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Proceeding Paper

Sonochemical Synthesis of Imidazo[1,2 α]pyridines via Groebke–Blackburn–Bienaymé Reaction Catalyzed by TSOH †

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Abstract

The synthesis of Imidazo[1, 2-α]pyridines (IMPs) analogs is a research field in constantly growing due potential applications of Groebke-Blackburn-Bienaymé (GBB) products in several fields, focus in the development of novel greener strategies. To date the ultrasound assisted synthesis of IMPs analogs via Groebke-Blackburn-Bienaymé reaction (GBBR) under green inexpensive catalysts such *p*-toluenesulfonic acid (TsOH) is practically unreported. In the present work, we describe the TsOH catalyzed GBB reaction assisted by ultrasound irradiation (USI) to access IMP analogs in excellent overall yields 77–91%.

Keywords: multicomponent reactions; GBB; Imidazo[1, 2-*a*]pyridine; USI

1. Introduction

Imidazo[1, 2-α]pyridines (IMPs) are considered privileged scaffolds in medicinal chemistry due the broad spectrum of pharmaceutical and biological applications (Figure 1). Several commercial drugs such as zolpidem, miroprofen, saripidem, zolidimide, olprinone and minodronic acid, incorporate the imidazo[1,2α]pyridine core in their structure (Figure 1) [1].

Isocyanide-based multicomponent reactions (IMCRs) have attracted significant interest in both academic and industry fields due to their efficiency, reducing the number of steps, minimizing waste during the purification of intermediates [2–4]. In addition, ultrasound irradiation (USI) in chemistry can alter reactivity, improve yields and selectivity, reduce reaction times, energy consumption and waste production, etc. [5].

The Groebke-Blackburn-Bienaymé reaction (GBBR) is the method of choice for the synthesis of IMPs [6,7]. In concordance with our research line focus in the design and development of novel GBBR protocols [8–12], herein is described the ultrasound assisted GBBR to the green synthesis of IMPs analogs under catalyst conditions. In 2024, Gámez-Montaño et al. (Scheme 1). developed a consecutive one-pot process by the GBBR followed by copper-catalyzed alkyne-azide Cycloaddition (CuAAC) assisted by alternative sustainable energies (ASE) such as ultrasonic or mechanical activation [11]. In 2025, we reported the sonochemical multicomponent synthesis of 2-(2′-hydroxyphenyl)imidazo[1,2-a]pyridine analogs (Scheme 1), that exhibited an intramolecular hydrogen-

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bonded eight-membered ring capable of excited-state intramolecular proton transfer (ESIPT) [12].

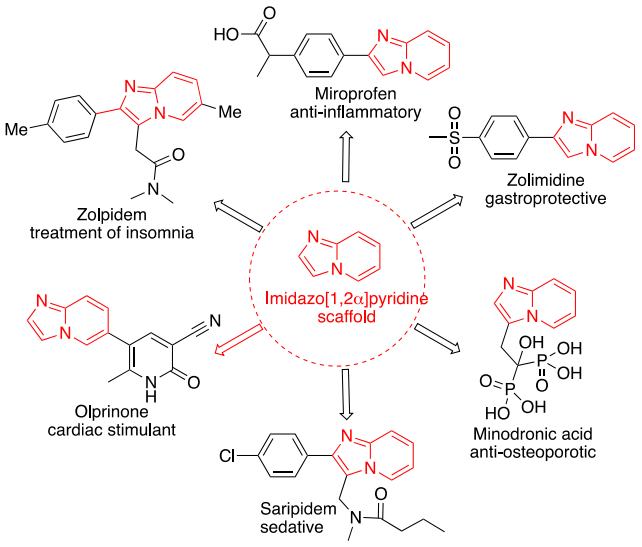
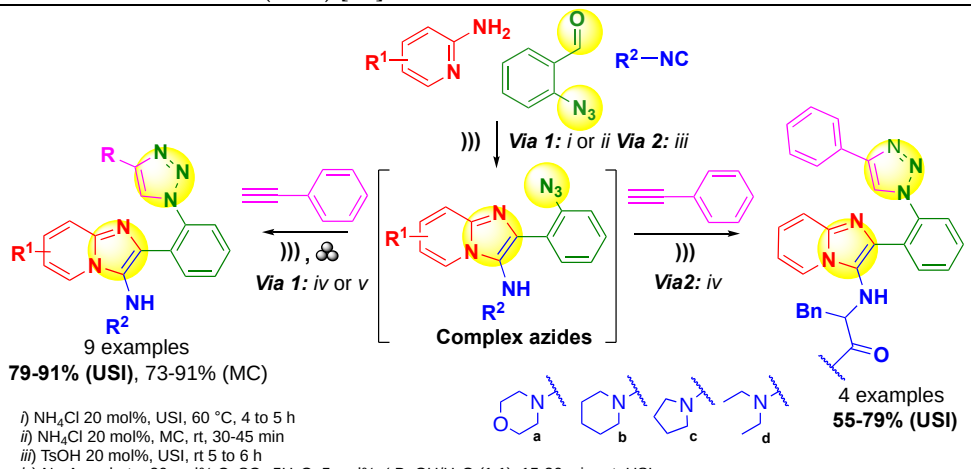


Figure 1. Commercialized drugs containing the imidazo[1,2-*a*]pyridine scaffold.

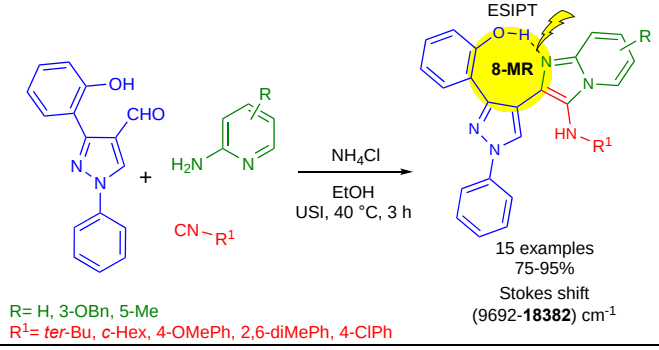
Our research group is pioneering in the innovation and development of novel one-pot GBBR protocols using alternative energy sources. To date the GBB synthesis of IMPs using inexpensive catalysts such as *p*-toluenesulfonic acid (TsOH) assisted by USI is practically unreported. In the present work, we describe the ultrasound assisted synthesis of IMP analogs catalyzed by TsOH.

PREVIOUS WORK

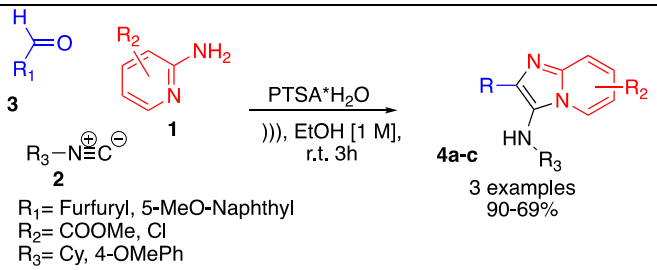
Gámez-Montaño R. et al. (2024) [11]



Gámez-Montaño R. et al. (2025) [12]



This work

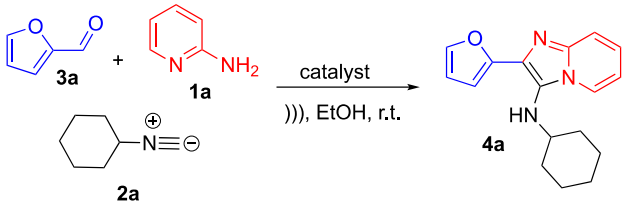


Scheme 1. Previous reports of synthesis of imidazo[1,2-*α*]pyridines.

2. Results and Discussion

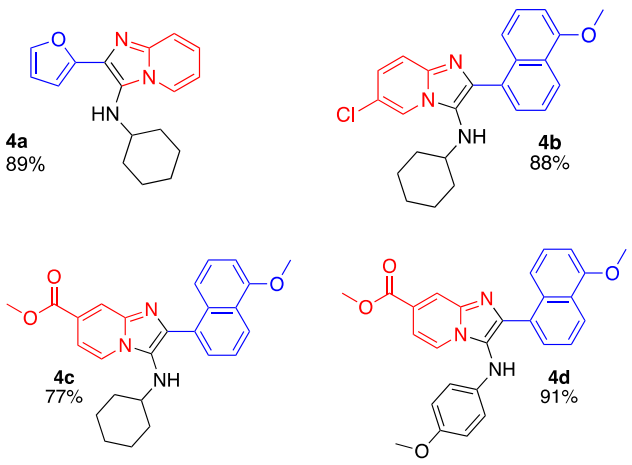
Initially we started the synthesis of N-cyclohexyl-2-(furan-2-yl)imidazo[1,2-*α*]pyridin-3-amine **4a** using furfural **3a** (1 mmol), 2-aminopyridine **1a** (1 mmol) and cyclohexyl isocyanide **2a** (1 mmol) in EtOH; green catalyst such as *p*-toluenesulfonic acid monohydrate (PTSA*H_2O) and ammonium chloride (NH_4Cl) were tested under USI conditions at room temperature (Table 1). We observed better yields using PTSA*H_2O, and the better yields were using 10% of catalyst PTSA*H_2O. A test without catalyst were carried out, no observing product formation.

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



Entry	Catalyst	Temperature	Time (h)	Yield (%)
1	PTSA*H_2O (5%)	t.a	3	80
2	PTSA*H_2O (10%)	t.a	3	89
3	PTSA*H_2O (20%)	t.a	3	75
4	NH_4Cl (5%)	t.a	3	64
5	NH_4Cl (10%)	t.a	3	88
6	NH_4Cl (20%)	t.a	2	77
7	----	t.a	3	------

After finding optimal conditions, a serie of IMPs **4a–d** were successfully synthesized in good to excellent yields (77–91%) (Scheme 2).



Scheme 2. Substrate Scope.

3. Experimental Section

3.1. General Information, Instrumentation and Chemicals

General Information: Commercially available starting materials were purchased from Sigma–Aldrich and used without further purification. Solvents were distilled and dried following standard procedures. IR spectra were recorded on a Perkin Elmer 100 FT-IR spectrometer (ν in cm^{-1}). ^{1}H and ^{13}C NMR spectra were acquired on Bruker spectrometers operating at 500 MHz. $CDCl_3$ was used as the solvent, and chemical shifts are reported in ppm. Coupling constants are reported in Hz. For ^{1}H NMR spectra, TMS at 0.0 ppm was used as the internal reference, and for ^{13}C NMR spectra, the central peak of $CDCl_3$ at 77.00 ppm served as the reference. Ultrasound-irradiated reactions were performed in sealed 10 mL tubes placed in the water bath of a Branson 1510 ultrasonic cleaner operating at 42 kHz ± 6%. Reaction progress was monitored by TLC, and spots were visualized under UV light at 254 or 365 nm.

3.2. General Procedure (GP)

In a sealed tube, to a solution of aldehyde (1.0 equiv.) in ethanol [1.0 M], aminopyridine (1.0 equiv.), isocyanide (1.0 equiv.), and PSTA*H_2O (10% mol) were sequentially added and the reaction mixture was sonicated at room temperature under 3 h. the solvent was dried and flash column chromatography was performed using silica gel (230–400 mesh) and mixtures of hexane and ethyl acetate were used as mobile phase.

3.3. Spectral Data

3.3.1. *N*-cyclohexyl-2-(furan-2-yl)imidazo[1,2-*α*]pyridin-3-amine (**4a**)

Compound **4a** (89% yield) was synthetized according to GP, using 2-aminopyridine, furfural and cyclohexyl isocyanide as compounds in GBBR., ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.46 (t, *J* = 4.3 Hz, 2H), 7.12 (d, *J* = 9.2 Hz, 1H), 6.84 (d, *J* = 3.0 Hz, 1H), 6.48 (d, *J* = 3.2 Hz, 1H), 3.58 (s, 1H), 2.88 (q, *J* = 7.4, 4.5 Hz, 1H), 1.81 (d, *J* = 11.5 Hz, 2H), 1.69 (d, *J* = 10.8 Hz, 2H), 1.58–1.45 (m, 1H), 1.20 (dq, *J* = 33.2, 10.9, 10.4 Hz, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.28, 142.29, 140.79, 130.38, 129.03, 126.15, 123.51, 118.01, 117.05, 111.73, 107.98, 97.69, 57.31, 34.08, 25.58, 24.90 ppm. HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $[C_{17}H_{19}N_3O + H^+]$ 282.1601, found 282.1616.

3.3.2. 6-Chloro-N-cyclohexyl-2-(5-methoxynaphthalen-1-yl)imidazo[1,2-*α*] pyridin-3-amine (**4b**)

Compound **4b** was synthetized according to GP, using 2-amino-5-chloropyridine, 5-methoxy-1-naphthaldehyde and cyclohexyl isocyanide. **4b** was obtained as an oil in 88% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28–8.26 (m, ^{1}H), 8.08–8.09 (m, 1H), 7.78–7.76 (m, 1H), 7.46–7.40 (m, 4H), 7.04 -7.02 (m, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 3.98 (s, 3H), 3.00 (d, *J* = 7.1 Hz, 1H), 2.59–2.51 (m, 1H), 1.53–1.50 (m, 2H), 1.41–1.30 (m, 3H), 0.91 (t, *J* = 10.8 Hz, 2H), 0.78 (q, *J* = 11.9 Hz, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.8, 139.9, 137.8, 133.1, 128.2, 127.2, 127.1, 125.9, 125.4, 125.30, 124.6, 124.0, 122.4, 120.7, 120.1, 118.0, 103.6, 56.4, 55.7, 33.9, 25.6, 24.6 ppm. HRMS (ESI-TOF) m/z $[M + H^+]+$ Calcd for $[C_{24}H_{24}ClN_3O + H^+]^+$ 406.1681, found 406.1696.

3.3.3. Methyl 3-(cyclohexylamino)-2-(5-methoxynaphthalen-1-yl)imidazo[1,2-*α*]pyridine-7-carboxylate (**4c**)

Compound **4c** was synthetized according to GP, using Methyl 2-aminopyridine-4-carboxylate, 5-methoxy-1-naphthaldehyde and cyclohexyl isocyanide. **4c** was obtained as

an oil in 77% yield. ^{1}H NMR 500 MHz, Chloroform-d) δ 8.35 (m, 2H), 8.14 (d, *J* = 7.1 Hz, 1H), 7.87–7.80 (m, 1H), 7.57 (d, *J* = 7.9 Hz, 1H), 7.54–7.43 (m, 3H), 6.91 (d, *J* = 7.8 Hz, 1H), 4.07 (s, 3H), 3.97 (s, 3H), 2.69 (m, 1H), 1.64–1.56 (m, 2H), 1.47 (m, 2H), 1.44–1.38 (m, 1H), 0.99 (m, 3H), 0.89 (m, 2H). ^{13}C NMR (126 MHz, $CDCl^{3}$) δ 166.0, 155.9, 139.7, 132.8, 128.4, 128.4, 127.2, 125.7, 125.3, 125.1, 122.4, 122.1, 120.0, 119.9 111.2, 103.5, 56.1, 55.6, 52.6, 33.8, 25.4, 24.5 ppm. HRMS (ESI-TOF) m/z $[M + H]^{+}$ Calcd for $[C_{26}H_{27}N_{3}O_{3} + H^{+}]^{+}$ 430.2125, found 430.2150.

3.3.4. Methyl 2-(5-methoxynaphthalen-1-yl)-3-((4-methoxyphenyl)amino)imidazo[1,2-*α*]pyridine-7-carboxylate (**4d**)

Compound **4d** was synthetized according to GP, using Methyl 2-aminopyridine-4-carboxylate, 5-methoxy-1-naphthaldehyde and 4-metoxy-phenyl-isocyanide. **4d** was obtained in 91% yield. ^{1}H NMR (500 MHz, Chloroform-d) δ 8.34 (*s*, 1H), 8.30–8.19 (*m*, 2H), 7.68 (d, *J* = 7.1 Hz, 1H), 7.49–7.38 (m, 3H), 7.33 (*dd*, *J* = 7.1, 1.6 Hz, 1H), 6.77–6.66 (*m*, 3H), 6.44–6.37 (m, 2H), 5.69 (s, 1H), 3.96 (*d*, *J* = 2.9 Hz, 6H), 3.72 (s, 3H). 13C NMR (126 MHz, $CDCl_{3}$) δ 165.97, 155.89, 153.75, 141.47, 140.79, 137.88, 132.70, 128.20, 126.97, 125.78, 125.66, 125.26, 125.21, 122.76, 122.54, 122.37, 122.16, 120.26, 115.21, 115.15, 111.18, 103.31, 77.30, 77.04, 76.79, 72.29, 61.79, 60.38, 55.65, 55.49, 52.48, 31.92, 30.58, 29.70, 22.69, 14.19, 14.11. ppm. HRMS (ESI-TOF) m/z $[M + H]^{+}$ Calcd for $[C_{27}H_{23}N_{3}O_{4} + H^{+}]$ 454.1736, found 454.1761.

4. Conclusions

The contributions of this work fall mainly in the synthetic and pharmacological fields. The GBB products could be to have applications in medicinal chemistry. This protocol offers several advantages, including excellent overall yields, the use of an alternative green energy source, short reaction times, eco-friendly solvents, inexpensive green catalysts, one-pot synthesis and operational simplicity. The scope of the developed strategy reported here corresponds to the current progress of the project, which will be further expanded and published in due course.

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Conflicts Of Interest: The authors declare no conflict of interest.

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