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FULL PAPER

A novel and simple strategy for the synthesis of γ-carboline

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This study introduces a novel and efficient approach for the oxidative aromatization of tetrahydro-γ-carboline using $CuCl_2.2H_2O$ and I_2, H_2O_2 in DMSO. This method was applied for all kinds of C-3 substituted tetrahydro-γ-carboline (THγC) units to access the corresponding aromatic γ-carbolines. With a 0.25 mol% $CuCl_2.2H_2O$ as a catalyst, THγC could be efficiently oxidized to γ-carboline at 100 °C with excellent yield. This protocol was also generalized for the aromatization of tetrahydro-β-carboline-3-carboxylic acid to corresponding β-carboline-3-carboxylic acid. The entire synthesized new compounds were characterized by using ^{1}HNMR, ^{13}CNMR and Mass spectroscopy technique. To the best of our knowledge, this is the first synthesis of γ-carbolines via an oxidative aromatization of THγC.

KEYWORDS

Fisher indole synthesis; tetrahydro-γ-carboline; aromatization; Copper chloride; Iodine.

Introduction

Carbolines are among the most intriguing alkaloids and are classified according to their position of N in the skeleton as α-, β-, γ-, or δ-carbolines [1]. The γ-Carboline alkaloids show a wide range of pharmaceutical activities such as CDK_4, CDK_2 inhibitors [2], antidepressants [3], neuroleptic [4], antipsychotic [5], Parkinson's disease [6], antitumor [7], antiarrhythmic [8], antiviral [9], osteoarthritides [10], antimicrobial activity [11], and anti-Alzheimer drugs [12]. Therefore, a great deal of attention from the scientific community, both academic and industrial ones, has been paid to γ-carboline for its synthesis. The γ-carboline skeleton is a significant synthetic intermediate for numerous medicinally important natural products and drug molecules (Figure 1). The remarkable biological properties of γ-carboline make it a synthetically critical unit.

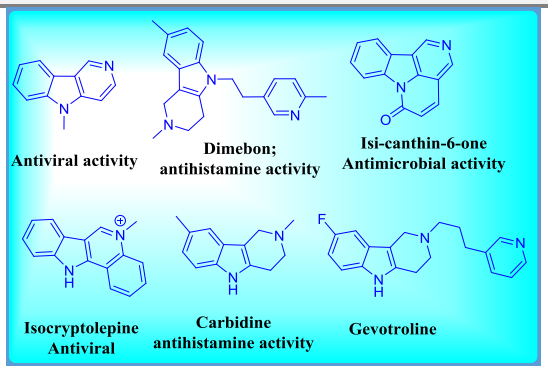
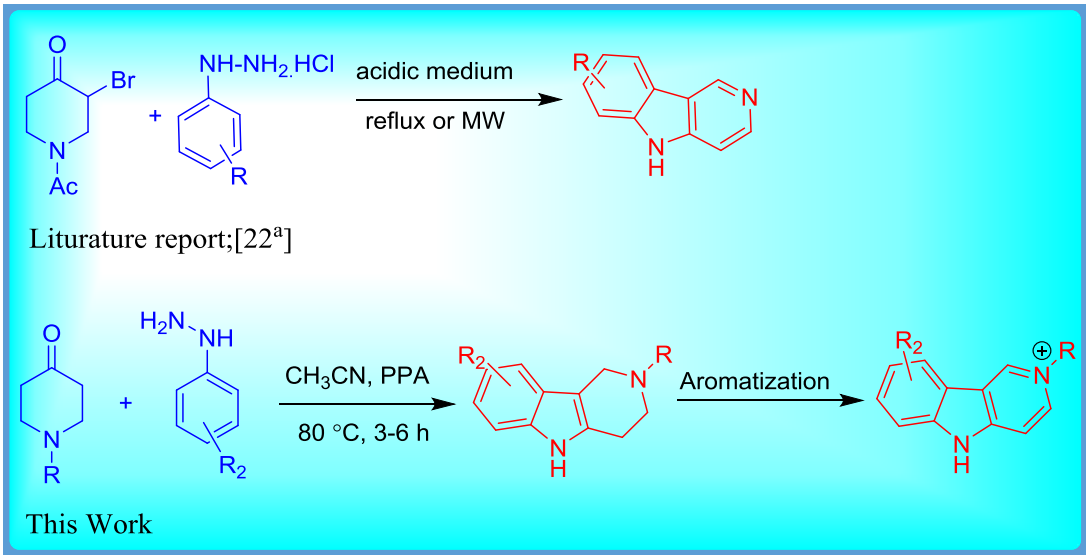


FIGURE 1 Bioactive γ-carboline

In the literature, synthesis of γ-carboline has been reported by many methods and reagents including Graebe - Ullmann procedure[13], Pictet-Spengler cyclization, Fischer annulation [14], ring closure of aldimine [15], Suzuki-Miyaura reaction [16], intermolecular Diels-Alder reaction [17], Pd-catalyzed annulation of alkynes [18], Ru-catalyzed [2+2+2] cycloaddition [19], Cu(I)-catalyzed asymmetric [3+3] cycloaddition [20], and intramolecular thermal electrocyclization strategy [21]. As the

literature attests, the synthesis of tetrahydro-γ–carboline *via* Fisher indole synthesis is a good priority for academic and industrial applications. A variety of different reactions on the Fisher indole synthesis of tetrahydro-γ-carboline have been developed over the past few decades [22]. To the best of our knowledge, no report is available for the transformation of tetrahydro-γ-carboline to aromatic γ-carbolines via sequential Fisher indole cyclization followed by aromatization (Scheme 2). $CuCl_2.2H_2O$ [23], iodine in DMSO [**24**] mediated notable organic transformations have been interesting areas of research.

The current study aimed at developing a new protocol for the synthesis of γ-carbolines using 0.25 mol% of $CuCl_2.2H_2O$ without any ligand and I_2, H_2O_2 in DMSO solvent.



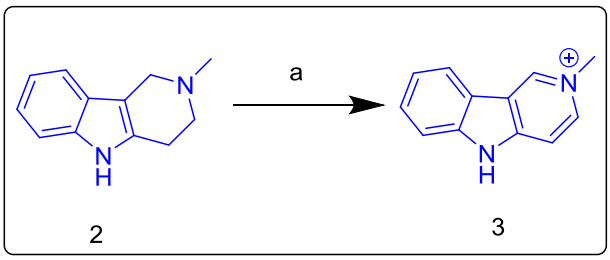
SCHEME 1 Synthesis of γ-carboline

Result and discussion

Accordingly, a series of tetrahydro-γ-carboline were synthesized my Fisher indole cyclization by the reaction of equimolar quantities of substituted arylhydrazines with *N*-protected- 4-piperidone. We initiated our studies by examining the reaction of tetrahydro-γ-carboline with $CuCl_2.2H_2O$ at 100 °C, as shown in Table 1. Initially, tetrahydro-γ-carboline 2I was treated with 0.01, 0.05 & 0.10 Equiv. $CuCl_2.2H_2O$ in DMSO at 100°C, 3I was isolated in 20 to 55 % yield (Table 1, Entry 1-3), while the minor yield was obtained at a lower reaction temperature.

Therefore, when the reaction was performed at 100 °C, with 0.25, 0.50 equiv. $CuCl_2.2H_2O$ in DMSO at 100 °C temperature, 3I with 77–78 % yield was obtained (Table 1, Entry 4, 5). Similarly, an increase in temperature or equiv. $CuCl_2.2H_2O$ in DMSO did not affect the return of 3I. After examining various conditions, the best outcome was obtained by using 0.25 mol% of $CuCl_2.2H_2O$ (Table 1, Entry 4). The isolated product was confirmed by ^{1}HNMR, ^{13}CNMR, and mass spectroscopy.

TABLE 1 Screening of reaction Conditions

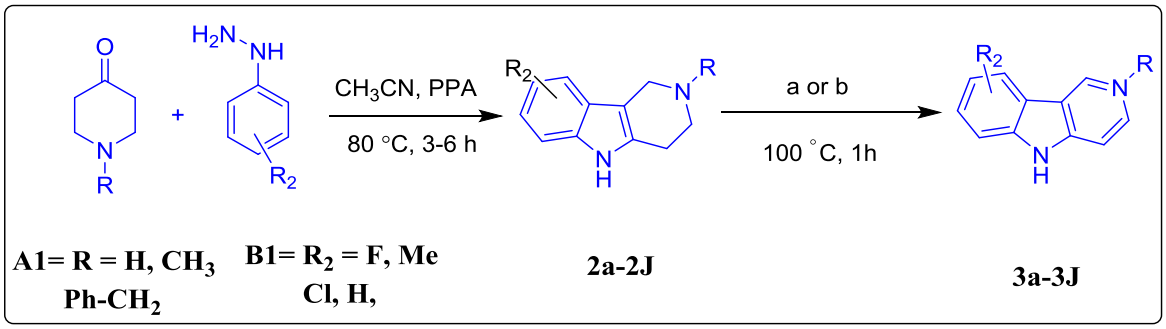


Entry	Catalyst equiv	Catalyst /solvent(a)	Time/h	Yield %(3)
1	0.01	$CuCl_2.2H_2O$/ DMSO	12	20
2	0.05	$CuCl_2.2H_2O$/ DMSO	12	34
3	0.10	$CuCl_2.2H_2O$/ DMSO	6	55
4	**0.25**	**$CuCl_2.2H_2O$/ DMSO**	2.5	77
5	0.50	$CuCl_2.2H_2O$/ DMSO	2	78
6	**0.25**	**I_2, H_2O_2/ DMSO**	2	76
7	0.50	**I_2, H_2O_2/ DMSO**	1.5	77

* a= Catalyst /solvent; the best condition is mentioned

Relying on our previous report, the I_2, H_2O_2 in DMSO is also a suitable reagent for the aromatization of tetrahydro-*β*-carboline, and multisubstituted cyclohexanone [24]. Therefore, I_2, H_2O_2 in DMSO at 100 °C was selected to do the reaction. When the aromatization of THγC was carried out using I_2, H_2O_2 in DMSO at 100 °C, it produced desired 3I with 74 % yield (Table 1, Entry 6, 7). Conspicuously, 74% yield of 3I with 0.25 mol% I_2 was obtained in just 2 h. However, no further significant improvement in yield was observed with 100 mol% of Iodine.

After having an optimized condition in our hand, we embarked on the newly established methods for the aromatization of various tetrahydro-*γ*-carboline derivatives, obtained by fisher indole synthesis of phenylhydrazine hydrochloride and appropriate 4-piperidone derivative. Accordingly, a series of substituted tetrahydro-*γ*-carboline which were treated with $CuCl_2.2H_2O$ (0.25 equiv) in DMSO at 100 °C and gave corresponding *γ*-carboline are summarized in Table 2, 3A-3J. Applying aromatization to the range of tetrahydro-*γ*-carbolines with electron-donating group led to good yields (up to 76%) (Tables 2, 3A, 3F, 3G, 3H, 3I), while applying aromatization to weekly deactivating group, such as fluoro-, chloro- resulted in the desired products in excellent yields (Scheme 2) (Tables 2, 3C, 3D, 3E, 3G, 3H). However, aromatization in the case of tetrahydro-*γ*-carboline with C-3 substituent like methyl and benzyl group gave *γ*-carbolines with 58% to 78% yield (Tables 2, 3E-3F, 3G, 3H, 3I, 3K, 3J).



SCHEME 2 Synthesis of *γ*-carboline; (a) $CuCl_2.2H_2O$ (0.25 equiv) b) I_2, H_2O_2, DMSO

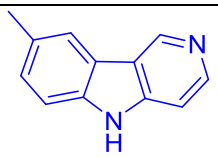
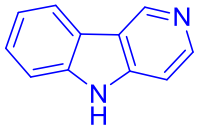
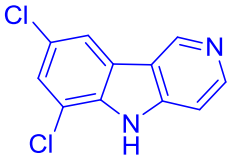
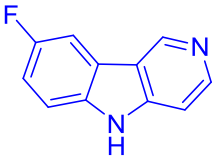
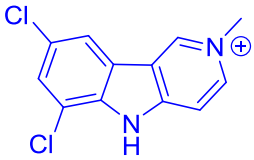
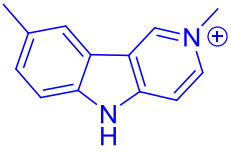
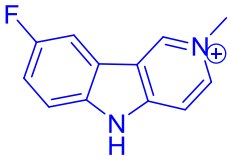
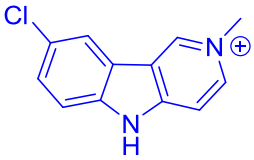
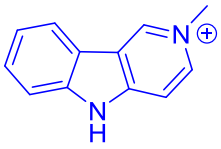
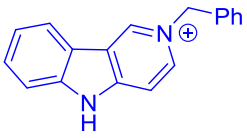
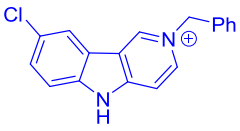
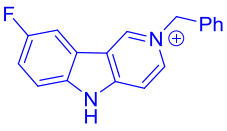
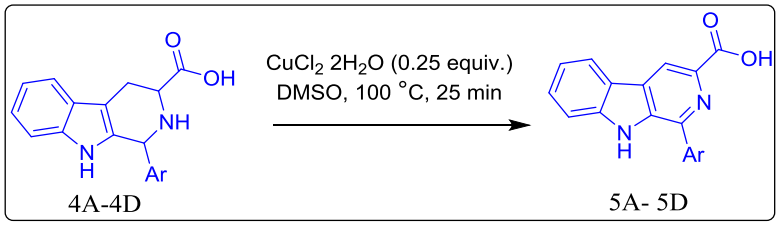
 3A, 74%	 3B, 80%	 3C, 75%	 3D, 76%
 3E, 67%	 3F, 78%	 3G,72%	 3H,74%
 3I, 78%	 3K, 58%	 3J, 61%	 3k, 60%

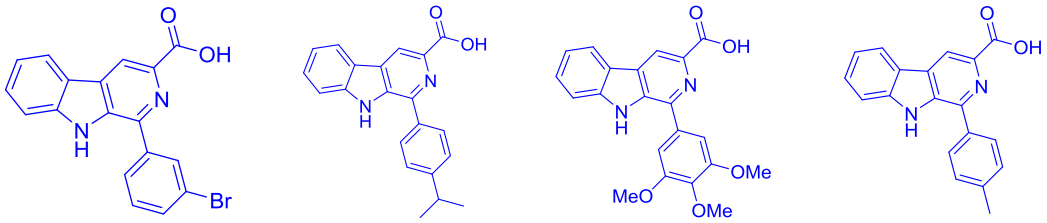
TABLE 2 Synthesis of γ-carboline

Subsequently, the THγC was subjected to aromatization using I_2, H_2O_2/ DMSO and it produced the desired γ-carboline with excellent yield. However, when the reaction was performed on the tetrahydro-γ-carboline having C-3 substituted with Methyl or benzyl group using I_2, H_2O_2/ DMSO condition, the response went smoothly like a simple experimental and workup procedure. We observed that when the experiment was performed on C-3-substituted tetrahydro-γ-carboline using $CuCl_2.2H_2O$ in DMSO, the desired product with fewer yields were provided. On the other hand, the reaction resulted in the formation of γ-carboline in a very good yield using I_2, H_2O_2/ DMSO at 100 °C. Indeed, the I_2, H_2O_2/ DMSO showed better result than the $CuCl_2.2H_2O$ in DMSO for the aromatization of C-3 substituted THγC. Moreover, THγC with free N-H reacted well to furnish the corresponding products with both of the reagents (Table 2. 3A, 3B, 3C, 3D).

The present method was also applied to the N-heterocyclic aliphatic scaffold-like THβC, quinoline and bioactive moieties. In our previous report [24d], a series of β-carboline-3-carboxylic acid was prepared by using iodine in DMSO/HCl. Likewise, when THβC was treated with $CuCl_2.2H_2O$ (0.25 equiv.) in DMSO at 100 °C, β-carboline-3-carboxylic acid with good yield was produced (Scheme 3). The scope and generality of oxidative aromatization of THβC were examined by employing various substituted THβC reaction substrates. The results are depicted in Table 3.



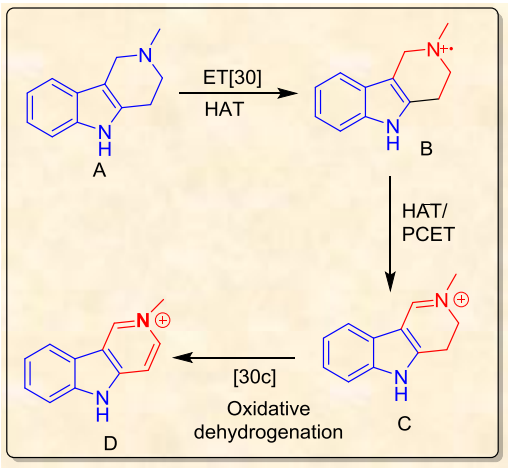
SCHEME 3 Synthesis of β-carboline



5A, 55% 5B, 56% 5C, 58% 5D, 58%

TABLE 3 *β*-carboline- 3-carboxylic acids

Mechanism: A possible mechanism for the $CuCl_2$-catalyzed oxidative conversion of THγCs to γ-carboline was proposed (Scheme 4). THγC **A** could first undergo $CuCl_2$-catalyzed oxidation of C-N single bond to C=N double bond via catalytic $CuCl_2$ electron transfer (ET) [30a] from the amine to the catalyst forming an ammonium radical cation intermediate **B** to produce 4,5-dihydro-γ-carboline **C** *via* hydrogen atom transfer **(HAT)** or proton-coupled electron transfer (**PCET**) mechanism[30c]. The iminium ion **C** could undergo $CuCl_2$ oxidative dehydrogenation to produce γ-carboline **D**, while the I_2, H_2O_2, in DMSO catalyzed mechanism proceeded via generation of HI in situ and sequential oxidative dehydrogenation to γ-carboline [24c, d].



SCHEME 4 A possible mechanism for the $CuCl_2$.$2H_2O$ catalyzed oxidative conversion of THγCs **A** to γ-carbolines **D**.

Conclusion

A direct and straightforward approach was developed for the synthesis of various γ-carbolines using $CuCl_2.2H_2O$ and I_2, H_2O_2, in DMSO as a mild oxidant. This method has some advantages as follows: a) The present process is metal-free and the experimental procedure is quite easy, so it is very safe and environmentally favorable; b) $CuCl_2$ and Iodine as the catalyst are cheap and harmless; (c) All results were obtained fell between good to excellent yields; (d) The reaction condition can tolerate numerous functional groups. Finally, this protocol has been utilized for the aromatization of various-heterocycles like tetrahydroquinoline, tetrahydro-isoquinoline and THβC.

The experiment

All the reagents were commercially available and used without further purification. All reagents were purchased from Acros (98-99% Purity), Alfa Aesar, and Avra chemical (98-99% purity), S.D. Fine chemical (97-98% purity). Analytical thin-layer chromatography was performed on silica gel using silica gel (100-200 mesh). The solvents were dried, and distilled over A4 molecular sieves before use. DMSO was dried over activated A4 molecular sieves before use. ^1H NMR, ^{13}C NMR spectra were recorded with tetramethylsilane (TMS) as internal standard at ambient temperature at Bruker 400, 500 MHz for ^1H NMR, and 100 and 125 MHz for

^{13}CNMR, GC-MS data collected on the AOS-20i Autoinjector Shimadzu GC/MS system mass spectrometer.

General procedure for the preparation of γ- carboline 3

General procedure A

What follows is the general procedure in relation to the solution of compound THγC (1 equiv) in DMSO, $CuCl_2$. $2H_2O$ (0.25 equiv.) was added, then the resulting mixture was heated at 100 °C temperature for 2 to 5 h. Next, the reaction mixture was allowed to cool at room temperature and quenched in ice-cold water; the crude product was extracted with ethyl acetate and dried under vacuum. The crude compound purified by column chromatography provided the desired compound with 71% yield.

General procedure B

Here, Iodine (0.25 equiv.) was added to the solution of compound THγC (1 equiv) in DMSO, followed by H_2O_2 (1 equiv.,). The resulting mixture was heated at 100 °C temperature for 1 to 5 h. The reaction mixture was then allowed to cool at room temperature. The added saturated solution sodium thiosulphate provided a solid crude filter and dried under vacuum. The crude compound purified by column chromatography gave the desired compound with 76% yield.

2-Methyl-5H-2l4-pyrido[4, 3-b]indole (3I): Brawn solid, 78% yield**,** ^{1}H NMR (500 MHz, DMSO) δ 11.92 (s, 1 H), 8.84 (s, 1 H), 8.45 (s, 3H), 8.33(d, J=7.8 Hz, 1 H), 7.96 (d, J=7.2 Hz, 1 H), 7.69 (d, J=7.1 Hz, 1 H), 7.65–7.58 (m, 1 H), 7.31 (d, J=6.9 Hz, 1 H), 7.21 (d, J=7.4 Hz, 1 H), 3.87 (s, 3 H).δ C (126 MHz, DMSO) 161.06, 142.82, 130.88, 130.51, 130.05, 122.79, 120.82, 114.97, 114.86, 114.59, 113.19, 55.94. Calculated Mass: 183.0922; Obtained mass; 183.0918.

6,8-Dichloro-2-methyl-5H-2l4-pyrido[4, 3-b]indole (3E), new compound

White solid, 67% yield, M.P., 179-184 °C, ^{1}H NMR (500 MHz, DMSO) δ 9.41 (s, 1 H), 8.25 (d, J=7.6 Hz, 2 H), 7.69 (d, J=6.7 Hz, 1 H), 7.64(s, 1H), 4.22 (s, 3 H). δ C (126 MHz, DMSO) 173.86, 152.67, 138.14, 136.47, 126.41, 125.53, 123.60, 121.84, 121.74, 119.95, 111.96, 46.05; calculated mass Exact Mass: 252.0221, Obtained Mass 252.0224.

2-Benzyl-5H-pyrido[4, 3-b]indol-2-ium (3K): 58% yield, ^{1}H NMR (500 MHz, DMSO) δ 13.14 (s, 1 H), 9.50 (s, 1 H), 7.84 (d, *J*=6.0 Hz, 1H), 7.64 – 7.51 (m, 4 H), 7.51 – 7.30 (m, 5 H), 5.06 (s, 2H).

General procedure for the preparation of β- carboline-3-carboxylic acid 5

A mixture of tetrahydro-*β*-carboline **5C** (1 equiv. 0.979 mmol) in DMSO, $CuCl_2$. $2H_2O$ (0.25 equiv.) was added and the resulting mixture was stirred at 100 °C temperature for 30 min. When TLC confirmed the consumption of starting material on TLC, the reaction was quenched with cold ice water. The crude product was purified by column chromatography using ethyl acetate, hexane and drop of methanol to obtain the desired compounds.

1-(3, 4, 5-Trimethoxyphenyl)-9H-pyrido[3, 4- b]indole-3-carboxylic acid (5C)[24d]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.31 (t, *J*=7.52 Hz, 1 H) 7.57 (t, *J*=7.64 Hz, 1 H) 7.69 (d, *J*=8.31 Hz, 1 H) 8.34 (d, *J*=7.83 Hz, 1 H) 8.86 (s, 1 H) 11.88 (s, 1 H); ^{13}C NMR (101 MHz, DMSO-d_6)

Supplementary data associated with this article (Full experimental details and characteristics for all new compounds and copies of ^{1}H NMR, ^{13}C NMR, and Mass spectral data) are available on the publisher's website.

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