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Molecular Iodine-Mediated Chemoselective Synthesis of Multisubstituted Pyridines through Catabolism and Reconstruction Behavior of Natural Amino Acids

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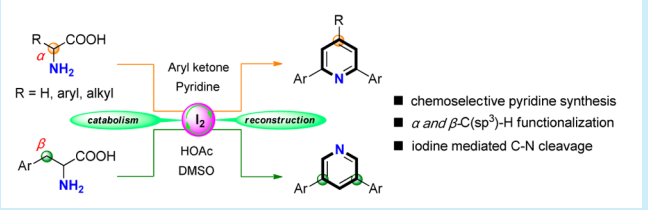
Supporting Information

ABSTRACT: A new process has been developed for the selective construction of 2,6-disubstituted, 2,4,6-trisubstituted, and 3,5-disubstituted pyridines based on the catabolism and reconstruction behaviors of amino acids. Molecular iodine was used as a tandem catalyst to trigger the decarboxylation−deamination of amino acids and to promote the subsequent formation of the pyridine products.



Amino acids hold an important place in the annals of ligand chemistry,[1] chiral catalysis,[2] and total synthesis.[3] They have also been used to develop an interesting array of synthetic methodologies, with the majority of these studies being focused on C−C bond-forming reactions via a decarboxylative coupling process.[4] However, nature is much more effective at affecting the chemical transformations of amino acids. These compounds are used in nature for many other reactions besides decarboxylative coupling reactions since amino acids are some of the most basic and versatile synthons available to living organisms. During the biosynthesis of alkaloids, amino acids can be catabolized into smaller fragments, which are subsequently used as building blocks to reconstruct the core skeletons of alkaloids under enzymatic conditions.[5] A representative example of this process is the biosynthesis of haouamine A, which is a pyridine-based alkaloid that is widely believed to be biogenetically derived from four identical tyrosine congeners[6] (Figure 1). The catabolism of these

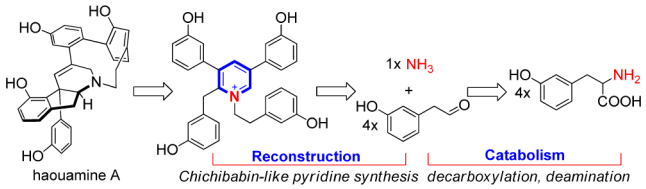


Figure 1. Biosynthesis protocol of haouamine **A**.

tyrosine derivatives through sequential decarboxylation and deamination reactions is thought to lead to the formation of the corresponding phenylacetaldehyde derivatives and ammonia, which might undergo a Chichibabin-type reaction to produce a pyridinium core.[7] To the best of our knowledge, there have been no reports concerning the use of the catabolism and reconstruction behaviors of natural amino acids as a leading strategy for the development of novel synthetic methodologies.

Pyridine is one of the most common N-containing aromatic ring systems[8] and can be found in a wide range of natural products, pharmaceuticals, and functional materials.[9] Pyridine rings are traditionally prepared from aldehydes and amines via multicomponent reactions[10] or transition-metal-catalyzed cycloaddition processes.[11] However, the application of these reactions can sometimes be limited by their requirements for the use of toxic aldehydes or the need for extensive workup procedures to remove residual metals. To address these limitations, research efforts have recently been directed toward the construction of pyridine skeletons via the oxidative cleavage of the C−N bonds of amine derivatives[12] (Figure 2, Column 1, left side). Herein, we report an unprecedented I_2-mediated reaction for the in situ cleavage of the unreactive C−N bonds[13] of natural amino acids to catabolize to the corresponding aldehydes and amines, which subsequently undergo a reconstruction process to afford 2,6-disubstituted, 2,4,6-trisubstituted, and 3,5-disubstituted pyridines in a single step. Given that the construction of pyridines from natural amino

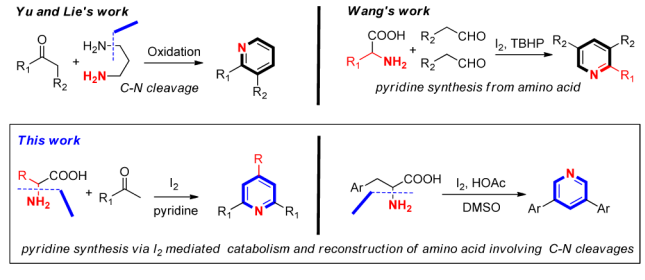


Figure 2. Selected examples of pyridine synthesis and a brief introduction of this work.

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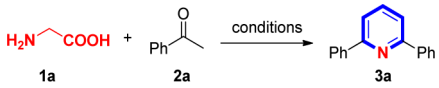
acids under mild condition represents a rare transformation[14] (Figure 2, Column 2, right side), this new method for the selective synthesis of multisubstituted pyridines from different kinds of amino acids will be of considerable practical value (Figure 2, Column 2).

We initially investigated the reaction of glycine (**1a**) with acetophenone (**2a**) as a model reaction in the presence of 1.0 equiv of I_2 at 100 °C in DMF. Several bases were screened against this transformation to optimize the reaction conditions (for optimization details, please see Supporting Information (SI)). The results of these screening experiments showed that pyridine was critical to the success of the transformation (Table 1, entry 1). When the solvent was switched from DMF to

Table 1. Optimization of the Reaction 1[a]



1a **2a** **3a**

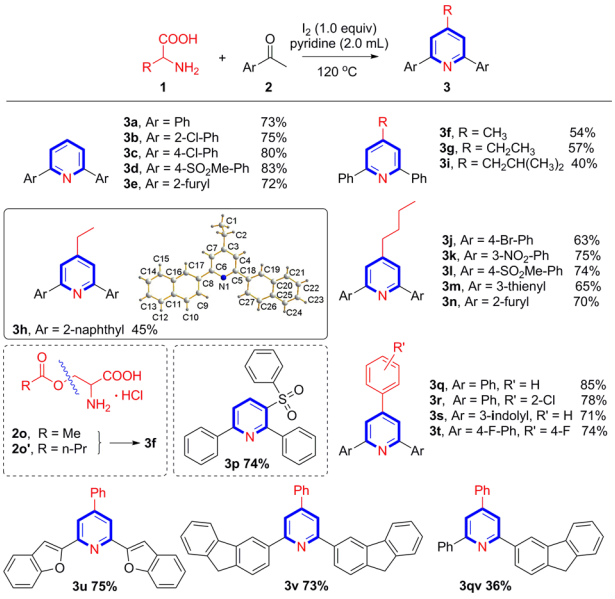
entry	solvent	I_2 (equiv)	additive (equiv)	temp (°C)	yield[b] (%)
1	DMF	1.0	Pyridine (2.0)	100	31
2	Pyridine	1.0	–	100	61
3	Pyridine	1.0	DBU (2.0)	100	trace
4	Pyridine	1.0	DMAP (2.0)	100	36
5	Pyridine	1.0	Cs_2CO_3 (1.0)	100	trace
6	Pyridine	1.0	K_2CO_3 (1.0)	100	23
7	Pyridine	1.0	KOH (2.0)	100	27
8	Pyridine	1.0	–	110	65
9	**Pyridine**	**1.0**	–	**120**	**73**
10	Pyridine	0.2	–	120	24
11	Pyridine	0.5	–	120	41
12	Pyridine	1.5	–	120	27

[a]Reaction conditions: **1a** (2.0 mmol, excessive dose), **2a** (2.0 mmol), additive, solvent (2.0 mL) for 12 h. [b]Isolated yields based on **2a**. Reactions were carried out in a pressure vessel.

pyridine, the yield of the desired product 2,6-diphenylpyridine (**3a**) increased significantly (Table 1, entry 2). Several other bases were also evaluated but found to be ineffective (Table 1, entries 3−7). The optimal temperature for this reaction was determined to be 120 °C (Table 1, entry 9). Notably, decreasing or increasing the loading of I_2 led to a reduction in the yield of the product, indicating that a loading of 1.0 equiv was optimal.

With the optimized conditions in hand, we proceeded to examine the scope of the reaction using a variety of different substrates (Scheme 1). Several alkyl-branched amino acids, including alanine (**3f**), 2-aminobutanoic acid (**3g**, **3h**), leucine (**3i**), and 2-aminohexanoic acid (**3j**−**n**), all reacted smoothly under the optimized conditions to produce the corresponding 2,4,6-trisubstituted pyridines in moderate yields. Unfortunately, the use of *O*-acetyl-L-serine hydrochlorideas (**2o**) or *O*-butyryl-L-serine hydrochlorideas (**2o′**) as substrates failed to provide the desired products. The unexpected cleavage of C−O bonds led to 4-methyl-2,6-diphenylpyridine (**3f**) being the major product. Furthermore, a wide range of acetophenones were screened under the optimized conditions. Acetophenones bearing an electron-withdrawing group on their phenyl ring reacted well and produced the desired pyridine products in good yields (e.g., **3d**, **3k**, **3l**). Acetophenone substrates bearing a halogen substituent on their benzene ring (e.g., 2-Cl, 4-Cl, 4-Br: **3b**, **3c**, **3j**) were well tolerated. Notably, 2-naphthyl methyl ketone also reacted smoothly to give the desired product (**3h**)

Scheme 1. Scanning of Substrate Scope of Reaction 1[a,b]



[a]Reaction conditions: **1** (2.0 mmol), **2** (2.0 mmol), I_2 (2.0 mmol), pyridine (2.0 mL), 120 °C for 12 h. [b]Isolated yields. Reactions were carried out in a pressure vessel.

in moderate yield (45%) which was unambiguously confirmed by X-ray crystallography (please see SI). The optimized conditions were also successfully applied to a wide variety of heteroaryl ketones, including furanyl, thienyl, indolyl, and benzofuryl methyl ketones, which generated the corresponding heterocyclic substituted pyridines in good yields (**3e**, **3n**, **3m**, **3s**, **3u**, respectively). It is noteworthy that the reaction of glycine with 1-phenyl-2-(phenylsulfonyl)ethan-1-one under the optimized conditions led to the unexpected cleavage of one of the two sulfonylbenzene groups and the formation of 2,3,6-trisubstituted pyridine (**3p**) as the main product in 74% yield. Several non-natural α-aromatic amino acids, such as 2-amino-2-phenylacetic acid and related derivatives, were found to be especially good substrates for this transformation (**3q**−**t** with good yields in most cases) because of the electron-withdrawing effect of their aromatic rings. Sterically hindered substituents were also employed, and the results were satisfactory (**3u** and **3v**). Cross-trapping product **3qv** could be obtained using **2a** (1.0 mmol) together with 1-(9*H*-fluoren-3-yl)ethanone (1.0 mmol) as substrates.

Having evaluated the scope of this new method, we turned our attention to the reaction of phenylalanine (**4a**) with acetophenone (**2a**). However, this reaction did not generate any of the desired product under the optimized conditions, but it did result in the formation of a small amount of 3,5-diphenylpyridine. Further investigation revealed that acetophenone did not participate in this transformation and that the 3,5-diphenylpyridine product was therefore formed as a consequence of the catabolism and homoreconstruction of phenylalanine through a C−N cleavage process. Because of this unusual transformation, we screened a variety of different solvents with the aim of improving the yield of the 3,5-diphenylpyridine product (for the optimization details, please see SI). Only DMSO gave a relatively meaningful yield (Table 2, entry 1). The optimal temperature for the reaction was determined to be 115 °C (Table 2, entry 2). The loading of I_2 was also examined. Addition of 0.2 equiv of I_2 led to a 20%

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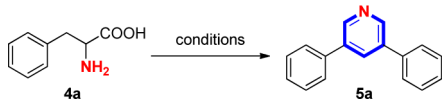
Table 2. Optimization of the Reaction 2[a]



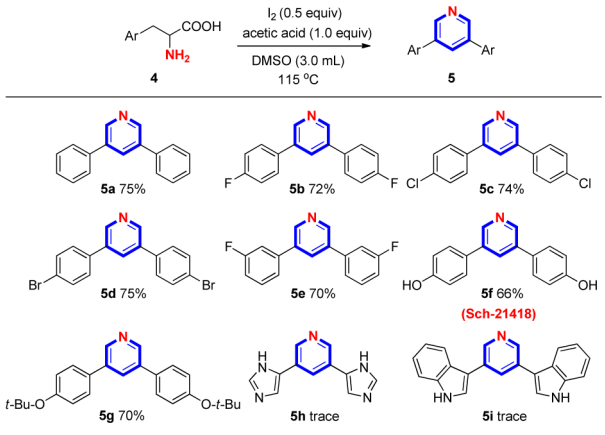
entry	I_2 (equiv)	additive (1.0 equiv)	temp (°C)	yield[b] (%)
1	1.0	–	100	31
2	1.0	–	115	46
3	0.2	–	115	20
4[c]	0.2	–	115	65
5	0.4	–	115	25
6	0.5	–	115	61
7	1.0	–	115	33
8	1.5	–	115	trace
9	0.5	K_2CO_3	115	25
10	0.5	NaOAc	115	trace
11	**0.5**	**HOAc**	**115**	**75**
12	0.5	acetic anhydride	115	70

[a]Reaction conditions: **4a** (1.0 mmol), I_2, additive, DMSO (3.0 mL) for 6 h. [b]Isolated yields. [c]Reaction time extented to 24 h. Reactions were carried out in a pressure vessel.

yield of the product (Table 2, entry 3). However, extension of the reaction time to 24 h lead to a 65% yield which means I_2 could be recycled by DMSO as a catalyst. The best result could be achieved when using 0.5 equiv of I_2 (Table 2, entry 6). An increased dose of I_2 lead to a dramatic reduction of desired product. Additives such as acids and bases have been scanned, and acetic acid was found to be optimal in reducing byproducts and improving the yield of **5a** (Table 2, entry 11).

Given that the yield of 3,5-diphenylpyridine achieved by this reaction was pleasing compared with that of "abnormal" *Chichibabin* pyridine synthesis,[15] we proceeded to investigate the scope of this conversion using a variety of phenylalanine derivatives bearing sensitive halogen substituents (4-F, 4-Cl, 4-Br, and 3-F; Scheme 2). All of these compounds gave the desired products in good yields. It is noteworthy that the reaction of tyrosine with a free hydroxyl group successfully furnished the interleukin-6 inhibitor Sch-21418[16] (**5f**) in 66% yield. The use of tyrosine derivatives bearing a *t*-Bu protecting group on their hydroxyl functionality gave **5g** (70%), which was

Scheme 2. Scanning of Substrate Scope of Reaction 2[a,b]

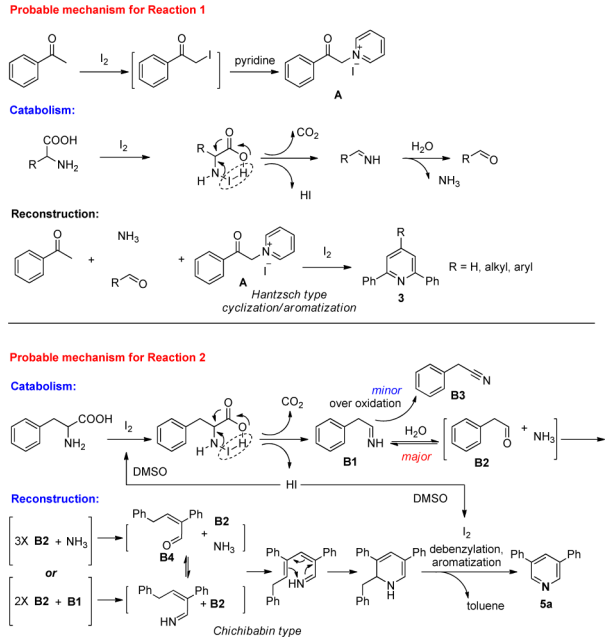


[a]Reaction conditions: **4** (2.0 mmol), HOAc (2.0 mmol), I_2 (1.0 mmol), DMSO (3.0 mL), 115 °C for 6 h. [b]Isolated yields. Reactions were carried out in a pressure vessel.

visualized as a white fluorescent dot by TLC. Unfortunately, histamine and tryptophan did not react in the same way.

The following control experiments were performed to provide some insight into the mechanisms of these reactions (for a detailed graphic, please see SI). For reaction 1, acetophenone was treated with 1.0 equiv of I_2 in the absence of an amino acid in pyridine under the standard conditions for 6 h. This reaction produced 1-(2-oxo-2-phenylethyl)pyridin-1-ium iodide (**A**) as a undissolved product in excellent yield. Given that the generation of the pyridinium ylide equivalent **A** would be an inevitable part of this reaction and pyridine was found to be critical to the success of this transformation, it seemed reasonable to assume that a pyridinium ylide was formed as a crucial intermediate during this reaction. The formation of **3q** in 71% yield from the reaction of amino acid **1q** with **A** in the absence of acetophenone provided further proof of this idea. However, the yield of this reaction was lower than that of the reaction shown in Scheme 3, which indicated

Scheme 3. Probable Mechanisms



that acetophenone played another role in the transformation. The subsequent reaction of **1q** with equal amounts of **A** and **2v** under the standard conditions gave the symmetrical products **3q** and **3v** in 7% and 34% yields, respectively. The cross-trapping product **3qv** was also obtained, as predicted, in a 45% yield. For reaction 2, we repeated the first reaction using 2-phenylethan-1-amine instead of phenylalanine (**4a**). However, this reaction failed to produce any trace of the desired product **5a** under standard conditions. This result suggests that the driving force for this reaction was the decarboxylation of the amino acid. The absence of a carboxyl group would make it difficult to activate the C–N bond at the α position, therefore preventing its oxidative cleavage by I_2. This result also suggests that this efficient I_2-mediated catabolism process is unique to amino acids. Furthermore, 2-phenylacetonitrile (**B3**), 2,4-diphenylbut-2-enal (**B4**), and toluene could be detected by GC-MS as intermediates.

Based on the results described above and previous research, we have proposed a plausible mechanism (Scheme 3). For

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reaction 1, the acetophenone substrate would be initially converted to 2-iodo-1-phenylethan-1-one, which would be trapped by pyridine to afford 1-(2-oxo-2-phenylethyl)pyridin-1-ium iodide (**A**). At the same time, I_2 would trigger the sequential decarboxylation and oxidation reactions of the amino acid substrate to generate the corresponding imine species, which would undergo a rapid hydrolysis reaction to give ammonia and the corresponding aldehyde. The ammonia, aldehyde, **A**, and residual acetophenone would converge via a Kröhnke type pyridine synthesis[17] to reconstruct the desired 2,6-disubstituted or 2,4,6-trisubstituted pyridine product in the presence of I_2. A similar mechanism would also occur for reaction 2 (with phenylalanine as an example). Followed by decarboxylation of carboxyl group, I_2 promoted the oxidation of the C−N bond to afford the unstable intermediate 2-phenylethan-1-imine (**B1**). After hydrolysis, phenylalanine catabolized to corresponding ammonia and 2-phenylacetaldehyde (**B2**). The combination of 3 equiv of **B3** with 1 equiv of ammonia (or 2 equiv of **B3** with 1 equiv of **B1**) would allow for the construction of the pyridine core in situ via a *Chichibabin*-type pyridine synthesis. Finally, the 3,5-disubstituted pyridine product could be obtained by a debenzylation/aromatizition process.[10a] This process would allow for the regeneration of a catalytic equivalent of I_2 in the presence of DMSO.

In summary, we have developed a novel method for the chemoselective synthesis of 2,6-disubstituted, 2,4,6-trisubstituted, and 3,5-disubstituted pyridines from natural amino acids. These transformations featured a catabolism and reconstruction reaction model including an unprecedented I_2-mediated oxidative cleavage of unreactive C−N bonds. In addition to the inherent value offered by this reaction as a biomimetic process, one of the main advantages of this environmentally benign method is that it avoids the direct use of toxic aldehydes and harsh conditions. Moreover, the transformation of biomass materials into synthetically valuable scaffolds is ecologically and economically beneficial.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03037.

Experimental procedures, product characterizations, crystallographic data, and copies of the ^1H and ^{13}C NMR spectra (PDF)

Crystallographic data for **3h** (CIF)

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Notes

The authors declare no competing financial interest.

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