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Efficient pyrido[1,2-*a*]benzimidazole formation from 2-aminopyridines and cyclohexanones under metal-free conditions

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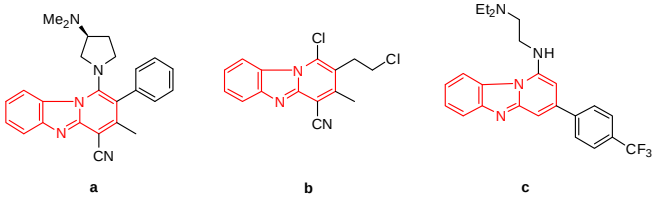
Yanjun Xie,[a] Jun Wu,[a] Xingzong Che,[a] Ya Chen,[a] Huawen Huang[a] and Guo-Jun Deng*[a,b]

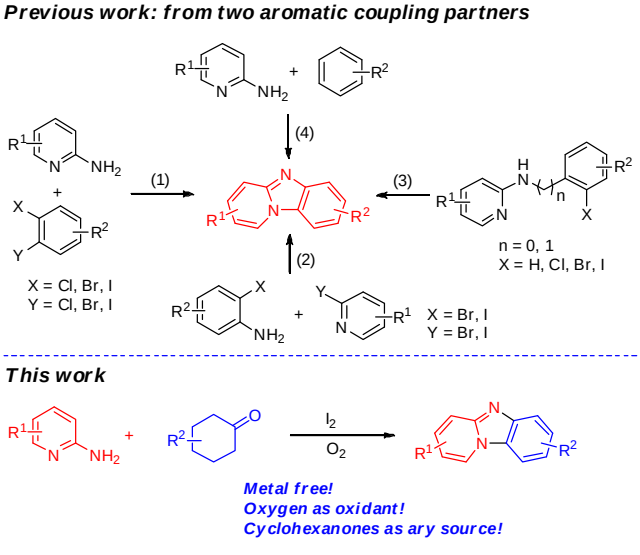
An efficient procedure for pyrido[1,2-*a*]benzimidazole preparation from 2-aminopyridines and cyclohexanones under metal-free conditions is described. Non-aromatic cyclohexanones were used as aryl source via dehydrogenation-aromatization process using molecular oxygen as the green oxidant.

Nitrogen-containing heterocycles are frequently found in natural products, pharmaceutical drugs, agrochemicals and functional materials.[1] Among them, pyrido[1,2-*a*]benzimidazoles which consist of three aromatic rings showed great potential as important drug candidates. For example, Rifaximin which widely used as antibiotic drug contains a pyrido[1,2-*a*]benzimidazole moiety.[2] Other pyrido[1,2-*a*]benzimidazole derivatives such as compounds **a-c** have been reported to possess antifungal activity via inhibition of *β*-1,6-glucan synthesis,[3] anticancer properties,[4] and antimalarial activity through inhibition of *Plasmodium* species,[5] respectively (Scheme 1).



Scheme 1 Selected important biologically active heterocycles containing pyrido[1,2-*a*]benzimidazole moiety.

Because of their important value in pharmaceuticals and material chemistry, the synthesis of pyrido[1,2-*a*]benzimidazole and its derivatives has attracted considerable interest. In general, four efficient synthetic routes were developed according to the manner of coupling partners (Scheme 2). The first route is mainly based the transition-metal-catalyzed one-pot nucleophilic substitution of 2-aminopyridines with *ortho*-dihalo arenes (Scheme 2, eqn 1).[6] The copper-catalyzed cascade C–N coupling of 2-halo anilines with 2-halo pyridines provided an alternative synthetic route (Scheme 2, eqn 2).[7] The third approach mainly based on the intramolecular cyclization of *N*-aryl-2-aminopyridines or *N*-benzyl-2-aminopyridines (Scheme 2, eqn 3).[8] Very recently, Antonchick and co-worker developed a metal-free annulation of arenes with 2-aminopyridine derivatives using $PhI(OAc)_2$ as the effective promoter (Scheme 2, eqn 4).[9] This strategy provided a straightforward access to pyrido[1,2- *a*]benzimizazole scaffold by avoiding functionalization of the aromatic substrates. All of these methods which are based on using two aromatic substrates have proven to be effective for the preparation of various substituted pyrido[1,2-*a*]benzimidazoles. However, as comparing with the extensively investigated imidazo[1,2-*a*]pyridines which have two aromatic rings,[10] environmentally benign and efficient synthetic routes for pyrido[1,2-*a*]benzimidazoles are still limited.



Scheme 2 Various procedures for pyrido[1,2-*a*]benzimidazole synthesis.

[a] *Key Laboratory of Environmentally Friendly Chemistry and Application of Ministry of Education, College of Chemistry, Xiangtan University, Xiangtan 411105, China; Fax: (+86)0731-5829-2251; Tel: (+86)0731-5829-8601; E-mail: gjdeng@xtu.edu.cn*
[b] *Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100080, China.*
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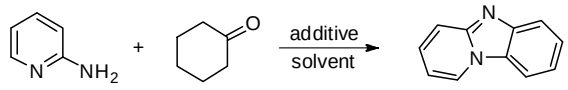
Cyclohexanones are commercially available, stable and widely used as raw materials to prepare many important bulk chemicals including aromatic phenols.[11] Recently, the Stahl group developed a strategy to selective convert cyclohexanones into phenols or cyclohexenones using Pd as the catalyst under mild reaction conditions.[12] We and others successfully trapped the dehydrogenation intermediates for further construction of C-C,[13] C-N,[14] C-O,[15] C-S[16] bonds as well as heterocycles[17] under oxidative conditions. In these transformations, cyclohexanones were used as a versatile aryl source via a dehydrogenation–tautomerization sequence.[18] Based on our previous research, we envision that it might be possible to prepare the biologically important nitrogen-containing imidazopyridines using cyclohexanones as the aryl source. Herein, we report a novel strategy for one-pot pyrido[1,2-*a*]benzimidazole formation from 2-aminopyridines and cyclohexanones under metal-free conditions using oxygen as the oxidant.[19]

Table 1 Optimization of the reaction conditions[a]



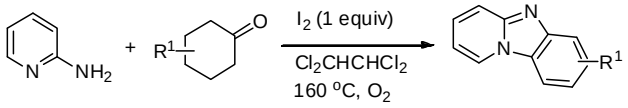
1a **2a** **3a**

entry	additive (equiv)	solvent	yield (%)[b]
1		1,1,2,2- tetrachloroethane	trace
2	KI (0.5)	1,1,2,2- tetrachloroethane	31
3	I_2 (0.5)	1,1,2,2- tetrachloroethane	48
4	NaI (0.5)	1,1,2,2- tetrachloroethane	27
5	I_2 (0.2)	1,1,2,2- tetrachloroethane	23
6	I_2 (1.0)	1,1,2,2- tetrachloroethane	92
7	I_2 (1.5)	1,1,2,2- tetrachloroethane	88
8	I_2 (1.0)	toluene	49
9	I_2 (1.0)	diglyme	25
10	I_2 (1.0)	*o*-DCB	70
11	I_2 (1.0)	DCE	79
12	I_2 (1.0)	NMP	54
13[c]	I_2 (1.0)	1,1,2,2- tetrachloroethane	73
14[d]	I_2 (1.0)	1,1,2,2- tetrachloroethane	76
15[e]	I_2 (1.0)	1,1,2,2- tetrachloroethane	21

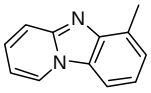
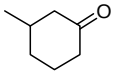
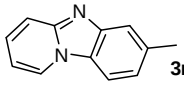
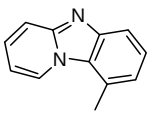
[a] Conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), solvent (0.9 mL), 160 °C, 24 h under oxygen unless otherwise noted. [b] GC yield based on **1a**. [c] 0.2 mmol of **2a** was used. [d] At 150 °C, [e] 24 h under air.

To get the optimized reaction conditions, we chose 2-aminopyridine (**1a**) and cyclohexanone (**2a**) as the model reaction in the absence of metal catalyst under an oxygen atmosphere (Table 1). When the reaction of 2-aminopyridine with 1.5 equiv. of cyclohexanone was performed in the absence of iodide-containing additive in 1,1,2,2-tetrachloroethane at 160 °C, no desired **3a** was formed as determined by GC-MS and ^{1}H NMR methods (entry 1). Gratifyingly, the starting materials were transformed into the desired product **3a** in 31% yield in the presence of KI (entry 2). Several iodide-containing chemicals were then investigated, and I_2 proved to be the most effective for this kind of transformation (entry 3). The amount of iodide-containing chemical is crucial to the reaction yield, and the desired product could be obtained in 92% yield when 0.2 mmol of I_2 was used (entry 6). Besides 1,1,2,2 tetrachloroethane, lower yield was obtained when the reaction was carried out in other organic solvents such as toluene, diglyme, *ortho*-dichlorobenzene, 1,2-dichloroethane and NMP (entries 8-12). The reaction yield was reduced to 76% when the reaction temperature was decreased to 150 °C (entry 14). Oxygen was necessary and much lower yield was obtained when the reaction was carried out in air (entry 15).

Table 2 Reaction of **1a** with various cyclohexanones (**2**)[a]



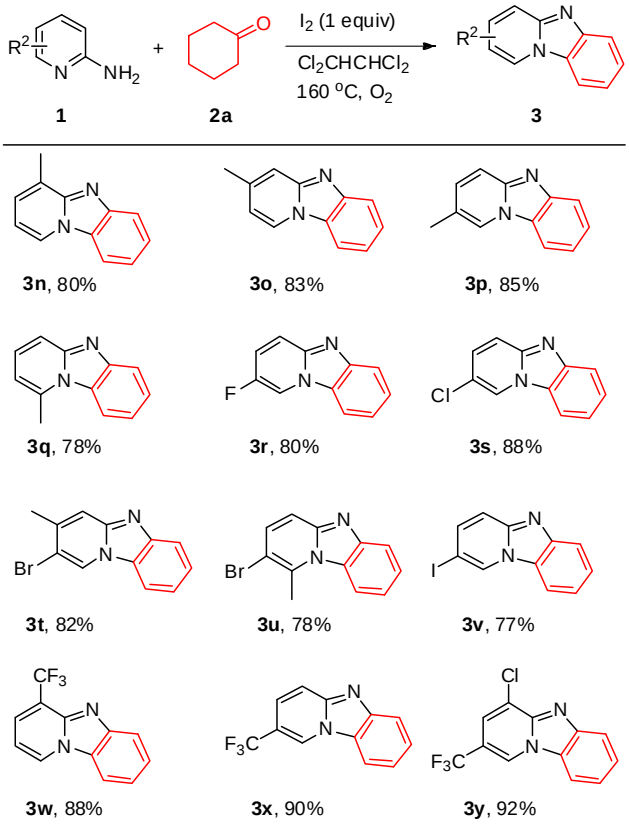
1a **2** **3**

entry	cyclohexanone		product		yield[b] (%)
1	R^1 = H	**2a**	**3a**		88 (78)[c]
2	R^1 = Me	**2b**	**3b**		89
3	R^1 = Et	**2c**	**3c**		87
4	R^1 = propyl	**2d**	**3d**		84
5	R^1 = isopropyl	**2e**	**3e**		83
6	R^1 = *tert*-butyl	**2f**	**3f**		83
7	R^1 = *n*-pentyl	**2g**	**3g**		86
8	R^1 = *tert*-pentyl	**2h**	**3h**		68
9	R^1 = Ph	**2i**	**3i**		88
10	R^1 = CO_2Et	**2j**	**3j**		83
11		**2k**		**3k**	64
12		**2l**	**3a**		76
13		**2m**		**3m**	88 (**3m**:**3m'** =3:2)
				**3m'**	

[a] Conditions: **1a** (0.2 mmol), **2** (0.3 mmol), I_2 (1.0 equiv.), 1,1,2,2-tetrachloroethane (0.9 mL), 160 °C, 24 h under oxygen. [b] Isolated yields based on **1a**. [c] Ten mmol scale reaction yield in parenthesis.

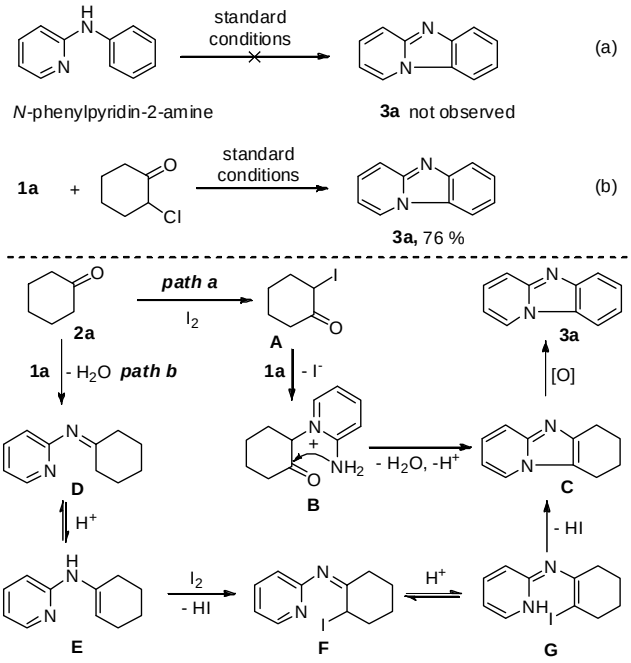
With the optimized reaction conditions in hand, we then investigated the scope of the reaction with respect to 2-aminopyridine and various cyclohexanones (Table 2). The model reaction of **1a** with **1b** gave the desired product **3a** in 88% isolated yield (Table 2, entry 1). When the same reaction was carried out on 10 mmol scale, **3a** was obtained in 78% isolated yield. Various 4-alkyl cyclohexanones smoothly reacted with 2-aminopyridine (**1a**) to give the corresponding products in good yields (entries 2-8). The chain length of alky substituents did not make much difference on the reaction yields. The desired product **3i** was obtained in 88% yield when 4-phenylcyclohexanone (**2i**) was treated with 2-aminopyridine (**1a**) under the optimized conditions (entry 9). To our delight, active ester group was well tolerated to afford the corresponding product **3j** in 83% yield (entry 10). A relatively lower yield of **3k** (64%) was obtained when a methyl group was located at the *ortho* position of cyclohexanone due to the steric effect (entry 11). When 2-chlorocyclohexanone (**2l**) was employed as the substrate, **3a** was obtained in 76% yield and no chloro-containing product (**3l**) could be observed (entry 12). When the methyl group was located at the *meta* position, a mixture of two isomers was isolated in a combined yield of 88% with a ratio of 3:2 (entry 13).

Table 3 Reaction of **2a** with various 2-aminopyridines (**1**)[a]



[a] Conditions: **1** (0.2 mmol), **2a** (0.3 mmol), I_2 (1.0 equiv.), 1,1,2,2-tetrachloroethane (0.9 mL), 160 °C, 24 h under oxygen, isolated yields based on **1**.

To further explore the scope of the reaction, a number of substituted 2-aminopyridine derivatives were employed to react with cyclohexanone (Table 3). In general, good to excellent yields were obtained under the standard reaction conditions. Varying the position of the methyl substituent on 2-aminopyridine had little effect on the outcome of the reaction and the corresponding products **3n**, **3o**, **3p**, and **3q** were all obtained in good yields. Halogen functional groups such as fluoro, chloro, bromo, and even iodo were well tolerated to give the corresponding products **3r**-**3v** in good to high yields. Pyridines bearing an electron-withdrawing trifluoromethyl group at different positions were smoothly reacted with **2a**, affording the corresponding products **3w** and **3x** in 88% and 90% yields, respectively. Finally, it was found that di-substituted 2-aminopyridine with chloro and trifluoromethyl groups was good substrate for this kind of transformation to give the desired product **3y** in 92% yield.



Scheme 3 Control experiments and plausible reaction pathway.

To have a better understanding of the reaction, a control experiment was performed. When *N*-phenylpyridine-2-amine which is a possible intermediate to give the final product via intramolecular Csp^2-H amination reaction was treated under the standard reaction conditions, no desired product **3a** could be obtained (Scheme 3a). This means the biaryl intermediate was not formed during the reaction process. As we previously mentioned, **3a** was obtained when 2-chlorocyclohexanone (**2l**) reacted with **1a** (Scheme 3b). This means the cyclohexanones may be iodinated firstly. Based on these observations and our previous research, the plausible reaction pathway is illustrated in Scheme 3. Cyclohexanone **2a** is iodinated with iodine to give 2-iodocyclohexanone (**A**).[17b, 17e] Nucleophilic substitution of 2-aminopyridine (**1a**) with **A** affords an intermediate **B**.[20] Subsequent tntramolecular cyclization of **B** provides 6,7,8,9 tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyridine (**C**). Alternatively,

condensation of **1a** with **2a** affords an imine intermediate **D**,[21] which can be further converted into intermediate **E** via isomerisation reaction. Iodination of **E** with iodine generates compound **F,** which can further isomerize into intermediate **G**. Intramolecular substitution of the iodo group with amine also provides **C**. Dehydrogenation-tautomerization of **C** under oxidative and acidic conditions affords the final product **3a**.[17, 22, 23]

Conclusions

In summary, we have developed a novel approach for the synthesis of nitrogen-containing pyrido[1,2-*a*]benzimidazoles from 2-aminopyridines and cyclohexanones under metal-free conditions. Iodine could smoothly mediate this kind of transformation without the aid of metal catalyst. Oxygen was used as an environmentally benign oxidant to give the corresponding products in good to high yields. The reaction showed good substrate scope and various functional groups such alkyl, ester, and halogens were well tolerated under the optimized reaction conditions. This method affords an efficient approach for biologically active nitrogen-containing heterocycles using non-aromatic cyclohexanones as the aryl source. The mechanism and synthetic applications of this reaction are under investigation.

Acknowledgements

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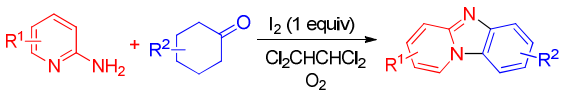
23 After completion of the reaction, the pH value of the reaction mixture is about 3.

Efficient pyrido[1,2-*a*]benzimidazole formation from 2-aminopyridines and cyclohexanones under metal-free conditions

Yanjun Xie,[a] Jun Wu,[a] Xingzong Che,[a] Ya Chen,[a] Huawen Huang[a] and Guo-Jun Deng[a,b] *



Pyrido[1,2-*a*]benzimidazole derivatives were selectively prepared from 2-aminopyridines and cyclohexanones under metal free conditions.