chemistry proceedings

MDPI

Proceedings Paper

Synthesis of Carbazolyl Imidazo[1,2-*a*] Pyridines via Groebke-Blackburn-Bienayme Reaction under Green Catalyst †

Alejandro Corona-Díaz, Mahanandaiah Kurva, Unnamatla M. V. Basavanag, Gustavo Rangel Porras and Rocío Gámez-Montaño *

Departamento de Química, Universidad de Guanajuato, Noria Alta S/N, Col. Noria Alta, Guanajuato 36050, Mexico; email (A.C.-D.); email (M.K.); email (U.M.V.B.); email (G.R.P.)

* Correspondence: rociogm@ugto.mx; Tel.:+52-473-732-0006 (ext. 8191)

† Presented at the 26th International Electronic Conference on Synthetic Organic Chemistry, 15–30 November 2022; Available online: https://ecsoc-26.sciforum.net/.

Abstract: Multicomponent reactions (MCR) are efficient and versatile modern synthetic tools, they also have several advantages such as high convergence, operational simplicity, atomic economy, friendly conditions and MCR products are obtained with good to excellent overall yields. The Groebke-BlackBurn-Bienaymé (GBB) multicomponent reaction based on isocyanide (IMCR) in the synthesis of imidazo[1,2-α]pyridines (IMPs) under green catalyst as montmorillonite K-10 has been little reported. Therefore, the present work describes the novel ultrasound irradiation (USI)-assisted one-pot synthesis for analogs of imidazo[1,2-α] pyridines (IMPs) incorporating the carbazole scaffold.

Keywords: one-pot synthesis; imidazo[1,2-α]pyridines (IMP); isocyanide-based multicomponent reactions (IMCR); USI

Citation: Corona-Díaz, A.; Kurva, M.; Basavanag, U.M.V.; Porras, G.R. Synthesis of Carbazolyl Imidazo[1,2-*a*] Pyridines via Groebke-Blackburn-Bienayme Reaction under Green Catalyst. *Chem. Proc.* **2022**, *4*, x. https://doi.org/10.3390/xxxxx

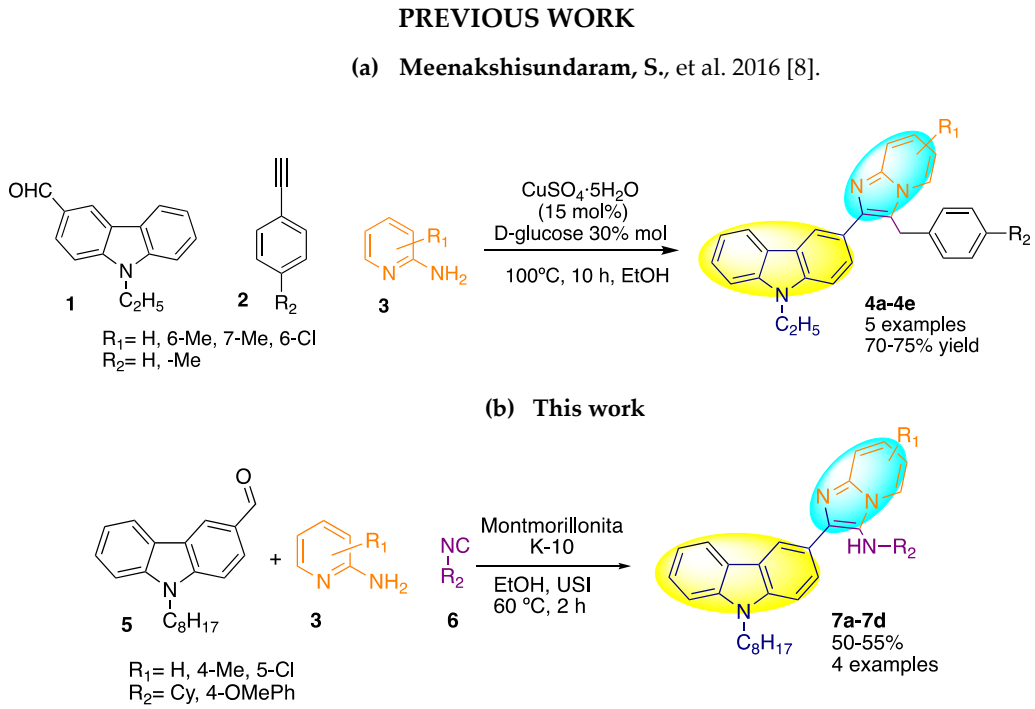
Academic Editor(s):

Published: 15 November 2022

1. Introduction

Carbazole imidazo[1,2-α]pyridines are a distinguished class of aromatic heterocyclics of interest because of the occurrence of its derivatives in biologically active compounds and the pharmacology that both parts of the system exhibit in common as antiviral, antimicrobial, anti-inflammatory and with applications in the field of optics. [1,2] Traditional procedures to synthetize imidazo [1,2-α]pyridines are: (i) condensation of 2-aminopyridines with α-halo carbonyl (ii) copper-catalyzed three component reactions of 2-aminopyridines, aldehydes, and alkynes, both inefficient and with several disadvantage in the conditions of reaction such as high temperature, low yields, expensive catalyst, and non-greener solvents, (iii) via Groebke-Blackburn-Bienaymé reaction (GBBR) that is an efficient methodologies to synthesize complex molecules from the simple materials with high atom economy. [3] Multicomponent reactions (MCRs) have gained a considerable attention among the organics chemists during the last decades being an efficient method in organic synthesis [4–8] and the GBBR has emerged as a very important multicomponent reaction with a high number of reports. [8,9]

Meenakshisundaram, S., et in 2016 reported the synthesis and anticancer activity of five molecules containing carbazole with imidazo[1,2-α] pyridine (Scheme 1), [8] Our group reported in 2018 the first efficient and mild USI assisted GBB based methodology for the green synthesis of new bound type bis-heterocyclic carbazolyl imidazo[1,2-α]pyridine-3- amines in excellent yields. [9] Herein, we report a one-pot GBBR strategy for the synthesis of carbazole imidazo[1,2-α]pyridine using montmorillonite as catalyst.

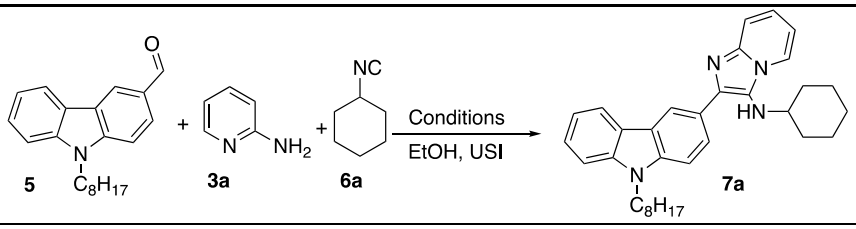


Scheme 1. (**a**) Previous work on the synthesis of series of five 3-imidazo[1,2-*α*]pyridine carbazoles by MCR (**b**) Ultrasound assisted one-pot synthesis of GBB products type bis-heterocycles

2. Results and Discussion

To synthetize the carbazolyl imidazo[1,2*α*] pyridines different conditions were studied to get the better yields, for the optimization of reaction conditions was used 9-octyl-9H-carbazole-3-aldehyde **5** (1 mmol), 2-aminopyridine **3a** (1 mmol), cyclohexyl isocyanide **6a** (1 mmol) in EtOH as a solvent and montmorillonite and USI (Table 1). Firstly, we made the GGBR at room temperature without catalyst and **7a** was obtained in 10% yield (Table 1, entry 1). When the reaction was heated to 60 °C **7a** is obtained in 30% yield (Table 1, entry 2). When the reaction was carried out using catalytic montmorillonite K-10 at room temperature, product **7a** was formed in 20% yields (Table 1, entry 3). Then, on heating at 60 °C with montmorillonite K-10, the yield of product **7a** increased to 50% (Table 1, entry 4).

Table 1. Optimization of reaction conditions **7a**.



Entry	Catalyst (10 mol%)	Temp (°C)	Time (h)	Yield (%) [b]
1	-	Rt	2	10
2	-	60	2	30
3	K-10 Montmorillonita	Rt	2	20
4	K-10 Montmorillonita	60	2	50

[a] All reactions were carried out in USI (42 kHz) using equimolar amounts of **5**, **3**a, and **6a**. [b] Isolated yield. Rt = room temperature.

The conditions showed in entry 4 were utilized to synthesize a series of four 3-imidazo[1,2-*α*]pyridine carbazoles bound type bis-heterocycles (Scheme 2). The versatility of the method was examined using different amino azines bearing both electron donating

and electron withdrawing groups, sterically crowded substituents as aliphatic and aromatic isocyanides. The products (**7a–d**) were obtained in moderate yields (50–55%). The compounds were purified using silica-gel column chromatography, the structure for isolated product was confirmed by ^{1}H and ^{13}C NMR (Figure 1).

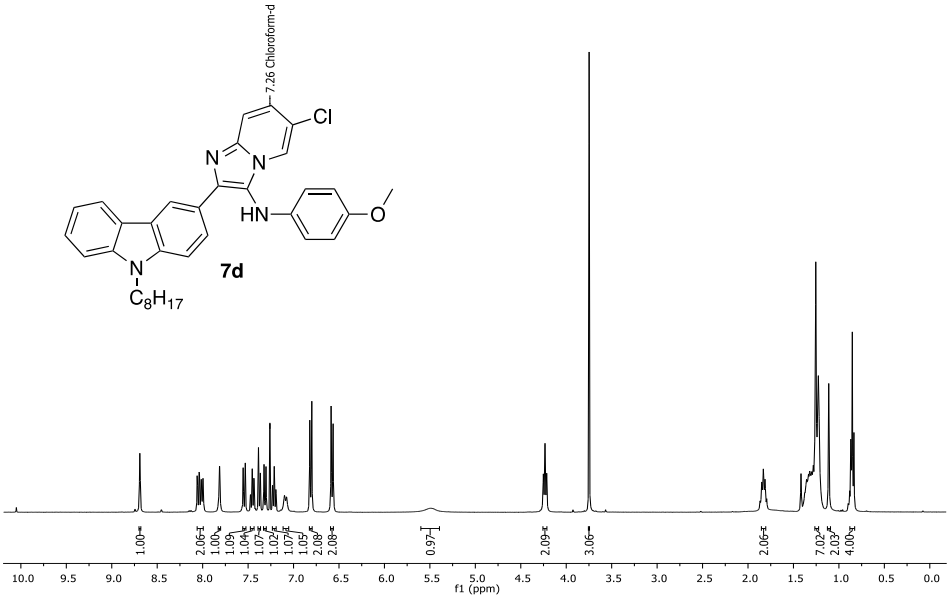
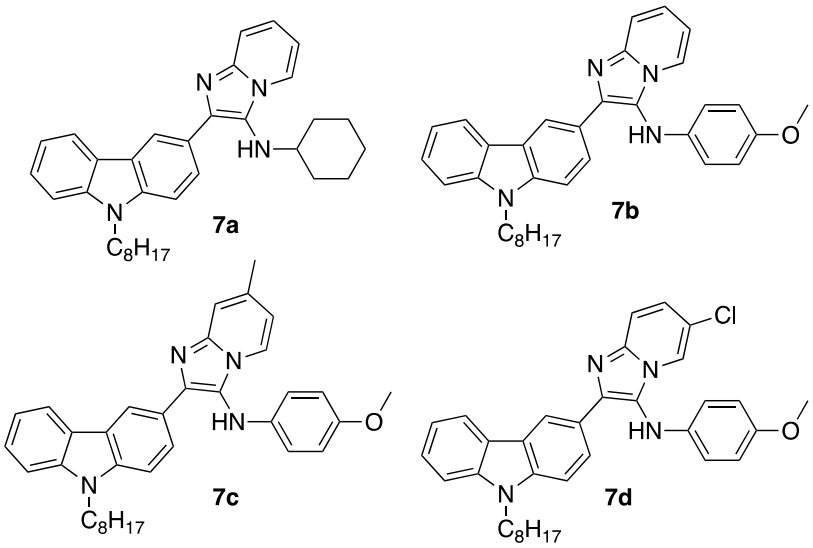


Figure 1. ^{1}H NMR spectrum of compound **7d**.



Scheme 2. Substrate Scope.

3. Experimental Section

3.1. General Information, Software, Instrumentation and Chemicals

^{1}H and ^{13}C NMR spectra were acquired on Bruker Advance III spectrometer (500 MHz). The solvent for NMR samples was $CDCl_3$. Chemical shifts are reported in parts per million (δ/ppm). Internal reference for NMR spectra is TMS at 0.00 ppm. Coupling constants are reported in Hertz (*J*/Hz). Multiplicities of signals are reported using the standard abbreviations: singlet (s), doublet (d), triplet (t), the quartet (q) and multiplet (m). NMR spectra were analyzed using the MestreNova software (version 6.0.2-5475). IR spectra were recorded on a Perkin Elmer 100 spectrometer by the ATR method using neat compounds. The wavelengths are reported in reciprocal centimeters ($_{max}$/cm^{-1}). FT-IR

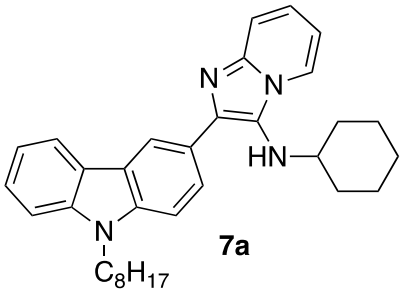
spectra were analyzed using the Report Builder software (Rev. 2.01). HRMS spectra were acquired on a MaXis-Impact ESI(+)-QqTOF Bruker mass spectrometer. HRMS spectra were analyzed using the data Analysis (Bruker, version 4.1). Ultrasound irradiated reactions were performed in sealed vials (10 mL) placed in a water bath of a Branson 1510 sonicator cleaner working at 42 kHz ± 6% frequencies. The reaction progress was monitored by TLC and the spots were visualized under UV light (254 or 365 nm). Melting points were determined on a Fisher-Johns apparatus and were uncorrected. The solvents were distilled and dried according to standard procedures. Commercially available reagents were purchased to Sigma-Aldrich and were used without further purification. Structure names and drawings were done using the ChemBioDraw Ultra software (version 16.0.1.4(61).

3.2. Synthesis and Characterization of the Carbazolyl-Imidazo[1,2-α]pyridine-3-Amines (7a-d)

General Procedure (GP): In a sealed vial (10 mL) for USI-assisted reactions, a solution of 9-octyl-9H-carbazole-3-carbaldehyde (1.0 equiv.) in EtOH [0.5 M] was placed. Then, 2-aminopyridine (1.0 equiv.), montmorillonite K-10 (0.1 equiv.) and the corresponding isocyanide (1.0 equiv.) were added sequentially. The vial was closed, and the reaction mixture was sonicated (42 kHz ± 6%) at 60 °C for 2 hours. Then, the solvent was removed by vacuum and purified by column chromatography by using silica gel of 230–400 mesh using hexane and ethyl acetate as eluent 6/4 v/v; to afford pure products**.** The solid products obtained from the reaction was filtered and washed with deionized water (10 mL) and used as such for analytical characterization. Specified details of each product are given below.

3.3. Spectral Data

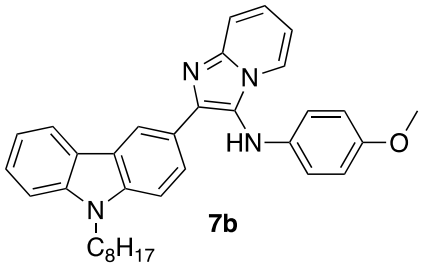
3.3.1. N-cyclohexyl-2-(9-octyl-9H-carbazol-3-yl) imidazo[1,2-α] pyridin-3-amine (7a)



7a

According to GP 9-octyl-9H-carbazole-3-carbaldehyde (100 mg, 0.325 mmol), 2-aminopyridine (30.6 mg, 0.325 mmol), cyclohexyl isocyanide (0.041mL, 0.325 mmol.), and montmorillonite K-10 (0.0325 mmol) in EtOH (0.5 M) to obtain black gummy paste; 50%; R_f = 0.3 (Hexane-AcOEt = 6/4 V/V); FT-IR (ATR) ν_{max}/cm^{-1} 3331, 3115, 2924, 1283, 1228, 1141; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.14–8.10 (m, 2H), 8.06 (d, J = 6.7 Hz, 1H), 7.55 (d, J = 8.9 Hz, 1H), 7.43–7.38 (m, 1H), 7.31 (d, J = 8.2 Hz, 2H), 7.21–7.17 (m, 1H), 6.99–6.93 (m, 1H), 6.66–6.61(m, 1H), 4.26–4.20 (m, 1H), 4.17–4.12 (m, 2H), 2.97–2.8 (m, 1H), 1.84–1.72 (m, 5H), 1.61–155 (m, 2H), 1.34–1.29 (m, 1H), 1.23–1.11(m, 8H), 1.09–1.01(m, 4H), 0.84–0.74(m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.8, 140.1, 125.8, 124.9, 124.2, 123.1, 123.0, 120.9, 119.3, 108.7, 57.0, 43.4, 34.2, 31.8, 29.7, 29.4, 29.2, 29.1, 27.4, 25.7, 24.8, 24.7, 22.6, 14.1; HR-MS (ESI+) m/z calculated for $[C_{33}H_{41}N_4]^+$ $[M+H]^+$: 493.3325, found 493.3343.

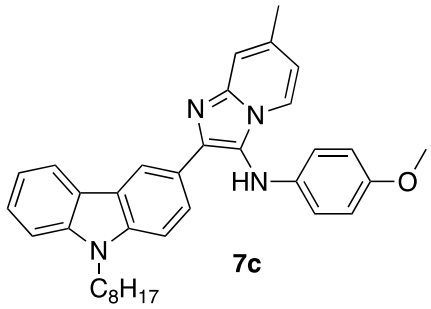
3.3.2. N-(4-methoxyphenyl)-2-(9-octyl-9H-carbazol-3-yl) imidazo[1,2-α] pyridin-3-amine (7b)



7b

According to GP 9-octyl-9H-carbazole-3-carbaldehyde (100 mg, 0.325 mmol), 2-aminopyridine (30.6 mg, 0.325 mmol), 4-Methoxy phenyl isocyanide (43.3 mg, 0.325 mmol) and montmorillonite K-10 (0.0325 mmol) in EtOH (0.5 M) to obtain pale brown solid; 53%; melting point = 115–117 °C; R_f = 0.3 (Hexane-AcOEt = 6/4 V/V); FT-IR (ATR) ν_{max}/cm^{-1} 3325, 3118, 2929, 1290, 1230, 1151; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.08 (d, J =8.5 Hz, 1H), 8.03 (d, J = 7.7 Hz, 1H), 7.79 (d, J =6.6 Hz, 1H), 7.63 (d, J = 8.3 Hz, 1H), 7.47–7.42 (m, 1H), 7.37 (d, J = 8.2 Hz, 1H), 7.30 (d, J =8.5 Hz, 1H), 7.23–7.14(m, 2H), 6.79 (d, J =8.7 Hz, 2H), 6.73–6.66 (m, 1H), 6.56 (d, J =8.73, 2H), 5.47 (s, 1H), 4.23 (d, J =6.8Hz, 2H), 3.73 (s, 3H), 1.83–1.77 (m, 2H), 1.41–1.16 (m, 9H), 1.12 (s, 1H), 0.91–0.81 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.5, 140.8, 140.2, 138.7, 125.7, 124.9, 123.2, 122.7, 120.8, 119.3, 119.0, 118.1, 115.3, 114.5, 108.7, 55.5, 43.2, 31.8, 29.4, 29.2, 29.0, 27.3, 22.6, 14.1; HR-MS (ESI+) m/z calculated for $[C_{34}H_{37}N_4O]^+$ $[M+H]^+$: 517.2961, found 517.2973.

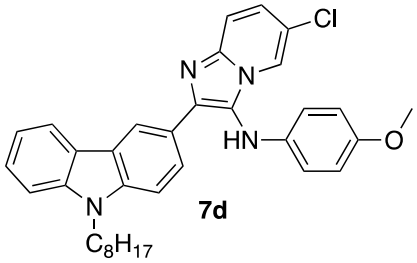
3.3.3. N-(4-methoxyphenyl)-7-methyl-2-(9-octyl-9H-carbazol-3-yl) imidazo[1,2-α] pyridin-3-amine (7c)



7c

According to GP 9-octyl-9*H*-carbazole-3-carbaldehyde (100 mg, 0. 325 mmol.), 4-Methyl-2-aminopyridine (35.1 mg, 0.325 mmol.), 4-Methoxy phenyl isocyanide (43.3 mg, 0.325 mmol) and montmorillonite K-10 (0.0325 mmol) to obtain white solid; 51%; melting point = 141–143 °C; R_f = 0.3 (Hexane-AcOEt = 6/4 V/V); FT-IR (ATR) ν_{max}/cm^{-1} 3335, 3120, 2934, 1286, 1230, 1151; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.10–8.0 (m,2H), 7.67 (d, *J* = 6.8 Hz, 1H), 7.47–7.41 (m, 1H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.6 Hz, 1H), 7.24–7.17 (m, 1H), 6.78 (d, *J* = 8.9 Hz, 2H), 6.56 (d, *J* = 8.92, 2H), 6.50 (d, *J* = 6.6Hz, 1H), 5.51 (s, 1H), 4.27–4.19 (m, 2H), 3.73 (s, 3H), 2.35 (s, 3H), 1.89–1.77 (m, 2H), 1.35–1.18 (m, 9H), 1.12 (s, 1H), 0.89–0.81 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.4, 140.7, 140.2, 139.1, 125.6, 124.9, 123.1, 123.0, 121.9, 120.7, 119.1, 118.9, 117.6, 115.3, 114.4, 108.6, 55.7, 43.2, 31.8, 31.3, 29.4, 29.2, 29.0, 27.3, 22.6, 21.4, 14.1; HR-MS (ESI+) *m*/*z* calculated for $[C_{35}H_{39}N_4O]^+$ $[M+H]^+$: 531.3118 found 531.3125.

3.3.4. 6-chloro-N-(4-methoxyphenyl)-2-(9-octyl-9H-carbazol-3-yl) imidazo[1,2-α] pyridin-3-amine (7d)



7d

According to GP 9-octyl-9*H*-carbazole-3-carbaldehyde (100mg, 0.325 mmol), 5-Chloro-2-aminopyridine (41.8 mg, 0.325 mmol) 4-Methoxy phenyl isocyanide (43.3 mg, 0.325 mmol) and montmorillonite K-10 (0.0325 mmol) to obtain pale white solid; 55%; melting point = 144–146 °C; R_f = 0.35 (Hexane-AcOEt = 6/4 V/V); FT-IR (ATR) ν_{max}/cm^{-1} 3321, 3119, 2927, 1288, 1238, 1147; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.08–7.98 (m, 2H), 7.81 (s, 1H), 7.54 (d, *J* =9.0Hz, 1H), 7.48–7.43 (m, 1H), 7.38 (d, *J* =8.2 Hz, 1H), 7.31 (d, *J* = 8.6Hz, 1H), 7.24-7.18 (m, 1H), 7.09 (d, *J* = 8.92, 1H), 6.81 (d, *J* = 8.9Hz, 2H), 6.58 (d, *J* = 8.9Hz, 2H), 5.49 (s, 1H), 4.29–4.17 (m, 2H), 3.75 (s, 3H), 1.88–1.78 (m, 2H), 1.28–1.19 (m, 7H), 1.11 (s, 2H), 0.89–0.82 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.7, 140.7, 140.3, 138.3, 125.8, 124.6, 123.1, 123.0, 120.6, 120.5, 119.2, 119.1, 118.6, 115.4, 114.6, 108.8, 108.7, 55.7, 43.2, 38.1, 29.4, 29.2, 29.0,27.3, 22.6, 14.1; HR-MS (ESI+) *m*/*z* calculated for $[C_{34}H_{36}ClN_4O]^+$ $[M+H]^+$: 551.2572 found 551.2545.

4. Conclusions

Was developed a mild USI assisted GBB based methodology for ecofriendly synthesis of bis-heterocyclic carbazolyl imidazo[1,2-α]pyridine-3-amines in good overall yields of 50–55%. Between its advantages the methodology uses green, available, cheap catalyst and solvent. This novel one-pot process allowed the synthesis of bound type bis-heterocycles containing two privileged scaffolds, which similar structure to other molecules reported with anticancer activity.

Author Contributions: All authors contributed equally to this work. All authors have read and agreed to the published version of the manuscript.

Funding:

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement:

Acknowledgments: A.C.D. thanks CONACYT, R.G.M. thanks CONACYT for financial support through CONACYT CB-2016-285622 and DAIP-UG, 005/2022 projects. Dr. Gustavo Rangel-Porras for providing montmorillonite catalyst. M.K (632715/338546), thanks CONACYT-México for a scholarship and Laboratorio Nacional de Caracterizacion de Propiedades Fisicoquímicas y Estructura Molecular (CONACYT-México, Project: 123732).

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

References

1. (a) Hiecke, M.; Rödl, C.B.; Wisniewska, J.M.; la Buscató, E.; Stark, H.; Zsilavecz, M.S.; Steinhilber, D.; Hofmann, B.; Proschak E. SAR-study on a new class of imidazo[1,2-*a*]pyridine-based inhibitors of 5-lipoxygenase. *Bioorg. M. Chem. Lett*. **2012**, 22, 1969-1975. (b) Ramachandran, S.; Panda, M.; Mukherjee, K.; Choudhury, NR.; Tantry, S.J.; Kedari, C.K.; Ramachandran, Sharma, S.; Ramya, V. K.; Guptha, S.; Sambandamurthy, V. K. Synthesis and structure activity relationship of imidazo[1,2-*a*]pyridine-8-carboxamides as a novel antimycobacterial lead series. *Bioorg. Med. Chem. Lett*. **2013**, 23 4996-5001. (c) Meng, Z.; J. Ciavarri, P.; McRiner, A.; Zhao, Y.; Zhao, L.; Reddy, P. A.; Zhang, X.; Fischmann, T. O.; Whitehurst, C.; Siddiqui, M. A., Potency switch

between CHK1 and MK2: Discovery of imidazo[1,2-*a*]pyrazine- and imidazo[1,2-*c*]pyrimidine-based kinase inhibitors *Bioorg. Med. Chem. Lett.* **2013**, 23, 2863-2867; (d) Bode, M.L.; Gravestock, D.; Moleele, S.S.; Westhuyzen, C.W.V.; Pelly, S.C.H.; Steenkamp, P.H.; Hoppe, C.; Khan, T.; Nkabinde, L.A. Imidazo[1,2-*a*]pyridin-3-amines as potential HIV-1 non-nucleoside reverse transcriptase inhibitors *Bioorg. Med. Chem*. **2011**, 19, 4227–4237.

2. Knölker, H.J.; Reddy, K.R. Chemistry, and biology of carbazole alkaloids. *Alkaloids* **2008**, 65, 1.
3. Groebke, K.; Weber, L.; Mehlin, F. Synthesis of Imidazo[1,2-*a*] annulated Pyridines, Pyrazines and Pyrimidines by a Novel Three-Component Condensation. *Synlett* **1998**, *6*, 661–663.
4. Pharande, S.G.; Rentería-Gómez, M.A.; Gámez-Montaño, R. Mechanochemical IMCR and IMCR-Post Transformation Domino Strategies: Towards the Sustainable DOS of Dipeptide-like and Heterocyclic Peptidomimetics. *New J. Chem.* **2022**.
5. Unnamatla, M.V.B.; Islas-Jácome, A.; Quezada-Soto, A.; Ramírez-López, S.C.; Flores-Álamo, M.; Gámez-Montaño, R. Multicomponent One-Pot Synthesis of 3-Tetrazolyl and 3-Imidazo[1,2-*a*]Pyridin Tetrazolo[1,5-a]Quinolines. *J. Org. Chem.* **2016**, *81*, 10576–10583.
6. Rentería-Gómez, M.A.; Islas-Jácome, A.; Pharande, S.G.; Vosburg, D.A.; Gámez-Montaño, R. Synthesis of Tris-Heterocycles via a Cascade IMCR/Aza Diels-Alder + CuAAC Strategy. *Front. Chem.* **2019**, *7*.
7. Pharande, S.G.; Corrales Escobosa, A.R.; Gámez-Montaño, R. Endogenous Water-Triggered and Ultrasound Accelerated Synthesis of 1,5-Disubstituted Tetrazoles via a Solvent and Catalyst-Free Ugi-Azide Reaction. *Green Chem.* **2017**, *19*, 1259–1262.
8. Meenakshisundaram, S., et al. Design, synthesis, and anticancer activity of novel hybrid compounds of imidazopyridine and quinoline/carbazole. *J. Chem. Pharm. Res.* **2016**, *8*, 576–582.
9. Kurva, M., Pharande, S. G., Quezada-Soto, A., & Gámez-Montaño, R. Ultrasound assisted green synthesis of bound type bis - heterocyclic carbazolyl imidazo[1,2-a]pyridines via Groebke-Blackburn-Bienayme reaction. *Tetrahedron Lett.* **2018**, *59*, 1596–1599.