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Triton-X-100 catalyzed synthesis of 1,4-dihydropyridines and their aromatization to pyridines and a new one pot synthesis of pyridines using visible light in aqueous media†

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Partha Pratim Ghosh, Prasun Mukherjee and Asish R. Das*

A realistic and convenient synthetic method has been developed for the facile synthesis of 1,4-dihydropyridine derivatives in the presence of the non-ionic surfactant Triton X-100, in an aqueous medium at room temperature. A greener method to synthesize pyridine derivatives has also been developed by the oxidation of 1,4-dihydropyridine derivatives with almost 100% yields and also in a one pot synthesis, employing an aldehyde, ethyl acetoacetate and ammonium acetate in an aqueous micellar medium by irradiation with potassium persulphate in the presence of visible light. The one pot protocol offered excellent yields of the targeted product in a very short period of time at room temperature and the non-ionic surfactant catalyst can be recovered very easily. We also observed that during the reaction there was the formation of micelles, or micelle-like colloidal aggregates, from the non-ionic surfactant and the reaction mixture in water, measured by dynamic light scattering and visualized through an optical microscope. The process is advantageous as ammonia is generated from an ammonium salt under absolutely neutral conditions and the product purification follows a group assistant purification chemistry process (GAP).

Introduction

Developing environmentally benign and economical syntheses is an active area of research that is being willingly pursued, and the avoidance of hazardous organic solvents follows the fundamental strategy to achieve the efficacy. The most attractive alternative to organic solvents is water, which has a perceived increasing popularity, due to being cheap and readily available, which have become major concerns in academia and industry and the need for green reactions is now globally putative.[1] In addition, reactions in aqueous media illustrate distinctive reactivities and unique selectivities that are not usually observed in organic media.[2] However, organic reactions in water are often limited in scope due to the poor solubility of the organic compounds. A possible new way to improve the solubility of substrates is the use of surface-active compounds that can form micelles.[3]

Under ambient conditions, surfactant molecules can aggregate in an aqueous phase to form micelles with a hydrophobic core and a hydrophilic corona. Lewis acidic or basic surfactant catalyzed reactions are commonly reported, but there are very few reports where non-ionic surfactants were used as the catalyst.[4] Non-ionic surfactants have the tendency to adsorb at interfaces and to form micelles, otherwise, their critical micelle concentration (CMC) is similar to the ionic surfactants.[5] However, the benefit of non-ionic surfactants (*e.g.* Triton X-100) is the absence of the electrical double layer, as formed by the ionic surfactants. Therefore, non-ionic surfactants are necessary model adsorbents for interfacial processes. Hence, we planned to utilize these properties of non-ionic surfactant for our present study.

In recent years, the swift assembly of molecular diversity is an important goal of synthetic organic chemistry and one of the key patterns of modern drug discovery. The tactics to address this contest involve the development of multicomponent reactions (MCRs), in which three or more reactants are combined together in a single reaction flask, to generate a product incorporating most of the atoms contained in the starting materials. In addition, MCRs in water are one of the most powerful tools for the atom efficient, time minimized, cost-advantageous and environmentally waste-free synthesis of bioactive motifs.[6]

Functionalized pyridine and 1,4-dihydropyridine derivatives have long been known as important biologically active compounds. 1,4-Dihydropyridines have been extensively used as calcium channel modulators,[7] and were developed as cardiovascular, antihypertensive and anticancer drugs, which include diludine, felodipine, isradipine, lacidipine, nitrendipine, nifedipine and nemadipine B (Fig. 1)[8] and their oxidized counterparts target a wide variety of biological receptors.[9] Due to the existence of pyridines in pharmaceuticals, agrochemicals, and natural products, their synthesis remains an area of intense current interest to the chemical community.[10] The corresponding pyridines of Hantzsch 1,4-dihydropyridines have been extensively studied in view of the significance of this reaction to the

Department of Chemistry, University of Calcutta, Kolkata-700009, India. E-mail: ardchem@caluniv.ac.in; ardas66@rediffmail.com; Fax: +913323519754; Tel: +913323501014 Tel: +919433120265

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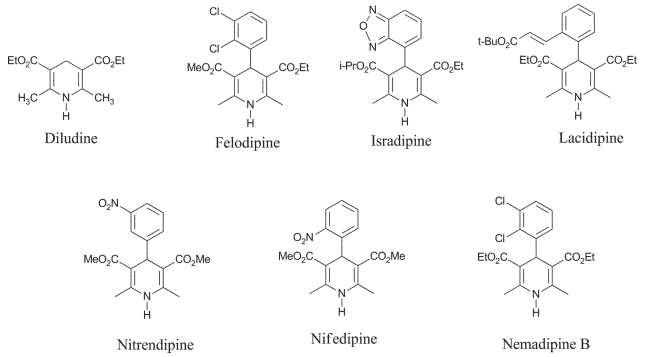
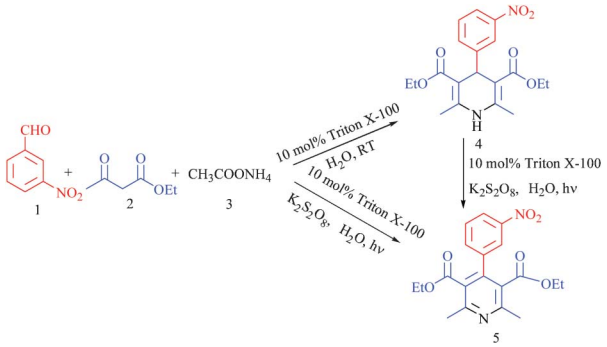


Fig. 1 Some bioactive dihydropyridines.



Scheme 1 One pot synthesis of 1,4-dihydropyridine, pyridine and the conversion of 1,4-dihydropyridine to pyridine.

metabolism of Hantzsch esters and to study the biologically important NADH redox processes.[11]

A variety of methods have been materialized to achieve the synthesis of this dihydropyridine and the pyridine nucleus. Despite some progress, most of the methods[12–16] suffer from a number of disadvantages, like using organic solvents, acidic reaction conditions, high reaction temperatures and low catalytic efficiencies. Surprisingly, very little is known about the surfactant catalyzed synthesis and light induced oxidations of 1,4-dihydropyridines and the one pot synthesis of pyridine derivatives.

Our group is involved in the utilization of visible light in chemical reactions, involving water as a reaction medium in organic multicomponent reactions (MCRs)[17] for the synthesis of various biologically important heterocyclic compounds. We wish to report herein a highly efficient procedure for the preparation of 1,4-dihydropyridine derivatives *via* a one pot, four component Hantzsch reaction,[18] using the non-ionic surfactant Triton X-100 in aqueous media at room temperature and a conceptually distinct approach to the synthesis of highly substituted pyridines *via* a one pot, three component reaction and oxidation of 1,4-DHP to the corresponding pyridines, with almost 100% yields within very few minutes. This approach is based upon the light induced synthesis of 1,4-dihydropyridine and its oxidation to the corresponding pyridines in the presence of potassium persulphate, $K_2S_2O_8$ (1 mmol) and Triton X-100 (10 mol%) in water at room temperature (Scheme 1).

Results and discussion

In order to optimize the reaction conditions and identify the best surfactant catalysts, the reaction was studied by employing surfactant catalysts with solvents, as well as under solvent-free conditions, with the hope of maximizing the product yield in short reaction times (Table 1). In our initial studies, we used 3-nitrobenzaldehyde **1** (1 mmol), ethyl acetoacetate **2** (2 mmol) and ammonium acetate **3** (1.5 mmol) as model substrates (Scheme 1) and these were stirred at room temperature in the presence of H_2O and ethanol as the solvents, without any catalyst. However, even after 24 h, the reaction failed to afford any product (Table 1, entries 1 and 2). The reactions were also restrained by using the anionic surfactant SDS (sodium dodecyl sulphate) as the catalyst (Table 1, entry 3). While the use of a cationic surfactant CTAB (cetyl trimethylammonium bromide) as a catalyst in aqueous media, provided a slight higher yield than the anionic surfactant (Table 1, entry 4) of the desired product. We then applied a non-ionic surfactant, Triton X-100 (10 mol%) as the catalyst in water. Eventually we achieved satisfaction because the reaction proceeded well, affording the desired product in a 96% yield within 2.5 h (Table 1, entry 5). Triton X-100 played an amazing catalytic role in this particular MCR in comparison to the other surfactants applied, which can be attributed to its high solubilizing capacity related to its hydrophobic character; in addition, the surfactant properties of Triton X-100 improve the reaction kinetics by increasing the interfacial area and also the aggregation number of the micelles. For the present investigation of micellar systems, the aggregation number follows the trend: Triton X-100 (N_{agg} = 143[19]) > CTAB (N_{agg} = 92[20]) > SDS (N_{agg} = 60[21]). An increase in the aggregation number results in an increase in the surface charge of the micellar units, which can subsequently create ambient conditions which optimize the reaction purity, yield and speed for the reaction to move forward.

Having evaluated Triton X-100 as the right choice of catalyst for the experiment, we then concentrated our attention on designing and also generalizing the promising conditions for the reaction. We firstly attempted some screening tests with Triton X-100. The quantity of the catalyst had a large effect on the formation of the desired product. The use of 15 mol% Triton X-100 diminished the quantity of the yield, whereas the yield of the product was much decreased when we used 5 mol% Triton X-100 (Table 1, entries 6 and 7). The yields of the desired product were also decreased when Triton X-100 was refluxed with water (Table 1, entry 8). Water showed superiority to the other solvents tested [ethanol (Table 1, entry 9), chloroform (Table 1, entry 10) and acetonitrile (Table 1, entry 11)], while under the solvent-free conditions (Table 1, entry 12) at room temperature, Triton X-100 failed to provide satisfactory outputs. Therefore, water was chosen as the solvent for this reaction as the maximum yield (96%) was obtained under aqueous conditions. Hence, these optimized conditions were followed for all experiments: taking 3-nitrobenzaldehyde (1 mmol), ethyl acetoacetate (2 mmol) and ammonium acetate (1.5 mmol) in the presence of 10 mol% Triton X-100 in aqueous media at room

Table 1 Screening of catalyst and solvents and reaction conditions[a]

Entry	Catalysts	Solvents	Conditions	Time (h)	Yields[b] (%)
1	—	H_2O	RT	24	—[c]
2	—	EtOH	RT	24	—[c]
3	SDS (10 mol%)	H_2O	RT	24	24
4	CTAB (10 mol%)	H_2O	RT	24	41
5	Triton-X-100 (10 mol%)	H_2O	RT	2.5	96
6	Triton-X-100 (15mol%)	H_2O	RT	2.5	86
7	Triton-X-100 (5mol%)	H_2O	RT	2.5	81
8	Triton-X-100 (10 mol%)	H_2O	reflux	2.5	66
9	Triton-X-100 (10 mol%)	EtOH	RT	2.5	54
10	Triton-X-100 (10 mol%)	$CHCl_3$	RT	2.5	59
11	Triton-X-100 (10 mol%)	CH_3CN	RT	2.5	44
12	Triton-X-100 (10 mol%)	—	RT	2.5	32

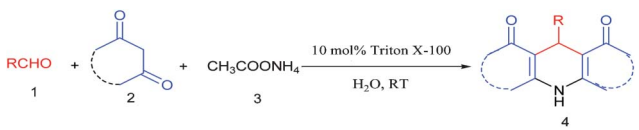
[a] All reactions were carried out with *m*-nitrobenzaldehyde (1 mmol), ethyl acetoacetate (1 mmol) and ammonium acetate (1.5 mmol) in 3 ml solvent. [b] Yield of isolated product. [c] Reaction failed to provide any product.

temperature (Scheme 1). Typically, a mixture of the substituted aldehyde (1.0 mmol), ethyl acetoacetate (2.0 mmol), ammonium acetate (1.5 mmol) and 10 mol% Triton X-100 in 3 ml water was stirred at room temperature for 2–3.5 h, which afforded a library of 1,4-dihydropyridines (**4a–z**) and polyhydroquinolines (**5**) derivatives in good to excellent yields (83–96%) (Table 2).

The scope of this study was then successfully extended to the oxidation of 1,4-dihydropyridine in water with almost 100% yields. The optimum conditions were 1,4-dihydropyridines in the presence of potassium persulphate, $K_2S_2O_8$ (1 mmol) and Triton X-100 (10 mol%) in water, irradiated with visible light at room temperature. The results obtained with various 1,4-dihydropyridines are given in Table 3.

Further experiments demonstrated that pyridine derivatives can be produced instead of dihydropyridines, when the reagents are irradiated with potassium persulphate in a one pot reaction, in

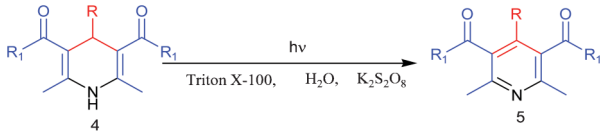
Table 2 Substrates scope for the synthesis of 1,4-dihydropyridine(**4a–4z**)



Entry	R	1,3-Diketones		Time (h)	Product	Yield (%)[a]
1	C_6H_5	Ethyl acetoacetate	Ethyl acetoacetate	2.5	4a	95
2	3-$NO_2C_6H_4$	Ethyl acetoacetate	Ethyl acetoacetate	2.5	4b	96
3	4-$MeOC_6H_4$	Ethyl acetoacetate	Ethyl acetoacetate	3	4c	93
4	4-HOC_6H_4	Ethyl acetoacetate	Ethyl acetoacetate	3	4d	89
5	4-ClC_6H_4	Ethyl acetoacetate	Ethyl acetoacetate	2.5	4e	94
6	4-FC_6H_4	Ethyl acetoacetate	Ethyl acetoacetate	2.5	4f	95
7	2-Furyl	Ethyl acetoacetate	Ethyl acetoacetate	2	4g	96
8	H	Ethyl acetoacetate	Ethyl acetoacetate	2	4h	95
9	n-Propyl	Ethyl acetoacetate	Ethyl acetoacetate	2.5	4i	88
10	2-Pyridyl	Ethyl acetoacetate	Ethyl acetoacetate	2.5	4j	85
11	4-$Me_2NC_6H_4$	Ethyl acetoacetate	Ethyl acetoacetate	3.5	4k	83
12	3-$NO_2C_6H_4$	Methyl acetoacetate	Methyl acetoacetate	3	4l	90
13	2,3-$Cl_2C_6H_3$	Methyl acetoacetate	Methyl acetoacetate	2.5	4m	91
14	C_6H_5	Acetyl acetone	Acetyl acetone	2.5	4n	90
15	4-$MeOC_6H_4$	Acetyl acetone	Acetyl acetone	3.5	4o	85
16	4-HOC_6H_4	Acetyl acetone	Acetyl acetone	3.5	4p	87
17	4-ClC_6H_4	Acetyl acetone	Acetyl acetone	3	4q	89
18	2-Furyl	Acetyl acetone	Acetyl acetone	2.5	4r	88
19	n-Propyl	Acetyl acetone	Acetyl acetone	2.5	4s	87
20	4-$NO_2C_6H_4$	Ethyl acetoacetate	Acetyl acetone	2.5	4t	88
21	4-FC_6H_4	Ethyl acetoacetate	Acetyl acetone	2	4u	87
22	4-$OMeC_6H_4$	Ethyl acetoacetate	Acetyl acetone	3	4v	84
23	4-$NO_2C_6H_4$	Dimedone	Ethyl acetoacetate	3.5	4w	92
24	4-$MeOC_6H_4$	Dimedone	Ethyl acetoacetate	3.5	4x	90
25	4-$NO_2C_6H_4$	Dimedone	Acetyl acetone	3.5	4y	87
26	4-$MeOC_6H_4$	Dimedone	Acetyl acetone	3.5	4z	88

[a] Isolated yield of the pure compound.

Table 3 Substrate scope for the oxidation of 1,4-dihydropyridine to pyridines (**5a–5g**).



Entry	R	R_1	Product(s)	Time (min)	Yields (%)[a]
1	H	OEt	5a	15	~100
2	4-$NO_2C_6H_4$	OEt	5b	15	~100
3	3-$NO_2C_6H_4$	OEt	5c	20	~100
4	4-$MeOC_6H_4$	OEt	5d	20	~100
5	4-MeC_6H_4	OEt	5e	15	~100
6	4-ClC_6H_4	OEt	5f	20	~100
7	C_6H_5	OEt	5g	20	~100

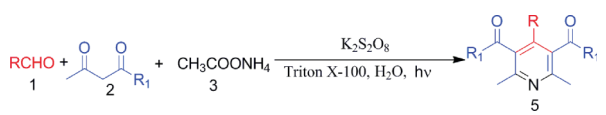
[a] Yield of the isolated products.

the presence of visible light with high yields, in a short period of time (Table 4). The structure of the 1,4-dihydropyridines and pyridines were confirmed by comparing their physical and spectral data with their reference data or elucidated by NMR spectroscopy (ESI†).

To test the generality of this reaction, a series of aromatic, aliphatic and heteroaromatic aldehydes were subjected to the optimal reaction conditions (Table 2). Ethyl acetoacetate, acetyl acetone and dimedone were also used for forming the dihydropyridine ring with ammonium acetate (acting as the ammonia donor), to access the corresponding 1,4-dihydropyridine derivatives. The reactions proceeded smoothly and provided excellent yields and tolerated unsubstituted benzaldehydes, and both electron-withdrawing and electron-donating *para*-substituted benzaldehydes.

The reusability of the catalyst was studied through the condensation of 3-nitrobenzaldehyde, ethyl acetoacetate and ammonium acetate. Upon completion of the reaction, the product was filtered and washed with water and the unused starting materials were extracted using diethyl ether and the separated micellar media were reused for the next cycle. The recycling could be followed five consecutive times with almost unaltered catalytic

Table 4 Substrates scope for the one pot synthesis of pyridines (**5a–5g**)



Entry	R	R_1	Product	Time (h)	Yields (%)[a]
1	H	OEt	5a	2	80
2	4-$NO_2C_6H_4$	OEt	5b	2	77
3	3-$NO_2C_6H_4$	OEt	5c	2.5	80
4	4-$MeOC_6H_4$	OEt	5d	3	80
5	4-MeC_6H_4	OEt	5e	2	77
6	4-ClC_6H_4	OEt	5f	2.5	82
7	C_6H_5	OEt	5g	2.5	78

[a] Yield of the isolated product.

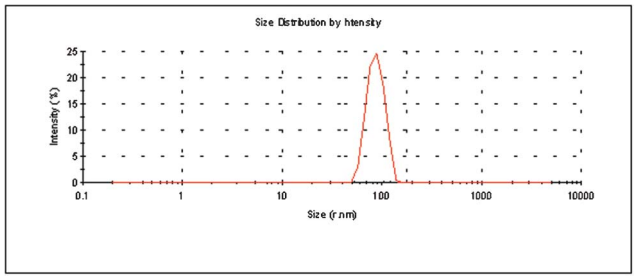


Fig. 2 DLS study of the reaction media showing formation of aggregates.

activity (recovery amount 91% and yield 87%, after the 5th run). The reactions were consistently carried out at the 1 mmol scale and no change of product yield was observed when scaled up to the 10 mmol scale at room temperature. The catalytic effect of micellar Triton X-100 in this reaction can be explained as follows: in the micellar solution, ethyl acetoacetate, aldehyde and ammonium acetate which are all hydrophobic, are forced inside the hydrophobic core of the micelles, thus allowing the reaction to take place more easily.

It is significant to mention that the addition of Triton X-100 in the reaction flask converted the initially suspended reaction mass into a homogeneous mixture, which on stirring became a yellowish turbid emulsion. This observation implies that there was formation of micelles or micelle-like colloidal aggregations. The average sizes of the colloidal particles formed from the non-ionic surfactant and the reaction mixture in water were measured by dynamic light scattering, and appeared to be about 100 nm in diameter (Fig. 2). Fig. 3 shows optical microscope (40×) images in the 10 mol% Triton X-100 and 3 ml water system of the reaction mixture; round structures can be clearly observed. As shown in the polarizing microscope image in Fig. 3a (before the addition of potassium persulphate) and Fig. 3b (after the addition of

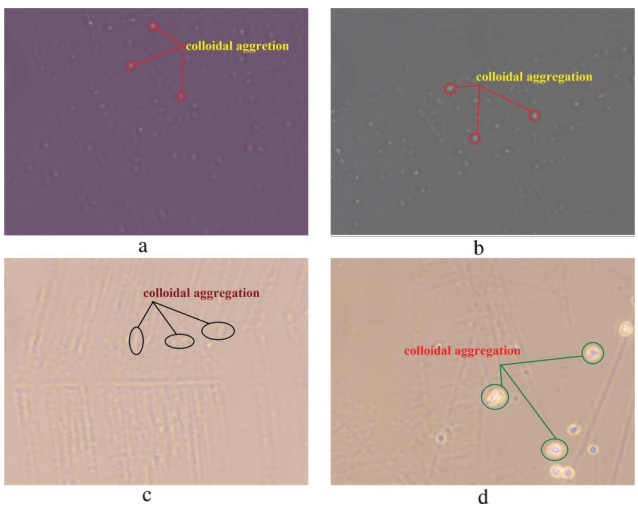


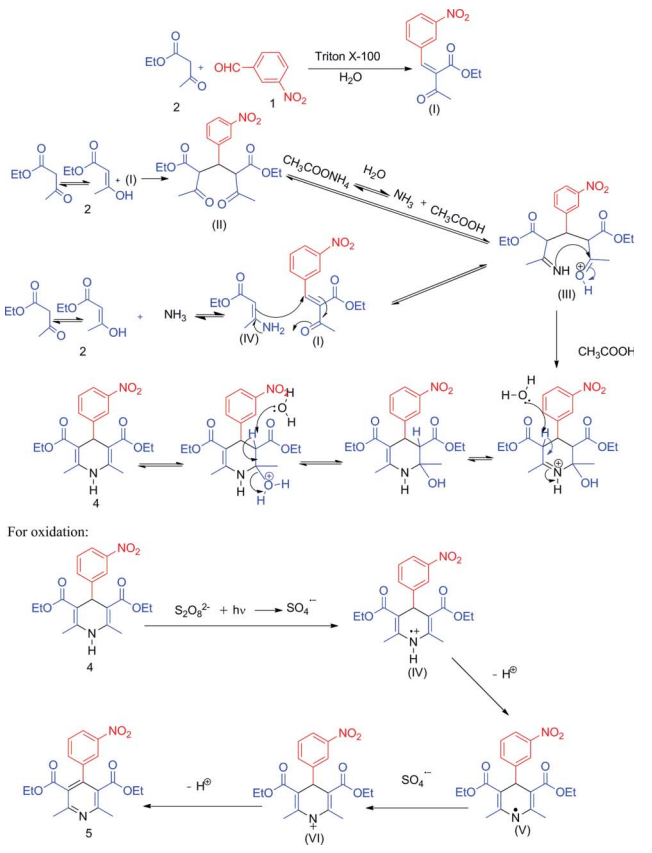
Fig. 3 Optical microscope images (25 μm at 40×) of nano-vesicle structures forming in emulsion samples: (a) without the addition of $K_2S_2O_8$ solution; (b) 15 min, (c) 1.5 h and (d) 2.5 h after $K_2S_2O_8$ addition.

potassium persulphate), only the shell part of the round structures is gleaming. Furthermore, we observed the growth process of these vesicles with the reaction progress over time, using the microscope. Before forming a vesicle, a cylindrical micellar-like structure was formed (Fig. 3c). It closed slowly and finally became spherical (Fig. 3d). The emulsion formation is attributed to the property of Triton X-100 as a surfactant, and this property should be important to accelerate the reaction rate. That is, these colloidal vesicles would function as effective reaction domains in water. The driving force of the reaction in the presence of micelles may be related to the hydrophobic forces which compress the reactants together in a highly compact arrangement of complexes, within a restricted hydrophobic domain.

Presumably, the reaction may proceed through the following mechanistic pathway, which is presented in Scheme 2. Initially, a Knoevenagel condensation occurs, by the coupling of the aldehyde (1) with the active methylene group of one equivalent of β-ketoester (2) to form intermediate (I). Then, intermediate (I) readily undergoes a nucleophilic addition from the enol form of the second equivalent of the β-ketoester, followed by a Michael addition, to generate 1,5-dioxo compound (II) in the micellar system. Ammonia and acetic acid generated from ammonium acetate (3) in the presence of water at room temperature, convert intermediate (II) into intermediate (III), which then undergoes a cyclocondensation and generates 1,4-dihydropyridine (4), following conventional acid catalysis (acetic acid from ammonium acetate). An alternative reaction pathway, that remains a possibility, is *via* the formation of intermediate (IV), an enamine ester, which is produced by the condensation of the second equivalent of the β-ketoester with ammonia in the micellar system, generates intermediate (III), following the condensation with intermediate (I), finally affording 1,4-dihydropyridine (4). We attempted to isolate; (i) intermediate (I) from the two component reaction of ethyl acetoacetate and 4-nitrobenzaldehyde (1 : 1), (ii) intermediate (II) from the three component reaction of ethyl acetoacetate and 4-nitrobenzaldehyde (2 : 1) and (iii) intermediate (IV), from the two component reaction between ethyl acetoacetate and ammonium acetate in the aqueous micellar system (in the presence of a catalytic amount of ammonium acetate (10 mol%)). Unfortunately, all these attempts produced no trace of the desired intermediates. The analysis of these results revealed that the intermediates (I), (II) and (IV) are very reactive towards the subsequent reaction under multicomponent reaction conditions in the micellar system. Consequently, whether the sequential reactions occur through the intermediate (I), (II) or (IV) could not be ascertained and evaluated in the present study. During the oxidation of 1,4-dihydropyridine derivatives, we used potassium persulphate, $K_2S_2O_8$, which is not a photocatalyst, however, photolysis of $S_2O_8^{2-}$ produces two sulphate radical anions (SO_4^{-}) with a quantum efficiency of unity,[22] and the formed SO_4^{-} can act as a strong oxidant in aqueous systems: initially a one electron transfer from 1,4-dihydropyridine to the radical anion (SO_4^{-}) gives a radical cation (IV), which loses a proton to form intermediate (V). Again a one electron transfer to the sulfate radical anion (SO_4^{-}), to form the intermediate (VI), subsequently results in the aromatized product (5) by homolysis.

It is also interesting to mention that for the one pot synthesis of pyridine, the sulphate radical anion did not oxidize the aldehyde, rather the reaction takes the desired course and pyridine derivatives are the sole isolable products under the attempted micellar reaction conditions.

From the stand point of green chemistry, it was positive to find that the final products could be isolated by filtration at the end of the reaction, due to their lower solubility in the TritonX-100–water mixture. Furthermore, their purity was high and did not require their preparation in an analytically pure form by single recrystallization, thus avoiding extraction steps and chromatographic separations. Therefore, we preferred water as the reaction medium over unsafe organic solvents, which decreased the chemical impurities, afforded an easy work-up procedure and avoided producing large volumes of waste from the discarded chromatographic static phases. Aromatic aldehydes with electron-donating and electron-withdrawing groups both participated in this reaction equally well; apparently, the nature and position of substitution on the aryl ring do not make much difference in reactivity. Similarly, aliphatic (Table 2, entries 8, 9 and 19) and heterocyclic aldehydes (Table 2, entries 7, 10 and 18) afforded excellent yields of the products, without forming any side-products.



Scheme 2 Plausible mechanism for the formation of 1,4-dihydropyridine and the corresponding pyridine.

Conclusions

In summary, a practical and convenient synthetic method in aqueous media using Triton X-100 as the surfactant catalyst (10 mol%) has been developed, for the facile synthesis of 1,4-dihydropyridines and polyhydroquinolines. We have also successfully developed a new and easy to perform method for the efficient oxidation of Hantzsch 1,4-dihydropyridines and a new one pot potentially efficient, absolutely clean, versatile, environment-friendly, light induced, green procedure for the synthesis of pyridines. The operational simplicity and excellent yields of the products in a short period of time at room temperature are the main advantages of this method, and furthermore, this procedure is cheap, safe and environmentally benign which makes this methodology a superior approach for the preparation of small molecules of medicinal concern.

Experimental

General procedure for the preparation of 1,4-dihydropyridines (4a–4z)

The aldehyde (**1**) (1 mmol), 1,3-diketone (**2**) (2 mmol) and ammonium acetate (**3**) (1.5 mmol) were added to a solution of Triton X-100 (10 mol%) in H_2O (3 mL), and the mixture stirred at room temperature. The resulting clear solution, that gradually became turbid, was stirred for the stipulated time mentioned in Table 2. After completion of the reaction (indicated by TLC), the free flowing solid mass was filtered and washed with water (20 ml) to afford the desired products as pale yellow solids. The products thus obtained were recrystallized from ethanol to give pure compounds as white or pale yellow crystals.

General procedure for the oxidation of 1,4-dihydropyridines to the corresponding pyridines (5a–5g)

A solution of 1,4-dihydropyridine (1 mmol) in Triton-X-100 (10 mol%) in 3 mL water was contained in a 25 mL glass vessel and potassium persulphate (1 mmol) was added. The reaction vessel was placed 10 cm away from the visible light source (150 W tungsten lamp of Philips, with a cut-off light filter to allow only $\lambda > 300$ nm), which had a water circulation jacket, maintaining the temperature of the reaction mixture at 25 °C for the required period of time (indicated by TLC) (temperature inside the flask 25 °C). After completion of the reaction, the free flowing solid was filtered off and washed with water (20 mL) to afford the desired product with almost 100% yield.

General procedure for the one pot synthesis of pyridines (5a–5g)

A solution of aldehyde (**1**) (1 mmol), ethyl acetoacetate (**2**) (2 mmol) and ammonium acetate (**3**) (1.5 mmol) in Triton-X-100 (10 mol%) in 3 mL water was taken in a 25 mL glass vessel and to this potassium persulphate (1 mmol) was added. The reaction vessel was placed 10 cm away from the visible light source (150 W tungsten lamp of Philips, with a cut-off light filter to allow only $\lambda > 300$ nm), which had a water circulation jacket, maintaining the temperature of the reaction mixture at 25 °C for the required period of time (temperature inside the flask 25 °C). After completion of the reaction (indicated by TLC), the free flowing solids were filtered and washed with water (20 ml) to afford the desired products as pale yellow solids. The products thus obtained were recrystallized from ethanol to get pure compounds as white or pale yellow crystals.

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