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A MILD AND EFFICIENT MICROWAVE-ASSISTED SOLVENT-FREE SYNTHESIS OF TETRAHYDRO- CARBOLINES SCAFFOLD

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ABSTRACT: A dynamic Solvent-free procedure for the synthesis of tetrahydro- carbolines scaffold via microwave-assisted synthesis based Pictet-Spengler reaction using catalyzed by Phosphoric acid supported on alumina (H3PO4/Al2O3) has been described. The remarkable features of these catalytic procedures are high conversions, shorter reaction times, straightforward experimental, effortless work-up procedures. Phosphoric acid supported on alumina as catalyst can be reused numerous times without significant loss of its catalytic activity. This one step reaction provides diverse tetrahydro- -carbolines that have utilize in medicinal and material chemistry.

INTRODUCTION: Synthesis of biologically and medicinally important organic compounds with improved methodologies and strategies have always been a matter of great interest for the synthetic chemists. tetrahydro- -carbolines compounds are among the oldest well recognized and most extensively studied moieties which enjoy great synthetic and biological importance in organic as well as medicinal chemistry . tetrahydro-carbolines moiety is one of the most effective, newly emerging class of heterocycles; as besides being well documented in a number of bioactive naturally occurring alkaloids such as annomontine, harmane, harmine and manzamines. it has also proved as a good synthon for the preparation of various hybrids showing many interesting and beneficial properties such as antibiotic agents, inhibitors of human NK-1 receptor, anti-cancer, antimicrobial, anti- malarial, and many more on the other hand, several of methodologies for the synthesis of tetrahydro-carbolines experience from drawbacks such as costly reagents, long reaction time, unsympathetic reaction conditions, occurrence of by-product, pitiable yield, tedious work-ups, inconvenient for industrial scale and complexity in isolation of products. Thus there is an ongoing quest for finding methodologies which are economically viable, simple to execute and produce desired compound with minimum side products.

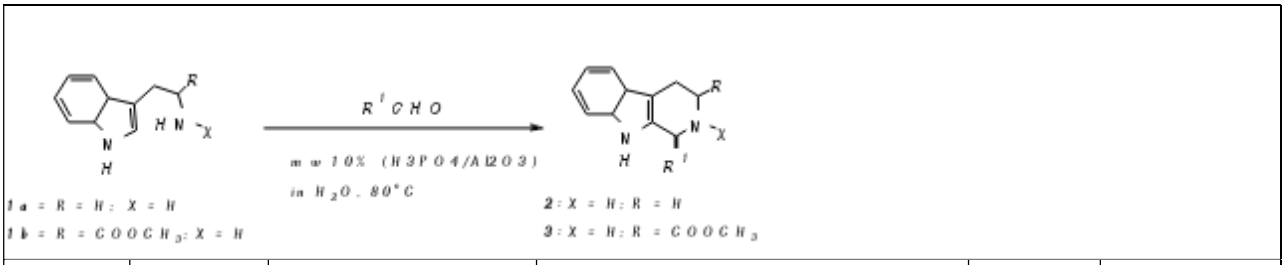
At some stage in our continuous efforts for the improvement of novel green protocols, has forced us to examine an alternate proficient method for the synthesis of tetrahydro- -carbolines. Herein, we wish to report a green procedure for the synthesis of tetrahydro- -carbolines under microwave- assisted Solvent-free conditions by using Phosphoric acid supported on alumina (H3PO4/Al2O3) as catalyst under milder reaction conditions. The advance of cleaner methodology is the majority important subject in green chemistry. In the middle of the several characteristic of green chemistry, the use of heterogeneous catalysts and substitution of volatile organic solvents with solvent-free reaction medium are of greatest concern. Heterogeneous organic reactions and solvent-free reactions have a lot of advantages such as: low costs, reduced pollution, and effortlessness process,

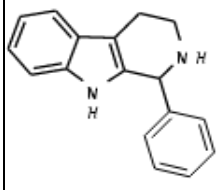
ease handling of catalyst, cleaner reactions, easier work up, decreasing corrosive problems, and reduced reaction times. We have synthesis of tetrahydro-carbolines derivatives via microwave-assisted Solvent-free Synthesis reaction.

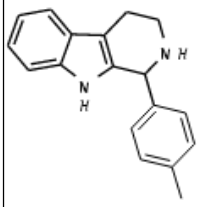
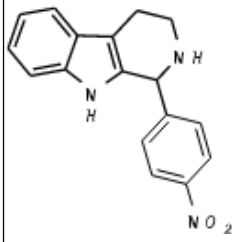
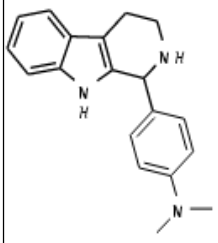
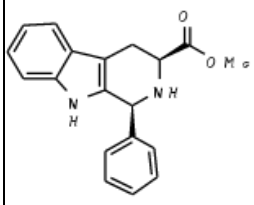
RESULTS AND DISCUSSION:

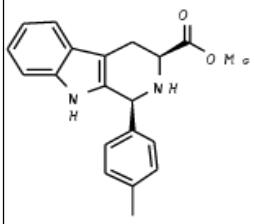
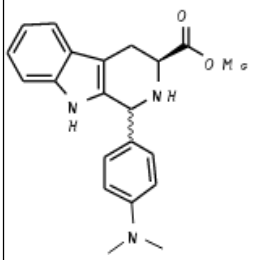
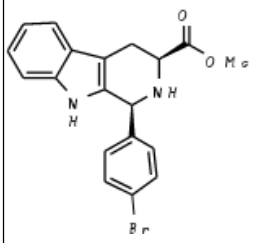
Initially, the two-component Pictet-Spengler reaction of freshly distilled benzaldehyde (1 mmol) and tryptamine (1mmol) was examined in water at 80oC temperature in the presence of a series of acid catalysts, traditionally used under Pictet-Spengler protocols. We were pleased to see that the Pictet-Spengler reactions in 10% (H3PO4/Al2O3) as catalyst, proceeded smoothly at 80oC temperature (Table 1). No cyclization, however, was observed when the reaction was carried out in water at room temperature in the presence of (H3PO4/Al2O3) as catalyst and as expected, the corresponding imine was isolated as the only product.

Table 1. The Pictet-Spengler reaction in (H3PO4/Al2O3) as catalyst:



Entry	Amine	R^1	Product[a]	Yield[b](%)	cis:trans[c]
Entry	Amine	R^1	Product[a]	Yield[b](%)	cis:trans[c]
1	1a	C6H5	 2a	75	-

2	1a	4-CH3-C6H4	 **2b**	64	-
3	1a	4-NO2-C6H4	 **2c**	72	-
4	1a	4-N(CH3)2C6H4	 **2d**	45	-
Entry	**Amine**	**R^1**	**Product[a]**	**Yield[b](%)**	**cis:trans[c]**
5	1b	C6H5	 **3a**	82	70:30

6	1b	4-CH3-C6H4	 **3b**	75	83:17
7	1b	4-N(CH3)2C6H4	 **3c**	72	60:40[d]
8	1b	4-Br-C6H4	 **3d**	77	80:20
Entry	**Amine**	**R^1**	**Product[a]**	**Yield[b](%)**	**cis:trans[c]**

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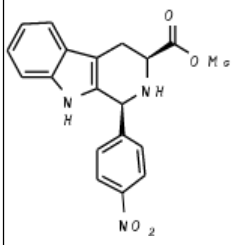
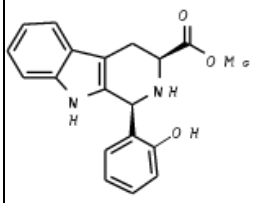
9	1b	4-NO2-C6H4	 **3e**	83	75:25
10	1b	2-OH-C6H4	 **3f**	68	90:10

[a]5 = Enantiomeric mixture, 6 = Diastereomeric mixture, 7 = Trans- isomer; b Yields are quoted for the pure isolated cis/trans mixture of diastereoisomoers; c As determined by integration of the 1HNMR spectrum (±3%), d Diastereomers not separated.

Reduction in the loading of (H3PO4/Al2O3) from 10 to 2% produced cyclized products in diminished yields. Endo cyclization in the presence of 2% (H3PO4/Al2O3) furnished the desired compound in only 33% yield. Use of other acid/Lewis acid catalysts traditionally used under Pictet- Spengler protocols such as p-TsOH and Yb(OTf)3 at room temperature failed to produce endo cyclized products. For both p-TsOH and Yb(OTf)3 catalyzed reactions, we observed an instant appearance of a sticky material, which upon trituration furnished imine in >96% purity instead of endo cyclized product. Interestingly, leaving this intermediate in 10% (H3PO4/Al2O3) for 45-60 minutes at 80oC temperature furnished the desired endo cyclized product 2a in quantitative yield.

For the characterization of the crude cyclized product 2a, initially we isolated the Pictet-Spengler product as a mixture of diastereomers to determine the yields and cis:trans ratios. This was followed by the separation of the cis and trans diastereomers by column chromatography and characterization using MS and NMR.

CONCLUSION: In summary, we have reported a tremendously proficient green approach for the synthesis of tetrahydro- -carbolines via microwave-assisted reaction catalyzed by H3PO4/Al2O3 catalyzed. This synthetic approach has a variety of amazing characteristics such as good yields, less reaction time, recyclability of catalyst and operational simplicity, ultimately foremost to a various collection of medicinally-relevant tetrahydro- -carbolines ring systems.

EXPERIMENTAL SECTION:

Synthesis of cyclized compounds via Pictet-Spengler Reaction:

To a 10% of (H3PO4/Al2O3) in water, tryptophan methyl ester (2.0 mmol) and aldehyde (2.0 mmol) were added at rt. The mixture was further stirred at 80oC temperature in microwave condition and the progress of reaction was monitored by TLC. Upon completion of the reaction, the (H3PO4/Al2O3) separate by filtration/solvent extraction method. The product was extracted using ethyl acetate and the organic layer was washed with water, brine solution and finally dried over anhydrous Na2SO4. It was then evaporated in vacuum to obtain a residue and purified by column chromatography to afford 2 and 3. For endo cyclized product 2, purification was carried out by flash column chromatography to afford cis/trans mixture of diastereoisomers. Care was taken to avoid separation of the isomers, to ensure that NMR would give accurate values for the cis:trans ratios. Finally, the mixture was again subjected to column chromatography on silica gel (200-400 mesh) using hexane/EtOAc (5:1) as eluent to separate both the isomers.

1-Phenyl-2,3,4,9-tetrahydro-1H- -carboline (2a):

Yield 75 %; gray solid; m.p. 160-161 oC; 1H NMR (CDCl3, 300 MHz) □ 7.64 (1H, br s), 7.57 (1H, dd, J = 5.5, 2.9 Hz), 7.38-7.32 (5H, m), 7.25-7.22 (1H, m), 7.19-7.11 (2H, m), 5.18 (1H, s), 3.43-3.36 (1H, m), 3.20-3.11 (1H, m), 3.00-2.82 (2H, m); 13C NMR (CDCl3, 75.5 MHz)141.86, 136.03, 134.48, 128.90, 128.68, 128.30, 127.43, 121.78, 119.43, 118.30, 110.99, 110.23, 58.09, 42.77, 22.57, IR (KBr) 3406, 2925, 2846, 1594 cm-1; MS (ES+) m/z: 270.1 (M+Na)+.

1-p-Tolyl-2,3,4,9-tetrahydro-1H- -carboline (2b)

Yield 64 %; Pale white; m.p135-137 oC; 1H NMR (CDCl3, 300 MHz) □ 7.94 (1H, br s), 7.60-7.57 (1H, m), 7.18-7.13 (7H, m), 5.10 (1H, s), 3.39-3.32 (1H, m), 3.17-3.08 (1H, m), 2.99-2.84 (2H, m), 2.39 (3H, s); 13C NMR (CDCl3, 75.5 MHz) □ 138.91, 138.05, 136.00, 134.81, 129.57, 128.57, 127.50, 121.73, 119.42, 1186.29, 110.97, 110.15, 57.85, 42.86, 22.63, 21.29, IR (KBr) 3426, 3309, 2924, 2852, 1595 cm-1; MS (ES+) m/z: 263.0 (M+H)+.

1-(4-Nitro-phenyl)-2,3,4,9-tetrahydro-1H- -carboline (2c):

Yield 72 %; yellow solid; m.p: 172-173 oC; 1H NMR (CDCl3, 300 MHz) □ 9.14 (1H, br s), 8.02 (2H, d, J = 8.7 Hz), 7.40-7.37 (3H, m), 7.14-7.12 (1H, m), 7.00-6.91 (2H, m), 5.15 (1H,), 3.08-2.96 (2H, m), 2.79–2.66 (3H, m); 13C NMR (CDCl3, 75.5 MHz) □ 149.80, 147.20, 136.10, 132.74, 129.38, 126.81, 123.34, 121.42, 118.87, 117.91, 110.98, 109.69, 56.47, 41.49, 22.15: IR (KBr) 3409, 2922, 2845, 1596, 1516, 1349 cm-1; MS (ES+) m/z294.1 (M+H)+.

4 Dimethyl-[4-(2,3,4,9-tetrahydro-1H- -carbolin-1-yl)-phenyl]-amine (2d):

Diastereomeric mixture (6:4) Yield 45 %; yellow sold; m.p: 143-144 oC; 1H NMR (CDCl3, 300 MHz) 8.02 (1H, br s), 7.55-7.52 (1H, m), 7.28-7.14 (5H, m), 6.66 (2H, d, J = 8.6 Hz), 5.36 (1H, s), 3.21-3.17 (1H, m), 3.05-3.01 (1H, m), 2.95-2.90 (7H, m), 1.86 (1H, br s); 13C NMR (CDCl3+DMSO, 75.5 MHz) □ 150.50, 136.07, 130.84, 129.80, 126.04, 124.28, 121.28, 118.63, 117.53, 111.77, 111.01, 107.91, 55.89, 40.08,

39.80, 19.70; IR (KBr) 3303, 2927, 2841, 1605 cm-1; MS (ES+) m/z: 292.1 (M+H)+; HRMS (EI+) C19H21N3 m/z calcd 291.1735 for [M]+ found 291.1737.

1-Phenyl-2,3,4,9-tetrahydro-1H- -carboline-3-carboxylic acid methyl ester (3a)
Cis isomer (6a): Yield 54 %; greenish white; m.p: 223-224 oC (litb. m.p 220-223 oC); 1H NMR CDCl3, 300 MHz) 7.58-7.55 (1H, m), 7.50 (1H, br s), 7.42-7.40 (5H, m), 7.24-7.14 (3H, m), 5.26 (1H, s), 4.0 (1H, dd, J = 11.1, 4.3 Hz), 3.84 (3H, s), 3.29-3.22 (1H, m), 3.08-3.03 (1H, m), 2.04 (1H, br s); 13C NMR (CDCl3, 75.5 MHz) 173.37, 140.91, 136.35, 134.85, 129.15, 128.80, 128.78, 127.30, 122.14, 119.82, 118.38, 111.11, 109.09, 58.88, 57.10, 52.41, 25.90, IR (KBr) 3393, 3335, 2948, 2950, 1739, 1595 cm-1; MS (ES+) m/z: 307 (M+H)+; Anal. Calcd for C19H18N2O2: C, 74.49; H, 5.92; N, 9.14 found C, 74.61; H, 5.72; N, 9.34.

Trans isomer (3a): Yield 23 %; off white; m.p: 175-176 oC (litb. m.p 176-178 oC); 1H NMR (CDCl3, 300 MHz) 7.57 (1H, br s), 7.60-7.57 (1H, m), 7.36-7.34 (3H, m), 7.28-7.20 (3H, m), 7.19-7.15 (2H, m), 5.40 (1H, s), 3.79 (1H, t, J = 6.1 Hz), 3.74 (3H, s), 3.28-3.26 (1H, m), 3.19-3.16 (1H, m); 13C NMR (CDCl3, 75.5 MHz) 174.26, 142.11, 136.37, 133.32, 128.90, 128.57, 128.28, 127.14, 122.11, 119.66, 118.38, 111.09, 108.60, 55.10, 52.64, 52.26, 24.82, IR (KBr) 3381, 2926, 2854, 1708, 1596 cm-1; MS (ES+) m/z: 307.1 (M+H)+.

p-Tolyl-2,3,4,9-tetrahydro-1H- -carboline-3-carboxylic acid methyl ester (3b):
Cis isomer (3b): Yield 61 %; white solid; m p. 42-144 oC; 1H NMR (CDCl3, 300 MHz) 7.55 (1H, dd, J = 5.5, 3.0 Hz), 7.46 (1H, br s), 7.30-7.28 (2H, m), 7.21-7.11 (5H, m), 5.23 (1H, s), 4.00 (1H, dd, J = 11.1, 4.2 Hz), 3.83 (3H, s), 3.28-3.21 (1H, m), 3.07-2.98 (1H, m), 2.39 (3H, s); 13C NMR (CDCl3, 75.5 MHz) 173.39, 138.52, 137.83, 136.25, 135.04, 129.74, 128.67, 127.26, 122.01, 119.71, 118.32, 111.07, 108.90, 58.47, 57.05, 52.38, 25.87, 21.33; IR (KBr) 3344, 2941, 2845, 1717, 1593 cm-1; MS (ES+) m/z: 321.1 (M+H)+, HRMS (EI+) C20H20N2O2 m/z calcd 320.1525 for [M]+ found 320.1527.

Trans isomer (3b): Yield 11 %; white solid; m.p: 174-176 oC; 1H NMR (CDCl3, 300 MHz) 7.77 (1H, br s), 7.59-7.56 (1H, m), 7.26-7.24 (2H, m), 7.20-7.11 (5H, m), 5.34 (1H, s), 4.00 (1H, t, J = 6.1 Hz), 3.74 (3H, s), 3.33-3.26 (1H, m), 3.18-3.11 (1H, m), 2.36 (3H, s); 13C NMR (CDCl3, 75 MHz) 174.28, 139.14, 138.03, 136.30, 133.56, 129.52, 128.48, 127.12, 122.01, 119.59, 118.34, 111.07, 108.80, 54.79, 52.55, 52.25, 24.85, 21.25; IR (KBr) 3287, 2949, 2843, 1744, 1595 cm-1; MS (ES+) m/z 321.1 (M+H)+.
1-(4-Dimethylamino-phenyl)-2,3,4,9-tetrahydro-1H- -carboline-3-carboxylic acid methyl ester (3c):
Diastereomeric mixture (3:2): Yield 72 %; yellow solid; mp 158-160 oC; 1H NMR (CDCl3, 300 MHz) 7.64 (1H, br s), 7.58-7.53 (3H, m), 7.28-7.19 (5H, m), 7.17-7.11 (7H, m), 6.74-6.67 (4H, m), 5.34 (1H, s), 5.17 (1H, s), 4.07-3.96 (2H, m), 3.82 (3H, s), 3.73 (3H, s), 3.31-3.02 (4H, m), 2.97 (6H, s), 2.95 (6H, s); 13C NMR (CDCl3, 75.5 MHz) 174.23, 173.47, 150.79, 150.44, 136.25, 136.17, 135.61, 131.58, 129.60, 129.55, 129.35, 127.27, 127.11, 121.76, 119.50, 118.17, 118.14, 112.72, 112.53, 111.05, 108.61, 108.26, 58.05, 57.04, 54.48, 52.29, 52.27, 52.14, 40.63, 25.89, 24.84; IR (KBr) 3368, 2922, 2847, 1735, 1610 cm-1; MS (ES+) m/z: 350.1 (M+H)+, HRMS (EI+) C21H23N3O2 m/z calcd 349.1790 for [M]+ found 349.1784.

1-(4-Bromo-phenyl)-2,3,4,9-tetrahydro-1H- -carboline-3-carboxylic acid methyl ester (3d)
Cis isomer (6d) Yield 58 %; white solid; mp: 160-161 oC; 1H NMR (CDCl3, 300 MHz) □ 7.58 (1H, br s), 7.55-7.49 (3H, m), 7.29-7.26 (1H, m), 7.25-7.21 (1H, m), 7.17-7.14 (3H, m), 5.32 (1H, s), 3.97 (1H, dd, J = 9.5, 4.2 Hz), 3.84 (3H, s), 3.23-3.22 (1H, m), 3.07-3.02 (1H, m); 13C NMR (CDCl3, 75.5 MHz) □ 173.23, 139.99, 136.40, 134.18, 132.25, 130.49,127.90, 122.71, 122.31, 119.92, 118.44, 111.14, 109.26, 58.27, 56.94, 52.46, 25.78. IR (KBr) 3399, 2933, 2849, 1735, 1595 cm-1; MS (ES+) m/z: 385.1 (M+), 386.2 (M+2)+.
Trans isomer (3d): Yield 14%; white solid; m p: 175-176 oC; 1H NMR (CDCl3, 300 MHz) 7.66 (1H, br s), 7.57 (1H, d, J = 8.07 Hz), 7.47 (2H, d, J = 8.25 Hz), 7.28-7.23 (1H, d, J = 9.93 Hz), 7.18-7.13 (4H, m), 5.38 (1H, s), 3.95 (1H, t, J = 6.0 Hz), 3.74 (3H, s), 3.32-3.25 (1H, m), 3.18 -3.11 (1H, m), 2.43 (1H, br s); 13C NMR (CDCl3, 75.5 MHz) □ 174.21, 141.17, 136.38, 132.79, 132.01, 130.29, 127.09, 122.34, 122.27, 119.82, 118.48, 111.12, 108.76, 54.47, 52.70, 52.32, 24.75, IR (KBr) 3343, 2923, 2850, 1708, 1594 cm-1; MS (ES+) m/z: 385.1 (M+), 387.0 (M+2)+, HRMS (EI+) C19H17BrN2O2 m/z calcd 384.0473 for [M]+ found 384.0500.
1-(4-Nitro-phenyl)-2,3,4,9-tetrahydro-1H- -carboline-3-carboxylic acid methyl ester (3e): cis isomer (3e): Yellow solid; Yield 43 %; m. p: 152-153 oC; 1H NMR (CDCl3, 300 MHz) □ 8.24 (2H, d, J = 8.7 Hz), 7.62 (2H, d, J = 8.3 Hz), 7.57 (1H, d, J = 8.7 Hz), 7.42 (1H, br s), 7.24-7.13 (3H, m), 5.40 (1H, s), 4.00 (1H, dd, J = 11.1, 4.2 Hz), 3.85 (3H, s), 3.31-3.25 (1H, m), 3.09- 3.00 (1H, m); 13C NMR (CDCl3, 75 MHz) 173.06, 148.44, 148.14, 136.57, 133.14, 129.75, 127.04, 124.23, 122.58, 120.10, 118.54, 111.22, 109.62, 58.21, 56.75, 52.55, 25.66; IR (KBr) 3406, 3313, 2914, 2848, 1732, 1597, 1518, 1347 cm-1; MS (ES+) m/z: 352 (M+H)+.

Trans isomer (3e): Yield 39 %; yellow solid; m.p: 205-207 oC; 1H NMR (CDCl3, 300 MHz) □ 8.21 (2H, d, J = 8.7 Hz), 7.60-7.51 (4H, m), 7.24-7.17 (2H, m), 5.56 (1H, s), 3.96 (1H, t, J = 5.9 Hz), 3.75 (3H, s), 3.29-3.27 (1H, m), 3.23-3.20 (1H, m); 13C NMR (CDCl3, 75.5 MHz) 172.92, 149.51, 146.27, 135.67, 131.63, 128.53, 125.73, 122.47, 120.63, 118.01, 117.03, 110.43, 106.66, 53.15, 51.28, 51.05, 24.05; IR (KBr) 3420, 3322, 2910, 2830, 1712, 1599, 528, 1326; MS (ES+) m/z: 352.0 (M+H)+; HRMS (EI+) C19H17N3O4 m/z calcd 351.1219 for [M]+ found 351.1247.
1-(2-Hydroxy-phenyl)-2,3,4,9-tetrahydro-1H- -carboline-3-carboxylic acid methyl ester (3f):
Cis isomer (3f): Yield 59 %; off white; m.p: 162-164 oC; 1H NMR (CDCl3, 300 MHz) 7.54-7.51 (1H, m), 7.54 (1H, brs s), 7.31-7.26 (2H, m), 7.21-7.12 (3H, m), 6.98-6.93 (1H, m), 6.86 (1H, d, J = 7.7 Hz), 5.37 (1H, s), 3.98-3.96 (1H, m), 3.89 (3H, s), 3.54-3.30 (1H, m), 3.14-2.98 (1H, m); 13C NMR (CDCl3, 75.5 MHz) 172.14, 157.69, 136.50, 132.39, 130.27, 128.50, 127.14, 123.45, 122.32, 119.93, 119.61, 118. 45, 118.01, 111.24, 107.92, 58.92, 56.63, 52.76, 24.94, IR (KBr) 3397, 3334, 2941, 2849, 1741, 1594 cm-1; MS (ES+) m/z: 323.1 (M+H)+; Anal. Calcd for C19H18N2O3, C, 70.79; H, 5.63; N, 8.69; found. C, 70.59; H, 5.53; N, 8.89.

Trans isomer (3f) Since the isomer was found in very low yield .It could not be isolated in sufficient quantity after column chromatography.

CONCLUSION: In summary, we have reported a extremely efficient green approach for the synthesis of thiazole-fused polyheterocycles via microwave-assisted Groebke- Blackburn- Bienayme reaction catalyzed by

H3PO4/Al2O3 catalyzed. This synthetic approach has various marvellous characteristics such as good yields, less reaction time, recyclability of catalyst and operational simplicity, ultimately foremost to a diverse array of medicinally-relevant Imidazo[2,1-b]thiazole ring systems.

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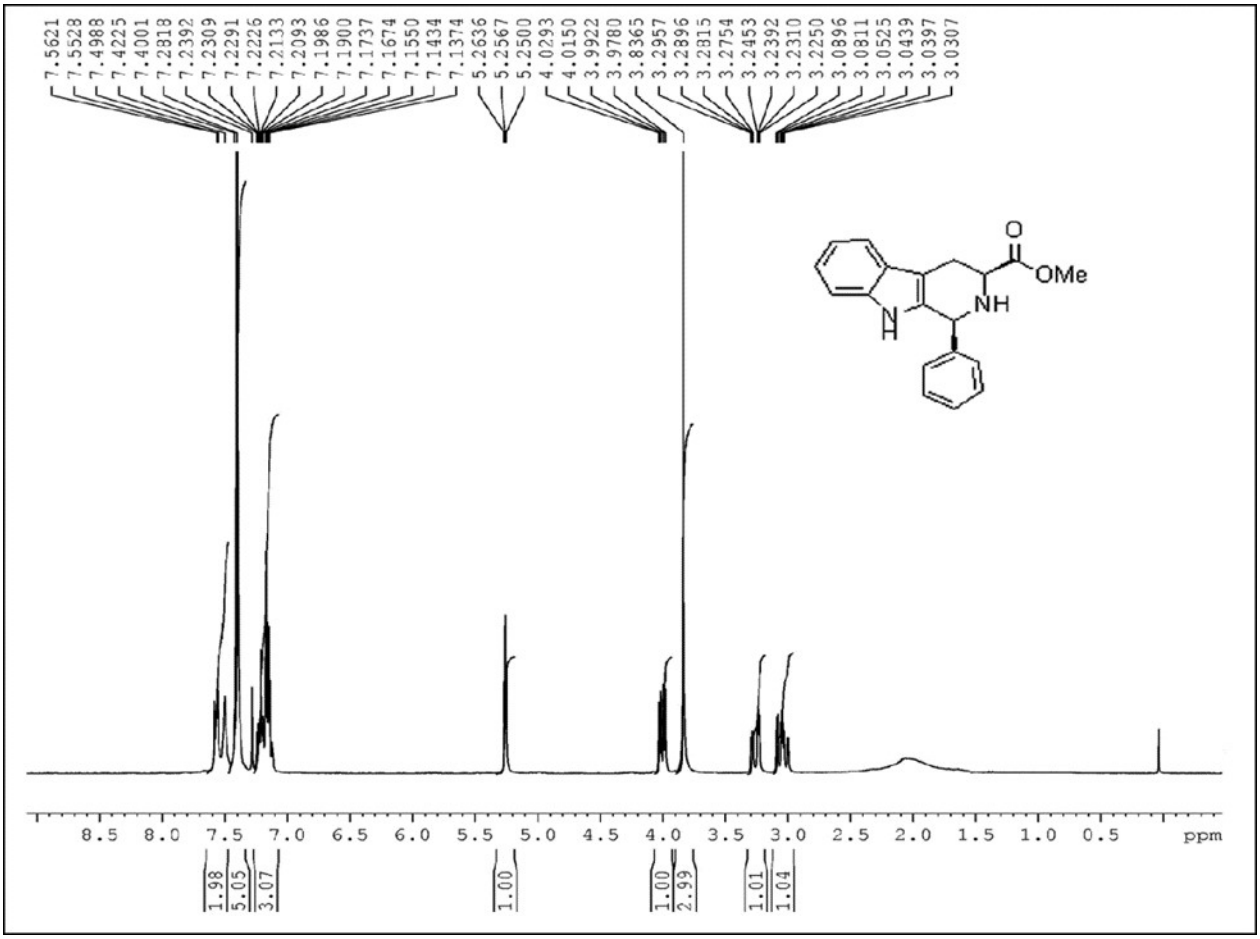

1H Spectra of 1-Phenyl-2,3,4,9-tetrahydro-1H-□-carboline-3-carboxylic acid methyl ester (3a). (Cis isomer).

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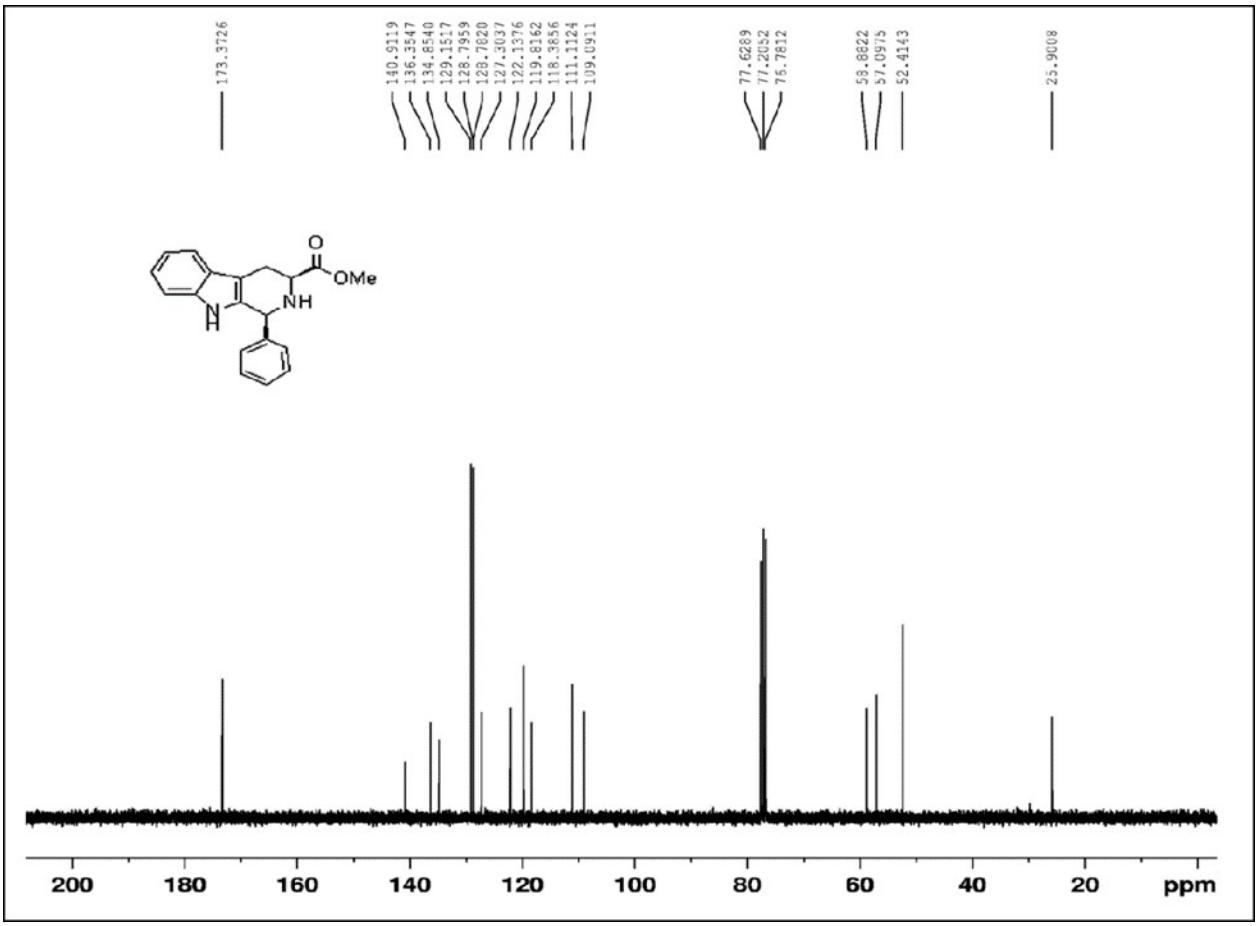

: 13C Spectra of 1-Phenyl-2,3,4,9-tetrahydro-1H-□-carboline-3-carboxylic acid methyl ester (3a). (Cis isomer).