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One Pot Synthesis of Imidazo[1,2-*a*] Pyridines via Groebke-Blackburn-Bienaymé Reaction †

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Abstract

The imidazo[1,2-*a*] pyridine (IMPs) scaffold has attracted considerable attention due to photophysical properties and their applications in medicinal, chemistry, and material sciences. Isocyanide based multicomponent reactions (I-MCR), particularly Groeke-Blackburn-Bienaymé reaction (GBBR), is considered as election synthetic one-pot process for synthesis of IMP analogs. Herein we described a novel ultrasound assisted one pot green synthesis of IMPs via GBBR, using water as election solvent. The approach aligns with the principles and metrics of green chemistry, and enables the efficient synthesis of highly fluorescent molecules. These compounds show potential applications in chemical sensing, optoelectronic devices, and bioimaging.

Keywords: imidazo[1,2-*a*]pyridines; Groebke-Blackburn-Bienaymé reaction; chemosensor

1. Introduction

Imidazo[1,2-*a*]pyridines (IMPs) are recognized as valuable structural frameworks in medicinal chemistry due to their diverse biological activities such as antifungal, antiviral, anticancer, antibacterial, anti-inflammatory, anthelmintic, analgesic, antitubercular, antipyretic, and antiepileptic. Particularly IMPs scaffolds, have attracted attention due to their versatile pharmacological and photophysical properties. Fluorescent chemical sensors are highly effective for analyzing various biological, industrial, and environmental analytes. Their strong selectivity, high sensitivity, fast photoluminescence response, cost-efficiency, and ability to detect low concentrations make them particularly useful, even for bioimaging applications [1]. These qualities make them highly promising chromophores for applications in chemosensors, bioimaging, and optoelectronics, as they can absorb light at specific wavelengths and emit fluorescence (Figure 1) [2].

The synthesis of new chemosensors for detecting heavy and transition metal ions is a research field in constantly growing. This is due to the significant impact on the environment and human health, these metal ions, such as cobalt, copper or zinc are crucial for various bodily functions and industrial applications; however, abnormal levels can pose health risks. Therefore, regulating their concentrations is vital to minimize harmful effects [3].

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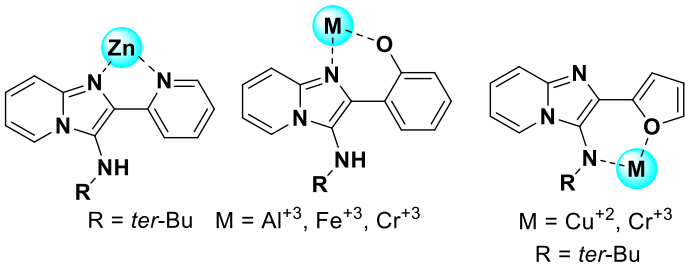
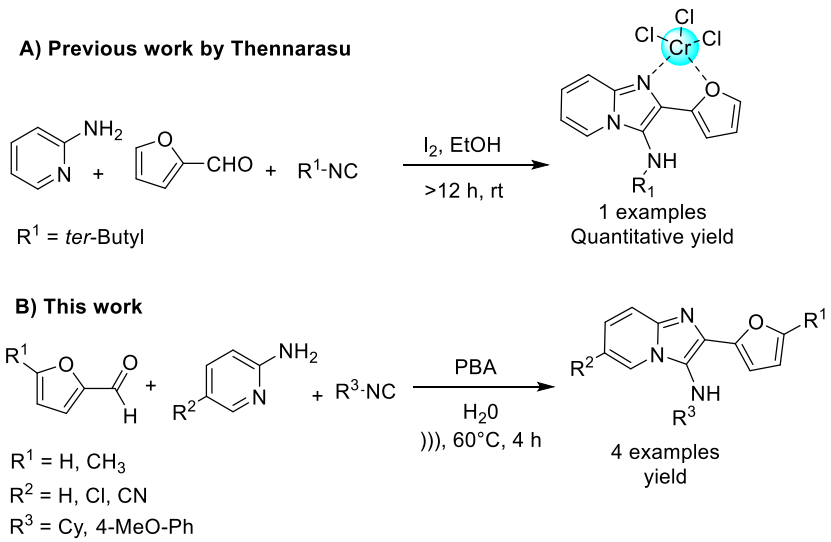


Figure 1. Chemosensors based on IMPs scaffold.

The synthesis of IMPs have been reported by several strategies, such as transition metal-catalyzed reactions, condensation processes, cyclization reactions, heteroannulation, and photocatalytic methods. However, these techniques often require harsh conditions, such as high temperatures and solvents that are not environmentally friendly, additionally lead to undesirable side products, long reaction times, high costs, and a limited scope, often resulting in low yields [4]. In this context the multicomponent reactions (MCRs) are consider the most efficient synthetic tools for the organic synthesis, due to advantages such as high overall yields and atomic economy, short reaction time, convergence and compatibility with a wide range of substrates with different structural characteristics resulting in a broad scope [5], in particular the isocyanide multicomponent reactions (IMCR) Groebke-Blackburn-Bienaymé reaction (GBBR) it's the best methodology to synthesize imidazo[1,2-*a*] pyridine-3-amines (IMPs) [6].

Our research line group is pioneer in the innovations and development of novel one-pot GBBR protocols using alternative energies sources (AES) allow the chemical activation accelerating reactions. Particularly the ultrasonic irradiation (USI) occur through the formation of bubbles, undergoes vigorous collapses by cavitation process generating energy, additionally enhancing solubility, selectivity, and reducing reaction times [7].

Following our research line focused on the design and development of novel sonochemical IMCR one-pot synthesis of fluorescent IMP analogs [8,9]. (Scheme 1) [10].



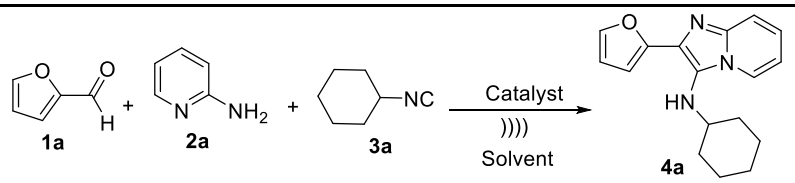
Scheme 1. Previously documented methods for IMP synthesis.

Herein we report the first ultrasound assisted one pot synthesis of potential IMPs chemosensors by GBBR.

2. Results and Discussion

Initially the synthesis of a furan-imidazo[1,2-a]pyridine-3-amine analogue **5a** was attempted by furfural **1a** (1 mmol), 2-aminopyridine **2a** (1 mmol), and cyclohexyl isonitrile **3a** (1 mmol) in the absence of catalyst and solvent under USI, after 4 h any product was observed (Table 1, Entry 1), next H_2O was employed such as green solvent, unfortunately only traces were identified (Entry 2), encouraged by this we decide to use NH_4Cl as catalyst in 5 to 10% mol, affording the desired product in 32 -50% of yield (Entries 3–4), then PBA was used such as catalyst, affording the desired product with 65% of yield (Entry 5), with the aim to increase yield the reaction was conducted at 60 °C, giving the desired product **5a** in 86% (Entry 6).

Table 1. Screening conditions for the synthesis of **4a**.



Entry [a]	Catalyst [b]	Solvent [1.0 M]	Time (h)	Yield [e]
1	---	---	4	---
2	---	H_2O	4	traces
3 [c]	NH_4Cl	H_2O	4	32
4	NH_4Cl	H_2O	4	50
5	PBA	H_2O	4	65
6 [d]	PBA	H_2O	4	86

[a] Furfural (**1a**, 1.0 equiv.), 2-aminopyridine (**2a**, 1.0 equiv.), and cyclohexyl isocyanide (**3a**, 1.0 equiv.); [b] 10 mol%; [c] 5 mol%, [d] 60 °C; [e] Isolated yields.

With the optimized conditions, we explored the scope of the methodology through variations of aminopyridine reagents. The respective imidazo[1,2-*a*]pyridine (**5a–d**, Figure 2) were synthesized under sonication in moderate to good yields (67–86%).

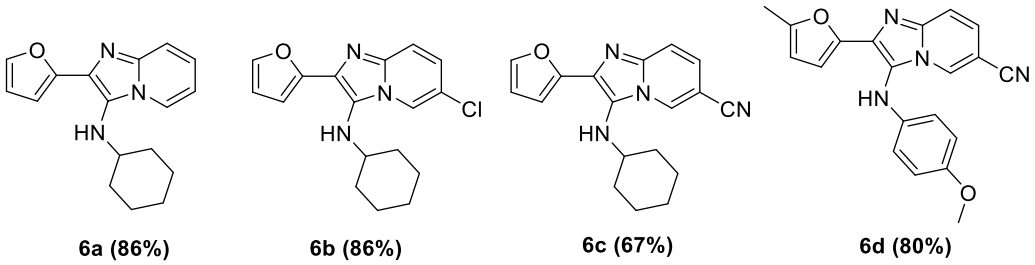


Figure 2. Substrate scope of imidazo[1,2-*a*]pyridine.

3. Experimental Section

3.1. General Information, Instrumentation, and Chemicals

The ^1H and ^{13}C NMR spectra were recorded using Bruker Avance III spectrometers operating at 500 MHz. Deuterated chloroform ($CDCl_3$) used as solvent. Chemical shifts are reported in parts per million (δ/ppm) and tetramethylsilane (TMS) at 0.0 ppm as the internal reference. Coupling constants (J) are reported in Hertz (Hz). The multiplicity are reported using the standard abbreviations: singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). Spectral data were processed using MestreNova software version 10.0.1–14719. High-resolution mass spectrometry (HRMS) were obtained using electrospray ionization (ESI) via the time-of-flight (TOF) method. Ultrasonic-assisted

reactions were carried out in 10 mL sealed vials immersed in a Branson 1510 ultrasonic bath operating at 42 kHz ± 6%. Reactions were monitored by thin-layer chromatography (TLC) and spots visualized under UV light (254 or 365 nm). Purification of the products was achieved by flash column chromatography on silica gel (230–400 mesh) using a gradient of hexanes with EtOAc (v/v) as the mobile phase. All reagents were purchased from Sigma-Aldrich and used without aditional purification. Chemical structures and nomenclature were generated by ChemBioDraw Ultra 13.0.2.3020 software package.

3.2. General Procedure (GP)

In a sealed vial (10 mL), was added aldehyde (1, 1.0 equiv.), 2-aminopyridine (**2**, 1 equiv.), and the appropriate isocyanide (**3**, 1 equiv.), and PBA (10% mol) were disolven in H_2O (1M) and the resulting mixture was sonicated (42 kHz ± 6%) at roof temperature for 4 h. The reactions were monitored by TLC, furthermore reactions were extracted with ethyl acetate and the crude reaction was purified by flash chromatography to afford the corresponding imidazo[1,2-*a*]pyridine.

3.3. Spectral Data

Characterization of the N-cyclohexyl-2-(furan-2-yl)imidazo[1,2-a]pyridin-3-amine (**5a**) was synthetized according to general procedure using 2-aminopyridine, furfural and cyclohexyl isocyanide. Was obtained as an oil in 86% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.97 (dd, *J* = 6.9, 0.8 Hz, 1H), 7.41 (dd, *J* = 6.5, 0.7 Hz, 2H), 7.02 (dd, *J* = 8.4, 7.3 Hz, 1H), 6.78 (d, *J* =3.2, 1H), 6.69 (t, *J* =6.5, 1H), 6.49–6.46 (m, 1H), 3.53 (s, 1H), 2.91–2.85 (m, 1H), 1.83–1.79 (m, 2H), 1.67–1.63 (m, 2H), 1.54–1.50 (m, 1H), 1.23–1.10 (m, 5H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 150.4, 141.8, 141.3, 128.1, 125.5, 123.8, 122.7, 117.2, 111.5, 111.4, 106.3, 57.0, 34.1, 25.7, 24.9 ppm. HRMS (ESI-TOF) m/z calcd. for $C_{17}H_{20}N_3O^+$ $[M + H]^+$ 282.1601, found 282.1616.

Characterization of the 6-Chloro-N-cyclohexyl-2-(furan-2-yl)imidazo[1,2-a]pyridin-3-amine (**5b**) was synthetized according to general procedure using 2-amino-5-chloropyridine, furfural and cyclohexyl isocyanide. Was obtained as an oil in 86% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 1.9 Hz, 1H), 7.43 (d, *J* = 1.5 Hz, 1H), 7.36 (d, *J* = 9.5 Hz, 1H), 7.00 (dd, *J* = 9.5, 2.0 Hz, 1H), 6.79 (d, *J* = 3.4 Hz, 1H), 6.46 (dd, *J* = 3.4, 1.8 Hz, 1H), 3.53 (s, 1H), 2.89 (t, *J* = 9.8 Hz, 1H), 1.81 (d, *J* = 10.7 Hz, 2H), 1.75–1.62 (m, 2H), 1.61–1.45 (m, 1H), 1.17 -1.12 (m, 5H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.1, 141.9, 140.3, 129.5, 126.0, 125.4, 120.8, 120.2, 117.8, 111.7, 107.0, 57.2, 34.2, 25.8, 25.1 ppm. HRMS (ESI-TOF) m/z calcd. for $C_{17}H_{19}ClN_3O$ $[M + H]^+$ 316.1211, found 316.1214.

Characterization of the 3-(Cyclohexylamino)-2-(furan-2-yl)imidazo[1,2-a]pyridine-6-carbonitrile (**5c**) was synthetized according to general procedure using 2-amino-5-cyanopyridine, furfural and cyclohexyl isocyanide. Was obtained as an oil in 67% yield. ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 8.39 (s, 1H), 7.48–7.44 (m, 2H), 7.12 (d, *J* = 9.2 Hz, 1H), 6.85 (s, 1H), 6.49–6.48 (m, 1H), 3.58 (s, 1H), 2.90 (t, *J* = 10.3 Hz, 2H), 1.81 (d, *J* = 11.5 Hz, 3H), 1.68 (d, *J* = 9.0 Hz, 3H), 1.57–1.56 (m, 2H), 1.26–1.11 (m, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 149.4, 142.5, 140.9, 130.5, 129.2, 126.3, 123.7, 118.2, 117.2, 111.9, 108.1, 97.8, 57.5, 34.2, 25.7, 25.1 ppm. HRMS (ESI-TOF) m/z calcd. for $C_{18}H_{19}N_4O^+$ $[M + H]^+$ 307.1553, found 307.1509.

Characterization of the 3-((4-Methoxyphenyl)amino)-2-(5-methylfuran-2-yl)imidazo[1,2-a] pyridine-6-carbonitrile (5d) was synthetized according to general procedure using 2-amino-5-cyanopyridine, 5-methylfurfural and 4-methoxyphenyl isocyanide. Was obtained as an oil in 80% yield. ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 8.17 (s, 1H), 7.58 (d, *J* = 9.3 Hz, 1H), 7.21 (dd, *J* = 9.3, 1.4 Hz, 1H), 6.72 (d, *J* = 8.8 Hz, 2H), 6.58 (d, *J* = 3.2 Hz, 1H), 6.46 (d, *J* = 8.9 Hz, 2H), 5.98 (d, *J* = 3.0 Hz, 3H), 5.50 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.5, 153.6, 146.0, 141.9, 137.3, 133.6, 128.8, 124.7, 119.7, 118.4, 116.8, 115.5, 115.5, 110.6, 108.1, 98.41, 55.8, 13.9

ppm. HRMS (ESI-TOF) *m*/*z* calcd. for $C_{20}H_{17}N_4O_2^+$ $[M + H]^+$ Calcd for 345.1346, found 345.1362.

4. Conclusions

The main contribution of this word falls in the multicomponent one-pot synthesis via GBBR towards IMPs incorporating the furan moiety as potential chemosensors. The one-pot GBB synthesis used water as green solvent, aligning with the principles of green chemistry. The scope of the develop strategy will be reported at this time

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