

Synthesis of New *bis* 1- and 5-Substituted 1*H*-Tetrazoles via Huisgen-Type 1,3-Dipolar Cycloadditions [†]

Roberto E. Blanco-Carapia ¹, Julio C. Flores-Reyes ¹, Yizrell Medina-Martínez ¹,
Perla Islas-Jácome ¹, Diego Pérez-Martínez ¹, Leticia Lomas-Romero ¹, Ilich A. Ibarra ^{2,*},
Alejandro Islas-Jácome ^{1,*} and Eduardo González-Zamora ^{1,*}

¹ Departamento de Química, Universidad Autónoma Metropolitana-Iztapalapa, San Rafael Atlixco 186, Col. Vicentina, C.P. 09340, Iztapalapa, Ciudad de México, Mexico; edreyblanco@gmail.com (R.E.B.-C.); flores.reyes.jc@gmail.com (J.C.F.-R.); i.srra12310@gmail.com (Y.M.-M.); permau26@gmail.com (P.I.-J.); dpm@xanum.uam.mx (D.P.-M.); llr@xanum.uam.mx (L.L.-R.)

² Laboratorio de Fisicoquímica y Reactividad de Superficies, Instituto de Investigaciones en Materiales, Universidad Nacional Autónoma de México, Circuito Exterior S/N, Ciudad Universitaria, C.P. 04510, Coyoacán, Ciudad de México, Mexico

* Correspondence: argel@unam.mx (I.A.I.); aij@xanum.uam.mx (A.I.-J.); egz@xanum.uam.mx (E.G.-Z.); Tel.: +52-55-5622-4595 (I.A.I.); +52-55-5804-4913 (A.I.-J. & E.G.-Z.)

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Abstract: The synthesis and characterization of one symmetrical *bis*-1-substituted-1*H*-tetrazole (69%) via a Huisgen-type 1,3-dipolar cycloaddition, as well as, one symmetrical *aza*-linked *bis*-5-substituted-1*H*-tetrazole (57%) via a classic Huisgen 1,3-dipolar cycloaddition followed by a reductive *aza*-coupling under greener reaction conditions are described. The main reason behind these tetrazole-based ligands is to construct novel Metal-Organic Framework (MOF) architectures to evaluate their CO₂ capture properties under relative humidity conditions. It is worthy to note that both herein reported products have not been synthesized nor isolated, anywhere. Besides, the synthesis of new ligands to fabricate novel MOFs with potential application in environmental remediation has become a highly valued field of opportunity for synthetic chemists and materials engineers.

Keywords: Symmetrical *bis*-tetrazole-based ligands; Huisgen 1,3-dipolar cycloadditions; MOFs chemistry; CO₂ capture properties

1. Introduction

Metal-Organic Frameworks (MOFs) [1], also known as Porous Coordination Polymers (PCPs) [2] are crystalline hybrid materials built from metal ions (discrete or clusters) linked coordinately by organic polydentate ligands (L^{*n*}), resulting in 1D, 2D, or 3D infinite architectures. These materials have found a wide range of interesting applications, among which it is worth highlighting their use as catalysts for organic transformations [3], chemosensors [4], proton-conducting materials [5], magnetic materials [6], as well as platforms for gas-storage [7], for example, hydrogen [8], oxygen [9] and methane [10]. However, their use for carbon dioxide capture has become a very attractive field of opportunity for environmental, synthetic, inorganic, and materials/polymers researchers [11]. Most of the known metals have been used successfully to fabricate MOFs [12]. However, the ligands are responsible of conferring their structural properties such as flexibility, porosity, thermal and

solvent resistance, pH susceptibility, as well as their topology [13]. Thus, the most used anionic linkers to synthesize MOFs for carbon dioxide capture contain carboxylate groups (RCOO^-), for example, there are many reports using *di*-, *tri*-, *tetra*- and *hexa*-carboxylated ligands [14].

Furthermore, during the last two decades, the number of publications describing the use of non-carboxylate-based ligands has increased rapidly. Among them, tetrazole-based ligands have gained much attention due mainly to the relative ease in their lab-handling and synthesis in comparison to other polydentate ligands, such as carboxylated ligands. Thus, the synthesis, characterization and use of polytetrazole-based ligands as precursors of novel and complex porous coordination polymers was reviewed masterfully by Gámez (up to 2011) [15] and Galli (up to 2018) [16].

Tetrazoles are 6π -aromatic *tetra*-nitrogen containing azoles are of high interest in various fields of science and technology [17]. From the substitution patterns in their aromatic ring systems, tetrazoles are classified into 1-, 2-, and 5-monosubstituted, as well as, 1,5- and 2,5-disubstituted tetrazoles [18], see Figure 1a. Among them, the 5-monosubstituted-1*H*-tetrazoles (5-S-1*H*-T) are the most important because can act as isosters (or bioisosters) of carboxylic acids as a result of the similarities in their physicochemical properties such as the acidity and the ability to present tautomeric forms to obtain 5-monosubstituted-2*H*-tetrazoles (5-S-2*H*-Ts). In the same context, their conjugate bases (RCN_4^- , tetrazolates) are considered as excellent carboxylate (RCOO^-) surrogates [19]. To coordinate metal ions, Xiong and co-workers reported that tetrazoles have seven modes (I–VII) through the four-nitrogen electron-donating atoms that allow them to serve as multidentate ligands or bridging building blocks in supramolecular assemblies [20], see Figure 1b.

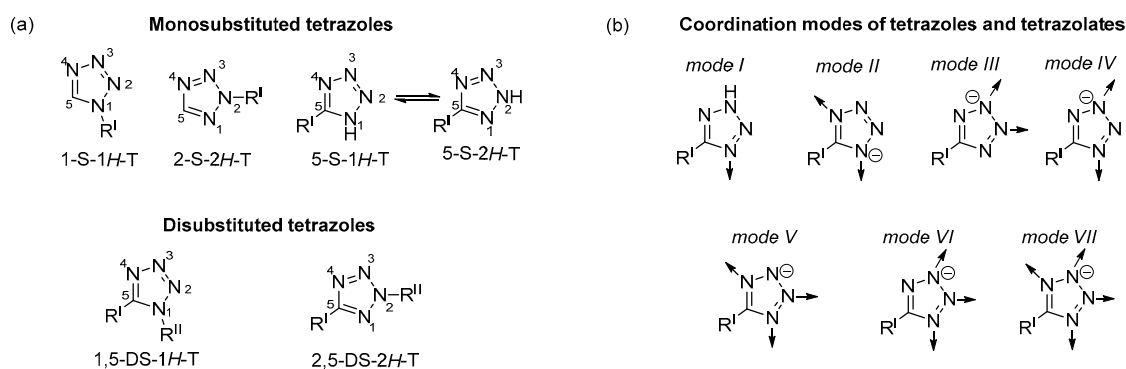


Figure 1. (a) Substitution patterns of tetrazoles. (b) Coordination modes of tetrazoles and tetrazolates.

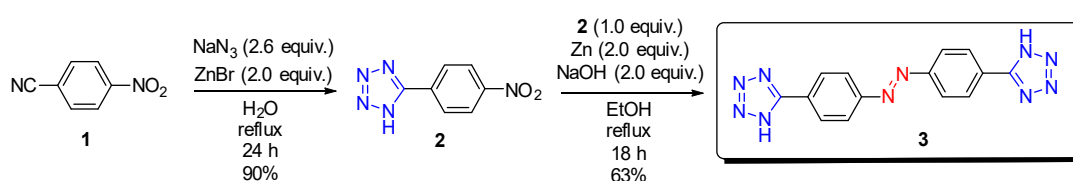
The classic method to synthesize efficiently monosubstituted-1*H*-tetrazoles is through Huisgen-type $[3 + 2]$ dipolar cycloadditions between organic nitriles and a source of the azide anion [21]. For example, Finnegan and co-workers reported the synthesis of 5-substituted-1*H*-tetrazoles (5-S-1*H*-T) by combining nitriles with sodium azide and ammonium chloride in DMF at reflux, giving good to excellent yields [22]. Despite the fact that this methodology was reported in 1958, it is still the most used strategy to obtain monosubstituted-tetrazoles, and most of the reported methods since then to date are considered variants of the Finnegan's method, for example, the greener synthesis reported by Demko and Sharpless in 2001, in which various organic nitriles reacted with sodium azide and zinc bromide in water as a solvent under reflux to give 5-substituted-1*H*-tetrazoles in excellent yields [23].

The stock of commercially available ligands to assemble new MOF architectures is limited. Thus, the aim of this communication is to describe the synthesis and characterization of two new ligands (MOF precursors), one symmetrical *bis*-1-substituted-1*H*-tetrazole and one symmetrical *aza*-linked *bis*-5-substituted-1*H*-tetrazole via efficient synthetic strategies involving Huisgen-type 1,3-dipolar cycloadditions. It is worth highlighting that both herein reported ligands have not been synthesized nor isolated, anywhere. Besides, the synthesis of new ligands to fabricate novel MOFs with potential application in environmental remediation such as for carbon dioxide capture has become a highly valued field of opportunity.

2. Results and Discussion

2.1. Synthesis of the (E)-1,2-bis(4-(1H-tetrazol-5-yl)phenyl)diazene (3)

The 4-nitrobenzonitrile (**1**) reacted with sodium azide and zinc bromide in water as a solvent under reflux for 24 h to give the 5-(4-nitrophenyl)-1H-tetrazole (**2**) with a yield of 90% via a Huisgen [3 + 2] cycloaddition using the protocol described by Demko and Sharpless as the synthetic methodology [23]. Then, two equivalents of the tetrazole **2** reacted in ethanol as a solvent under reflux for 18 h to synthesize the symmetrical *bis*-5-substituted-1H-tetrazole (**3**) with a yield of 63% via a Zn(0)-assisted reductive *aza*-coupling, see Scheme 1. As it can be seen, the yield for the two steps was 57%, which is excellent considering the complexity of the symmetrical bidentate ligand, the linker functional group is an *aza*-bond, and only two experimental steps were required for its total synthesis. In the same context, it is important to highlight the use of green conditions because eco-friendly solvents (water and ethanol) were used in both processes.



Scheme 1. Huisgen/*aza*-coupling strategy towards the new symmetrical *bis*-5-*S*-1H-Tetrazole **3**.

The tetrazole **2** and *bis*-tetrazole **3** were characterized by their physicochemical properties, as well as by spectroscopic techniques, see the Experimental Section for further details. Figure 2 shows the ^1H and ^{13}C NMR spectra of the product **2**, and Figure 3 shows the ^1H and ^{13}C NMR spectra of the product **3**. For the tetrazole **2**, it is worth noting that the A^2B^2 system for the phenyl ring at 8.32 ppm, see Figure 2a, and the peak at 156.8 ppm typical for the C-5 of the tetrazole ring, see Figure 2b. Moreover, for the *bis*-tetrazole **3** (bidentate ligand for MOFs), it has a double A^2B^2 system for their symmetrical aromatic phenyl rings at 8.08 ppm, see Figure 3a. In the same way, there is a peak at 160.6 ppm, which can be attributed to both, C-5 and C-20 of their symmetrical tetrazole rings, see Figure 3b.

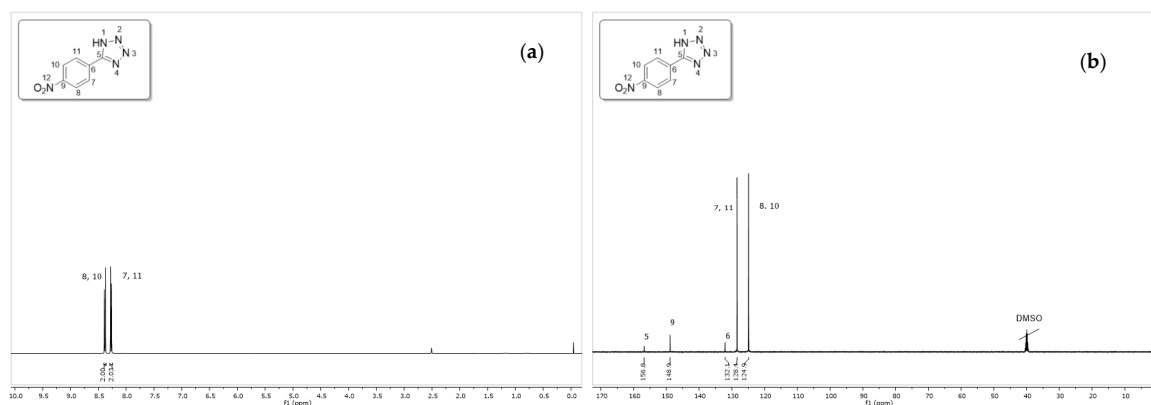


Figure 2. (a) ^1H NMR spectrum of the tetrazole **2**. (b) ^{13}C NMR spectrum of the tetrazole **2**.

3. Conclusions

Two new symmetrical tetrazole-containing ligands with potential application as precursors of new MOFs were synthesized successfully via short and efficient strategies based on Huisgen-type [3 + 2] cycloadditions. The use of solvents like water, EtOH, or AcOH makes both synthetic methodologies greener, resulting in low costs, eco-friendly conditions, and high yields. The first attempts to synthesize new porous coordination polymers are being performed and the results will be communicated soon.

4. Experimental Section

4.1. General Information, Instrumentation and Chemicals

¹H and ¹³C NMR spectra were acquired on a Bruker Advance III (500 MHz) spectrometer. The solvent was deuterated dimethyl sulfoxide (d⁶-DMSO). Chemical shifts are reported in parts per million (δ/ppm). The internal reference for NMR spectra is with respect to tetramethyl silane (TMS) at 0.0 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 data were treated using the MestReNova software (12.0.0–20080). IR spectra were acquired on a Bruker Tensor 27 spectrophotometer. The absorbance peaks are reported in reciprocal centimeters (cm^{−1}). Reaction progress was monitored by thin layer chromatography (TLC) on precoated Kieselgel 60 F₂₅₄ plates and the spots were visualized under UV light (254 or 365 nm). Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Structural drawings were created using the ChemDraw professional software (15.0.0.106). All starting materials were purchased from Sigma-Aldrich and were used without further purification. The solvents were distilled and dried according to standard procedures.

4.2. Synthesis of the 5-(4-nitrophenyl)-1H-tetrazole (2)

In a 100-mL round-bottomed flask equipped with a magnetic stirring bar, 1.48 g (1.0 equivalent) of the 4-aminobenzonitrile, 0.84 g (2.6 equivalent) of sodium azide and 2.25 g (2.0 equivalent) of zinc bromide were added sequentially into 40 mL of water. The reaction mixture was stirred at room temperature for 10 minutes before the temperature was raised to put the system under reflux using an oil bath as the heating system. The reaction progress was monitored by TLC. At the time the starting reagent disappeared, the reaction was stopped (24 h). After the reaction system reached room temperature, 15 mL of HCl solution [2 M] was added, and the mixture was stirred vigorously for 15 minutes. When the agitation was stopped, a crystalline precipitate was formed, which was filtered and washed with hot water (70 °C), methanol, ethyl acetate, and acetone (2 × 10 mL per solvent). The compound **2** was dried for 14 h, obtaining 1.72 g of a white crystalline solid in a yield of 90%; *R*_f = 0.28 (AcOEt–EtOH, 3:2 *v/v*); mp = 207–209 °C; ¹H NMR (500 MHz, d⁶-DMSO): δ 8.38 (d, *J* = 9.0 Hz, H-8, H-10, 2H), 8.27 (d, *J* = 9.0 Hz, H-7, H-11, 2H) ppm; ¹³C NMR (125 MHz, d⁶-DMSO): δ 156.8 (C-5), 148.9 (C-9), 132.1 (C-6), 128.4 (C-7, C-11), 124.9 (C-8, C-10) ppm; HRMS [M+H]⁺ Calculated for C₇H₆N₅O₂⁺ = 192.0521, found = 192.0516.

4.3. Synthesis of the (E)-1,2-bis(4-(1H-tetrazol-5-yl)phenyl)diazene (3)

In a 100-mL round-bottomed flask equipped with a magnetic stirring bar, 0.5 g (1.0 equivalent) of the 5-(4-nitrophenyl)-1H-tetrazole, 0.34 g (2.0 equivalent) of zinc, and 0.20 g (2.0 equivalent) of sodium hydroxide in 12.5 mL of ethanol and 5 mL of water were sequentially added. The reaction mixture was refluxed for 24 h. At the end of this time, the presence of an orange spot by TLC indicated that the azo-coupling had been completed successfully. Once the reaction mixture reached room temperature, the zinc was filtered, and to new crude, 20 mL and 15 mL of water and ethyl acetate were added, respectively. Then, the extraction was carried out using 8 mL of ethyl acetate, then the organic phase was concentrated to dryness under reduced pressure, and the reaction crude was purified by a silica column using a mixture of dichloromethane (DCM) with MeOH (3:2 *v/v*) as eluent.

The product was collected and concentrated to a vacuum, obtaining an orange solid, which was recrystallized using ethyl acetate. Finally, 0.57 g of an orange crystalline solid (**3**) was obtained in 63% yield; $R_f = 0.11$ (AcOEt–EtOH, 3:2 v/v); mp = 224–226 °C; ^1H NMR (500 MHz, $\text{d}^6\text{-DMSO}$): δ 8.21 (d, $J = 8.7$ Hz, H-8, H-10, H-15, H-19, 4H), 7.95 (d, $J = 8.7$ Hz, H-7, H-11, H-16, H-18, 4H) ppm; ^{13}C NMR (125 MHz, $\text{d}^6\text{-DMSO}$): δ 160.6 (C-5, C-20), 151.5 (C-9, C-14), 135.8 (C-6, C-17), 127.0 (C-7, C-11, C-16, C-18), 123.4 (C-8, C-10, C-15, C-19) ppm; HRMS $[\text{M}+\text{Na}]^+$ Calculated for $\text{C}_{14}\text{H}_{10}\text{N}_{10}\text{Na}^+$ = 341.0988, found = 341.0982.

4.4. Synthesis of the bis(4-(1H-tetrazol-1-yl)phenyl)sulfane (**5**)

In a 50-mL round-bottomed flask equipped with a magnetic stirring bar, 1.08 g of 4,4'-thiodianiline (1.0 equivalent), 1.5 g of sodium azide (4.5 equivalent) and 5.5 mL of trimethyl orthoformate (10 equivalent) were added sequentially into 10 mL of acetic acid. The reaction mixture was placed in an oil bath and the temperature was raised to 90 °C (reflux). The reaction progress was monitored by TLC and was stopped after being stirred for 24 h. The reaction mixture was cooled to room temperature and the precipitate was collected by filtration, washed with cold distilled water, and dried at room temperature. Then, 1.11 g of a gray powder (**5**) was obtained in a yield of 69%; $R_f = 0.23$ (Hex–AcOEt, 2:3 v/v); mp > 250 °C; ^1H NMR (500 MHz, $\text{d}^6\text{-DMSO}$): δ 10.1 (s, H-16, H-18, 2H), 7.98 (d, $J = 8.8$ Hz, H-1, H-3, H-9, H-11, 4H), 7.67 (d, $J = 8.8$ Hz, H-4, H-6, H-8, H-12, 4H) ppm, ^{13}C NMR (125 MHz, $\text{d}^6\text{-DMSO}$): δ 142.7 (C-16, C-18), 136.4 (C-5), 133.4 (C-2), 132.7 (C-4, C-6, C-8, C-12), 122.7 (C-1, C-3, C-9, C-11) ppm; HRMS $[\text{M} + \text{H}]^+$ Calculated for $\text{C}_{14}\text{H}_{11}\text{N}_8\text{S}^+$ = 323.0827, found = 323.0812.

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