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A direct synthesis of β-carbolines via a three-step one-pot domino approach with a bifunctional Pd/C/K-10 catalyst

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ABSTRACT

A rapid, microwave-assisted synthesis of β-carbolines via a successive condensation/cyclization/dehydrogenation approach is described. This methodology involves the coupling of various tryptamines with aromatic aldehydes/glyoxals. The product imine undergoes a Pictet–Spengler cyclization followed by a final dehydrogenation to yield β-carbolines in a three-step domino reaction. The use of the bifunctional catalyst Pd/C/K-10 combined with microwave irradiation enabled the synthesis of β-carbolines in short reaction times and in good to excellent yields.

β-Carboline scaffolds are present in a wide range of biologically active compounds of both natural and synthetic origin.[1] β-Carboline alkaloids isolated from different sources have been used for the treatment of various diseases. Examples include (−)-isocyclocapitelline **(1)** that shows anti-cancer activity,[2] sempervirine **(2)** that is cyctostatic and anti-HIV active,[3] 3,10-dibromofascaplysin (**3**), a marine alkaloid that exhibits antifungal, antiviral, and anticancer activity,[4] and tribulusterine (**4**), isolated from a famous traditional Chinese herbal medicine, *Tribulus terrestris*, that is used for liver ailments (Fig. 1).[5] Recently reported alkaloids isolated from *Korean Tunicate* were found to have antibacterial activity.[6] Due to the broad biological activity, the synthesis of β-carbolines has received considerable attention.[7] Over the years, many synthetic methods have been developed for these heterocycles; however, most of the reported methods involve multiple steps.[8] In particular, these methods involve cyclization and oxidation as separate steps, with the latter requiring a stoichiometric amount of oxidant and long reaction times.

Our earlier investigations proved that the solid acid-catalyzed cyclization processes are very effective for the construction of various heterocycles such as pyrroles, indoles, and carbazoles.[9] Our recent studies also revealed that the combination of cyclization and catalytic oxidation reactions can be effectively employed for the synthesis of pyrazoles or pyridines in a two-step one-pot condition by using a bifunctional noble metal/solid acid catalyst.[10]

Continuing our efforts in developing new methods for the synthesis of important heterocycles, herein, we report the first direct, one-pot synthesis of the β-carboline core. This approach is based on a new pathway, namely, solid acid-catalyzed coupling and cyclization followed by a catalytic oxidation (dehydrogenation). The first step is the coupling between aldehyde and amine to form an

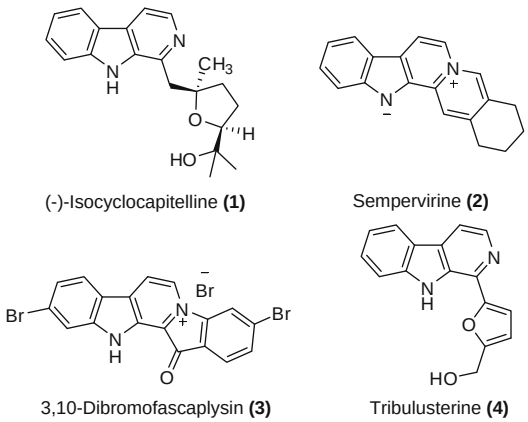

Figure 1. Representative β-carboline-based natural products.

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imine that readily undergoes Pictet–Spengler cyclization under acidic conditions to form tetrahydro-β-carboline followed by oxidative aromatization to form β-carboline in a three-step one-pot process using a special bifunctional noble metal/solid acid catalyst. The combination of heterogeneous catalysis and microwave irradiation, a highly eco-friendly approach, results in excellent yields and reduced reaction times.

First, we focused on finding a suitable catalyst that could provide high yields and desired selectivities. Optimization studies were carried out using tryptamine and benzaldehyde as starting materials. Based on our previous findings, we chose montmorillonite K-10 as a solid acid catalyst, while we evaluated Pt and Pd as metals for dehydrogenation. The reactions were carried out in a CEM Discover microwave reactor and in a pressure vessel under conventional heating. The results are shown in Table 1.

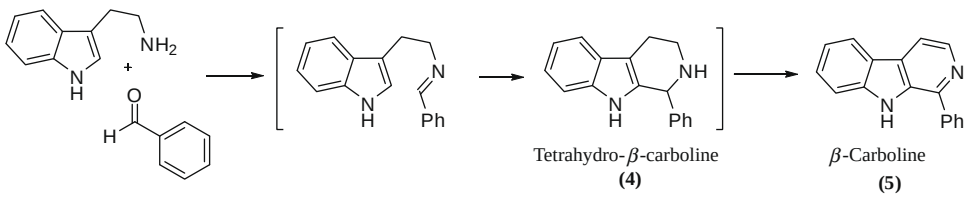
First, we tried several acid catalysts such as Al_2O_3, AcOH, and K-10. The data show that the reaction is strongly catalyst dependent; catalysts with moderate acidity provided comparatively low yields (Table 1, entries 10 and 13). Under conventional heating conditions, K-10 provided only cyclized saturated product (**4**) (Table 1, entry 2), however, under microwave conditions it gave a substantial amount of aromatic compound **(5)** (Table 1, entry 3). It appears that K-10 itself is capable of carrying out oxidation at a higher temperature; however, it would require long reaction times and higher temperatures for complete conversion to aromatic product. This results in low product yields due to possible product decomposition. As an alternative, the combination of a metal and K-10 provided excellent results. Although Pd gave higher selectivities toward the aromatic compound **(5)** (Table 1, entry 7), both Pt and Pd were effective in dehydrogenation. Pd content was crucial: 5% Pd/C/K-10 provided 38% of **(5)** (Table 1, entry 12), while 10% Pd/C/K-10 provided 100% selectivity for the aromatic product (Table 1, entries 5, 6 and 7). Also, the reaction was optimized as a function of time and temperature. Apparently at 130 °C, we obtained the best yield and selectivity.

Based on the above results (Table 1), we concluded that the best combination was 10% Pd/C/K-10 catalyst at 130 °C. Based on our previous investigations, the 1:1.2 equiv of tryptamine to benzaldehyde ratio was selected. After determining these optimized parameters, we decided to broaden the scope of this approach and illustrate the applicability of our methodology by using various substituted tryptamines and aromatic aldehydes. Table 2 summarizes the results. The data show that reactions occurred efficiently in short reaction times (20–55 min.), providing high selectivities and isolated yields (68–91%). In addition, the reactions proceeded without any byproduct formation, and even after extended time of irradiation, the products did not undergo secondary reactions. The substituents on tryptamine rings did not show any remarkable effect. Tryptophan, however, provided the corresponding β-carboline by undergoing decarboxylation under similar reaction conditions (Table 2, entries 13–16).[11]

Encouraged by the above results, we further extended the scope of our methodology with a variety of substituted aromatic glyoxals. Table 3 summarizes the results. These data indicate the usefulness of our method. Various tryptamines readily underwent cyclization/dehydrogenation with glyoxals to form the corresponding β-carboline derivatives. As indicated in Table 3, glyoxals showed higher reactivity as compared to aldehydes; the reaction rates were much faster, and we achieved excellent yields in 2–12 min of irradiation.

The proposed mechanism involved contribution from both the K-10 and Pd. The first step is a coupling between primary amino group and aldehyde to form an imine. This imine underwent cyclization by the traditional Pictet–Spengler pathway (Scheme 1).[12] K-10 helps to activate the carbonyl group and facilitate the imine formation as well as cyclization. K-10 is a well known and widely used solid acid catalyst in organic transformations.[13] It offers several advantages over classical liquid acids; solid, non-corrosive, inexpensive, and easily reusable. Also, its high surface area (220–270 m^2/g) ensures excellent reaction rates. The Hammett acidity (H_o) value for K-10 is ~−8, indicating strong acidity. It is also an excellent catalyst for microwave-assisted organic synthesis.[14] Finally, the metal component carried out the catalytic oxidative aromatization via dehydrogenation.

Table 1
Synthesis of β-carboline core under various experimental conditions from tryptamine and benzaldehyde

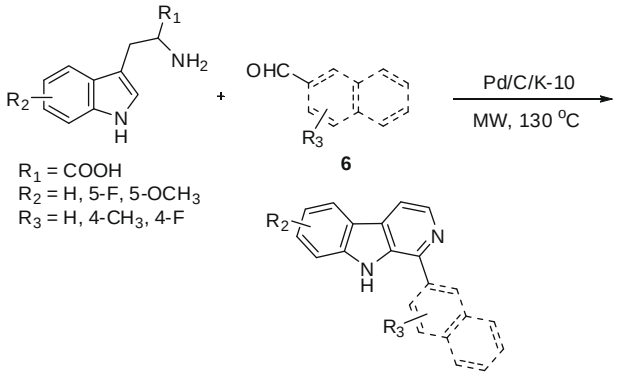


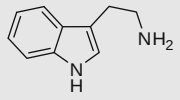
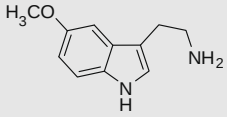
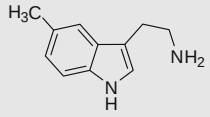
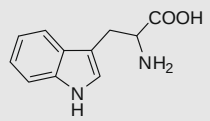
Tetrahydro-β-carboline **(4)** β-Carboline **(5)**

Entry	Catalyst	Temperature (°C)	Conditions[a]	Time (min)	Conversion[b] (%)	Selectivity[b] (%) **4/5**
1[c]	—	160	Conventional heating	120	0	0/0
2[c]	K-10	160	Conventional heating	120	37	100/0
3	K-10	160	MW	60	70	65/35
4	10% Pt/C/K-10	160	MW	60	85	21/79
5	10% Pd/C/K-10	160	MW	60	88	0/100
6	10% Pd/C/K-10	150	MW	45	93	0/100
7	10% Pd/C/K-10	130	MW	45	93	0/100
8	10% Pd/C/K-10	120	MW	45	85	8/92
9	5% Pt/Al_2O_3	130	MW	45	78	20/80
10	5% $Pd/C/Al_2O_3$	130	MW	45	47	8/92
11[c]	10% Pd/C/K-10	130	Conventional heating	720	75	18/82
12	5% Pd/C/K-10	130	MW	45	90	62/38
13[c]	10 Pd/AcOH	130	Conventional heating	120	15	9/91

[a] 1:1.2 equiv tryptamine/benzaldehyde ratio used.
[b] Determined by GC, based on residual tryptamine.
[c] Reactions were carried out in a pressure vessel.

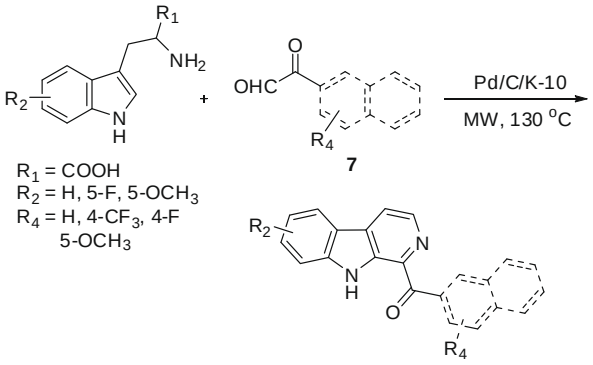
Table 2
Synthesis of β-carbolines from tryptamines in the presence of Pd/C/K-10 catalyst

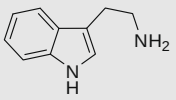
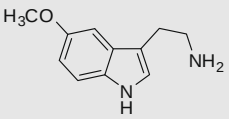
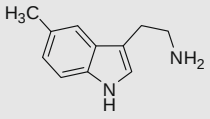
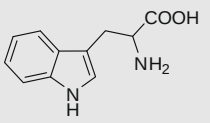


Entry	Tryptamines	6	Time (min)	Yield[a] (%)
1		PhCHO	45	89
2		4-CH_3–C_6H_4CHO	35	78
3		4-F–C_6H_4CHO	30	90
4		Naphth-2-yl-CHO	30	82
5		PhCHO	35	85
6		4-CH_3–C_6H_4CHO	30	91
7		4-F–C_6H_4CHO	25	90
8		Naphth-2-yl-CHO	40	80
9		PhCHO	50	75
10		4-CH_3–C_6H_4CHO	45	81
11		4-F–C_6H_4CHO	40	88
12		Naphth-2-yl-CHO	55	70
13		PhCHO	25	68
14		4-CH_3–C_6H_4CHO	35	71
15		4-F–C_6H_4CHO	20	88
16		Naphth-2-yl-CHO	45	83

[a] Isolated yields after flash chromatography.

Table 3
Synthesis of β-carbolines from tryptamines in the presence of Pd/C/K-10 catalyst

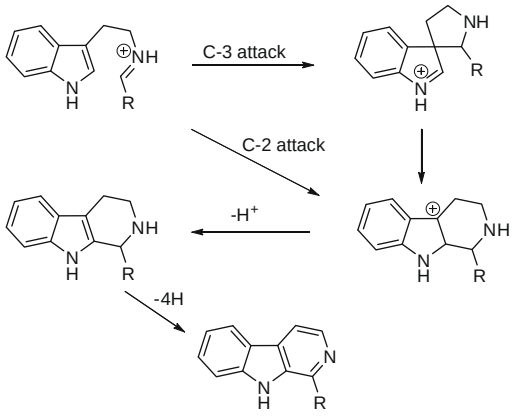


Entry	Tryptamines	7	Time (min)	Yield[a] (%)
1		PhCOCHO	5	94
2		4-$CF_3C_6H_4$COCHO	2	96
3		4-FC_6H_4COCHO	10	91
4		6-OCH_3-Naphth-2-yl-COCHO	5	80
5		PhCOCHO	2	93
6		4-$CF_3C_6H_4$COCHO	6	90
7		4-FC_6H_4COCHO	7	94
8		6-OCH_3-Naphth-2-yl-COCHO	5	92
9		PhCOCHO	4	95
10		4-$CF_3C_6H_4$COCHO	8	93
11		4-FC_6H_4COCHO	5	89
12		6-OCH_3-Naphth-2-yl-COCHO	9	90
13		PhCOCHO	5	85
14		4-$CF_3C_6H_4$COCHO	10	81
15		4-FC_6H_4COCHO	12	83
16		6-OCH_3-Naphth-2-yl-COCHO	7	79

[a] Isolated yields after flash chromatography.

In summary, we have developed an effective and direct microwave-assisted, three-step one-pot method for the synthesis of β-carbolines from tryptamines and aromatic aldehydes or glyoxals. We have also proved the usefulness of a bifunctional catalyst (Pd/C/K-10) for the one-pot cyclization/dehydrogenation reaction. The combination of solid acid-catalysis, heterogeneous catalytic oxidative aromatization, and microwave irradiation provided excellent selectivities and yields in short reaction times. In addition to efficiency and effective catalysis, the very limited energy consumption and its waste-free nature make the process very attractive as an environmentally benign synthesis of these important heterocycles.

General experimental procedure: Tryptamine (100 mg, 0.62 mmol) and benzaldehyde (76 μL, 0.75 mmol) were dissolved in 3 mL CH_2Cl_2 in a round bottomed flask. Catalyst was prepared by mixing 21 mg 10%Pd/C and 500 mg of K-10. The catalyst was mixed with the above reaction mixture, and a few drops of MeOH were added to dissolve the tryptamine. After 5 min of stirring the solvent was removed. The dry mixture was transferred to a reaction vial and irradiated in the CEM Discover Benchmate microwave reactor for the specified time. After the reaction was complete, CH_2Cl_2 was added to the reaction mixture and the catalyst was filtered. The filtrate was concentrated, and the residue was subjected to column chromatography.



Scheme 1. Proposed mechanism for the Pd/C/K-10-catalyzed synthesis of β-carbolines via cyclization–dehydrogenation domino sequence.

Acknowledgments

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Supplementary data

Experimental procedures and spectral data for all compounds are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.143.

References and notes

1. (a) Trujillo, J. I.; Meyers, M. J.; Anderson, D. R.; Hegde, S.; Mahoney, M. W.; Vernier, W. F.; Buchler, I. P.; Wu, K. K.; Yang, S.; Hartmann, S. J.; Reitz, D. B. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4657; (b) Winkler, J. D.; Londregan, A. T.; Ragains, J. R.; Hamann, M. T. *Org. Lett.* **2006**, *8*, 3407; (c) Costa, E. V.; Pinheiro, M. L. B.; Xavier, C. M.; Silva, J. R. A.; Amaral, A. C. F.; Souza, A. D. L.; Barison, A.; Campos, F. R.; Ferreira, A. G.; Machado, G. M. C.; Leon, L. L. P. *J. Nat. Prod.* **2006**, *69*, 292.
2. (a) Phuong, N. M.; Van Sung, T.; Porzel, A.; Schmidt, J.; Merzweiler, K.; Adam, G. *Phytochemistry* **1999**, *52*, 1725; (b) Hartung, J.; Drees, S.; Geiss, B.; Schmidt, P. *Synlett* **2003**, 223.
3. (a) Potts, K. T.; Mattingly, G. S. *J. Org. Chem.* **1968**, *33*, 3985; (b) Gribble, G. W.; Barden, T. C.; Johnson, D. A. *Tetrahedron* **1988**, *44*, 3195; (c) Lipinska, T. *Tetrahedron Lett.* **2002**, *43*, 9565.
4. (a) Segraves, N. L.; Robinson, S. J.; Garcia, D.; Said, S. A.; Fu, X.; Schmitz, F. J.; Pietraszkiewicz, H.; Valeriote, F. A.; Crews, P. *J. Nat. Prod.* **2004**, *67*, 783; (b) Zhidkov, M. E.; Baranova, O. V.; Balaneva, N. N.; Fedorov, S. N.; Radchenko, O. S.; Dubovitskii, S. V. *Tetrahedron Lett.* **2007**, *48*, 7998.
5. (a) Wu, T.-S.; Shi, L.-S.; Kuo, S.-C. *Phytochemistry* **1999**, *50*, 1411; (b) Li, C.-Y.; Lee, E.-J.; Wu, T.-S. *J. Nat. Prod.* **2004**, *67*, 473; (c) Bremner, J. B.; Sengpracha, W.; Southwell, I.; Bourke, C.; Skelton, B. W.; White, A. H. *Aust. J. Chem.* **2004**, *57*, 273.
6. Wang, W.; Nam, S.-J.; Lee, B.-C.; Kang, H. *J. Nat. Prod.* **2008**, *71*, 163.
7. (a) Cain, M.; Mantei, R.; Cook, J. M. *J. Org. Chem.* **1982**, *47*, 4933; (b) Trudell, M. L.; Fukada, N.; Cook, J. M. *J. Org. Chem.* **1987**, *52*, 4293; (c) Hudlicky, T.; Rinner, U.; Finn, K. J.; Ghiviriga, I. *J. Org. Chem.* **2005**, *70*, 3490; (d) Busacca, C. A.; Eriksson, M. C.; Dong, Y.; Prokopowicz, A. S.; Salvagno, A. M.; Tschantz, M. A. *J. Org. Chem.* **1999**, *4*, 4564; (e) Wu, T. Y. H.; Schultz, P. G. *Org. Lett.* **2002**, *4*, 4033.
8. (a) Zhang, H.; Larock, R. C. *Org. Lett.* **2001**, *3*, 3083; (b) Bonnet, D.; Ganesan, A. *J. Comb. Chem.* **2002**, *4*, 546; (c) Yeh, W.-P.; Chang, W.-J.; Sun, M.-L.; Sun, C. M. *Tetrahedron* **2007**, *63*, 11809; (d) Lee, S.-C.; Choi, S. Y.; Chung, Y. K.; Park, S. B. *Tetrahedron Lett.* **2006**, *47*, 6843; (e) Ivanov, I.; Nikolova, S.; Statkova-Abeghe, S. *Heterocycles* **2005**, *65*, 2483; (f) Garcia, M. D.; Wilson, A. J.; Emmerson, D. P. G.; Jenkins, P. R. *Chem. Commun.* **2006**, 2586; (g) Kusurkar, R. S.; Goswami, S. K. *Tetrahedron* **2004**, *60*, 5315.
9. (a) Abid, M.; Spaeth, A.; Török, B. *Adv. Synth. Catal.* **2006**, *348*, 2191; (b) Abid, M.; Landge, S. M.; Török, B. *Org. Prep. Proced. Int.* **2006**, *35*, 495; (c) Abid, M.; De Paolis, O.; Török, B. *Synlett* **2008**, 410; (d) Landge, S. M.; Berryman, M.; Török, B. *Tetrahedron Lett.* **2008**, *49*, 4505.
10. Landge, S. M.; Schmidt, A.; Outerbridge, V.; Török, B. *Synlett* **2007**, 1600.
11. (a) Rönner, B.; Lerche, H.; Bergmüller, W.; Freilinger, C.; Severin, T.; Pischetsrieder, M. *J. Agric. Food. Chem.* **2000**, *48*, 2111; (b) Maki, Y.; Kimoto, H.; Fujii, S.; Nishida, M.; Cohen, L. A. *J. Fluorine. Chem.* **1989**, *43*, 189; (c) Song, Y.; Wang, J.; Teng, S. F.; Kesuma, D.; Deng, Y.; Duan, J.; Wang, J. H.; Qi, R. Z.; Sim, M. M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1129.
12. (a) Narayanan, K.; Schindler, L.; Cook, J. M. *J. Org. Chem.* **1991**, *56*, 359; (b) Ungemach, F.; DiPierro, M.; Weber, R.; Cook, J. M. *J. Org. Chem.* **1981**, *46*, 164; (c) Gremmen, C.; Willemse, B.; Wanner, M. J.; Koomen, G.-J. *Org. Lett.* **2000**, *2*, 1955.
13. (a) Szöllösi, G.; Török, B.; Baranyi, L.; Bartók, M. *J. Catal.* **1998**, *179*, 619; (b) Kantam, M. L.; Choudary, B. M.; Reddy, C. V.; Rao, K. K.; Figueras, F. *Chem. Commun.* **1998**, 1033; (c) Török, B.; London, G.; Bartók, M. *Synlett* **2000**, 631; (d) Ebitani, K.; Ide, M.; Mitsudome, T.; Mizugaki, T.; Kaneda, K. *Chem. Commun.* **2002**, 690; (e) Abid, M.; Török, B. *Adv. Synth. Catal.* **2005**, *347*, 1797.
14. (a) Balogh, M.; Laszlo, P. *Organic Chemistry Using Clays*; Springer: Berlin/Heidelberg, 1993; (b) Varma, R. S.; Dahiya, R.; Kumar, S. *Tetrahedron Lett.* **1997**, *38*, 2039; (c) Kappe, C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH, 2005; (d) Li, A.; Li, T.; Ding, T. *Chem. Commun.* **1997**, 1389; (e) Polshettiwar, V.; Varma, R. S. *Acc. Chem. Res.* **2008**, *41*, 629.