Graphical Abstract

Copper-Catalyzed Four-component Synthesis of Imidazo[1,2-*a*]pyridines *via* Sequential Reductive Amination, Condensation and Cyclization

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Copper-Catalyzed Four-component Synthesis of Imidazo[1,2-*a*]pyridines via Sequential Reductive Amination, Condensation, and Cyclization

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Abstract: A novel and efficient four-component approach for the synthesis of 2,3-disubstituted imidazo[1,2-*a*]pyridines is described. The copper-catalyzed reductive amination of 2-bromopyridine by sodium azide followed by sequential condensation and cyclization with aldehydes and isocyanides afforded the corresponding imidazo[1,2-*a*]pyridines in good yields.

Keywords: Copper-catalyzed, Imidazo[1,2-*a*]pyridine, Reductive amination, 2-Bromopyridine, Aldehyde, Isocyanide, Sodium azide.

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Introduction

The imidazo[1,2-*a*]pyridine core is an important biologically active, nitrogen-containing heterocyclic scaffold due to its extensive applications in medicinal chemistry and material science.¹ Antibacterial,² antifungal,³ antiviral,⁴ antineoplastic,⁵ antitumor⁶ and antiulcer⁷ properties have been reported for imidazo[1,2-*a*]pyridine derivatives. Additionally, the imidazo[1,2-*a*]pyridine subunit has been widely used in medicinal chemistry. For example, zolpidem, zolimidine, and alpidem are commercially available drugs based on the imidazo[1,2-*a*]pyridine scaffold for use as sedative, anxiolytic and gastroprotective agents, respectively (Fig. 1).

Figure 1. Representative commercially available imidazo[1,2-*a*]pyridine-based drugs

Because of their pharmacological importance, the development of novel synthetic approaches for the preparation of imidazo[1,2-*a*]pyridine derivatives has gained significant attention, and as a result, many synthetic routes for this valuable scaffold have been reported in the literature.⁸ Typical approaches include the heterocyclization of 2-aminopyridine with α -haloketones,⁹ α,β -unsaturated carbonyl compounds¹⁰ or α -diazoketones.¹¹ Also, several three-component condensation reactions have been reported including the coupling reaction of 2-aminopyridine and aldehydes with isocyanides¹² or alkynes,¹³ and the condensation between 2-aminopyridine, isocyanides, and benzyl halides¹⁴ or benzyl alcohols¹⁵ (Scheme 1).

Scheme 1. General approaches for the synthesis of imidazo[1,2-*a*]pyridines

Recently, the synthesis of fused *N*-heterocycles using the copper-catalyzed reductive amination of aryl halides by sodium azide as a convenient nitrogen source, has been widely applied in organic synthesis.¹⁶ Due to the pharmacological value of imidazo[1,2-*a*]pyridines, and in continuation of our research regarding the preparation of nitrogen-containing compounds,¹⁷ herein, we report a novel and efficient approach for the synthesis of imidazo[1,2-*a*]pyridines **5**, *via* the four-component condensation of 2-bromopyridine **1**, sodium azide **2**, aldehydes **3**, and isocyanides **4**, in the presence of CuI as a catalyst and L-proline as a ligand, in DMSO at 100 °C (Scheme 2). To the best of our knowledge, this is the first report on the synthesis of imidazo[1,2-*a*]pyridines using 2-bromopyridine instead of 2-aminopyridine.

Scheme 2. Four-component synthesis of imidazo[1,2-*a*]pyridines

Result and Discussion

We began with the model reaction of 2-bromopyridine **1**, sodium azide **2**, benzaldehyde **3a**, and cyclohexyl isocyanide **4a**, in the presence of CuI, in dry DMSO at 100 °C, which led to the isolation of product **5a** in 33% yield (Table 1, entry 1). In order to improve the yield of **5a**,

various experimental conditions were screened by varying the ligands, copper catalysts, solvents and temperatures (Table 1). Firstly, screening the ligands 1,10-phenanthroline, pipecolic acid and L-proline (Entries 2–4), revealed that the yield significantly increased in the presence of a ligand. Among them, L-proline was found to be the most suitable ligand (Entry 4). Various copper salts including CuBr, CuCl, CuCl₂ and Cu₂O (Entries 5–8), were screened and the highest yield was obtained with CuI (compare entries 4 and 5–8). Several solvents including DMF, 1,4-dioxane and toluene were tested (Entries 9–11), where DMSO proved to be the most effective (compare entries 4 and 9–11). Finally, decreasing or increasing the reaction temperature did not lead to any further improvement in yield (Entries 12 and 13).

Table 1. Optimization of conditions for the four-component synthesis of **5a**^a

Entry	Catalyst	Ligand	Solvent	Temp. (°C)	Yield (%) ^b
1	CuI	—	DMSO	100	33
2	CuI	1,10-Phenanthroline	DMSO	100	58
3	CuI	Pipecolic acid	DMSO	100	64
4	CuI	L-proline	DMSO	100	78
5	CuBr	L-proline	DMSO	100	70
6	CuCl	L-proline	DMSO	100	66
7	CuCl ₂	L-proline	DMSO	100	62
8	Cu ₂ O	L-proline	DMSO	100	52
9	CuI	L-proline	DMF	100	60
10	CuI	L-proline	1,4-Dioxane	100	10
11	CuI	L-proline	Toluene	100	5
12	CuI	L-proline	DMSO	80	63
13	CuI	L-proline	DMSO	120	69

^a Reagents and conditions: **1** (1 mmol), **2** (2 mmol), **3a** (1 mmol), **4a** (1 mmol), Cu-source (0.05 mmol), ligand (0.1 mmol), solvent (3 mL), 3 h.

^b Isolated yield.

With the optimized conditions for the synthesis of imidazo[1,2-*a*]pyridines in hand, we then investigated the substrates scope. Aromatic aldehydes with either electron-withdrawing or electron-donating substituents, regardless of their position on the phenyl ring, provided the corresponding products **5** in good yields (Table 2).¹⁸

Table 2. Substrate scope for the four-component synthesis of imidazo[1,2-*a*]pyridines^a

Entry	Aldehyde	Isocyanide	Product	Yield (%) ^b
1	3a	4a		78
2	3b	4a		81
3	3c	4a		79
4	3d	4a		82
5	3e	4a		76

6	3f	4a	5f	81
7	3a	4b	5g	88
8	3f	4b	5h	84
9	3b	4b	5i	84
10	3c	4b	5j	85

^a Reagents and conditions: **1** (1 mmol), **2** (2 mmol), **3** (1 mmol), **4** (1 mmol), CuI (0.05 mmol), L-proline (0.1 mmol), DMSO (3 mL), 110 °C, 3 h.

^b Isolated yield.

A plausible mechanism for the formation of imidazo[1,2-*a*]pyridines **5** is illustrated in Scheme 3. Based on recent reports that sodium azide act as an ammonia surrogate to prepare primary amines in the copper-catalyzed reductive amination of aryl halides,¹⁶ it is reasonable to assume that, initially, reductive amination of 2-bromopyridine **1** using sodium azide in the presence of the copper catalyst produced 2-aminopyridine **7**. Subsequently, condensation of 2-aminopyridine **7** with the aldehyde furnishes imine intermediate **8**. Next, nucleophilic addition of the isocyanide to imine **8**, followed by intramolecular cyclization leads to the formation of intermediate **10** which tautomerizes to afford the desired product **5** (Scheme 3).

Scheme 3. Plausible mechanism for the four-component synthesis of imidazo[1,2-*a*]pyridine **5**.

Conclusion

In summary, we report a new and efficient, one-pot, four-component approach for the synthesis of 2,3-disubstituted imidazo[1,2-*a*]pyridines *via* the copper-catalyzed reductive amination of 2-bromopyridine with sodium azide followed by sequential condensation-cyclization with aldehydes and isocyanides. To date, this is the first report on the synthesis of imidazo[1,2-*a*]pyridine using 2-bromopyridine instead of 2-aminopyridine.

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18. *General procedure for the preparation of compounds 5a–j, exemplified with 5a:* A mixture of 2-bromopyridine (1 mmol), NaN₃ (1 mmol), benzaldehyde (1 mmol), cyclohexyl isocyanide (1 mmol), CuI (0.05 mmol) and L-proline (0.1 mmol), in dry DMSO (3 mL) was stirred in a sealed vessel under air for 3 hours at 100 °C. After reaction completion (TLC), the reaction mixture was cooled, quenched with water (20 mL), and extracted with EtOAc (3 × 20 mL). The extract was washed with 30% NaCl solution (V/V), dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by column chromatography using

petroleum ether/ethyl acetate (3:1) as eluent to afford the pure product **5a**. *N-cyclohexyl-2-phenylimidazo[1,2-*a*]pyridin-3-amine (5a)*: m.p. 198–200 °C (lit.¹⁴ 195–197 °C); ¹H NMR (DMSO-*d*₆, 500 MHz): δ = 1.05–1.71 (10H, m), 2.82–2.87 (1H, m), 4.80 (1H, d, *J* = 6.0 Hz), 7.15 (3H, m), 7.20 (2H, d, *J* = 8.0 Hz), 7.44 (3H, m), 8.38 (1H, d, *J* = 7.0 Hz) ppm; ¹³C NMR (DMSO-*d*₆, 125 MHz): δ = 20.8, 28.36, 30.0, 55.6, 110.7, 116.3, 123.6, 123.8, 127.5, 128.5, 129.2, 132.5, 136.0, 137.9, 140.9.