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Research Article

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Ultrasound-Promoted Synthesis of Tetrahydro-*β*-Carbolines Using Triton-X 100 Catalyst *via* Pictet-Spengler Reaction

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Abstract: An ultrasound-promoted efficient synthesis of novel tetrahydro-*β*-carbolines by condensation of tryptamine and aryl/ heteroaryl aldehydes in the presence of Triton X-100 catalyst at 70^{o}C in aqueous media is accomplished *via* Pictet-Spengler reaction. In general, ultrasound irradiation offered the advantages of high yield, clean reaction, simple methodology and short reaction time compared to conventional methods. The structures of novel compounds were confirmed by IR, ^{1}H NHR, ^{13}C NMR and elemental analysis.

Keywords: Tetrahydro-*β*-carboline; Aryl/heteroaryl aldehydes; Tryptamine; Triton X-100; Tryptamine/ Ultrasonic irradiation.

1. INTRODUCTION

The popularity of employing ultrasonic irradiation in organic synthesis has tremendously increased in recent years to the simplicity, rapidity, high turnover and green nature of the reactions [1]. This can be considered as a processing aid in terms of energy conservation and waste minimization compared to conventional heating. Many C-C bond forming reactions in organic synthesis have been accelerated using ultrasound irradiation [2]. The tetrahydro-*β*-carboline/ *β*-carboline ring system is an important structural motif found in various bioactive natural products and pharmaceutical agents. They act as anti-HIV [3-5], antitumor [6-9], antimalarial [10-12], antibacterial [13-14] and excellent binding agents towards 5-hydroxy serotonin receptors [15-18], monoamine oxidase [19] and benzodiazepine receptors [20-23] in the central nervous system. Pictet-Spengler reaction is the most widely followed method to access tetrahydro-β-carbolines. Mechanistically, the Pictet -Spengler reaction occurs when an aryl ethyl amine such as tryptamine undergoes condensation with an aldehyde to afford an imine intermediate, which undergoes a 6-endo cyclization to furnish the requisite cyclic product tetrahydro-*β*-carboline [24].

Since its discovery [25], many different sets of reaction conditions such as Lewis acids [26-27], Bronsted acids [28-29], Organocatalysts [30], enzymatic [31], RTILs [32-34], DES [35] and microwave conditions [36-37] have been reported. While these are prompt with short reaction times and excellent yields, they are environment non-benevolent. Hence, the identification of environmentally benign and cost effective catalyst is of current interest for the synthetic chemists. Recently, non-ionic surfactant have identified as catalysts due to their properties like rapid dissolution , non-denaturing, chemical stability in the presence of dilute acids, bases and salts, low aquatic toxicity, and readily biodegradable. In this view we identified Triton X-100 catalyst and used as catalyst for the preparation of tetrahydro-*β*-carbolines. Triton X-100 is one of the most commonly used surfactant for solubilization of liquid membranes [38]. It is also used as an emulsifier, wetting agent, depressant and complexing agent in both aqueous and non aqueous media.

In the continuation of our efforts to develop various biologically important compounds in greener methods, we report here a highly efficient procedure for the preparation of tetrahydro-*β*-carbolines in good yields by the condensation of tryptamine and aldehydes *via* Pictet-Spengler reaction using non-ionic surfactant catalyst Triton X-100 (10mol%) in aqueous media under ultrasound irradiation.

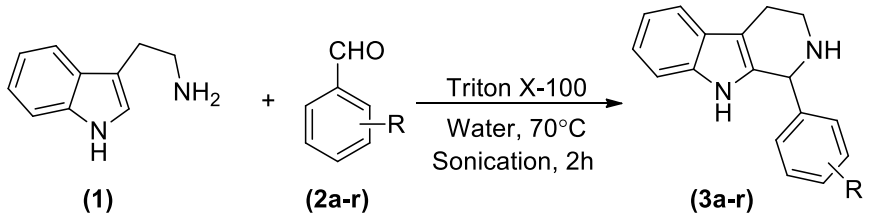
2. EXPERIMANTAL

2.1. General

All reagents were purchased from Sigma-Aldrich and were used without further purification. Double distilled water used as solvent, sonochemical reactions were carried out on Power sonic 405 micro process controlled bench-top ultrasonic cleaner with a frequency of 40 KHz and an output power of 350 W. Melting points were determined in open capillaries using EZ-Melt automated melting point apparatus. The IR spectra were recorded on Bruker Alpha-EcoATR-FTIR interferometer with single reflection sampling module equipped with ZnSe crystal and the absorptions were reported in wavenumbers (cm^{-1}). NMR spectra were recorded on Bruker 400MHZ NMR spectrometer operating at 400MHZ for ^{1}H NMR, 100 MHZ for ^{13}C NMR by recording in $CDCl_3$ and referenced to TMS (^{1}H and ^{13}C). Mass spectra were recorded on a JEOL GCMATE II GC-MS spectrophotometer at IIT-SAIF, Chennai. Elemental analysis was performed on a Thermo Finnigan Instrument. Elemental analysis was performed on a Thermo Finnigan Instrument. All solvents used for spectroscopic and other physical studies were reagent grade and were further purified by literature methods.

2.2. General procedure for the synthesis of compound tetrahydrocarboline derivatives (3a-r):

In a typical experiment, tryptamine **(1),** respective aldehydes **(2a-r)** and Triton X -100 (10 mol%) were taken in water in a round bottomed flask. The resulting mixture was subjected to ultrasonic irradiation at 70ºC and progress of the reaction was monitored by thin layer chromatography (TLC). After completion of the reaction, the reaction mixture was extracted with ethyl acetate and dried over anhydrousNa_2SO_4, filtered. The filtrate was evaporated under reduced pressure. The resulting product was purified by column chromatography on silica gel as absorbent and ethyl acetate & hexane (1:2) as an eluent to get pure products. Structures of all the products were confirmed by analytical and spectral data.



(1) (2a-r) (3a-r)

Entry	Substrate	Time (h)	Entry	Substrate	Time (h)
3a	(4-Cl)Ph	2	**3j**	(4-OH)(3-OMe)Ph	3
3b	(4-Me)Ph	2	**3k**	(4-Piperidinyl)Ph	2
3c	(4-NO_2)Ph	4	**3l**	2-Furyl	2
3d	(4-OMe)Ph	2	**3m**	2-Thiophenyl	2.5
3e	(4-OH)Ph	2	**3n**	2-Pyrrolyl	2
3f	(4-$N(CH_3)_2$)Ph	3	**3o**	4-Pyridinyl	2
3g	(4-F)Ph	2	**3p**	(2-Methyl)-4-Pyridinyl	3
3h	(2-Br)Ph	3	**3q**	5-Indolyl	2
3i	(2-OH)Ph	3	**3r**	1,3-benzo[*d*]dioxole-5-yl	2

Scheme 1: Synthesis of tetrahydro-β-carboline

2.2.1. 1-(4-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (3a): Yield: 92%; white solid; mp 206–207 °C; IR (ZnSe): 1742 (C=O) cm^{-1};; ^{1}HNMR (400 MHz, $CDCl_3$): δ 12.46 (s, 1H), 7.41-7.37 (m, 3H), 7.24-7.03 (m, 5H), 5.28 (s, 1H), 3.97-3.94 (m,1H), 3.21-3.18 (m, 1H), 2.68-2.87 (m, 2H),1.68 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$,): δ 139.26, 136.45, 136.27, 134.77, 129.25, 128.85, 127.52, 122.10, 121.98, 119.28, 118.97, 114.03, 111.10, 107.54, 62.02, 43.42, 26.80 ppm; LCMS m/z: 282(M+). Anal. Calcd for $C_{17}H_{15}ClN_2$ (%): C, 72.21; H, 5.35; Cl, 12.54; N, 9.91; Found: C, 72.18; H, 5.34; Cl, 12.52; N, 9.88.

2.2.2. 1-(p-tolyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (3b): Yield: 86%; pale yellow solid; mp 136–138 °C; IR (ZnSe): 1738 (C=O) cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 12.23(s, 1H), 7.58-7.52 (m, 2H), 7.44-7.38 (m, 3H), 7.32-7.20 (m, 3H), 12.23(s, 1H), 5.38 (s, 1H), 3.42-3.39 (m, 2H), 3.24-3.21 (m, 2H), 2.42 (d, 2H), 2.28 (s, 1H) ppm, 1.91 (s,1H); ^{13}C NMR (100 MHz, $CDCl_3$,): δ 138.42, 137.56, 136.22, 134.12, 130.48, 129.34, 126.72, 122.84, 120.24, 116.46, 113.52, 108.43, 64.28, 51.14, 22.81, 21.54 ppm; LCMS m/z: 262(M+). Anal. Calcd for $C_{18}H_{18}N_2$ (%): C, 82.41; H, 6.92; N, 10.68; Found: C, 82.39; H, 6.89; N, 10.66.

2.2.3. 1-(4-nitrophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (3c): Yield: 94%; yellow solid; mp 172–173 °C; IR (ZnSe): 1734 (C=O) cm^{-1};; ^{1}HNMR (400 MHz, $CDCl_3$): δ 12.29 (s, 1H), 8.32 (m, 2H), 7.52 (m, 1H), 7.35-7.31 (m, 4H), 5.46 (s, 1H), 3.46-3.38 (m, 2H), 2.92-2.87 (m, 2H), 1.98 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$,): δ 146.82, 145.48, 136.24, 134.18, 128.25, 123.54, 120.56, 118.94, 110.26, 109.65, 62.28, 46.42, 24.26 ppm; LCMS m/z: 293(M+). Anal. Calcd for $C_{17}H_{15}N_3O_2$ (%): C, 69.61; H, 5.15; N, 14.33; O, 10.91; Found: C, 69.58; H, 5.13; N, 14.32. O, 10.87.

2.2.4. 1-(4-methoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (3d): Yield: 89%; pale yellow solid; mp 205–206 °C; IR (ZnSe): 1740(C=O) cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 12.43 (s, 1H), 8.10 (d, 2H), 7.52 (d, 2H), 6.90-7.32 (m, 4H), 5.40 (s, 1H), 3.86 (s, 3H), 3.3 (m, 1H), 3.08 (m, 1H), 2.62-2.85 (m, 2H),

1.95 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$,): δ 159.46, 136.54, 134.96, 132.28, 130.06, 127.54, 121.89, 120.51, 118.32, 113.96, 111.23, 109.16, 62.20, 55.98, 45.26, 22.08 ppm; LCMS m/z: 278(M+). Anal. Calcd for $C_{18}H_{18}N_2O$ (%): C, 77.67; H, 6.52; N, 10.06; O, 5.75; Found: C, 77.65; H, 6.48; N, 10.05; O, 5.71.

2.2.5. 4-(2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenol (3e): Yield: 88%; pale yellow solid; mp 192–193 °C; IR (ZnSe): 1736 (C=O) cm^{-1};; ^{1}HNMR (400 MHz, $CDCl_3$): δ 12.39 (s, 1H), 7.92 (d, 2H), 7.32 (d, 2H), 6.96-6.93 (m, 4H), 5.46 (s, 1H), 4.21 (s, 1H), 3.08-3.06 (m, 2H), 2.86-2.82 (m, 2H), 1.92 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$,): δ 153.38, 140.82, 136.53, 132.48, 130.65, 127.42, 121.36, 120.43, 118.49, 115.72, 110.26, 108.39, 60.15, 45.26, 22.08 ppm; LCMS m/z: 264(M+). Anal. Calcd for $C_{17}H_{16}N_2O$ (%): C, 77.25; H, 6.10; N, 10.60; O, 6.05; Found: C, 77.23; H, 6.08; N, 10.57; O, 6.04.

2.2.6. N,N-dimethyl-4-(2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)aniline (3f): Yield: 84%; yellow solid; mp 205-206°C; IR (ZnSe): 1746 (C=O) cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 12.39 (s, 1H), 7.78 (d, 2H),7.26 (d, 2H), 6.84-6.82 (m, 4H), 5.68 (s, 1H), 3.42-3.39 (m,2H), 3.26 (s, 6H), 2.72-2.69 (m, 2H), 2.02 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$,): δ 152.24, 138.62, 135.26, 132.02, 128.22, 127.86, 122.38, 120.42, 118.56, 112.72, 111.48, 108.02, 60.20, 44.56, 40.06, 22.82 ppm; LCMS m/z: 291(M+). Anal. Calcd for $C_{19}H_{21}N_3$ (%): C, 78.32; H, 7.26; N, 14.42; Found: C, 78.28; H, 7.24; N, 14.39.

2.2.7. 1-(3-fluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (3g): Yield: 89%; pale yellow liqid; mp 183-188°C; IR (ZnSe): 1740 (C=O) cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 12.42 (s, 1H), 7.48-7.42 (m, 4H), 7.26-7.20 (d, 2H), 6.82-6.80 (d, 2H), 5.84 (s, 1H), 3.42-3.40 (m, 2H), 2.86-2.84 (m, 2H), 1.78 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$,): δ 164.24, 141.32, 136.62, 134.28, 130.46, 128.20, 123.12, 121.92, 120.54, 118.86, 115.02, 114.34, 112.28, 110.08, 60.84, 45.92, 22.25 ppm; LCMS m/z: 266(M+). Anal. Calcd for $C_{17}H_{15}FN_2$ (%): C, 76.67; H, 5.68; F, 7.13; N, 10.52; Found: C, 76.64; H, 5.67; F, 7.10; N, 10.49.

2.2.8. 1-(2-bromophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (3h): Yield: 86%; yellow solid; mp 198-199°C; IR (ZnSe): 1746 (C=O) cm^{-1};; ^{1}HNMR (400 MHz, $CDCl_3$): δ 12.36 (s, 1H),7.56-7.52 (d, 2H), 7.48-7.34 (m, 4H), 7.22 (s, 2H), 5.52 (s, 1H), 3.26-3.21 (m, 2H), 2.85-2.82 (m, 2H), 1.74 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$,): δ 140.26, 137.02, 134.52, 132.64, 131.48, 129.82, 127.36, 126.92, 125.74, 122.86, 120.48, 119.02, 112.24, 109.82, 58.02, 46.32, 22.45 ppm; LCMS m/z: 326(M+). Anal. Calcd for $C_{17}H_{15}BrN_2$ (%): C, 62.40; H, 4.62; Br, 24.42; N, 8.56; Found: C, 62.37; H, 4.60; Br, 24.38; N, 8.54.

2.2.9. 2-(2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenol (3i): Yield: 82%; yellow solid; mp 212-213°C ; IR (ZnSe): 1742 (C=O) cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 12.63 (s, 1H), 7.82-7.79 (m, 4H), 7.68 (s, 1H), 7.42 (s, 1H), 6.96 (s, 1H), 6.86 (s, 1H), 5.42 (s, 1H), 3.94 (s, 1H), 3.09-2.97 (m, 2H), 2.84-2.79 (m, 2H), 1.88 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$,): δ 158.48, 138.52, 134.68, 131.02, 130.43, 127.82, 126.34, 122.32, 120.26, 119.65, 118.82, 118.48, 111.56, 108.27, 56.65, 45.20, 20.80 ppm; LCMS m/z: 264(M+). Anal. Calcd for $C_{17}H_{16}N_2O$ (%): C, 77.25; H, 6.10; N, 10.06; O, 6.05; Found: C, 77.23; H, 6.08; N, 10.05; O, 6.01.

2.2.10. 2-methoxy-4-(2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenol (3j): Yield: 85%; yellow solid; mp 185–186°C; IR (ZnSe): 1732 (C=O) cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 12.39 (s, 1H), 7.84-7.79 (m, 3H), 7.65 (s, 1H), 7.46 (s, 1H), 7.24 (s, 1H), 7.02 (s, 1H), 5.26 (s, 1H), 4.28-4.24 (m,1H), 3.94 (s, 3H), 3.12-3.09 (m, 2H), 2.64-2.60 (m, 2H), 1.98 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$,): δ 156.42, 145.56, 138.42, 136.26, 133.34, 128.04, 121.82, 120.96, 119.17, 118.84, 117.34, 116.24, 112.36, 109.72, 62.22, 56.84, 43.40, 22.76 ppm; LCMS m/z: 294(M+). Anal. Calcd for $C_{18}H_{18}N_2O_2$ (%): C, 73.45; H, 6.16; N, 9.52; O, 10.87; Found: C, 73.41; H, 6.13; N, 9.50; O, 10.84.

2.2.11. 1-(4-(piperidin-1-yl)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (3k): Yield: 92%; yellow solid; mp 222-223°C; IR (ZnSe): 1730 (C=O) cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 12.42 (s, 1H), 7.42-7.21 (m, 6H), 6.76 (m, 2H), 5.28 (s, 1H), 3.54-3.42 (m,4H), 2.86-2.74 (m, 4H), 1.74-1.68 (m, 6H), 1.64 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$,): δ 152.56, 148.42, 136.82, 134.28, 127.84, 127.52, 122.06, 121.62, 119.81, 117.92, 112.54, 110.78, 108.84, 62.02, 51.18, 44.22, 26.84, 24.56, 22.36 ppm; LCMS m/z: 331(M+). Anal. Calcd for $C_{22}H_{25}N_3$ (%): C, 79.72; H, 7.60; N, 12.68; Found: C, 79.69; H, 7.58; N, 12.64.

2.2.12. 1-(furan-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (3l): Yield: 95%; yellow solid; mp 209-210°C; IR (ZnSe): 1748 (C=O) cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 12.29 (s, 1H), 7.58-7.14 (m, 5H), 6.92 (s, 1H), 6.38 (s, 1H), 5.34 (s, 1H), 3.26-2.98 (m, 4H), 1.92 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$,): δ 152.06, 143.42, 136.27, 134.02, 128.20, 122.55, 119.88, 119.07, 118.03, 112.20, 109.89, 102.54, 60.02, 44.42, 22.32 ppm; LCMS m/z: 238(M+). Anal. Calcd for $C_{15}H_{14}N_2O$ (%): C, 75.61; H, 5.92; N, 11.76; O, 6.71; Found: C, 75.59; H, 5.88; N, 11.74; O, 6.68.

2.2.13. 1-(thiophen-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (3m): Yield: 85%; pale yellow solid; mp 170–172 °C; IR (ZnSe): 1741 (C=O) cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 12.54 (s, 1H), 7.42-7.08 (m, 5H), 7.04 (s, 1H), 6.92 (s, 1H), 5.28 (s, 1H), 3.18-2.84 (m,4H), 1.86 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$,): δ 142.36, 136.32, 131.22, 128.52, 126.25, 125.82, 124.35, 122.02, 119.38, 118.52, 112.25, 102.04, 60.12, 44.54, 22.06 ppm; LCMS m/z: 254(M+). Anal. Calcd for $C_{15}H_{14}N_2S$ (%): C, 70.83; H, 5.55; N, 11.01; O, 12.61; Found: C, 70.79; H, 5.54; N, 10.99; O, 12.58.

2.2.14. 1-(1H-pyrrol-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (3n): Yield: 90%; yellow solid; mp 194–195°C; IR (ZnSe): 1735 (C=O) cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 12.45 (s, 1H), 8.12 (s, 1H), 7.34-6.82 (m, 5H), 6.94 (s, 1H), 6.21 (s, 1H), 5.26 (s, 1H), 3.09-2.76 (m, 4H), 1.90 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$,): δ 136.45, 129.32, 128.94, 122.22, 119.88, 119.20, 118.72, 114.03, 111.62, 111.32, 107.54, 102.32, 54.52, 44.42, 21.58 ppm; LCMS m/z: 237(M+). Anal. Calcd for $C_{15}H_{15}N_3$ (%): C, 75.92; H, 6.37; N, 17.71; Found: C, 75.89; H, 6.35; N, 17.67.

2.2.15. 1-(pyridin-4-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (3o): Yield: 93%; yellow solid; mp 186–187 °C; IR (ZnSe): 1742 (C=O) cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 12.64 (s, 1H), 8.52 (d, 2H), 7.32-7.06 (m, 6H), 5.28 (s, 1H), 3.14 (s,1H), 3.02 (s, 1H), 2.54 (d, 2H), 1.89 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$,): δ 152.32, 145.04, 136.86, 135.75, 128.16, 122.92, 120.04, 118.52, 112.26, 110.02, 58.84, 45.26, 21.48 ppm; LCMS m/z: 249(M+). Anal. Calcd for $C_{16}H_{15}N_3$ (%): C, 77.08; H, 6.06; N, 16.85; Found: C, 77.04; H, 6.04; N, 16.83.

2.2.16. 1-(2-methylpyridin-3-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (3p): Yield: 87%; yellow solid ; mp 204-205°C; IR (ZnSe): 1730 (C=O) cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 12.39 (s, 1H), 8.48 (s, 1H), 7.89 (s, 1H), 7.34 (d, 2H), 7.21 (s, 1H), 7.12 (s, 1H), 6.68 (s, 1H), 5.36 (s, 1H), 3.02 (d, 2H), 2.67-2.63 (d,2H), 2.53 (m, 3H), 1.84 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$,): δ 160.28, 148.32, 138.46, 136.06, 134.22, 134.02, 128.14, 122.20, 119.34, 118.26, 112.12, 109.82, 60.26, 45.25, 22.04, 21.56 ppm; LCMS m/z: 263(M+). Anal. Calcd for $C_{17}H_{17}N_3$ (%): C, 77.54; H, 6.51; N, 15.96; Found: C, 77.51; H, 6.47; N, 15.94.

2.2.17. 1-(1H-indol-5-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (3q): Yield: 92%; yellow solid; mp 172–173 °C; IR (ZnSe): 1746 (C=O) cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 12.42 (s, 1H),7.54-7.28 (m, 4H), 7.22 (d, 2H), 7.12 (t, 3H), 6.82 (s, 1H), 5.82 (s, 1H), 2.98 (d, 2H), 2.48 (d, 2H), 1.94 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$,): δ 141.98, 136.45, 135.54, 133.17, 129.25, 128.25, 125.02, 124.28, 122.36,

118.96, 118.25, 114.66, 111.82, 109.56, 102.54, 58.82, 45.22, 21.52 ppm; LCMS m/z: 287(M+). Anal. Calcd for $C_{19}H_{17}N_3$ (%): C, 79.41; H, 5.96; N, 14.62; Found: C, 79.39; H, 5.92; N, 14.59.

2.2.18. 1-(benzo[d][1,3]dioxol-5-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (3r): Yield: 88%; yellow solid; mp 196–197°C; IR (ZnSe): 1737 (C=O) cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 12.56 (s, 1H), 7.24 (s, 1H), 7.12 (t, 3H), 7.02 (d, 2H), 6.92 (s, 1H), 5.94 (m, 2H), 5.26 (s, 1H), 3.14 (d, 2H), 2.72 (d, 2H), 1.83 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$,): δ 150.02, 146.24, 135.82, 134.96, 133.84, 121.90, 121.68, 119.52, 118.69, 113.82, 111.76, 110.02, 108.58, 102.26, 60.46, 44.42, 22.08 ppm; LCMS m/z: 292(M+). Anal. Calcd for $C_{18}H_{16}N_2O_2$ (%): C, 73.95; H, 5.52; N, 9.58; O, 10.95; Found: C, 73.93; H, 5.50; N, 9.54; O, 10.93.

3. RESULTS AND DISCUSSION

To explore the scope of catalyst concentration, comparative study of ultrasound to conventional heating and temperature conditions of the present method, we have taken synthesis of 1-(4-chlorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole **(3a)** from tryptamine **(1)** and substituted benzaldehyde **(2a)** (**Scheme 1**) as a model.

3.1. Optimization of catalyst concentration against compound 3a

Initially efforts were made towards the catalytic evaluation of triton X-100 towards the synthesis of tetrahydro-*β*-carbolines. In an initial endeavor, the reaction was carried out using 5mol% of Triton X-100 catalyst using 1 equivalent of each of tryptamine and aldehyde. These were stirred at 70ºC in water under ultrasound irradiation. After 4 h only 65% of the expected product **3a** was obtained. The same reaction was then carried out using 10mol% of triton X-100 under similar conditions. Surprisingly a significant improvement was observed and the yield of 3a was dramatically increased to 92%, stirring mixture for only 2 h. This shows that the catalyst can plays a major role in optimization of the product yield. Even after increasing the catalyst concentration above 10 mol%, the yields of the products did not improve. So it is established that the 10 mol% of catalyst is sufficient to catalyze and bring it to completion. The results are listed in **Table1**.

Table 1. Catalytic activity evaluation for the synthesis of 3a

Entry	Catalyst (mol%)	Time (hrs)	Yield (%)[a]
1	5	4	65
2	10	2	92
3	15	2	92
4	20	2	92

[a]Isolated yield

3.2. Effect of temperature for the synthesis of 3a

The effect of temperature was studied for synthesis of compound **3a** at various temperatures ranging from 60-90ºC and observed that the high yield (92%)was obtained at 70ºC under ultrasonic

condition in 2h (Table 2, Entry 2). Further enhancement of the reaction temperature had not shown any impact on the reaction time and yield.

Table 2. Influence of the temperature for the synthesis of 3a

Entry	Temperature	Time (hrs)	Yield (%)[a]
1	60	3	83
2	70	2	92
3	80	2	87
4	90	2	78

[a]Isolated yield

3.3. Method optimization

In sequence, we compared the effect of ultrasound to conventional heating methods by investigating the synthesis of compounds **3a-d** at 70°C for the improved yields and reaction times. In sonication result we identified the excellent yields and shorter reaction times with sonication method as summarized in **Table 3**.

Table 3: Comparative study on conventional and ultrasound-promoted synthesis of **3a-d**

Entry	Conventional heating (70°C)		Ultrasonic irradiation (70°C)	
	Time(h)	Yield(%)[a]	Time(h)	Yield(%)[a]
3a	9	75	2	92
3b	9	72	2	90
3c	12	70	4	94
3d	10	65	2	89

[a]Isolated yield

Tryptamine **(1)** reacts well with aryl/ heteroaryl aldehydes having both electron-donating and electron-withdrawing substituents to furnish tetrahydro-*β*-carbolines. Triton X-100 proved effective in catalyzing the 6-*endo* cyclization of aldehydes such as salicylaldehyde **(3i),** 2-Bromo benzaldehyde **(3h)** and 4-dimethyl amino benzaldehyde **(3f)** under sonication. These aldehydes failed to produce the cyclized product in desired yield under conventional based bronsted acid catalysis and often produced the oxidized products under harsher reaction conditions. This disadvantage has been overcome by the use of Triton X-100 catalyst.

3.4. Comparative study with previous reports

To show the merit of the present work in comparison with the previously reported, we compared results of Triton X- 100 with other catalysts in the synthesis of tetrahydro-*β*-carbolines. As shown in **Table 4**, Triton X-100 act as effective catalyst with respect to reaction times, yields and the obtained products.

Table 4. Comparison of the results of using Triton X-100 with other catalysts

Entry	Catalyst	Reaction Conditions	Time (h)	Yield (%)[a]
1	Cyanuric chloride	DMSO, N_2	5	89
2	Montmorillonite	Water, 120ºC	18	82
3	1,1,1,3,3,3-hexafluoro-2-propanol	RT, N_2	2	85
4	Molecular iodine	Acetonitrile	4	80
5	Triton X- 100	Water, 70ºC	2	92

[a]Isolated yield

In all cases, the products were obtained in good yield, but in the case of 4-nitro benzaldehyde, low yield has been obtained and hence continuing the reaction for 4 h instead of 2 h and the yields were improved to 94%. The reaction was carried out with a wide variety of aromatic and heterocyclic aldehydes bearing various substituents under optimized conditions. All the products were purified by column chromatography and were characterized by elemental analysis, ^{1}H NMR, IR, ^{13}C NMR and mass spectral data.

4. CONCLUSION

In conclusion, this is the first report on the green and efficient synthesis of tetrahydro-*β*-carbolines obtained by the catalytic action of a non-ionic surfactant Triton-X 100. The merit of this protocol is the formation of Triton X-100 micellar spheres in water medium under ultrasound irradiation conditions. The ability of each individual spheres to host the aggregates of the substrates made them to react easily and helps them to form the product easily. Hence, the reaction of tryptamine with various aldehydes has been facilitated the formation of desired products in good yields via Pictet-Spengler reaction. As a future insight, this strategic understanding will offer the researcher to focus more on the catalytic activity of Triton X-100 in designing of new reactions which involve in the synthesis of drugs and natural compounds in an eco-friedly approach.

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