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Synthesis of imidazo[1,2*a*]pyridines via three-component reaction of 2-aminopyridines, aldehydes and alkynes

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ABSTRACT

A novel three-component reaction towards the synthesis of imidazo[1,2*a*]pyridines was independently developed based on 2-aminopyridines, aldehydes and alkynes, and thereby imidazo[1,2*a*]pyridines were obtained in acceptable yields by the CuSO4/TsOH catalyzed three-component reaction.

During the past decades, multicomponent reactions (MCRs) to form several bonds in a single-step-cascade synthesis manner[1] and to integrate several different fragments into one molecule attracted much attention and achieved great progress.[2] In view of atom-economics, step-efficiency, and structural diversity in terms of green chemistry and drug discovery, developing new MCRs, especially those toward 'bias' scaffolds remains very active in current process chemistry and medicinal chemistry. As a 'bias' scaffold, imidazo[1,2*a*]pyridine unit has widely occurred in various bioactive molecules and clinically applied drugs,[3] such as Zolpidem to treat insomnia, Alpidem as an anxiolytic agent, Olprinone to treat acute heart failure, and Minodronic acid to treat osteoporosis. To date, several synthetic approaches to imidazo[1,2*a*]pyridines have been reported,[4] and among them the popular approaches utilized in medicinal chemistry are: (1) coupling reaction of 2-aminopyridine with α-halocarbonyl compounds; (2) one-pot condensation of 2-aminopyridines, aldehydes, and isonitriles, since a variety of starting materials are either commercially available or easily synthesized. However, both of them remain limited either to 3-amino imidazo[1,2*a*]pyridines,[5] or to stepwise available precursors and long reaction time (up to 10 days).[6] Therefore, it is highly desirable to explore a novel approach to imidazo[1,2*a*]pyridines, especially in a single-step-cascade synthesis manner with multiple components.

Logically speculating along the known three-component approach to the 3-amino imidazo[1,2*a*]pyridines, we hypothesize whether or not the isonitrile could be replaced by its isosteric surrogate the alkyne, and thereby the novel approach to 3-alkyl imidazo[1,2*a*]pyridines could become possible with 2-aminopyridine, aldehydes, and alkynes (Fig. 1).

If so, the simplified process should possibly include: (1) condensation of 2-aminopyridine and aldehyde to form imine; (2) nucleophilic attack of alkyne to imine to form propargyl amine; (3) intramolecular nucleophilic attack of nitrogen in pyridine ring to the triple bond possibly in *5-exo-dig* (attack to C-*a*) or *6-endo-dig* way (attack to C-*b*); (4) aromatic isomerization of the cyclic intermediate (Fig. 2).

Recently, a number of methodologies have been disclosed on transitional-metal-mediated formation of chiral or achiral propargyl amines with amines, aldehydes, and alkynes,[7] or cycloisomerization toward heterocycles with alkynes tethering intramolecular nucleophiles;[8] meanwhile, in principle the *5-exo-dig* cyclic intermediate produced in step 3 could be preferably isomerized into the thermodynamic stable heteroarenes, whereas the *6-endo-dig* one could not; and thus we reason that the designed approach could be feasible. Herein, we are willing to present our preliminary effort and complementary information on this issue, although most recently an elegant method based on the similar strategy has been developed by Chernyak and Gevorgyan in the course of our research.[9]

According to the designed route toward the synthesis of imidazo[1,2*a*]pyridines, we initially screened the different transitional metal catalysts in the model reaction, including Cu, Fe, In, Pd, Zn, Ag, etc., most of which occurred in alkyne-participated formation of propargyl amines or cycloisomerization.[7,8] Consequently, we found Cu or Ag might be the promising catalyst for the reaction.

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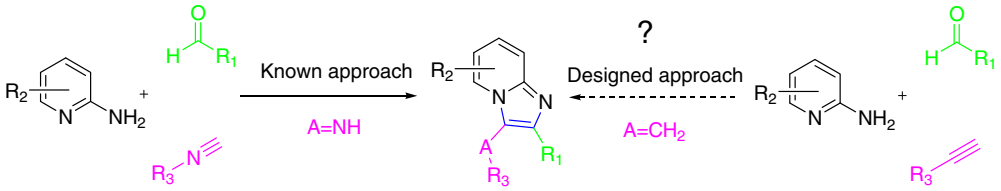


Figure 1. The designed approach for imidazo[1,2-*a*]pyridines.

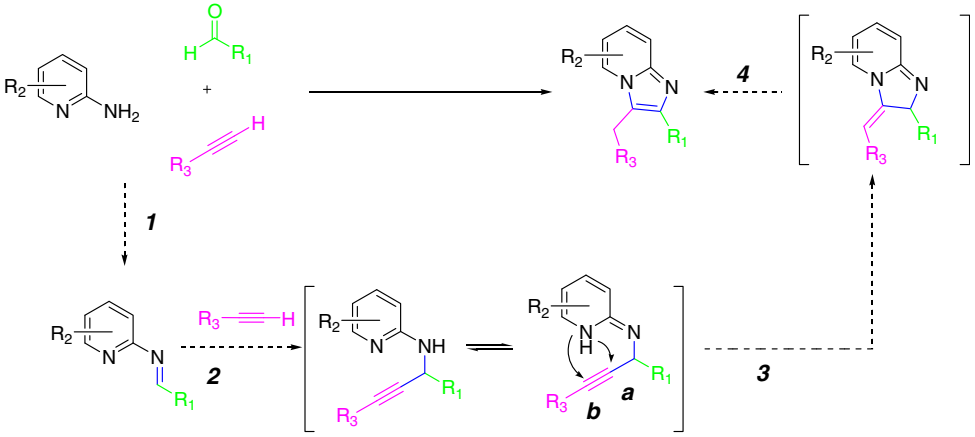
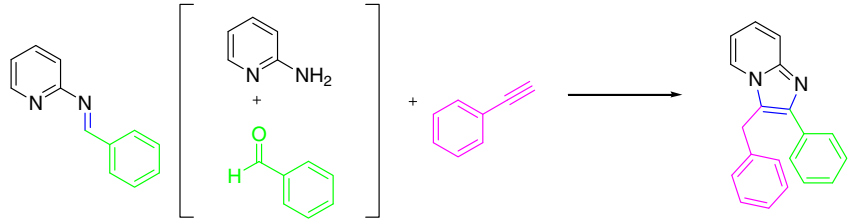


Figure 2. The simplified process for synthesis of imidazo[1,2-*a*]pyridines.

Table 1
Screening the catalysts in the two- or three-component reaction[a]



Entry	Catalysts (mol%)	Yield[b] (%)	
		2C Reaction	3C Reaction
1	$CuSO_4$	30	Trace
2	$Cu(OTf)_2$	42	35
3	CuCN	20	9
4	AgOTf	34	12
5	$Ag(O_2CCF_3)$		9
6	Ag_2O		Trace
7	$AgNO_3$		6
8	$AgBF_4$		7
9	CuI		Trace
10	CuCl		Trace
11	CuBr		Trace
12	Cu_2O		Trace
13	CuOAc		4
14	$CuBr_2$		8
15	$Cu(acac)_2$		Trace

[a] Two-component reaction (2CR) conditions: *N*-benzylidenepyridin-2-amine (0.5 mmol), acetylene (0.5 mmol), catalyst (10 mol %), toluene (2 mL), 18 h; Three-component reaction (3CR) condition: 2-aminopyridine (1.0 mmol), benzaldehyde (1.0 mmol), acetylene (1.0 mmol), catalyst (10 mol %), toluene (5 mL), 110 °C, 18 h.
[b] Isolated yield.

Next, we examined in detail the different Cu or Ag salts in the two- (*N*-benzylidenepyridin-2-amine and 1-ethynylbenzene: 2CR) or three-component reaction (aminopyridine, benzaldehyde, and ethynylbenzene: 3CR) and the results are shown in Table 1. In

Table 2
Screening the co-catalysts in the two- or three-component reaction[a]

Entry	Catalysts	Additive	Yield[b] (%)	
			2CR	3CR
1	$Cu(OTf)_2$		42	35
2	$Cu(OTf)_2$	TsOH	54	45
3	$Cu(OTf)_2$	$PhCO_2H$	65	50
4	$Cu(OTf)_2$	4-HO–$C_4H_6CO_2H$	63	
5	$Cu(OTf)_2$	BINOL	38	
6	$Cu(OTf)_2$	4A MS		31
7	$Cu(OTf)_2$	CF_3SO_3H		47
8	$Cu(OTf)_2$	Ti(*i*-OPr)$_4$		39
9	$CuSO_4$		30	Trace
10	$CuSO_4$	$PhCO_2H$		24
11	$CuSO_4$	TsOH		60[c]
12	$CuSO_4$	CF_3SO_3H		45
13	$CuSO_4$	D-camphor acid		54
14	CuCN	TsOH		39
15	CuI	TsOH		30
16	AgOTf	TsOH		15

[a] Two-component reaction (2CR) conditions: *N*-benzylidenepyridin-2-amine (0.5 mmol), acetylene (0.5 mmol), catalyst (10 mol %), additive (10 mol %) if required, toluene (2 mL), 18 h; Three-component reaction (3CR) condition: 2-aminopyridine (1.0 mmol), benzaldehyde (1.0 mmol), acetylene (1.0 mmol), catalyst (10 mol %), additive (10 mol %) if required, toluene (5 mL), 110 °C, 18 h.
[b] Isolated yield.
[c] When TsOH (0.02 mmol) used, yield: 45%; solvent optimized for the 3CR (dioxane: 51%; DMF: 41%; EtOH: 40%); the ratio for the acetylene verus aldehyde or amine (1 equiv, 60%; 1.2 equiv, 57%; 1.5 equiv, 52%).

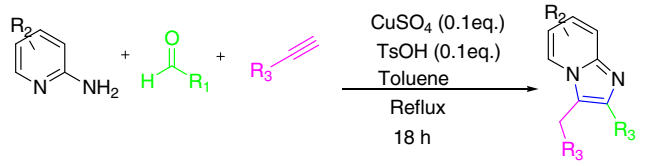
the case of two-component reaction, Cu^{II}, Cu^{I}, or Ag^{I} has been demonstrated to catalyze the reaction to some extent (20–42%, entries 1–4 in Table 1) and resulted in the desired product, which was identified by the routine physical spectrum and monocrystal X-ray diffraction.[10] In our case, Cu^{II} salts appeared to display better than Cu^{I} salts or Ag^{I} salts in the formation of propargyl amine and cycloisomerization.[9] Despite a rewarding yield ($Cu(OTf)_2$: 42%) in hand, several attempts failed to improve the reaction by enhancing activities of the metal catalyst with some mono-, bi-, or tri-dentate ligands containing nitrogen or phosphorus atom. Additionally, the efforts to expand those catalysts from 2CR to 3CR have also been proved to be disappointing, and in 3CR most of Cu^{II}, Cu^{I}, or Ag^{I} salts dramatically hampered the reaction and led to extremely low yields except $Cu(OTf)_2$ (35%).

Considering that both the nonbeneficial electronic effect of 2-aminopyridine and the soft acidity of the copper or silver salt do not favor the formation of the imine, the reason for lower yields obtained in 3CR than in 2CR is that the in situ formation of the imine is possibly difficult under the above-mentioned condition. Thus additives to possibly benefit the formation of the imine were examined, and the results are shown in Table 2. In order to avoid the additives interfering the subsequential processes, the two-component reaction was investigated prior to the three-component reaction.

Brønsted acids, such as TsOH or benzoic acid[11], were observed to co-catalyze the two-component reaction with $Cu(OTf)_2$ and led to significantly increased yields, especially benzoic acid could enable the yield up to 65% versus 42% (entries 1 and 3 in Table 2), however, the weaker Brønsted acid such as BINOL had no beneficial effect on the transformation (entries 1 and 5 in Table 2). It suggested that the strong Brønsted acid might, to some extent, activate nucleophilic addition of the alkyne to the imine due to protonation of the imine[14] or inhibition of coordination of the pyridine nitrogen to copper, whereas the weaker acids could not.

Unexpectedly, when the strong Brønsted acid combined with $Cu(OTf)_2$ in the three-component reaction, only a slightly lower yield (45% vs 54% for TsOH; 50% vs 65% for $PhCO_2H$, entries 2–3 in Table 2) was offered. Screening other strong Brønsted acids, Lewis acids, or drying agents as a co-catalyst did not significantly improve the 3CR (entries 1 and 6–8 in Table 2). Fortunately, $CuSO_4$, instead of $Cu(OTf)_2$, combined with Brønsted acids such as TsOH, improved the 3CR dramatically with a yield of 60% versus trace in the 2CR (entries 9–13 in Table 2). Such a synergeric effect of TsOH was also observed with Cu^{I} salts but not Ag^{I} salt in 3CR (entries 14–16 in Table 2). Having screened the sorts and amounts of several other acids, the ratio of the reagents and solvents, we found that the product was obtained in 60% yield under the optimized condition for the 3CR (see entries 10–13 and footnote c in Table 2).

Table 3
Synthesis of some imidazo[1,2*a*]pyridines[a]



Entry	R_1	R_2	R_3	Yield[b] (%)
1	Ph	H	Ph	60
2	4-CH_3–C_6H_4	H	Ph	56
3	4-OCH_3–C_6H_4	H	Ph	58
4	4-OMOM–C_6H_4	H	Ph	55
5	4-Cl–C_6H_4	H	Ph	66
6	4-F–C_6H_4	H	Ph	62
7	4-CF_3–C_6H_4	H	Ph	64
8	4-HO–C_6H_4	H	Ph	n.d.
9	4-Me_2N–C_6H_4	H	Ph	n.d.
10	3-Cl–C_6H_4	H	Ph	59
11	3-CF_3–C_6H_4	H	Ph	64
12	3-NO_2–C_6H_4	H	Ph	49
13	2-Cl–C_6H_4	H	Ph	55
14	2-Br–C_6H_4	H	Ph	n.d.
15	Ph	H	4-CH_3–C_6H_4	57
16	Ph	H	4-OCH_3–C_6H_4	46
17	Ph	H	4-F–C_6H_4	60
18	Ph	5-CH_3	Ph	68
19	Ph	3-F	Ph	55
20	*cyclo*-C_6H_{10}	H	Ph	53
21	Et_2CH	H	Ph	28
22	$CH_3CH_2CH_2$	H	Ph	n.d.
23	H[a]	H	$CONMe_2$	n.d.
24	H[c]	H	CO_2Et	n.d.

[a] Three-component reaction (3CR) condition: 2-aminopyridine (1.0 mmol), aldehydes (1.0 mmol), acetylenes (1.0 mmol), $CuSO_4$/TsOH (10/10 mol %), toluene (5 mL), 110 °C, 18 h.
[b] Isolated yield; n.d. means not determined.
[c] Paraformaldehyde is used.

Under the optimized condition, the reaction mixtures showed, by TLC analysis, that the residues included the product, the unreactive imine, and benzaldehyde as well as several minor unidentified residues. Furthermore, among the minor residues, the possible intermediates such as the propargyl amine or the allene amine[15] could not be found by LC–MS analysis. Prolonging the reaction time or increasing the amount of $CuSO_4$/TsOH did not ameliorate the reaction, but decreasing the amount of the catalyst indeed led to a lower yield. Notwithstanding, considering that the single-step-cascade synthesis includes at least three steps (condensation for imine, nucleophilic addition of alkyne, and cycloisomerization), the yield is acceptable (average 85%/per step).

With the optimized condition in hand, the scope and limitation of the reaction were finally examined[12] and the results are shown in Table 3. In most cases of aromatic aldehydes and aromatic alkynes, the three-component reaction proceeded smoothly under the condition and the corresponding products were offered in moderate yields (46–68%, entries 1–19, Table 3), and the condition was compatible with various function groups including

acid-sensitive, reductive, and coupling-sensitive groups (MOM, NO_2, Cl). The electronic effect seemed to have a slight influence on the reaction since either the electron-withdrawing or the electron-donating groups on the different aromatic ring resulted in the hardly discriminate yields (entries 2–3, 6 and 15–19). However, bromo, dimethylamino, or phenolic hydroxy existing in substrates was indeed observed to intervene the reaction (entries 8–9 and 14 in Table 3), possibly due to coupling reaction (Br) or coordinative inactivation (Me_2N or OH with Cu^{II}). The reaction with aliphatic aldehydes, instead of aromatic aldehydes, seems to be promising because cyclohexanecarbaldehyde resulted in 53% yield, while some low boiling-point aliphatic aldehydes appeared to be problematic and led to lower yields (entries 21–22 in Table 3). An attempt to employ 2-aminopyridine and paraformaldehyde with aliphatic alkynes, such as *N*,*N*-dimethylpropiolamide or ethyl propiolate (entries 23–24 in Table 3) aiming to the synthesis of Zolpidem[4e] or Mindronic acid,[13] failed to obtain the desired products, that indicates the disadvantage of the current method.

In conclusion, we have independently explored a novel approach to the synthesis of imidazo[1,2*a*]pyridines via three-component reaction of 2-aminopyridines, aldehydes, and alkynes, and imidazo[1,2*a*]pyridines are obtained in acceptable yields by the $CuSO_4$/TsOH-catalyzed three-component reaction, and the reaction could tolerate a variety of functional groups on the aromatic moieties but remains incompatible with hydroxy, dialkylamino, and bromo existing in the substrates.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.05.139.

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