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Synthesis of Imidazo[1,2-a]pyridine-chromones via microwave-assisted Groebke-Blackburn-Bienaymé Reaction†

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Abstract: A serie of imidazo[1,2-*a*]pyridine-chromones were synthesized by microwave-assisted Groebke–Blackburn–Bienaymé reaction (GBBR) under eco-friendly conditions (20 mol% ammonium chloride catalyst in EtOH). Chromones and imidazo[1,2-*a*]pyridines are a privileged cores of high interest in medicinal chemistry.

Keywords: multicomponent reactions; imidazo[1,2-a]pyridine; GBBR; chromone; green chemistry

1. Introduction

Imidazo [1,2,a]pyridines have been intensively investigated since the beginning of the 20th century, it has been of great interest in medicinal research science and wide variety of biologically active compounds and many commercially available drugs such as zolpidem (**1**), olprinone (**2**) and soraprazan (**3**) containig this core [1]. Also in the development of fluorescent dyes and OLED´s, because of their luminescent properties [2].

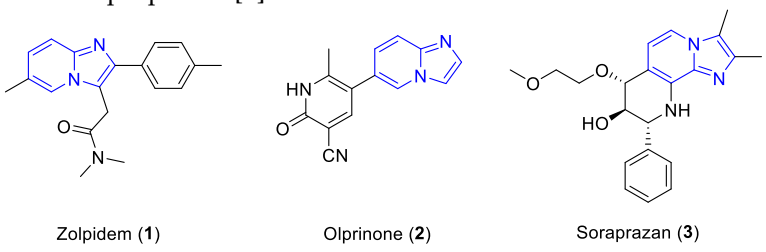


Figure 1. Some representative drugs with imidazo[1,2,a]pyridine core.

On the other hand chromones are present in natural products, this core is of great interest in medicinal chemistry and are present in various compounds showing different biological activities such as antiparasitic (**4**), anticancer (**5**), antiplatelet (**6**), antiparkinson, an antimicrobials, to mention some [3].

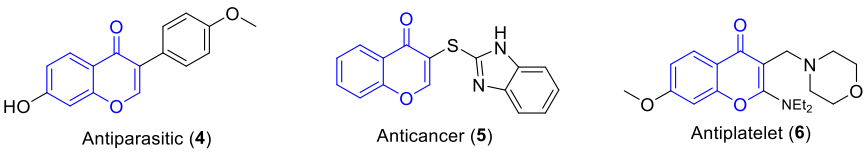
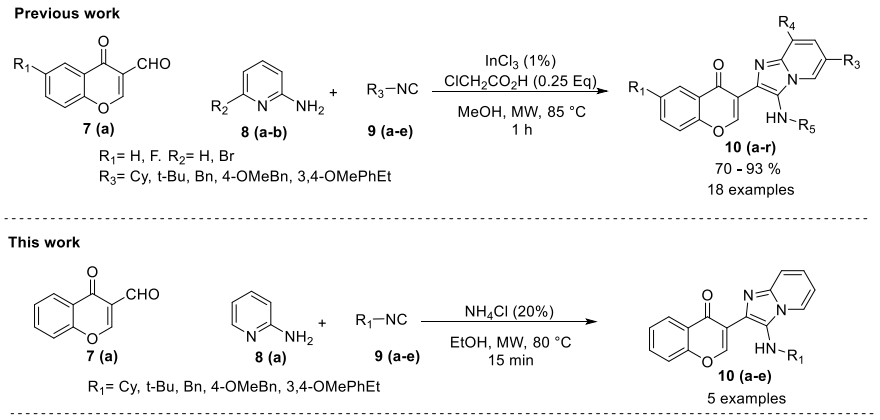


Figure 2. Bioactive chromone compounds.

A method to acces of imidazo[1,2-*a*]pyridine core it is through a multicomponent reaction GBBR [4]. Several conditions are reported, employing various catalyst, like to Lewis acids, Brönsted acids, organic bases, solid supported and inorganic salts. Frequently these catalysts are expensive and long reaction times were required [5].

In a previous report, the synthesis of chromone and imidazo[1,2-*a*]pyridine were performed under non-green conditions [6]. Actually, our research group is interested in development of eco-friendly methodologies based on I-MCR´s (isocyanide-based multicomponent reactions) for the synthesis of complex heterocyclic compounds. Herein we describe the microwave assisted synthesis of imidazo[1,2-*a*]pyridin-chromones from 2-amino-pyridines, 3-formyl-chromone and isocyanides using green catalyst and solventas and eco-friendly method. (scheme 1).

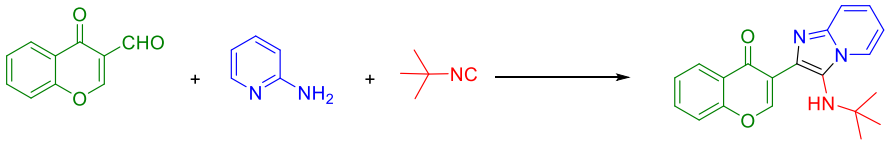


Scheme 1. Previous report and our work.

2. Results and Discussion

First, a model reaction was conducted using 3-formylchromone (**7**), amidine (**8**) and *tert*-butyl isocyanide (**9a**) to optimize reaction conditions. The results are shown in Table 1. As our intention was to develop an eco-friendly method, we chose EtOH as solvent. Initially, we performed the GBBR at room temperature without catalyst, however no reaction took place. Then, we decide assisted the reaction with other sources energy.as ultrasonic but the product was observed in traces, then staying in the margin of eco-friendly method, we tried NH_4Cl as catalyst. Carried out the reaction at the same condition, (ultrasound-assisted and NH_4Cl 20%), the product **10a** was isolated in 23 %. When the reaction was performed under microwave-assisted with NH_4Cl, the yield increased to 36 % and the reaction time decreased to 15 min.

Table 1. Reaction optimizing conditions **10a**.

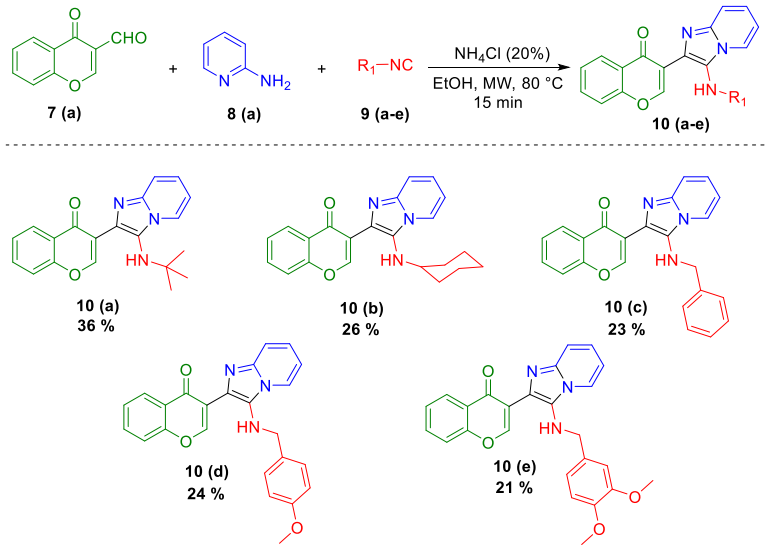


Entry[a]	Solvent	Catalyst	Temperature	Time	Yield[c]
1	EtOH [0.5 M]	---	r.t.	4 h	N.R.
2	EtOH [0.5 M]	---	60° C,)))	3 h	Traces
3	EtOH	NH_4Cl	60° C,)))	5 h	23 %

	[0.5 M]	(20%)			
4[b]	EtOH [0.5 M]	NH_4Cl (20%)	80 °C, MW	15 min	36 %

[a] Reactions performed with 1.0 equiv. 3-formyl-chromone (**7**), 1.2 equiv. of 2-amine-pyridine (**8**), 1.2 equiv. of *tert*-butylisocyanide (**9a**) and 0.02 equiv. of NH_4Cl. [b]All Microwave assisted reactions was performed to 100 W. [c]Isolated yield. r.t. = room temperature.,))) = Ultrasound assisted. MW = Microwave assisted.

After optimizing the conditions, we explored the reaction scope with different isocyanides (**9**), as cyclohexyl, benzyl and phenethyl moieties (**a-e**). The respective products **9a–e** (scheme 2**)** were obtained in yields (21–36%).



Scheme 2. Substrate scope.

Figure 3. ^{1}H NMR spectra for 3-(3-(tert-butyl-amino)imidazo[1,2-a]pyridin-2-yl)-4H-chromen-4-one (**10a**).

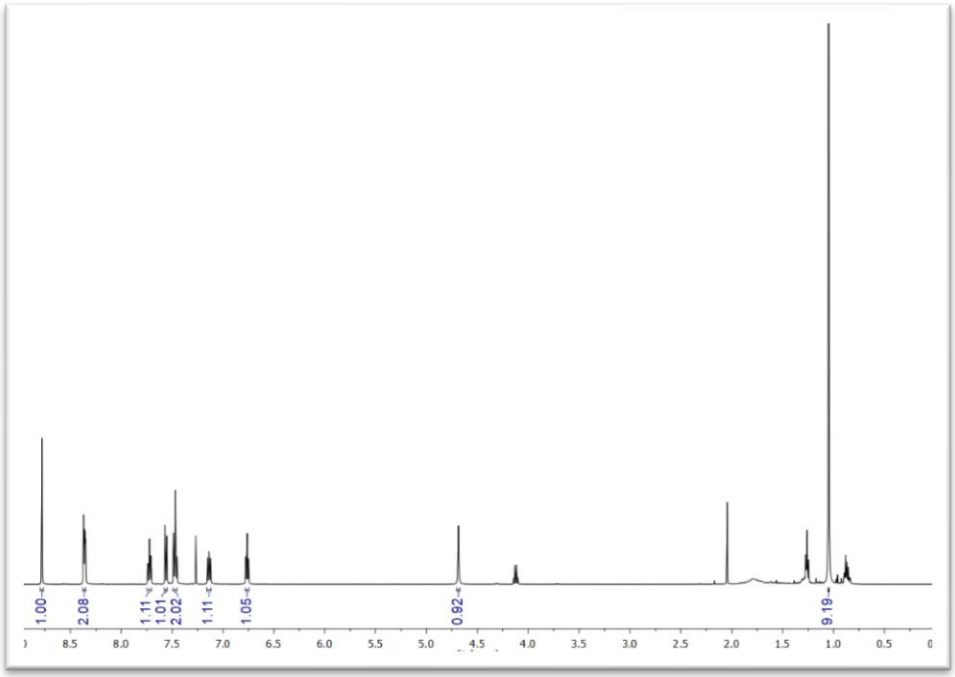


Figure 3. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS) spectrum of 3-(3-(tert-butylamino)imidazo[1,2-a]pyridin-2-yl)-4H-chromen-4-one (**10a**).

3. Experimental Section

3.1. General information, Instrumentation, and Chemicals

^{1}H and ^{13}C NMR spectra were acquired on Bruker Avance III spectrometers (500 and 125 MHz respectively). The solvent used was deuterated chloroform ($CDCl_3$). Chemical shifts are reported in parts per million (δ/ppm). The internal reference for ^{1}H NMR spectra is trimethylsilane at 0.0 ppm. The internal reference for ^{13}C NMR spectra is $CDCl_3$ 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). NMR spectra were analyzed using the MestreNova software version 12.0.0–20080. IR spectra were acquired on a Perkin Elmer 100 spectrometer using an Attenuated Total Reflectance (ATR) method with neat compounds. The absorbance peaks are reported in reciprocal centimeters (υ_{max}/cm^{-1}). Microwave assisted reactions were performed in closed vessel mode using a monomodal CEM Discover unit. Reaction progress was monitored by Thin-Layer Chromatography (TLC) on precoated silica-gel 60 F_{254} plates and the spots were visualized under UV light at 254 or 365 nm. Mixtures of hexane with ethyl acetate (EtOAc) were used to run TLC and for measuring retention factors (R_f). Flash column chromatography was performed using silica gel (230–400 mesh) and mixtures of hexane with EtOAc in different proportions (v/v) as the mobile phase. All reagents were purchased from Sigma-Aldrich and were used without further purification. Chemical names and drawings were obtained using the ChemBioDraw Ultra 13.0.2.3020 software package.

3.*2. General procedure*

In a MW vial (10mL) equipped with a magnetic stirring containing a solution of 3-formyl-chromone (1.0 equiv.) in EtOH [0.5 M], 2-amino-piridyne (1.2 equiv.) and NH_4Cl (0.02 equiv.) were sequentially added and the reaction mixture was MW heated (100W, 80 °C) for 20 min, then the corresponding isocyanide (1.2 equiv.) was added and the reaction mixture was performed at the same condition for 15 minutes. The solvent was removed until dryness and the crude was immediately purified by silica gel column chromatography using a mixture of hexanes with ethyl acetate (7/3 V/V) to afford the corresponding imidazo[1,2-*a*]pyridine-chromones **10a-e**.

Synthesis and characterization of the 3-(3-(tert-butylamino)imidazo[1,2-a]pyridin-2-yl)-4H-chromen-4-one (**10a**)

According to the GP, 3-formylchromone (51 mg, 0.292 mmol), 2-aminopyridine (33 mg, 0.35 mmol), NH_4Cl (3 mg, 0.058 mmol) and *tert*-butylisocyanide (39.58 μL, 0.35 mmol) were reacted together in EtOH (2.0 mL) to afford the compound **10a** (35 mg, 36%) as pale yellow solid; R_f = 0.17 (Hexanes-AcOEt = 7/3 V/V); FT-IR (ATR)n_{max}/cm^{-1} 3281, 2926, 1629, 1138; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ 8.80 (s, 1 H), 8.36 (d, *J* = 7.0 Hz, 2 H), 7.73-7.67 (m, 1 H), 7.55 (d, *J* = 8.4 Hz, 1 H), 7.51-7.42 (m, 2 H), 7.16-7.10 (m, 1 H), 6.78-6.73 (m, 1 H), 4.70 (bs, 1 H), 1.05 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$; 25 °C; TMS): δ 176.7, 156.6, 156.4, 142.7, 133.9, 130.4, 128.2, 126.5, 125.5, 124.4, 124.3, 124.1, 121.6, 118.1, 116.9, 111.0, 56.0, 29.3; HRMS (ESI+): *m*/*z* calcd. for $C_{20}H_{20}N_3O_2^+$ 334.1556, found 334.1553.

Synthesis and characterization of the 3-(3-(cyclohexylamino)imidazo[1,2-a]pyridin-2-yl)-4H-chromen-4-one (**10b**)

According to the GP, 3-formylchromone (51 mg, 0.292 mmol), 2-aminopyridine (33 mg, 0.35 mmol), NH_4Cl (3 mg, 0.058 mmol) and cyclohexylisocyanide (43.51 μL, 0.35 mmol) were reacted together in EtOH (2.0 mL) to afford the compound **10a** (27 mg, 26%) as brown solid; R_f = 0.15 (Hexanes-AcOEt = 7/3 V/V); FT-IR (ATR)n_{max}/cm^{-1} 3278, 2920, 1629, 1143; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ 8.82 (s, 1 H), 8.37 (dd, *J* = 8.0, 1.5 Hz, 1 H), 8.12 (dt, *J* = 6.9, 1.2 Hz, 1H), 7.75-7.70 (m, 1 H), 7.56 (dd, *J* = 8.4, 0.6 Hz, 1 H), 7.51-7.44 (m, 2 H), 7.15-7.10 (m, 1 H), 6.81-6.75 (m, 1 H), 5.17 (d, *J* = 9.1 Hz, 1 H), 2.72-2.61 (m, 1 H), 1.83 (d, *J* = 9.3 Hz, 2 H), 1.66 (d, *J* = 5.2 Hz, 2 H), 1.51 (d, *J* = 5.9 Hz, 1 H), 1.19-1.06 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$; 25 °C; TMS): δ 177.3, 156.8, 156.7, 142.4, 134.1, 129.9, 127.6, 126.8, 125.8, 124.6, 124.2, 123.5, 121.1, 118.6, 117.4, 111.6, 56.6, 34.0, 25.5, 25.0; HRMS (ESI+): *m*/*z* calcd. for $C_{22}H_{22}N_30_2^+$ 360.1712, found 360.1737.

Synthesis and characterization of the 3-(3-(benzylamino)imidazo[1,2-a]pyridin-2-yl)-4H-chromen-4-one (**10c**)

According to the GP, 3-formylchromone (34 mg, 0.195 mmol), 2-aminopyridine (22 mg, 0.234 mmol), NH_4Cl (2 mg, 0.039 mmol) and benzylisocyanide (28.49 μL, 0.234 mmol) were reacted together in EtOH (2.0 mL) to afford the compound **10c** (17 mg, 23%) as orange solid; R_f = 0.12 (Hexanes-AcOEt = 7/3 V/V); FT-IR (ATR)n_{max}/cm^{-1} 3289, 2836, 1629, 1148; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ 8.45 (s, 1 H), 8.28 (d, *J* = 8.0 Hz, 1 H), 8.17 (d, *J* = 6.8 Hz, 1 H), 7.72-7.67 (m, 1 H), 7.49 (d, *J* = 8.2 Hz, 2 H), 7.46-7.42 (m, *J* = 7.5 Hz, 1 H), 7.17-7.12 (m, 1 H), 7.00-6.94 (m, 5 H), 6.82-6.78 (m, 1 H), 5.48 (t, *J* = 7.2 Hz, 1H), 3.99 (d, *J* = 7.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$; 25 °C; TMS): δ 176.3, 156.0, 142.2, 139.4, 133.7, 129.1, 128.7, 128.2, 128.0, 127.0, 126.3, 125.4, 124.2, 124.0, 122.7, 120.1, 118.1, 117.3, 111.7, 52.5; HRMS (ESI+): *m*/*z* calcd. for $C_{23}H_{18}N_30_2^+$ 368.1399, found 368.1401.

Synthesis and characterization of the 3-(3-((4-methoxybenzyl)amino)imidazo[1,2-a]pyridin-2-yl)-4H-chromen-4-one (**10d**)

According to the GP, 3-formylchromone (34 mg, 0.195 mmol), 2-aminopyridine (22 mg, 0.234 mmol), NH_4Cl (2 mg, 0.039 mmol) and 4-methoxybenzylisocyanide (35 mg, 0.234 mmol) were reacted together in EtOH (2.0 mL) to afford the compound **10c** (19 mg, 24%) as orange solid; R_f = 0.11 (Hexanes-AcOEt = 7/3 V/V); FT-IR (ATR) ν_{max}/cm^{-1} 3295, 2932, 1629, 1461; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ 8.29 (s, 1 H), 7.79 (dd, *J* = 8.2, 2.8 Hz, 1 H), 7.65-7.60 (m, 1 H), 7.47-7.34 (m, 3 H), 7.13-7.05 (m, 2 H), 6.63 (d, *J* = 8.3 Hz, 2 H), 6.25 (d, *J* = 8.3 Hz, 2 H), 4.77 (bs, 1 H), 3.90 (s, 2 H), 3.47 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$; 25 °C; TMS): δ 174.8, 161.1, 158.8, 158.6, 157.0, 151.8, 130.4, 130.3, 126.7, 125.3, 122.4, 122.2, 120.5, 120.4, 120.3, 115.6, 113.4, 111.1, 110.9, 55.3, 55.1; HRMS (ESI+): *m/z* calcd. for $C_{24}H_{20}N_3O_3^+$ 398.1505, found 398.1505.

Synthesis and characterization of the 3-(3-((3,4-dimethoxyphenethyl)amino)imidazo[1,2-a]pyridin-2-yl)-4H-chromen-4-one (**10e**)

According to the GP, 3-formylchromone (34 mg, 0.195 mmol), 2-aminopyridine (22 mg, 0.234 mmol), NH_4Cl (2 mg, 0.039 mmol) and 3,4-dimethoxyphenetylisocyanide (41 mg, 0.234 mmol) were reacted

together in EtOH (2.0 mL) to afford the compound **10e** (18 mg, 21%) as pale yellow oil; R_f = 0.10 (Hexanes-AcOEt = 7/3 V/V); FT-IR (ATR)n_{max}/cm^{-1} 3281, 2926, 1629, 1138; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ 8.77 (s, 1 H), 8.26 (d, *J* = 7.9 Hz, 1 H), 7.95 (d, *J* = 6.9 Hz, 1 H), 7.74-7.68 (m, 1 H), 7.54 (d, *J* = 8.4 Hz, 1 H), 7.50-7.43 (m, 2 H), 7.15-7.09 (m, 1 H), 6.77-6.72 (m, 1 H), 6.65-6.60 (m, 3 H), 5.44 (t, *J* = 7.0 Hz, 1 H), 3.78 (s, 3 H), 3.75 (s, 3 H), 3.19 (q, *J* = 7.0 Hz, 2 H), 2.71 (t, *J* = 7.1 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$; 25 °C; TMS): δ 176.3, 156.1, 156.0, 148.8, 147.4, 141.9, 133.8, 131.9, 130.2, 126.4, 126.3, 125.5, 124.2, 123.9, 122.9, 120.7, 120.5, 118.3, 117.2, 112.0, 111.5, 111.1, 55.8, 49.2, 36.4; HRMS (ESI+): *m*/*z* calcd. for $C_{24}H_{20}N_3O_3^+$ 442.1767, found 442.1798.

4. Conclusions

We have developed an efficient microwave-assisted GBB protocol for the eco-friendly synthesis of imidazo[1,2,a]pyridine-chromones, in short reactions time under green catalyts.

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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