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Proceeding Paper

One-Pot Synthesis of Tetrazole-Triazole *Bis*-Heterocycles via Ugi-Azide Reaction †

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Abstract: Bioisosteres of amide bonds such as 4,5-disubstituted-1,2,3-triazoles (4,5-DS-1,2,3-Ts) and 1,5-disubstituted tetrazoles (1,5-DST) are present in compounds with important biological activities like antineoplastic, antibacterial, antifungal and antiparasitic; and antifungal, antiparasitic, antiviral, and anti-inflammatory. In the present work, we describe the synthesis of tetrazole-triazole bis-heterocycles via the Ugi-Azide strategy. The target molecules were synthesized with moderate yields, under mild conditions, employing 2*H*-1,2,3-triazole aldehyde as input.

Keywords: tetrazole; triazole; *bis*-heterocycles; Ugi-Azide

1. Introduction

Multicomponent reactions (MCRs) have proven to be efficient synthetic tools compared to traditional multistep syntheses. They are defined as one-pot processes where three or more reagents interact together under the same reaction conditions [1]. MCRs are considered domino reactions [2].

MCR products are complex and exhibit great molecular diversity, allowing the generation of libraries of compounds with importance for several fields such as optics, agrochemistry, and medicinal chemistry, among others [3]. Heterocyclic chemistry is an important topic in the MCR field, where heterocycles can be either synthesized via a multicomponent process or via MCR-post transformation or functionalized via MCRs [4].

Among MCRs, those based on isocyanide chemistry (IMCRs) are among the more important and widely used, due to the versatility of isocyanide to react as a nucleophile and electrophile at the same carbon [5]. Ugi reaction is one of the well-known IMCRs [6]. however several variations have been reported, for example, Ugi-Azide, where carboxylic acid is replaced with hydrazoic acid. This reaction is the method of choice for 1,5-disubstituted tetrazole synthesis [7].

Tetrazoles are heterocyclic compounds formed by 4 nitrogen atoms with potential applications in medicine, agriculture, chemistry, and pharmacology, among others [8]. In medicinal chemistry, two types of tetrazoles are highlighted: 5-substituted-tetrazole and 1,5-disubstituted tetrazole, the latter being considered as a biosiostere of amide bond. This property is associated with bond angles and lengths, and it is beneficial as it improves the metabolic resistance to peptidases [9].

On the other hand, 1,2,3-triazoles are 5-membered heterocycles with 3 nitrogen atoms. In recent years, they have attracted interest from several fields due to their antineoplastic, antibacterial, antifungal, antiviral, and antiparasitic potential [10]. From the medicinal chemistry point of view, 1,4 and 1,5-disubstituted-1,2,3-triazoles are capable of

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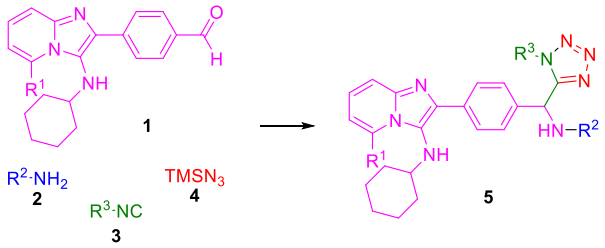
mimicking *trans* and *cis* amide bonds, respectively, which provides a high metabolic resistance [11].

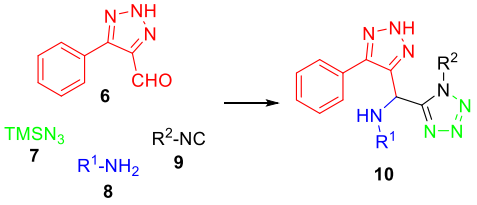
Bis-heterocycles are hybrid molecular systems where two heterocycles are present [12]. Their connectivity can be either linked, spaced, bound, fused, or merged [13]. Among the plethora of this kind of compounds, those which incorporate nitrogen heterocycles are highlighted, because around 59% of the FDA-approved drugs until 2014 contained at least one nitrogen heterocycle [14].

The incorporation of a heterocycle as part of the components in an IMCRs process such as the Ugi-Azide reaction is an important alternative to the construction of *bis*-heterocycles with linked connectivity, like 1,5-disubstituted-tetrazole-1,5-disubstituted-triazole.

(**A**). Closer work by Sharisa, A. et. al. (2013) [15].



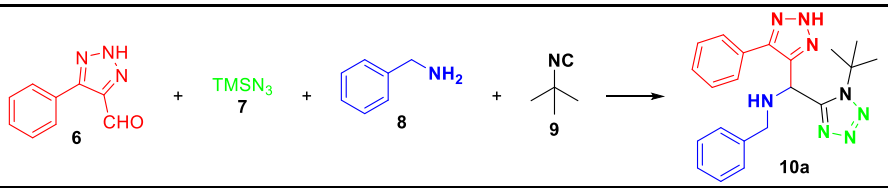
(**B**). This work



2. Results and Discussion

The present work, it is presented the synthesis of a small library of *bis*-heterocycles containing the 1,5-disubstituted 1,2,3-triazole and 1,5-disubstituted tetrazole moieties via the Ugi-Azide reaction. For the reaction optimization, 5-phenyl-2*H*-1,2,3-triazole-4-carbaldehyde (**6**) trimethylsilylazide (**7**), benzylamine (**8a**) and *tert*-butyl isocyanide (**9a**) were chosen as components, to synthesize *bis*-heterocycle **10a**. In Table 1, the optimization experiments are described.

Table 1. Screening conditions for the synthesis of target molecule **16a**.



Entry	Solvent	Time	Yield
1	EtOH	24 h	59%
2	H_2O	48 h	NR
3	-	48 h	NR

In the first experiment, ethanol was used as a solvent for the Ugi Azide reaction for 24 h, at room temperature, obtaining a moderate yield of 59%. Further optimization of the reaction was attempted by using water as a solvent, and with a solvent-free experiment, however, neither of the two reactions proceeded, as the starting materials were recovered.

Taking the experiment with ethanol as the optimized condition, the reaction scope was evaluated, varying the amine and isocyanide components.

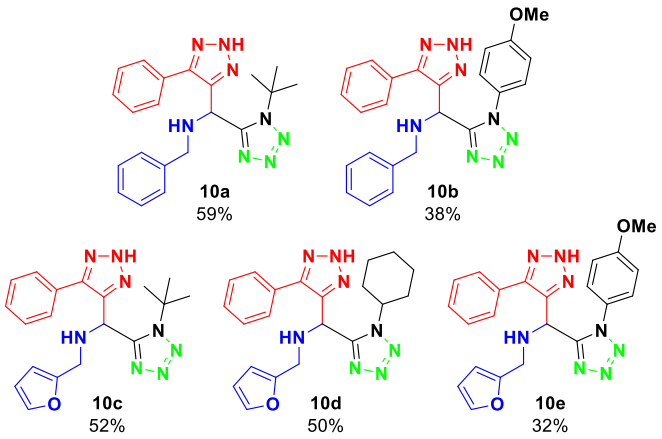


Figure 1. Substrate scope.

3. Conclusions

The incorporation of a nitrogen heterocycle in one of the components in an IMCR is an efficient strategy for the functionalization of heterocycles. It is highlighted that the target molecules incorporate *bis*-heterocycles in their structure. The developed strategy is the first report on the use of 5-phenyl-2*H*-1,2,3-triazole-4-carbaldehyde as a component in the Ugi-Azide reaction. The developed procedure has advantages such as being carried out under mild and environmentally friendly reaction conditions, using a green solvent.

4. Experimental Section

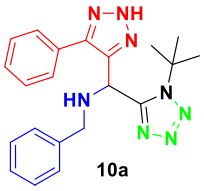
4.1. General information, Chemicals, and Instrumentation

Bruker Avance III spectrometers (500 and 125 MHz, respectively) were used for acquisition of 1H and 13C NMR spectra. Deuterated chloroform ($CDCl_3$) was used as the solvent for NMR experiments. Chemical shifts (δ) are given in ppm relative to tetramethylsilane (TMS). Coupling constants are reported in Hertz (Hz). Multiplicities of the signals are described using standard abbreviations: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). NMR spectra were analyzed using MestReNova software version 12.0.0-20080. Reaction progress was monitored by thin-layer chromatography (TLC) on pre-coated silica gel F254 aluminum sheets. The spots were visualized under UV light at 254 nm. Column chromatography was performed using silica gel (230–400 mesh) as a stationary phase. Mixtures of hexanes and ethyl acetate were used as mobile phases for column chromatography and in TLC for reaction progress monitoring. All reagents were purchased from Sigma Aldrich and were used without further purification. Chemical names and drawings were obtained using the ChemDraw 22.2.0.3300 software package.

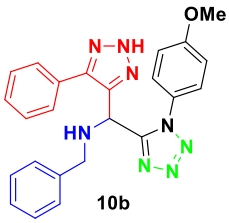
4.2. General Procedure

In a sealed vial, 5-phenyl-2*H*-1,2,3-triazole-4-carbaldehyde (**6**, 1.0 equiv.), trimethylsilylazide (**7**, 1.0 equiv.), amine (**8a-b**, 1.0 equiv.) and isocyanide (**9a-c**, 1.0 equiv.) were dissolved in EtOH (0.5 M) and stirred for 24 h at room temperature. The solvent was evaporated under reduced pressure and the product was purified by flash chromatography using mixtures of ethylacetate in hexanes as mobile phase and silica gel as stationary phase to obtain the corresponding *bis*-heterocycles **10a-e**.

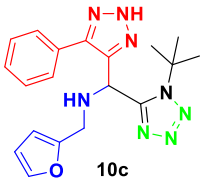
4.3. Spectral Data



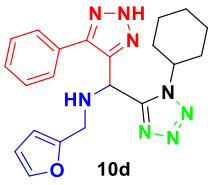
***N*-benzyl-1-(1-(*tert*-butyl)-1*H*-tetrazol-5-yl)-1-(5-phenyl-2*H*-1,2,3-triazol-4-yl)-methanamine (10a):** Yellow solid; ^{1}H (500 MHz, $CDCl_3$) δ 7.58 (m, 2H), 7.35 (m, 3H), 7.27 (m, 3H), 7.21 (m, 3H), 5.53 (s, 1H), 3.86 (d, *J* = 12.7 Hz, 1H), 3.75 (d, *J* = 12.7 Hz, 1H), 1.44 (s, 9H).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.55, 144.12, 141.20, 138.30, 129.62, 129.91, 128.85, 128.80, 128.43, 128.01, 127.55, 61.98, 51.63, 49.33, 29.60.



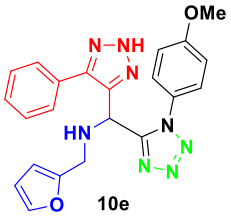
***N*-benzyl-1-(1-(4-methoxyphenyl)-1*H*-tetrazol-5-yl)-1-(5-phenyl-2*H*-1,2,3-triazol-4-yl)-methanamine (10b).** Yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ 7.22 (m, 7H), 7.09 (m, 3H), 6.97 (d, J = 6.9 Hz, 2H), 6.69 (d, J = 6.9 Hz, 2H), 5.34 (s, 1H), 3.79 (d, J = 4.8 Hz, 2H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.83, 155.23, 138.10, 129.12, 128.75, 128.66, 128.57, 128.44, 127.78, 127.41, 126.28, 125.56, 114.60, 55.55, 51.23, 47.02.



1-(1-(*tert*-butyl)-1*H*-tetrazol-5-yl)-*N*-(furan-2-yl-methyl)-1-(5-phenyl-2*H*-1,2,3-triazol-4-yl)-methanamine (10c): brown solid; ^{1}H NMR (400 MHz, CD_3OD) 7.65 (m, 2H), 7.50 (m, 1H), 7.44 (m, 3H), 6.37 (m, 1H), 6.19 (d, J = 3.1 Hz, 1H), 5.61 (s, 1H), 3.98 (d, J = 14.3 Hz, 1H), 3.83 (d, J = 14.4 Hz, 1H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, CD_3OD) δ 155.76, 153.74, 143.87, 130.13, 130.01, 129.03, 111.46, 109.78, 63.36, 50.20, 44.27, 29.69.



1-(1-cyclohexyl-1*H*-tetrazol-5-yl)-*N*-(furan-2-yl-methyl)-1-(5-phenyl-2*H*-1,2,3-triazol-4-yl)-methanamine (10d): colorless oil: ^{1}H NMR (400 MHz, CD_3OD) 7.65 (m, 2H), 7.50 (m, 1H), 7.44 (m, 3H), 6.37 (m, 1H), 6.19 (d, J = 3.1 Hz, 1H), 5.61 (s, 1H), 3.98 (d, J = 14.3 Hz, 1H), 3.83 (d, J = 14.4 Hz, 1H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, CD_3OD) δ 155.76, 153.74, 143.87, 130.13, 130.01, 129.03, 111.46, 109.78, 63.36, 50.20, 44.27, 29.69.



***N*-(furan-2-yl-methyl)-1-(1-(4-methoxyphenyl)-1*H*-tetrazol-5-il)-1-(5-phenyl-2*H*-1,2,3-triazol-4-yl)-methanamine (10e):** Colorless oil: ^{1}H NMR (500 MHz, CD_3OD) 7.33 (m, 1H), 7.26 (t, J = 7.2 Hz, 1H), 7.21 (t, J = 7.4 Hz, 2H), 7.12 (d, J = 7.3 Hz, 2H), 6.85 (d, J = 8.9 Hz, 1H), 6.67 (d, J = 8.9 Hz, 1H), 6.22 (m, 1H), 6.01 (d, J = 2.8 Hz, 1H), 5.29 (s, 1H), 3.86 (d, J = 14.6 Hz, 1H), 3.82 (d, J = 14.5 Hz, 1H), 3.68 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 161.18, 155.39, 152.12, 142.43, 128.47, 127.49, 126.26, 125.35, 114.34, 109.98, 108.27, 54.72, 46.78, 42.76.

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