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Microwave Assisted Attractive and Rapid Process for Synthesis of Octahydroquinazolinone in Aqueous Hydrotropic Solutions

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Abstract

We demonstrate here the synthesis of octahydroquinazolinone derivatives through one-pot, three-component condensation reactions of various aryl aldehydes, with a dimedone and urea in 50 % aqueous hydrotropic solution (Sodium *p*-Toluene Sulfonate) under microwave irradiation. This method exhibits efficient and environmentally benign methodology with simple reaction workup for the rapid synthesis of library of octahydroquinazolinones. Moreover, the reaction medium can be easily separated from the product and subsequently reused many times. The present method is of great interest in the context of environmentally greener and safer processes.

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Keywords: Hydrotrope; Microwave; Aqueous Medium; Octahydroquinazolinone.

1. Introduction

Octahydroquinazolinone derivatives have been attracted considerable interest because of their potential anti-bacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* Kidwai et al. (2005). In addition, these are widely used in pharmaceuticals and agrochemicals and also considered as a calcium antagonist Yarim et al. (2003). The most widely used method for the synthesis of octahydroquinazolinones is classical one pot multi-component 'Biginelli reaction' involving aromatic aldehydes, dimedone and urea, using different acid

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catalysts Hassani et al (2006). Several other modified processes have also been applied for this reaction using ionic liquids, boron compounds, TMSCl and various heterogeneous catalysts Joseph et al. (2006). Although some of these catalysts afford good to excellent yields, many of them suffers from various drawbacks such as the use of expensive catalysts, harmful reaction conditions which are difficult to handle especially on large scale and most of these methods require longer reaction times, uses strongly acidic conditions, and also suffer from the formation of many side products.

From ecological and green chemistry point of view the use of water as a reaction media have been attracted increasing attention since, it is harmless, safe and environmentally benign Holmberg et al. (2003). The low solubility of organic compounds in water can often be overcome by using hydrotropes, which are highly water soluble surface active organic salts that at higher concentration enhance the solubility of sparingly soluble as well as practically insoluble organic compounds in aqueous medium. The hydrotropes are characterized by an amphiphilic association structure Ekwall et al. (1975). It forms aggregation in aqueous solutions that are reminiscent of surfactant micelles and the formation of associated structures is responsible for hydrotropic effect. The characteristic aggregation of hydrotrope induces the origin of the solubilization process of sparingly soluble hydrophobic compound in water in analogy to a micillization process Balasubramanian et al. (1989). The ability of hydrotrope to increase the solubility of organic compounds in water is strongest, when the hydrotrope concentration called 'Minimum Hydrotrope Concentration (MHC)' is sufficient to induce the formation of associated structure and after which solubilities remain unchanged Srinivas et al. (1998). Aggregation and MHC are the exact mechanism of solubilisation of organic compounds in water by hydrotropes Horvath-Szabo et al. (2001). The potential use of hydrotropes in industry was stressed in 1946 by McKee et al. (1946), and are found a huge number of applications in various field such as separation sciences, drug solubilisation and nanocarrieres for poorly soluble drugs Tavare et al. (1996). They are also used as a reaction medium for many organic transformations Kumbhar et al (2012).

As hydrotropes are usually salts, their aqueous solutions are likely to assists dielectric heating in microwave radiation enhancing the reaction rate Rashinkar et al (2010). Although the use of hydrotropes is barely exploited field, it won't be wonder if their aqueous solutions will occupy a unique position in microwave assisted organic synthesis. The main advantages of microwave heating are very fast heating, absence of inertia, ease of use i.e. power regulation easy with an instantaneous control, better homogeneity in temperature with quick transfer of energy into the whole mass without superficial heating and selective heating of the polar molecules Varma et al. (2002).

We have recently established the compatibility of aqueous hydrotropic solution as safer solvent for ultrasound irradiation and microwave assisted reactions for the synthesis of medicinally important compounds Kamble et al. (2012). In continuation of our effort to tap the barely exploited potential of hydrotropes in organic synthesis, we report herein the use of different hydrotropes for efficient synthesis of octahydroquinazolinones under microwave irradiation.

2. Experimental Section

Infrared spectra were recorded on a Perkin-Elmer FTIR spectrometer and the samples were examined as KBr discs ~5% w/w. NMR spectra were recorded on a Bruker Avon 300 MHz spectrometer using $CDCl_3$ as solvent and TMS as an internal reference. Melting points were determined in an open capillary and are uncorrected. All the chemicals were obtained from Aldrich, Sd-fine chem and used without further purification. Sodium *p*-Toluene Sulfonate (NaPTSA) was synthesized by following the procedures reported in the literature Vogel et al. (1996).

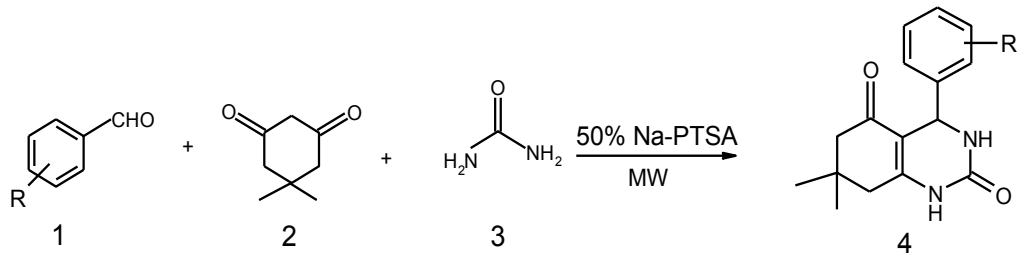
General procedure for synthesis of octahydroquinazolinones

A mixture of aryl aldehyde (1 mmol), dimedone (1 mmol) and urea (1 mmol) was stirred in round bottom flask containing aqueous 50 % hydrotropic solution (5 mL) to form a clear solution. The resulting solution was irradiated by microwave till the completion of reaction. After completion of the reaction as monitored by TLC, the mixture was diluted with water (20 mL). The obtained solid was filtered, washed with water, dried and recrystallized from

ethanol affording the corresponding products of high purity.

3. Results and discussion

We initially focused our attention on the selection of appropriate hydrotrope for the present work. Initially the condensation of benzaldehyde (1), dimedone (2), and urea (3) were employed for the synthesis of octahydroquinazolinone (4) in 50 % aqueous hydrotropic solution under microwave (Scheme 1).



Scheme 1: Synthesis of octahydroquinazolinone in aqueous hydrotropic solution

The different hydrotropes such as Sodium Benzene Sulphonate (NaBS), Sodium *p*-Xylene Sulphonate (NaXS) and Sodium *p*-Toluene Sulphonate (NaPTS) were selected for this purpose (Table 1.1). We opted to use 50 % (w/v) aqueous solutions of selected hydrotropes as a solvent, since this concentration was suitable for the maximum solubilization of organic compounds Friberg et al. (1996). On completion of the reaction, reaction mixture was diluted with water, and the filtration of reaction mixture followed by recrystallization of solid afforded the corresponding product of a high purity. For comparison the model reaction was performed at room temperature, though the reaction did occur at room temperature, longer reaction time was required as compared to microwave.

As excellent results were obtained for NaPTS, we employed this particular hydrotrope for subsequent studies. Next, we have studied the effect of concentration of hydrotrope on reaction yield under microwave irradiation. Thus the model reaction was carried out with various concentrations of NaPTS. As shown in fig 1.1, the yield of product varied dramatically with respect to hydrotrope concentration and was maximum (90 %) at 50% hydrotropic concentration, since this concentration was suitable for the maximum solubilization of organic compounds in water.

Table 1.1: Screening of various hydrotropes for the synthesis of octahydroquinazolinone[a]

Entry	Hydrotrope	With MW[b]		Room Temp[c]	
		Time (min)	Yield [d] (%)	Time (h)	Yield [d] (%)
1	Sodium *p*-Toluene Sulphonate (NaPTS)	20	90	4	88
2	Sodium *p*-Xylene Sulphonate (NaXS)	20	70	4	65
3	Sodium Benzene Sulphonate (NaBS)	45	40	4	40

[a] Reaction conditions: Benzaldehyde (1.0 mmol), dimedone (1.0 mmol), urea (1 mmol), 50% aqueous hydrotropic solution (5 mL).
[b] Reactions under microwave irradiation.
[c] Reactions at room temperature.
[d] Isolated yields after purification.

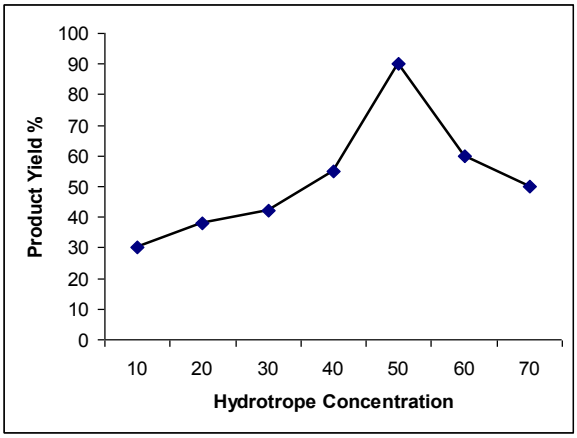


Fig 1.1. Effect of NaPTS concentration on octahydroquinazolinone synthesis under microwave

The higher activity of NaPTS is attributed to its overall planar structure with presence of more balanced hydrophobic and hydrophilic regions that give rise to a self-association configuration offering a microenvironment of lowered polarity stabilizing the reactants through a cooperative effect. The overall planar structure and the resulting effect of NaPTS was rationalized by comparing its X-ray diffraction data simulated from the crystal structure data available in the literature Gnanendran et al. and Rovetto et al. (Fig 1.2).

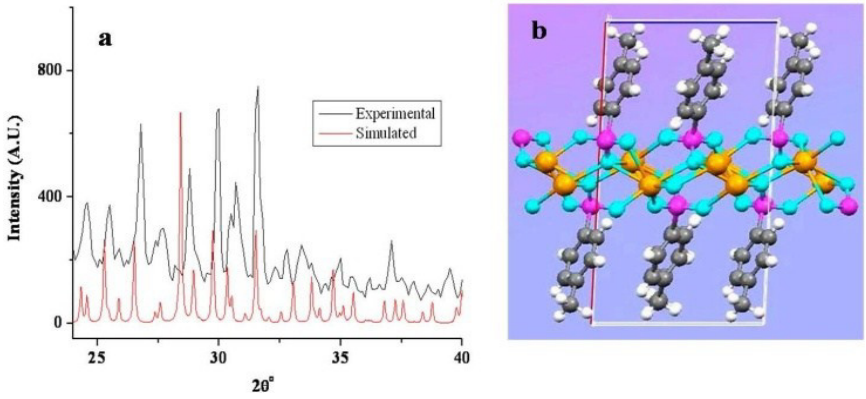


Fig 1.2. XRD pattern and crystallographic structure of NaPTS

The three-dimensional crystal structure of the NaPTS based on the crystallographic information reported by Reinke et al.(1999) is displayed in the Fig 1.2 viewed along the ‘b’ axis, and thus from the X-ray diffraction data we have confirmed the phase purity and monoclinic crystal structure of NaPTS. The absence of extra reflections other than the monoclinic phase indicates that the sample is free from any crystalline impurities originating from other phases. This was supported by Scanning Electron Microscopic study (Fig.1.3) and it was observed that the particles have sheet like morphology or layered structure, which is useful in stacking mechanism of hydrotrope. This morphology helps in the aggregation property of hydrotrope in aqueous medium for the solubilisation of organic compounds.

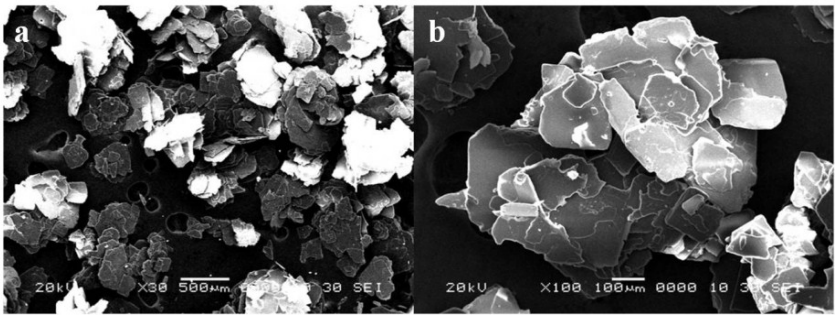
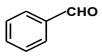
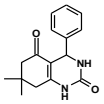
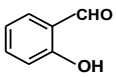
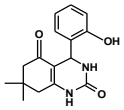
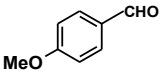
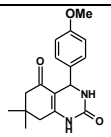
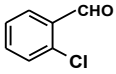
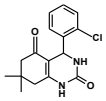
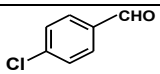
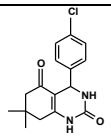
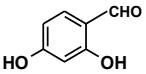
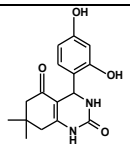
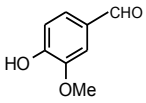
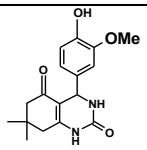
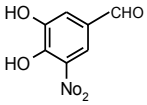
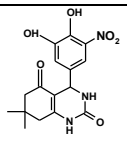
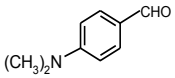
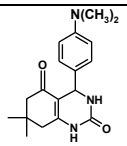
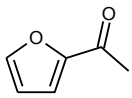
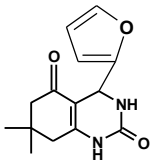


Fig 1.3. Scanning Electron Microscopy (SEM) image of NaPTS (a) normal view, and (b) magnified view

After the selection of an appropriate hydrotrope and optimized conditions, a series of aryl aldehydes were treated with dimedone and urea in 50% aqueous NaPTS solution under microwave (Table 1.2). With both electron-poor and electron-rich benzaldehydes the corresponding octahydroquinazolinone compounds were obtained in good to excellent yields. The reaction of sterically hindered 2-substituted benzaldehydes even gave higher yields highlightening the general applicability of this protocol. All the synthesized compounds were ascertained on the basis of IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy.

Table 1.2: Microwave assisted synthesis of octahydroquinazolinone in 50% aqueous NaPTS solution[a]

Entry	Aldehyde	Product[b]	Time (min)	Yield[c] (%)	M.P.[d] (°C)
1			20	89	290-292 [292]
2			25	88	265-267 [268]
3			28	80	244-247 [248]
4			23	82	282-285 [285]
5			30	85	304-306 [> 300]
6			32	85	225-227 [230]

7			35	83	188-190 [192]
8			30	86	192-196 [196]
9			32	83	260-263 [262]
10			30	85	262-265 [266]

[a] Reaction conditions: Aryl aldehydes (1.0 mmol), dimedone (1.0 mmol), urea (1 mmol), 50% aqueous hydrotropic solution (5 mL) under microwave irradiation.
[b] All products were analyzed by ^{1}H NMR, ^{13}C NMR, and mass spectroscopy.
[c] Isolated yields after purification.
[d] Literature values in parenthesis.

Another important feature of hydrotropic medium was its easy recovery from the reaction mixture and its recyclability. The reusability of hydrotropic solution was studied for model reaction and it was observed that it can be reused at least five times (Fig.1.4).

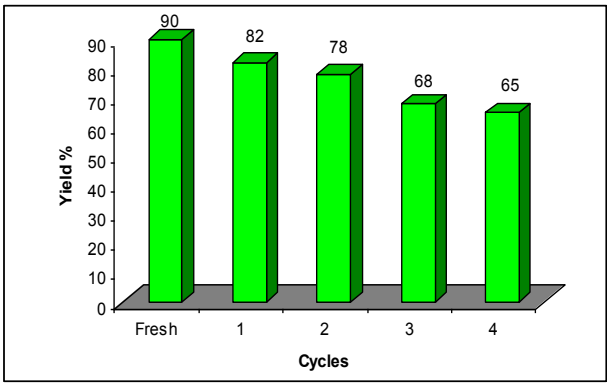


Fig.1.4. Recyclability of Hydrotrope

Conclusion

Aqueous solution of hydrotrope represents the unique property of an alternative reaction media for synthesis of octahydroquinazolinone under microwave irradiation. Besides being a cheap, non-toxic, non-flammable and environment friendly, aqueous hydrotropic solutions possess the other physico-chemical characteristics required to

be an alternative greener solvents for many organic transformations. Within the framework of green chemistry this method offers several significant advantages such as high conversions, easy handling, cleaner reaction profile and shorter reaction time making it useful and attractive process for the rapid synthesis. The easy recovery of products from the hydrotropic solution makes this protocol an attractive synthetic methodology.

Acknowledgments

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