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Proceeding Paper

Multicomponent one-pot synthesis of imidazo[1,2-*a*]pyridine functionalized with azides †

Diana García-García [1], Jorge Alejandro Tovar-Rosales [1], Indhira A. González-Gámez [2] and Rocío Gámez-Montaño [1,*]

[1] Departamento de Química, Universidad de Guanajuato, Noria Alta S/N, Col. Noria Alta, Guanajuato 36050, Mexico; diana13g@hotmail.com (D.G.-G.); joralextovar@hotmail.com (J.A.T.-R.)
[2] Arkansas State University Campus Querétaro, km 17.5 Estatal 100, Colón 76270, Querétaro, Mexico; indhi.08.agg@gmail.com
* Correspondence: rociogm@ugto.mx; Tel.: +52-473-732-006 (ext. 8191)
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Abstract: Imidazo[1,2-a]pyridine (IMPs) are valuable heterocycles, present in bioactive compounds and drugs. Analogs that incorporate azide moieties are useful intermediates in organic synthesis and can be used as synthetic platforms to access more complex products. Isocyanide-based multicomponent reaction such as Groebke-Blackburn-Bienaymé (GBB-3CR) are versatile tools to synthesized IMPs, in which orthogonal reagents included into components to increase its synthetic potential. Herein we developed a one-pot process to access IMPs functionalized with azides under mild conditions, which are synthetic platforms for further post-transformations.

Keywords: imidazo[1,2-a]pyridine, azides, IMCR, GBB-3CR, one-pot

1. Introduction

Imidazo[1,2-*a*]pyridine are nitrogen fused heterocycles which are acknowledged as privileged molecules due their wide range of properties in medicinal chemistry, including anti-diabetic, anti-cancer, anti-viral, anti-ulcer, anti-microbial, anti-IHV, hypnotic, analgesic and antipyretic activities [**1**]. These scaffolds are also valuable for other fields like bioimaging, probes or chemosensors, due to their optoelectronic properties, which include high quantum yields, large Stokes shifts, and good stability [**2,3**].

On the other hand, organic azides are valuable intermediates in organic synthesis for constructing diverse nitrogen-containing heterocycles via intra- or intermolecular C-N and N-N bond formation. This are not found in nature, to our knowledge, only the antiviral drug zidovudine incorporates this group [**4**].

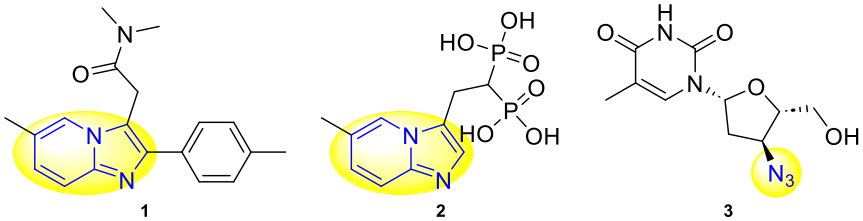

Figure 1. Bioactive molecules containing imidazo[1,2-a]pyridine scaffold and azide group.

One-pot processes that include multicomponent reactions are the most efficient, robust, and sustainable synthetic tools for the synthesis of valuable molecules. Among these, isocyanide-based multicomponent reactions stand out as the most versatile and effective tools for the synthesis of heterocyclic molecules directly or via post-transformation.

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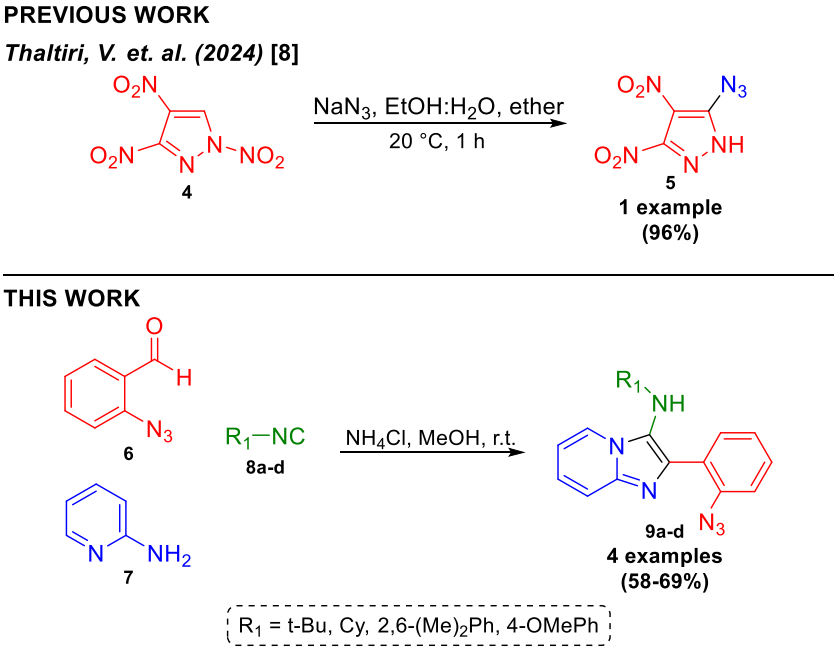
Specifically, the Groebke-Blackburn-Bienaymé reaction (GBB-3CR) is the most effective tool for accessing IMPs. This reaction involves an aldehyde or ketone, an amidine and an isocyanide, with Lewis or Bronsted acid catalysis. The reactivity of the endocyclic nitrogen in the amidine component allows the intramolecular nitrilium ion trapping, leading to the formation of the heterocyclic scaffold, whereas the acid component is not incorporated in the final products as in classical Ugi reaction [**5-7**].



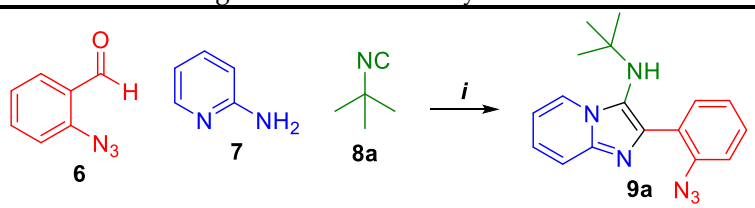
Scheme 1. Previous report of synthesis of IMPs functionalized with azides.

Herein we developed the one-pot synthesis under mild conditions to access IMPs functionalized with azide, using ammonium chlorine as a catalyst. The resulting GBB products could serve as synthetic platforms for further post-transformations.

2. Results and Discussion

The synthesis of imidazo[1,2-a]pyridine (**9a**) was made via GBB-3CR reaction between 2-azidobenzaldehyde (**6**), 2-aminopyridine (**7**), and *tert*-butyl isocyanide (**8a**), in MeOH as solvent. We used green catalysts, ammonium chloride and *p*-toluensulfonic acid, which resulted in moderate yields at room temperature (**Table 1**, **entries 1-2**). Since a higher yield was obtained with ammonium chloride, it was selected for the synthesis of GBB-3CR product.

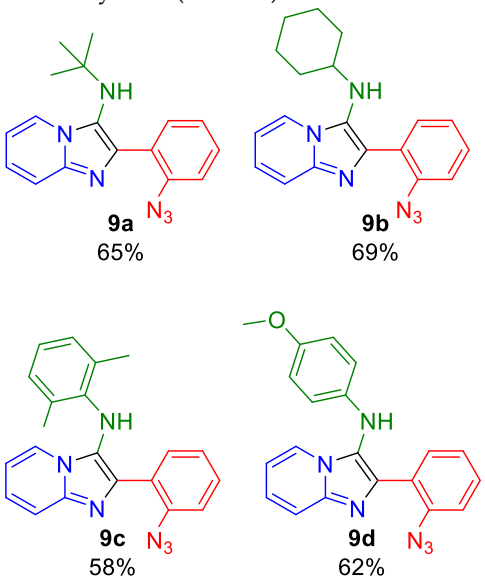
Table 1. Screening conditions for the synthesis of molecule **xa**.



Entry	Solvent	Catalyst (20 mol%)	Temperature	Time	Yield (%)
1	**MeOH**	**NH_4Cl**	**r.t.**	**24 h**	**65**
2	MeOH	p-TsOH	r.t.	24 h	59

In **Scheme 2**, a series of imidazo[1,2-a]pyridine (**9a-d**) is depicted, which was synthesized under the optimized conditions. The effect of the stereo-electronic nature of the isocyanide

component was evaluated, employing aliphatic and aromatic isocyanides. Finally, products were obtained in moderate yields (**58-69%**).



Scheme 2. Synthesis of imidazo[1,2-a]pyridine scope.

3. Experimental Section

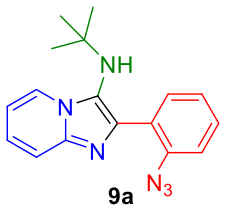
3.1 General Information, Intrumentation and Chemicals

^{1}H and ^{13}C NMR spectra were acquired on Bruker Advance III spectrometer (500 MHz). The solvent used for NMR spectroscopy was deuterated chloroform ($CDCl_3$). Chemical shifts (δ) are given in ppm relative to tetramethylsilane (TMS). Coupling constants are reported in Hertz (Hz). Multiplicities of the signals are reported using standard abbreviations: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). NMR spectra were analyzed using MestReNova software version 14.2.0-26256. Reaction progress was monitored by thin-layer chromatography (TLC) on pre-coated silica gel F254 aluminum sheets, and the spots were visualized under UV light at 254 nm. Column chromatography was performed using silica gel (230-400 mesh) as stationary phase. Mixtures of hexanes and ethyl acetate were used as mobile phase for column chromatography and in TLC for reaction progress monitoring and measuring retention factors (R_f). All reagents were purchased from Sigma Aldrich and were used without purification.

3.2 General Procedure

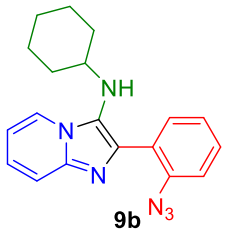
In a sealed vial, 2-azidobenzaldehyde (**6**, 1.0 equiv.), 2-aminopyridine (**7**, 1.0 equiv.), isocyanide (**8a-d**, 1.0 equiv.) and ammonium chloride (0.2 equiv.) were dissolved in MeOH (1.0 M) and stirred at room temperature for 24 h. The solvent was removed, and the crude was purified by flash chromatography using silica gel and mixtures of ethyl acetate in hexanes as mobile phase and silica gel as stationary phase to afford the corresponding imidazo[1,2-a]pyridine (**9a-d**).

3.3 Spectral Data



2-(2-azidophenyl)-N-(tert-butyl)imidazo[1,2-a]pyridine-3-amine (**9a**)

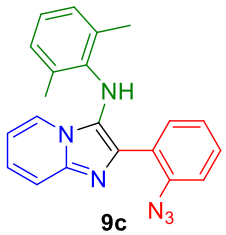
Brown oil, R_f = 0.24 (40 % ethyl acetate in hexanes), ^{1}H (500 MHz, $CDCl_3$, 25 °C, TMS): δ 8.37 – 8.26 (m, 1H), 7.82 – 7.75 (m, 1H), 7.75 – 7.67 (m, 1H), 7.42 – 7.36 (m, 1H), 7.26 – 7.18 (m, 3H), 6.90 – 6.80 (m, 1H), 3.60 (s, 1H), 0.88 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) 141.6, 137.0, 134.8, 132.3, 129.5, 126.4, 125.5, 125.3, 125.1, 123.7, 118.2, 116.7, 112.0 56.0, 29.8.



9b

2-(2-azidophenyl)-N-cyclohexylimidazo[1,2-a]pyridine-3-amine (**9b**)

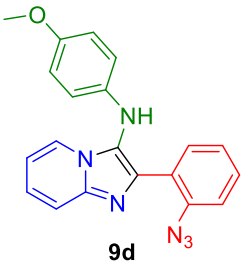
Brown oil, R_f = 0.24 (40 % ethyl acetate in hexanes), ^{1}H (500 MHz, $CDCl_3$, 25 °C, TMS): δ 8.13 (dt, J = 6.9, 1.3 Hz, 1H), 7.78 (dd, J = 7.7, 1.7 Hz, 1H), 7.54 (dd, J = 9.1, 1.3 Hz, 1H), 7.43 (td, J = 7.7, 1.6 Hz, 1H), 7.30-7.24 (m, 2H), 7.13 (dd, J = 9.1, 1.3 Hz, 1H), 6.80 (td, J = 6.7, 1.2 Hz, 1H), 3.78-3.71 (m, 1H), 2.68-2.61 (m,1H), 1.74-1.69 (m, 1H), 1.64-1.56 (m, 2H), 1.52-1.45 (m, 1H), 1.15-0.97 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) 142.0, 137.0, 133.7, 132.5, 129.2, 127.2, 126.7, 125.5, 123.8, 123.0, 118.4, 117.6, 111.7, 56.8, 34.2, 25.8, 24.9.



9c

2-(2-azidophenyl)-N-(2,6-dimethylphenyl)imidazo[1,2-a]pyridine-3-amine (**9c**)

Brown oil, R_f = 0.19 (40 % ethyl acetate in hexanes), ^{1}H (500 MHz, $CDCl_3$, 25 °C, TMS): δ 7.64 (dt, J = 6.8, 1.2 Hz, 1H), 7.61-7.57 (m, 2H), 7.38-7.34 (m, 1H), 7.20-7.11 (m, 3H), 6.88 (d, J = 7.4 Hz, 2H), 6.76-6.69 (m, 2H), 5.75 (s, 1H), 1.91 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) 141.4, 139.9, 137.8, 134.3, 131.9, 129.5, 129.4, 126.8, 126.4, 125.2, 123.7, 123.1, 122.4, 121.6, 118.2, 117.9, 112.3, 18.4.



9d

2-(2-azidophenyl)-N-(4-methoxyphenyl)imidazo[1,2-a]pyridine-3-amine (**9d**)

Brown oil, R_f = 0.17 (40 % ethyl acetate in hexanes), ^{1}H (500 MHz, $CDCl_3$, 25 °C, TMS): δ 7.80 (dt, *J* = 6.7, 1.2 Hz, 1H), 7.72 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.65 (dt, *J* = 9.1, 1.1 Hz, 1H), 7.40-7.34 (m, 1H), 7.24- 7.16 (m, 3H), 6.78 (td, *J* = 6.7, 1.1 Hz, 1H), 6.72 (d, *J* = 8.9 Hz, 2H), 6.42 (d, *J* = 9.0 Hz, 2H), 5.97 (s, 1H), 3.70 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 153.6, 142.6, 138.3, 137.5, 135.5, 132.2, 129.6, 126.1, 125.3, 124.6, 123.3, 121.4, 118.6, 117.9, 115.2, 115.1, 112.2, 55.8.

4. Conclusions

Finally, the present work contributes in the design and development of novel green multicomponent one-pot synthesis via GBB-3CR, under mild conditions. The orthogonal reagents in GBB-3CR allow to increase synthetic potential of a series of imidazo[1,2-a]pyridine functionalized with azides.

Author Contributions: Conceptualization, R.G.-M.; methodology, D.G.-G., J.A.T.-R. and I.A.G.-G.; software, D.G.-G.; validation, R.G.-M.; formal analysis, R.G.-M.; investigation, D.G.-G.; resources, R.G.-M.; data curation, D.G.-G.; writing—original draft preparation, D.G.-G.; writing—review and editing, R.G.-M.; visualization, R.G.-M.; supervision, R.G.-M.; project administration, R.G.-M.; funding acquisition, R.G.-M. All authors have read and agreed to the published version of the manuscript.

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