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COMMUNICATION

Energy Efficient Pfitzinger Reaction: A Novel strategy with Surfactant catalyst

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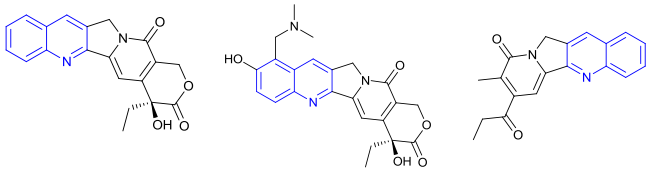
A novel energy efficient method for Pfitzinger reaction catalysed by a surfactant, cetyltrimethylammonium hydroxide has been demonstrated. Catalyst being surfactant in nature makes substrate soluble in aqueous media fastening interaction of catalyst with substrate. More increase in the rate of reaction and more than 78% of energy saving was observed under ultrasonic irradiation.

Quinoline is a backbone of many natural products (Fig. 1) such as alkaloids[1] and several pharmaceuticals[2], agrochemicals[3] and dyestuffs[4]. In coordination chemistry, quinolines are used to chelate metallic ions as N-donor ligands[5]. This scaffold has been reported to possess wide range of pharmacological activities including antiprotozoal[6], antitubercular[7], anticancer[8], antipsychotics[9], anti-inflammatory[10], antioxidant[6], anti-HIV[11], antifungal[12], as efflux pump inhibitors[13] and for treatment of neurodegenerative diseases[14] and lupus[15] etc.

Quinoline is also a part of several clinically used drugs, where their major occurrence is among antimalarial drugs (Fig 2). Other commercially available drugs containing quinoline ring are fluoroquinolone antibiotic ciprofloxacin (and its analogues), pitavastatin (cholesterol lowering agent), lenvatinib (kinase inhibitor for cancer) (Fig. 2) and its other structural analogues (such as carbozantinib, bosutinib), tipifarnib 70 (farnesyl transferase inhibitor for leukemia), saquinavir (antiretroviral), bedaquiline (anti-TB), etc. The 2-(2-fluorophenyl)-6,7-methylenedioxy quinolin-4-one monosodium phosphate (CHM-1-P-Na) is a preclinical anticancer agent, showing excellent antitumor activity in a SKOV-3 xenograft nude mice model[16, 17].



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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

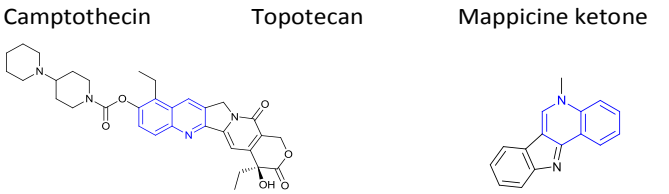
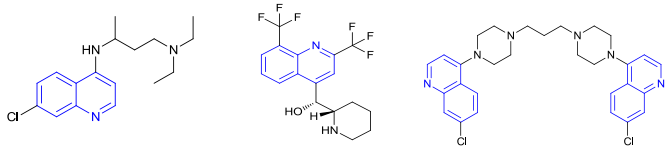


Fig. 1 Structures of natural products containing quinoline ring



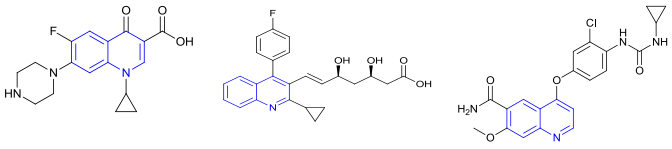


Fig. 2 Chemical structures of quinoline containing drugs

Several 'Name Reactions' have been reported for the synthesis of quinoline: (a) Combes quinoline synthesis; (b) Skraup synthesis; (c) Conrad-Limpach synthesis; (d) Povarov reaction; (e) Doebner reaction; (f) Doebner-Miller reaction; (g) Gould-Jacobs reaction; (h) Reihm synthesis; (i) Knorr quinoline synthesis; (j) Pfitzinger reaction; (k) Friedländer synthesis; (l) Niementowski quinoline synthesis; (m) Meth-Cohn synthesis; and (n) Camps quinoline synthesis[18]. However, conventional way of carrying out some of these methods suffer from drawbacks such as hazardous organic solvents, high cost, longer reaction time, low selectivity, and use of excessive amounts of base. Therefore, this necessitates the development of facile and environmentally benign methods for the synthesis of quinolines.

Here we have explored environmentally benign route for Pfitzinger reaction for the synthesis of quinoline-4-carboxylic acids. Traditional Pfitzinger reaction involves reaction of isatin

with ketone catalysed by strong bases such as NaOH, KOH[19] which are difficult to recycle which further leads to the generation of highly basic effluent. Therefore we thought of using basic catalyst which is recyclable and facilitates solubility of water insoluble substrates in to water. Cetyltrimethyl ammonium hydroxide (CTAOH) forms micelles in water[20] which solubilises organic substrates in to water. Micelles are proficient in bringing together the reactants within their small volumes. They can also stabilize and orient substrates in order to change the reactivity of substrates. Therefore, they can modify the reaction rates. It facilitates the use of water as a solvent for organic reactions. In our effort for conservation of energy required for the chemical reaction processes, we have also made use of ultrasound as a nonconventional energy source to accelerate the rate of reaction.

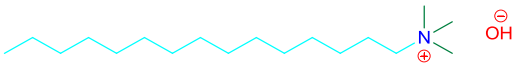
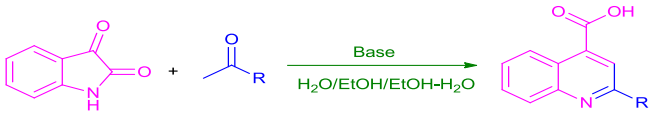


Fig. 3 Structure of Cetyltrimethylammonium hydroxide (CTAOH)

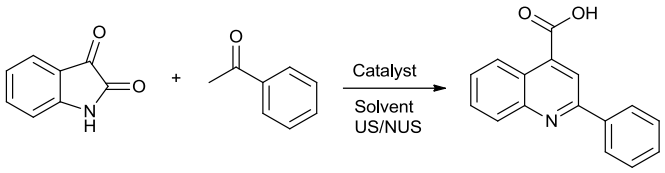
Scheme 1 General Pfitzinger reaction for the synthesis of quinoline-4-carboxylic acid



In order to study the catalytic effect of CTAOH for Pfitzinger reaction, isatin was reacted with acetophenone to give 2-phenylquinoline-4-carboxylic acid **3a**. Reaction did not take place when isatin was reacted with acetophenone in absence of catalyst. Pfitzinger reaction takes place by basic hydrolysis of isatin to isatoic acid therefore strong basic catalyst is needed to trigger this reaction[19]. Among various bases tested for this reaction CTAOH was found to be efficient basic catalyst which gave 2-phenylquinoline-4-carboxylic acid 3a with 94 % yield with water as a suitable solvent (table 1). 0.5 equivalents of CTAOH gave highest yield of 2-phenylquinoline-4-carboxylic acid. CTAOH being surfactant solubilises reactants in water through micelle formation[21-23]. This homogenization of reactants in solvent increases contact with catalyst therefore increases rate and yield of the reaction system. Though reactants have good solubility in ethanol water acted as a good reaction media due to easy separation of product, higher rate of hydrolysis of isatin than in ethanol[24]. Thus CTAOH fastens the rate of reaction. After extraction of product aqueous media containing dissolved CTAOH could be reused for the next batch of reaction. Further to explore the generality of the optimized reaction conditions various derivatives of quinoline-4-carboxylic acids were synthesised (Table 2).

To enhance the rate of reaction and productivity we carried out the same reaction under ultrasonic condition. Rate acceleration in ultrasound assisted reaction is due to the collapse of acoustic cavitation bubbles that generates localised temperature and pressure[25]. This also avoids the need to provide external heat. When isatin was reacted with acetophenone under ultrasonic conditions (ultrasound frequencies of 22 kHz, at 40% amplitude, at RT), compound 3a was obtained in 2.5 hr where as it required 10 hr under conventional thermal condition (80 °C) (Table 1). It is noteworthy to mention here that under ultrasonic conditions rate and efficiency of the reaction are more than those of the conventional thermal condition.

Table 1 Optimization of reaction parameters for the synthesis of quinoline-4-carboxylic acid

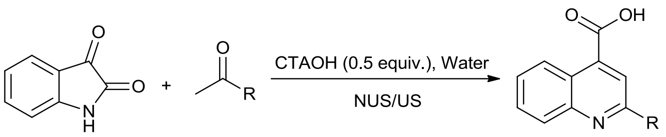


Entry	Base	Solvent	US yield (%)[a]	NUS yield (%)[b]
1	-	Water	nr[c]	Nr
2		Ethanol	Nr	Nr
3	KOH	Water	65	59
4		Ethanol	63	57
5		Water-ethanol (1:1)	66	62
6	$Ca(OH)_2$	Water	58	54
7		Ethanol	59	56
8		Water-ethanol (1:1)	62	57
9	$(CH_3)_3CO^-K^+$	Water	55	50
10		Ethanol	50	45
11		Water-ethanol (1:1)	58	54
12	TEA[d]	Water	20	14
13		Ethanol	25	21
14		Water-ethanol (1:1)	23	19
15	ChOH	Water	56	49
16		Ethanol	60	58
17		Water-ethanol (1:1)	55	51
18	CTAOH	Water	95	94
19		Ethanol	94	92
20		Water-ethanol (1:1)	93	92
21	CTAOH (0.5 equiv.)	Water	95	94
21	CTAOH (1.5 equiv.)	Water	93	92

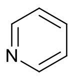
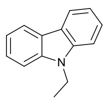
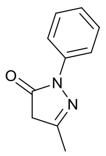
a: Ultrasound reaction condition: Isatin (0.01 mol), acetophenone (0.01 mol), base (0.01 mol), solvent (5mL) at ultrasound frequencies of 22 kHz, at 40% amplitude, at rt.
b: Non-ultrasound reaction condition: Isatin (0.01 mol), acetophenone (0.01 mol), base (0.01 mol), solvent (5 mL) at 80 °C.
c: No reaction, d: Triethylamine

A number of different methyl ketones were chosen to access the scope of the reaction method (Table 2). All the reactions were carried out under set reaction conditions and continued till the completion of reaction, indicated by thin layer chromatography. Under this method simple and functionalized methyl ketones easily reacted with isatoic acid formed after hydrolysis of isatin giving corresponding 2-substituted quinoline-4-carboxylic acids with good yield.

Table 2 Synthesis of quinoline-4-carboxylic acid derivatives



1 2 3

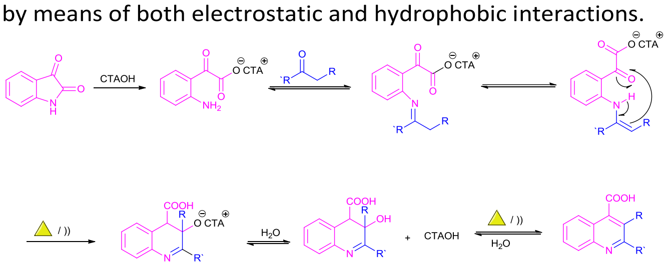
Entry	R	3	Time (hr)		Energy (KJ)		Yield (%)
			NUS	US	NUS	US	
1	C_6H_5	3a	10	2.5	17.7	3.8	95
2	*p*-CH_3-C_6H_5	3b	10.5	3.0	18.4	4.5	80
3	*p*-Cl-C_6H_5	3c	9	2.75	15.5	4.0	82
4	*p*-Br-C_6H_5	3d	10	3.0	16.7	4.2	78
5	*p*-OCH_3-C_6H_5	3e	11	4.0	19.0	5.9	77
6	*p*-NH_2-C_6H_5	3f	13	4.5	22.8	6.7	75
7	*p*-NO_2-C_6H_5	3g	7	2.0	12.0	2.9	85
8	*o*-OH-C6H_5	3h	13	4.5	22.9	6.7	79
9		3i	18	6.5	31.9	9.8	89
10		3j	15	6.0	24.4	8.2	78
11	CH_3	3k	13	4.0	24.2	6.4	88
12		3l	14	4.5	23.8	6.5	85

Reaction condition: Isatin (0.01 mol), acetophenone (0.01 mol), CTAOH (0.005 mol), water (5.0 mL).
NUS: non ultrasound US: ultrasound

The method to obtain quinoline-4-carboxylic acid derivatives (3a–3m) under ultrasonic irradiation offers several significant advantages including faster reaction rates, higher purity, higher yields, and lower temperature. In comparison with conventional methods, the main advantage of ultrasound application is the significant decrease in the reaction times. Thus, while conventional heating method requires 7-18 h for the completion of this reaction, ultrasonic irradiation affords the respective products in only 2-7 h. These results support the assumption that the energy provided by ultrasound accelerates these reactions. The difference in reaction times may be a consequence of the specific effects of ultrasound that is cavitation, a physical process that creates, enlarges, and implodes gaseous and vaporous cavities in an irradiated liquid, thus enhancing the mass transfer and allowing chemical reactions to occur. The creation of hot spots in the reaction mixture produces intense local temperatures and high pressures generated inside the cavitation bubble and its interfaces when it collapses. Under these conditions, very reactive chemical species are produced, with a very short lifetime, thus facilitating synthesis of quinoline-4-carboxylic acids (3a–3l) in shorter time.

Energy efficiency has been calculated and compared using CTAOH in the conventional (NUS) and ultrasound (US) methods. Method for energy calculation have been reported by Singh et al.[26] (see Supporting Information) shows the calculation of the energy of the two methods: conventional (NUS) and ultrasound (US) method used for the synthesis of quinoline-4-carboxylic acid derivatives. The energy utilized for the synthesis is the total energy supplied (kJ) per unit weight of the material processed/obtained (g). The time required for the synthesis of compound **3a** is 10 hr for the NUS method and 2.5 hr for the US method. Total energy required per unit weight of the material processed to synthesize compound **3a** is 17.76 kJ/g for the NUS method and 3.79 kJ/g for the US method. It was observed that the US method saved more than 78 % energy as compared to the NUS method.

The mechanism of CTAOH catalysed formation of 2-substituted quinoline-4-carboxylic acids can be explained on the basis of mechanism reported in the literature[19] (Scheme 2). The isatin 1 is converted by the action of CTAOH into the salt of isatoic acid 2, which condense with ketone 3 with the release of water. The latter undergo cyclization through the CO and CH_2 groups and are converted into the salt of quinolone-4-carboxylic acid, which further gives corresponding product 5. Most micellar catalyzed reactions are supposed to occur in the Stern layer[27] (Fig. 4). Micelles can attract an organic substrate by means of both electrostatic and hydrophobic interactions.



Scheme 2 Plausible mechanism for CTAOH catalysed Pfitzinger reaction

The recyclability of CTAOH was investigated in the synthesis of compound 3a from the reaction of isatin and acetophenone. After separation of the product, the aqueous layer containing the CTAOH was reused in the next run without further purification. Same reaction of isatin and acetophenone was carried out in spent aqueous layer under the same reaction conditions. The yield was found to be decreased by 10 % by the

fourth recycle (Fig. 5(A)). This decrease in the yield may be due to loss of catalytic aqueous system during work up procedure. To obtain constant yield in every cycle we thought of topping up catalyst to overcome this loss during work up procedure. We carried out various reactions with spent aqueous media of previous reaction by adding additional 2-10% of catalyst. It was found that addition of 10% of catalyst in every recycle of catalytic aqueous system gives yield of the product equivalent to the fresh catalytic system.

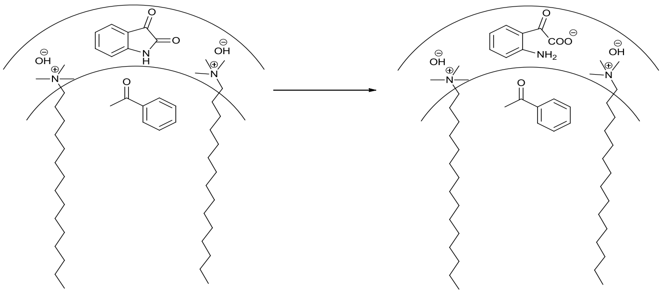


Fig. 4 Micellar catalyzed reaction at stern layer

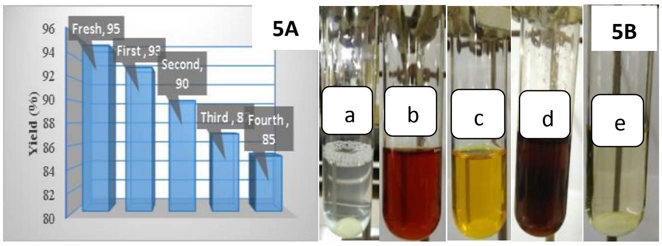


Fig. 5 (A) Bar graph showing recyclability of CTAOH aqueous solution. **(B)** Aqueous CTAOH solution (a) before addition of reactants, (b) after addition of isatin, (c) after addition of acetophenone, (d) after reaction, (e) spent aqueous CTAOH solution after separation of product.

Conclusions

In conclusion, we have explored catalytic activity of CTAOH for the Pfitzinger reaction of 2-substituted quinoline-4-carboxylic acid synthesis. CTAOH being surfactant in nature increases solubility of reactants in water by entrapping substrate molecules in to the micelles. Ultrasonic irradiation was found to reduce reaction time, temperature and make this method energy efficient when compared with conventional thermal method. Synergistic effects of both CTAOH and ultrasound make this method green with silent features including operational simplicity, use of water as a solvent, improved reaction rates, high yields of products and avoidance of the use of hazardous acids or bases.

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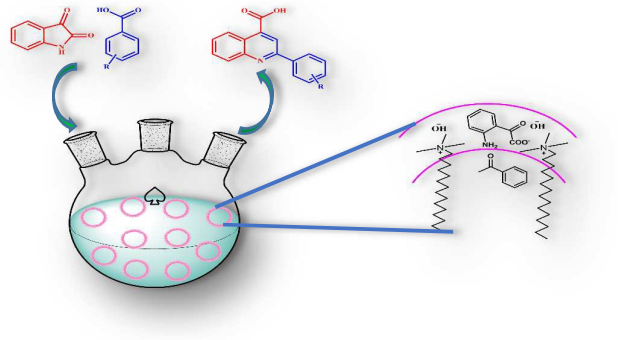
Graphical Abstract



A novel ultrasound assisted synthesis rout for quinolone-4carboxylic acid catalysed by surfactant.