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SYNTHESIS OF 4-ARYL SUBSTITUTED CANTHIN-6-ONE WITH β-CARBOLINE SKELETON VIA PICTET-SPENGLER CONDENSATION AND CYCLIZATION REACTION

(Sintesis 4-Aril Gantian Kantin-6-One dengan Rangka β-Karbolina Melalui Kondensasi Pictet-Spengler dan Tindak Balas Kitaran)

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Abstract

This study presents a comprehensive synthesis of 4-aryl substituted canthin-6-one through a versatile Pictet-Spengler condensation and subsequent cyclization, involving the formation of 1-aroyl substituted β-carbolines as pivotal intermediates. β-Carbolines, as indole alkaloids, serve as fundamental building blocks with diverse biological activities. In particular, canthin-6-one and its derivatives exhibit a wide range of promising biological properties, which include anti-cancer, antibacterial, anti-inflammatory, and cytotoxic effects, thus making them valuable in pharmaceutical and medicinal chemistry applications. The method outlined herein involves the utilization of readily available starting materials in a direct reaction sequence, resulting in an efficient and moderate-yield access to 4-aryl substituted canthin-6-one. Synthesizing canthine was initiated by forming the intermediates, 1-aroyl substituted β-carbolines via Pictet-Spengler condensation of different substituted aromatic glyoxals with 5-hydroxy tryptophan in the presence of trifluoroacetic acid. This synthesis route avoids the formation of tetrahydro-β-carbolines. Subsequently, the series of 1-aroyl substituted β-carboline intermediates were cyclized to yield the desired 4-aryl substituted canthin-6-one derivatives. The reaction mechanism and key intermediates are discussed, providing insights into the synthesis pathway. The structure of the synthesized compounds were confirmed by using Infrared Radiation (IR) and Nuclear Magnetic Resonance (NMR) spectroscopy. This research not only contributes to the understanding of synthetic methodologies but also paves the way for the development of novel compounds with promising pharmaceutical properties.

Keywords: β-carboline, Pictet-Spengler condensation, cyclization, canthin-6-one

Abstrak

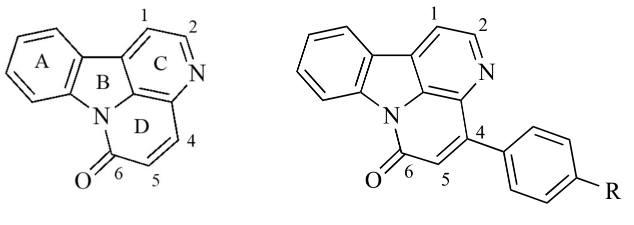
Kajian ini membentangkan sintesis komprehensif 4-aril digantikan kantin-6-satu melalui pemeluwapan Pictet-Spengler serba boleh dan kitaran seterusnya, melibatkan pembentukan 1-aroil digantikan β-karbolin sebagai perantaraan penting. β-karbolina, sebagai alkaloid indole, berfungsi sebagai blok binaan asas dengan pelbagai aktiviti biologi. Khususnya, kantin-6-satu dan derivatifnya mempamerkan pelbagai sifat biologi yang menjanjikan, termasuk kesan anti-kanser, antibakteria, anti-radang dan sitotoksik, dengan itu menjadikannya berharga dalam aplikasi kimia farmaseutikal dan perubatan. Kaedah yang digariskan di sini melibatkan penggunaan bahan permulaan yang sedia ada dalam urutan tindak balas langsung, menghasilkan akses hasil yang cekap dan sederhana kepada 4-aril digantikan kantin-6-satu. Mensintesis kantin telah dimulakan dengan membentuk perantaraan, β-karbolina yang digantikan 1-aroil melalui kondensasi Pictet-Spengler bagi glioksal aromatik tersubstitusi berbeza dengan triptofan 5-hidroksi dengan kehadiran asid trifluoroasettik. Laluan sintesis ini mengelakkan pembentukan tetrahidro-β-karbolina. Selepas itu, siri perantaraan β-karbolina yang digantikan 1-aroil telah dikitar untuk menghasilkan derivatif 4-aril digantikan kantin-6-satu yang dikehendaki. Mekanisme tindak balas dan perantaraan utama dibincangkan, memberikan pandangan tentang laluan sintesis. Struktur sebatian yang disintesis telah disahkan dengan menggunakan spektroskopi sinaran inframerah (IR) dan resonans magnetik nuklear (NMR). Penyelidikan ini bukan sahaja menyumbang kepada pemahaman metodologi sintetik tetapi juga membuka jalan untuk pembangunan sebatian baru dengan sifat farmaseutikal yang menjanjikan.

Kata kunci: β-karbolina, kondensasi Picter-Spengler, kitaran, kantin-6-satu

Introduction

In field of medicinal chemistry, the search of novel compounds with therapeutic potentials never ends. Within this dynamic field, the synthesis of heterocyclic molecules has emerged as a promising pathway, offering new scaffolds for drug discovery. One such class of heterocycles, β-carbolines, has garnered increasing attention due to their diverse biological activities and potential applications in pharmaceutical research. In this work, we investigate the complex area of organic synthesis and chemical transformation to unlock the diverse potentials of β-carboline belongs to the indole alkaloid family and consists of an indole structure fused to a pyridine ring [1]. The structure of β-carboline is similar to that of tryptamine, with the ethylamine chain reconnected to the indole ring via an extra carbon atom, to produce a tricyclic ring structure [2]. Extensive studies on β-carboline have revealed exceptionally diverse biological efficacy of this natural compound.

β-Carboline has been isolated from *Peganum harmala*, a plant used as an emmenagogue and a digestive tract medicine, which is also known to evoke hallucinations. β-Carboline plays an important role in biological activities like antiparasitic, antitumor, antiviral, anti-inflammatory, and antibacterial. Although these alkaloids are highly represented in terrestrial species, large amounts of β-carboline are also isolated from marine invertebrates such as tunicates, bryozoans, soft corals, and sponges [3]. Canthine-6-one (Figure 1a) alkaloids belong to the tetracyclic subclass of β-carboline alkaloids with the addition of D ring, and have a peri-fused indolo[3,2,1-de][1,5]naphthyridine structure. They are widely found in Rutaceae and Simaroubaceae families. There are a lot of compounds that have been isolated due to their diversity in biological activities that act as anticancer, antibacterial, antifungal, anti-inflammatory, and cytotoxic agents [4]. The 4-aryl substituted canthin-6-one (Figure 1b) is one of the derivatives of β-carboline which consists of canthine as its monomer [5]. It is commonly formed by the cyclization of intermediate 1-substituted β-carboline. The derivatives of β-carboline with aroyl substitution at the C1 position were known to exhibit potent anti-inflammatory, anti-malarial, anti-cancer, anti-phospholipase, P-glycoprotein-inducer, and anti-microbial activities [6].



(a) (b)

Figure 1. (a) Canthine-6-one structure and (b) 4-Aryl substituted canthin-6-one structure

Numerous efforts have been made to synthesize not only the parent structure of β-carboline but also a variety of synthetic β-carboline derived compounds due to their notable impact in life. One of the well-known reactions that has been used to prepare β-carboline is the Pictet-Spengler reaction. To date, it has remained as one of the most powerful methods for the formation of this ring system via C-C bond formation using indole-based compound as the starting material [7]. This reaction is the most direct, and efficient synthetic method for the construction of advantaged and widely synthesized pharmacophores such as tetrahydro-isoquinolines (THIQs), tetrahydro-β-carbolines (THβCs), and polyheterocyclic frameworks [8]. The application of the Pictet-Spengler condensation reaction was the most reported method to synthesize THβCs with the aid of strong Brønsted acids to promote the ring closure of the imine [9]. Generally, Pictet-Spengler reaction can be characterized by the formation of iminium salt after an acid-catalyzed condensation of β-arylethylamine with an aldehyde or a ketone, followed by ring closure [10]. This method continues to be a prominent focus of research over the years as scientists continue to refine the methodology by applying novel reaction conditions.

However, in this study, we attempted in a more practical and convenient synthesis of the aromatic β-carbolines using 5-hydroxytryptophan and various aromatic glyoxals in the desired Pictet-Spengler reaction, followed by formation of 4-aryl substituted canthin-6-one via cyclization. This work details the efficient Pictet-Spengler condensation catalyzed by TFA, without the use of expensive metal catalysts, prolonged reaction hours or critical reaction conditions. Thus, we report herein the successful application of this versatile method for the synthesis of naturally occurring 4-aryl substituted canthin-6-one derivatives using 5-hydroxy-L-tryptophan as the starting material.

Materials and Methods

Procedure for the synthesis of intermediate 1-formyl-β-carbolines (2a-e)

To a stirred suspension of 5-hydroxy-L-tryptophan (5.69 mol, 1.3 equiv.) in 1.0 equiv. of p-toluenesulfonic acid monohydrate (TFA) (1.5 equiv.), glyoxal (4.38 mol, 1.0 equiv.) in methanol (50 ml) was added. Then, the solution was heated to 50°C for 4 hours and the presence of phenylglyoxal was monitored by TLC analysis until it was completely consumed. The reaction mixture was poured into water and the precipitate was filtered and purified by silica gel column chromatography eluted with a gradient of acetone and petroleum ether (1:1) to afford **2a-e**.

Procedure for the synthesis of 4-aryl substituted canthin-6-ones (3a-e)

The intermediate compounds **2a-e** (2.13 mol, 1.0 equiv.) in THF (5 mL) was added into NaH solution (60% dispersion in mineral oil) and stirred at 0°C for 15 minutes. Then, acetic anhydride (1.54 mol, 1.5 equiv.) was added into the stirred solution and heated at 70°C for 3 hours. The reaction was monitored by using TLC analysis, and upon completion, the reaction mixture was quenched with water (50 mL), extracted with ethyl acetate (2 x 50 mL) and dried over anhydrous Na_2SO_4. The organic layer was evaporated and purified by silica gel column chromatography eluted with a gradient of n-hexane and EtOAc (8:2) to obtain **3a-e**.

Results and Discussion

(6-hydroxy-9H-pyrido[3,4-b]indol-1-yl)(phenyl)methanone (**2a**). Yield: 53%, yellow solid. IR ν cm^{-1}: 3500, 3423, 1697cm^{-1}. ^{1}H-NMR (400 MHz, METHANOL-D4) ppm: δ 7.86 (dt, J = 8.4, 1.8 Hz, 2H), 7.59-7.54 (m, 3H), 7.29-7.27 (m, 1H), 7.17-7.06 (m, 2H), 6.01 (s, 1H), 3.65-3.53 (m, 2H), 3.23-3.12 (m, 1H). ^{13}CNMR δ (100 MHz, METHANOL-D4): 191.8, 163.0, 141.8, 137.2, 137.1, 135.9, 133.6, 131.0, 130.0, 129.0, 122.0, 120.3, 118.6, 113.6, 113.1, 55.7.

(6-hydroxy-9H-pyrido[3,4-b]indol-1-yl)(4-hydroxyphenyl)methanone (**2b**). Yield: 30%, light brown solid. IR ν cm^{-1}: 3499, 3456, 1678cm^{-1}. ^{1}H-NMR (400 MHz, METHANOL-D4) ppm: δ 12.18 (br s, 1H), 9.68 (br s, 1H), 9.23 (br s, 1H), 8.68 (d, J = 4.6 Hz, 1H), 8.51 (d, J = 7.4 Hz, 1H), 8.43 (d, J = 5.5 Hz, 2H), 8.32 (d, J = 3.6 Hz, 1H), 7.87 (d, J = 6.7 Hz, 1H), 7.52 (dd, J = 8.0 Hz, 3.2 Hz, 1H), 7.12 (d, J = 3.3 Hz, 2H). ^{13}CNMR δ (100 MHz, METHANOL-D4): 170.8, 165.0, 143.9, 138.2, 136.1, 135.2, 133.2, 131.8, 130.0, 129.0, 122.0, 120.8, 118.4, 113.6, 114.5.

(6-hydroxy-9H-pyrido[3,4-b]indol-1-yl)(4-methoxyphenyl)methanone (**2c**). Yield: 42%, brown solid. IR ν cm^{-1}: 3492, 3432, 1642, 1621cm^{-1}. ^{1}H-NMR (400 MHz, METHANOL-D4) ppm: δ 8.34 (d, J = 4.4 Hz, 1H), 8.15 (m, 3H), 7.51 (d, J = 8.4 Hz, 1H), 7.49 (d, J= 8.0 Hz, 1H), 7.10 (d, J = 4.9 Hz, 1H), 7.01 (d, J = 7.4 Hz, 2H), 4.60 (s, 1H), 3.85 (s, 3H). ^{13}CNMR δ (100 MHz, METHANOL-D4): 163.5, 151.5, 136.8, 136.1, 135.9, 133.8, 136.5, 130.0, 121.2, 118.7, 117.9, 112.2, 105.5, 100.3, 54.6.

(6-hydroxy-9H-pyrido[3,4-b]indol-1-yl)(4-bromophenyl)methanone (**2d**). Yield: 57%, brown solid. IR ν cm^{-1}: 3443, 3389cm^{-1}. ^{1}H-NMR (400 MHz, METHANOL-D4) ppm: δ 12.09 (br s, 1H), 9.19 (br s, 1H), 8.51 (d, J = 5.2 Hz, 1H), 8.44 (d, J = 4.4 Hz, 1H), 8.31 (d, J = 7.0 Hz, 1H), 8.15 (d, J = 5.5 Hz, 2H), 7.82 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 5.4 Hz, 2H), 7.60 (t, J = 4.1 Hz). ^{13}CNMR δ (100 MHz, METHANOL-D4): 192.8, 141.9, 137.4, 136.6, 136.0, 133.0, 131.3, 131.2, 129.2, 126.5, 122.0, 120.4, 120.2, 119.3, 113.2.

(6-hydroxy-9H-pyrido[3,4-b]indol-1-yl)(4-nitrophenyl)methanone (**2e**). Yield: 60%, brown solid. IR ν cm^{-1}: 3443, 3389cm^{-1}. ^{1}H-NMR (400 MHz, METHANOL-D4) ppm: δ 12.09 (br s, 1H), 9.19 (br s, 1H), 8.51 (d, J = 5.2 Hz, 1H), 8.44 (d, J = 4.4 Hz, 1H), 8.31 (d, J = 7.0 Hz, 1H), 8.15 (d, J = 5.5 Hz, 2H), 7.82 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 5.4 Hz, 2H), 7.60 (t, J = 4.1 Hz). ^{13}CNMR δ (100 MHz, METHANOL-D4): 192.8, 141.9, 137.4, 136.6, 136.0, 133.0, 131.3, 131.2, 129.2, 126.5, 122.0, 120.4, 120.2, 119.3, 113.2.

10-hydroxy-4-phenyl-6H-indolo[3,2,1-de][1,5]naphthyridin-6-one (**3a**). Yield: 30%, light yellow solid. IR ν cm^{-1}: 3364.7, 3046.1, 1671.2, 1646.3, 1629.9, 686.6, 709.5 cm^{-1}. ^{1}H-NMR (400 MHz, METHANOL-D4) ppm: δ 8.60 (1H, d, J = 5.0 Hz, HCN), 8.31 (2H, dd, J = 8.5, 1.6 Hz, CH), 8.11 (1H, d, J = 5.5 Hz, CH), 7.91 (1H, d, J = 2.3 Hz, CH), 7.61-7.50 (5H, m, CH), 7.34-7.32 (1H, m, CH). ^{13}CNMR δ (100 MHz, METHANOL-D4): 118.8, 145.3, 132.5, 123.4, 114.5, 112.6, 128.1, 131.3, 138.1, 210.0.

10-hydroxy-4-(4-hydroxyphenyl)-6H-indolo[3,2,1-de][1,5]naphthyridin-6-one (**3b**). Yield: 16%, light brown solid. IR ν cm^{-1}: 3364.7, 3046.1, 1671.2, 1646.3, 1629.9, 686.6, 709.5 cm^{-1}. ^{1}H-NMR (400 MHz, METHANOL-D4) ppm: δ 8.60 (1H, d, J = 5.0 Hz, HCN), 8.31 (2H, dd, J = 8.5, 1.6 Hz, CH), 8.11 (1H, d, J = 5.5 Hz, CH), 7.91 (1H, d, J = 2.3 Hz, CH), 7.61-7.50 (5H, m, CH), 7.34-7.32 (1H, m, CH). ^{13}CNMR δ (100 MHz, METHANOL-D4): 118.8, 145.3, 132.5, 123.4, 114.5, 112.6, 128.1, 131.3, 138.1, 210.0.

10-hydroxy-4-(4-methoxyphenyl)-6H-indolo[3,2,1-de][1,5]naphthyridin-6-one (**3c**). Yield: 23%, brown solid. IR ν cm^{-1}: 3364.7, 3046.1, 1671.2, 1646.3, 1629.9, 686.6, 709.5 cm^{-1}. ^{1}H-NMR (400 MHz, METHANOL-D4) ppm: δ 8.60 (1H, d, J = 5.0 Hz, HCN), 8.31 (2H, dd, J = 8.5, 1.6 Hz, CH), 8.11 (1H, d, J = 5.5 Hz, CH), 7.91 (1H, d, J = 2.3 Hz, CH), 7.61-7.50 (5H, m, CH), 7.34-7.32 (1H, m, CH). ^{13}CNMR δ (100 MHz, METHANOL-D4): 118.8, 145.3, 132.5, 123.4, 114.5, 112.6, 128.1, 131.3, 138.1, 210.0.

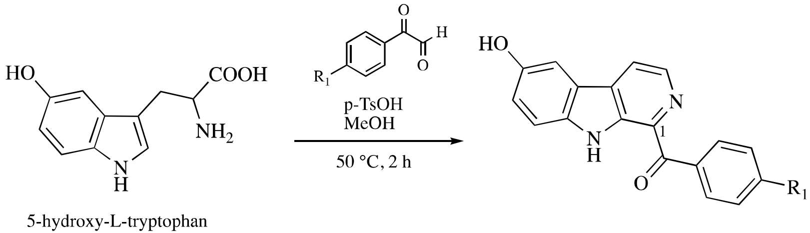
10-hydroxy-4-(4-bromophenyl)-6H-indolo[3,2,1-de][1,5]naphthyridin-6-one (**3d**). Yield: 34%, brown solid. IR ν cm^{-1}: 3443, 3389cm^{-1}. ^{1}H-NMR (400 MHz, METHANOL-D4) ppm: δ 12.09 (br s, 1H), 9.19 (br s, 1H), 8.51 (d, J = 5.2 Hz, 1H), 8.44 (d, J = 4.4 Hz, 1H), 8.31 (d, J = 7.0 Hz, 1H), 8.15 (d, J = 5.5 Hz, 2H), 7.82 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 5.4 Hz, 2H), 7.60 (t, J = 4.1 Hz). ^{13}CNMR δ (100 MHz, METHANOL-D4): 192.8, 141.9, 137.4, 136.6, 136.0, 133.0, 131.3, 131.2, 129.2, 126.5, 122.0, 120.4, 120.2, 119.3, 113.2.

10-hydroxy-4-(4-nitrophenyl)-6H-indolo[3,2,1-de][1,5]naphthyridin-6-one (**3e**). Yield: 41%, brown solid. IR ν cm^{-1}: 3364.7, 3046.1, 1671.2, 1646.3, 1629.9, 686.6, 709.5 cm^{-1}. ^{1}H-NMR (400 MHz, METHANOL-D4) ppm: δ 8.60 (1H, d, J = 5.0 Hz, HCN), 8.31 (2H, dd, J = 8.5, 1.6 Hz, CH), 8.11 (1H, d, J = 5.5 Hz, CH), 7.91 (1H, d, J = 2.3 Hz, CH), 7.61-7.50 (5H, m, CH), 7.34-7.32 (1H, m, CH). ^{13}CNMR δ (100 MHz, METHANOL-D4): 118.8, 145.3, 132.5, 123.4, 114.5, 112.6, 128.1, 131.3, 138.1, 210.0.

The Pictet-Spengler reaction is indeed a valuable chemical transformation for the synthesis of β-carboline ring systems, and it is particularly useful when the starting materials are tryptophan or tryptophan derivatives. This reaction involves the process of acid-catalyzed condensation of β-carboline with an aldehyde, a ketone or a glyoxal, resulting in the formation of a C-C bond and a series of analogues with a β-carboline ring system. This method has been widely used by chemists in producing new canthine derivatives. Subsequently, it continues with endo cyclization reaction between a carbon nucleophile of a sufficiently reactive aromatic moiety and an activated iminium ion resulting in formation of N-heterocyclic ring through a new C-C bond that directly forms tetrahydro-β-carboline. The tetrahydro-β-carboline (THβC) continues to undergo aromatization to form fully aromatic β-carboline [11,12]. It is important to note that the approach continues to be a prominent topic of research as chemists continue to improve the methodology by applying new reaction conditions. Several groups have been investigating the detailed mechanistic features of this reaction over the years [13].

Meanwhile, in our study, by performing the versatile route of Pictet-Spengler reaction where p-TsOH.H_2O was used as catalyst and methanol was used a medium, this simple method produces a fully aromatic β-carboline instead of the tetrahydro β-carboline. Two reactions were performed to convert intermediate 1-aroyl β-carbolines into 4-aryl substituted canthin-6-ones. In this study, a useful approach for the preparation of 1-aroyl β-carboline derivatives via acid-mediated coupling of 5-hydroxy-L-tryptophan and substituted phenylglyoxal's was described. As a result, the conversion of 5-hydroxy-L-tryptophan and phenylglyoxals directly to 1-substituted β-carboline in the presence of acid via a single step Pictet-Spengler reaction. This strategy refines the scope of Pictet-Spengler cyclization as the THβC intermediate directly oxidized to the targeted β-carboline in one-pot oxidation reaction, which also allows for product diversification at C-1 position.

Scheme 1. The synthesis of 5-hydroxy-L-tryptophan with different substituted phenylglyoxals



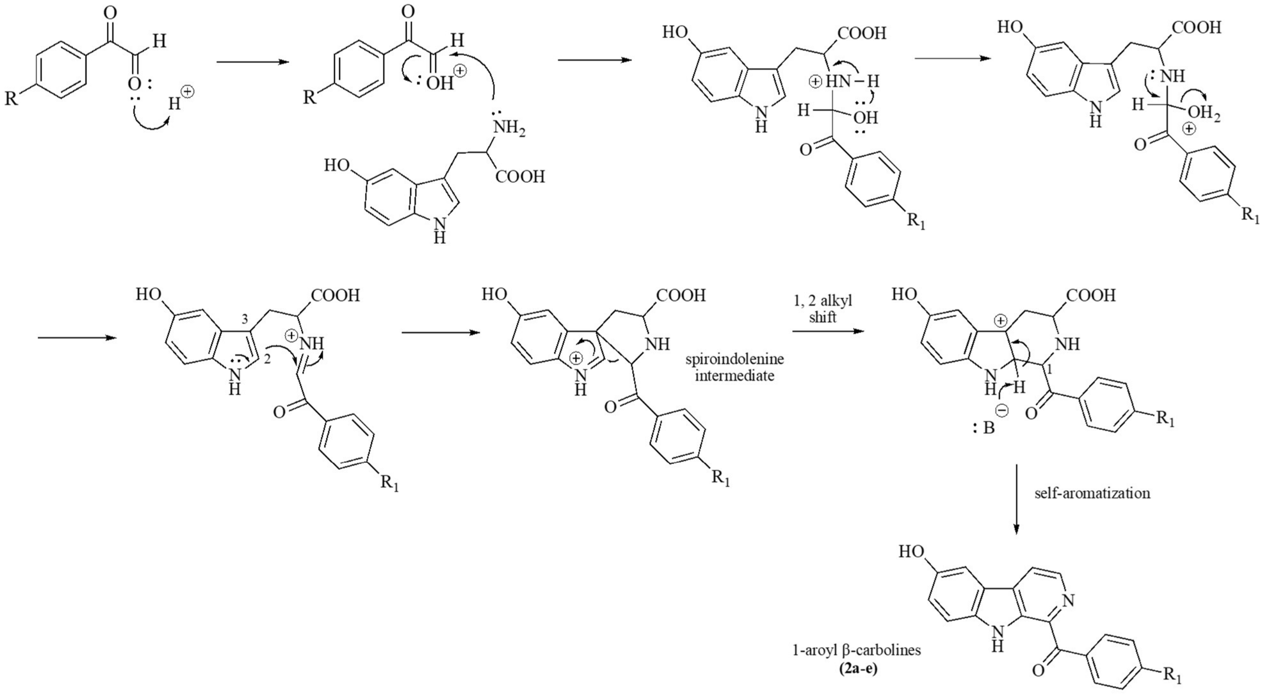
5-hydroxy-L-tryptophan
1

Intermediate 1-aroyl-β-carbolines
2a-e

Entry	R_1	Yield (%)
2a	H	53
2b	OH	30
2c	OCH_3	42
2d	Br	57
2e	NO_2	65

This approach is concise and most preferred due to its simplicity since no heat is involved to drive the reaction. Based on the results obtained, a general conclusion on the electronic effects of electron-withdrawing group (EWG) and electron-donating (EDG) could be deduced. The inductive and resonance effects cause the yields to vary correspondingly. Having EDG as substituent reduced the electrophilicity of the carbonyl carbon, resulting in a weaker reactivity with the nucleophile and hence, gave lower yield products (**2b** and **2c**) than that of using standard phenylglyoxal (**2a**). On the contrary, phenylglyoxal bearing electron-withdrawing group (**2d** and **2e**) gave higher product as anticipated. Despite being to an inductive electron-withdrawing group, halogens are activators since their ability to donate electrons to the aromatic ring via resonance is much greater.

The reaction mechanism occurs by the initial formation of iminium ion followed by electrophilic addition at the C-2 position to directly yield the six-membered ring intermediate. However, both carbon-2 and -3 of 5-hydroxy-L-tryptophan are nucleophilic. Therefore, the reaction can also proceed by the attack of carbon-3 to yield a spiroindolenine intermediate that would then undergo a 1,2-alkyl shift to form the product as depicted in Scheme 2. Both mechanisms have been proven to be true, yet the prevailing mechanism is still unknown [14].

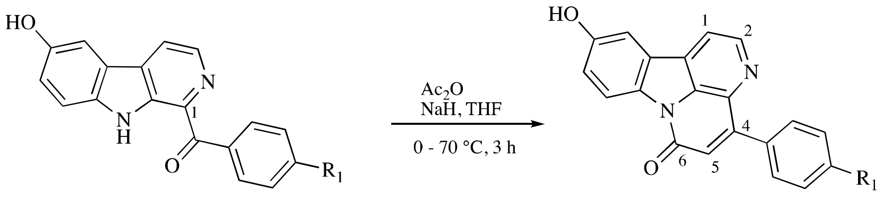


Scheme 2. Mechanism of Pictet-Spengler reaction with electrophilic addition using phenylglyoxal at carbon-3

Having the series of intermediates 1-aroyl β-carbolines (**2a-e**), the synthesis of 4-aryl substituted canthin-6-ones was performed through the cyclization in dry reaction condition for 3 hours as shown in Scheme 3. The use of sodium offers the advantage of the reaction being carried out in a nonhydrolytic solvent. It was thought that the use of sodium hydride would offer similar advantage and simultaneously would be safer and easier to handle than using the metal. The intermediate compounds (**2a-e**) were reacted with acetic anhydride in the base by using THF as the medium to get the desired target compounds in lower yields.

The synthesis of compounds (**3a-e**) was achieved by intramolecular nucleophilic substitution. The reaction mechanism begins by addition reaction whereby the nucleophilic amine of the intermediate compound attacked the acetic anhydride to form new C-C bond. Accordingly, a series of proton transfers, electron movement and intramolecular cyclization led to the formation of an Aldol intermediate via enolate ion formation. A more stable enone form of the anticipated product was eventually obtained by elimination of water.

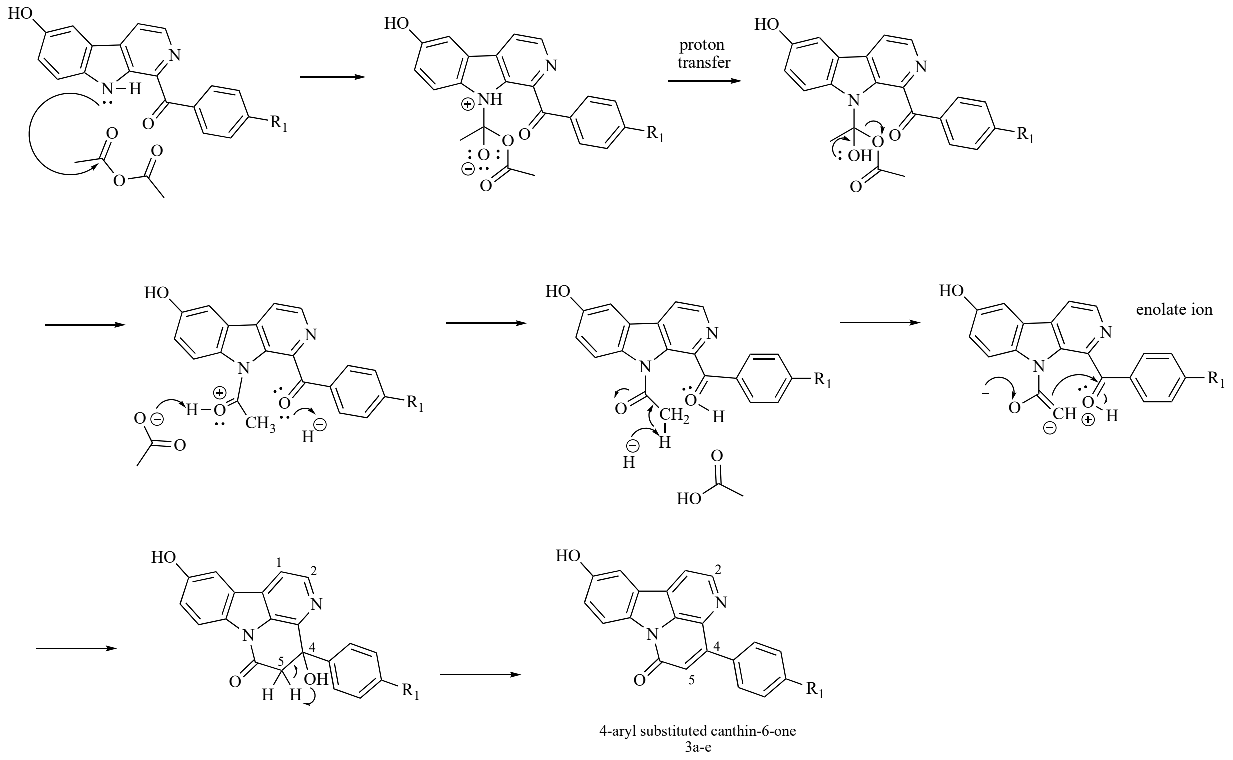
Scheme 3. Cyclization of tetrahydro-β-carboline intermediates



Intermediate 1-aroyl-β-carbolines
2a-e

4-aryl substituted canthin-6-one
3a-e

Entry	**R1**	**Yield (%)**
3a	H	30
3b	OH	15
3c	OCH_3	23
3d	Br	34
3e	NO_2	41



Scheme 4. Mechanism of Pictet-Spengler reaction with electrophilic addition using phenylglyoxal at carbon-3

Dighe et al. [6], had successfully discovered an effective iodine-mediated oxidative Pictet-Spengler reaction in DMSO using terminal alkynes as a substitute the glyoxal to produce an intermediate of 1-aroyl-β-carboline, then it underwent cyclization to yield 4-aryl substituted canthin-6-ones. Shashikant et al. [15] their investigations by reacting 1 with phenylacetylene in the presence of 50 mol of iodine in DMSO as the medium at 100℃ for 6 hours to yield **2a-e**. They continued their study and discovered that reacting of substituted 1-aroyl β-carbolines **2a-e** with Ac_2O in the presence of NaH as the base in THF at 70℃ for 12 hours produced the desired products in a good yield of **3a-e** in 83%. However, by employing the same procedure, we only managed to get the 4-aryl substituted canthin-6-ones in much lower yields (15-41%). This is due to the substituents on C-1 which influences the reactivity of the nucleophilic substitution in both reactions. The reaction time also affects the product yields.

Conclusion

In conclusion, we have successfully synthesized a series of 4-aryl substituted canthine-6-one derivatives through a versatile Pictet-Spengler condensation from 5-hydroxy tryptophan and subsequent cyclization using NaH, involving the formation of 1-aroyl β-carbolines as pivotal intermediates in moderate yields. This alternative is an improved Pictet-Spengler reaction in producing 1-substituted β-carboline in which tetrahydro-β-carboline. Further application of the scope and mechanism of reaction in the study towards total synthesis of novel canthine-6-one and other additional biologically active natural products are currently in progress.

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