Synthesis of Imidazo[1,2-α]pyridine-Chromones via Microwave-Assisted Groebke-Blackburn-Bienaymé Reaction †

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Abstract: A series of imidazo[1,2-α]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-α]pyridines are a privileged core of high interest in medicinal chemistry.

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

1. Introduction

Imidazo [1,2,α]pyridines have been intensively investigated since the beginning of the 20th century, they have been of great interest in medicinal research science and a wide variety of biologically active compounds and many commercially available drugs, such as zolpidem (1), olprinone (2), and soraprazan (3), containing this core [1–4] (Figure 1). They have also been used in the development of fluorescent dyes and OLED’s, because of their luminescent properties [5,6].

![Figure 1. Some representative drugs with imidazo [1,2,α]pyridine core.](image)

On the other hand chromones are present in natural products, this core is of great interest in medicinal chemistry and it is present in various compounds showing different biological activities such as antiparasitic (4), anticancer (5), antiplatelet (6), antiparkinson, and antimicrobial, to mention some [7–11] (Figure 2).

The method to access imidazo[1,2-α]pyridine core is through a multicomponent reaction GBBR [12]. Several conditions are reported, employing various catalysts, such as Lewis acids, Brönsted acids, organic bases, solid-supported, and inorganic salts. Frequently, these catalysts are expensive and long reaction times were required [13].
In a previous report, the synthesis of chromone and imidazo[1,2-α]pyridine was performed under non-green conditions [14]. Actually, our research group is interested in the 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-α]pyridin-chromones from 2-amino-pyridines, 3-formyl-chromone, and isocyanides using a green catalyst and solvents and an 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 a catalyst, however, no reaction took place. Then, we carried out an assisted the reaction with other sources of energy, such as ultrasonic, but the product was observed in traces, then staying in the margin of the eco-friendly method, we tried NH₄Cl as a catalyst. After carrying out the reaction in the same conditions, (ultrasound-assisted and NH₄Cl 20%), the product 10a was isolated in 23%. When the reaction was performed using microwave-assisted synthesis with NH₄Cl, the yield increased to 36%, and the reaction time decreased to 15 min. Figure 3 show the 1H NMR spectra for the representative imidazo[1,2-α]pyridine 10a.

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

**Figure 2. Bioactive chromone compounds.**
Table 1. Reaction optimizing conditions 10a.

| Entry | Solvent [0.5 M] | Catalyst | Temperature | Time | Yield c |
|-------|----------------|----------|-------------|------|---------|
| 1     | EtOH           | ---      | r.t.        | 4 h  | N.R.    |
| 2     | EtOH           | ---      | 60 °C, ))) 3 h | Traces |
| 3     | EtOH           | NH₄Cl (20%) | 60 °C, ))) 5 h | 23%   |
| 4 b   | EtOH           | NH₄Cl (20%) | 80 °C, MW 15 min | 36%   |

\(^a\) Reactions performed with 1.0 equivalent 3-formyl-chromone (7), 1.2 equiv. of 2-amine-pyridine (8), 1.2 equiv. of tert-butylisocyanide (9a) and 0.02 equivalent of NH₄Cl. \(^b\) All microwave-assisted reactions were performed to 100 W. \(^c\) Isolated yield. r.t. = room temperature. ))) = Ultrasound-assisted. MW = Microwave-assisted.

Scheme 2. Substrate scope.
3. Experimental Section

3.1. General Information, Instrumentation, and Chemicals

$^1$H and $^{13}$C NMR spectra were acquired using 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 ($\nu_{\text{max}}$/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 to measure 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 (GP)

In a microwave-assisted (MW) vial (10 mL) 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$_4$Cl (0.02 equiv.) were sequentially added and the reaction mixture was MW heated (100 W, 80 °C) for 20 min, then the corresponding isocyanide (1.2 equivalent) was added and the reaction mixture was performed in the same conditions for 15 min. The solvent was removed until dry 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$_4$Cl (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)$\nu$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$_3$O$_2$+ 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$_4$Cl (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 10b (27 mg, 26%) as brown solid, R$_f$ = 0.15 (Hexanes-AcOEt = 7/3 V/V); FT-IR (ATR)$\nu$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, 1 H), 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$_3$O$_2$+ 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$_4$Cl (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)$\nu$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, 1 H), 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$_3$O$_2$+ 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$_4$Cl (2 mg, 0.039 mmol) and 4-methoxybenzylisocyanide (28.49 µL, 0.234 mmol) were reacted together in EtOH (2.0 mL) to afford the compound 10d (19 mg, 24%) as orange solid, R$_f$ = 0.11 (Hexanes-AcOEt = 7/3 V/V); FT-IR (ATR)$\nu$max/cm$^{-1}$ 3295, 2932, 2836, 1629, 1148; $^1$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, 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$_{24}$H$_{20}$N$_3$O$_3$+ 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), NH₄Cl (2 mg, 0.039 mmol) and 3,4-dimethoxyphenethylisocyanide (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) ν_max/cm⁻¹ 3281, 2926, 1629, 1138; ¹H NMR (500 MHz, CDCl₃, 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); ¹³C NMR (125 MHz, CDCl₃, 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 C₂₄H₂₀N₃0₃+ 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 reaction time under a green catalyst.

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