

Synthesis of Tetrakis-Tetrazole via a Repetitive MCR [†]

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Abstract: The synthesis of novel and complex molecules of tetrakis-tetrazole was done via a Ugi-azide repetitive reaction from easily accessible starting materials in good yields. The use of orthogonal bifunctional reagents in isocyanide-based multicomponent reactions (IMCR) allowed the synthesis of structurally complex molecules in one pot manner. The molecules herein synthesized could have applications such as use as chelating agents and organocatalysts.

Keywords: tetrakis-tetrazole; Ugi-azide; I-MCR; chelating agents

1. Introduction

Multicomponent reactions (MCRs) are one of the most efficient synthetic tools used in organic chemistry, which incorporate three or more reactants into a single step reaction, and offer advantages over traditional linear multistep synthesis. MCRs accelerate the exploration of chemical space by reducing the number of experimental steps and purification process required to access a target product. The atom economy of MCR further improves the sustainability of the chemical processes [1]. Among the most well-known are those in which an isocyanide reagent is incorporated in the process.

The synthesis of molecules containing several 1,5-disubstituted tetrazoles (1,5-DS-T's) cores has been reported little in the literature [2,3] (Figure 1). Encouraged for this precedent, we are interested in the synthesis of this molecules (Figure 1).

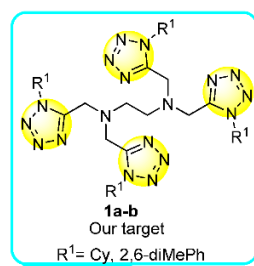


Figure 1. Target compounds.

There are several reported approaches for the synthesis of tetrazoles from nitriles, amides, thioamides, ketones, amines, and alkenes. One of the most common methods of synthesis involves the [3 + 2] cycloaddition between hydrazoic acid and organic nitriles [4]. In this context is noteworthy that IMCR process via the Ugi-azide of 4CR allows to access to molecules that contain several tetrazole cores providing several advantages as atom economy, operational simplicity, convergency, diversity, and complexity [5].

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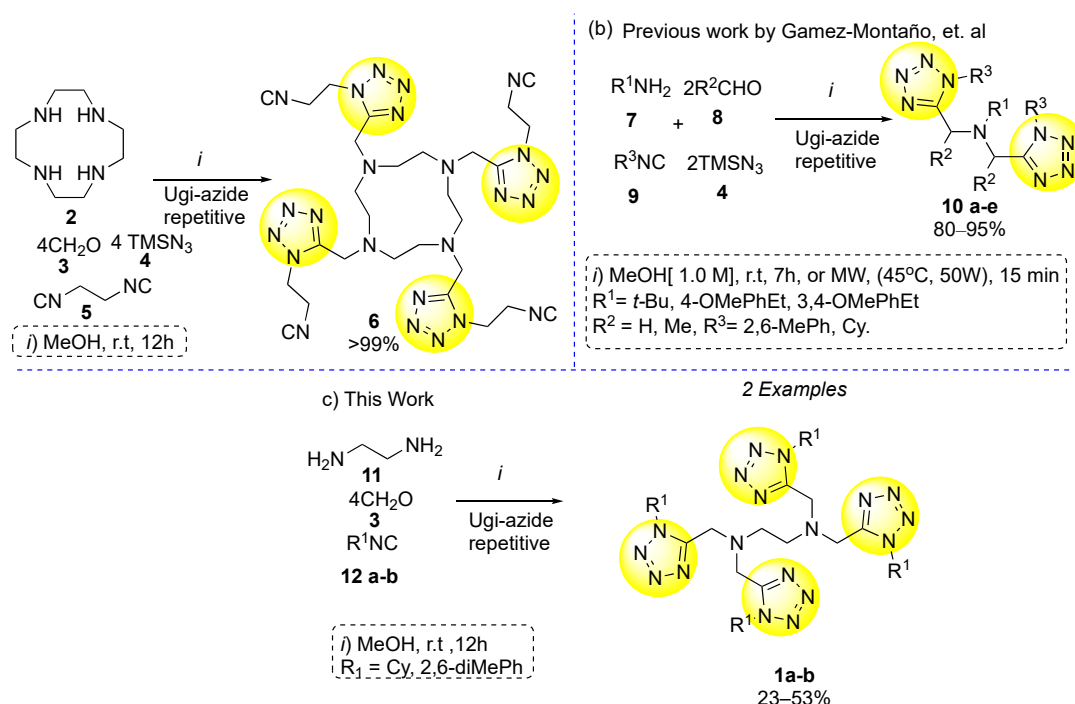
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In this context, Dömling et.al. in 2016 [6] reported a Ugi tetrazole reaction to the synthesis of a novel macrocyclic cyclen derivative containing four tetrazole cores; compared to our work, their methodology is highly restricted by the type of starting materials that they use in their process (Scheme 1a). On the other hand, the current work is an extension of our previous work published in 2015 where we reported the first synthesis of bis-1,5-disubstituted-1H-tetrazoles (bis-1,5-DS-1H-T) under mild conditions via Ugi-azide repetitive process [7] (Scheme 1b). Following the same line of research and as a part of our ongoing efforts in the development of new and versatile methodologies via I-MCR toward the synthesis of molecules containing privileged heterocyclic peptidomimetics (PHPs) as tetrazoles and/or complex 1,5-DS-1H-T, in the present work, we report the synthesis of two novel molecules tetrakis-tetrazole (**1a–b**) through a domino process via the Ugi-azide repetitive process (Scheme 1c).



Scheme 1. Previous work and our work. (a) Previous work by Dömling, et. al., (b) previous work by Gámez-Montaño, et. al., and (c) this work.

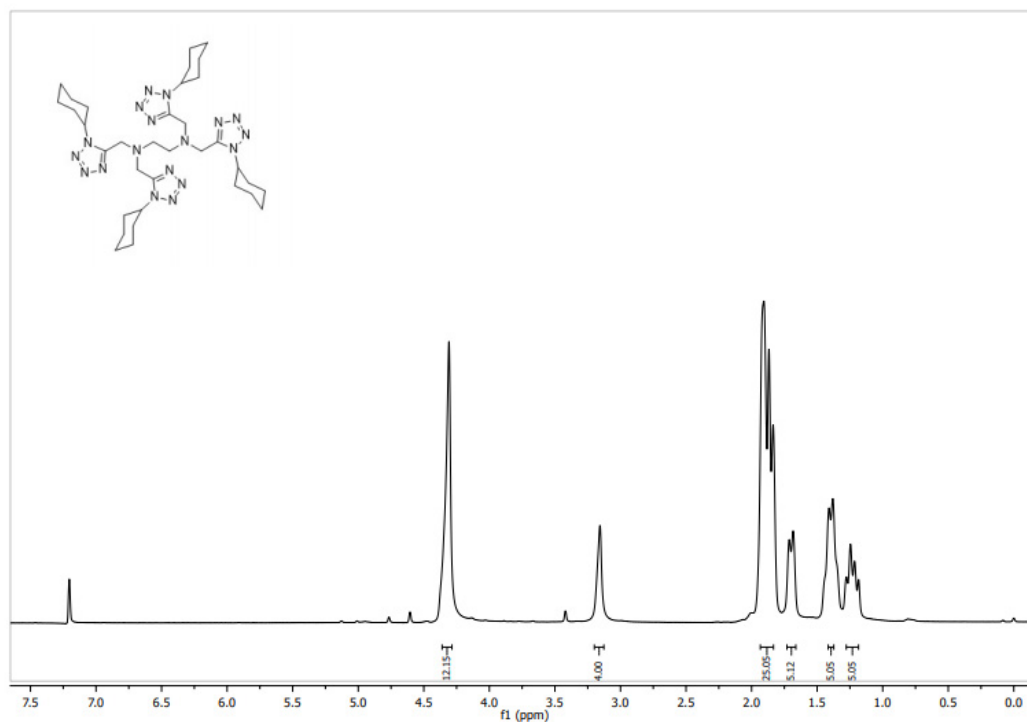
2. Results and Discussion

We began our experimental study by optimizing the Ugi-azide repetitive reaction, selecting *N*-tetrakis((1-cyclohexyl-1H-tetrazol-5-yl)methyl)ethane-1,2-diamine (**1a**) as our model to optimize the one-pot process. First, the formation of Ugi-azide repetitive product was attempted by the simple mixing of paraformaldehyde (4 equiv.) (**3**), ethylenediamine (1 equiv.) (**11**), azidotrimethylsilane (4 equiv.) (**4**), and cyclohexyl isocyanide (4 equiv.) (**12a**). The reaction using a mixture of toluene/MeOH (1:1) as solvent (Entry 1, Table 1) resulted in obtaining of only traces of the desired product and decomposition of the reaction mixture when we used conventional heat (Entry 2, Table 1), while the same reaction with MeOH at room temperature for 12 h was more fruitful (Entry 3, Table 1). Indeed, initial studies without the catalyst afforded the desired products in lower yields. On the other hand, in presence of catalytic amounts of NaOH (10 %mol), the yield of this reaction was improved (Entry 4, Table 1). The course of reactions was monitored by TLC and the structure of isolated product was confirmed by analysis of ^1H y ^{13}C NMR (Figures 2 and 3).

Table 1. Reaction optimizing conditions **1a**.

Entry	Solvent	Catalyst	Temperature	Source Energy	Time (h)	Conversion
1	PhMe/MeOH	–	r.t	–	12	Traces
2	PhMe/MeOH	–	90	Conventional heat	3	Decomp
3	MeOH	–	r.t	–	12	12%
4	MeOH	NaOH	r.t	–	12	28%

Decomp = decomposition.

**Figure 2.** ¹H NMR spectrum of compound **1a**.

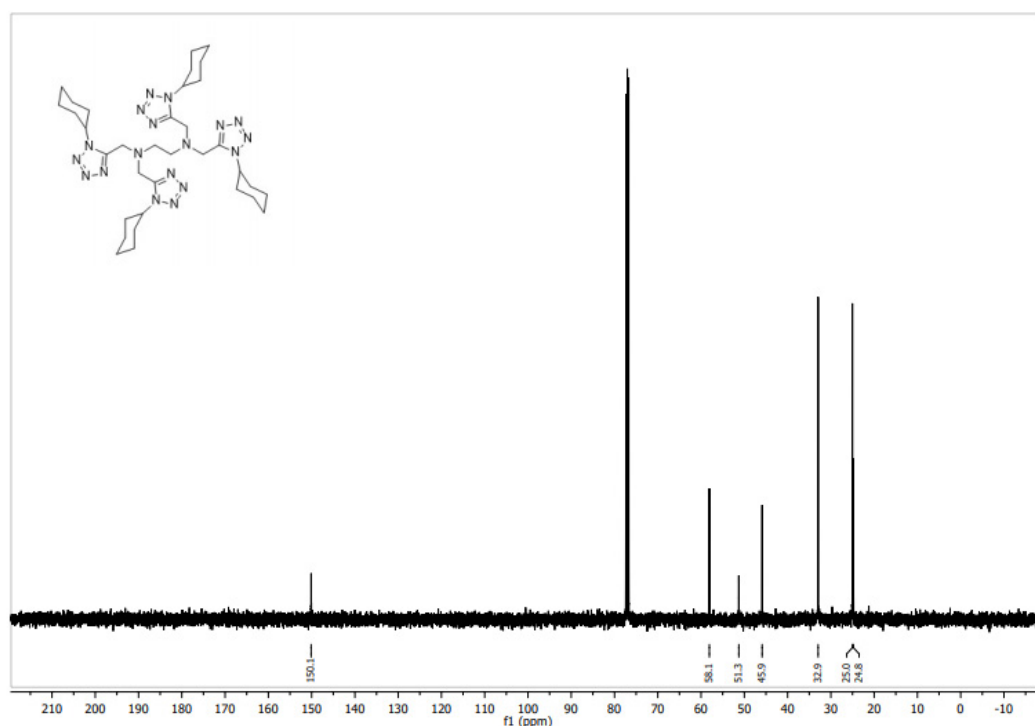
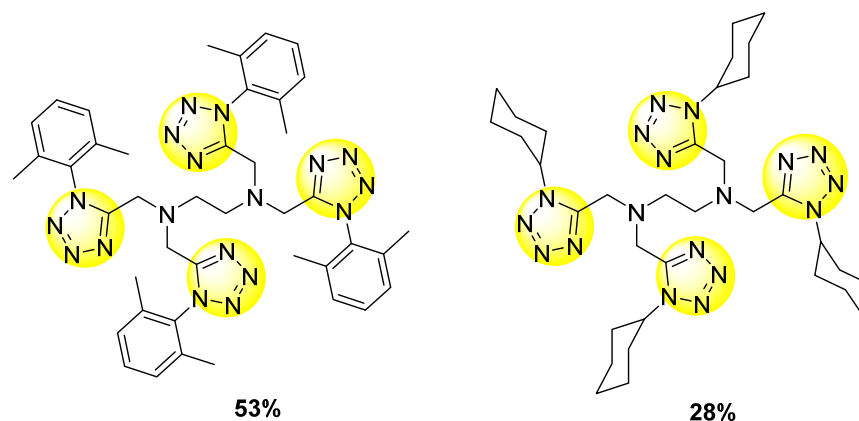


Figure 3. ^{13}C NMR spectrum of compound **1a**.

In fact, after some optimization of the reaction conditions, we could obtain the desired products (**1a–b**) in 28% and 53%, respectively, overall yields (Scheme 2). The versatility of the developed methodology was examined using two different isocyanides as aryl and alkyl (**12a–b**) and bifunctional amine (ethylenediamine).



Scheme 2. Substrate scope.

3. Experimental Section

General Information. ^1H and ^{13}C NMR spectra were acquired on a 500 MHz spectrometer. The solvent for NMR samples was CDCl_3 . Chemical shifts are reported in parts per million (δ/ppm). Internal reference for NMR spectra was tetramethylsilane at 0.00 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 version 10.0.1-14719. The reaction progress was monitored by TLC, and the spots were visualized under UV light (254 or 365 nm). Flash column chromatography was performed using silica gel

(230–400 mesh) and mixtures in different proportions of hexanes with ethyl acetate as mobile phase. Chemical names and drawings were obtained using the ChemBioDraw Ultra 13.0.2.3020 software package.

General method: paraformaldehyde (4 equiv.) (**3**), ethylenediamine (1 equiv.) (**11**), azidotrimethylsilane (4 equiv.) (**4**), isocyanide (4 equiv.) (**12a–b**) and NaOH (10 %mol) was dissolved in MeOH (1 M) were placed in a 10 mL round bottom flask. The mixture was stirred at room time for 12 h. Then, the solvent was removed to dryness and the crude was recrystallized in a mixture of MeOH/DCM/Hex for obtain the desired products (**1a–b**) (Figure 4).

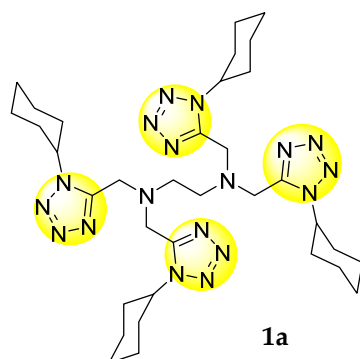


Figure 4. N-tetrakis((1-cyclohexyl-1H-tetrazol-5-yl)methyl)ethane-1,2-diamine (**1a**).

White solid (51 mg, 28%); $R_f = 0.27$ (Hexanes-EtOAc = 7/3 v/v); ^1H NMR (500 MHz, CDCl_3) δ 4.24 (s, 12H), 3.15 (s, 4H), 1.94–1.83 (m, 25H), 1.69–1.58 (m, 5H), 1.47–1.33 (m, 5H), 1.22–1.11 (m, 5H) ^{13}C NMR (126 MHz, CDCl_3) δ 150.1, 58.1, 51.3, 45.9, 32.9, 25.0, 24.8.

4. Conclusions

Two new tetrakis-tetrazole were synthesized via a domino process through the Ugi-azide repetitive reaction, under mild green conditions in moderate to good overall yields (28–53%). The use of the bifunctional groups allows us to obtain complex molecules with likely application as a chelating agent and organocatalysts.

Author Contributions: All authors contributed equally to this work. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflicts of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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