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Oxidative Trimerization of Amino Acids: Selective Synthesis of 2,3,5-Trisubstituted Pyridines

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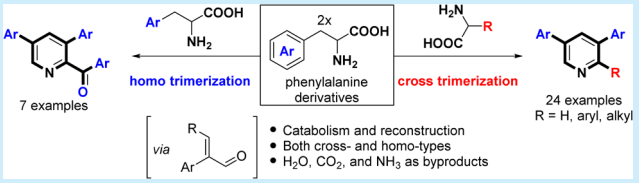
Supporting Information

ABSTRACT: An oxidative trimerization of three amino acids has been realized to furnish 2,3,5-trisubstuitued pyridines in both cross- and homo-trimerization types. This method is capable of converting simple linear biomass material to heterocycles, which features in the assembly of three amino acid branched chains into one aromatic ring. Molecular iodine triggers the sequential decarboxylation and deamination of amino acids and then promotes the selective formation of new C−N and C−C bonds.



Trimerization is a broadly existing and stimulating molecular behavior in chemistry.[1−3] This thermodynamically favorable conversion is a powerful maneuver to assemble three individual molecules into one linear or circular target through an entropy-decreasing process.[1b] Compared with the other oligomerization processes,[2] cyclotrimerization attracts more attention due to its capability of generating functionalized ring-closure products.[3] Comprehensive research has focused on the cyclotrimerization of alkynes[3a] and olefins[3b] to produce aromatic rings. Furthermore, extensive investigations have disclosed trimerizations of other small-molecule synthons that are similar in reaction models but differ in mechanisms. Examples include the trimerization of isocyanates,[3c] trifluoroacetones,[3d] quinols,[3e] aldehydes,[3f] nitriles,[3g] and others[3h−l] (Figure 1A).

However, as one of the most common and versatile synthons, amino acids are infrequently used as trimerization precursors. The trimerization behaviors of amino acids are present in nature. For example, vicibactin can be biogenerated from three naturally occurring ornithines via metabolic sequences (Figure 1B).[4] Previous endeavors using amino acids to prepare cyclic compounds by chemical means are few,[5,6] and the direct preparation of aromatic rings through trimerization of these renewable resources has yet to be reported. By simulating biological catabolism approaches, we found that amino acids can be activated by specific oxidizing agents in situ. With this arsenal, we have disclosed an unexpected oxidative cyclization reaction of phenylalanine to afford 3,5-disubstituted pyridines.[6] However, we failed to achieve higher oligomers since the third amino acid branched chain was not inserted into the final aromatic ring. Inspired by a better understanding of amino acid reactivity from our prior studies, this work focuses on the successful execution of the 2:1 cross-trimerization of amino acids to afford 2,3,5-trisubstituted pyridines.[7] Moreover, we accomplish the homotrimerization of

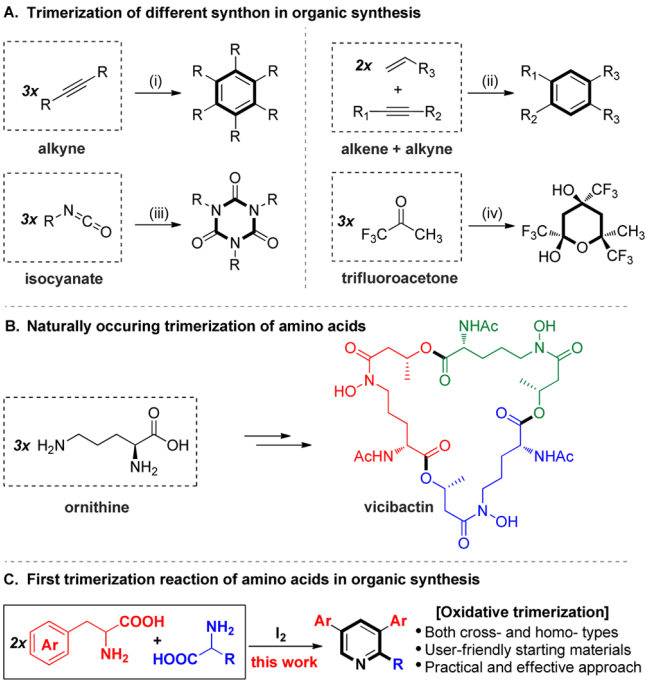


Figure 1. Trimerization behaviors in nature and organic synthesis.

phenylalanine to fill the research gap by switching the catalytic system (Figure 1C).

The cross-trimerization reaction, which leads to a higher diversity of products, was first investigated. Reactions of phenylalanine (**1a**) and 2-amino-2-(2-chlorophenyl)acetic acid (**2b**) were conducted for scanning the conditions (Table 1).

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Table 1. Reaction Optimization[a]

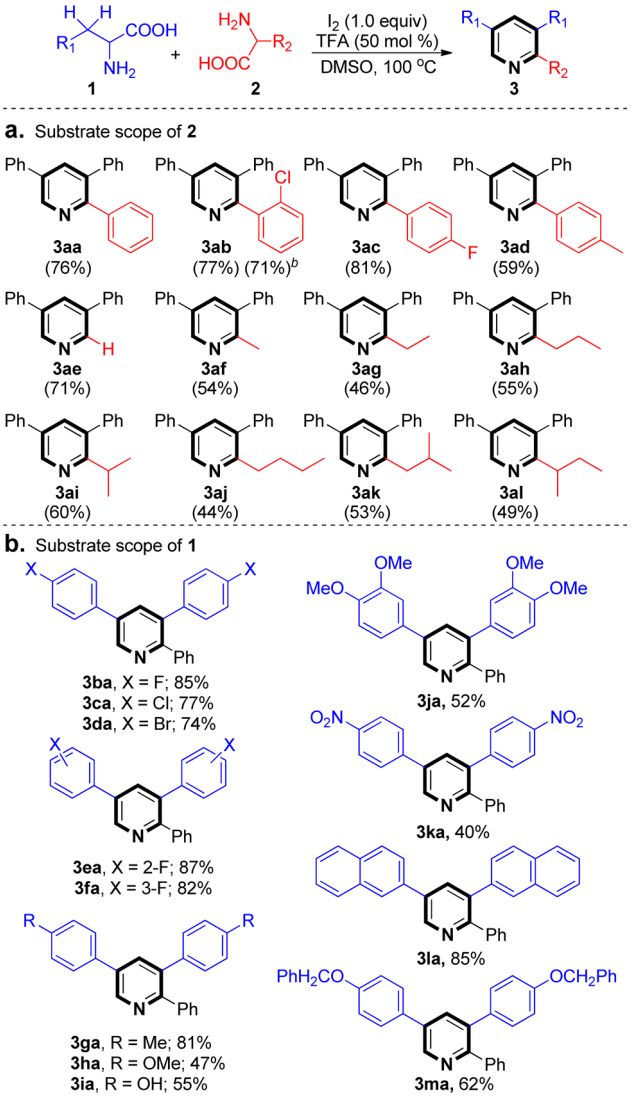
entry	I_2 (equiv)	acid (equiv)	1a/2b	temp (°C)	3ab[b] (%)	4 (%)
1	1.0		**2:1**	100	<10	61
2	1.0		**1:1**	100	32	40
3	1.0		**1:1.3**	100	37	29
4[c]	1.0	**HI (0.5)**	1:1.3	100	45	
5	1.0	**sulfanilic acid (0.5)**	1:1.3	100	<10	
6	1.0	**TfOH (0.5)**	1:1.3	100	55	
7	***1.0***	***TFA (0.5)***	***1:1.3***	***100***	*77*	***<10***
8	**0.2**	TFA (0.5)	1:1.3	100	<15	
9	**1.5**	TFA (0.5)	1:1.3	100	44	
10	1.0	TFA (0.5)	1:1.3	**rt**	trace	trace
11	1.0	TFA (0.5)	1:1.3	**60**	trace	trace
12	1.0	TFA (0.5)	1:1.3	**80**	38	
13	1.0	TFA (0.5)	1:1.3	**120**	66	
14	1.0	TFA (**0.2**)	1:1.3	100	33	
15	1.0	TFA (**1.0**)	1:1.3	100	75	<10

[a]Reaction conditions: **1a** (1.0 mmol), **2b**, acid, I_2, and DMSO (3.0 mL) were combined in a pressure vessel and then stirred at 100 °C for 6 h. TfOH = trifluoromethanesulfonic acid, TFA = trifluoroacetic acid. [b]Isolated yields. [c]Using hydriodic acid, 57 wt % solution in H_2O.

Inspired by our previous studies, 1.0 equiv of oxidizing agent I_2 was added, and DMSO was used as the solvent. When the substrates ratio was determined as **1a**/**2b** = 2:1, a formal dimerized product **4** was isolated as the predominant product (entry 1). When a 1:1 ratio of **1a**/**2b** was used, **3ab** was obtained in low yield (entry 2, 32%). The generation of byproduct **4** still affects the reaction efficiency. Excess **2b** (**1a**/**2b** = 1:1.3) weakens the formal dimerization and also induces the cross-trimerization reaction to enhance the chemoselectivity (entry 3). It was found that Brφnsted acid further improved the yield of **3ab**. As a result, several acids were investigated (entries 4−7), and trifluoroacetic acid (TFA) was chosen as the optimal one with both high yield and selectivity. Next, we screened the loading of I_2 (entries 7−9). The results show that a stoichiometric amount of I_2 was decisive. However, the use of excessive iodine was detrimental to the yield (entry 9, 44%). The optimal reaction temperature was investigated. Under low-temperature conditions (entries 10−12), the reaction medium stays heterogeneous due to the poor solubility nature of amino acids in cold solvent. Thus, the transformation is difficult to trigger. However, a high temperature was ineffective (entry 13, 66%). At last, the loading of TFA was evaluated (entry 14 and 15). The results show that a 50 mol % amount of acid was optimal in the cross-trimerization.

With the optimal conditions set, we tested the scope of the reaction (Scheme 1). Substrate **2** bearing aromatic-ring branched chains achieved the desired products in good yields (59−81%). Sensitive groups such as halogens were tolerated under these mild conditions, allowing further modifications (**3ab**, 77%; **3ac**, 81%). Moreover, conducted on 10 mmol scale, this reaction allows gram-scale preparation of **3ab** in 71% yield. When electron-donating substrate 2-amino-2-(*p*-tolyl)acetic acid was used as the substrate, the conversion provided **3ad** smoothly (59%). In addition, naturally occurring amino acids with alkyl branched chains performed well in this conversion

Scheme 1. Scope of Amino Acids in Cross-trimerization[a]



[a]Reaction conditions: **1** (1.0 mmol), **2** (1.3 mmol), TFA (50 mmol %), I_2 (1.0 mmol), and DMSO (3.0 mL) were combined in a pressure vessel and then stirred at 100 °C for 6 h. Isolated yields. [b]Conducted on 10 mmol scale, isolated yield.

(**3ae**−**al**) to achieve cross-trimerized products in moderate yields (44−71%). The substrate scope of **1** was further examined. Phenylalanine derivatives bearing halogen groups in all positions of aromatic rings provided the desired products (**3ba**−**fa**) with little difference in yields (74−87%). Both electron-donating and electron-withdrawing substituents on the aromatic rings (**3ga**−**ka**, 40−81%) were compatible. Notably, tyrosine was a valuable candidate in this reaction, providing a trisubstituted pyridine with two hydroxyl groups (**3ia**, 55%). Furthermore, the reaction using sterically hindered substituents such as naphthalene and benzyl groups proceeded well (**3la**, 85%; **3ma**, 62%).

From the above understanding of the scope in cross-trimerization, we focused on the homotrimerization behavior of three phenylalanines. When we used 2.3 equiv of phenylalanines under standard conditions without addition of **2**, the major product obtained was formal homodimerization product **4**. The third amino acid branched chain could not be inserted into the target product. We suggest that **4′** is unstable under

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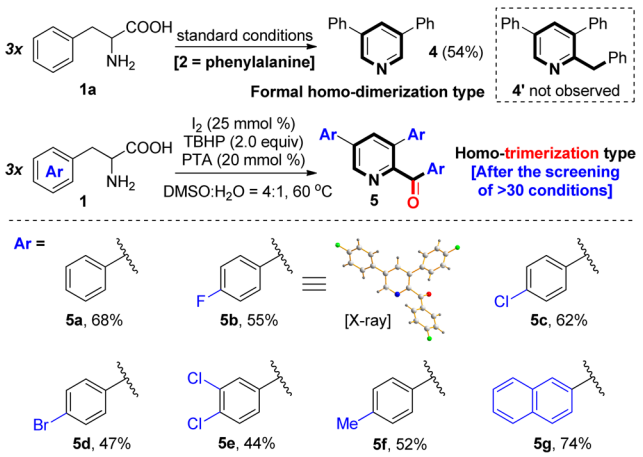
these oxidative conditions. After extensive optimization of the reaction conditions (see the Supporting Information (SI)), homotrimerization was achieved to obtain **5** as a stable product instead of **4′**. The reaction was conducted at 60 °C with *tert*-butyl hydroperoxide (TBHP) and phosphotungstic acid (PTA) as combined additives (Scheme 2). On the basis of previous

Scheme 2. Homo-trimerization of Phenylalanine.[a]

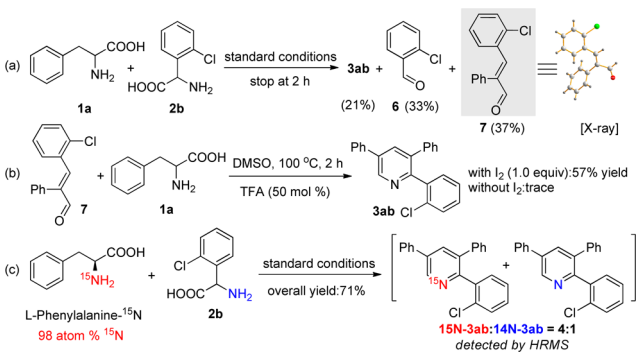


[a]Reaction conditions: **1** (1.0 mmol), phosphotungstic acid (PTA) (20 mmol %), *tert*-butyl hydroperoxide (TBHP) (2.0 equiv), I_2 (25 mmol %), and DMSO/H_2O = 4:1 (3.0 mL) were combined in a pressure vessel and then stirred at 60 °C for 6 h. Isolated yields.

studies, this homotrimerized product was afforded by further iodination and Kornblum oxidation of in situ generated **4′**[8] (for the mechanism, see the SI). Moreover, additional examples were synthesized[7d] to further verify this oligomeric selectivity. Bearing halogen groups (−F, −Cl, −Br, −Cl_2), **5b−e** could be obtained in medium yields (44−62%). Substrates with electron-donating groups (−Me) remain applicable (**5f**, 52%). 2-Amino-3-(naphthalen-2-yl)propanoic acid with a bulky electron-withdrawing groups reacted smoothly to afford **5g** in 74% yield. Structures of both cross- (**3da**) and homo-trimerization (**5b**) products were further confirmed by X-ray diffraction.

To illustrate the reaction mechanism, various control experiments were performed (Scheme 3). The reaction of **1a** and **2b** was conducted and stopped at 2 h, and three major products, **3ab**, 2-chlorobenzaldehyde (**6**), and *α,β*-unsaturated aldehyde (**7**) were isolated. I_2 triggered the catabolism of **2b** to afford **6** as an intermediate. Treating **7** with **1a** under standard conditions afforded **3ab** in the presence of I_2 with 57% yield,

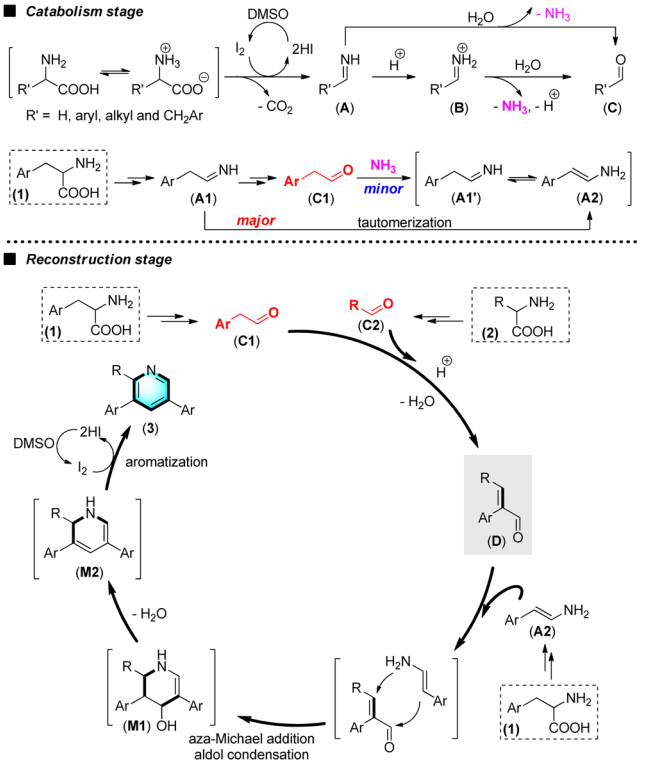
Scheme 3. Control Experiments



which determined that **7** is a vital intermediate to achieve the trimerization. The yield was poor because **1a** would undertake competing formal dimerization under these conditions in the absence of excessive amounts of **2**. Furthermore, I_2 is critical to achieve this step. Next, the origin of the nitrogen atom in the pyridine product was investigated. L-Phenylalanine-^{15}N was employed under the standard conditions to furnish ^{15}N-**3ab** and ^{14}N-**3ab** with 4:1 selectivity. The result of the isotope experiment suggests that the source of the nitrogen atom in pyridine comes from phenylalanine as a major pathway. A nitrogen-transfer process in which the nitrogen source is derived from phenylglycine could not be excluded.

On the basis of the above results and related reports,[6,7,9] a preliminary mechanism proposal is proposed in Scheme 4. The

Scheme 4. Mechanistic Proposal



reaction began with an I_2-promoted decarboxylation and oxidation reaction of amino acid to produce imine intermediate **A**. Then, rapid hydrolysis occurred to transform **A** or corresponding ammonium cation **B** into aldehyde species **C**. This tandem process is the catabolism stage of amino acids. According to that, phenylalanine (**1**) and phenylglycine (**2**) generated phenylacetaldehyde (**C1**) and benzaldehyde (**C2**), respectively. **C1** could further react with dropped ammonia to give **A1′** and **A2** as a couple of tautomers. Two catabolism products, **C1** and **C2**, underwent an aldol condensation to afford *α,β*-unsaturated aldehyde (**D**). Linear dimer **D** was then attacked by enamine (**A2**) in an aza-Michael addition followed by aldol condensation to give **M1**. Subsequently, ring-closure product **M1** underwent elimination and oxidation under the assistance of I_2 and TFA. Finally, aromatic product **3** was obtained by oxidative aromatization from regenerated I_2. This sequential three-component trimerization process was termed the reconstruction pathway.

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In conclusion, we demonstrate a straightforward pyridine synthesis from three amino acids. This new reaction reveals unusual cross- and homo-trimerization behaviors of amino acids which have potential synthetic utilities. This transformation, driven by nonfossil carbon renewable resources, features high chemoselectivity and good compatibility and is user-friendly. Mechanistically, I_2 activates amino acids in situ via decarboxylation and deamination reactions to afford α,β-unsaturated aldehyde intermediate. I_2 further assists the subsequent tandem process as a terminal oxidant to achieve consecutive C−C and C−N bond formations. 2,3,5-Trisubstituted pyridines with diversified substitution patterns could be readily prepared.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01232.

Experimental procedures, product characterization, crystallographic data, and ^1H and ^{13}C spectra (PDF)
X-ray data for compound **3ba** (CIF)
X-ray data for compound **5b** (CIF)
X-ray data for compound **7** (CIF)

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Notes

The authors declare no competing financial interest.

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