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# Synthesis of Imidazo[1,2-*a*]pyridines via Multicomponent GBBR Using α-isocyanoacetamides †

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**Abstract:** Six novel imidazo[1,2-*a*]pyridines were synthesized by Groebke–Blackburn–Bienaymé reactions (GBBRs) under eco-friendly conditions (10 mol% ammonium chloride catalyst in EtOH at room temperature) with moderate to good yields (76–44%) using 2-isocyano-1-morpholino-3-phenylpropan-1-one. This is the first successful use of this type of α-isocyanoacetamide in a GBBR, as these reactive isonitriles readily undergo ring-chain tautomerization, as reported in other IMCRs (isonitrile-based multicomponent reactions). The product structures contain a peptidomimetic imidazo[1,2-*a*]pyridine scaffold linked to an α-aminomorpholide and are of interest to medicinal chemists.

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

## 1. Introduction

Nitrogen-fused heterocycles are becoming more popular because of their wide range of pharmacological and biological properties. Among them, nitrogen-fused azoles such as imidazo[1,2-*a*]pyridines have attracted interest over the past decade due to their widespread applications in medicinal chemistry, organometallics, optics, and materials science [1]. These scaffolds are present in many commercially available drugs such as olprinone (cardiotonic agent), miroprofen (analgesic), DS-1 (GABA receptor agonist), zolimidine (peptic ulcers), GSK812397 (HIV infection), and minodronic acid (osteoporosis) [2–4]. Imidazo[1,2-*a*]pyridines are termed as non-benzodiazepine drugs because they possess similar pharmacological properties to benzodiazepines but differ structurally; examples include alpidem (**1**, anxiety), zolpidem (**2**, insomnia), saripidem (**3**, sedative), and necopidem (**4**, anxiolytic) [5,6]. Additionally, the synthesis of bioimaging probe **5** for benzodiazepine receptors has recently been reported [7]. All of the examples mentioned above contain an amide fragment in their structures (Figure 1).

The most common methodologies for the synthesis of imidazo[1,2-*a*]pyridines are (i) the condensation of 2-aminopyridines with α-halo carbonyl compounds [8], which suffers from limitations such the scarcity of commercially available α-halo carbonyl compounds and their lachrymatory properties; (ii) copper-catalyzed three-component reactions of 2-aminopyridines, aldehydes, and alkynes [9]; and (iii) Grobke–Blackburn–Bienaymé reactions (GBBRs) between an aldehyde, a 2-aminoazine, and an isocyanide [10–12].

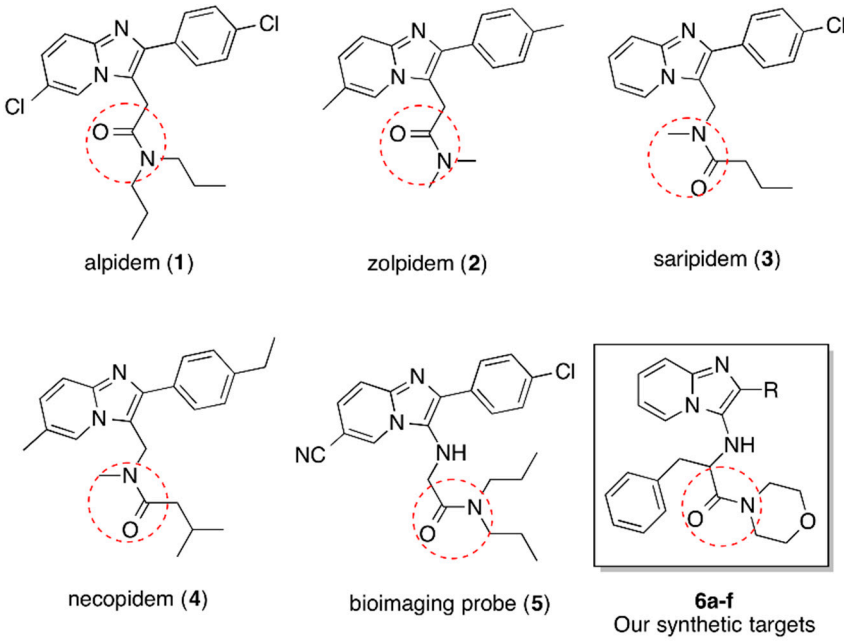
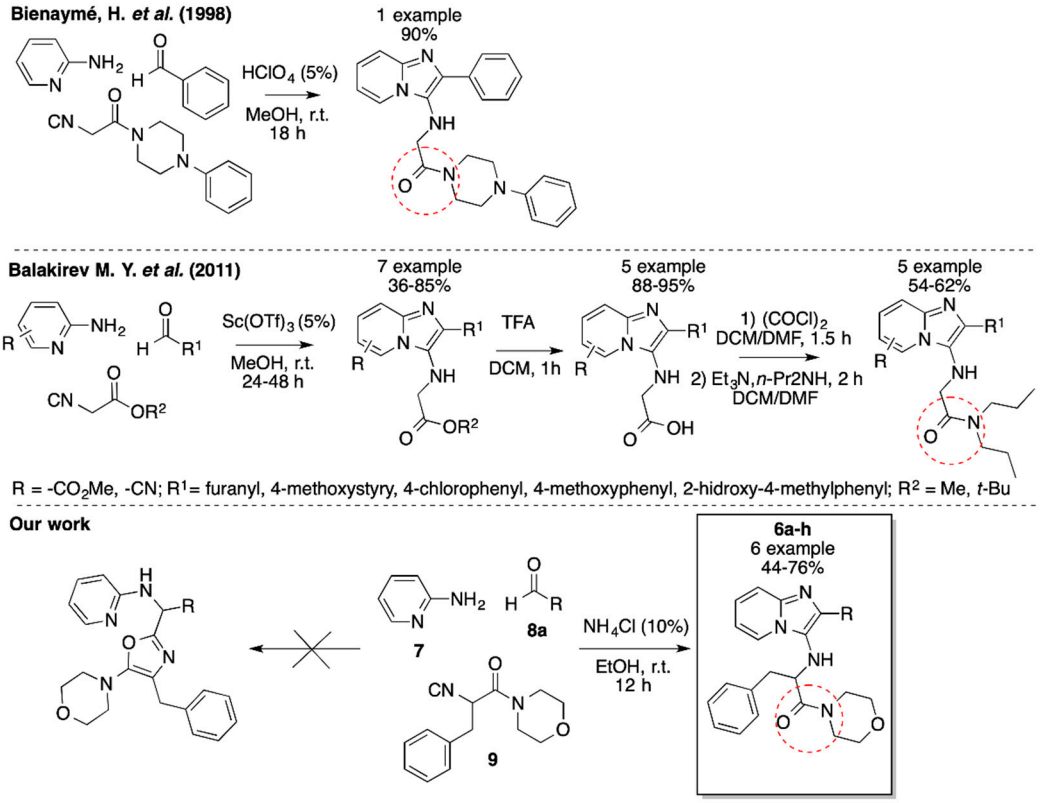



**Figure 1.** Selected imidazo[1,2-*a*]pyridines with pharmacological activity and our synthetic targets.

In modern synthetic chemistry, there is an urgent need to design and develop new green and efficient methodologies to synthesize complex molecules from simple materials with high atom economy. The isocyanide-based multicomponent reaction (IMCR) is a powerful tool that plays a central role in the synthesis of heterocycles [13]. The GBBR is one of the most common and efficient methodologies to synthesize imidazole analogues and the method of choice to synthesize imidazo[1,2-*a*]pyridine-3-amines. Normally, this reaction requires a solvent and a catalyst [5,6]. Various GBBR procedures have been reported, using catalysts such as Lewis acids, Bronsted acids, solid supports, organic bases, and inorganic salts [14]. Each of these methodologies has drawbacks such as high temperature, low yields, expensive catalysts, and/or non-green solvents. The design and development of improved GBBR procedures using green solvents and catalysts at room temperature is an underexplored field. There are few GBBR reports available towards imidazo[1,2-*a*]pyridine-3-amines describing the use of green catalysts [15,16]. For these reasons, it is necessary to increase efforts to develop new, efficient, mild methodologies using green, inexpensive, and readily available catalysts and solvents.

*α*-isocyanoacetamides present exceptional reactivity because they can undergo intramolecular ring closure. For this reason, they have been extensively explored in certain IMCRs as an Ugi three component reaction [17]. On the other hand, the use of this type of isonitrile in GBBRs is practically unexplored; in fact, there is only one such previous report, by Bienaymé in 1998 (see Scheme 1) [12].

The methodology described here allows the one-pot synthesis of new imidazo[1,2-*a*]pyridine-3-amines that incorporate a peptidomimetic amide fragment in the isonitrile reactant. To the best of our knowledge, the only other published method for access to this type of compound uses a synthesis strategy of GBBR followed by deprotection and peptide coupling steps (Scheme 1, Valakirev, M.Y. et al.) [7]. Therefore, the methodology described here is attractive due to the use of green reaction conditions and access to the final products in a single stage.

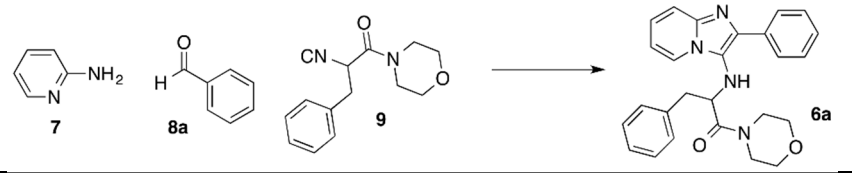



**Scheme 1.** Previous reports and our work.

## 2. Results and Discussion

In order to develop green conditions for the GBBR, we started the synthesis of imidazo[1,2-*a*]pyridine-3-amine analogue **6a** by reacting equimolar amounts of 2-aminopyridine (**7**), benzaldehyde (**8a**), and 2-isocyano-1-morpholino-3-phenylpropan-1-one (**9**). In concordance with our main line of research, green conditions were studied to optimize the reaction. Initially we performed the GBBR under neat conditions at room temperature, generating product **6a** in poor yield (10%) after 5 h (Entry 1, Table 1) [18]. When the reaction was performed in water as solvent (Entry 2), only 8% of compound **6a** was obtained. Changing the solvent to EtOH (Entry 3) increased the yield to 46%. Seeking a green, inexpensive, and easily available catalyst, we decided to try the reaction with a catalytic amount of $NH_4Cl$ at room temperature [19]. This raised the product yield to 72% (Entry 4). The use of iodine and montmorillonite (K-10) as catalysts in GBBR is well-documented [20–24], so we decided to try those catalysts in our methodology. Unfortunately, catalytic iodine or montmorillonite at room temperature resulted in lower yields of 49% and 66%, respectively (Entries 5–6). We then tested phenyl phosphinic acid, which is not a known catalyst for the GBBR, but this catalyst did not result in an improved yield (67%, Entry 7). Performing the $NH_4Cl$-catalyzed reaction at 60 °C lowered the yield of product **6a** to 49% (Entry 8, Table 1), which can be attributed to the low stability of this isocyanide in acidic media at elevated temperatures. Indeed, we detected the corresponding oxazole **13**, resulting from chain-ring tautomerization of isocyanide **9**, as a by-product.

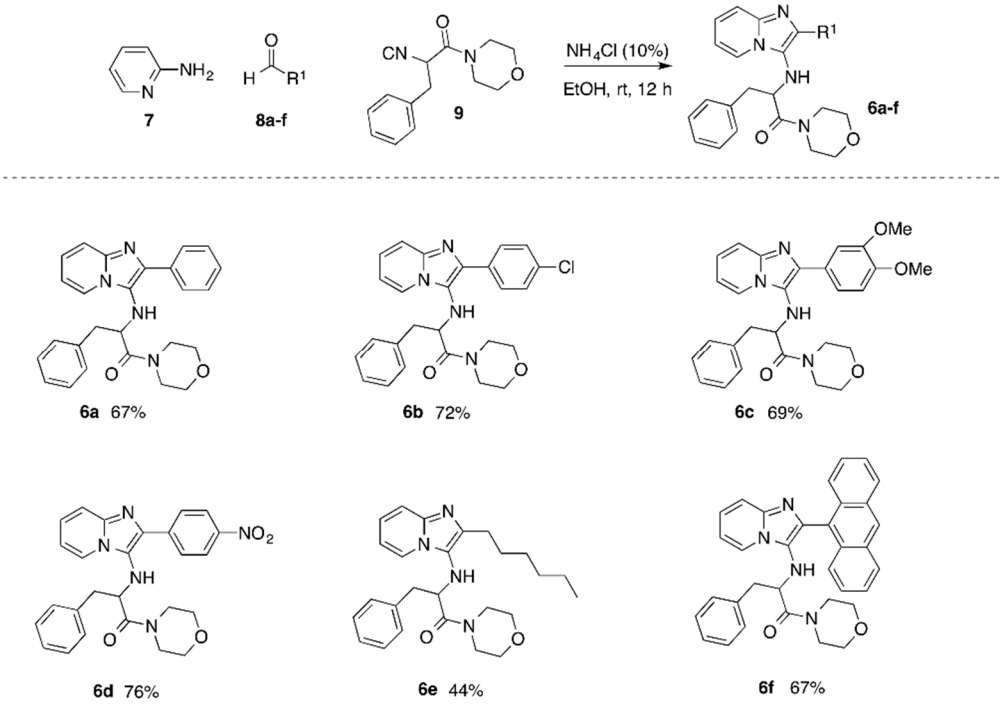
**Table 1.** Screening conditions for synthesis of imidazo[1,2-*a*]pyridine-3-amine **6a**.




| Entry [a] | Solvent [b] | Aditive | T (°C) | Yield (%) [c] |
|---|---|---|---|---|
| **1** | --- | --- | rt | 10 |
| **2** | $H_2O$ | --- | rt | 8 |
| **3** | EtOH | --- | rt | 46 |
| **4** | **EtOH** | **$NH_4Cl$** | **rt** | **72** |
| **5** | EtOH | $I_2$ | rt | 49 |
| **6** | EtOH | K-10 | rt | 66 |
| **7** | EtOH | Phenyl phosphinic acid | rt | 67 |
| **8** | EtOH | $NH_4Cl$ | 60 | 49 |

[a] All reactions were carried out using equimolar amounts of **7**, **8a**, and **9** for 12 h. [b] [1.0 M] [c] Isolated yield. rt = room temperature. In all reactions, oxazole **13** was detected as a by-product.

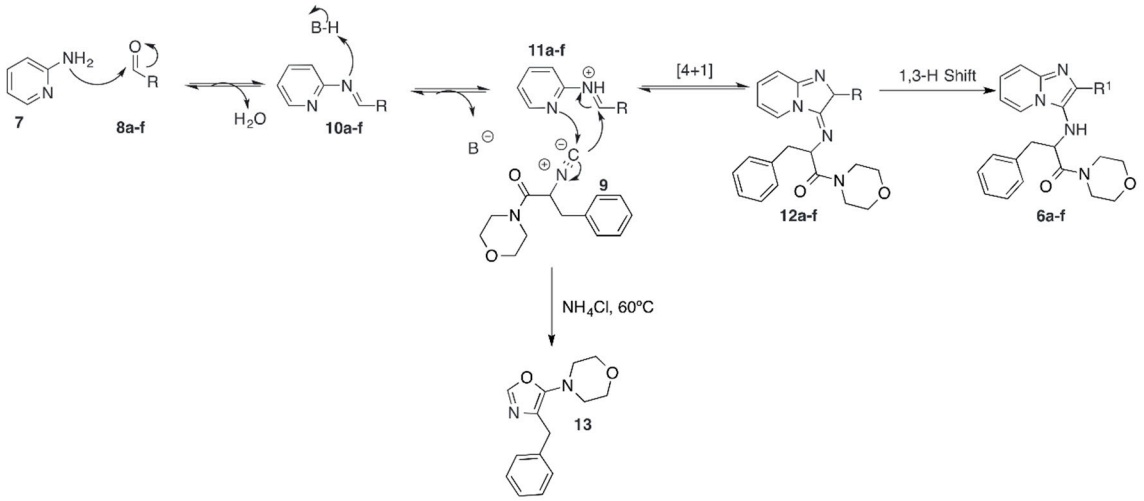
Using our optimized conditions, we synthesized the series of imidazo[1,2-*a*]pyridines (**6a–f**) shown in Scheme 2. The versatility of the developed methodology was examined using different benzaldehydes bearing both electron-donating and electron-withdrawing groups (**8a–d**), and also 9-anthracenecarboxaldehyde (**8e**) and heptanaldehyde (**8f**). The respective products **6a–f** were obtained in moderate to good yields (44–76%).




**Scheme 2.** Sustrate scope.

A plausible reaction mechanism involves the initial formation of a Schiff base (**10a–f**) via the condensation of the corresponding aldehyde (**8a–f**) with 2-aminopyridine (**7**), which is accompanied by a (nonconcerted) [4+1] cycloaddition between the protonated Schiff base (**10a–f**) and the isonitrile (**9**) to give the intermediate **12a–f**. A subsequent prototropic shift generates the aromatic, fused imidazo[1,2-*a*]pyridine (**6a–f**, Scheme 3).

Figures 2 and 3 show the $^{1}H$ and $^{13}C$ NMR spectra for the representative imidazo[1,2-*a*]pyridine **6a**. In the $^{13}C$ NMR, the carbonyl carbon signal appears at 172.1 ppm, which confirms the formation of the GBBR product and not the formation of the oxazole by an intramolecular ring closure in the isonitrile. All of the other key signals are readily observed in these spectra.




**Scheme 3.** Plausible reaction mechanism involved in the GBBR toward imidazo[1,2-*a*]pyridines **6a-h**.

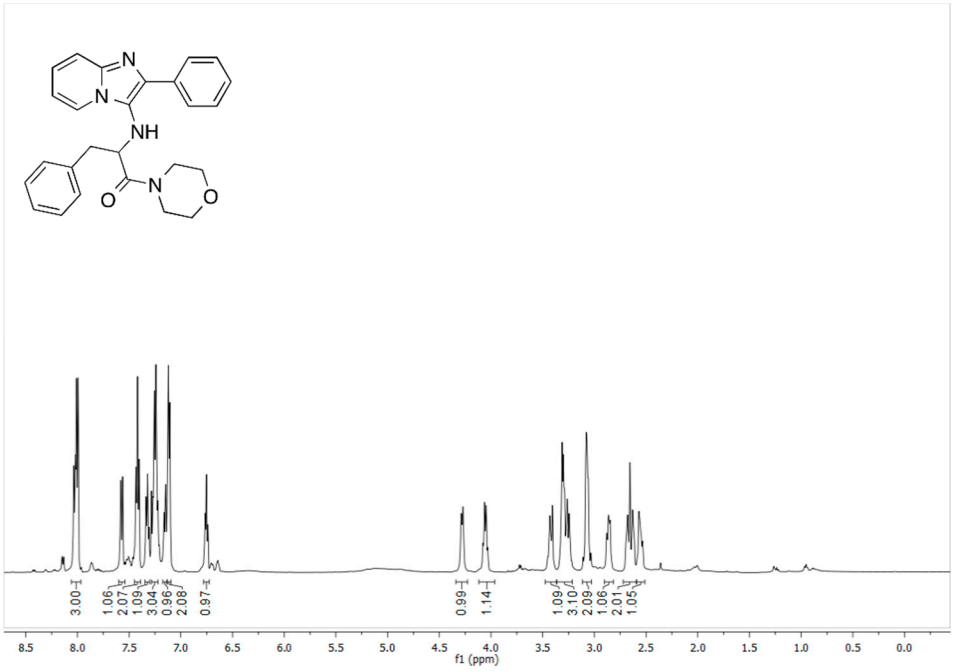



**Figure 2.** $^{1}H$ NMR spectrum of imidazo[1,2-*a*]pyridine **6a**.

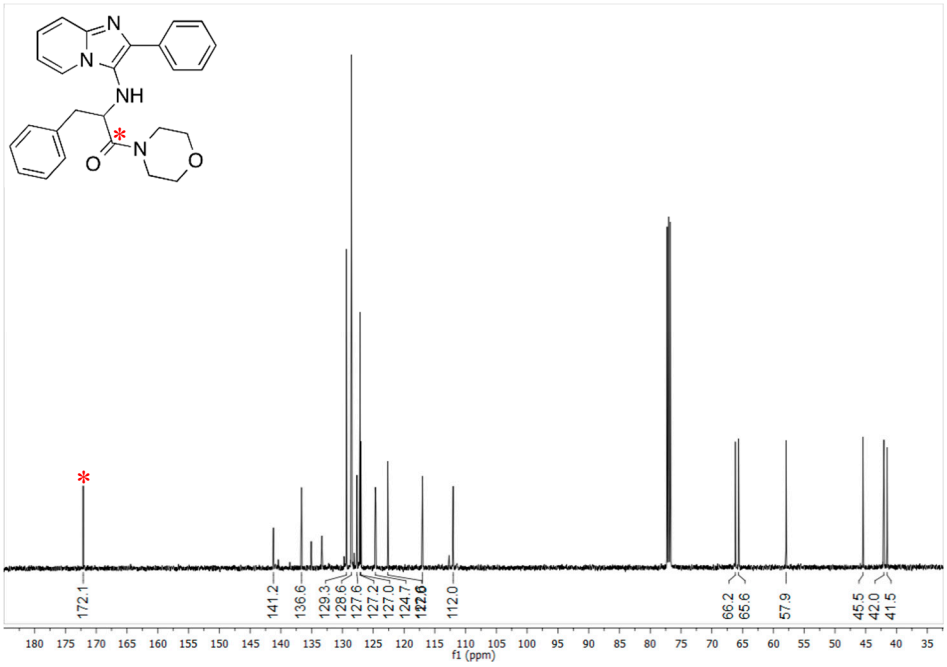



**Figure 3.** $^{13}$C NMR spectrum of imidazo[1,2-*a*]pyridine **6a**.

## 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 or 400 MHz). 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 10.0.1–14719. 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 ($\upsilon_{max}/cm^{-1}$). 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. The purity for all the synthesized products (up to 99%) was assessed by NMR.

### *3.2. Synthesis and Characterization of the Imidazo[1,2-a]pyridine 6a-f*

General procedure (GP): 2-Aminopyridine (**7**) (1.0 equiv.), the corresponding aldehyde **8a–f** (1.0 equiv.), 2-isocyano-1-morpholino-3-phenylpropan-1-one (**9**), and $NH_4Cl$ (10% mol) were placed in a 10-mL sealed vial equipped with a magnetic stirring bar in ethanol [1.0 M]. Then, the mixture was stirred at room temperature (rt) for 12 h. The solvent was removed by rotary evaporation. The residue was purified by flash chromatography using mixtures of hexane–EtOAc (v/v) in different proportions to afford the corresponding imidazo[1,2-*a*]pyridine **6a–f**.

1-Morpholino-3-phenyl-2-((2-phenylimidazo[1,2-*a*]pyridin-3-yl)amino)propan-1-one (**6a**)

According to the GP, 2-aminopyridine (26.0 mg, 0.276 mmol), benzaldehyde (29.0 mg, 0.276 mmol), 2-isocyano-1-morpholino-3-phenylpropan-1-one (67.0 mg, 0.276 mmol), and $NH_4Cl$ (1.5 mg,

0.027 mmol) were reacted together in EtOH (0.276 mL) to afford the imidazo[1,2-*a*]pyridine **6a** (80.0 mg, 67%, rt) as a white solid; m.p. 142–144 °C; $R_f$ = 0.22 (hexane–EtOAc = 2:3 v/v); FT-IR (ATR) $\upsilon_{max}$/cm$^{-1}$ 1631 (C = O); $^1$H NMR (500 MHz, $CDCl_3$, 25 °C): δ 8.06–7.97 (m, 3H), 7.57 (d, *J* = 9.0 Hz, 1H), 7.45–7.39 (m, 2H), 7.35–7.30 (m, 1H), 7.29–7.22 (m, 3H), 7.18–7.13 (m, 1H), 6.79–6.73 (m, 1H), 4.35–4.23 (m, 1H), 4.12–3.96 (m, 1H), 3.47–3.36 (m, 1H), 3.36–3.21 (m, 3H), 3.12–3.03 (m, 2H), 2.90–2.82 (m, 1H), 2.73–2.59 (m, 2H), 2.59–2.51 (m, 1H); $^{13}$C NMR (126 MHz, $CDCl_3$, 25 °C): δ 172.1, 141.2, 136.6, 129.3, 128.6, 127.6, 127.2, 127.0, 124.7, 124.6, 122.6, 117.0, 112.0, 66.3, 65.8, 58.0, 45.6, 42.2, 41.5.

2-((2-(4-Chlorophenyl)imidazo[1,2-*a*]pyridin-3-yl)amino)-1-morpholino-3-phenylpropan-1-one (**6b**)

According to the GP, 2-aminopyridine (21.0 mg, 0.220 mmol), 4-chlorobenzaldehyde (31.0 mg, 0.220 mmol), 2-isocyano-1-morpholino-3-phenylpropan-1-one (54.0 mg, 0.220 mmol), and $NH_4Cl$ (1.0 mg, 0.022 mmol) were reacted together in EtOH (0.220 mL) to afford the imidazo[1,2-*a*]pyridine **6b** (68.0 mg, 72%, rt) as a white solid; m.p. 81–82 °C; $R_f$ = 0.27 (hexane–EtOAc = 2:3 v/v); FT-IR (ATR) $\upsilon_{max}$/cm$^{-1}$ 1618 (C = O); $^1$H NMR (500 MHz, $CDCl_3$, 25 °C): δ 8.03 (d, *J* = 6.7 Hz, 1H), 7.96 (d, *J* = 7.9 Hz, 1H), 7.55 (d, *J* = 8.9 Hz, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.30–7.25 (m, 3H), 7.19–7.08 (m, 3H), 6.91–6.72 (m, 1H), 4.37–4.17 (m, 1H), 4.08–3.96 (m, 1H), 3.47–3.40 (m, 1H), 3.38–3.29 (m, 2H), 3.28–3.21 (m, 1H), 3.12–3.02 (m, 2H), 2.91–2.85 (m, 2H), 2.75–2.68 (m, 2H), 2.65–2.59 (m, 1H); $^{13}$C NMR (126 MHz, $CDCl_3$, 25 °C): δ 172.2, 141.3, 136.6, 134.0, 133.5, 131.1, 129.5, 128.8, 128.7, 128.4, 127.2, 125.0, 124.8, 122.8, 117.1, 112.3, 66.2, 65.6, 57.9, 45.5, 42.0, 41.5.

2-((2-(3,4-Dimethoxyphenyl)imidazo[1,2-*a*]pyridin-3-yl)amino)-1-morpholino-3-phenylpropan-1-one (**6c**)

According to the GP, 2-aminopyridine (18.0 mg, 0.192 mmol), 3,4-dimethoxybenzaldehyde (32.0 mg, 0.192 mmol), 2-isocyano-1-morpholino-3-phenylpropan-1-one (47.0 mg, 0.192 mmol), and $NH_4Cl$ (1.0 mg, 0.019 mmol) were reacted together in EtOH (0.200 mL) to afford the imidazo[1,2-*a*]pyridine **6c** (81.0 mg, 69%, rt) as a brown gum; $R_f$ = 0.1 (hexane–EtOAc = 2:3 v/v); FT-IR (ATR) $\upsilon_{max}$/cm$^{-1}$ 1628 (C = O); $^1$H NMR (500 MHz, $CDCl_3$, 25 °C): δ 8.05 (d, *J* = 6.7 Hz, 1H), 7.74–7.62 (m, 2H), 7.57 (d, *J* = 8.3 Hz, 1H), 7.28–7.20 (m, 4H), 7.16–7.08 (m, 2H), 6.91 (d, *J* = 8.3 Hz, 1H), 6.84–6.79 (m, 1H), 4.47–4.25 (m, 1H), 4.19–3.99 (m, 4H), 3.94 (s, 3H), 3.47–3.42 (m, 1H), 3.36–3.27 (m, 3H), 3.11–3.06 (m, 2H), 2.95–2.90 (m, 1H), 2.75–2.66 (m, 2H), 2.64–2.54 (m, 1H); $^{13}$C NMR (126 MHz, $CDCl_3$, 25 °C): δ 171.2, 153.3, 151.6, 142.0, 143.5, 131.1, 129.5, 128.3, 128.7, 128.4, 127.2, 125.0, 124.8, 122.8, 117.1, 112.3, 66.2, 65.6, 57.9, 56.7, 56.3 45.5, 42.0, 41.5.

1-Morpholino-2-((2-(4-nitrophenyl)imidazo[1,2-*a*]pyridin-3-yl)amino)-3-phenylpropan-1-one (**6d**)

According to the GP, 2-aminopyridine (19.0 mg, 0.198 mmol), 4-nitrobenzaldehyde (30.0 mg, 0.198 mmol), 2-isocyano-1-morpholino-3-phenylpropan-1-one (49.0 mg, 0.198 mmol), and $NH_4Cl$ (1.0 mg, 0.019 mmol) were reacted together in EtOH (0.200 mL) to afford the imidazo[1,2-*a*]pyridine **6d** (72.0 mg, 76%, rt) as a orange solid; m.p. 110–113 °C; $R_f$ = 0.22 (hexane–EtOAc = 2:3 v/v); FT-IR (ATR) $\upsilon_{max}$/cm$^{-1}$ 1615 (C = O); $^1$H NMR (500 MHz, $CDCl_3$, 25 °C): δ 8.25–8.13 (m, 4H), 7.33–7.14 (m, 8H), 6.91–6.79 (m, 1H), 4.59–4.36 (m, 1H), 4.13–3.99 (m, 1H), 3.53–3.44 (m, 1H), 3.40–3.24 (m, 3H), 3.17–3.03 (m, 2H), 2.97–2.89 (m, 1H), 2.84–2.63 (m, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$, 25 °C): δ 171.3, 142.1, 134.6, 133.0, 132.4, 132.1, 129.9, 128.9, 128.8, 128.2, 127.6, 125.1, 124.3, 122.0, 117.8, 112.4, 66.3, 65.8, 58.0, 45.9, 42.5, 41.9.

2-((2-Hexylimidazo[1,2-*a*]pyridin-3-yl)amino)-1-morpholino-3-phenylpropan-1-one (**6e**)

According to the GP, 2-aminopyridine (26.0 mg, 0.280 mmol), heptanaldehyde (32.0 mg, 0.280 mmol), 2-isocyano-1-morpholino-3-phenylpropan-1-one (68.0 mg, 0.280 mmol), and $NH_4Cl$ (1.5 mg, 0.028 mmol) were reacted together in EtOH (0.280 mL) to afford the imidazo[1,2-*a*]pyridine **6e** (54.0 mg, 44%, rt) as a brown oil; $R_f$ = 0.22 (hexane–EtOAc = 2:3 v/v); FT-IR (ATR) $\upsilon_{max}$/cm$^{-1}$ 1631 (C = O); $^1$H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.54 (d, *J* = 8.9 Hz, 1H), 7.42–7.36 (m, 1H), 7.32–7.22 (m, 3H), 7.21–7.16 (m, 3H), 7.14–7.08 (m, 3H), 4.10 (d, *J* = 9.5 Hz, 1H), 3.79 (q, *J* = 8.0 Hz, *J* = 16.2 Hz, 1H), 3.65–3.58 (m, 2H), 3.55–3.44 (m, 2H), 3.27–3.16 (m, 1H), 3.07–3.01 (m, 1H), 2.98–2.86 (m, 4H), 2.59 (t, *J* = 7 7 Hz, 2H), 1.70–1.62 (m, 1H), 1.62–1.55 (m, 1H), 1.34–1.17 (m, 7H), 0.84–0.79 (m, 3H),; $^{13}$C NMR (126 MHz,

$CDCl_3$, 25 °C): δ 172.2, 134.0, 133.5, 131.1, 129.5, 128.8, 128.7, 128.4, 127.2, 125.0, 124.8, 122.8, 66.3, 65.8, 58.0, 45.6, 42.2, 38.8, 31.5, 29.4, 29.0, 28.7, 22.7, 22.5, 14.0.

2-((2-(Anthracen-9-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)-1-morpholino-3-phenylpropan-1-one(**6f**)

According to the GP, 2-aminopyridine (19.0 mg, 0.203 mmol), 9-anthracenecarboxaldehyde (42.0 mg, 0.203 mmol), 2-isocyano-1-morpholino-3-phenylpropan-1-one (50.0 mg, 0.203 mmol), and $NH_4Cl$ (1.0 mg, 0.020 mmol) were reacted together in EtOH (0.200 mL) to afford the imidazo[1,2-*a*]pyridine **6f** (72.0 mg, 67%, rt) as a yellow solid; m.p. 186–187 °C; $R_f$ = 0.22 (hexane–EtOAc = 2:3 v/v); FT-IR (ATR) $\upsilon_{max}/cm^{-1}$ 1640 (C = O); $^1H$ NMR (500 MHz, $CDCl_3$, 25 °C): δ 8.57 (s, 1H), 8.14–8.04 (m, 2H), 8.02–7.93 (m, 1H), 7.88–7.79 (m, 1H), 7.77–7.72 (m, 1H), 7.70–7.64 (m, 1H), 7.55–7.48 (m, 2H), 7.46–7.40 (m, 2H), 7.28–7.20 (m, 1H), 7.14–7.05 (m, 3H), 6.97–6.83 (m, 1H), 6.65–6.56 (m, 2H), 4.31–4.16 (m, 1H), 3.63–3.58 (m, 1H), 3.22–3.04 (m, 4H), 2.74–2.66 (m, 1H), 2.62–2.50 (m, 3H), 2.45–2.32 (m, 1H); $^{13}C$ NMR (126 MHz, $CDCl_3$, 25 °C): δ 173.0, 141.2, 140.2, 137.6, 135.0, 132.5, 132.1, 129.9, 129.4, 128.7, 127.7, 127.4, 126.2, 124.0, 123.9, 123.5, 118.1, 115.3, 67.1, 66.6, 57.0, 45.9, 42.1, 41.3.

## 4. Conclusions

In conclusion, we have developed an efficient and mild GBBR-based methodology for the green synthesis of new imidazo[1,2-*a*]pyridine-3-amines in good yields using α-isocyanoacetamides that incorporate a peptidomimetic amide fragment in the isonitrile component. These results can be interpreted as a reactivity study, the GBBR versus the Ugi three component reaction based on the use of chain ring tautomerizable isonitriles, and as can be seen, iminium ion trapping is the kinetic step favored over the oxazole ring formation. To the best of our knowledge, this is the first example of this reaction using a green, readily available, inexpensive catalyst ($NH_4Cl$) and solvent (EtOH) at room temperature. In addition, the compounds were synthesized in a single step, an improvement over previous multi-stage efforts. This methodology allows the synthesis of imidazo[1,2-*a*]pyridine-3-amines containing amide substituents that are structurally similar to established drug molecules.

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