



AQUEOUS CTAB CATALYZED EFFICIENT SYNTHESIS OF POLYHYDROQUINOLINES

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Abstract:

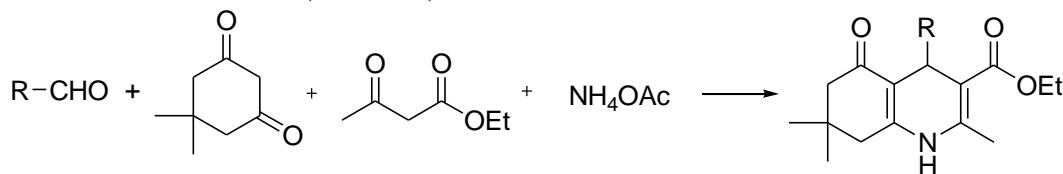
Simple, green and one pot four component synthetic route has been developed for the synthesis of polyhydroquinolines by allowing the condensation of aryl aldehydes, dimedone, ethyl acetoacetate and ammonium acetate using cheaper micellar catalyst, cetyl trimethyl ammonium bromide (CTAB) in water. The role of CTAB in the rate acceleration of the cyclocondensation has been discussed.

Keywords: Polyhydroquinoline, Micellar catalysis, Green synthesis.

INTRODUCTION:

Polyhydroquinolines are 1,4-dihydropyridines derivatives combined with single ring. 4-Substituted 1,4-dihydropyridines (1,4-DHPs) are well known for their Ca^{2+} channel blocker activity and known as one of the most important classes of drugs used for the treatment of cardiovascular diseases, including hypertension.¹ 1,4-Dihydropyridines possess a wide variety of biological activities, such as antitumor, vasodilator, bronchodilator, anti-atherosclerotic, geroprotective, hepatoprotective and antidiabetic² etc. 1,4-dihydropyridine derivatives exhibited several medicinal applications which include neuroprotectant, activity,³ platelet anti-aggregatory activity⁴ and cerebral antiischemic activity useful in the treatment of Alzheimer's disease.⁵ In addition they have been emerged as chemo sensitizers in tumor therapy.⁶ These facts clearly underlines the remarkable potential of dihydropyridine derivatives as a source of valuable medicaments.⁷

In view of the medicinal as well as synthetic importance of polyhydroquinoline derivatives, a wide variety of conventional methods were reported for their synthesis,⁸⁻¹³ many of these methods use conventional heating and refluxing approaches in the presence of an organic solvents. The straightforward approach for obtaining polyhydroquinolines involves the one pot four component cyclocondensation of aldehyde, dimedone, ethyl acetoacetate and ammonium acetate (**Scheme: 1**)



Scheme: 1

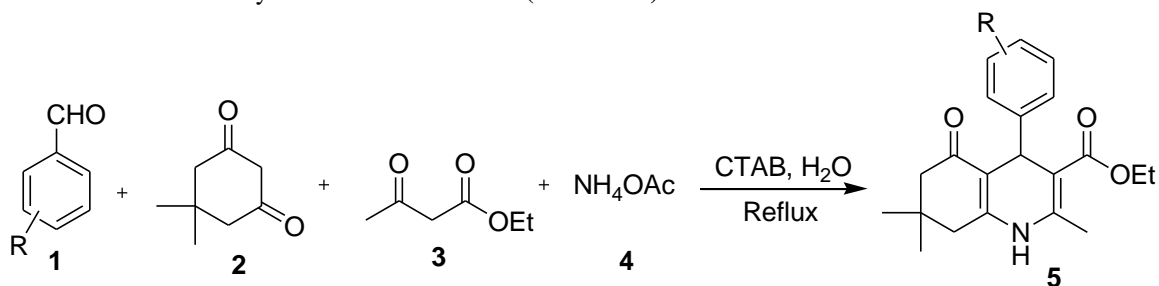
Number of attempts were made to make this approach more convenient and efficient, which involved use of microwave energy,¹⁴ TMSCl,¹⁵ ionic liquids,¹⁶ polymers,¹⁷ Yb(OTf)₃,¹⁸ ZnO-nanoparticle¹⁹ and Bakers' yeast.²⁰ Zinc modified beta zeolite/MW,²¹ Silica Sulfuric Acid²² are also used for the process of synthesis of polyhydroquinolines with the hope to make it more convenient rapid and environmentally benign.

These approaches, however, accompanied with long reaction times, the use of a huge quantity of volatile organic solvents and generally leading to low yields. The catalysts employed were specially synthesized by

following long synthetic procedures; sometimes these catalysts are very expensive. Some of the routes have problem of solid waste management. Therefore, it is necessary to develop an efficient, versatile and preferably green method for the synthesis of polyhydroquinoline avoiding the use of organic solvents.

Considering all above facts about the significance of polyhydroquinolines and drawbacks in the conventional as well as many of the modified protocols, it is necessary to develop rapid efficient and green method for the value added product such as polyhydroquinolines. In continuation of our earlier efforts to accelerate the synthetic routes leading to bioactive molecules with the help of biomimetic catalysts, here it was planned to carry one-pot four component cyclocondensation using cheap and easily accessible surfactant cetyl trimethyl ammonium bromide (CTAB) as acatalyst in water as reaction medium to obtain efficiently high yield of polyhydroquinolines in short time.

Considering the diverse applications of polyhydroquinolines and lacunas with the reported synthetic routes, here an one pot four component synthesis of polyhydroquinolines has been developed by allowing cyclocondensation of substitute aryl aldehydes, dimedone, ethyl acetoacetate and ammonium acetate in aqueous micellar (5 mol%) solution of CTAB as a catalyst and reaction medium. (Scheme: 2)



Scheme: 2

RESULTS AND DISCUSSION:

To find the best experimental conditions the investigations were started by performing one pot four component synthesis of polyhydroquinoline by allowing the cyclocondensation of p-bromobenzaldehyde (1g), dimedone, ethyl acetoacetate and ammonium acetate using aqueous micellar (5 mol%) solution of CTAB as catalyst and reaction medium. This reaction was considered as a model reaction.

Table 1: Optimization for appropriate reaction temperature^a

Entry	Reaction temperature (°C)	Yield ^b (%)
1	Room temperature	Nd
2	60	38
3	80	64
4	Reflux	77
5	Reflux without CTAB	Nd

^aReaction conditions: p-bromobenzaldehyde (5 mmol), dimedone (5 mmol), ethylacetoacetate (5mmol) ammonium acetate (6 mmol) in aqueous micellar (5 mo%) solution of CTAB (5 ml).

^bIsolated yields NdExpected product not detected

Initially to find the appropriate reaction temperature for efficient conversion of reactants in to product, the model reaction of p-bromobenzaldehyde (5 mmol), dimedone (5 mmol) ethylacetoacetate (5 mmol) and ammonium acetate (6mmol) was performed in aq. micellar solution of CTAB (Table 1). The use of aq. solution of CTAB at room temperature did not gave the desired product. When the same reaction was carried at elevated temperature, it was observed that reactants are converted in to corresponding cyclocondensed product, polyhydroquinoline; but the yields were not satisfactory (Table 1, entry 2, 3). Hence the reaction temperature was further increased to reflux condition, and the yield of the desired cyclocondensed product was found to be increased to 77%.

Table 2: Optimization for appropriate amount of CTAB^a

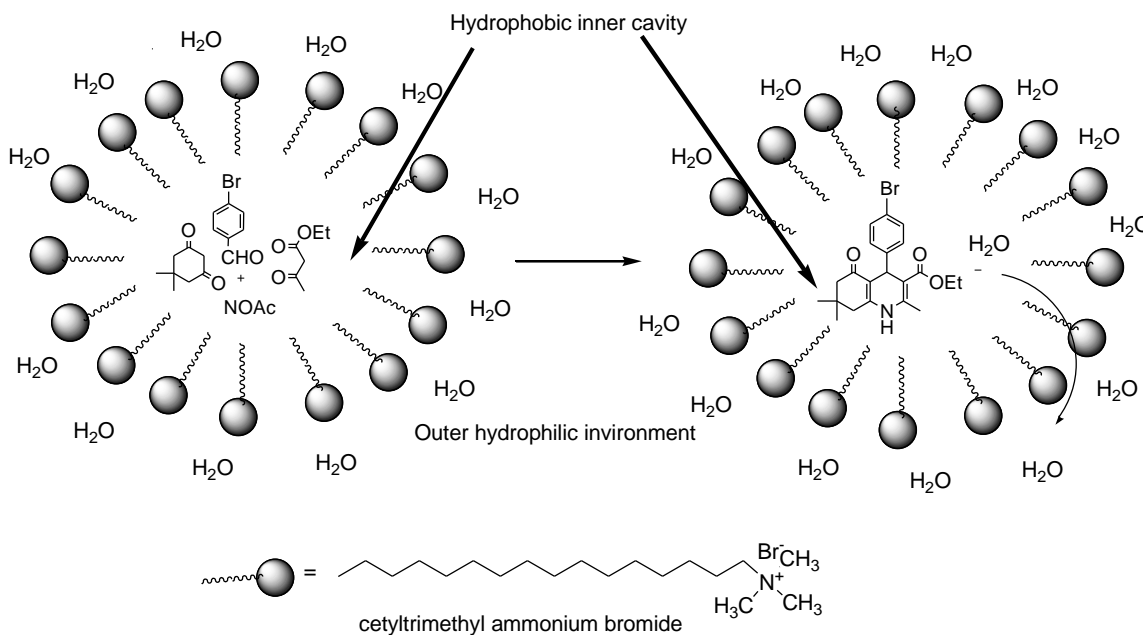
Entry	CTAB mol%	Yield ^b (%)
1	1	Trace
2	2	45
3	5	78
4	10	78

^aReaction conditions: p-bromobenzaldehyde (5 mmol), dimedone (5 mmol), ethylacetoacetate (5mmol) ammonium acetate (6 mmol) in aqueous micellar solution of CTAB (5 ml) at reflux condition.

^bIsolated yields

To optimize the appropriate amount of surfactant CTAB, the model reaction was run with different amount of catalysts such as 1, 2, 5 and 10 mol% at reflux condition. 5 mol% was found to be the appropriate amount of CTAB in 5 ml water for the conversion of reactants into product (**Table 2**). The same reaction when carried without CTAB at same reaction conditions, formation of the desired product was not observed even after 12 h (**Table 1, entry 5**).

CTAB is an emulsifying agent, which catalyzes this reaction by forming micellar aggregates in water in presence of substrate molecules. This micell formation plays an important role in acceleration of the reactions, as it provides hydrophobic inner cavity to allow the reactant molecules to come in the close proximity and react with each other. A possible mechanism for the reaction consists of a two-step sequence involving the micelle-promoted formation of product (**Scheme: 3**).


Scheme: 3

To test the generality of this reaction, a series of substituted aromatic aldehydes were subjected with dimedone, ethyl acetoacetate and ammonium acetate by using water as solvent at reflux temperature with stirring. Polyhydroquinolines with corresponding substitutions were obtained in better to excellent yields.

EXPERIMENTAL SECTION:

General procedure for the synthesis of polyhydroquinoline:

To the stirred mixture of aryl aldehyde (5 mmol), dimedone (5 mmol), ethyl acetoacetate (5 mmol) and ammonium acetate (6 mmol), micellar solution of CTAB (5 mol %) was added. The resulting reaction mass was

further stirred at reflux temperature. The progress of the reaction was monitored by thin layer chromatography using pet ether: ethyl acetate (2:8) as solvent system. After 1.5 h of reaction, the reaction mass was poured on crushed ice. The solid obtained was filtered and crystallized from absolute ethanol to obtain the pure products.

Spectral data of representative compound of the series:

Compound (5g): Ethyl 4-(4-bromophenyl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate

¹H NMR (500 MHz, CDCl₃): δppm= 0.917 (s, 3H), 1.087 (s, 3H), 1.173 (t, 3H, *J*= 7 Hz), 2.122-2.359 (m, 7H), 4.042 (q, 2H, *J*= 7 Hz), 5.004 (s, 1H), 6.240 (s, 1H), 7.169 (d, 2H), 7.301 (d, 2H).

¹³C NMR (125 MHz, CDCl₃): δppm = 14.38, 19.59, 27.29, 29.60, 32.88, 36.48, 41.21, 50.85, 60.10, 105.82, 111.93, 119.97, 130.03, 131.11, 143.87, 146.26, 148.46, 167.38 and 195.69.

HR-MS (ESI⁺ mode) (*m/z*): calculated for C₂₁H₂₄BrNO₃ [M+ K]⁺ : 456.0571, found : 458.0545 (M+2).

Table 3: Aqueous phase synthesis of polyhydroquinoline derivatives through Hantzsch reaction catalysed by CTAB micelles^a

Entry	R	Product ^b	Yield ^c (%)	M. P. (°C)
1	C ₆ H ₅	5a	72	202-204
2	2-ClC ₆ H ₄	5b	69	204-206
3	4-ClC ₆ H ₄	5c	81	245-247
4	4-OHC ₆ H ₄	5d	74	230-232
5	4-NO ₂ C ₆ H ₄	5e	75	244-245
6	4-CH ₃ C ₆ H ₄	5f	83	261-262
7	4-BrC ₆ H ₄	5g	78	252-254
8	3-NO ₂ C ₆ H ₄	5h	65	175-177
9	2-Furyl	5i	71	246-248
10	4-N(CH ₃) ₂ C ₆ H ₄	5j	77	230-231
11	4-OCH ₃ C ₆ H ₄	5k	80	255-257

^aReaction conditions: Aryl aldehyde (5 mmol), dimedone (5 mmol), ethylacetoacetate (5mmol) ammonium acetate (6 mmol) in 5 mol% aqueous micellar solution of CTAB (5 ml) at reflux condition.

^bThe known polyhydroquinoline derivatives synthesized by this method are having their melting points and spectral data in good agreement with those reported in the literature.²³

^cIsolated yields

CONCLUSIONS:

In summary, a practical and convenient synthetic method in aqueous media using CTAB as the surfactant catalyst (5 mol%) has been developed for the facile synthesis of polyhydroquinolines. The operational simplicity, excellent yields of the products, and high chemoselectivity are the main advantages of this method, and furthermore, this procedure is cheap, safe and environmentally benign.

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