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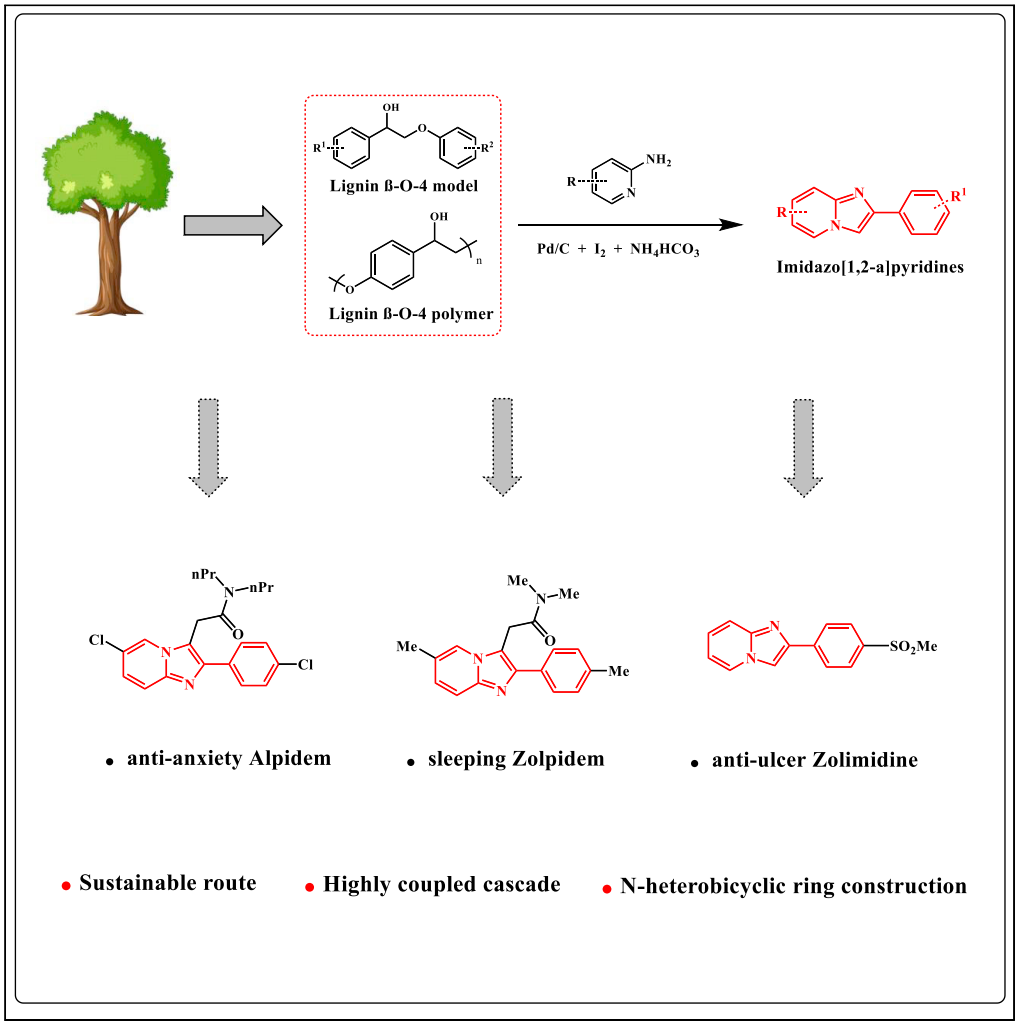

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Highlights

The conversion of β-O-4 model compounds to imidazo[1,2-a]pyridines

Highly coupled cascade reaction

Drug skeletons

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Imidazo[1,2-a]pyridine derivatives synthesis from lignin β-O-4 segments via a one-pot multicomponent reaction

Luxian Guo,[1,2,4] Yangming Ding,[1,4] Hua Wang,[1] Yuxuan Liu,[1] Qian Qiang,[1,2] Qi Luo,[1,3] Fei Song,[1,3] and Changzhi Li[1,2,5,*]

SUMMARY

The catalytic conversion of lignin into N-containing chemicals is of great significance for the realization of value-added biorefinery concept. In this article, a one-pot strategy was designed for the transformation of lignin β-O-4 model compounds to imidazo[1,2-a]pyridines in yields up to 95% using 2-aminopyridine as a nitrogen source. This transformation involves highly coupled cleavage of C-O bonds, sp^3C-H bond oxidative activation, and intramolecular dehydrative coupling reaction to construction of N-heterobicyclic ring. With this protocol, a wide range of functionalized imidazo[1,2-a]pyridines sharing the same structure skeleton as those commercial drug molecules, such as Zolimidine, Alpidem, Saripidem, etc., were synthesized from different lignin β-O-4 model compounds and one β-O-4 polymer, emphasizing the application feasibility of lignin derivatives in N-heterobicyclic pharmaceutical synthesis.

INTRODUCTION

With accelerating consumption of fossil resources and the increasing environmental concerns, lignocellulosic biomass as a renewable and abundant source of chemicals and fuels has recently attracted substantial attention.[1–5] Lignin, a major component of lignocellulose and a complex plant-derived heteropolymer, is a unique precursor for aromatic compounds.[6–8] However, most lignin in the paper and pulp industry has been discarded or burnt as a low-value fuel,[9] which not only wastes renewable resources, but also poses different environmental concerns. Lignin valorization has therefore become a major topic in biomass conversion field and would play an important role in improving the economics of the overall biorefinery associated with addressing the problem of environmental impacts. So far, great efforts have been devoted to selective cleavage of C-O and C-C linkages to obtain phenols,[2,10–14] arenes,[15] cycloalkanes,[16,17] aromatic aldehydes,[18] ketones,[19–21] acids,[22] and benzoquinones.[23] The above mentioned products are limited to C, H, O-containing compound.

Nitrogen-containing aryl compounds are typically value-added chemicals in the synthesis of biologically active pharmaceuticals and valuable materials.[24–27] Recently, the conversion of lignin and lignin-derived compounds into N-containing products appears as a direction for lignin valorization.[28–30] Li et al. described an efficient palladium-catalyzed formal cross-coupling of phenols with various amines and anilines to form aryl amines.[31] Wang et al. converted lignin models and preoxidized lignin to isoxazole and aromatic nitrile.[32] Maes et al. depicted a method that coverts lignin-derived 4-propylguaiacol to 3,4-dialkoxyanilines via a Beckmann rearrangement.[33] Han et al. reported Pd-catalyzed coupling of aryl ethers and morpholines to 4-cyclohexylmorpholines.[34] In our recent paper, we have accomplished the direct conversion of lignin β-O-4 dimers into benzylamines in the presence of organic amines overPd/C, and the potential of "lignin to benzylamines" was demonstrated by a two-step process.[24] More recently, heterocyclic aromatic compounds, such as pyrimidines,[26] functionalized quinolines,[25] and quinoxalines[27] have been synthesis from lignin β-O-4 segments via a one-pot multicomponent reaction. Of which, important marine alkaloid meridianin derivatives[26] and an important drug compound AG1295[27] were obtained, showcasing good examples for the valorization of lignin to pharmaceutical molecules.

Imidazo[1,2-a]pyridine derivatives are essential ingredients for marketed medicines such as anti-ulcer Soraprazan and Zolimidine,[35] vasodilator Olperinonr,[36] anti-anxiety Alpidem and Saripidem,[37] and sleeping

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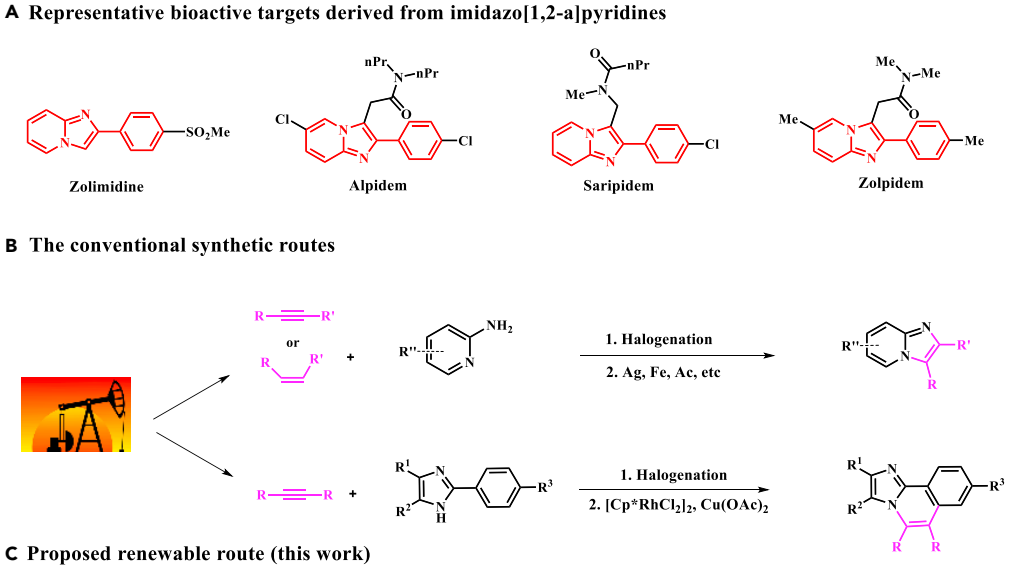


Scheme 1. Synthetic strategies to imidazo[1,2-a]pyridines

(A) Representative bioactive compounds derived from imidazo[1,2-a]pyridines.

(B) Current petroleum-based synthetic routes to imidazo[1,2-a]pyridines.

(C) The proposed renewable route in this work.

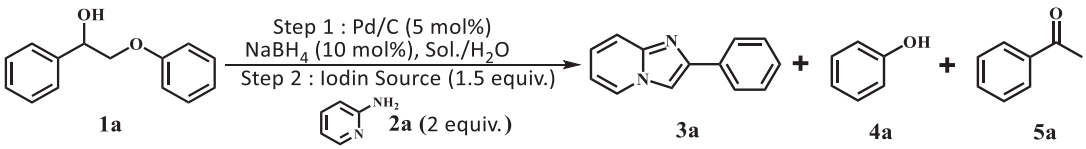
Zolpidem (Scheme 1A). In addition, the heterobicyclic skeleton of imidazo[1,2-a]pyridine has high fluorescence activity, which can be used in the research of genetic fluorescent markers.[38] Normally, The traditional synthesis methods of imidazo[1,2-a]pyridine derivatives are based on the construction of imidazole ring, which typically uses pyridines and olefins/alkynes as the starting materials via halogenation followed by *in-situ* generation of imidazole ring.[39,40] In another route, imidazo[1,2-a]pyridines can also be constructed based on the formation of pyridine ring through halogenation of alkynes coupled with nucleophilic addition of imidazole[41–43] (Scheme 1B). The above methods for the synthesis of imidazo[1,2-a]pyridine derivatives prevailingly rely on fossil-based feedstock and transition metal catalysts. Moreover, a great number of these progresses require multi-step synthetic routes, complicated ligands which suffer from high processing cost, low overall efficiency, and excessive waste emission. Hence, efficient strategy for the selective conversion of renewable feedstock such as lignin into such kind of products is highly desirable for cost-effective biorefinery conception and the sake of sustainable chemical industry.

Ketones are important type of substrates for the construction of imidazole skeleton.[44–46] Previous literature[47–49] including our own[19,50] have shown the possibility from lignin to aromatic ketones. It therefore provides us a potential choice using lignin β-O-4 segments as a renewable substrate for imidazo[1,2-a]pyridine production. Enlightened by the above cases, in this work, a one-pot two-step synthesis method of imidazo [1,2-a]pyridine derivatives from β-O-4 model compounds, by far the most frequent linkage in almost all types of lignin, using 2-aminopyridine as nitrogen source, commercial available Pd/C as catalyst and iodine as a promoter was developed (Scheme 1C). Such a strategy involves highly coupled cleavage of C-O bonds, dehydrative condensation, sp^3C-H bond oxidative activation, and intramolecular dehydrative coupling reaction. Moreover, a β-O-4 polymer that mimicking natural lignin, was successfully converted to imidazo[1,2-a]pyridine derivative based on this catalytic route.

RESULTS AND DISCUSSION

Our exploration started from the reaction of typical lignin β-O-4 model compound 2-(2-methoxyphenoxy)-1-phenylethanol 1a with 2-aminopyridine 2a to afford 2-phenylimidazo[1,2-a]pyridine 3a. This transformation is

Table 1. Conversion of β-O-4 model compound 1a with 2-aminopyridine 2a at different conditions

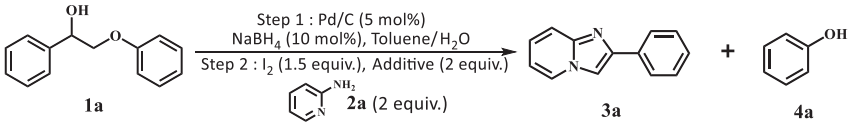


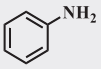
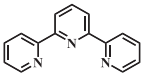
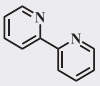
Entry[a]	Iodine Source	Solvent	3a Yield (%)	4a Yield (%)	5a Yield (%)
1	–	EtOAc/H_2O	0.0	95.3	92.6
2	KI	EtOAc/H_2O	0.0	94.8	85.1
3	CuI	EtOAc/H_2O	0.0	95.7	89.7
4	KIO_3	EtOAc/H_2O	31.5	96.1	trace
5	$NaIO_3$	EtOAc/H_2O	23.4	94.7	trace
6	KIO_4	EtOAc/H_2O	28.8	96.4	trace
7	$NaIO_4$	EtoAc/H_2O	26.6	96.0	trace
8	I_2	EtOAc/H_2O	40.0	95.3	–
9	I_2	CH_2Cl_2/H_2O	2.3	45.6	14.3
10	I_2	t-AmOH/H_2O	10.8	38.1	16.5
11	I_2	CH_3CN/H_2O	22.0	60.1	36.0
12	I_2	THF/H_2O	33.6	65.0	38.5
13	I_2	Toluene/H_2O	60.5	96.8	–

[a]Reaction conditions: Step 1: 1a (0.2 mmol), 5 wt% Pd/C (5 mol%), $NaBH_4$ (10 mol%) in water (0.5 mL), toluene (1.5 mL), 140°C, t = 2 h. Step 2: 2a (0.4 mmol), iodine source (0.35 mmol), 140°C, t = 15 h. Yield was determined by GC-FID using dodecane as an internal standard.

anticipated to have two major steps, namely cleavage of 1a to afford ketone intermediate acetophenone 5a, which then reacts with 2a to provide targeted product 3a. As Pd/C is a typical catalyst for C-O bond cleavage,[49,51,52] it is used in this work for dissembling of 1a. According to Samec et al. research, addition of catalytic amount of hydrogen source could activate Pd/C catalyst through a low energy barrier pathway.[47] Hence, 10 mol% $NaBH_4$ (based on 1a) was employed as hydrogen source to activate Pd/C. Because water is a good solvent for $NaBH_4$, it was selected as an integral solvent in the reaction. On the other hand, organic solvent is required to dissolve β-O-4 model compound. Therefore, a mixed solvent system containing water and organic solvent was adopted for this one-pot transformation. Our initial experiment was conducted without iodine source, it was found that no target product was generated (Table 1, entry 1), instead, C-O bond cleavage products 4a and 5a were obtained in excellent yields of 95.3% and 92.6%, respectively. In organic synthesis, molecular iodine has been used extensively in various reactions.[53,54] It can act as a mild oxidizing reagent,[55–57] and has mild Lewis acidic properties.[58,59] Molecular iodine has the lowest homolytic dissociation energy among the nonradioactive halogens (151 kJ/mol). After astatine, iodine has the lowest electronegativity among the halogens. Therefore it is much easier to generate the monocationic iodine species ('I^+') *in situ* than monocationic bromine or chlorine derivatives.[60] Das et al.[61] have reported that iodine source can promote the C-N bond formation between 2-aminobenzyl alcohol/2-aminobenzamide and different coupling partners (such as nitriles, aldehydes and ketones) to construct imidazole ring. Enlightened by this finding, we therefore added iodine in the reaction system, and obtained 40.0% of 3a yield (Table 1, entry 8). This encourages us to further screen different iodine sources. As shown in Table 1, this reaction is very sensitive to iodine species. In detail, iodine anions cannot promote the generation of 3a, the reactions in the presence of KI and CuI gave similar results to that without iodine source (Table 1, Entries 1–3), whereas it proceeded well in the presence of I_2, KIO_3, $NaIO_3$, KIO_4 and $NaIO_4$promotors (Table 1, Entries 4–8), indicating that the promotors containing iodine cations could also catalyze the reaction, albeilt they showed lower activity than iodine (Table 1, entry 8 vs. entries 4–7), which might due that these promotors have weaker electrophilicity than I_2. Therefore, I_2 was employed as a promotor in the subsequent reactions. To further improve the yield of 3a, the solvent system was then screened. Under the same conditions, the solvent mixture containing polar-aprotic solvents such as CH_2Cl_2, CH_3CN, tetrahydrofuran (THF) and ethyl acetate (EtOAc) gave 3a yield no more than 40% (Table 1, entries 8–12). Polar-protic solvent tert-amyl alcohol (t-AmOH) also provided 3a yield of 22%. Specifically, much higher 3a yield (60.5%), with 96.8% yield of phenol 4a (Table 1, entry 13) were obtained in toluene/water mixture (See Tables S1 and S2 for the screening of temperature and different solvents).

Table 2. Screening of Amine additives



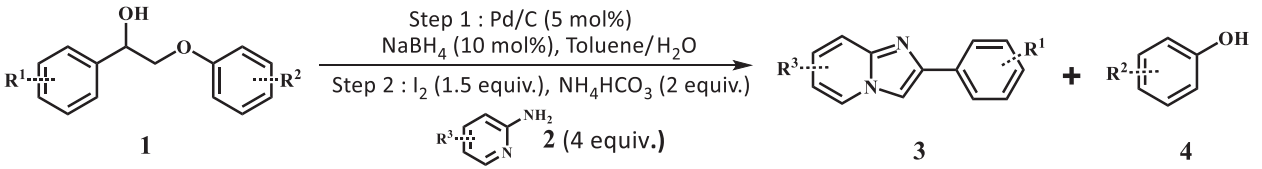
Entry[a]	Additive	3a Yield (%)	4a Yield (%)
1	–	60.5	96.8
2	NH_4Cl	47.3	96.5
3	NH_4OAc	62.5	95.9
4	NH_4HCO_3	71.6	96.3
5		43.5	95.2
6		61.5	94.1
7		68.1	93.4
8[b]	NH_4HCO_3	89.5	96.8

[a]Unless otherwise specified, the reaction conditions are: Step 1: 1a (0.2 mmol),5 wt% Pd/C (5 mol%), $NaBH_4$ (10 mol%) in water (0.5 mL), toluene (1.5 mL), 140°C, t = 2 h. Step 2: 2a (0.4 mmol), I_2 (0.35 mmol), additive (0.4 mmol), 140°C, t = 15 h. Yield was determined by GC-FID using dodecane as an internal standard.
[b]1a (0.2 mmol), 2a (0.8 mmol), NH_4HCO_3 (0.4 mmol).

It should be noted that the yield of 4a was always higher than 3a in all reactions, probably because 4a from depolymerization of lignin does not participate in downstream transformation, while the formation of 3a requires more steps from 1a. To sum up, the above experiments demonstrated the possibility for the conversion of lignin β-O-4 model compound into imidazo[1,2-a]pyridine derivatives. Yang[62] and Kapoor[63] disclosed that both amines and inorganic ammonium additives can promote the reaction.[62] Accordingly, several organic amines and inorganic ammoniums were added in the reaction system with the aim to further improve the conversion efficiency. It is gratifyingly to note that most of these additives gave better conversion results except for ammonium chloride and aniline (Table 2). Amongst all these additives, ammonium bicarbonate (NH_4HCO_3) exhibited the greatest acceleration effect, providing 3a in yield of 71.6% (Table 2, entry 4). We speculate that ammonium bicarbonate additive can promote the cyclization reaction[63] of acetophenone and aminopyridine in the presence of I_2, by releasing NH_3 to capture HI, a byproduct generated from the iodination of C_α in acetophenone, which will be further discussed in the following mechanism study. After optimizing the molar ratio of 1a and 2a (Tables S3 and S4), 3a yield up to 89.5% could be achieved (Table 2, entry 8).

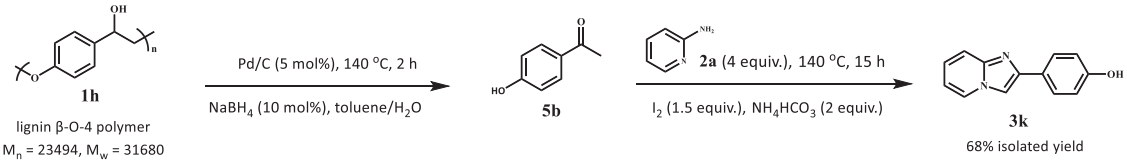
To examine the generality of this route, the activity of various lignin β-O-4 model compounds was explored. Substrates 1 with different functional groups on the aryl ring (Table 3) are found as fragments in different types of lignin.[26] Under optimized reaction condition, all β-O-4 model compounds were completely consumed to afford the corresponding imidazo[1,2-a]pyridines and monophenols, whereas the yields and selectivity showed some diversity. In detail, when β-O-4 model compounds 1a-1g containing different methoxy groups reacted with 2a, moderate to good isolated yields (64–89.5%) of imidazo[1,2-a]pyridines 3a-3c, with excellent yields (95–99%) of phenol derivatives 4a-4c were achieved (Table 3, entries 1–7), indicating that the formation of imidazo[1,2-a]pyridine heterobicycles occurred associated with selective C-O bond breaking and C-N bond construction. Compared with the β-O-4 model compound bearing no functional group, methoxyl substitution on the O-terminal aryl ring had slight negative impact on the product yield (Table 3, entry 1 versus entries 4–5), whereas methoxyl group on the C-terminus aryl ring exhibited greater negative influence on the reaction efficiency (74–80%) (Table 3, entry1 vs. entries 6–7). It is also

Table 3. Scope of lignin β-O-4 model compounds and aminopyridine for the synthesis of imidazo[1,2-a]pyridines



Entry[a]	Sub.1	Sub.2	3 Yield (%)	4 Yield (%)	Entry	Sub.1	Sub.2	3 Yield (%)	4 Yield (%)
1	1a	2a	3a 89.5%	4a 97%	8	1a	2b	3d 93%	4a 96%
2	1b	2a	3b 74%	4b 99%	9	1a	2c	3e 95%	4a 96%
3	1c	2a	3c 64%	4b 97%	10	1a	2d	3f 92%	4a 97%
4	1d	2a	3a 86%	4b 98%	11	1a	2e	3g 94%	4a 96%
5	1e	2a	3a 83%	4c 99%	12	1a	2f	3h 91%	4a 95%
6	1f	2a	3b 80%	4a 95%	13	1a	2g	3i 90%	4a 96%
7	1g	2a	3c 69%	4a 95%	14	1a	2h	3j 87%	4a 95%

[a]Reaction conditions: for step 1: 1a (0.2 mmol), 5 wt% Pd/C (5 mol%), $NaBH_4$ (10 mol%) in water (0.5 mL), toluene (1.5 mL), 140°C, t = 2 h. Forstep 2: 2a (0.8 mmol), I_2 (0.35 mmol), NH_4HCO_3 (0.4 mmol), 140°C, t = 15 h. Yield refers to isolated yield.



Scheme 2. Conversion of lignin β-O-4 polymer to imidazo[1,2-a]pyridine derivative 3k

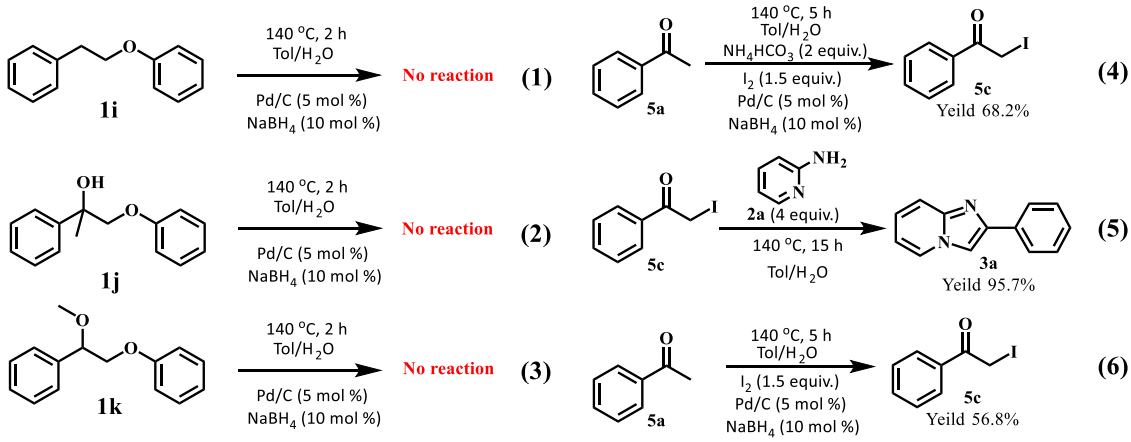
found that, the yields of heterocycle products were 89.5%, 86%, 74% and 64%, respectively, when the methoxyl groups of β-O-4 model compounds gradually increased from 0 to 4 (Table 3, entries 1, 4, 2, and 3). Overall, the more methoxyl groups on the aryl rings, the greater the negative impact on the reaction performance. Notwithstanding, this route leads to the successful cleavage of various β-O-4 model compounds and to the synthesis of imidazo[1,2-a]pyridines in a one-pot manner with fairly good yields. It is worth noting that all the prepared imidazo[1,2-a]pyridine molecules share the same structure skeleton as those commercial drug molecules (Scheme 1A), such as Zolimidine,[35] Alpidem,[61] Saripidem,[37] etc. It therefore can be expected that themselves, or after proper modification,[61] could have similar biological activity to above-mentioned drug molecules.

This reaction system has also proven to be effective for a broad range of aminopyridines. As shown in Table 3, seven aminopyridines have been successfully employed in the transformation, providing corresponding imidazo[1,2-a]pyridine products 3d-3j in high yields of 87%–95% (Table 3, entries 8–14). Aminopyridines possessing either electron-donating group (Table 3, entries 8–12,14) or electron-withdrawing group (Table 3, entry 13) on pyridine ring can react well with β-O-4 model compound to obtain excellent yield of imidazo[1,2-a]pyridines. Taking together, this one-pot catalytic system has proven to be effective not only for a variety of β-O-4 model compounds, but also for a broad range of aminopyridines. Lignin model compounds and aminopyridines with different functional groups are compatible to afford good to excellent yields of imidazo[1,2-a]pyridines, which thus offers an interesting opportunity for the valorization of lignin major segments to value-added N-heterobicyclic compounds.

To further determine the compatibility of the developed route, a β-O-4 polymer 1h (number-average molecular weight M_n = 23494, weight-average molecular weight M_w = 31680) that mimicking natural lignin was prepared and was then used as a substrate for the synthesis of imidazo[1,2-a]pyridine derivative. Under the same treatment condition as that in Table 3, 1h first underwent Pd/C-catalyzed C-O bond cleavage to afford *p*-hydroxyacetophenone 5b.

Subsequently, 5b reacted with 2-aminopyridine 2a in the presence of NH_4HCO_3/I_2, and the corresponding target product 3k was obtained in 68% overall yield (isolated) based on β-O-4 polymer (Scheme 2). Product 3k is very similar in structure to Zolimidine,[37] a commercially marketed anti-ulcer drug. Therefore, the above results further manifest the potential of this route in the synthesis of value-added N-heterobicyclic drug molecular from lignin β-O-4 polymer.

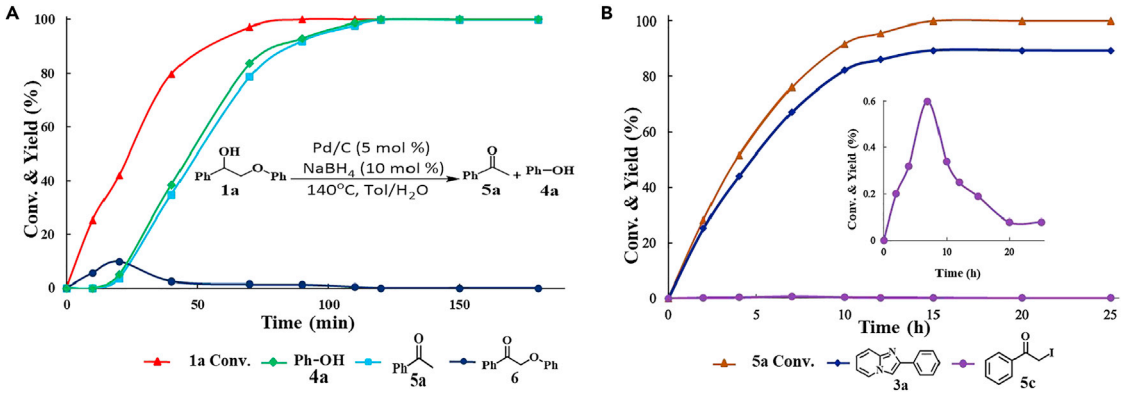
To understand the whole reaction scheme in depth, and to clarify the roles of different functional groups in β-O-4 aryl ethers, several comparative experiments were carried out to determine the possible reaction intermediates. For the first step, viz. the depolymerization of C-O bonds in β-O-4 model compounds, substrate 1i without substituted functional group in side chain cannot initiate any reaction over Pd/C in the presence of $NaBH_4$ at 140°C, which is in sharp contrast to the reaction of 1a (Scheme 3, Reaction 1 versus Table 3, entry 1), implying that the hydroxyl group at C_α position should play a key role. Substrate 1j, in which the C_α position is blocked by a methyl group, also did not react under the same condition (Scheme 3 and Reaction 2), suggesting the hydrogen at C_α position is involved in the reaction. The same result was obtained on compound 1k (Scheme 3 and Reaction 3), which contains a methoxyl group in the C_α position, indicating that the proton of hydroxyl group at the C_α position also plays an important role in the reaction. The above three experiments show that both the proton of hydroxyl group and the hydrogen at C_α position are involved in C-O bond breaking. According to the above cases and literature,[47] a plausible reaction pathway for the cleavage of C-O bonds of β-O-4 model compounds (taking 1a as an example) is proposed: the reaction begins with the dehydrogenation of 1a to produce intermediate 2-phenoxy-1-phenylethanone 6 and Pd/C-adsorbed hydrogen.[47] This hydrogen participates in the subsequent cleavage of C-O bonds via an intramolecular hydrogenolysis step to generate another intermediate acetophenone 5a, with phenol 4a as a final product. The



Scheme 3. Control experiments

following time course experiment using 1a as the substrate gives direct evidence on the proposed pathway. As shown in Scheme 4A, at the very beginning of the reaction (10 min), the conversion of 1a only provided 6, and the yield of 6 increased fast at the initial stage but then quickly decreased after 20 min. In parallel, 5a and 4a appeared after 10 min and the corresponding yields increased very slow at the initial stage (from 0 to 20 min) with increasing of the reaction time. Of interest, after 20 min, with the consuming of 1a, the yield of 6 showed a decline trend whereas the yields of both 4a and 5a increased faster than before. Apparently, 2-phenoxy-1-phenylethanone 6 would be a plausible intermediate for the generation of 4a and 5a.

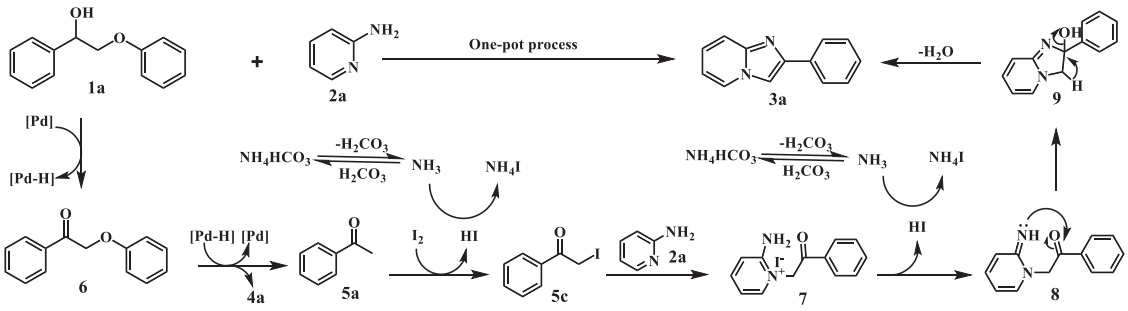
For the second step, to produce imidazo[1,2-a]pyridine compounds, we also carried out several comparative experiments to catch the possible reaction intermediates. First, treatment of acetophenone 5a alone under otherwise identical conditions yielded 68.2% of 2-iodo-1-phenylethanone 5c within 5 h (Scheme 3 and Reaction 4), indicating that the reaction of 5a with iodine to form 5c may be one step of the reaction. This assumption was confirmed by the reaction using 5c and 2a as the substrates, which afforded 95.7% of 3a, a slightly higher yield than that in Table 2, entry 8 using 1a as the substrate. According to the above facts, a plausible reaction pathway for the conversion of 5a to 3a is proposed: the reaction begins with the electrophilic substitution of α-H on acetophenone by I_2 to produce intermediate 5c. This intermediate then reacts with 2-aminopyridine 2a via a cascade cyclization-dehydration step to generate 3a as a final product. Aforementioned experiments in Table 2 have demonstrated the acceleration effect of NH_4HCO_3 on the whole transformation. Two comparative experiments in Scheme 3 Reactions 4 and 6) further showed that NH_4HCO_3 additive can promote the formation of intermediate 5c, namely the electrophilic substitution of acetophenone by I_2, because the reaction in Reaction 6 without NH_4HCO_3 gave lower



Scheme 4. Time course reactions

(A) Time course profile of compound 1a conversion overPd/C.

(B) Time course profile of compound 5a conversion.



Scheme 5. The plausible mechanism of the transformation of 1a to 3a

yield of 5c (56.8%) than Reaction 4 (68.2%) under the same conditions. The time course profile of 5a conversion (Scheme 4B) showed that 5a was almost quantitatively converted to 3a in the end, and 5c yield appeared a volcanic trend with the increase of time, indicating it is an intermediate during the transformation. Noting that only a very low yield of 5c was observed, one can expect 5c is rapidly converted into 3a once it is generated. Therefore, 5c formation might be a rate-determining step in the reaction.

Based on all above results, the possible mechanism of the whole transformation is proposed in Scheme 5. The dehydrogenation of 1a overPd/C forms intermediate 6 and [Pd-H] species,[47] then the *in-situ* generated [Pd-H] species participates the cleavage of the C-O bond of intermediate 6 to afford 5a and 4a. After adding I_2 in the reaction mixture, intermediate 5a reacts with I_2 via sp^3C-H bond oxidative activation to form another intermediate 2-iodo-1-phenylethanone 5c and HI. In this step, NH_4HCO_3 can promote the reaction via neutralization of HI through releasing NH_3. Once 5c is generated, a fast intermolecular nucleophilic substitution of 5c by 2-aminopyridine 2a occurs to obtain compound 7, which then releases intermediate 8 and HI via an intramolecular electron transfer. NH_4HCO_3further consumes HI and intermediate 8 undergoes an intramolecular cyclization to afford 9, which finally is dehydrated to targeted product 3a.

In conclusion, we have developed a route for the effective synthesis of imidazo[1,2-a]pyridines from lignin β-O-4 model compounds via a one-pot multicomponent transformation in the presence of pyridine, I_2 and Pd/C. The developed method shows versatility in production of various imidazo[1,2-a]pyridine derivatives by varying β-O-4 model compounds and the substituted aminopyridines. The feasibility for the production of imidazo[1,2-a]pyridine derivatives from lignin-related polymer has also been demonstrated. A highly coupled cascade pathway, including cleavage of C-O bonds, sp^3C-H bond oxidative activation and dehydration aromatization reaction has been established. The methodology described here makes it possible to build a bridge between renewable lignin and heterobicyclic aromatic compounds, thus providing a petroleum-independent choice for value-added fine chemicals and pharmaceutical molecules.

Limitations of the study

Unless otherwise specified, there are no limitations in this study.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2023.106834.

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AUTHOR CONTRIBUTIONS

C.L. conceived the project. L.G. and Y.D. contributed to the experimental studies and analyzed the data. H.W., Y.L., Q.Q., Q.L., and F.S. synthesized some of the intermediates. C.L. supervised the research. C.L. and L.G. contributed to the original draft of the manuscript, which was revised by all authors.

DECLARATION OF INTERESTS

There are no conflicts to declare.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Chemicals, Peptides, and Recombinant Proteins		
Pd/C	Cat. No. 75992	Sigma-Aldrich
Iodine	CAS: 12190-71-5	Mackun
2-phenylimidazo[1,2-a]pyridine	CAS: 4249-72-3	Mackun
NH_4HCO_3	CAS: 1066-33-7	Aladdin
$NaBH_4$	CAS: 1066-33-7	Aladdin
2-aminopyridine	CAS: 504-29-0	Mackun

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Changzhi Li (licz@dicp.ac.cn).

Materials availability

This study did not generate new unique reagents.

All reagents were purchased from commercial sources (Mackun, Aladdin, Sigma-Aldrich) and used without purification unless otherwise mentioned. Lignin model compounds 1a-1g were synthesized according to the literature.[19] 2-Phenoxyphenylethane was extracted according to the literature.2 2-methoxy-1-phenoxy-1-phenylethane was extracted according to the literature.[47] 2,3 A lignin-related polymer was synthesized according to the literature.[47] The products were purified by column chromatography over silica gel (200–400 size). Thin layer chromatography (TLC) analyses were conducted with glass-backed silica gel plates and visualized by UV light (254 nm). Flash column chromatography was performed using Qingdao Haiyang silica gel (200–300 mesh) with freshly distilled solvents. Gas chromatography (GC) analysis was performed on an Agilent 7890B gas chromatograph with a HP-5 MS column (quartz capillary column, 30 m × 0.25 mm × 0.25 μm). GC-MS analysis was carried out on a SHIMADZU GC-MS QP2020 NX with a HP-5 MS column (quartz capillary column, 30 m × 0.25 mm × 0.25 μm). NMR spectra were recorded on a Bruker 400 MHz or Bruker 700 MHz NMR spectrometer with TMS as the internal standard. Multiplicities are given as: s (singlet), d (doublet), t (triplet), q (quartet), brs (broad singlet), dd (doublets of doublet), dt (doublets of triplet), td (triplets of doublet) or m (multiplet).

Data and code availability

- This study does not generate new unique reagent.
- This paper does not report original code.
- Any additional information required to reanalyze the data reported in this paper can be obtained from the lead contact upon request.

METHOD DETAILS

Typical procedure for the Imidazo[1,2-a]pyridine synthesis from lignin β-O-4 model compound

Lignin model compound (0.2 mmol), Pd/C (22 mg, 0.01 mmol), magnetic stir bar, and Toluene (1.5 mL) were placed in the pressure tube (10 mL), next to the mixture freshly prepared $NaBH_4$ water solution (0.5 mL, 0.092M) was added. The mixture was sealed and heated to 140°C (oil bath temperature) for 2h. After the reaction, the solution was cooled to room temperature, Aminopyridine (4 equiv.), I_2 (89 mg, 0.35 mmol) and NH_4HCO_3(31.6 mg, 0.4 mmol) was added to the mixture. The mixture was sealed and heated to 140°C (oil bath temperature) for 15h. After the reaction, the solution was cooled to room temperature. The reaction mixture was quenched with NaS_2O_3 and extracted with ethyl acetate (3 × 15 mL) and dried

over anhydrous Na_2SO_4. The organic phase was analyzed by GC to determine the yield of imidazo[1,2-a] pyridines. Then the solvent was evaporated under reduced pressure, and the crude products were purified by column chromatography using petroleum ether/ethyl acetate (8:1) to obtain the desired products.

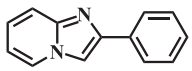
Procedure for cleavage of a lignin-related polymer

A lignin-related polymer was synthesized according to the literature.[47] Procedure for cleavage of the polymer: the lignin related polymer 1h (27.4 mg), Pd/C (22 mg), magnetic stir bar, and toluene (1.5 mL) were placed in the pressure tube (10 mL), then freshly prepared $NaBH_4$ water solution (0.5 mL, 0.092 M) was added. The mixture was then heated at 140°C for 2 h. After cooling the reaction mixture to room temperature, 1 mL dodecane EtOAc solution (10.8 mg/mL), and 5 mL EtOAc were added in the recation. Gas chromatography was employed to determine the yield of 5b using dodecane as internal standard.

Procedure for conversion of lignin-related polymer to 3k

The lignin related polymer (27.4 mg), Pd/C (22 mg), magnetic stir bar, and toluene (1.5 mL) were placed in the pressure tube (10 mL), next to the mixture freshly prepared $NaBH_4$ water solution (0.5 mL, 0.092M) was added. The mixture was then heated at 140°C for 2 h. After that, the solution was cooled to room temperature, 2a (75.2 mg), I_2 (89 mg) and NH_4HCO_3(31.6 mg) was added in. The mixture was sealed and heated to 140°C for another 15 h. After reaction, the solution was cooled to room temperature. The reaction mixture was quenched with NaS_2O_3 and extracted with ethyl acetate (3 × 15 mL) and dried over anhydrous Na_2SO_4. Then the solvent was evaporated under reduced pressure, and the crude products were purified by column chromatography using petroleum ether/ethyl acetate to obtain the desired product 3k in isolated yield of 68%.

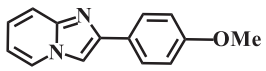
Characterization data for the products



3a

2-phenylimidazo[1,2-a]pyridine (3a)

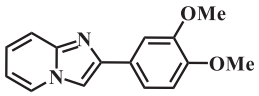
White solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.10 (d, 1H, J = 6.8 Hz), 7.95 (d, 2H, J = 7.6 Hz), 7.85 (s, 1H), 7.64 (d, 1H, J = 8.8 Hz), 7.43 (t, 2H, J = 7.6 Hz), 7.33 (t, 1H, J = 7.6 Hz), 7.17 (t, 1H, J = 8.0 Hz), 6.77 (t, 1H, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 145.8, 145.5, 133.5, 129.9, 128.7, 128.4, 128.0, 126.0, 125.6, 124.8, 117.4, 112.5, 108.1.



3b

2-(4-methoxyphenyl)imidazo[1,2-a]pyridine (3b)

Dark yellow solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.07 (m, 1H), 7.87 (dd, 2H, J1= 8.4 Hz, J2 = 1.2 Hz), 7.74 (d, 1H, J = 4.4 Hz), 7.60 (d, 1H, J = 9.2 Hz), 7.13 (m, 1H), 6.96 (dd, 1H, J1 = 8.4 Hz, J2 = 1.2 Hz), 6.74 (m, 1H), 3.84 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 159.5, 145.6, 145.5, 127.2, 126.3, 125.4, 124.5, 117.2, 114.1, 112.2, 107.2, 55.3.

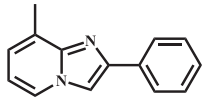


3c

2-(3,4-Dimethoxyphenyl)imidazo[1,2-a]pyridine (3c)

Yellow solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.84 (s, 1H), 7.74-7,72 (m, 1H), 7.61-7.54 (m, 1H), 7.48 (dd, J = 8.3, 1.6 Hz, 1H), 7.23 (t, J = 8.1 Hz, 2H), 6.96 (d, J = 8.3 Hz, 1H), 6.84 (t, J = 8.1 Hz, 1H), 4.03 (s, 3H), 3.95 (s, 3H);

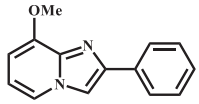
^{3}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 150.8, 149.0, 145.4, 144.2, 126.6, 125.0, 123.3, 118.6, 116.2, 112.5, 111.6, 110.0, 109.9, 56.0, 55.9.



3d

8-methyl-2-phenylimidazo[1,2-a]pyridine (3d)

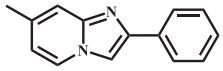
Yellow solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.97 (m, 3H), 7.82 (s, 1H), 7.44 (td, 2H, J1 = 7.6 Hz, J2 = 1.6 Hz), 7.32 (m, 1H), 6.93 (dt, 1H, J1 = 6.8 Hz, J2 = 0.8 Hz), 6.66 (t, 1H, J = 6.8 Hz), 2.67 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 146.2, 145.1, 134.0, 128.6, 127.7, 127.5, 126.1, 123.3, 123.2, 112.3, 108.5, 17.1.



3e

8-Methoxy-2-phenylimidazo[1,2-a]pyridine (3e)

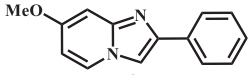
Yellow viscous liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 4.01 (s, 3H), 6.41 (d, J = 7.5 Hz, 1H), 6.64 (t, J = 7 Hz,1H), 7.30 (t, J = 7 Hz, 1H), 7.40 (t, J = 8 Hz, 2H), 7.71 (d, J = 6.5 Hz,1H), 7.80 (s, 1H), 8.00 (d, J = 7.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 54.7, 99.6, 108.1, 111.2, 117.4, 125.1, 126.7, 127.5, 132.5, 139.0, 143.8, 147.9.



3f

7-methyl-2-phenylimidazo[1,2-a]pyridine (3f)

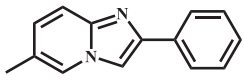
Light yellow solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.98 (d, 1H, J = 6.8 Hz), 7.94 (m, 2H), 7.77 (s, 1H), 7.42 (m, 3H), 7.32 (m, 1H), 6.60 (dd, 1H, J1 = 6.8 Hz, J2 = 1.2 Hz), 2.39 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 146.0, 145.3, 135.7, 133.7, 128.7, 127.8, 125.9, 124.7, 115.8, 115.1, 107.5, 21.4.



3g

7-Methoxy-2-phenylimidazo[1,2-a]pyridine (3g)

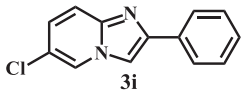
White solid;.^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.93–7.88 (m, 3H), 7.67 (s, 1H), 7.42 (t, J = 7.8 Hz, 2H),7.30 (t, J = 7.4 Hz, 1H), 6.90 (d, J = 2.4 Hz, 1H), 6.48 (dd, J =7.4, 2.5 Hz, 1H), 3.85 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 157.9, 147.1, 145.5, 133.9, 128.6, 127.6, 125.9, 125.7, 107.4,106.8, 94.7, 55.4.



3h

6-methyl-2-phenylimidazo[1,2-a]pyridine (3h)

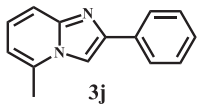
White solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.93 (m, 2H), 7.85 (m, 1H), 7.74 (d, 1H, J = 0.4 Hz), 7.52 (d, 1H, J = 9.6 Hz), 7.42 (m, 2H), 7.30 (m, 1H), 7.00 (dd, 1H, J1 = 9.6 Hz, J2 = 2.0 Hz), 2.29 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 145.3, 144.6, 133.8, 128.6, 127.8, 127.7, 125.9, 123.3, 122.0, 116.7, 107.8, 18.0.



3i

6-chloro-2-phenylimidazo[1,2-a]pyridine (3i)

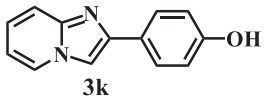
White solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.12 (d, 1H, J = 1.2 Hz), 7.92 (m, 2H), 7.79 (s, 1H), 7.56 (d, 1H, J = 9.6 Hz), 7.43 (t, 2H, J = 7.6 Hz), 7.34 (m, 1H), 7.11 (dd, 1H, J1 = 9.6 Hz, J2 = 1.6 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 146.7, 144.0, 133.2, 128.7, 128.2, 126.0, 123.3, 120.5, 117.8, 108.4.



3j

5-methyl-2-phenylimidazo[1,2-a]pyridine (3j)

Clear liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.98 (d, J = 7.7 Hz, 2H), 7.73 (s, 1H), 7.54 (d, J = 9.1 Hz, 1H), 7.42 (t, J = 7.6 Hz, 2H), 7.34 – 7.29 (m, 1H), 7.13 (dd, J = 9.1, 6.8 Hz, 1H), 6.60 (d, J = 6.8 Hz, 1H), 2.60 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 145.7, 134.3, 133.9, 128.7, 127.9, 126.0, 124.9, 114.9, 111.7, 105.3, 18.8.



3k

4-(imidazo[1,2-a]pyridin-2-yl)phenol (3k)

Brown solid; ^{1}H NMR (d_6-DMSO, 400 MHz) δ (ppm) 9.65 (s, 1H), 8.48 (d, 1H, J = 6.4Hz), 8.21 (s, 1H), 7.78 (d, 2H, J = 8.8 Hz), 7.53 (d, 1H, J = 8.8 Hz), 7.20 (m, 1H), 6.85 (m, 3H). ^{13}C NMR (d_6-DMSO, 100 MHz) δ (ppm) 157.4, 144.9, 144.6, 127.0, 126.7, 124.9, 124.5, 116.3, 115.5, 112.0, 107.6.