

A One-Pot Process for the Synthesis of Alkyne-3-tetrazolyl-tetrazolo [1,5-*a*] Quinolines [†]

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Abstract: An efficient synthesis of alkyne-3-tetrazolyl-tetrazolo[1,5-*a*] quinolones via a one-pot isocyanide-based multicomponent reaction (IMCR) process: I-MCR Ugi-azide/S_NAr/ring-chain azido tautomerization was performed under eco-friendly conditions. We report the one-pot synthesis of tris-heterocycles containing a tetrazolo[1,5-*a*] quinoline connected to a 1,5-disubstituted-tetrazole (1,5-DS-T). The synthesis of these compounds is of great interest in synthetic and medicinal chemistry because these heterocycles are considered privileged scaffolds and their preparation and evaluation may lead to the discovery of novel bioactive molecules.

Keywords: isocyanide based multicomponent reaction; Ugi-azide; tetrazolo [1,5-*a*] quinolones; ring-chain azido tautomerization; one-pot process; alkyne moiety

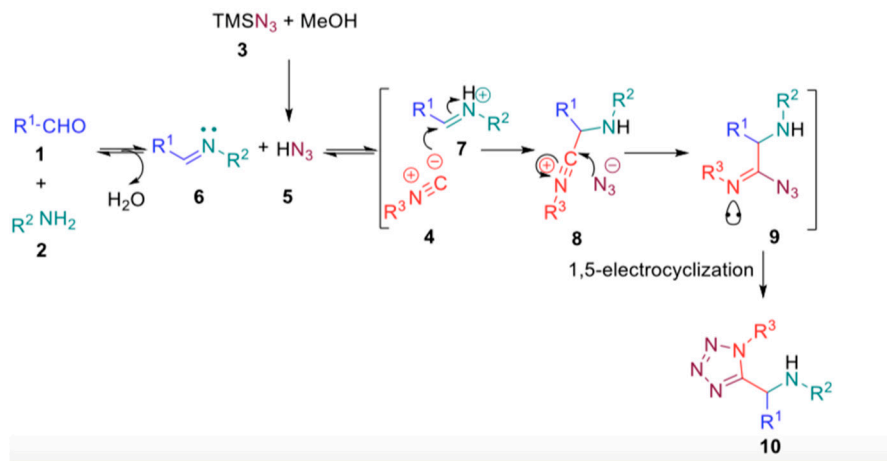
1. Introduction

Bis-heterocycles are molecules that can be formed by connecting two heterocyclic scaffolds via fusion, by a directed bond, or via a multi-bond linked, bound, or spacer [1]. The purpose behind the combination of two heterocycles is to improve their potential applications in different areas, such as chelating agents and metal ligands, and particularly in the development of bioactive molecules and drugs [2–5]. Many bis-heterocycles can be synthesized using multicomponent reactions (MCRs). A multicomponent reaction is a domino process in which three or more compounds react with each other in one pot to produce the products in such a way that the majority of the atoms of the reactants are incorporated into the final products. MCRs therefore offer great possibilities for molecular diversity by reducing step time and effort.

There are a number of advantages that make one-pot transformations popular for organic chemists: the procedures are generally simple, saving time and resulting in high atom economies. The one-pot process can be carried out through multi-step sequential processes where the consecutive steps take place under the same reaction conditions [6,7]. The 1,5-disubstituted tetrazoles (1,5-DS-T's) are bioisosteres of the *cis*-amide bond in peptides as a result of the similarities in their physicochemical properties [8–10]. They are an important class of heterocycles with a wide range of applications in coordination chemistry, agriculture, photoimaging agents, and medicinal chemistry [11].

The main routes for the synthesis of 1,5-DS-T's are [3 + 2] intermolecular cycloadditions [12–15] between azides and nitriles and Ugi-azide reactions (UA) [16,17]. The UA was reported first by Ugi in 1961. The carboxylic acid used in the classical Ugi reaction is replaced by hydrazoic acid (generated in situ from NaN₃ or TMSN₃). The proposed mechanism of this one-pot, four-component reaction

(Scheme 1) involves a condensation between an amine and an aldehyde to give Schiff base **6**, which after protonation by HN_3 and nucleophilic attack with isocyanide **4**, affords intermediate **8**. Subsequent nucleophilic attack with N_3^- gives intermediate **9**. Finally, an intramolecular electrocyclicization occurs to afford 1,5-DS-T's **10** [18–20].



Scheme 1. Ugi-azide reaction mechanism.

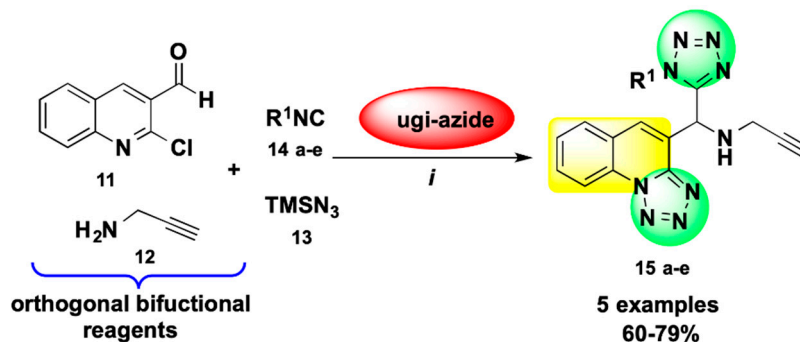
Tetrazolo [1,5-*a*] quinoline is the core moiety of various compounds with interesting pharmacological properties like anticancer [21], antifungal [22], antibacterial [23], and anti-inflammatory properties [23]. Due to the above-mentioned medicinal importance of tetrazolo [1,5-*a*] quinoline and 1,5-DS-T moieties individually, there has been an increased interest in the synthesis of *bis*-heterocycles containing the 1,5-DS-T moiety over the past decade.

Herein, we report the synthesis of fused *bis*-heterocycles type linked containing tetrazolo [1,5-*a*] quinoline linked to 1,5-DS-T moieties. It is noteworthy that the one-pot synthesis of 1,5-DS-T with linked heterocycle has been little-explored, but 1,5-DS-T bound to tiadiazoles [24], chromone [25], and quinoline [26] have been prepared previously.

2. Results and Discussion

In this work, we described the synthesis of five alkyne-3-tetrazolyl-Tetrazolo[1,5-*a*] quinoline via a one-pot I-MCR process: Ugi-azide/ $\text{S}_{\text{N}}\text{Ar}$ /ring-chain azido tautomerization under eco-friendly conditions with good yields (60–79%).

The synthetic methodology involved a sequential combination of 2-chloroquinoline-3-carboxaldehyde (**11**) with one equivalent of propargyl amine (**12**), two equivalents of azidotrimethylsilane (**13**), and one equivalent of isocyanide (**14**) in MeOH at room temperature (Scheme 2).



$\text{R}^1 = \text{t-Bu, Cy, Bn, 2,6-diMePh, TosMIC}$
i) MeOH, 8–12h, r.t.

Scheme 2. Strategy for the synthesis of alkyne-3-tetrazolyl-tetrazolo[1,5-*a*] quinolines.

We selected the *N*-((1-Cyclohexyl-1H-tetrazol-5-yl)(tetrazolo[1,5-*a*]quinolin-4-yl)methyl)prop-2-yn-1-amine (**5a**) as our model target to optimize the one-pot process Ugi-azide/S_NAr/ring-chain azido tautomerization. Thus 2-chloroquinoline-3-carbaldehyde (**11**) was combined sequentially with one equivalent of propargyl amine (**12**), cyclohexyl isocyanide (**14a**), and two equivalents of azidotrimethylsilane (**13**) using the Ugi-azide standard conditions (MeOH, rt) as starting point. The product **15a** was isolated in 70% after 6 h (Entry 1, Table 1). Then, we decided to study the effect of temperature. Thus, the reaction was performed in methanol at reflux at 70 °C after 6 h (Entry 2, Table 1), where the product **15a** was synthesized in 20%. In this context, we used microwaves (Entry 3, Table 1) and ultrasound (US) (Entry 4, Table 1) as irradiation methods in order to reduce the reaction time and eventually to increase the yields, but the experiment was not successful with respect to the experiment at room temperature, the reaction time decreased, but the yield was lowered from 54% and 40% respectively.

Table 1. Screening conditions.

Entry	Solvent	t (h)	T (°C)	Yield (%)
1	MeOH	6	rt	70
2	MeOH	6	70	20
3	MeOH	1	85 ^a	54%
4	MeOH	1.5	60 ^b	40%

^a MW (100 W) ^b US (42 kHz).

After an exploration of the reaction conditions varying the temperature and irradiation methods, optimal conditions for preparing alkyne-3-tetrazolyl-tetrazolo[1,5-*a*] quinolines **15a–e** were found. Using the optimal conditions (MeOH, rt, 8–12 h), we synthesized the compounds with good yields (60–79%) (Table 2). As seen in Scheme 2, a good reaction scope was found. The stereoelectronic nature of substituents in the isocyanide moiety varied from alkyl to aryl and benzyl substituents. Steric and electronic effects from the isocyanide impacted the yields of the corresponding compounds. When the poorly nucleophilic 2,6-dimethylphenyl isocyanide was used, the yield was slightly lower in comparison with cyclohexyl and *t*-butyl isocyanides analogs.

Table 2. Substrate scope.

15	R ¹	Yield (%)
15a	Cy	79
15b	<i>t</i> -Bu	74
15c	2,6-diMePh	68
15d	Bn	64
15e	TosMIC	60

With respect to screening conditions, higher yields were observed at room temperature. When we used microwave or ultrasound irradiation, the time of reaction was shorter (1 and 2 h, respectively), but the yields were lower in comparison with the room temperature reaction.

Finally, all the products were characterized by the classical spectroscopic techniques (see the experimental section). The product 15a (Figure 1) was chosen to show ^1H and ^{13}C spectra (Figures 2 and 3).

3. Experimental Section

General Information: ^1H and ^{13}C NMR spectra were acquired on Bruker Advance III (Fällande, Uster, Switzerland) spectrometer (500 MHz). The solvent for NMR samples was deuterated chloroform (CDCl_3). Chemical shifts are reported in parts per million (δ/ppm). Internal reference for NMR spectra is tetramethylsilane (TMS) at 0.00 ppm. The internal reference for ^{13}C NMR spectra is expressed with respect to CDCl_3 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). IR spectra were acquired on Perkin Elmer 100 spectrometer with Attenuated Total Reflectance (ATR) accessory using neat compounds. The wavenumbers are reported in reciprocal centimeters ($\nu_{\text{max}}/\text{cm}^{-1}$). HRMS spectra were acquired via electrospray ionization (ESI) in positive ion mode and recorded via the time-of-flight (TOF) method. Reactions at reflux were performed in round-bottomed flasks using a recirculation system mounted on a sand bath with electronic temperature control. Microwave-assisted reactions were performed on CEM DiscoverTM Synthesis Unit without pressure sensor in close vessel mode. Ultrasound irradiated reactions were performed on Branson model 1510 ultrasonic cleaner working at $42 \text{ kHz} \pm 6\%$ frequencies. The reaction progress was monitored using Thin-Layer Chromatography (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 were used as the mobile phase. Melting points were determined on Cole-Parmer Electrothermal Programmable Digital Melting Point apparatus.

General procedure (GP): 2-Chloroquinoline-3-carboxaldehyde **11** (0.52 mmol, 1.0 equiv), propargyl amine **12** (0.52 mmol, 1.0 equiv.), azidotrimethylsilane **13** (1.12 mmol, 2.0 equiv.), and isocyanide **14** (0.052 mmol, 1.0 equiv.) were dissolved in MeOH in a round-bottom flask equipped with a magnetic stirrer bar. The resulting mixture was stirred for 8–12 h at room temperature. The solvent was evaporated under reduced pressure until dryness, and the organic layer was purified using flash chromatography eluting with hexanes-EtOAc (7/3 *v/v*) as eluent to afford compounds **15a–e**.

Spectral Data

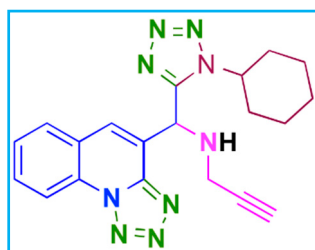


Figure 1. Molecule 15a.

N-((1-Cyclohexyl-1H-tetrazol-5-yl)(tetrazolo[1,5-a]quinolin-4-yl)methyl)prop-2-yn-1-amine (15a). Pale yellow solid (112.0 mg, 79%); mp = 173–174 °C; Rf = 0.29 (Hexanes-EtOAc = 1/1 *v/v*); ^1H NMR (500 MHz, CDCl_3) δ 8.68 (d, $J = 8.4 \text{ Hz}$, 1H), 8.28 (s, 1H), 8.01 (d, $J = 7.9 \text{ Hz}$, 1H), 7.93–7.88 (m, 1H), 7.76–7.72 (m, 1H), 6.17 (s, 1H), 4.99–4.90 (m, 1H), 3.63–3.52 (m, 1H), 2.88 (s, 1H), 2.32 (t, $J = 2.4 \text{ Hz}$, 1H), 2.26–2.21 (m, 1H), 7.93–7.88 (m, 1H), 2.15–1.94 (m, 5H), 1.84–1.79 (m, 1H), 1.60–1.48 (m, 2H), 1.42–1.32 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 153.3, 146.6, 131.6, 131.5, 130.3, 129.4, 128.4, 123.8,

123.3, 116.8, 80.2, 73.3, 58.5, 50.3, 36.4, 33.3, 32.9, 25.4, 25.3, 24.9; FT-IR (ATR) $\nu_{\max}/\text{cm}^{-1}$ 3340 (N-H), 1616 (N=H), 1279 (N=N=N); HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $\text{C}_{20}\text{H}_{22}\text{N}_9$ 388.1992, found 388.1985.

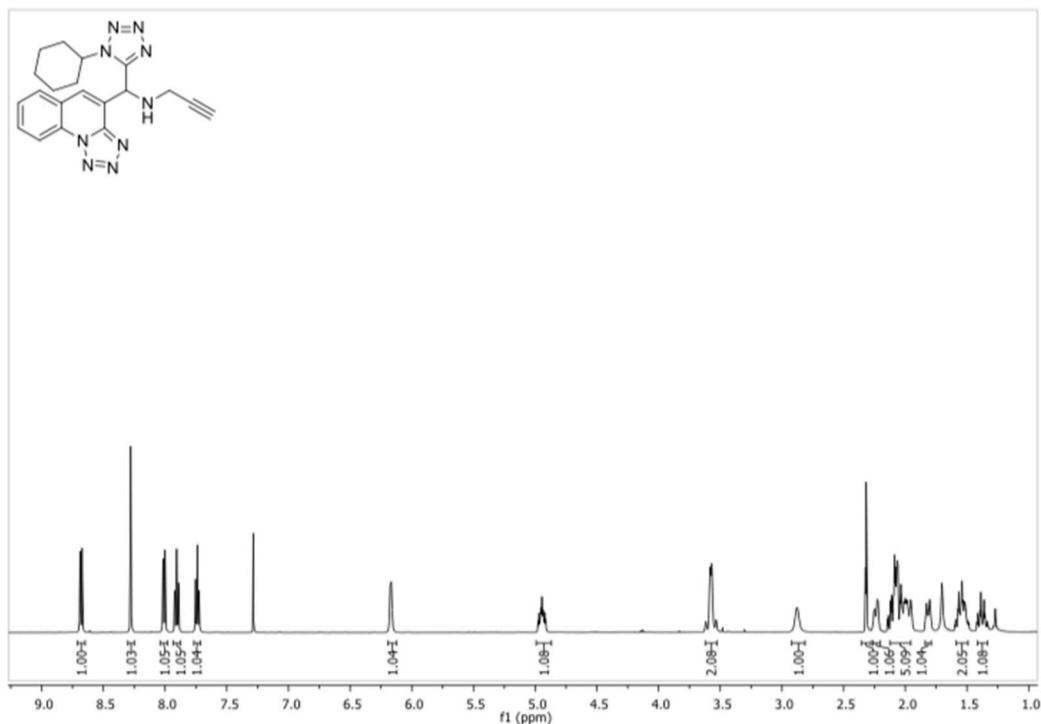


Figure 2. ^1H NMR spectrum of compound 15a.

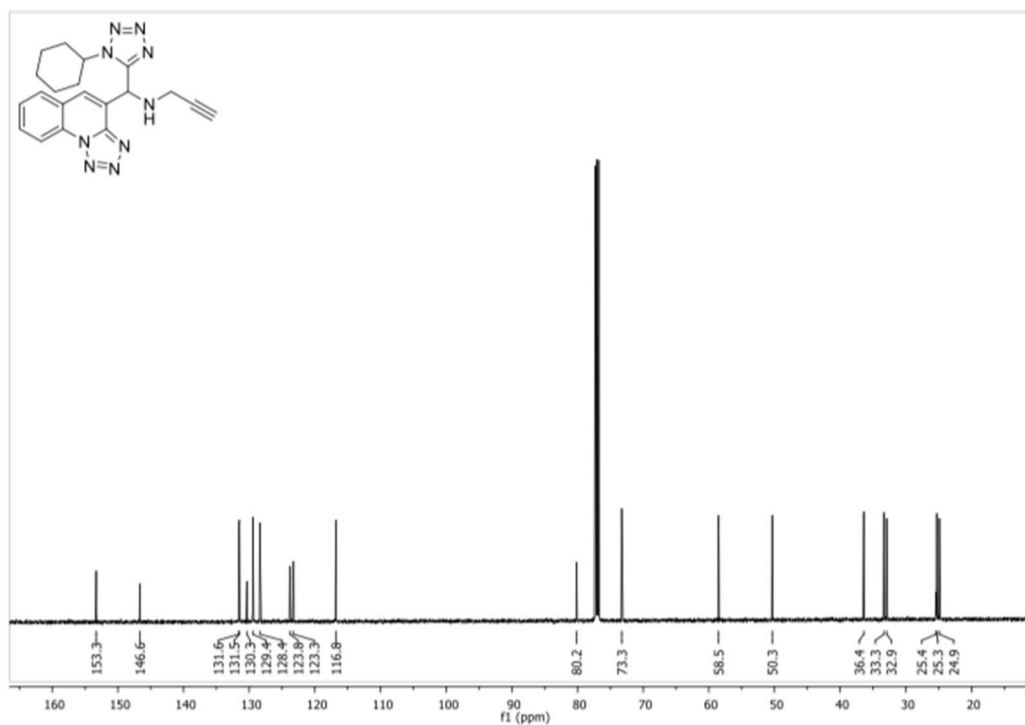


Figure 3. ^{13}C NMR spectrum of compound 15a.

4. Conclusions

A series of five alkyne-3-tetrazolyl-tetrazolo[1,5-*a*]quinolines was synthesized with good yields (60–79%) in one pot under eco-friendly conditions at room temperature. This work represents a contribution in the synthesis of fused bis-heterocycles (15a–e) containing 1,5-DS-T and tetrazolo[1,5-

a]quinoline. The use of the bifunctional groups allowed us to obtain highly functionalized molecules with enormous potential in post-transformations for the generation of more complex molecules.

Author Contributions: All authors contributed equally to this work.

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Conflicts of Interest: The authors declare no conflict 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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