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One Pot Synthesis of Imidazo[1,2-*a*]pyridines via Groeke-Blackburn-Bienaymé Reaction-CuAAC Assisted by MW †

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Abstract: Bis-heterocyclic compounds containing imidazo[1,2-a]pyridines (IMPs) are privileged heterocyclic drug scaffolds due to their potential applications. The Groebke-Blackburn-Bienaymé reaction (GBBR) are greener alternative to synthesize IMPs. On the other hand 1,2,3-triazole scaffolds are biososteres of the trans amide, its incorporation in bioactive molecules provides advantages such as resistance to cleavage mediated by proteases and improved stability, in this context the CuAAC reaction is the most efficient approach to synthesize 1,4-disustituted-1,2,3-triazoles. Herein we described a novel one pot synthesis of IMPs by the GBBR-CuAAC strategy assisted by microwave irradiation.

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

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1. Introduction

The imidazo[1,2-*a*]pyridines (IMPs) have been identified as a highly versatile building block in synthetic organic chemistry, due to their diverse biological activities such as antifungal, antiviral, anticancer, antibacterial, anti-inflammatory, anthelmintic, analgesic, antituberculosis, antipyretic and antiepileptic. Additionally several IMPs have been studied for their optical properties with their possible applications in cell imaging, metal sensing and OLEDs [1]. Bis-heterocyclic compounds combine two heterocyclic cores with different connectivity such as linked, bound, spaced or fused [2]. In particular *bis*-heterocycles containing IMPs are privileged heterocyclic drug scaffolds [3].

On the other hand the 1,2,3-triazole scaffolds are biososteres of the *trans*-amide bond [4], and they are of great interest in the design of novel heterocycles compounds with potential applications in medicinal chemistry, its incorporation provides advantages such as resistance to proteases and improved stability under hydrolytic, oxidative, and reducing conditions [5]. IMPs connected to 1,4-disustituted-1,2,3-Ts (1,4-DS-1,2,3-Ts) have been reported for their biological properties (Figure 1) [6].

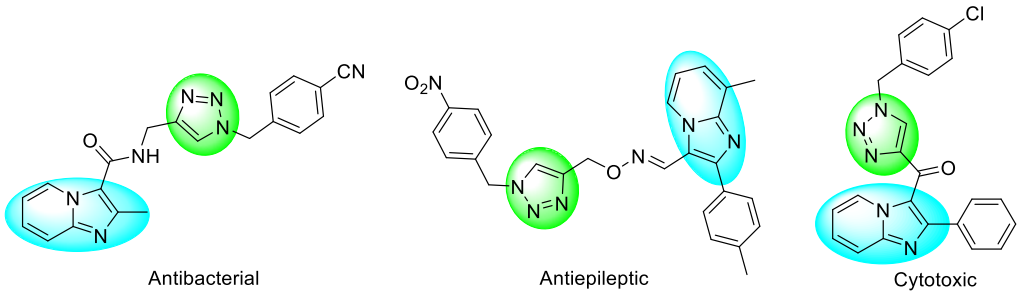
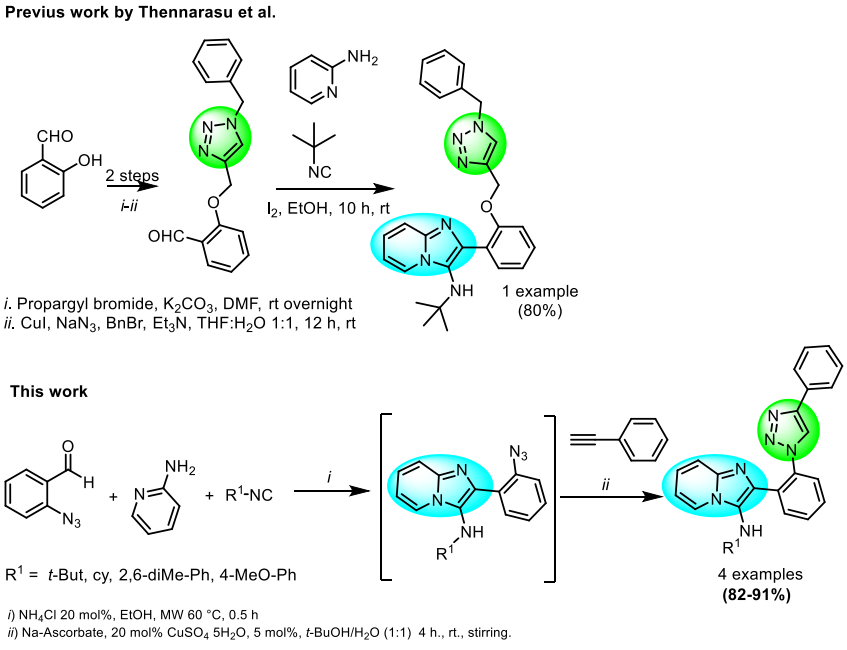


Figure 1. Biological activities of IMPs connected to 1,4-DS-1,2,3-Ts.

The most common methods to synthetized IMP implies transition metal-catalyzed, condensation reactions, cyclization reactions, heteroannulation and photocatalytic reactions. Nevertheless, in the majority of instances, they are subjected to harsh conditions, such as high temperatures, non-ecofriendly solvents, sideproducts, long reaction time, expensive, low yields and limited scope [7].

In this context the multicomponent reactions (IMCRs) represent the most efficient synthetic tools for the organic synthesis, exhibiting high overall yields, convergence, atomic economy and broad scope [8], for example the IMCR Groebke-Blackburn-Bienaymé reaction (GBBR) attracted the scientific community, since its discovery it's the best methodology to synthesize imidazo[1,2-*a*] pyridine-3-amines [9]. The use of alternative energy source (AES) in GBB allowed chemical activation as well as accelerated and cleaner reactions, for example the MW irradiation allowed homogeneous and efficient temperature increase by the effect of dielectric heating [10].

On the other hand, 1,3-dipolar Copper-catalyzed Alkyne-Azide Cycloaddition (CuAAC) is the most efficient approach to synthesize 1,4-DS-1,2,3-TS [11]. The IMCR coupled with post-transformations strategy has emerged as a research field for the synthesis of novel molecules, with potential application in several fields [12]. As far as our survey of the literature is concerned, few reports of the synthesis of IMPs connected to 1,4-DS-1,2,3-Ts by IMCR processes have been reported (Scheme 1) [13].



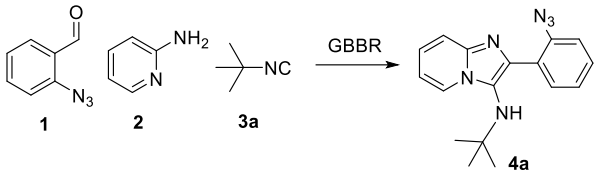
Scheme 1. Previous reports of synthesis of IMPs connected to 1,4-DS-1,2,3-Ts.

Herein we report the synthesis one pot of bis-heterocyclic IMPs-1,4-disustituted-1,2,3-triazoles by GBBR-CuAAC strategy assisted by AES.

2. Results and Discussion

The optimization of the reactions was conducted by use of orthogonal 2-azidobenzaldehyde (1), 2-aminopyridine (2), and tert-butyl isocyanide (3a), employing NH_4Cl [14] as green catalyst under conventional conditions (Table 1, Entry 1), giving the desired product at a 82% yield. To decrease the reaction time, the procedure was conducted at 60 °C, resulting in 8 h with a comparable yield (Entry 2). The reaction was performed with the assistance of MW energy source, which yielded the desired product in a more efficient manner, with a yield of 89% and a reduction in the reaction time to 30 min (Entry 3).

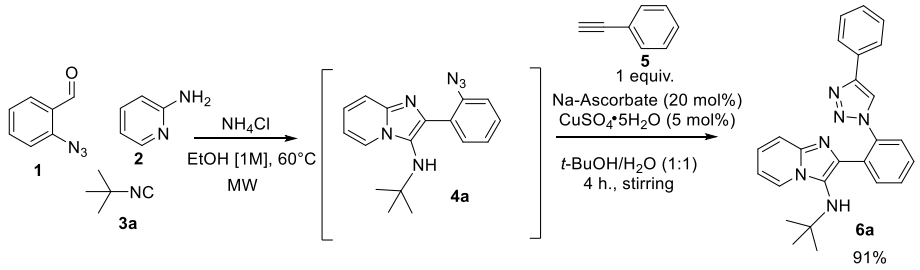
Table 1. Screening conditions for the synthesis of **4a.**



Entry [a]	Catalyst [b]	Solvent [1.0 M]	Time (h)	Temp °C	Yield [d]
1	NH_4Cl	EtOH	24	rt	82
2	NH_4Cl	EtOH	8	60	80
3 [c]	NH_4Cl	EtOH	0.5	60	89

[a] 2-azidobenzaldehyde (1, 1.0 equiv.), 2-aminopyridine (2, 1.0 equiv.), tert-butyl isocyanide (3a, 1.0 equiv.); [b] 20 mol%; [c] MW (150 W); [d] Isolated yields.

After optimizing the conditions, we explored the one pot reaction to synthetize **6a** via GBBR/CuAAC strategy, according with the Sharpless conditions for the click reaction (Scheme 2) [11].



Scheme 2. One-pot optimization for the synthesis of via GBBR/CuAAC strategy.

Aditionally we explored the versatility of the methodology through variations of isocyanide reagents. The respective imidazo[1,2-*a*]pyridine-1,2,3-triazoles (**6a–d**, Figure 2) synthesized under AES were obtained in good yields (82–91%).

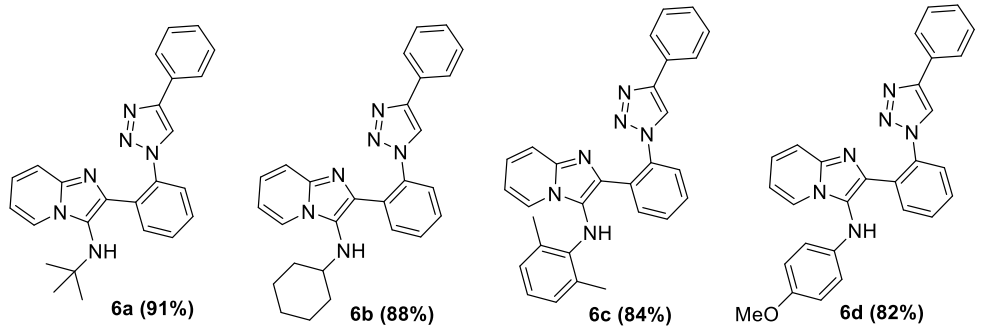


Figure 2. Substrate scope of imidazo[1,2-*a*]pyridine-1,2,3-triazoles.

3. Experimental Section

3.1. General Information, Instrumentation, and Chemicals

The ^{1}H and ^{13}C NMR spectra were acquired on Bruker Avance III spectrometers (500 MHz). Deuterated chloroform ($CDCl_3$) was used. Chemical shifts are reported in parts per million (δ/ppm). The internal reference for NMR spectra was tetramethylsilane (TMS) at 0.0 ppm. Coupling constants are reported in Hertz (J/Hz). Multiplicities of signals are reported using the standard abbreviations: singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). NMR spectra were analyzed using MestreNova software version 10.0.1-14719. IR spectra were acquired on a Perkin Elmer 100 spectrometer. High-resolution mass spectrometry (HRMS) samples were ionized in Electrospray ionization (ESI) mode and recorded via the time-of-flight (TOF) method. 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 Kieselgel 60 F254 plates and spots were visualized under UV light at 254 or 365 nm. Mixtures of hexanes with ethyl acetate (EtOAc) were used as eluents for TLC and for measuring retention factors (Rf). Flash column chromatography was performed using silica gel (230–400 mesh) and mixtures of hexanes with EtOAc in different proportions (*v*/*v*) as mobile phase. Melting points were determined on an electrothermal apparatus and were uncorrected. All starting materials 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 MW sealed-tube 10 mL equipped with a magnetic stirring bar, was added azidobenzaldehyde (1, 1.0 equiv.), 2-aminopyridine (**2**, 1 equiv.), the corresponding isocyanide (**3a**–**d**, 1 equiv.), and NH_4Cl (20% mol) were disolven in EtOH (1M) and the reaction mixture was MW heated (150 W, 60 °C) for 30 min. The reactions were monitored by TLC and once the starting materials disappeared, the solvent was removed to dryness and the residue was diluted in tert-BuOH/H_2O (1:1 *v*/*v*) [0.3 M], and the phenylacetylene (**5**, 1.0 equiv.) was added. Sodium ascorbate (0.20 equiv.) and $CuSO_4$*$5H_2O$ (0.05 equiv.) were added sequentially. Then, the vial was closed, and the reaction mixture was stirred at room temperature and monitored by TLC. Once the starting material disappeared, the reaction mixture was diluted in water (5.0 mL) and extracted with ethyl acetate (2 × 10 mL). The organic layer was washed with water (2 × 10 mL) and brine (2 × 10 mL). The new organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford the crude product. The residue was purified by flash chromatography to afford the corresponding imidazo[1,2-a]pyridines-1,2,3-triazole **6a**–**d**.

3.3. Spectral Data

*3.3.1. Characterization of the N-(tert-*butyl)-2-(2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)phenyl) imidazo[1,2-*a*]pyridin-3-amine(**6a**)

Brown oil, 91%; R_f = 0.32 (Hexanes/EtOAc, 3:7); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.27–8.21(m, 1H), 7.93–7.88 (m, 1H), 7.83 (s, 1H), 7.78–7.70(m, 3H), 7.70–7.60 (m, 3H), 7.40–7.28 (m, 4H), 6.95–6.87 (m, 1H), 2.70 (s, 1H), 0.92 (s, 9H).; ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ 147.8, 140.8, 135.9, 132.8, 130.2, 130.0(2), 128.8, 128.6, 128.4, 127.2, 126.5, 126.1, 125.8, 124.1, 122.1, 116.0, 113.2, 55.9, 29.9.; HRMS (ESI^+):*m*/*z* calcd. for $C_{25}H_{25}N_6^+$ $[M + H]^+$ 409.2135, found 409.2133.

3.3.2. Characterization of the N-cyclohexyl-2-(2-(4-phenyl-1H-1,2,3-triazol-1-yl)phenyl) Imidazo [1,2-a]pyridin-3-amine (**6b**)

Brown oil, 88%; R_f = 0.33(hexanes/EtOAc, 3:7); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 8.04–8.00 (m,1H), 7.85 (s, 1H), 7.82–7.78 (m, 1H), 7.72–7.67 (m, 3H), 7.64–7.58 (m, 3H), 7.38–

7.33 (m, 2H), 7.30–7.27 (m, 1H), 7.22–7.18 (m, 1H), 6.84–6.68 (m, 1H), 2.67 (s, 1H), 2.63–2.55 (m, 1H), 1-59–1.49 (m, 4H), 1.48–1.43 (m, 1H), 1.06–1.02 (m, 2H), 0.98–0.93 (m, 2H), 0.89–0.84 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 147.6, 141.0, 136.0, 132.5, 130.1, 129.9, 129.6, 129.0, 128.8, 128.2, 127.0, 126.3, 125.8, 125.5, 123.3, 122.0, 116.7, 112.6, 56.3, 33.6, 25.5, 24.4; HRMS (ESI^+):*m*/*z* calcd. for $C_{27}H_{27}N_6^+$ $[M + H]^+$ 435.2292, found 435.2306.

3.3.3. Characterization of the N-(2,6-Dimethylphenyl)-2-(2-(4-phenyl-1H-1,2,3-triazol-1-yl)phenyl) Imidazo[1,2-a]pyridin-3-amine (**6c**)

Brown oil, 84%; Rf = 0.30(hexanes/EtOAc, 3:7); 1H NMR (500 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.76–7.71 (m, 2H), 7.61–7.54 (m, 2H),7.53–7.44 (m, 4H),7.40–7.35 (m, 2H), 7.32–7.26 (m, 1H), 7.14–7.07 (m, 1H), 6.86–6.79 (m, 2H), 6.70–6.74 (m, 1H), 6.67–6.62 (m, 1H), 5.15 (s, 1H), 1.79 (s, 6H); 13C NMR (126 MHz, CDCl3, 25 °C): δ 147.5, 141.2, 140.0, 136.4, 133.9, 132.1, 130.2, 129.9, 129.5, 129.3(2), 128.9, 128.3, 126.9, 125.8, 125.6, 124.1, 123.9, 122.5, 122.9, 122.1, 121.6, 117.7, 112.4, 18.2; HRMS (ESI^+):*m*/*z* calcd. for $C_{24}H_{25}N_6^+$ [M + H]+ 457.2135, found 457.2142.

3.3.4. Characterization of the N-(4-Methoxyphenyl)-2-(2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)phenyl) Imidazo[1,2-*a*]pyridin-3-amine (**6d**)

Brown oil, 82%; R_f = 0.29(hexanes/EtOAc, 3:7); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.89 (s, 1H), 7.77–7.72 (m, 3H), 7.67 (d, *J* = 6.8 Hz, 1H), 7.58–7.49 (m, 4H), 7.40–7.35 (m, 2H),.7.33–7.28 (m, 1H),.7.18 (t, *J* = 6.8 Hz, 1H), 6.72 (t, *J* = 6.8 Hz, 1H), 6.62 (d, *J* = 8.8 Hz, 2H), 6.26 (d, *J* = 8.8 Hz, 2H), 5.34 (s, 1H); 3.65 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ 153.3, 147.5, 142.5, 137.9, 135.8, 135.4, 132.3, 130.2, 129.9, 129.8, 129.3, 128.8, 128.2, 126.2, 125.7, 124.9, 123.4, 122.0, 121.5, 117.8, 114.9, 114.6, 112.3, 55.6.HRMS (ESI^+):*m*/*z* calcd. for $C_{28}H_{23}N_6O^+$ $[M + H]^+$ 459.1927, found 459.1934.

4. Conclusions

This is a contribution for the multicomponent one-pot processes in the design of novel drug scaffolds like analogs of IMPs incorporating conformationally restricted bioisostere of amide bond. The bis-heterocycles containing privileged IMP and triazole cores, adding aggregate value increasing their possible applications in medicinal chemistry. The developed strategy contributes to the multicomponent and click chemistry fields.

Author Contributions: writing—original draft preparation, investigation, M.A.R.-G.; investigation, D.C.-R.; resources, formal analysis, A.C.-D.; methodology, writing original manuscript, R.G.-M. All authors have read and agreed to the published version of the manuscript.

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