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Solvent-Free Synthesis of Imidazo [1,2-*a*] pyridin-tetrazolo [1,5-*a*] Quinolines via an IMCR One-Pot Process †

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Abstract: A solvent-free and catalyst-free synthesis of fused bis-heterocycles containing imidazo[1,2-*a*]pyridine and tetrazolo[1,5-a]quinoline frameworks is reported via a one-pot process. This Groebke–Blackburn–Bienaymé reaction (GBBR)/SNAr/ring-chain azido tautomerization cascade proceeds under eco-friendly conditions. The tetrazolo[1,5-*a*]quinoline and imidazo[1,2-*a*]pyridine scaffolds are present in various compounds with interesting pharmacological properties and could lead to the discovery of novel bioactive molecules.

Keywords: isocyanide-based multicomponent reactions; Groebke–Blackburn–Bienaymé reaction; tetrazolo[1,5-a]quinolines; ring-chain azido tautomerization; one-pot process

1. Introduction

Fused *bis*-heterocycles are important compounds which consist of the fusion of one heterocyclic ring to second heterocycle. Combining two such privileged structures in one chemical entity leads to a hybrid molecule, which in some cases can serve as multiple ligands for one or more biological targets. This is an emerging approach in drug discovery that could generate a lead compound that is more effective than its individual components [1].

The art of generating structural complexity is inexorably linked with the development of novel and efficient synthetic strategies. To this end, multicomponent reactions (MCRs) have emerged as an effective means to prepare complex heterocyclic frameworks. Time saving, simple experimental procedures that form several bonds in one step are among the exceptional characteristics of these reactions [2–4]. Isocyanide-based MCRs (IMCRs) are the most important subclass of MCRs due to the high functional-group tolerance and versatility of isocyanides.

Multicomponent reactions (MCR) play essential roles in heterocyclic chemistry: (i) To synthesize heterocycles directly, (ii) to synthesize heterocycles via MCR/cyclization processes, (iii) to use heterocycles as substituents in the starting components, and (iv) to functionalize heterocycles with other heterocyclic systems [5–7].

In this note, we report the *one-pot*, solvent-free synthesis of fused bis-heterocycles containing the tetrazolo[1,5-*a*]quinoline core bound to an imidazo [1,2-*a*] pyridine frameworks. Tetrazolo[1,5-*a*]quinoline is the core of various compounds with anticancer [8], antifungal [9], antibacterial [10], and anti-inflammatory [10] properties. The imidazo[1,2-*a*] pyridine ring system has been shown to possess a broad range of useful pharmacological activities, including antibacterial [11], antimicrobial [12], anti-inflammatory [13], antitubercular [14], anxiolytic (Alpidem) [15], hypnotic (Zolpidem) [16], and antiulcer (Zolmidine) [17] activity. Recently, some imidazo[1,2-*a*]pyridine have been reported as

candidates for fluorescent probes, which can be used for fluorescence imaging in clinical diagnostics and biomedical research [18,19]. There are various methods to synthetize imidazo[1,2-*a*]pyridines [20], but the Groebke–Blackburn–Bienaymé reaction (GBBR) is the current and most efficient method to synthesize imidazo[1,2-*a*]pyridines [21].

Solvent-free heterocyclic synthesis (SFHS) is an important synthetic procedure from the perspective of green and sustainable chemistry. This approach can help to reduce the amounts of undesired hazardous chemicals (including solvents) used, increase selectivity towards the desired product(s), and also enhance the rate of many organic reactions. In addition, solvent-free methods are of great interest because the procedures can be cleaner, safer and easier to perform than traditional protocols [22].

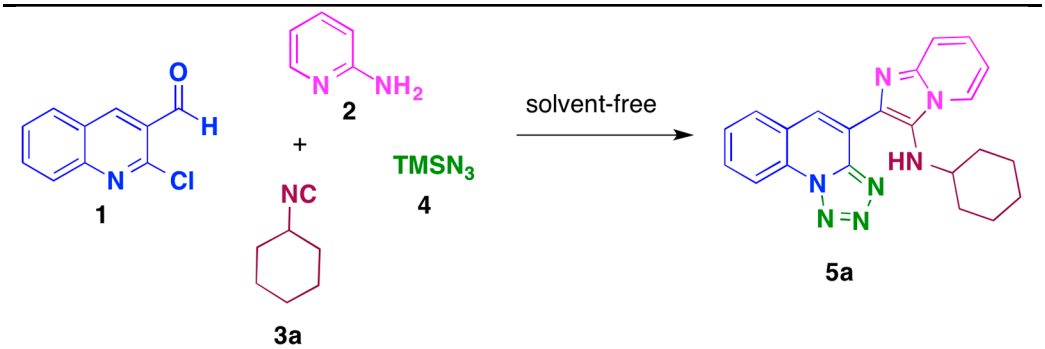
Recently we reported a green, endogenous water-triggered, solvent- and catalyst-free ultrasound-assisted one-pot Groebke–Blackburn–Bienaymé reaction/SNAr/ring-chain azido tautomerization strategy to synthesize pairs of fused bis-heterocycles linked to one another. More specifically, there were imidazo or benzo[d]imidazo[2,1-*b*]thiazoles connected to 1,5-disubstituted tetrazoles (1,5-DsT) fused to quinoline [23]. In continuation of our research interests in the development of environmentally friendly methodologies, we wish to report herein a methodology for the solvent-free for the synthesis of imidazo[1,2-*a*]pyridines via a one-pot Groebke–Blackburn–Bienaymé reaction/ SNAr /ring-chain azido tautomerization process.

2. Results and Discussion

In this work, we describe the synthesis of five compounds containing a 3-imidazo[1,2-*a*]pyridine linked to a tetrazolo[1,5-*a*] quinolone via a one-pot process: GBBR/SNAr/ring-chain azido tautomerization under eco-friendly conditions in good to excellent yields (79–96%).

In 2016 we reported the synthesis of the same compounds using MeOH as solvent [24]. In concordance with our main line research we decided to make a greener process, and for this reason we elected to explore solvent-free conditions and selected N-cyclohexyl-2-(tetrazolo[1,5-*a*]quinolin-4-yl)imidazo[1,2-*a*]pyridin-3-amine (5a) as our model target to optimize the one-pot process GBBR/SNAr/ring-chain azido tautomerization. Thus 2-chloroquinoline-3-carbaldehyde (1) was combinated sequentially with one equivalent of 2-aminopyridine (2), cyclohexyl isocyanide (3a), and azidotrimethylsilane (4) under solvent-free conditions. Using mechanochemical grinding at room temperature, only traces of the desired bis-heterocycle 5a was isolated in traces because the starting materials were not consumed (Entry 1, Table 1). We then decided to conduct the process using ultrasound (US) irradiation at 60 °C, which gave the bis-heterocycle 5a in 71% after 1.5 h (Entry 2, Table 1). Performing the reaction at 70 °C (but without US), the yield was increased to 96% in 3h (Entry 3, Table 1).

Table 1. Screening Conditions.

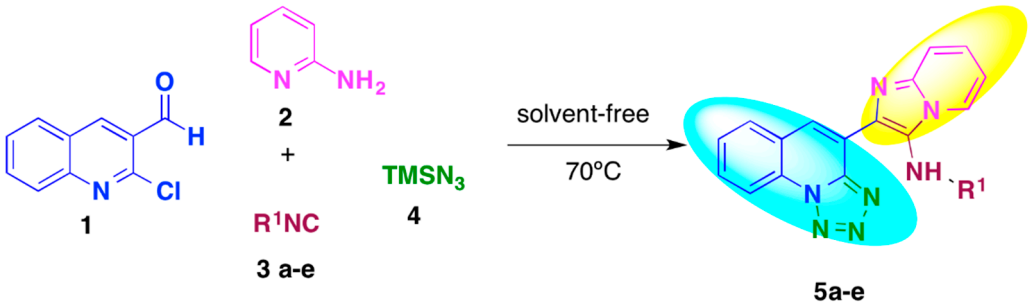


Entry	*t* (h)	T °C	Yield (%)
1	0.25	r.t [a]	trace
2	1.5	60 [b]	71%
3	**3**	**70**	**96%**

[a] grinding [b] US (42 kHz).

By using the optimized conditions (solvent-free, heating at 70 °C for 3 h) we synthesized a series of 3-imidazo[1,2-*a*]pyridine-tetrazolo[1,5-*a*]quinolines(5a–e, Table 2). As seen in Table 2, good to excellent yields were obtained (79–96%). All the products obtained were characterized by ^{1}H NMR and ^{13}C NMR (Figure 1, Figure 2).

Table 2. Substrate Scope.



Compound	R ^{1}	Yield (%)
5a	*c*-Hex	96
5b	*t*-Bu	90
5c	4-OMePh	94
5d	Bn	83
5e	2,6-diMePh	79

3. Experimental Section

General Information: ^{1}H and ^{13}C NMR spectra were acquired on Bruker Advance III (Fällande, Uster, Switzerland) spectrometers (400 or 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 was tetramethylsilane (TMS) 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). IR spectra were acquired on PerkinElmer 100 spectrometer with Attenuated Total Reflectance (ATR) accessory using neat compounds. The wavelengths are reported in reciprocal centimeters (ν_{max}/cm^{-1}). HRMS spectra were acquired via electrospray ionization (ESI) in positive ion mode and recorded via the time-of-flight (TOF) method. Heated reactions (without ultrasound) were performed using a sand bath. Ultrasound-irradiated reactions were performed on Branson model 1510 ultrasonic cleaner working at 42 kHz ± 6% frequencies. The reaction progress was monitored by 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 as mobile phase. Melting points were determined on Cole-Parmer Electrothermal Programmable Digital Melting point apparatus.

General method: 2-Chloroquinoline-3-carboxaldehyde 1 (0.52 mmol, 1.0 equiv), 2-aminopyridine **2** (0.52 mmol, 1.0 equiv.), the corresponding isocyanide 3 (0.52 mmol, 1.0 equiv.) and azidotrimethylsilane (0.52 mmol, 1.0 equiv) were placed into a 10 mL vial equipped with a magnetic stirrer bar for the appropriate reaction time at 70 °C in a sand bath. The crude product was purified by flash chromatography using hexane-EtOAc (1/1 v/v) as eluent to afford compounds (5a–e).

4. Spectral Data

N-Cyclohexyl-2-(tetrazolo[1,5-a]quinolin-4-yl)imidazo[1,2-*a*]pyridin-3-amine (5a). Yellow solid (134 mg, 96%); mp = 204–206 °C; R*f* = 0.19 (hexanes-EtOAc = 7/3; *v*/*v*); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.19 (d, *J* = 6.9 Hz, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.80–7.66 (m, 1H), 7.62–7.57 (m, 2H), 7.22–7.18 (m, 1H), 6.88–6.85 (m, 1H), 3.36 (d, J = 6.5 Hz, 1H), 2.69 (s, 1H), 1.72–1.66 (m, 2H), 1.60–1.53 (m, 2H), 1.47–1.42 (m, 1H), 1.08–0.99 (m, 4H), 0.95–0.83 (m, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 149.0, 147.2, 141.9, 140.8, 133.6, 130.6, 128.6, 128.4, 127.9, 127.3, 127.2, 126.9, 124.2, 123.0, 117.6,

111.9, 56.6, 33.9, 25.6, 24.5; FT-IR (ATR, ν_{max}/cm^{-1}) 3274 (N − H), 1632 (C=N); HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{22}H_{21}N_7$ 384.1931, found 384.1929.

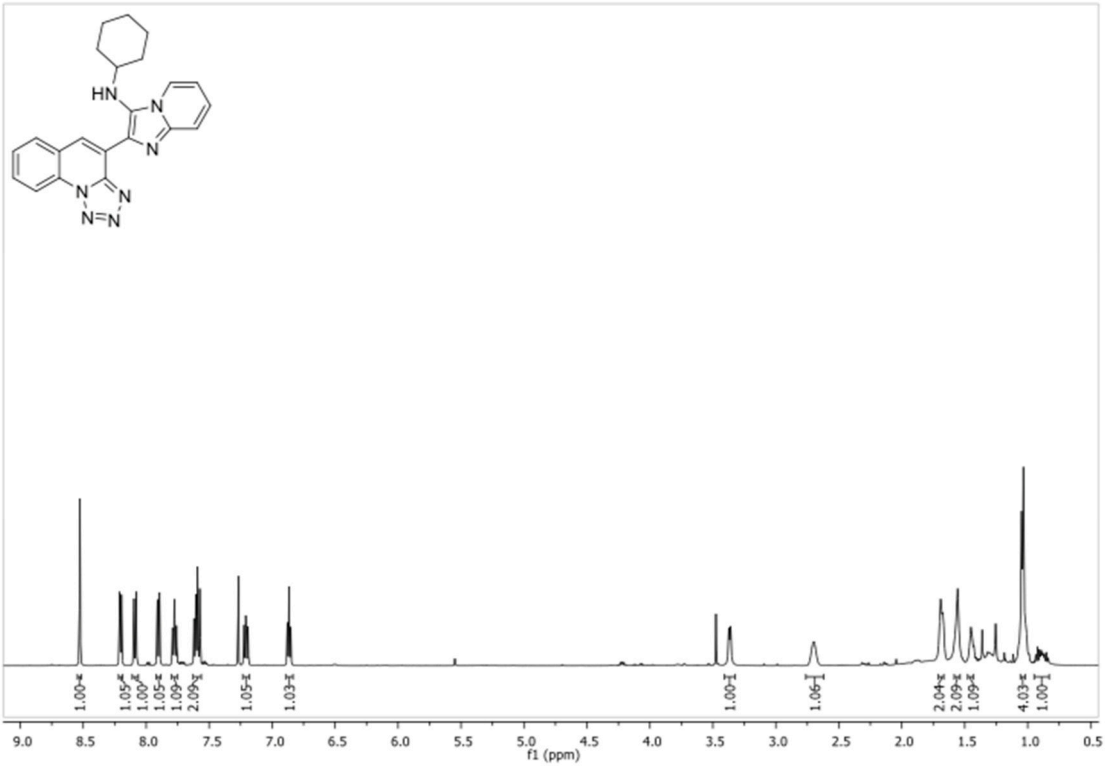


Figure 1. ^{1}H NMR spectrum of compound **5a**.

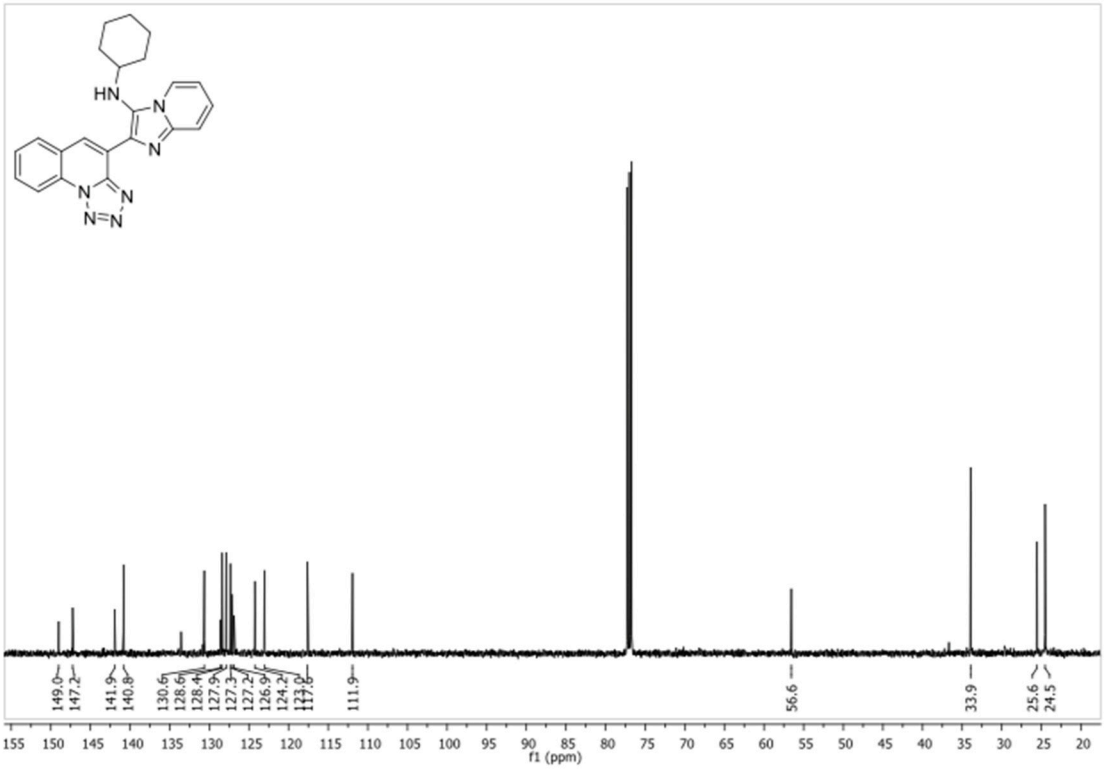


Figure 2. ^{13}C NMR spectrum of compound **5a**.

5. Conclusions

In conclusions, the methodology herein described represents sustainable process for the synthesis of fused *bis*-heterocycles. The yields obtained for the 3-imidazo[1,2-*a*] pyridine-tetrazolo[1,5-*a*]quinolines under solvent-free conditions are improved when compared to our previously reported method from 2016 [20].

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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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