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Transition-Metal-Free Tandem Chlorocyclization of Amines with Carboxylic Acids: Access to Chloroimidazo[1,2-α]pyridines

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Supporting Information

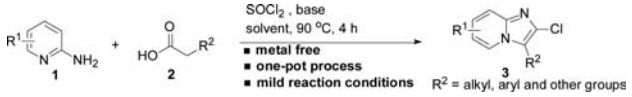
ABSTRACT: An efficient one-pot and transition-metal-free chlorocyclization cascade of 2-aminopyridines with aliphatic carboxylic acids is reported. This transformation provides a novel approach to 2-chloro- or 3-chloro-substituted imidazo[1,2-α]pyridines with a broad range of substrate scopes.

Polysubstituted imidazo[1,2-α]pyridines (IPYs) are well established as privileged scaffolds which are commonly encountered in many biologically active natural products and medicinal molecules.[1] In the past decades, much significant progress toward transition-metal-catalyzed synthesis of IPY derivatives has been achieved.[2] Palladium,[3] copper,[4] gold,[5] and silver catalysts,[6] etc., have been widely employed to develop various synthetic strategies for rapidly assembling these compounds. However, most transition-metal salts are environmentally unfriendly to different extents, and removal of trace amounts of residual metal from pharmaceutical precursors such as IPYs generally still suffers from high cost and complicated purifying procedures. Therefore, developing metal-free synthetic reactions will provide a direct and powerful tool to meet these challenges.

On the other hand, halogenated IPYs belong to a class of important building blocks and versatile synthons,[7] which could be further converted to more complex organic molecules through cross-coupling reactions.[8] Nevertheless, existing methods for furnishing 2- or 3-halogen-substituted IPYs were rarely reported. To date, only previous works by Paudler and Alcaide described a cyclocondensation and electrophilic chloration reaction to make these halogenated heteroaromatic ring monomers, which derived from α-amino alcohols[9] and imidazo[1,2-α]pyridine 1-oxides,[10] respectively. Recently, Jiang also developed a copper-catalyzed synthesis of 2-halo-substituted IPYs employing haloalkynes as halogen sources.[11] Thus, it can be seen that the common features of the above-mentioned strategies involved the use of complex organic reagents and transition-metal salts. From the viewpoint of green and step-economic strategy, developing an efficient one-pot and transition-metal-free approach to halogenated IPYs that allows for using cheap and readily available starting materials is highly desirable. Herein, we described a novel chlorocyclization cascade of 2-aminopyridines with aliphatic carboxylic acids (ACA) to rapidly furnish halogenated IPYs by using thionyl chloride as halogen sources, in which the chlorine atom was regioselectively introduced into the 2-position of IPYs (Scheme 1).

To begin, we tried to screen various chlorine sources (3.0 equiv) including $POCl_3$, PCl_5, CO_2Cl_2, and $SOCl_2$ to explore the possibility of intermolecular chlorocyclization of 2-aminopyridine **1a** (0. 1 mmol) with propionic acid **2a** (0.1 mmol) in the presence of pyridine (2.0 equiv) in toluene (2.0 mL) at 90 °C for 8 h (Table 1, entries 1−4). To our delight, we soon found that $SOCl_2$ could give us the desired 2-chloro-3-methyl-imidazo[1,2-*a*]pyridine **3a** in 27% yield (entry 4). Although the reaction yield is very poor, this positive result greatly stimulated us to evalulate the solvent effect to further improve the reaction conversion (entries 4−8), and the corresponding solvent screening indicated that chloroform could serve as the most suitable solvent to provide 68% yield **3a** (compare entries 4−7 with 8). Subsequently, a significant improvement of the reaction (85% yield of **3a**) was achieved by employing triethylamine (TEA) as base (compare entries 8−12 with 13). It is worth noting that further changing the equivalence of $SOCl_2$ led to a decreased conversion of **1a** to some degree (compare entries 14 and 15 with 13). Finally, the best yield of **3a** (85%) was obtained at 90 °C for 8 h by using 3.0 equiv of a $SOCl_2$/TEA (2.0 equiv) reaction system (compare entries 15−17 with 13) (see the Supporting Information for the more details about screening of reaction conditions).

Scheme 1. One-Pot and Metal Free Approach to Functionalized 2-Chloroimidazo[1,2-α]pyridines



With the optimized reaction conditions established, we next investigated the scope of the current procedure by testing various 2-aminopyridines with propionic acid **2a**. As shown in Scheme 2, the reactivity of 2-aminopyridine **1** was remarkably dependent on the electronic properties of the substituents from pyridine ring (**3a**−**f**). For example, 5-substituted pyridines with an electron-donating group or halogen atom provided 84−88% yields of 2-Cl-substituted IPYs (**3a**−**d**), but the electron-poor pyridyl ring gave 38−59% yields of IPY (**3e** and **3f**). On the other hand, the present chlorocyclization could also be successfully applied to a

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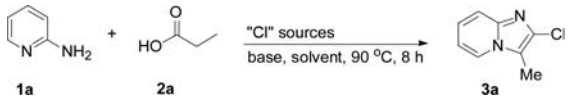
Table 1. Optimization of the Reaction Parameters[a]



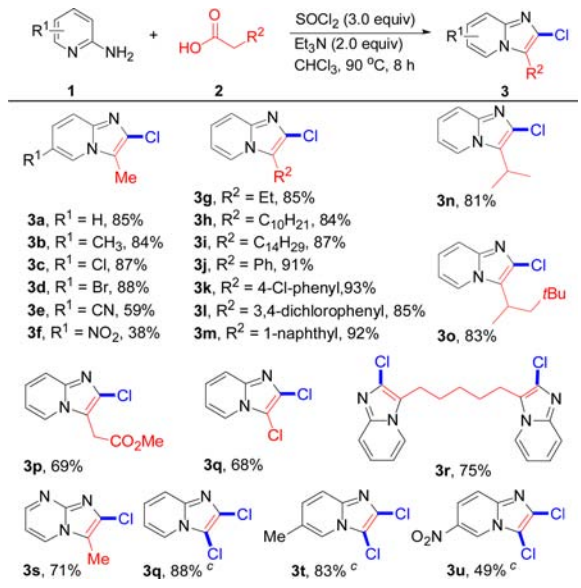
entry	"Cl" sources	base	solvent	yield[b] (%)
1	$POCl_3$	pyridine	toluene	
2	PCl_5	pyridine	toluene	
3	CO_2Cl_2	pyridine	toluene	
4	$SOCl_2$	pyridine	toluene	27
5	$SOCl_2$	pyridine	ethyl acetate	42
6	$SOCl_2$	pyridine	CH_3CN	16
7	$SOCl_2$	pyridine	THF	10
8	$SOCl_2$	pyridine	$CHCl_3$	68
9	$SOCl_2$	Na_2CO_3	$CHCl_3$	72
10	$SOCl_2$	$NaHCO_3$	$CHCl_3$	65
11	$SOCl_2$	DABCO	$CHCl_3$	77
12	$SOCl_2$	DBU	$CHCl_3$	79
13	$SOCl_2$	TEA	$CHCl_3$	85
14	$SOCl_2$	TEA	$CHCl_3$	77[c]
15	$SOCl_2$	TEA	$CHCl_3$	74[d]
16	$SOCl_2$	TEA	$CHCl_3$	47[e]
17	$SOCl_2$	TEA	$CHCl_3$	79[f]

[a]Unless otherwise noted, all of the reactions were carried out first using carboxylic acid (**2a**) (0.10 mmol) and the "Cl" source (0.30 mmol) in solvent (2.0 mL) at 90 °C for 2 h. After the mixture was cooled to room temperature, base (2.0 equiv) and 2-aminopyridine (**1a**) (0.10 mmol) were added to the reaction mixture, the corresponding mixture was stirred at 25 °C for 3 h, the reaction temperature was increased to 90 °C again, and the corresponding mixture stirred for another 3 h. [b]Isolated yield. [c]2.0 equiv of $SOCl_2$ was used. [d]4.0 equiv of $SOCl_2$ was used. [e]The reaction temperature was 80 °C. [f]The reaction temperature was 100 °C.

wide range of ACA with 2-aminopyridine **2a**. Different kinds of α-alkyl groups (**3g−i,n−o**), α-aryl groups (**3j−m**), α-ethoxylcarbonylmethyl groups (**3p**), and α-chloro-substituted (**3q**) acetic acid derivatives could easily enable assembly of the desired 2-Cl-substituted IPYs in good to excellent yields, regardless of whether electron-withdrawing or electron-donating groups or sterically hindered groups (**3n** and **3o**) were introduced into aliphatic carboxylic acid molecules. Moreover, this reaction protocol was well tolerated with dicarboxylic acids and 2-aminopyrimidine, which could be efficiently converted to the corresponding fused heteroarene **3r** and **3s** in 75% and 71% yields, respectively. Interestingly, when acetic acid was employed as the substrate in this reaction system, electron-rich or electron-defecient 2,3-dichloro-substituted IPYs could be produced smoothly in moderate to good yields (**3q**, **3t** ,and **3u**). The structure of 2, 3-dichloro-imidazo [1,2-α]pyridine **3q** was already unambiguously assigned by its single-crystal X-ray analysis (see the Supporting Information for more details).

Considering that amides could possibly isomerize to imines under base conditions,[12] we further explored the chlorocyclization reactivity of 2-aminopyridines with ketones under our standard conditions, in which ketoimines were first prepared via a one-pot process in toluene at 110 °C in the presence of concd H_2SO_4 (10 mol %) for 12 h. Gratifyingly, this procedure could rapidly assemble another kind of polysubstituted IPYs employing α-aryl methyl ketones **4** as starting materials, in which the chlorine atom was regioselectively introduced into the C3-position of IPYs (Scheme 3, **5a−l**).[13] When we switched α-aryl methyl ketone to α-phenyl ethyl ketone, only 2-phenyl-3-methyl

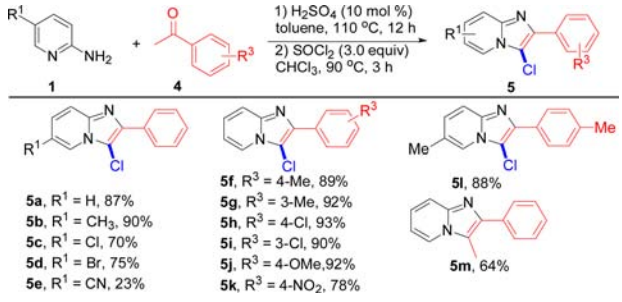
Scheme 2. Substrate Scope for the Tandem Chlorocyclization of Amines with Carboxylic Acids[a,b]



[a]Unless otherwise noted, all of the reactions were carried out first using carboxylic acid (**2**) (0.10 mmol) and $SOCl_2$ (0.30 mmol) in $CHCl_3$ (2.0 mL) at 90 °C for 2 h. After the reaction mixture was cooled to room temperature, Et_3N (2.0 equiv) and amine (**1**) (0.10 mmol) were added to the reaction mixture, the corresponding mixture was stirred at 25 °C for 3 h, and the reaction temperature was increased to 90 °C again, and the corresponding mixture was stirred for another 3 h. [b]Isolated yield. [c]Acetic acid was subjected to the standard reaction system.

IPY (**5m**) was formed in 64% yield, and no halogen-substituted product was observed.

Scheme 3. Substrate Scope for the Tandem Chlorocyclization of Amines with Ketones[a,b]



[a]Unless otherwise noted, all the reactions were carried out first using amine (**1**) (0.1 mmol) and ketone (**2**) (0.10 mmol) and H_2SO_4 (10 mol %) in toluene (2.0 mL) at 110 °C for 12 h. After the solvent was removed and the mixture was cooled to room temperature, $SOCl_2$ (3.0 equiv) and $CHCl_3$ (2.0 mL) were added to the reaction mixture and the corresponding mixture was stirred at 90 °C for 3 h. [b]Isolated yield.

The corresponding synthetic application of halogen-substituted IPY is shown in Scheme 4. For example, 2-chloro-IPY **3j** could be easily converted into 2,3-diaryl-IPY (**7**) through a traditional Pd-catalyzed cross-coupling strategy (eq 1). More importantly, 2, 3-dichloro-IPY (**3q**) could also efficiently couple with diphenylphosphine oxide (**8**) to construct C−P bond in the presence of Ag(I) salts[14] and furnish 78% yield of 2-chloro-3-(diphenylphosphinoyl)-IPY (**9**),[15] which belongs to an

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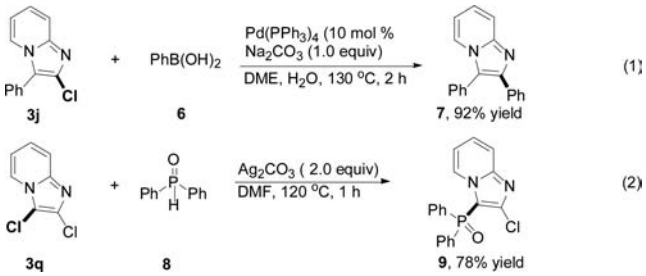
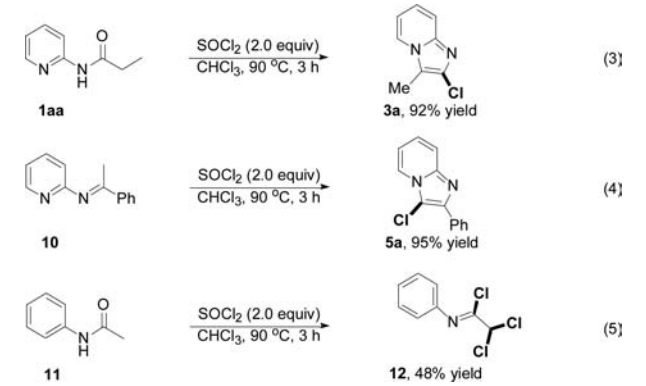
Scheme 4. Synthetic Application for This Transformation



important synthetic intermediate[16] for making biological active molecules (eq 2). Existing synthetic approaches to this kind of phosphino group-containing heteroarene generally require tedious reaction steps and harsh reaction conditions.[16]

Finally, several controlled reactions were conducted to better understand the possible reaction mechanism (Scheme 5). As

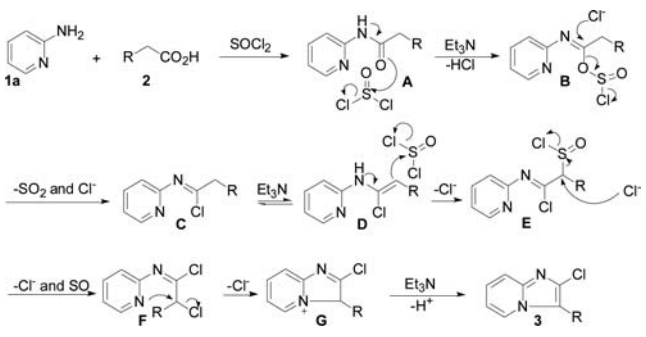
Scheme 5. Controlled Experiments



anticipated, when *N*-(2-pyridyl)amide **1aa** and *N*-(2-pyridyl)-ketoimine **10** were successively subjected to the standard reaction system, 2-chloro- and 3-chloro-substituted IPY could be obtained in 92% yield (eq 3, **3a**) and 95% yield (eq 4, **5a**), respectively. These results demonstrated that amides and imines were involved in the chlorocyclization process of 2-aminopyridines. Meanwhile, employing *N*-phenyl amide **11** as a substrate only led to the formation of 2,2-dichloro-*N*-phenylacetimidoyl chloride **12** (eq 5), and this transformation further implied imino chlorides could also possibly be derived from *N*-(2-pyridyl)amides.

On the basis of the above-mentioned controlled experments, a plausible mechanism for the chlorocyclization cascade of 2-aminopyridines with ACA is proposed in Scheme 6. First, thionyl

Scheme 6. Possible Mechanism for Chlorocyclization Cascade



chloride promoted the intermolecular amidation of 2-aminopyridine (**1a**) with ACA (**2**) to produce *N*-(2-pyridyl)amide **A** by converting acids to acid chlorides, and then the lone-pair electrons from amide nitrogen of **A** triggered the nucleophilic attack to sulfinyl sulfur to lead to the formation of chlorosulfurous acid ester (**B**), which could be attacked by Cl^- via SN_2 process to produce imino chloride (**C**) with the release of SO_2. Subsequently, alkenyl chloride (**D**) derived from imine/enamine isomerization of **C** could nucleophilically attack $SOCl_2$ again, followed by substitution with Cl^- to afford active imino chloride **F**.[17] Finally, the intramolecular cyclization/aromatization of **F** generated the desired 2-chloro-substituted imidazo[1,2-α]pyridine **3**.

In conclusion, we have developed an efficient one-pot and transition-metal-free strategy for the chlorocyclization cascade of 2-aminopyridines with aliphatic carboxylic acids or ketones to rapidly assemble 2-chloro- and 3-chloro-substituted imidazo[1,2-α]pyridines, respectively. This method is compatible with a wide range of readily available substrates. Further studies on the reaction mechanism and synthetic application of this transformation are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01868.

Details for experiments conditions, characterization data, copies of ^1H and ^{13}C NMR spectra for all isolated compounds (PDF)
Single crystal data of **3q** (CIF)
Single crystal data of **5f** (CIF)
Single crystal data of **9** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(13) For the single crystal information of **5f**, see the Supporting Information.

(14) For this novel Ag-catalyzed C−P bond formation reaction, we are currently exploring its possible mechanism and will report it in due course.

(15) For the single crystal information of **9**, see the Supporting Information.

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(17) Possibly, the chemical stability of *N*-(2-pyridyl)imino chloride **F** is poorer than that of *N*-phenylimino chloride **12**, so we did not obtain the corresponding spectral data about intermediate **F**.

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