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Letter

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Highly Regioselective, Acid Catalyzed, Three-Component Cascade Reaction for the Synthesis of 2-aminopyridine-Decorated Imidazo[1,2-*a*]pyridine

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ABSTRACT: A highly regioselective acid-catalyzed three-component reaction of 2-aminopyridine and 3-phenylpropiolaldehyde for the construction of imidazo[1,2-*a*]pyridine has been developed. This strategy provides a broad range of substrates and represents an efficient approach to give various 2-aminopyridine-decorated imidazo[1,2-a]pyridine in good yields.

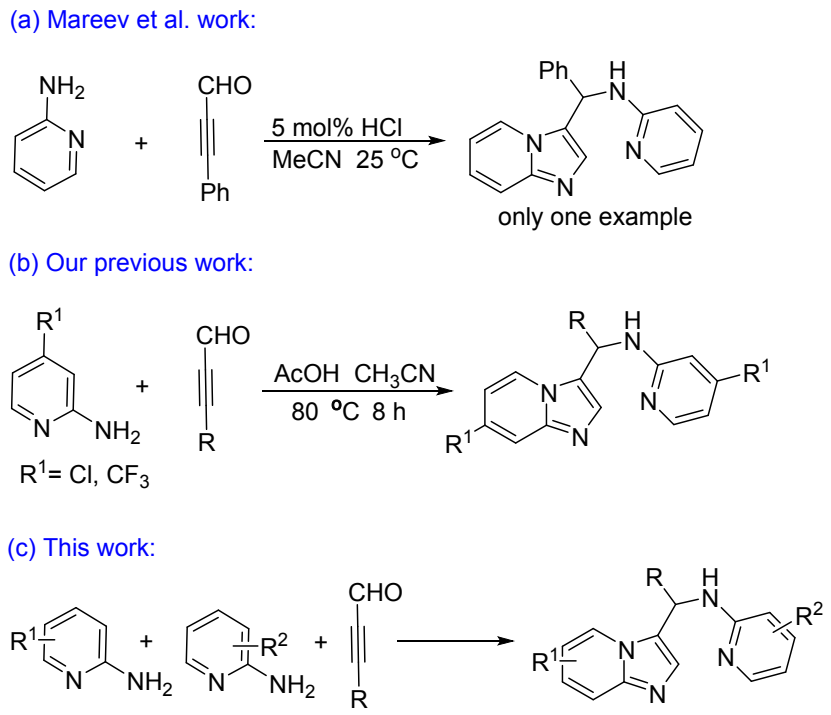
KEYWORDS: *Pivalic acid*, *2-aminopyridine*, *three-component reaction*, *imidazo[1,2-a] pyridine*

Considerable efforts have been devoted to developing new Imidazo[1,2-*a*]pyridine-based heterocycles compounds[1-4], that is, a single compound that displays the coexistence or synergism of two or more properties including obvious inhibitory effects on many target enzymes[5-7] and good bioactivity in the aspect of anti-tumor[8-12], anti-virus[13-15], anti-bacterial[16-18], anti-tuberculosis[19,20], anti-inflammatory[21], antiulcer[22], anti-diabetic[23], antipsychotic[24,25], etc. 3-Substituted imidazo[1,2-a]pyridines are of particular interest, because of their potential applications in many commercially available drugs such as necopidem, alpidem, saripidem, minodronic acid. The versatility and value of these Imidazo[1,2-*a*]pyridine derivatives for a wide range of applications feeds the continuous synthetic drive for novel and better synthetic strategies, including oxidative cross-coupling, multi-component reaction[26-34]. Despite the fact that much progress has been made in the synthesis of these derivatives, there still remains great challenges for synthetic organic chemists in developing a facile approach for the direct synthesis of 3-2-aminopyridine-decorated imidazo[1,2-a]pyridines. For example, Mareev[35] et al. first reported the synthesis of 3-[2-pyridylamino(phenyl) methyl]imidazo[1,2-a]pyridine by employing phenylpropynal and 2-aminopyridine (Scheme 1, a). Unfortunately, only one product has been synthesized under their protocol. Subsequently, we disclosed an efficient one-pot methodology for the synthesis of these compounds via AcOH catalysis (Scheme

1, b) and a series of imidazo[1,2-α]pyridines were obtained in high to excellent yields[36]. However， there are still some limitations and inconveniences of this protocol. The substituted pyridine-2-amine used to undergo a Michael type addition to finish the transformation should be the same as the one reacted with the aldehyde to form the imine intermediate during the first step of the reaction. This seriously restricted the further application of a diversity oriented synthesis.

Therefore, the development of new catalytic systems to achieve two different 2-aminopyridine reactions for the direct construction of multifunctional imidazo[1,2-*a*]pyridines is still of great importance. In this context, our group envisions to construct 2-aminopyridine-decorated imidazo[1,2-*a*]pyridine derivatives via a three-component reaction of 2-aminopyridines and 3-phenylpropionaldehyde.

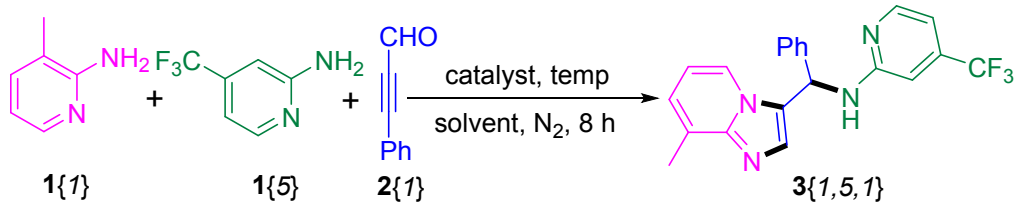
Scheme 1 Syntheses of N-(imidazo[1,2-a]pyridin-3-yl(phenyl) methyl)2-aminopyridine



In the beginning, the model reaction of 2-amino-3-methylpyridin **1**{*1*}, 5-(trifluoromethyl)-2-aminopyridine **1**{*5*} and 3-phenylpropiolaldehyde **2**{*1*} were conducted to determine the suitable reaction conditions[37]. The results are described in Table 1. The desired product **3**{*1,5,1*} was not obtained without any catalysts in dioxane at room temperature (entry 1). We then attempted to increase the yield of product **3**{*1,5,1*} by adding variety of catalysts. Using 5 mol % PivOH in dioxane at room temperature afforded a yield of 42% (entry 2), but the addition of benzoic acid,

AcOH, TsOH, TFA, $ZnCl_2$, $FeCl_3$, $FeCl_2$, showed that the product **3**{*1,5,1*} was formed in relatively lower yield or not detected (entries 3-10). It is interesting to note that the temperature changes significantly affect the yield. The results indicated that the reaction at 60 °C was the most suitable (entry 2, 9-13). In order to improve the reaction efficiency, we evaluated the influence of various solvents. Among the solvents, we were delighted to find that the product **3**{*1,6,1*} was readily formed in 92 % yield in CH_2Cl_2. Other solvents, such as DMSO, DMF, or toluene, did not lead to any improved result (entries 14-19).

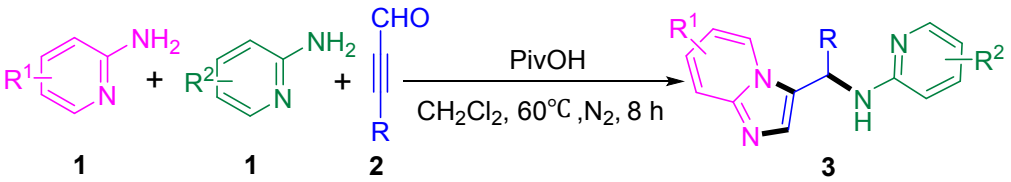
Table 1. Optimization of the reaction conditions[a]



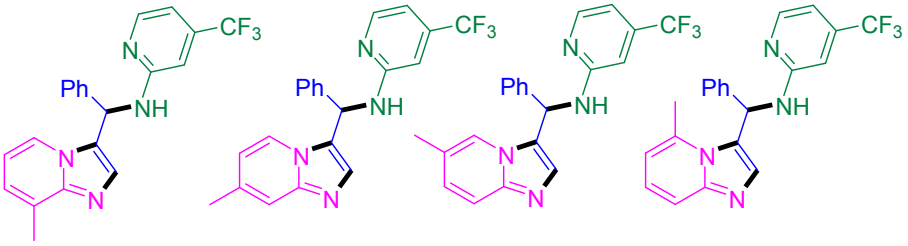
Entry	Catalyst	Solvent	T (oC)	Yield b (%)
1		1,4-dioxane	rt	N.P.
2	PivOH	1,4-dioxane	rt	42
3	Benzoic Acid	1,4-dioxane	rt	28
4	$AlCl_3$	1,4-dioxane	rt	30
5	AcOH	1,4-dioxane	rt	14
6	TsOH	1,4-dioxane	rt	17
7	TFA	1,4-dioxane	rt	14
8	$ZnCl_2$	1,4-dioxane	rt	trace
9	$FeCl_3$	1,4-dioxane	rt	trace
10	$FeCl_2$	1,4-dioxane	rt	N.P.
11	PivOH	1,4-dioxane	60	67
12	PivOH	1,4-dioxane	80	65
13	PivOH	1,4-dioxane	100	64
14	PivOH	DMSO	60	23
15	PivOH	DMF	60	<5
16	PivOH	CH_2Cl_2	60	92
17	PivOH	toluene	60	32
18	PivOH	DCE	60	56
19	PivOH	THF	60	62

[a] Reaction conditions: **1**{*1*} (0.5 mmol), **1**{*5*} (0.5 mmol), **2**{*1*} (0.6 mmol), catalyst (5 mol %), and solvent (2 mL), carried out in a sealed tube (25 mL); [b] Determined by GC analysis.

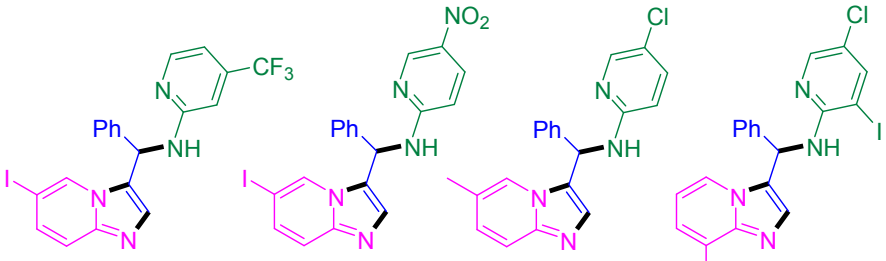
Scheme 2 **Synthesis of Imidazoles using different 2-aminopyridine and alkynal**



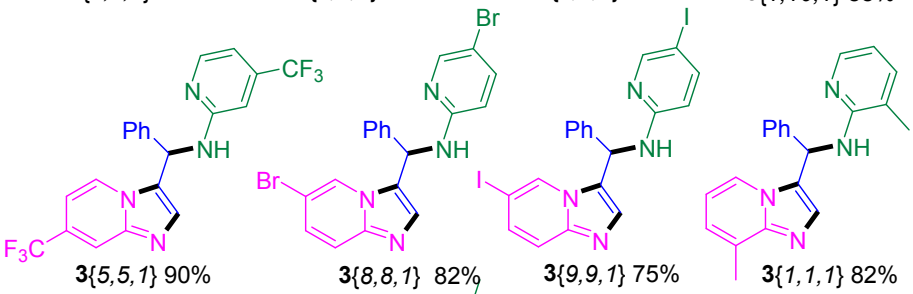
1 1 2 3



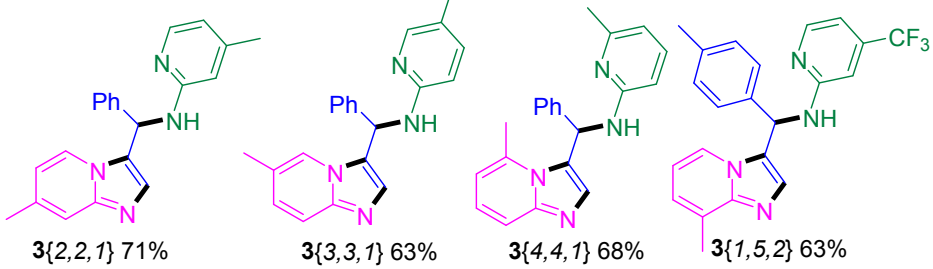
3{1,5,1} 92% 3{2,5,1} 83% 3{3,5,1} 82% 3{4,5,1} 77%



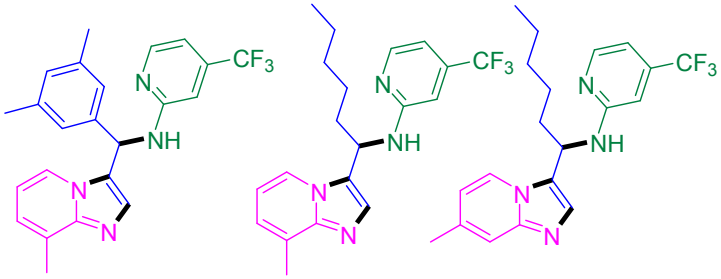
3{5,5,1} 79% 3{9,7,1} 81% 3{3,7,1} 70% 3{1,10,1} 88%



3{5,5,1} 90% 3{8,8,1} 82% 3{9,9,1} 75% 3{1,1,1} 82%



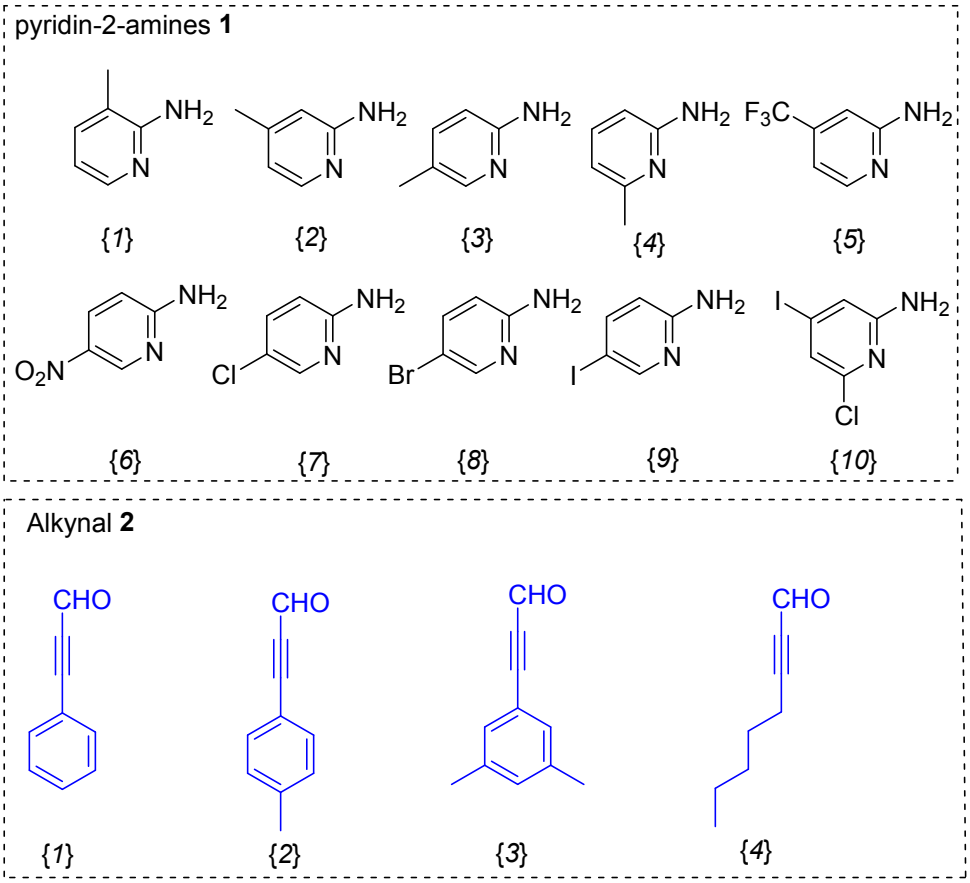
3{2,2,1} 71% 3{3,3,1} 63% 3{4,4,1} 68% 3{1,5,2} 63%



3{1,5,3} 66% 3{1,5,4} 65% 3{2,5,4} 70%

[a] Isolated yields.

Table 2. Structural diversity of 2-aminopyridine 1 and alkynal 2

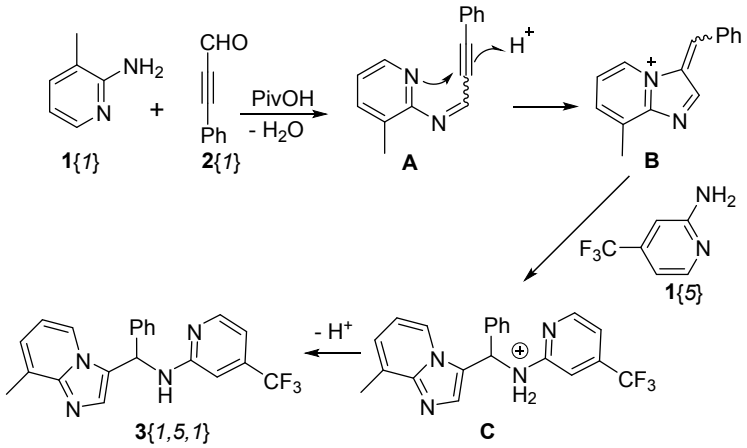


Under the optimized reaction conditions, we examined a series of amino pyridines and alkynals to probe the scope of this PivOH-catalyzed, three-component transformation. The structural diversity of the starting materials are summarized in Table 2. To our delight, a wide range substituted groups of aminopyridines all gave the corresponding imidazo[1,2-*a*]pyridine with great efficiency. The results are shown in Scheme 2. It was pleasing to find that methyl-substituted and iodized pyridine-2-amine successfully reacted with **1**{*5*} and **2**{*1*} under the optimized conditions to generate the corresponding product **3**{*1,5,1*}, **3**{*2,5,1*}, **3**{*3,5,1*}, **3**{*4,5,1*}, **3**{*5,5,1*} with good yield of 79-92%. 5-NO_2 and 5-I or 5-methyl and 5-Cl monosubstituted aminopyridine also give the corresponding product **3**{*9,7,1*} or **3**{*3,7,1*} in 81% or 70% yields, respectively. Additionally, the pyridine-2-amine substituted both with 5-Cl and 3-I reacted with **1**{*1*} and **2**{*1*} under the same conditions to generate the product **3**{*1,10,1*} with yield of 88%. It is no surprise that the electron-withdrawing groups (4-CF_3, 5-Br, 5-I) on the pyridine ring exhibit a beneficial effect for the improvement of yield and the desired product **3**{*5,5,1*}, **3**{*8,8,1*}, **3**{*9,9,1*} were obtained with the yield of 75-90%. With a electron donating group on the pyridine ring such as 3-methyl, 4-methyl, 5-methyl and 6-methyl,

reacted with **2**{*1*} stably to afford the expected products **3**{*1,1,1*}, **3**{*2,2,1*}, **3**{*3,3,1*}, **3**{*4,4,1*} in good isolated yield. Subsequently, a variety of alkyls were also tested as the substrate with various substituted 2-aminopyridines. For instance, 3-(p-tolyl)propiolaldehyde **2**{*2*} and 3-(3,5-dimethylphenyl)propiolaldehyde **2**{*3*} reacted with **1**{*1*} and **1**{*5*} afforded products **3**{*1,5,2*}, **3**{*1,5,3*} in good yields. Then, when oct-2-ynal **2**{*4*} was tested as substrate, the corresponding product **3**{*1,5,4*}, **3**{*2,5,4*} was also isolated. These results clearly show that this scheme is general and suitable for the reaction of various substituted 2-aminopyridines and various alkynals. The molecular structure of product **3**{*1,5,1*} was determined by X-ray crystallography (Figure S1).

On the basis of the above results, a plausible mechanism for this transformation is described in Scheme 3. Initially, PivOH promotes dehydration of **2**{*1*} by **1**{*1*} to afford intermediate imine A, which then cyclizes to intermediate B via an intramolecular nucleophilic attack on the triple bond by the lone electron pair of the nitrogen atom on the pyridine ring. Intermediate B then is converted to Intermediate C via nuclephilic attack of **1**{*5*} on its exocyclic double bond. Subsequent proton loss finally affords product **3**{*1,5,1*}.

Scheme 3 **Possible mechanism**



In summary, we have developed an efficient and general PivOH-catalyzed approach to prepare imidazole derivatives. This three-component reaction of 2-aminopyridines and ynals has been demonstrated by the preparation of a broad range of functionalized imidazoles in moderate to good yields. This transformation provides a convenient route for the formation of C–N bonds to prepare amino-modified imidazo[1,2-*a*]pyridines.

ASSOCIATED CONTENT

Supporting Information

Details of experimental and analytical procedures, along with spectroscopic data for

synthesized compounds. Crystallographic data for **3**{*1,5,1*} (CCDC 1868963).

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Notes

The authors declare no competing financial interest.

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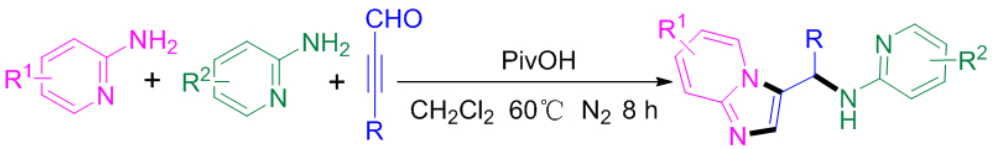
(37) Synthesis of **3**{*1,5,1*} according to the following procedure: A 25 mL sealed tube was charged with a stirring bar, and added 3-methylpyridin-2-amine **1**{*1*} (0.081g, 1.0 equiv), 4-(trifluoromethyl)pyridin-2-amine **1**{*5*} (0.054g, 1 equiv), 3-phenylpropiolaldehyde **2**{*1*} (0.078g, 1.2 equiv), PivOH (0.005g, 5% equiv), CH_2Cl_2 (2 mL). The reaction was carried out at 60 ^{O}C stirring for 8 h and monitored by TLC. The reaction mixture was then diluted with EtOAc and water, extracted with EtOAc. The organic layers were washed with brine and dried over $MgSO_4$, evaporated under reduced pressure. The crude mixture was purified by Thin layer chromatography silica gel plate (eluted with petroleum ether : ethyl acetate = 2 : 1) to give **3**{*1,5,1*} in 92% yield (175.8 mg).



A highly regioselective acid-catalyzed three-component reaction of 2-aminopyridine and 3-phenylpropiolaldehyde for the construction of imidazo[1,2-a]pyridine has been developed. This strategy provides a broad range of substrates and represents an efficient approach to give various 2-aminopyridine-decorated imidazo[1,2-a]pyridine in good yields.

285x41mm (72 x 72 DPI)