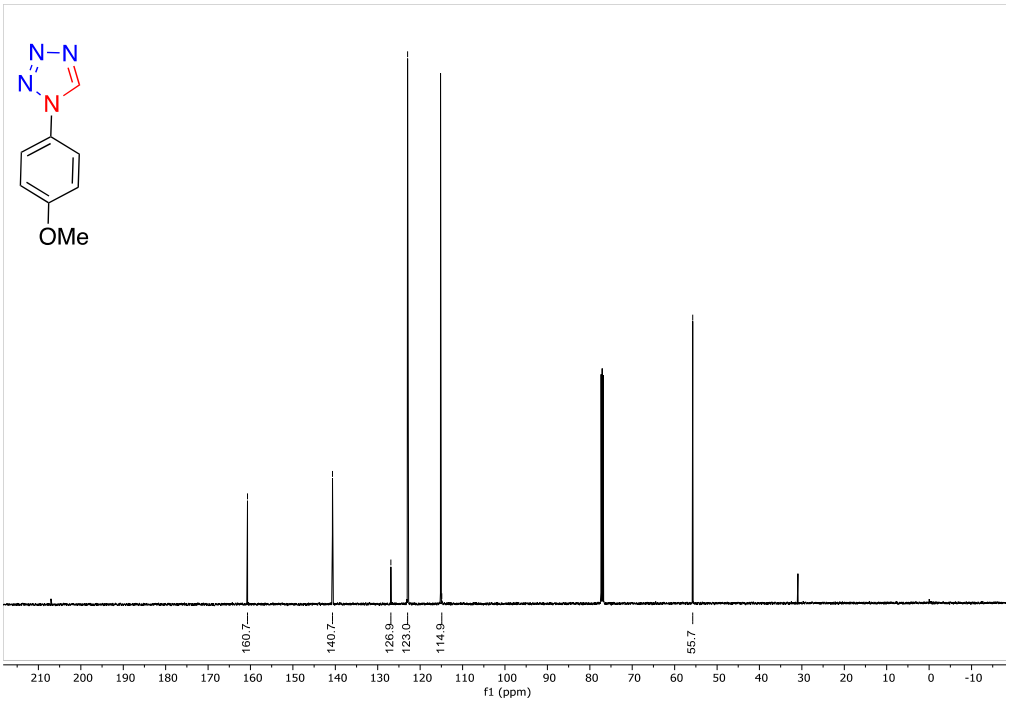


Figure 3. ^{13}C NMR spectrum of 1-ST **10e**.

3. Conclusions

A serie of five 1-ST**s** in good overall yields (46–63%) were synthesized, via a novel IMCCR under mild conditions at RT, achieving the generation of nitrogen heterocycles in a one-pot process, avoiding the formation of by-products to minimize waste production contributing directly to the area of green chemistry, besides the products herein described

may find applications in various fields, but mainly in medicinal chemistry, since they contain a tetrazole moiety.

4. Experimental Section

4.1. General Information, Instrumentation, and Chemicals

^{1}H and ^{13}C 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 versión 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 (υ_{max}/cm^{-1}). 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.

4.2. Synthesis and Characterization of 1-substituted 1H-1,2,3,4-tetrazoles (10 a-e)

General procedure (GP): In a dry 10 mL flask was charged with an isocyanide (1 mmol), $TMSN_3$ (2 mmol) and H_2O (2 mmol). The reaction mixture was placed in at room temperature for 1 h. The resulting crude products were diluted with DCM (2 mL) and filtered through small Na_2SO_4 bed to remove traces of water. The resulting filtrate kept as it is at room temperature for evaporation to afford pure products. In some cases, to remove the traces of isocyanide, wash of 2mL EtOAc: Hex (0.5/9.5 *v*/*v*) was given.

Spectral Data

1-(tert-butyl)-1H-tetrazole (10a): Based on GP, 0.068 cm^3 ter-butyl isocyanide (0.60 mmol), 0.159 cm^3 $TMSN_3$ (1.20 mmol) and 0.021 cm^3 H_2O (1.20 mmol) were reacted together to afford 68 mg (90%) as a white solid. Melting range 42–44 °C; 1H NMR (500 MHz, CDCl3) δ 8.61 (s, 1H), 1.72 (s, 9H); 13C NMR (126 MHz, CDCl3) δ 139.91, 59.75, 29.93; FT-IR (ATR) υ_{max}/cm^{-1} 1583.0 (C=N), 1273.3 (N-N=N); HRMS (ESI+): m/z calcd. for $C_5H_{11}N_4^+$ 149.0797, found 149.0802.

1-(Cyclohexil)-1H-tetrazole (10b): Based on GP, 0.068 cm^3 ter-butyl isocyanide (0.46 mmol), 0.123 cm^3 $TMSN_3$ (0.91 mmol) and 0.016 cm^3 H_2O (0.91 mmol) were reacted together to afford 68 mg (90%) as a brown oil. ^{1}H NMR (500 MHz, CDCl3) δ 8.63 (s, 1H), 4.55–4.47 (m, 1H), 2.30–2.23 (m, 2H), 1.99–1.92 (m, 2H), 1.86–1.76 (m, 2H), 1.54–1.43 (m, 2H), 1.38–1.23 (m, 2H); ^{13}C NMR (126 MHz, CDCl3) δ 140.67, 58.82, 33.08, 24.82; FT-IR (ATR) υ_{max} /cm^{-1} 1612.6(C=N),1281.1(N-N=N); HRMS (ESI+): *m*/*z* calcd. for $C_7H_{13}N_4^+$ 152.1062, found 152.1078.

***1-(2,6-dimethylphenyl)-1H-tetrazole (10c)*:** Based on *GP*, 50 mg 2,6-dimethyl phenyl isocyanide (0.38 mmol), 0.114 cm^3 TMSN3 (0.76 mmol) and 0.015 cm^3 H_2O (0.76 mmol) were reacted together to afford 62 mg (84%) as a yellow-white solid. Melting range 98–100 °C; ^{1}H NMR (500 MHz, CDCl3) δ 8.69 (s, 1H), 7.38 (d, *J* = 7.6, 1H), 7.23 (d, *J* = 7.6 Hz, 2H), 1.98 (s, 6H); ^{13}C NMR (126 MHz, CDCl3) δ 143.67,135.50, 132.43, 131.08, 129.02, 17.57; FT-IR (ATR) υ_{max} /cm^{-1} 3031.4 (*Aromatic* C-H *Stretch*), 2942.0 (C-H *Stretch*), 1612.3 (C=N),1281.51(N-N=N); HRMS (ESI+): *m*/*z* calcd. for $C_9H_{11}N_4^+$ 175.0978, found 175.0988.

***1-phenethyl-1H-tetrazole (10d)*:** Based on *GP*, 50 mg phenethyl isocyanide (0.38 mmol), 0.102 cm^3 $TMSN_3$ (0.76 mmol) and 0.013 cm^3 H_2O (0.76 mmol) were reacted together to afford 65 mg (98%) as a light brown solid. Melting range 67–69 °C; 1H NMR (500 MHz, CDCl3) δ 8.12 (s, 1H), 7.25–7.19 (m, 3H), 6.97 (d, *J* = 6.7 Hz, 2H), 4.61 (t, *J* = 6.9 Hz, 2H), 3.16 (t, *J* = 6.9 Hz, 2H); 13C NMR (126 MHz, CDCl3) δ 142.68, 136.13, 129.24, 128.73, 127.67, 49.85, 36.27; FT-IR (ATR) υ_{max}/cm^{-1} 3051.2 (*Aromatic* C-H *Stretch*), 2945.1 (C-H

Stretch), 1613.2 (C=N), 1275.3 (N-N=N); HRMS (ESI+): *m*/*z* calcd. for $C_9H_{11}N_4^+$ 175.0978, found 175.0982.

***1-(4-methoxyphenyl)-1H-tetrazole (10e)*:** Based on GP, 50 mg 4-methoxy phenyl isocyanide (0.37 mmol), 0.099 cm^3 TMSN3 (0.75 mmol) and 0.013 cm^3 H_2O (0.75 mmol) were reacted together to afford 59 mg (90%) as a light brown solid. Melting range 118–119 °C, 1H NMR (500 MHz, CDCl3) 8.91 (s, 1H), 7.59 (d, J = 10 Hz, 2H), 7.06 (d, J = 10 Hz, 2H), 3.88 (s, 3H); 13C NMR (126 MHz, CDCl3) δ 160.88, 140.72,127.08, 123.12, 115.34, 55.87; FT-IR (ATR) υ_{max} /cm 3051.0 (*Aromatic* C-H *Stretch*), 2942.8 (C-H *Stretch*), 1603.1 (C=N), 1280.5 (N-N=N), 1046.2 (C-O *Stretch*); HRMS (ESI+): m/z calcd. for $C_8H_9N_4O^+$ 177.0770, found 177.0782.

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