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FeCl₃-catalyzed sequential cyclization for the construction of 12-aryl 5,7dihydropyrido[2,3-*b*:6,5-*b*']diindoles

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ABSTRACT

A facile approach to prepare 12-aryl 5,7-dihydropyrido[2,3-*b*:6,5-*b*']diindoles via tandem cyclizations is described. FeCl₃ is used as the catalyst for the reaction between *o*-aminophenylacetonitriles and aromatic aldehydes, generating 5,7-dihydropyrido[2,3-*b*:6,5-*b*']diindoles derivatives in moderate to high yields.

Available online Keywords: FeCl₃ Tandem cyclizations Aminophenylacetonitrile Aromatic aldehyde 5,7-Dihydropyrido[2,3-b:6,5-b']diindole

 α -carboline represents a core scaffold that occur in a number of natural products, some of which exhibit a wide range of biological and pharmacological activities, such as high cytotoxicity, anticancer properties and CNS activities.^[1] For example, grossularine-1 and grossularine-2 marine alkaloids isolated from Dendrodoa grossularia, possess high cytotoxicityagainst solid human tumour cell lines.^[2] Similarly, N,N-didesmethylgrossularine-1 Indonesian from ascidian Polycarpa aurata exhibits inhibitory activity against tumour necrosis factor (TNF-a) production.^[3] Furthermore, mescengricin from a culture of Streptomyces griseoflavus has shown significantly prevent L-glutamate toxicity (Figure 1).^[4] Besides medical applications, carboline derivatives have been used as electronic transport units in host materials, bacause of their promising electronical and photophysical properties.^[5]



R= 3-indolyl or p-hydroxyphenyl

Grossularines

Mescengricin

Figure 1. Biological active molecules containing α -carboline structure.

Owning to the α -carbolines' marked biological and photoelectrical activities, much effort has been devoted to the synthesis of the privileged α -carboline scaffold.^[6] Recently, a series of useful methods including modified Graebe–Ullman

reaction of triazoles,^[7] intramolecular hetero Diels-Alder cycloaddition-aromatization,^[8] transition metal-catalyzed coupling-cyclization,^[9] as well as annulation of pyridine ring to indole derivative,^[10] have been reported. Notably, Langer et al. developed an efficient two-step procedure for the preparation of 5,7-disubstituted 5,7-dihydro-pyrido[2,3-b:6,5-b']diindoles, via a double Suzuki cross-coupling reaction followed by a fourfold Buchwald-Hartwig amination reaction (Scheme 1a).^[11] The electrochemical and photochemical properties of 5,7-dihydro-pyrido[2,3-b:6,5-b']diindoles were investigated in their work. However, methodologies previously reported conditions required the synthesis to include noble metal catalysts, strong acidic conditions, multi-steps and/or specific oxidants.

In the past few years, the employ of iron salts as the catalyst or promoter in synthetic chemistry has sparked tremendous interest in the scientific community.^[12] Owning to iron salts' low price, non-toxicity and environmentally benign character, iron salts show great advantages in terms of sustainable chemistry and represent an attractive alternative to other noble metals.^[13] Our previous work has been focused on heterocyclic synthesis and cascade reaction.^[14] Recently, we developed two facile protocols for the synthesis of α -carbolines via FeCl₃-promoted tandem cyclization process.^[15] Herein, we report a novel FeCl₃-catalyzed synthetic method to 12-aryl 5,7-dihydropyrido[2,3-b:6,5b'diindoles via the reaction between o-aminophenylacetonitrile and aromatic aldehydes (Scheme 1b). In the presence of FeCl₃, three heterocyclic rings can be formed through a sequential cycloaddition-Friedel-Crafts-alkylation-condensationdehydrogenation process at once.

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Scheme 1 (a) Synthesis of 5,7-disubstituted 5,7-dihydro-pyrido[2,3-b:6,5-b']diindoles *via* the Pd-catalyzed two-step couplings; (b) FeCl₃-catalyzed synthesis of 12-aryl 5,7-dihydropyrido[2,3-*b*:6,5-*b*']diindoles discussed in this work.

Initially, we applied $Fe(OTf)_3$ as the catalyst to the model reaction of 2-(2-(methylamino)phenyl)aceto-nitrile 1a with benzaldehyde 2a. To our delight, the desired product 12-phenyl 5,7-dihydropyrido[2,3-b:6,5-b]diindoles 3a was obtained in 72% yield after 4 h at 110°C (Table 1, entry 1). This reaction underwent tandem cycloaddition-Friedel-Crafts alkylationcondensation-dehydrogenation process. Encouraged by the result, other iron/copper salts were investigated, such as FeCl₃, FeCl₃·6H₂O, Cu(OTf)₂ and Cu(OAc)₂·2H₂O (Table 1, entries 2-5). It could be found that FeCl₃ was the best choice, giving rise to the product 3a in 78% yield (Table 1, entry 2). Bronsted acid (TfOH) was also tried, but only 31% yield was obtained (Table 1, entry 6). Lowered temperatures result in a dramatic drop in yield (Table 1, entries 7 and 8). No product was observed in the absence of any iron salts (Table 1, entry 9). The result indicates that iron salts play an important role in the tandem cyclizations procedures. Subsequently, the effect of solvents in this transformation was evaluated [ClCH2CH2Cl, PhCl, 1,4-dioxane, DMF and DMSO] (Table 1, entries 10-14). The result revealed that toluene was the most suitable solvent. When the amount of FeCl₃ was inhanced to 20 mol%, **3a** was isolated in a comparable yield (Table 1, entry 15, 77%).

Table 1 Optimization of reaction conditions.^a



e-proo	18			
11	FeCl ₃	PhCl	110	68
12	FeCl ₃	1,4-dioxane	110	55
13	FeCl ₃	DMF	110	39
14	FeCl ₃	DMSO	110	43
15°	FeCl ₃	toluene	110	77

^aReaction conditions: **1a** (0.5 mmol), **2a** (0.2 mmol), catalyst (10 mol%), solvent (1 mL), 110 °C under air, 4 h. ^bIsolated yields of **3a**. ^cCatalyst (20 mol%).

With the optimized conditions in hand (see entry 2 in Table 1), the substrate scope for the reactions of *o*-aminophenylacetonitrile **1a** with various ArCHO **2** was then studied (Table 2). As for the ArCHO **2**, when the phenyl containing *p*-, *m*-, or *o*-Me substituent, the reaction proceeded smoothly, producing the 12aryl 5,7-dihydropyrido[2,3-b:6,5-b']diindoles **3b-d** in 68-83% yields under standard conditions. ArCHO with tertiary butyl group could also take part in the reaction (**3e**), but strong electron-donating groups (MeO or Me₂N) resulted in lower yields (65% of **3f** and 41% of **3g**).

Table 2
The reaction of o-aminophenylacetonitrile 1
with

ArCHO 2.^{a,b}
Image: Comparison of the second second



^aReaction conditions: **1a** (0.5 mmol), **2** (0.2 mmol), FeCl₃ (10 mol%), toluene (1 mL), 110 °C under air, 4 h. ^bIsolated yields of **3**.

The strong electron-withdrawing group CN on the benzene ring was also tolerant, and the corresponding product **3h** was obtained in 71% yield. Other halogenated ArCHO could also participated in the reaction, forming the products **3i-o** in good yields. Heteroaryl aldehyde were also tolerant in this reaction and showed 59% yields (**3p**). Then we investigated the effect of the substituent groups on the NH₂ of **1**. Methyl- and ethylamino substituted **1** could also take part in the cyclizations, forming the products **3q-y** in good yields. When 2-(2-

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aminophenyl)acetonitriles 1 contained Br atom, the reaction went soomthly to give 3z in 75% yield. However, when alkyl aldehyde (heptaldehyde or cyclohexanecarbaldehyde) was used as the substrate, no desired product was obtained.

Moreover, to expand the practicality of this synthesis method, a gram-scale reaction of **1a** (25 mmol) and **2b** (10 mmol) was carried out, and the desired product **3b** was obtained in 61% yield (2.12 gram).

To explore photophysical properties of synthesized compounds, we performed UV-Vis absorption and fluorescence measurements of selected compounds 3g, 3h, 3i, 3t and 3x. The UV-Vis absorption spectra show absorption bands with maxima around 300 nm and 370 nm exhibiting analogous fine structures (Figure 2). As for the fluorescence emission spectra, the fluorescence intensity of *N*-Me substituted products (3t and 3x) was distinctly lower than *N*-H products (3g, 3h and 3i) (Figure 3). It could be attributed to the resonance of the fused ring structure, which was suppressed by the *N*-Me group.



Figure 2. UV-Vis absorption spectra of 3g, 3h, 3i, 3t and 3x (10 μ M in MeOH).



Figure 3. fluorescence emission spectra ($\lambda_{ex} = 360$ nm) of **3g**, **3h**, **3i**, **3t** and **3x** (1 μ M in MeOH).

To gain insight into the mechanism, two control experiments were carried out. As described in Scheme 3a, when only 1q was carried out in the standard conditions, the result was complicated. But indol-2-amine A could be determined by GC-MS (Scheme

2a). Furthermore, when indol-2-amine hydrochloride was treated with base, and then added into the reaction under the standard conditions, 52% yield of 3q was observed as well (Scheme 2b). This result probably indicated that indol-2-amine **A** would be the key intermediate for this tandem process.



Scheme 2 Control experiments.

Furthermore, it was found that Schiff base was generated in the reaction process by TLC, which could gradually release aldehyde. Based on the result and other works,^[15b,16] a plausible reaction pathway is proposed in Figure 4. Firstly, **1a** generated intermediate **A** through intramolecular cyclization under the catalysis of iron salt. Intermediate **A** rapidly reacted with **2a** to form intermediate **B** by activation of FeCl₃. Then intermediate **C** was generated through tautomerization, which underwent Fridel-Crafts reaction producing intermediate **D**. Subsequently, an intramolecular nucleophilic addition process occured to give intermediate **E**. Because of the instability of **E**, the release of a molecule of NH₃ from **E** generated **F**. Finally, the target product **3a** was formed via an aromatization process.



Figure 4. Proposed reaction pathway to 12-aryl 5,7-dihydropyrido[2,3-*b*:6,5-*b*]diindoles.

In summary, we herein reported a novel method for the synthesis of 12-aryl 5,7-dihydropyrido[2,3-b:6,5-b']diindoles through tandem cycloaddition-Friedel-Crafts alkylationcondensation-dehydrogenation reaction. In the presence of cheap of FeCl₃. а variety multisubstituted 12-aryl 5.7dihydropyrido[2,3-b:6,5-b]diindoles were obtained in moderate to high yields. The synthetic method developed here represents a practical strategy to construct five-ring fused heterocyclic scaffold.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/

References

- (a) H. Raza, R.S. King, R. B. Squires, F. P. Guengerich, D. W. Miller, J. P. Freeman, N.P. Lang and F. F. Kadlubar, Metabolism of 2-amino-alpha-carboline-A food-borne heterocyclic amine mutagen and carcinogen by human and rodent liver microsomes and by human cytochrome P4501A2, Drug Metab. Dispos., 1996, 24, 395-400; (b) A. Jaromin, A. Kozubek, K. Suchoszek-Lukaniuk, M. Malicka-Blaszkiewicz W. Peczynska-Czoch and L. Kaczmarek, Liposomal formulation of DIMIQ potential antitumor indolo[2,3b]Quinoline agent and its cytotoxicity on hepatoma Morris 5123 cells, Drug Deliv., 2008, 15, 49-56.
- [2] W. Peczyskaczoch, F. Pognan, L. Kaczmarek and J. Boratynski, Synthesis and structure-activity relationship of methylsubstituted indole[2,3-B]quinlines- novel cytotoxic, DNA topoisomerase- II inhibitors, J. Med. Chem., 1994, 37, 3503-3510.
- [3] T. Oda, J.-S. Lee, Y. Sato, Y. Kabe, S. Sakamoto, H. Handa, R.E.P. Mangindaan and M. Namikoshi, Inhibitory Effect of N,N-Didesmethylgrossularine-1 on Inflammatory Cytokine Production in Lipopolysaccharide-Stimulated RAW 264.7 Cells, Mar. Drugs, 2009, 7, 589-599.
- [4] J.-S. Kim, K. Shin-ya, K. Furihata, Y. Hayakawa and H. Seto, Structure of mescengricin, a novel neuronal cell protecting substance produced by Streptomyces griseoflavus, Tetrahedron Lett., 1997, 38, 3431-3434.
- (a) Y. H. Son, Y. J. Kim, M. J. Park, H.-Y. Oh, J. S. Park, J. H. [5] Yang, M. C. Suh, J. H. Kwon, Small single-triplet energy gap materials for phosphorescent blue and white bipolar host organic light emitting diodes, J. Mater. Chem. C, 2013, 1, 5008-5014; (b) C. W. Lee, Y. Im, J. A. Seo and J. Y. Lee, Carboline derivatives with an ortho-linked terphenyl core for high quantum efficiency in blue phosphorescent organic lightemitting diodes, Chem. Commun. 2013, 49, 9860-9862; (c) C. W. Lee, Y. Im, J.-A. Seo and J. Y. Lee, Thermally stable carboline derivative as a host material for blue phosphorescent organic light-emitting diodes, Org. Electron., 2013, 14, 2687-2691; (d) C. W. Lee and J. Y. Lee, Above 30% external quantum efficiency in blue phosphorescent organic lightemitting diodes using pyrido[2,3-b]indole derivatives as host materials, Adv. Mater., 2013, 25, 5450-5454.
- [6] T. Iwaki, A. Yashuara, and T. Sakamoto, Novel synthetic strategy of carbolines via palladium-catalyzed amination and arylation reaction, J. Chem. Soc., Perkin Trans. 1 1999, 1505–1510.
- [7] P. Vera-Luque, R. Alajarin, J. Alvarez-Builla and J. J. Vaquero, An improved synthesis of alpha-carbolines under microwave irradiation, Org. Lett., 2006, 8, 415-418.
- [8] A. Tahri, K. J. Buysens, E. V. van der Eycken, D. M. Vandenberghe and G. J. Hoornaert, Synthesis of alphacarbolines and beta-carbolinones via intramolecular Diels-Alder reactions of 2(1H)-pyrazinones, Tetrahedron, 1998, 54, 13211-13226; (b) Z.Y. Ma, F. Ni, G. H. C. Woo, S.-M. Lo, P.

M. Roveto, S. E. Schaus and J. K. Snyder, An intramolecular inverse electron demand Diels-Alder approach to annulated alpha-carbolines, Beilstein J. Org. Chem., 2012, 8, 829-840; (c) N. L. Chavan, S. K. Nayak and R. S. Kusurkar, A rapid method toward the synthesis of new substituted tetrahydro alpha-carbolines and alpha-carbolines, Tetrahedron, 2010, 66, 1827-1831.

- [9] S. Hostyn, G. Van Baelen, G. L. F. Lemière and B. U. W. Maes, Synthesis of alpha-carbolines starting from 2,3-dichloropyridines and substituted anilines, Adv. Synth. Catal., 2008, 350, 2653-2660; (b) J. K. Laha, P. Petrou and G. D. Cuny, One-pot synthesis of alpha-Carbolines via sequential palladium-catalyzed aryl amination and intramolecular arylation, J. Org. Chem., 2009, 74, 3152-3155; (c) D. Basavaiah and D. M. Reddy, Baylis-Hillman acetates in organic synthesis: convenient one-pot synthesis of alpha-carboline framework a concise synthesis of neocryptolepine, Org. Biomol. Chem., 2012, 10, 8774-8777.
- [10] C. Bonini, M. Funicello and P. Spagnolo, Novel alphacarboline synthesis using tandem aza-Wittig-electrocyclization reaction of indol-2-yl phosphorane with enone, Synlett, 2006, 10, 1574-1578; (b) A. S. Kumar and R. Nagarajan, Synthesis of alpha-carbolines via Pd-catalyzed amidation and Vilsmeir-Haack reaction of 3-acetyl-2-chloroindoles, Org. Lett., 2011, 13, 1398-1401; (c) A. S. Kumar, P. V. A. Rao and R. Nagarajan, Synthesis of pyrido[2,3-b]indoles and pyrimidoindoles via Pd-catalyzed amidation and cyclization, Org. Biomol. Chem., 2012, 10, 5084-5093.
- [11] L. Ohlendorf, J. E. D. Velandia, K. Kónya, P. Ehlers, A. Villinger and P. Langer, Synthesis and properties of 5,7-disubstituted 5,7-dihydropyrido [2,3-b:6,5-b']diindoles, Adv. Synth. Catal. 2017, 359, 1758–1769; (b) Q. T. Hung, N. N. Thang, D. H. Hoang, T. T. Dang, K. Ayub, A. Villinger, S. Lochbrunner, G.-U. Flechsig, P. Langer, Synthesis and properties of 5,7-Dihydropyrido[3,2-b:5,6-b ']diindoles Eur. J. Org. Chem. 2015, 1007-1019.
- [12] C. Bolm, J. Legros, J. L. Paih, and L. Zani, Iron-catalyzed reactions in organic synthesis Chem. Rev., 2004, 104, 6217-6254; (b) Y. Song, X. S. Tang, X. M. Hou, Y. J. Bai, Advances of iron(III) chloride-catalyzed organic reactions, Chin. J. Org. Chem., 2012, 32, 76-89.
- [13] Correa, O. G. Mancheno and C. Bolm, Iron-catalysed carbonheteroatom and heteroatom-heteroatom bond forming processes, Chem. Soc. Rev., 2008, 37, 1108-1117.
- [14] L. Tang, P. F. Wang, Y. Fan, X. K. Yang and C. F. Wan, Heterogeneous palladium-catalyzed hydrogen-transfer cyclization of nitroacetophenones with benzylamines: access to C-N bonds, Chemcatchem, 2016, 8, 3565-3569; (b) B. Wang, W. B. Ye, Z. C. Yan, C. F. Wan, H. Q. Hou and Z. Y. Wang, A new catalyst-free synthesis of 2,3-dicarboxylic ester quinoline derivatives, Chin. J. Org. Chem., 2018, 38, 504-508; (c) W. B. Ye, Z. C. Yan, C. F. Wan, H. Q. Hou and Z. Y., A new decarboxylation/methylation process of cinnamic Acids, Acta Chimica Sinica, 2018, 76, 99-102; (d) Z. C. Yan, C. F. Wan, Z. G. Zha and Z. Y. Wang, The synthesis of imidazo[1,5a]quinolines via a decarboxylative cyclization under metal-free Conditions, RSC Adv 2018, 8, 23058-23065; (e) L. D. Hu, L. F. Gao, C. F. Wan and Z. Y. Wang, A practical iodine-catalyzed sequential process: assembly of imidazo[1,5-a]pyridines from aldehydes, Acta Chim Sinica, 2012, 71, 1603-1606.
- [15] Z.-C Yan, C.-F. Wan, J.-Y. Wan and Z.-Y. Wang, An efficient iron-promoted synthesis of 6H-indolo [2,3-b]quinolines and neocryptolepine derivatives, Org. Biomol. Chem., 2016, 14, 4405-4408; (b) Y. M. Xu, X. Q. Chen, Y. Q. Gao, Z. C. Yan, C.

F. Wan, J. B. Liu and Z. Y. Wang, Synthesis of trifluoromethyl and ester group substituted α -carbolines via iron-catalyzed tandem cyclization reaction, J. Org. Chem. 2020, 85, 4354–4364.

[16] (a) U. Jana, S. Maiti and S. Biswas, An FeCl₃-catalyzed highly C3-selective Friedel-Crafts alkylation of indoles with alcohols,

Highlights

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Tetrahedron Lett., 2007, 48 ,7160-7163; (b) Y.-C. Wang, J.-B. Liu, H. Zhou, W. Xie, P. Rojsitthisak and G. Qiu, Ortho-Hydroxylative ipso Cyclization of N-arylpropiolamide, J. Org. Chem. 2020, 85, 1906-1914.

aromatic aldehydes.

• Three heterocyclic rings can be formed through a sequential cycloadditions.

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