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FULL PAPER

Citric Acid Catalyzed Aqua Mediated Multicomponent Synthesis of Tetrahydropyridines and its Antioxidant Activities

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Abstract:

Tetrahydropyridine derivatives are one of the most demanding molecules due to its great applications in medicinal and synthetic chemistry. Here we have designed a new way to synthesize a series of tetrahydropyridine derivatives using citric acid. In this methodology, five-component reaction of 1,3-diketones, substituted amines and aldehydes is done in the presence of citric acid extracted from lemon juice. High atom economy, green and mild conditions, high to moderate yields and shorter reaction times were the key features of this methodology. Later, we have discussed the antioxidant activities of our compounds. It is observed that compound **4a**, **4b**, **4e**, **4f**, **4i** and **4l** were quite effective to show good antioxidant activity.

Keywords: antioxidants; multicomponent reactions; citric acid; tetrahydropyridine

1. Introduction

Recently, synthetic researchers and medicinal chemists are focusing on one of the important tasks of synthesizing highly functionalized *N*-heterocycles with potent biological activities [1-4]. Tetra hydropyridine, a nitrogen containing moiety is abundantly found in diverse synthetic bioactive molecules as well as including natural products. A variety of medicinal, pharmacological and biological activities are effectively shown by tetrahydropyridine derivatives [5-6], for example, GABA receptor [7], neurotoxic activity [8], antibacterial [9], anti-inflammatory [10], antimalarial [11], and oral antagonistic [12]. A surplus of evolutionary procedures and ways, recognizing the excellence of tetrahydropyridine as biologically being active is presented in the recent literatures, demonstrating the several ways for furnishing funtionalised Tetrahydroppyridines [13-15]. Multicomponent reactions (MCRs) are very widely known methodology to produce miscellaneous and unnaturally fresh compounds in a single pot, with atomic efficiency and step economic way [16-18]. In order to generate various highly functionalized heterocycles via MCRs technique, imines are established as one of the flexible and multipurpose intermediate. Hence, MCRs including *in-situ* generation of imines had achieved significant consideration in current years [19].

As prolongation of our research work in the progress and evolution of synthetic methodologies for obtaining diverse heterocycles via MCRs [20-25], the intension was to investigate aromatic aldehyde, variety of amines, and 1,3-di carbonyl reagents for obtaining a broad range of substituted tetrahydropyridines utilizing imine-based single pot reactions in association with small amount of citric acid extracted from lemon juice. Till now, an immense reports are submitted in the literature, explaining numerous methods for the single-pot synthesis of multi substituted tetrahydropyridines utilizing supported boron

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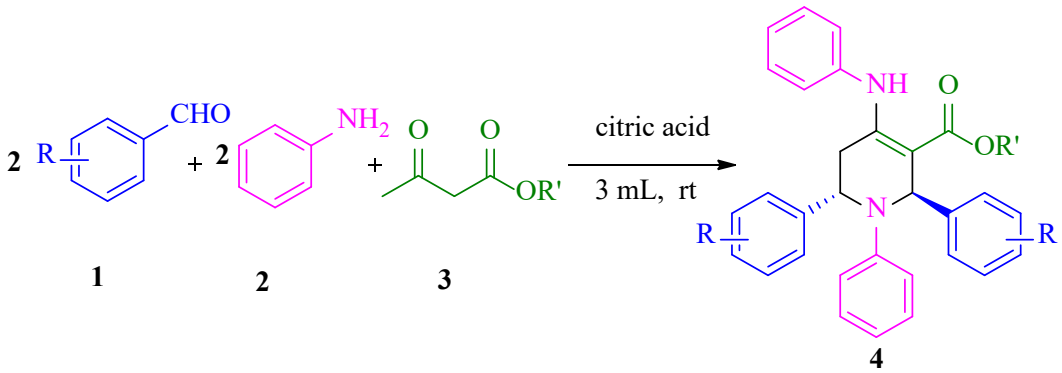
trifluoride ($BF_3 \cdot SiO_2$) [26], CAN [27], tetrabutyl ammonium tribromide [28], $InCl_3$ [29], bromodimethyl sulfonium bromide [30], I_2 [31], silicaphenylboronic acid [32], $ZrOCl_2.8H_2O$ [33], L-proline/TFA [34], and as catalyst $LaCl_3 \cdot 7H_2O$ [35]. But a number of methods reported in past are accompanied with few and more drawbacks for instance high cost of catalyst or constraint of catalyst grounding preceding to apply, time-consuming reaction, use of conventional unfriendly organic solvents and many more. Therefore, the advancement in use of MCRs has created awareness towards an easy and less complex strategy employing easily accessible catalyst for the well-organized formation of functionalized tetrahydropyridines, with much more scope. Citric acid has recognized as an effective catalyst for an assortment of many organic reactions in advancing years because of its easy accessibility and minor toxicity assay.

Use of naturally and easily available catalyst for organic transformation is achieving enormous significance in the last few years. In this regard, citric acid is proved as one of the most efficient biodegradable, non-toxic, low-cost and environmentally benign catalyst which keeps the potential of performing the role of ideal catalyst. It is relatively strong organic acid which is present as a natural constituent of a variety of citrus fruits such as lemon, orange, pear peach and fig etc. Due to its widespread presence, it has been used as a softener in detergent, as anticoagulant blood preservatives, as a complexing agent in metal treatment and for sequestering in Industrial processes. Despite of its huge application, only a few reports exemplify its catalytic applications in organic synthesis. Therefore, we tried to develop a green protocol by synthesizing tetrahydropyridine derivatives from single-pot reaction of 1,3-diketone, substituted amines and aldehydes in association with citric acid as biodegradable organocatalyst in aqueous medium under mild conditions (**Scheme 1**).



Scheme 1. Citric acid catalyzed synthesis of tetrahydropyridine derivatives.

2. Results and Discussion

2.1 Chemistry

For the present reaction, we have extracted citric acid from lemon juice from the reported conventional method [36]. To check the feasibility of the methodology, we tried to optimize the reaction with different catalysts and solvents. For this, we chosen the five component reaction of 1 mmol of methyl acetoacetate as 1,3-dicarbonyl compound, with 2 equiv. of each, 4-methylbenzaldehyde and aniline respectively as our model reaction (Table 1). Initially, model reaction was treated without any catalyst and solvent for 24 hrs, however it failed to give the expected product **1** (entry 1, Table 1). Later, the reaction was carried out in association with 10 mol% of Lewis acid catalyst $FeCl_3$ under neat condition; here also we got only traces of product (entry 2, Table 1). Afterwards, we treated the same model reaction with 10 mol% $FeCl_3$ in ethanol and fortunately, got an increased amount of desired product **1** (30% yield) after 8 hrs (entry 3, Table 1). Later, we used lemon juice (3 mL) directly in the reaction without any solvent but didn't get any satisfactory results. However, in presence of water as solvent, the same reaction gave the desired product with a yield of 45% after 5 hrs (entry 4-5, Table 1). Encouraged with this result, we tried 10 mol% citric acid extracted from lemon juice in neat as well in the presence of

different solvents like water, ethanol, acetonitrile, THF and DCM etc. (entry 7-12, Table 1). A very good result has been observed as 94% yield within 1.5 hrs (entry 5, Table 1) once the reaction was done in aqueous medium. The synthesized product was then totally analyzed by IR, ^{1}H and ^{13}C NMR spectroscopy. The presence of NH and C=O functionalities were confirmed by observing the absorption bands at 3230 and at 1659 cm^{-1}, respectively.

Table 1. Optimization for the preparation of tetrahydropyridine.[a]

Entry	Catalyst	Solvent	Time (hrs)	Yield (%)[a]
1	----	Neat	24	NR[b]
2	$FeCl_3$ (10 mol%)	Neat	12	Traces
3	$FeCl_3$ (10 mol%)	Ethanol	8	30%
4	Lemon juice (3 ml)	Neat	8	Traces
5	Lemon juice (3 ml)	Water	5	45 %
6	Acetic acid (3 ml)	Water	4.5	65 %
7	Citric acid (10 mol%)	Neat	3.5	Traces
8	**Citric acid (10 mol%)**	**Water**	**1.5**	**94 %**
9	Citric acid (10 mol%)	Ethanol	2	86 %
10	Citricacid (10 mol%)	Acetonitrile	4	66 %
11	Citric acid (10 mol%)	THF	6	42%
12	Citric acid (10 mol%)	DCM	8	60%

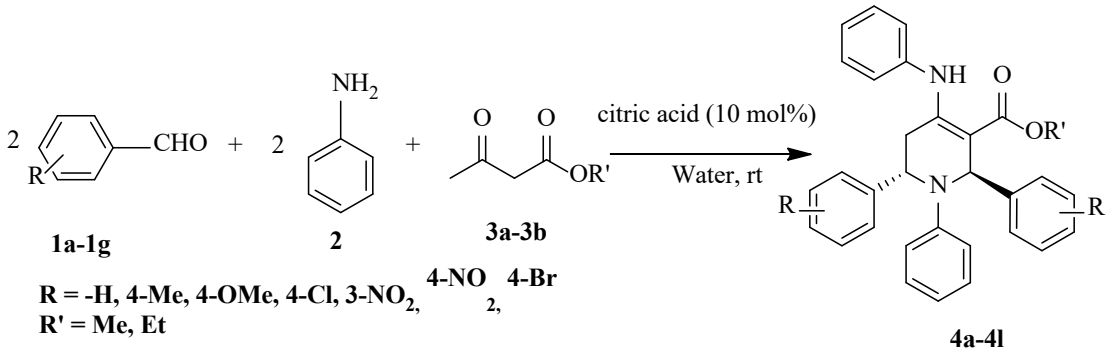
[a]Isolated Yield; [b]No reaction

Also, the ^{1}H NMR signal appeared at 10.25 for NH, 21 aromatic protons in the range of 7.20-6.29, 1, CH proton at 5.11, and 9 protons for CH_3 in the range of 3.91-2.30 ppm, clearly showed the formation of the product. Along with this, ^{13}C NMR signals appeared at 168.4, 156.2, 147.6, 147.2, 146.9, 140.9, 139.5, 137.9, 136.6, 135.7, 129.4, 128.9, 128.7, 126.6, 126.3, 125.8, 125.7, 116.1, 112.9, 112.4, 98.5, 98.3, 58.3, 27.9, 55.5, 54.9, 50.9, 50.6, 34.3, 33.6, 21.3, 20.9, 20.5 ppm shows the confirmation of the product **4a** formation. Encouraged by this result, we checked out the role of various other catalysts and different solvents systematically on the model reaction for the preparation of tetrahydropyridines **4a** in terms of shorter reaction time and better yield. However, in case acetic acid the result obtained was quite good and the yield of product was more than 65% in 4.5 hrs (entry 6). Further attempts were made with our extracted citric acid from lemon juice, which is slightly stronger than acetic acid to get better yield in less time duration. Citric acid (10 mol%) used with various solvents provided the best result with water within time duration of 1.5 hours (entry 7-12, Table 1) which proved it as an appropriate catalyst in terms of yield and reaction time.

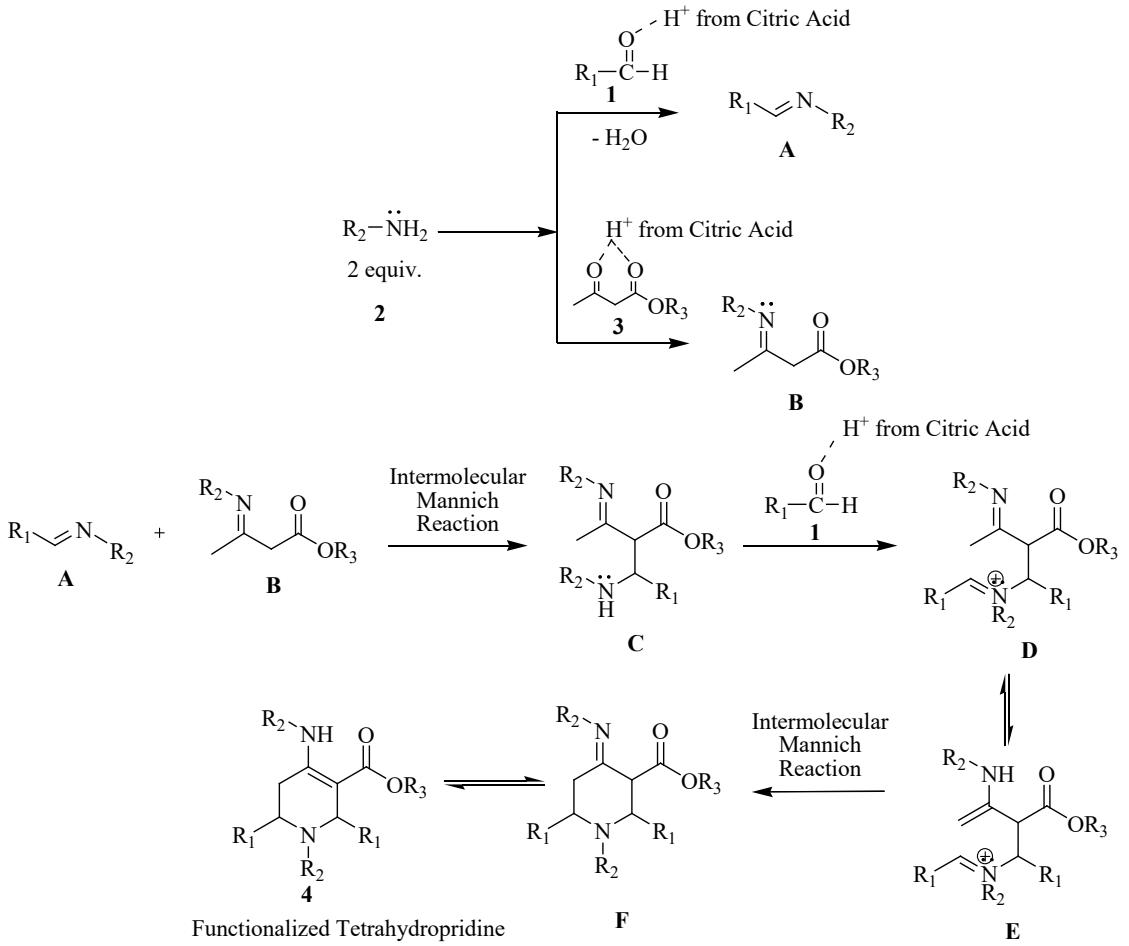
After achieving the optimal set-up, substrate scope of the given in Scheme 2 was examined and encapsulated in Figure 1. A broad array of substituted aldehydes in cooperation with electron donating as well as withdrawing groups such as –H, 4–Me, 4-Br, 4-Cl, 3-NO_2, 4-NO_2 and 4-OMe with aniline and different methyl or ethyl substituted 1,3-dicarbonyl compounds (*β*-ketoesters) were tested under the optimized conditions (compounds **4a-4j**, Figure 1). All reactions went smoothly and given good to excellent yield. However, when we use 4-NO_2, 3-NO_2 substituted aldehydes with aniline and methyl acetoacetate, it gave a low yield of 32 and 38% respectively (compounds **4k** and **4l**). Although, when we have done the reaction with benzyl amine an aliphatic amine, respective tetrahydropyridine was obtained in traces but the mixture could not be isolated. Also, when the reaction was done with cinnamaldehyde, the reaction was failed to give our expected product. All the products were well analyzed by general spectroscopic techniques like IR, ^{1}H NMR, and ^{13}C NMR.

The possible mechanism for the above MCR has been illustrated in Scheme 3. Mechanistically, the product forms through the formation of imine and enamine intermediates. At first 1 equiv. amine **2** reacts with 1 equiv. of aldehyde to produce *in situ* imine **A**, on the same time another equiv. of amine reacts with *β*- ketoeseter **3** through H^+ provided by citric acid to form enamine intermediate **B**. In the very next step reaction between imine **A** and enamine **B** leads to the intermediate **C** via an intermolecular Mannich

Reaction. The intermediate **C** then reacts with another equiv. of aldehyde **1** to provide intermediate **D** which can further tautomerized and due to the formation of intermolecular H-bonding a stable intermediate **E** is formed. This newly formed stable intermediate immediately undergoes intermolecular Mannich reaction and provides the intermediate **F**. In the final step tautomerization of **F** yield the desired product **4**. From the mechanistic study, it is clear that the role of citric acid is to provide the H^+ and to increase the electrophilicity of aldehyde.



Scheme 2. Synthesis of tetrahydropyridine derivatives. Reactions of 2 equiv. aldehyde, 2 equiv. amine and 1 equiv. *β*-keto esters were done by using 10 mol% citric acid as catalyst and water as a solvent at room temperature.



Scheme 3. Possible approach for the preparation of tetrahydropyridines.

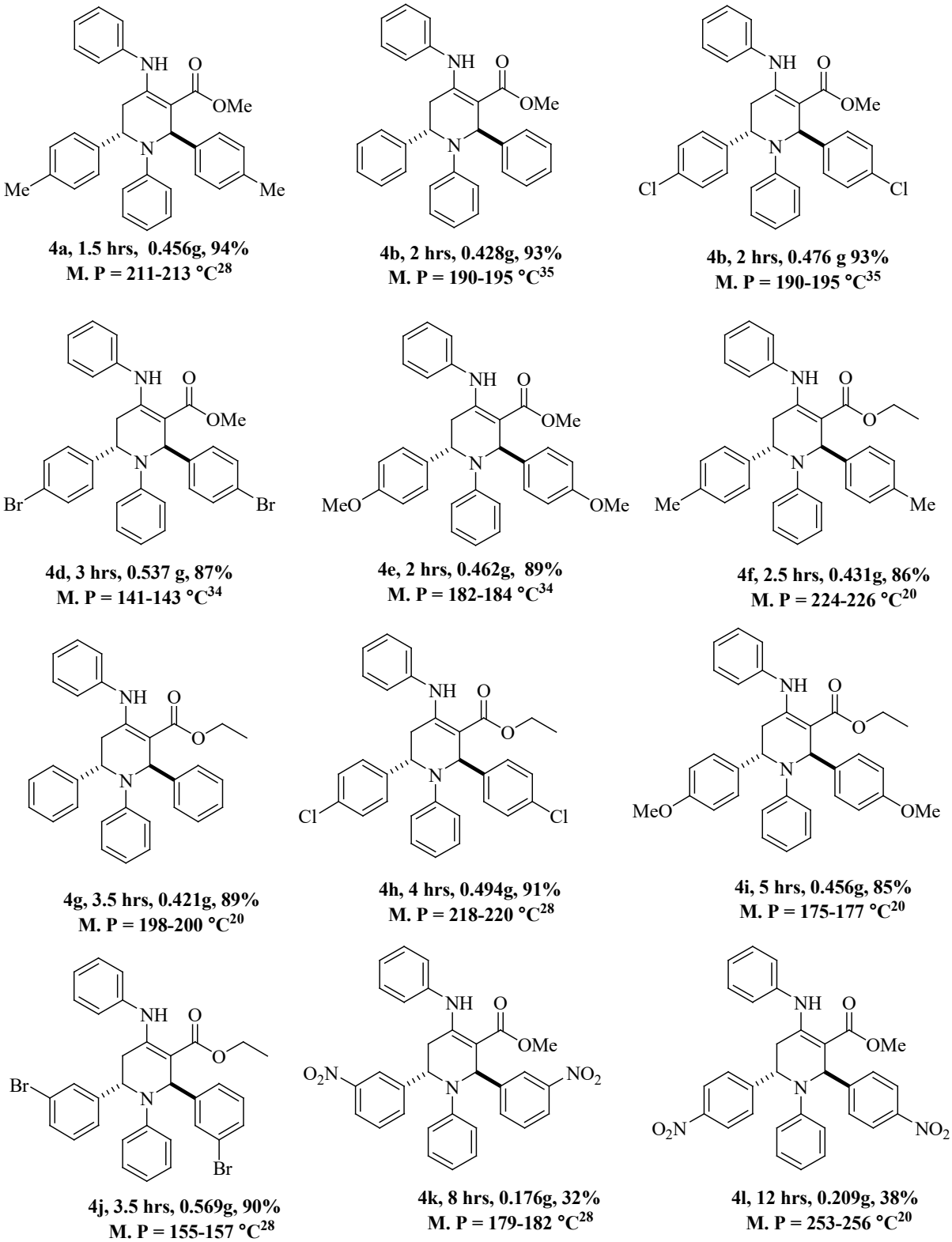


Figure 1. Synthesized compounds.

2.2 Antioxidant assay

After synthesis and characterization of these novel tetrahydropyridine derivatives, their antioxidant assay was evaluated by ABTS free radical assay. Free radical scavenging ability of chloroform solutions of all synthesized compounds against ABTS was determined spectrophotometrically at 734 nm. However notable *in vitro* antioxidant activity was only

observed in case of **4e**, which is 0.067 including -OCH_3 substituent, with %radical inhibition of 72% (72%).

All the compounds were tested to check their antioxidant activity against ABTS assay. However, only products **4a, 4b, 4e, 4f, 4i** and **4l** were able to show very good activity while others were failed to show the activity. Figure 2 shows the inhibitory effects of Standards (GA and AA), Control ($CDCl_3$) and products **4a, 4b, 4e, 4f, 4i and 4l**.

Table 2. Results of various antioxidants assays for **4a, 4b, 4e, 4f, 4i and 4l** compounds.

	1st Reading	2nd Reading	3rd Reading	Average	% Inhibition
ABTS	0.421	0.42	0.422	0.421	
Control-$CDCl_3$	0.241	0.242	0.24	0.241	
Ascorbic acid	0.002	0.002	0.002	0.007	
Gallic acid	0.007	0.007	0.007	0.002	
4a	0.113	0.111	0.112	0.112	53.52% ± 0.038
4b	0.161	0.159	0.16	0.16	33.61% ± 0.041
4e	**0.067**	**0.069**	**0.067**	**0.067**	**72.20% ± 0.044**
4f	0.14	0.139	0.139	0.139	42.32% ± 0.024
4i	0.129	0.13	0.128	0.129	46.47% ± 0.032
4l	0.176	0.176	0.177	0.175	27.38% ± 0.121

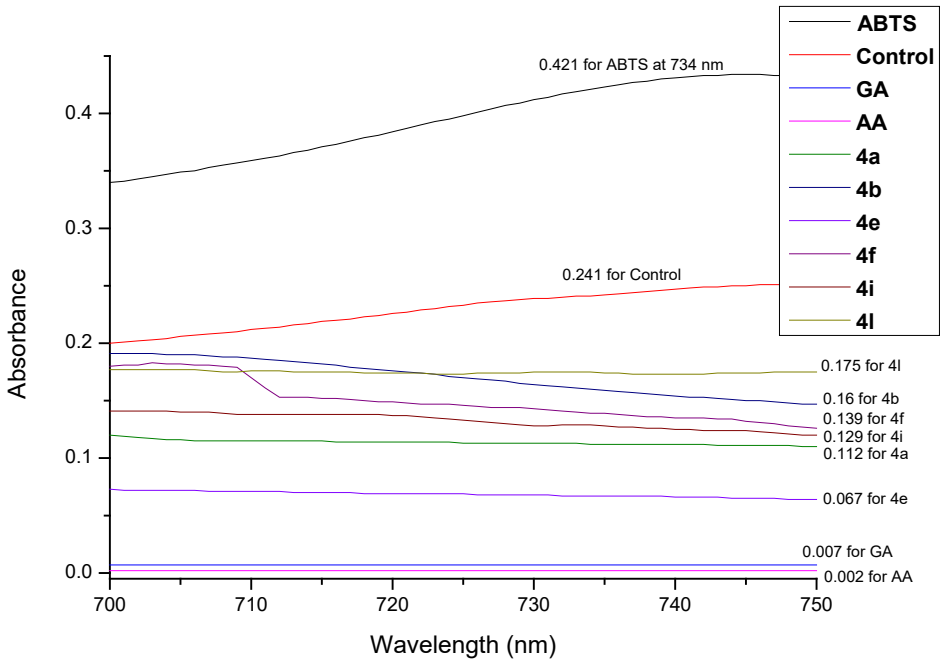


Figure 2. Antioxidant assay for the product **4a, 4b, 4e, 4f, 4i** and **4l.**

3. Material and Methods

The reagents, ABTS, Potassium persulfate (PPS), Gallic Acid (GA), Ascorbic Acid (AA) and the solvents of analytical grade were utilized in this work without any further purification. Melting points of newly synthesized compounds were diagnosed by digital melting point device. Reaction progress and purity of compounds were determined by thin layer chromatography (TLC) technique using UV/Iodine as visualizing agent. The IR spectra of all the synthesized products were obtained on a Perkin-Elmer FTIR

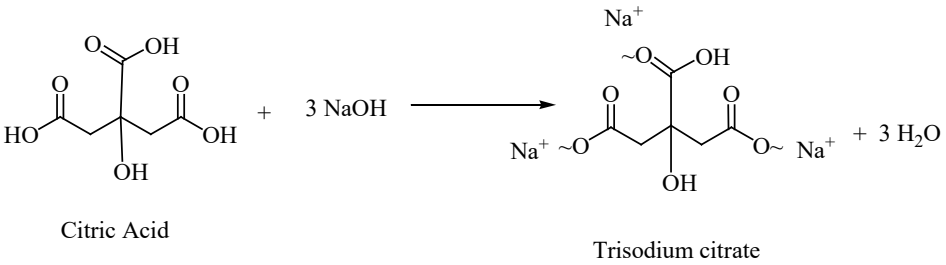
spectrophotometer. UV-Spectra were observed by using Shimadzu UV-Visible spectrophotometer. To record ^{1}H and ^{13}C NMR of all newly synthesized molecules, Shimadzu Brucker Advance Neo 500 MHz NMR spectrometer was used in deuterated chloroform ($CDCl_3$). The chemical shifts values were reported on delta scale by using tetramethylsilane (TMS) as standard in ppm. Known compounds were carefully checked with the previously reported data in the literature.

3.1 General procedure for the extraction of citric acid as catalyst from lemon juice

For the extraction of Citric acid from Lemon juice, a conventional method already mentioned in many literatures was used. Citric acid was traditionally produced by extracting it from fruits but now a days, it is produced using a fungus similar to the process of production of alcohol using yeast.

The first step was to remove the lemon juice approximately 30 mL, by manually chopping each lemon into halves and juicing it. After taking 30 mL of lemon juice in a 250 mL beaker, a glass stirring rod was added to the beaker and then added 10 % by weight (10 g NaOH pellets dissolved in 90 mL of water) NaOH solution. The addition of NaOH solution was drop wise and slow with continuous stirring, until the content in beaker reaches the pH 8 or 9, indicated by a distinctive color change (yellow to orange) as the solution was changing from acidic to basic medium leading to the formation of trisodium citrate solution.

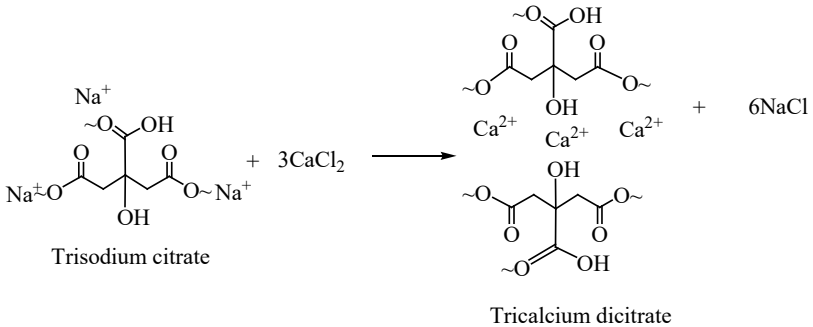
The basic reaction occurring here was neutralization of citric acid, depicted as in reaction 1.



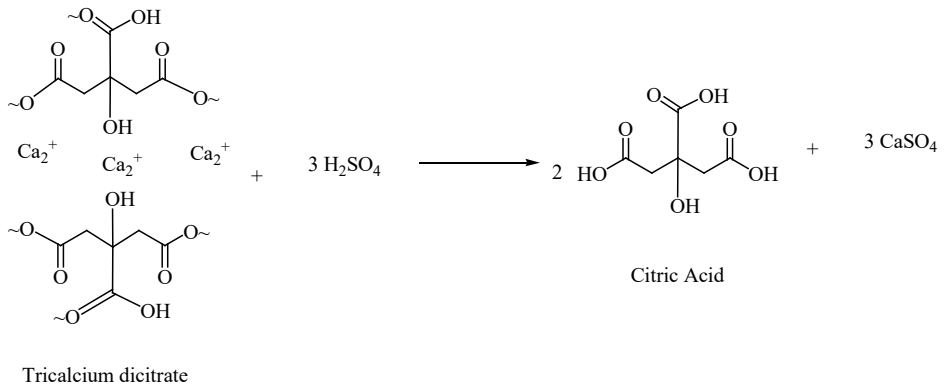
Reaction 1. Neutralization reaction.

As trisodium citrate is soluble in water so it will remain dissolved in solution. Citric acid is a 3-carboxyl group containing acid so it requires 3 NaOH to get fully neutralized. With the increase in pH from 2-3 to 8 or 9 the solubility of many particles decreased leading to the formation of solid residue in beaker's content. Using gravity filtration process the content in beaker was filtered thoroughly, the solid residue was discarded, and filtrate (sodium citrate) was taken in beaker for further reactions.

Afterwards a solution of calcium chloride $CaCl_2$ was prepared by solubilizing 0.96 g of $CaCl_2$ in 4.6 mL of water and this solution of calcium chloride was added in to the sodium citrate solution present in beaker and mixed thoroughly using glass stirrer. In order to get the reaction going the solution was heated up to the point till it starts boiling. As the solution temperature rises there was the formation of white colored calcium dicitrate precipitates. The reaction involved in the formation of calcium dicitrate formation is given in reaction 2.



Reaction 2. Double Displacement reaction.



Reaction 3. Formation of citric acid from dicitrate.

In next step, using vacuum filtration the precipitated calcium citrate was retrieved, accompanied with three times washing with hot distilled water. After transferring the precipitates of calcium citrate into a beaker, a heavily diluted solution of sulphuric acid, H_2SO_4 (prepared by dissolving 5.2 mL of sulphuric acid in 50 mL water) was added in to the beaker slowly and thoroughly mixed using glass rod. The reaction taking place was given as Reaction 3. Here in this, formation of insoluble calcium sulphate and 2 molecules of citric acid take place. The precipitated calcium sulphate was separated using vacuum filtration setup and washed couple of times with distilled water so as to retrieve all amount of citric acid entrapped within solid residue of calcium sulphate.

The filtrate retrieved was heated so as to boil off all the water content present in it and obtain a concentrated form of citric acid. On getting concentrated the solution shows slight yellow coloration. In last step this solution was filtered and then allowed to cool down overnight in open, leading to crystal formation. The isolated yield of citric acid was 0.89 g which is about 83%.

3.1.1 Characterization details of citric acid

Crystalline solid; 72%; M. P.: 157-158 ^{0}C; IR (ν, cm^{-1}): 3492, 3286, 1742, 1697, 1388, 1356, 1240, 1215, 1171, 1138, 1084, 934, 880. 779.

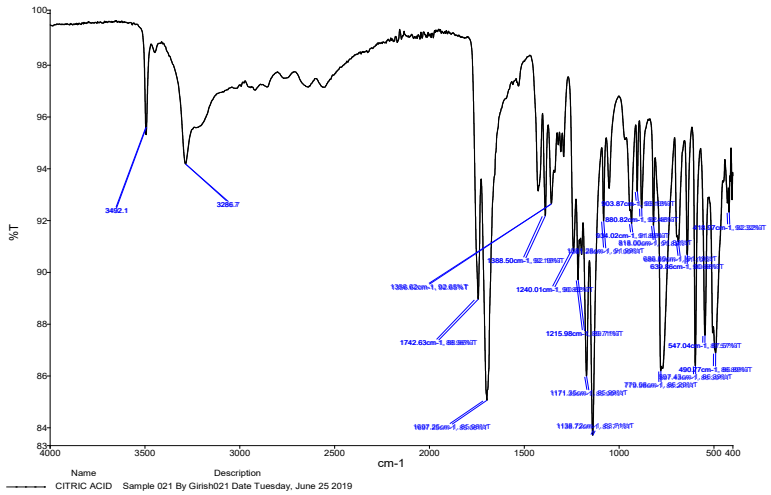


Figure 2. IR spectrum of citric acid.

3.1.2 Synthetic procedure adopted for the preparation of bioactive tetrahydropyridine derivatives

Initially, 2 mmol of substituted aldehyde and 2 mmol of amine is taken in a 25 mL RB, and a catalytic amount, 1 mL of citric acid retrieved from lemon juice. This mixture was stirred for 15 minutes in the absence of solvent. Afterwards, *β*-

ketoester (1 mmol) was supplied into the mixture taken in RBF with continuous stirring. After 30 minutes water was added in the mixture and continuous stirring was done till the end of reaction. Reaction progress was checked carefully and indicated by TLC. Later at the end of reaction, solid precipitates were formed, which was simply filtered and recrystallized in ethanol or ethyl acetate and subsequently dried to gain the pure product. Spectroscopic data of all newly reported molecules are explained below.

Compound 4a: White Solid; Yield: 0.458 g, 94%; IR (ν, cm^{-1}): 3249, 3020, 2941, 2918, 2866, 1715, 1654, 1593, 1444, 1374, 1244, 1192, 1076, 976, 852, 787; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.25 (s, 1H), 7.20 (d, *J* = 8.0 Hz, 3H), 7.08-7.03 (m, 12H), 6.58 (t, *J* = 8.0 Hz, 1H), 6.52 (d, *J* = 8.0 Hz, 2H), 6.39 (s, 1H), 6.29 (d, *J* = 8.0 Hz, 2H), 5.11 (s, 1H), 3.91 (s, 3H), 2.32 (s, 3H), 2.30 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.4, 156.2, 147.6, 147.2, 146.9, 140.9, 139.5, 137.9, 136.6, 135.7, 129.4, 128.9, 128.7, 126.6, 126.3, 125.8, 125.7, 116.1, 112.9, 112.4, 98.5, 98.3, 58.3, 27.9, 55.5, 54.9, 50.9, 50.6, 34.3, 33.6, 21.3, 20.9, 20.5 ppm;

Compound 4b: White Solid; Yield: 0.427 g, 93%; IR (ν, cm^{-1}): 3253, 3062, 3025, 1659, 1579, 1495, 1374, 1248, 1076, 1029, 928, 740, 698, 581; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.26 (s, 1H), 7.32-7.26 (m, 2H), 7.23-7.03 (m, 13H), 6.59 (t, *J* = 8.0 Hz, 1H), 6.52 (d, *J* = 8.0 Hz, 1H), 6.45 (s, 1H), 6.27-6.26 (m, 2H), 5.14 (s, 1H), 3.92 (s, 3H), 2.88-2.84 (m, 1H), 2.77-2.74 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.5, 156.2, 155.9, 147.3, 147.0, 144.3, 142.7, 138.3, 138.0, 128.9, 128.8, 128.6, 126.6, 126.3, 125.8, 125.7, 115.9, 115.4, 112.7, 97.7, 97.6, 58.2, 57.9, 56.0, 55.2, 51.7, 51.2, 50.9, 33.6 ppm.

Compound 4e: White Solid; Yield: 0.462 g, 89%; IR (ν, cm^{-1}): 3151, 2978, 2885, 1649, 1593, 1449, 1360, 1244, 1174, 1066, 1029, 824, 763, 698, 525; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.27 (s, 1H), 7.21 (d, J = 8.0 Hz, 3H), 7.10 (d, J = 8.0 Hz, 3H), 7.06 (d, J = 8.0 Hz, 4H), 6.80 (d, J = 8.0 Hz, 4H), 6.60-6.52 (m, 3H), 6.35 (d, J = 8.0 Hz, 2H), 5.08 (s, 1H), 3.91 (s, 3H), 3.77 (s, 3H), 3.75 (s, 3H), 2.86-2.82 (m, 1H), 2.76-2.73 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.6, 158.7, 158.0, 157.3, 156.3, 150.7, 146.9, 137.9, 135.8, 134.6, 130.7, 129.1, 128.8, 127.7, 127.4, 125.6, 123.8, 116.0, 115.3, 113.9, 112.9, 98.0, 97.8, 57.7, 57.5, 55.2, 54.5, 54.4, 50.9, 50.8, 33.7 ppm.

Compound 4f: White crystalline solid; Yield: 0.432 g, 86%; IR (ν, cm^{-1}): 3165, 3039, 2988, 2880, 1645, 1584, 1495, 1365, 1244, 1169, 1066, 1024, 945, 861, 745; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.29 (s, 1H), 7.23-7.20 (m, 3H), 7.08-7.03 (m, 10H), 6.58 (t, *J* = 8.0 Hz, 1H), 6.53-6.52 (m, 3H), 6.41 (s, 1H), 6.29 (d, *J* = 8.0 Hz, 1H), 5.11 (s, 1H), 4.46-4.41 (m, 1H), 4.34-4.28 (m, 1H), 2.88-2.84 (m, 1H), 2.77-2.74 (m, 1H), 2.32 (s, 3H), 2.27 (s, 3H), 1.46-1.43 (m, 3H) ppm; ^{13}C NMR (500 MHz, $CDCl_3$): δ = 168.3, 156.0, 147.1, 142.0, 141.0, 139.9, 139.7, 136.7, 136.6, 128.9, 128.3, 126.9, 126.5, 125.9, 125.7, 115.9, 115.0, 112.9, 112.2, 98.4, 98.0, 59.8, 59.6, 57.9, 57.6, 54.9, 54.2, 33.6, 33.0, 21.1, 21.0, 20.9, 14.8, 14.3 ppm.

3.1.3 Antioxidant assay

Antioxidant assay was calculated via ABTS free radical cation ($ABTS^{\bullet+}$) scavenging activity, using procedure presented by Re et al. (1998) [37] with slight modifications [38].

Initially, the stock solution was prepared by mixing equal volume of ABTS and PES solutions i.e. adding up 2 mL of each 7 mmol of 2, 2'-azinobis-(3-ethylbenzothiazoline-6-sufonic acid) (ABTS) solution and 2 mmol of potassium persulphate (PPS) solution and then the stock solution was left to react (partial oxidation of ABTS) undisturbed up to 12-16 hours in dark leading to the generation of ABTS free radical cations ($ABTS^{\bullet+}$) in stock solution.

For the investigation of antioxidant properties in the synthesized derivative compounds, the 1 mL of ABTS radical cation ($ABTS^{\cdot+}$) stock solution was diluted with 22 mL of methanol and incubated for 7 minutes before starting the analysis. The sample dilutions were prepared by dissolving 1 mg of derivative compound in 1 mL of the solvent mixture of methanol and chloroform in 1:1 ratio by volume, respectively.

The diluted ABTS radical cation ($ABTS^{\cdot+}$) stock solution recorded an absorbance of 0.421 at wavelength 734 nm. Afterwards, 1ml of diluted ABTS radical cation ($ABTS^{\cdot+}$) stock solution was take out in a test tube frequently followed by adding 1 mL of sample dilution prepared, and then percentage inhibition was calculated by recording absorbance value of the mixture at 734 nm.

The percentage (%) inhibition was calculated using relation given below:

$$I\ \%\ [\text{ABTS free radical}] = [(A_C - A_S)/A_C] \times 100$$

4. Conclusions

In conclusion, we have described an interesting MCR having new and efficient methodology for synthesizing highly functionalized tetrahydropyridines in aqueous medium at room temperature using citric acid (10 mol %) as catalyst. This methodology accessible various advantages with environmentally benign, simple procedure, single step atom economy, water as green solvent, short reaction time, avoid column chromatography, good to excellent yield and no-toxic by-products etc. These features make this methodology a useful and attractive strategy in multicomponent reaction. The synthesized products contain important bioactive moieties and expected that they may exhibit other potent biological activities.

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