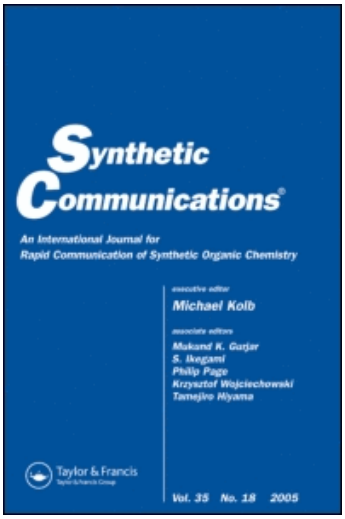

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FACILE AND EFFICIENT ONE-POT SYNTHESIS OF β-CARBOLINES

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Initial formation of tetrahydrocarboline 3 from tryptophan methyl ester 1 and aldehyde 2 by Pictet–Spengler reaction, followed by treatment with trichlorocyanuric acid, provides a facile and efficient route for a one-pot synthesis of β-carbolines with excellent yields.

Keywords: β-Carboline; one pot; synthesis

INTRODUCTION

β-Carbolines are a large class of natural indole alkaloids widely distributed in nature, including in various plants,[1] fungi,[2] marine creatures,[3] and animal as well as human tissues and body fluids.[4] These compounds have been afforded a great deal of attention recently because of their wide range of biological activities, such as hypnotic, anxiolytic, antimicrobial,[5] antiviral,[6] antitumor,[7] anticonvulsant,[8] and parasiticidal[9] activities. Base on their simple structure features, some β-carbolines were synthesized, and many synthetic methods have also been developed.[10] The classical methods are mainly based on two strategies: (1) Bischler–Napieralski route,[11] which involves the conversion of dihydro-β-carboline, generated from carboxylic acids (anhydride) and tryptophan (tryptamine), to β-carboline by oxidation using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), $KMnO_4$, SeO_2, and so on, and (2) the Pictet–Spengler route,[12] wherein the tetrahydro-β-carboline produced by the condensation reaction of tryptophan (tryptamine) with aldehyde is treated with oxidative reagents, leading to the formation of β-carboline. Other methods are also used for the synthesis of β-carboline, such as the Fisher indolization reaction and aromatization reactions of aryl hydrazine and cyclohexanone;[13] oxime formation, electrocyclization, and aromatization reactions of 3-vinyl indole;[14] palladium-catalyzed cross-coupling reaction of *tert*-butylimines of N-substituted 3-iodoindole-2-carboxaldehydes;[15] aza-Wittig reaction and

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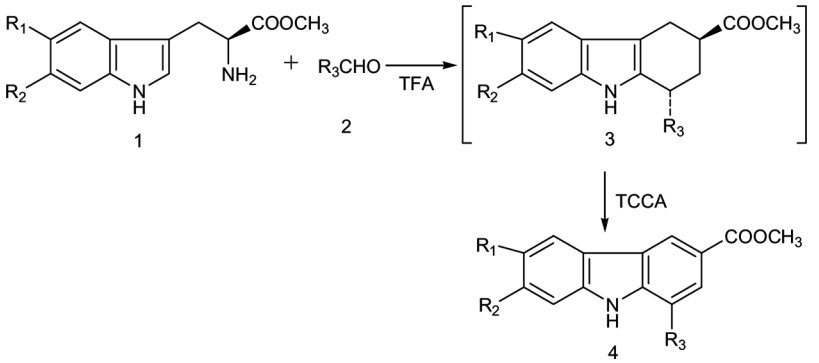
electrocyclic ring closure of 3-azidoindole;[16] and Friedel–Crafts acylations and cyclization of 3-substituted indole.[17] Most of the available methods have poor yields, require special material, or utilize expensive reagents to achieve the reported yield. Therefore, the need for large quantities of β-carboline prompted us to develop a facile and effective method. In this article, we report a synthetic method of β-carboline that can be carried out in one step under mild conditions.

RESULTS AND DISCUSSION

In our study, the Pictet–Spengler route was selected from among two classical methods. As we know, the tetrahydro-β-carboline can be easily obtained by the reaction of tryptophan with aldehydes in good yield, but the subsequent aromatizing step is always troublesome. It is the key issue in the synthesis of carboline in good yield. There are many methods for dehydrogenation of tetrahydro-β-carboline to β-carboline using MnO_2, DDQ, SeO_2, and Pd/C,[18] but none is satisfactory because of either harsh reaction conditions or poor yield. During the course of our study, TCCA (trichlorocyanuric acid) was reported as a mild dehydrogenating reagent of indoline and tetrahydro-β-carboline.[18] TCCA is a mild dehydrogenating reagent and has many advantages, such as low cost, easy accessibility (even on a large scale), high solubility, and environmental friendliness. Because of its high solubility in organic solvent, we successfully applied this agent to synthesis of β-carboline in one pot from tryptophan methyl ester and aldehyde. The synthetic route is shown in Scheme 1.

In this article, the one-pot method involved the preparation of tetrahydro-β-carboline **3** from substituted tryptophan methyl ester **1** and substituted aldehyde **2** by the Pictet–Spengler reaction. In the Pictet–Spengler reaction, methylene dichloride and trifluoroacetic acid (TFA) as solvent and catalyst, respectively, and in most cases the reaction was completed within 2 days at room temperature. Then dichloromethane (DCM) was moved away under a pressure reduction, and tetrahydro-β-carboline **3** obtained was directly added dropwise to the reagent TCCA (dissolved in DMF) at less than 0 °C. The aromatizing reaction was carried out at room temperature, and in most cases the reaction was completed within 2 h. The respective β-carbolines can be precipitated by pouring crushed ice. The yields and melting points of various substituted β-carbolines prepared are summarized in Table 1.



Scheme 1. Synthetic route to β-carboline.

Table 1. Yields and melting points of various β-carbolines

Compound	R_1	R_2	R_3	Yield (%)	Mp (°C)
4a	H	H	H	80	143–146
4b	H	H	Methyl	84	152–154
4c	H	H	Ethyl	80	161–162
4d	H	H	n-Propyl	82	169–171
4e	H	H	Isoropyl	81	149–152
4f	H	H	Cyclopentyl	82	171–172
4g	H	H	*Trans*-1-butenyl	84	173–175
4h	CH_3	H	4′-Trifuoromethylphenyl	91	192–194
4i	H	H	2-Pyridyl	87	172–174
4j	F	H	2-Furyl	85	169–172
4k	H	F	5-Acetoxymethyl-2-furyl	88	165–169
4l	CH_3O	H	2-Thioyl	86	171–173
4m	H	H	2-Indoly	87	180–181
4n	H	H	2-Benzo[b]furyl	87	173–175
4o	CH_3O	H	2-Quinolyl	88	181–183
4p	H	H	2-Naphthyl	90	178–180

In conclusion, the method described in this article is a mild, facile, and efficient process for a one-pot synthesis of β-carbolines. A large-scale production of β-carbolines has been afforded, which confirms the simplicity of the method. Application of this strategy to other biologically β-carboline alkaloids is in progress.

EXPERIMENTAL

Instruments and Materials

Thin-layer chromatography (TLC) was conducted on silica-gel F254 plates and detected under ultraviolet (UV) light. The melting points were measured using an X-type micro-melting-point apparatus and are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ with a Bruker AM-400 or Bruker DRX-500 instrument using tetramethylsilane (TMS) as an internal standard (chemical shifts in δ ppm). Mass spectra (MS) were taken on VG Auto Spec-3000. All reagents and solvents were commercially obtained and of analytical grade.

General Procedure for Synthesis of Compound 4

Compounds **1** (10 mmol) and **2** (10 mmol) were added to dry dichloromethane (DCM, 20 mL) under N_2, and later TFA (0.18 mL, 2.5 mmol) was added slowly over 10 min. After stirring for 2 days at room temperature, the DCM was removed under reduced pressure, and the mixture was taken up in 20 mL of DMF and neutralized with triethylamine (TEA). Another 4.5 mL of TEA and 10 mmol TCCA (dissolved in 10 mL of DMF) were added slowly, keeping the temperature at less than 0 °C. When addition was completed, the mixture was allowed to slowly warm up to room temperature and stirred for 2 h at this temperature to complete the reaction. Later, crushed ice was added, and the resulting product was precipitated from ice water, filtered, washed with water, dried, and recrystallized from methanol to give compound **4**.

Selected Data

Compound 4a. β-Carboline-3-carboxylic methyl ester, yellow solid, 1.80 g. Yield: 80%, mp: 143–146 °C, $C_{13}H_{10}N_2O_2$, FAB^+-MS m/z: 227 $(M+1)$; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.91 (1H, s), 8.77 (1H, s), 8.13 (1H, d, $J=8.0$ Hz), 7.58 (1H, d, $J=8.0$ Hz), 7.52 (1H, t, $J=7.2$ Hz), 7.31 (1H, t, $J=7.2$ Hz), 3.99 (3H, s).

Compound 4b. 1-Methyl-β-carboline-3-carboxylic methyl ester, $C_{14}H_{12}N_2O_2$, yellow solid, 2.01 g. Yield: 84%, mp: 152–154 °C; FAB^+-MS m/z: 241 $(M+1)^+$; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.50 (1H, s), 8.78 (1H, s), 8.16 (1H, d, $J=8.0$ Hz), 7.59 (1H, d, $J=8.0$ Hz), 7.54 (1H, t, $J=7.2$ Hz), 7.32 (1H, t, $J=7.2$ Hz), 4.01 (3H, s), 2.38 (3H, s).

Compound 4c. 1-Ethyl-β-carboline-3-carboxylic methyl ester, yellow solid, 2.03 g. Yield: 80%, mp: 161–162 °C, $C_{15}H_{14}N_2O_2$, FAB^+-MS m/z: 255 $(M+1)^+$; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.91 (1H, s), 8.77 (1H, s), 8.13 (1H, d, $J=8.0$ Hz), 7.58 (1H, d, $J=8.0$ Hz), 7.52 (1H, t, $J=7.2$ Hz), 7.31 (1H, t, $J=7.2$ Hz), 3.99 (3H, s), 3.13 (2H, q, $J=7.2$ Hz), 1.29 (3H, t, $J=7.2$ Hz).

Compound 4d. 1-n-Propyl-β-carboline-3-carboxylic methyl ester, yellow solid, 2.19 g. Yield: 82%, mp: 169–171 °C, $C_{16}H_{16}N_2O_2$, FAB^+-MS m/z: 269 $(M+1)^+$; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.52 (1H, s), 8.78 (1H, s), 8.13 (1H, d, $J=7.6$ Hz), 7.82 (1H, d, $J=7.6$ Hz), 7.52 (1H, t, $J=7.2$ Hz), 7.30 (1H, t, $J=7.2$ Hz), 3.97 (3H, s), 1.67 (2H, t, $J=7.2$ Hz), 1.36–1.32 (2H, m), 0.67 (3H, t, $J=6.4$ Hz).

Compound 4e. 1-Isopropyl-β-carboline-3-carboxylic methyl ester, yellow solid, 2.17 g. Yield: 81%, mp: 149–152 °C, $C_{16}H_{16}N_2O_2$, FAB^+-MS m/z: 269 $(M+1)^+$; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.80 (1H, s), 8.22 (1H, d, $J=7.5$ Hz), 7.67 (1H, d, $J=8.0$ Hz), 7.47 (1H, t, $J=7.5$ Hz), 7.37 (1H, t, $J=7.5$ Hz), 4.09 (3H, s), 3.68 (1H, m), 1.56 (6H, d, $J=7.0$ Hz).

Compound 4f. 1-Cyclopentyl-β-carboline-3-carboxylic methyl ester, yellow solid, 2.41 g. Yield: 82%, mp: 171–172 °C, $C_{18}H_{18}N_2O_2$, FAB^+-MS m/z: 295 $(M+1)^+$; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.20 (1H, s), 8.72 (1H, s), 8.15 (1H, d, $J=7.6$ Hz), 7.64 (1H, d, $J=8.0$ Hz), 7.55 (1H, t, $J=7.2$ Hz), 7.29 (1H, t, $J=7.2$ Hz), 4.01 (3H, s), 3.73 (1H, m), 2.15 (4H, m), 1.92 (2H, m), 1.76 (2H, m).

Compound 4g. *Trans*-1-(1′-butenyl)-β-carboline-3-carboxylic methyl ester, yellow solid, 2.35 g. Yield: 84%, mp: 173–175 °C, $C_{17}H_{16}N_2O_2$, FAB^+-MS m/z: 281 $(M+1)^+$; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.80 (1H, s), 8.22 (1H, d, $J=7.5$ Hz), 7.67 (1H, d, $J=8.0$ Hz), 7.47 (1H, t, $J=7.5$ Hz), 7.37 (1H, t, $J=7.5$ Hz), 6.67 (1H, d, $J=12.6$ Hz), 6.62 (1H, d, $J=12.6$ Hz), 4.09 (3H, s), 2.00 (2H, m), 1.06 (3H, t, $J=6.0$ Hz).

Compound 4h. 1-(4′-Trifuoromethylphenyl)-6-methyl-β-carboline-3-carboxylic methyl ester, yellow solid, 3.49 g. Yield: 91%, mp 192–194 °C, $C_{21}H_{15}N_2O_2F_3$, FAB^+-MS m/z: 385 $(M+1)^+$; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.86 (1H, s), 8.20 (2H, d, $J=7.5$ Hz), 8.01 (1H, s), 7.85 (2H, d, $J=7.5$ Hz), 7.54 (1H, t, $J=7.0$ Hz), 7.42 (1H, d, $J=8.0$ Hz), 4.05 (3H, s), 2.56 (3H, s).

Compound 4i. 1-(2′-Pyridyl)-β-carboline-3-carboxylic methyl ester, yellow solid, 2.63 g. Yield: 87%, mp: 172–174 °C, $C_{18}H_{13}N_3O_2$, FAB^+-MS m/z: 304 $(M+1)^+$;^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.84 (1H, s), 8.31 (1H, d, $J=8.0$ Hz), 8.28 (1H, d, $J=8.0$ Hz), 8.12 (1H, s), 7.86 (1H, d, $J=7.6$ Hz), 7.68 (1H, d, $J=7.6$ Hz), 7.62 (2H, t, $J=7.2$ Hz), 7.32 (2H, t, $J=6.5$ Hz), 3.76 (3H, s).

Compound 4j. 1-(2′-Furyl)-6-fuoro-β-carboline-3-carboxylic methyl ester, yellow solid, 2.48 g. Yield: 85%, mp: 168–172 °C, $C_{17}H_{12}N_2O_3$, FAB^+-MS m/z: 293 $(M+1)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.61 (1H, s, br), 8.79 (1H, s), 8.18 (1H, d, $J=8.0$ Hz), 7.63–7.59 (2H, m), 7.44 (1H, d, $J=2.5$ Hz), 7.36 (1H, t, $J=7.0$ Hz), 6.67 (1H, d, $J=1.0$ Hz), 4.06 (3H, s).

Compound 4k. 1-(5′-Aceoxylmethyl-2′-furyl)-7-fuoro-β-carboline-3-carboxylic methyl ester, yellow solid, 3.36 g. Yield: 88%, mp 165–169 °C, $C_{20}H_{15}FN_2O_5$, FAB^+-MS m/z: 383 $(M+1)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.37 (1H, s, br), 8.73 (1H, s), 8.22 (1H, dd, $J=1.2$ Hz, 8.8 Hz), 7.71 (1H, dd, $J=2.0$ Hz, 9.2 Hz), 7.31 (1H, d, $J=3.6$ Hz), 7.31 (1H, dt, $J=2.0$ Hz, 9.2 Hz), 6.63 (1H, d, $J=3.6$ Hz), 5.26 (2H, s), 4.02 (3H, s), 2.18 (3H, s).

Compound 4l. 1-(2′-Thioyl)-6-methoxyl-β-carboline-3-carboxylic methyl ester, yellow solid, 2.90 g. Yield: 86%, mp: 171–173 °C, $C_{18}H_{14}N_2O_3S$, FAB^+-MS m/z: 339 $(M+1)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.79 (1H, s), 8.76 (1H, s), 7.79 (1H, d, $J=3.6$ Hz), 7.62 (1H, d, $J=2.4$ Hz), 7.53 (1H, t, $J=5.2$ Hz), 7.49 (1H, s), 7.26 (1H, d, $J=4.0$ Hz), 7.24 (1H, d, $J=4.0$ Hz), 4.06 (3H, s), 3.95 (3H, s).

Compound 4m. 1-(2′-Indoly)-β-carboline-3-carboxylic methyl ester, yellow solid, 2.96 g. Yield: 87%, mp: 180–181 °C, $C_{21}H_{15}N_3O_2$, FAB^+-MS m/z: 342 $(M+1)^+$; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 10.02 (1H, s), 8.88 (1H, s), 8.70 (1H, d, $J=8.0$ Hz), 7.76 (1H, d, $J=8.0$ Hz), 7.68 (1H, d, $J=6.5$ Hz), 7.58 (2H, t, $J=7.5$ Hz), 7.52 (1H, d, $J=6.5$ Hz), 7.48 (2H, t, $J=7.5$ Hz), 6.94 (1H, s), 3.94 (3H, s).

Compound 4n. 1-(2′-Benzofuryl)-β-carboline-3-carboxylic methyl ester, yellow solid, 2.89 g. Yield: 87%, mp: 173–175 °C, $C_{21}H_{14}N_2O_3$, FAB^+-MS m/z: 343 $(M+1)^+$; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 11.05 (1H, s), 8.36 (1H, s), 8.05 (1H, d, $J=8.5$ Hz), 7.98 (1H, d, $J=8.0$ Hz), 7.78 (2H, t, $J=7.5$ Hz), 7.48 (1H, d, $J=6.5$ Hz), 7.32 (1H, d, $J=6.5$ Hz), 7.20 (2H, t, $J=7.5$ Hz), 6.79 (1H, s), 4.09 (3H, s).

Compound 4o. 1-(2′-Quindyl)-6-methoxyl-β-carboline-3-carboxylic methyl ester, yellow solid, 3.37 g. Yield: 88%, mp: 181–183 °C, $C_{23}H_{17}N_3O_3$, FAB^+-MS m/z: 384 $(M+1)^+$; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 11.82 (1H, s), 9.02 (1H, d, $J=8.5$ Hz), 8.39 (1H, s), 8.36 (1H, d, $J=8.0$ Hz), 8.28 (1H, d, $J=8.5$ Hz), 7.90 (1H, d, $J=8.0$ Hz), 7.78 (2H, t, $J=7.5$ Hz), 7.68 (1H, d, $J=6.5$ Hz), 7.32 (1H, d, $J=6.5$ Hz), 4.08 (3H, s), 3.91 (3H, s).

Compound 4p. 1-(2′-Naphthyl)-β-carboline-3-carboxylic methyl ester, yellow solid, 3.16 g. Yield: 90%, mp: 178–180 °C, $C_{23}H_{16}N_2O_2$, FAB^+-MS m/z: 353 $(M+1)^+$; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 9.89 (1H, s), 8.45 (1H, d, $J=8.5$ Hz), 8.24 (1H, d, $J=8.5$ Hz), 8.22 (1H, s), 8.18 (1H, d, $J=8.0$ Hz), 7.96

(1H, d, $J = 8.0$ Hz), 7.78 (2H, t, $J = 7.5$ Hz), 7.65 (1H, d, $J = 6.5$ Hz), 7.51 (H, t, $J = 7.5$ Hz), 7.45 (1H, d, $J = 6.5$ Hz), 7.32 (2H, t, $J = 6.5$ Hz), 4.09 (3H, s).

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