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Microwave-Assisted Synthesis of Bis-Heterocycles Containing the Imidazo[1,2-a]Pyridine by Groebke-Blackburn-Bienaymé Reaction †

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Abstract: A series of six fused *bis*-heterocycles having imidazo[1,2-a]pyridine bound with quinoline were synthesized by microwave-assisted Groebke-Blackburn-Bienaymé reaction (GBBR) under green catalysis. The GBB products are privileged scaffolds and their synthesis is of great interest in synthetic and medicinal chemistry.

Keywords: imidazo[1,2-a]pyridine; Groebke-Blackburn-Bienaymé reaction (GBBR); 2-Chloro-3-formyl-quinoline

1. Introduction

Nitrogen is considered a key element with a vital role in bioactive compounds providing a noticeable range of activities [1]. Heterocycles containing nitrogen atoms possess several pharmaceutical properties. For instance, the quinoline core has received much attention in medicinal chemistry resulting from their activities e.g., anti-tuberculosis [2], antibacterial [3], antifungal [4], antimalarial [5], anti-HIV [6], and anti-inflammatory [7] activities. As a result of their pharmacological and biological properties of bioactive compounds incorporated quinoline ring system, the 2-chloroquinoline-3-carbaldehyde has been applied as an aldehyde moiety in multicomponent reactions as Ugi-4CR [8–10], Ugi-azide [11], and Groebke-Blackburn-Bienaymé (GBBR) [11–13].

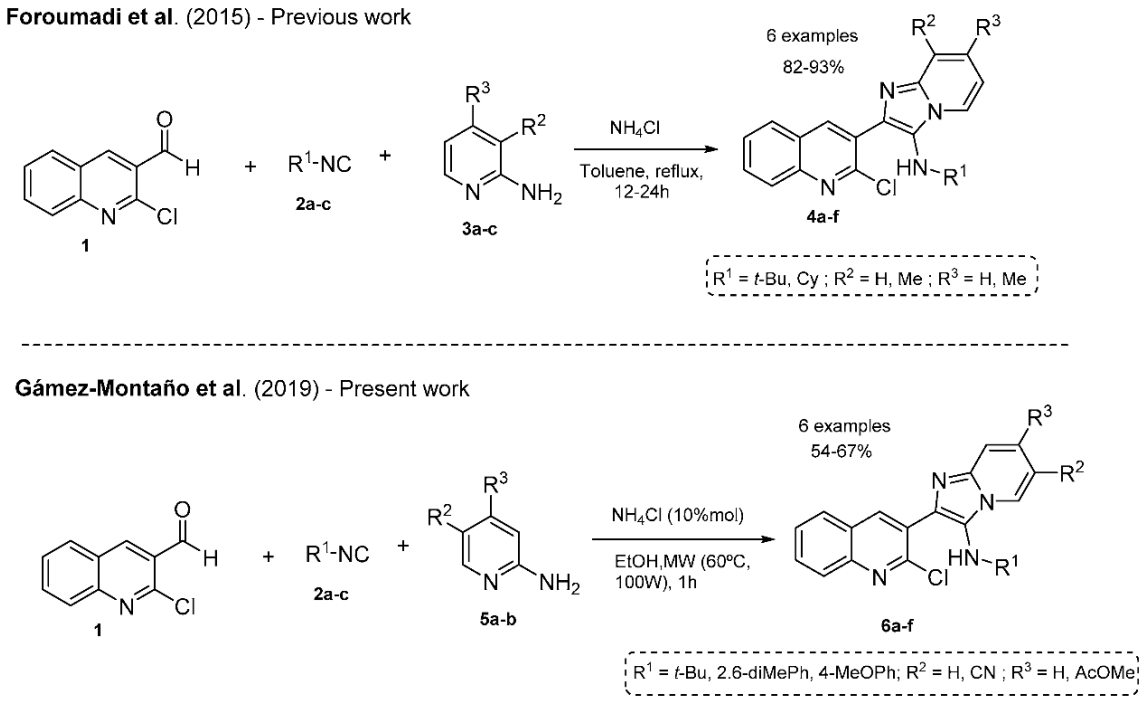
Among them, *bis*-heterocycles have attracted much attention due to their numerous applications in many fields, such as organic synthesis, optics, materials, and polymer sciences, agrochemistry, and mainly in medicinal chemistry [14]. The research towards finding novel applications is supported on the basic principle, a union makes force [15]. Two heterocycles can be suitably placed to construct complex products having potential new or enhanced known properties.

Imidazo[1,2-a]pyridine core is present in a lot of drugs, useful in various treatments of brain diseases and CNS-related disorders. For example, zolpidem is the most prescribed drug for insomnia [15]. The GBBR is one of the highest important classes of isocyanide-based multicomponent reactions (I-MCRs) and the most efficient methods for the synthesis of fused imidazole analogs. GBBR usually requires a solvent and catalyst. In this context, GBBR methodologies using various green catalysts, such as Lewis acids, Bronsted acids, solid-supported organic bases and inorganic salts have been reported [16]. It is highlighted that the reported methodologies have some drawbacks such as high temperature, low yields, expensive catalyst and non-greener solvents.

Microwave irradiation (MW) plays a central role in synthetic organic chemistry mainly to decrease reaction times. Herein the goal is to develop an efficient protocol for the synthesis of new

heterocyclic scaffolds containing imidazole and quinoline cores under ecofriendly conditions. MW offers several benefits over conventional methods including short reaction time and yield enhancements.

Foroumadi and co-workers reported in 2015 the synthesis of imidazo[1,2-a]pyridine in moderate yields (82–93%) via a GBBR using NH_4Cl in stoichiometric quantities and hard conditions (Scheme 1) [17]. Our methodology has some advantages, for example, the synthetic process worked well under green catalyst. Besides short reaction times and MW energy source.



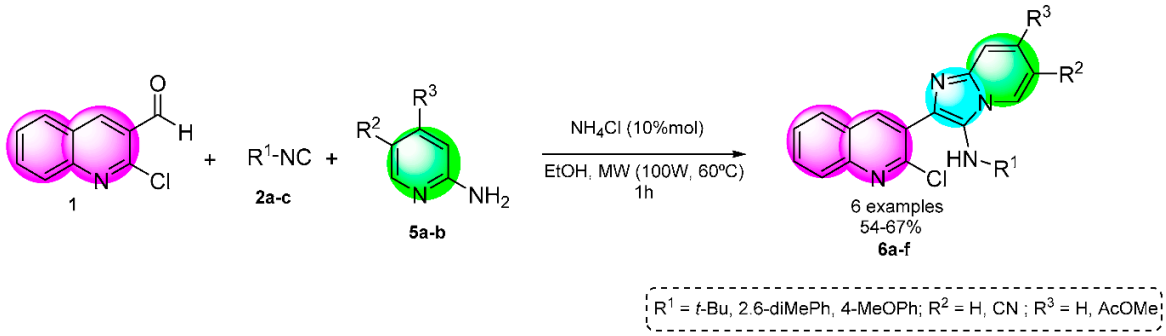
Scheme 1. Previous works related to the synthesis of imidazo[1,2-a]pyridines analogs.

The principal objective in our research group during the last years has been to develop versatile and efficient I-MCR-based methodologies to synthesize a series of novel unsymmetrical *bis*-heterocycles containing privileged nucleus in medicinal chemistry [10–12,18].

As a part of our research program in the development of green or eco-friendly IMCR strategies herein, we describe the one-pot synthesis of new unsymmetrical *bis*-heterocycles via the GBBR under mild conditions. The target molecules containing two different complex heterocycles such as imidazo[1,2-a]pyridine bound with quinoline moiety.

2. Results and Discussion

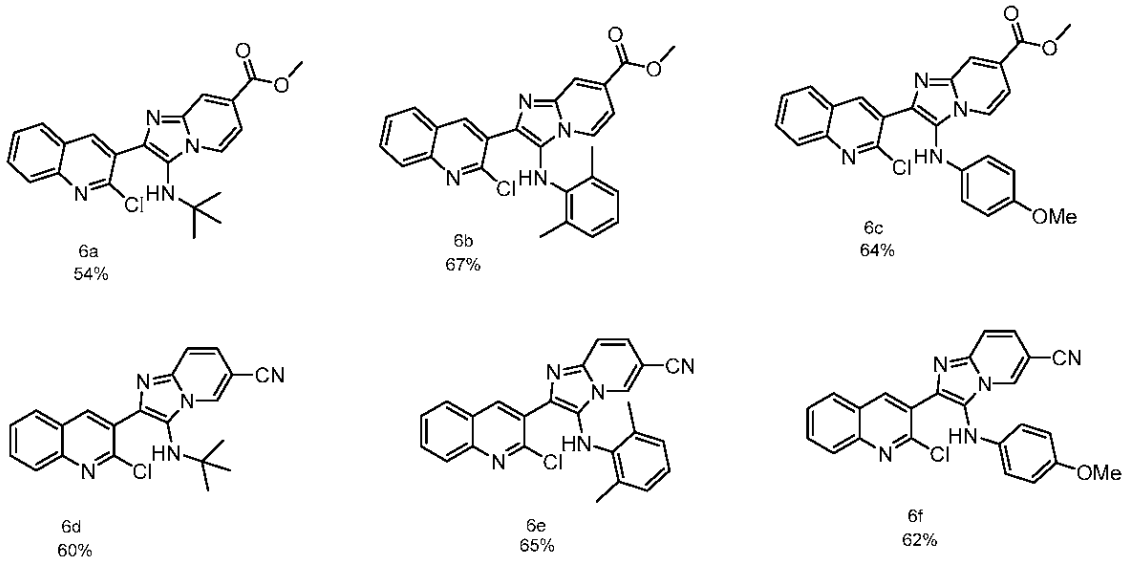
Following our interests in the efficient synthesis of *bis*-heterocycles containing frameworks of interest in medicinal chemistry, our work consists of the synthesis of six new analogs of 2-chloroquinoline imidazo[1,2-a]pyridine which were synthesized in moderate to good yields (54–67%) via GBBR under mild green conditions (Scheme 2).



Scheme 2. Strategy for the synthesis of analogs of 2-chloroquinoline imidazo[1,2-a]pyridine.

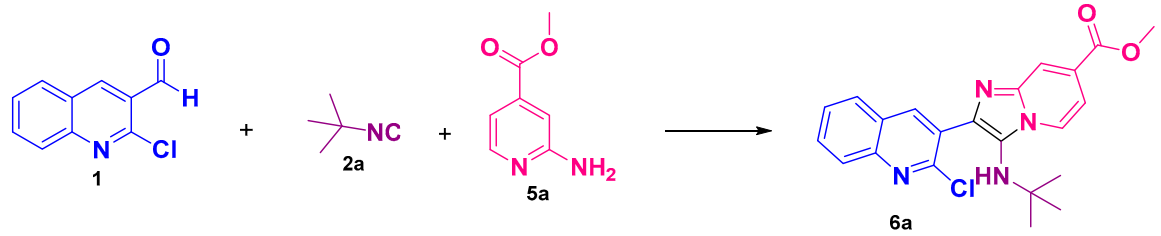
In order to find the optimum conditions for the GBBR involved in the synthetic strategy toward unsymmetrical bound-type bis-heterocycles **6a**, 2-chloro-3-formylquinoline (**1**) was reacted sequentially with one equivalent of methyl-2-aminopyridine-4-carboxylate (**5a**), tertbutyl isocyanide (**2a**) which were selected as the model reaction (Table 1). According to our main line of research, green solvents, moderate temperatures, and green catalysts were studied to optimize the reaction conditions. Firstly, we performed the GBBR at room temperature in water (Table 1, entry 1) but the starting materials remained completely unconsumed. When the reaction was carried out in ethanol without catalyst at r.t (Table 1, entry 3), the product **6a** was obtained in 13% yield. Due to the low yields obtained, we decided to use a catalyst and we decided to try a reaction using NH_4Cl in 10% mol which is a green, inexpensive and easily available catalyst. In the literature, there are many reports of the use of NH_4Cl in GBBR in stoichiometric amounts and longer reaction times were required. In 2018, we reported for the first time of NH_4Cl in GBBR in a catalytic amount [18]. The TLC of the reaction with NH_4Cl revelated that the product yield was increased. Under MW at 60 °C in EtOH and NH_4Cl, the yield was better than USI 54 and 42% of **6a** respectively. The course of the reaction was monitored by TLC and characterized by ^1H y ^{13}C NMR.

Using optimized conditions, a series of six new 2-chloroquinoline imidazo[1,2-a]pyridine were synthesized (shown in Scheme 3). The versatility of the developed methodology was examined using different isocyanides such as aryl and alkyl (**2a–c**) and two different aminoazines with withdrawing groups. The respective products **6a–f** were obtained in moderate to good yields (54–67%).



Scheme 3. Substrate scope.

Table 1. Reaction optimizing conditions **6a**.



Entry	Solvent	Catalyst	T (°C)	Time(h)	Yield (%)
1	H_2O	----------	r.t	8	n.r
2	H_2O	----------	r.t USI	3	n.r
3	EtOH	----------	r.t	8	13
4	EtOH	----------	r.t USI	4	18
5	EtOH		60 USI	4	26
6	EtOH	NH_4Cl	USI	4	35
7	EtOH	NH_4Cl	60 USI	2	42
8	**EtOH**	**NH_4Cl**	**60 MW**	**1**	**54**

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 is 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 (Mestrelab Research, S.L., Santiago de Compostela, Spain). 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 (PerkinElmer Inc., Waltham, MA, USA).

General method: 2-Chloroquinoline-3-carboxaldehyde **1** (0.365 mmol, 1.0 equiv), 2-aminopyridine derivatives with withdrawing groups **5a–b** (0.365 mmol, 1 equiv), isocyanide **2a–c** (0.365 mmol, 1 equiv) and NH_4Cl 10%mol in MeOH (1M) were placed in a 10 mL vial equipped with a magnetic stirring bar. The reaction mixture was MW-heated at 60 °C (100 W) for 1h. Then, the solvent was removed to dryness and the crude was purified by silica-gel column chromatography using mixtures of hexanes with ethyl acetate (1/1; *v*/*v*) to afford products **6a–f**.

Spectral data: *2-(2-Chloroquinolin-3-yl)-3-((4-methoxyphenyl)amino)imidazo[1,2-a]pyridine-6-carbonitrile* (**6f**): yellow solid (97.0 mg, 62%); Rf = 0.32 (Hexanes-EtOAc = 1/1 *v*/*v*); ^1H NMR (500 MHz, CDCl3) δ 8.36 (s, 1 H), 8.25 (s, 1 H), 8.0–7.98 (m, 1 H), 7.78–7.68 (m, 1 H), 7.57–7.54 (m, 1 H), 7.34–7.31 (m, 1 H), 6.73–6.70 (m, 2 H), 6.45–6.43 (m, 2 H), 3.70 (s, 3 H); ^{13}C NMR (126 MHz, CDCl3) δ 154.3, 153.1, 148.6, 147.4, 141.4, 140.9, 140.2, 137.5, 136.7, 131.3, 129.5, 128.3, 127.9, 127.6, 126.8, 126.2, 124.7, 123.2, 119.0, 116.5, 115.4,115.3,108.0, 98.9, 56.6. (Figures 1–3).

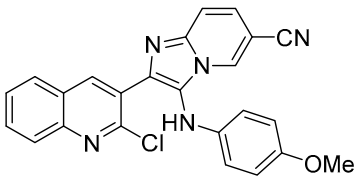


Figure 1. Compound **6f.**

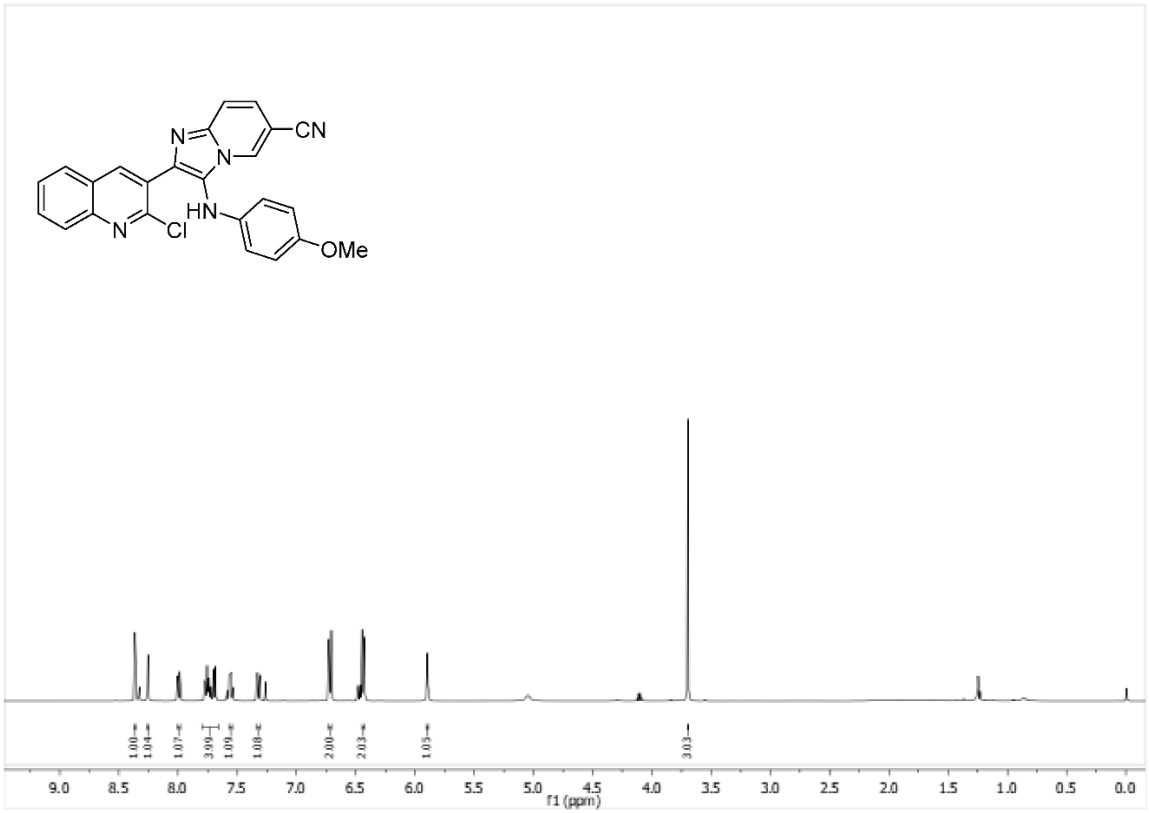


Figure 2. [1]H NMR spectrum of compound **6f**.

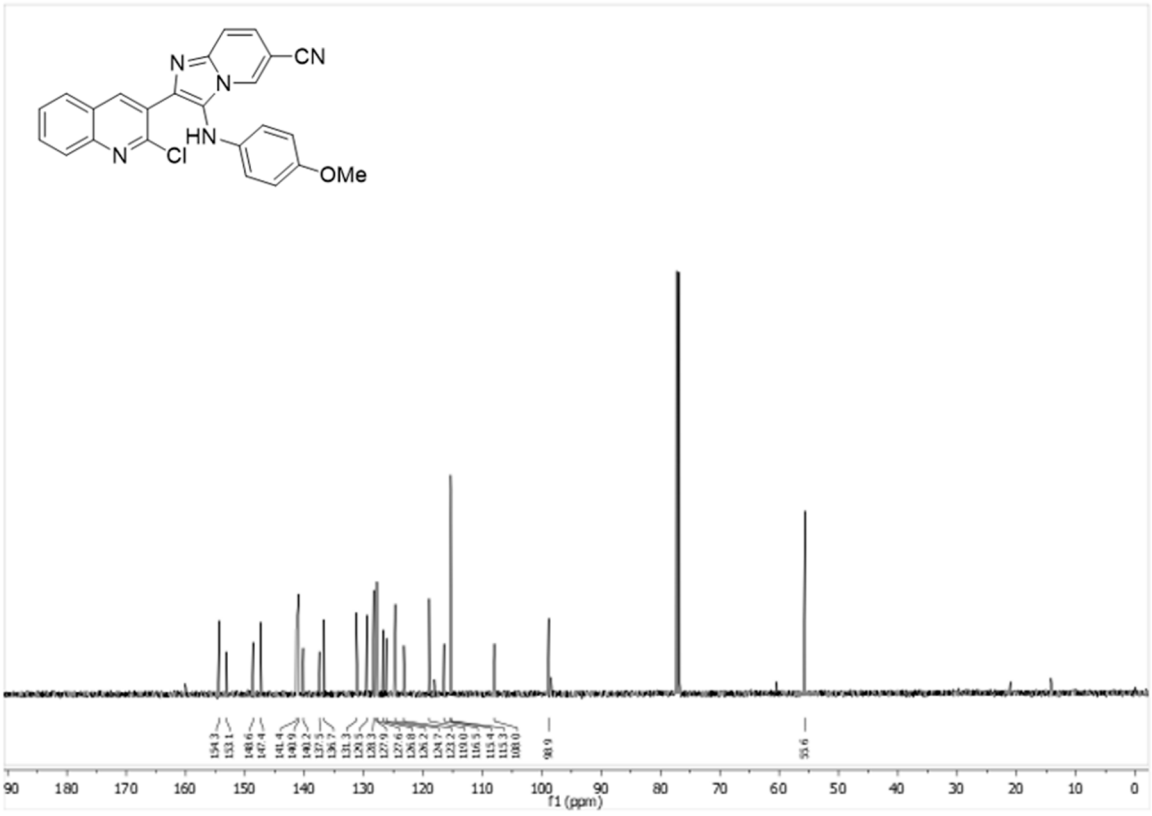


Figure 3. [13]C NMR spectrum of compound **5c**.

4. Conclusions

In conclusions, herein we described GBBR protocol under green catalyst for the synthesis of *bis*-heterocycles containing privileged nucleus in medicinal chemistry.

Additionally, this strategy has advantages in comparison with previous works due to the strategy herein described takes place under mild and green conditions.

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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