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IONIC LIQUID ASSISTED FRIEDLANDER SYNTHESIS OF QUINOLINE DERIVATIVES

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Abstract

The synthesis of protic ionic liquid tris-(2-hydroxy-ethyl)-ammonium formate (TEAOHF) was synthesized by known synthetic procedures. TEAOHF was characterized by spectroscopic data, thermogravimetric studies and temperature dependent of conductivities. The synthesized ionic liquid TEAOHF was used as catalyst in the synthesis of quinoline derivatives under solvent free condition at moderate 70 °C temperature. The present catalytic system has advantages of having neat reaction conditions, simple procedure, easy workup, excellent yields, high reaction rate and eco-friendly to nature.

Keywords: Protic ionic liquid, Quinoline derivatives, Triethanolammonium salt, Friedlander synthesis, Solvent free conditions.

1. Introduction

Ionic liquids although not new to synthetic chemistry, the interest in the field of ionic liquids is a decade old. Ionic liquids are salts having melting point below 373 K. The application of ionic liquids in synthetic organic chemistry have gained much more importance owing to their properties which make it capable to be used as solvent or catalysts. These liquid-solids have properties such as minimum vapour pressure, robustness, non-flammable, high mechanical strength, ability to conduct and ability to excellent ability to dissolve organic / inorganic substrates [1–5]. Ionic liquids can be obtained by chemical interaction of Brönsted acid to the Brönsted base, thus by proton transfer reaction. The ionic liquids are often salts of organic and inorganic cationic or anionic species, therefore, their imperfect crystallisation avert them to have perfect crystal structure resulting low melting point [6].

Protic ionic liquids are generally N or P containing organic positive ions. The structural studies of N containing protic ionic liquids with various anions revels that proton H(N) associated with ammonium cation forms hydrogen bond with oxygen atom of hydroxyl group and forms intermolecular hydrogen bonding [7–12]. Enamours work is being done on protic ionic liquids in research community as they are cost effective and easy to prepare. Furthermore, such ionic liquids have biodegradable nature [13] as its decayed product is used by microorganisms and plants [14-15]. Theses PILs have several applications in biochemistry field such as the delignification of biomass [16-17], extraction processes [18], purification of bioactive chemicals by phase transfer mechanism [19-20] and in synthetic organic field [21]. PILs due to their thermal and electrochemical properties are used in proton exchange membrane (PEM) [22-23]. These protic molten salts also find applications in fuel cells. [24-25].

Quinolines are nitrogen containing heterocyclic compound having unambiguous role in the field of medicinal chemistry. Quinolines and its derivatives have tremendous applications in pharmaceutical industries such as anti-bacterial [26], anti-tubercular [27], anti-malarial [28], anti-HIV [29], anti-HCV [30], antitumor [31], anti-cancer [32] and many other biological activities [33].

Owing to its high demand many synthetic routs have been developed for synthesis of these class of compounds. While surveying through literature we found various methods for synthesis of quinolines by using catalysts such as phosphoric acid using microwave condition [34], palladium – carbon system [35], nanocrystalline sulfated zirconia [36], Iodine [37], Ionic liquids [38], and various transition metals [39]. However, all above methods requires special reaction setup, or use of expensive catalysts or solvent system, harsh reaction conditions and tedious reaction workup procedures which limit use of such protocols.

Studies of literature revels that various triethanolammonium salt have been explored for organic transformations, but triethanolammonium salt of formic acid have hardly been explored. Therefore, in view of abovesaid facts and in continuation of new methodologies for nitrogen containing bioactive heterocycles [38-40] in present work, we demonstrate solvent free Friedlander synthesis of quinoline derivatives by reaction of aromatic amino aldehydes with active methylene compounds by using eco-friendly protic tri-(2-hydroxyethyl)ammonium formate (TEAOHF) as ionic liquid.

2. Experimental section

2.1 *Methods and Material*

All solvents and chemicals were purchased from S. D. Fine chemicals and used as commercial anhydrous grade without further purification. For melting points determination open capillary tube technique was used, and are uncorrected. The progress of the reaction was monitored by thin layer chromatography. Column chromatography was performed with silica gel (80-120 mesh). 1H NMR and ^{13}C NMR were recorded on Avance-300 MHz spectrometer in $CDCl_3$ solvent and TMS as an internal standard. Mass spectra were obtained on Polaris Q Thermoscintific GC-MS. The FT-IR spectra of the compounds were recorded on a Schimandzu IR Tracer 100 device in the region of 4000–500 cm^{-1} using KBr pellets. Thermogravimetric measurement was obtained from TGA 50 series instrument. The sample placed into a platinum crucible was heated in argon flow at the rate of 10 K min^{-1}. The conductivity values were recorded on Equiptronic EQ 664.

2.2. *Synthesis of protic ionic liquid triethanolammonium salt of formic acid (TEAOHF)*

The PILs were prepared by known synthetic pathways [41-43]. The ionic liquid triethanolammonium salt of formic acid (TEAOHF) was obtained by direct neutralization of equimolar quantities of triethanolamine with formic acid. A round bottom flask containing 10 mmol of tris(2-hydroxyethyl)amine was kept in ice bath to expel out heat of neutralisation. In to the flask 10 mmol of formic acid was added dropwise over a period of 20 min. After ensuring proper mixing of two, it was stirred at elevated temperature 60 °C for 10 hours in an inert argon atmosphere. The obtained ionic liquid was dehydrated using rotavapor, followed by drying under high vacuum at 100 °C to collect colourless viscous protic ionic liquid as triethanolammonium salt of formic acid (TEAOHF).

2.3. *General procedure for synthesis of quinoline derivatives 3 (a-l).*

The quinoline derivatives were prepared by mixing 2-aminoarylbenzophenone (1 mmol) and active methylene dicarbonyl compound (1 mmol) in presence of 12 mole % of protic ionic liquid tris-(2-hydroxy-ethyl)-ammonium formate (TEAOHF) under solvent free conditions. The reaction mixture was stirred at room temperature initially followed by stirring at 70 °C using oil bath. The reaction progress was monitored by TLC. After completion of reaction as indicated by TLC, reaction mixture was cooled to room temperature and ice-cold water was added to it. The reaction mixture was extracted in dichloromethane. The organic product was collected in organic layer and ionic liquid in aqueous phase. The separated organic layer was dried over sodium sulphate under reduced pressure. The crude product was purified further by coloumn chromatography using silica gel and ether /EtOAc (9 : 1, v/v) solvent system. The purified product was then characterised using melting point and spectroscopic data.

2.4. *Characterisation data*

2.4.1. *Tris-(2-hydroxy-ethyl)-ammonium formate* (**TEAOHF**): Yield 78 %, M.p. 68 °C. FTIR(KBr) υ(cm^{-1}): 3350, 3080, 2910, 2800, 2640, 1790, 1510, 1350, 1090; 1H NMR (300 MHz, $CDCl_3$):δ 10.11 (*s*, 1H, formate ion), 7.28 (*s*, 1H, NH), 5.16 (*s*, 1H, OH), 3.37 (*m*, 2H, OCH_2), 2.71 (*m*, 2H, OCH_2); 13C NMR (75 MHz, $CDCl_3$):δ 188.2, 60.8, 59.4.

2.4.2 *1-(2,6-Dimethyl-4-phenyl-quinolin-3-yl)-ethanone* (**3a**): Yield 94 %, M.P. 117 °C. 1H NMR (300 MHz, $CDCl_3$):δ 7.65 – 7.80 (*m*, 2H, ArH), 7.49 – 7.62 (*m*, 2H, ArH), 7.30-7.32 (*m*, 1H, ArH), 7.15 – 7.24 (*m*, 2H, ArH), 7.06 – 7.13 (*m*, 2H, ArH) 2.76 (*s*, 3H, $COCH_3$), 2.70 (*s*, 3H, $NCCH_3$), 1.79 (*s*, 3H, $ArCH_3$); 13C NMR (75 MHz, $CDCl_3$):δ 201.1, 158.3, 151.0, 146.7, 139.6, 135.4,

134.8, 133.1, 131.7, 129.8, 128.2, 127.9, 125.5, 25.0, 23.8, 15.7. ESI-MS: *m/z* 276.238 [M+H]; Anal. Calcd. for $C_{19}H_{17}NO$: C, 75.89; H, 7.07; N, 5.32%; Found: C, 75.78; H, 7.13; N, 5.24 %.

2.4.3. *1-(6-Chloro-2-methyl-4-phenyl-quinolin-3-yl)-ethanone* (**3b**): Yield 91%, M.P. 152 °C. The compound **3b** was confirmed by comparing melting with those reported in literature [44 – 45].

2.4.4. *1-(2-Methyl-4-phenyl-quinolin-3-yl)-ethanone* (**3c**): Yield 89 %, M.P. 112 °C. The compound **3c** was confirmed by comparing melting with those reported in literature [44 – 45].

2.4.5. *1-(2-Methyl-6-nitro-4-phenyl-quinolin-3-yl)-ethanone* (**3d**): Yield 84 %, M.P. 162 °C. 1H NMR (300 MHz, $CDCl_3$):δ 8.09 – 8.30 (*m*, 4H, ArH), 7.02 – 7.29 (*m*, 5H, ArH), 2.71 (*s*, 3H, $COCH_3$), 2.65 (*s*, 3H, $NCCH_3$); 13C NMR (75 MHz, $CDCl_3$):δ 200.8, 161.6, 149.5, 148.1, 145.0, 136.4, 134.9, 134.1, 132.5, 131.8, 130.4, 129.7, 129.0, 128.6, 22.1, 13.5. ESI-MS: *m/z* 307.319 [M+H]; Anal. Calcd. for $C_{18}H_{14}N_2O_3$: C, 70.58; H, 4.61; N, 9.15 %; Found: C, 70.61; H, 4.59; N, 9.13 %.

2.4.6. *2,6-Dimethyl-4-phenyl-quinoline-3-carboxylic acid methyl ester* (**3e**): Yield 95 %. M.P. 123 °C. 1H NMR (300 MHz, $CDCl_3$):δ 7.79 – 8.86 (*m*, 2H, ArH), 7.65 – 7.71 (*m*, 2H, ArH), 7.35 – 7.45 (*m*, 2H, ArH), 7.15 – 7.24 (*m*, 3H, ArH), 3.96 (*s*, 3H, OCH_3), 2.75 (*s*, 3H, $NCCH_3$), 1.85 (*s*, 3H, $ArCH_3$); ESI-MS: *m/z* 292.114 [M+H]; Anal. Calcd. for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81 %; Found: C, 78.31; H, 5.91; N, 4.78 %.

2.4.7 *6-Chloro-2-methyl-4-phenyl-quinoline-3-carboxylic acid methyl ester* (**3f**): Yield 87 %, M.P. 132 °C. The compound **3f** was confirmed by comparing melting with those reported in literature [44 – 45].

2.4.8 *2-Methyl-4-phenyl-quinoline-3-carboxylic acid methyl ester* (**3g**): Yield 90 %, M.P. 105 °C. The compound **3g** was confirmed by comparing melting with those reported in literature [44 – 45].

2.4.9 *2-Methyl-6-nitro-4-phenyl-quinoline-3-carboxylic acid methyl ester* (**3h**): Yield 85 %. M.P. 147 °C. 1H NMR (300 MHz, $CDCl_3$):δ 8.88 – 8.99 (*m*, 2H, ArH), 7.68 – 7.79 (*m*, 2H, ArH), 7.41 – 7.61 (*m*, 5H, ArH), 3.95 (*s*, 3H, OCH_3), 2.55 (*s*, 3H, $NCCH_3$); ESI-MS: *m/z* 322.328 [M+H]; Anal. Calcd. for $C_{18}H_{14}N_2O_4$: C, 67.07; H, 4.38; N, 8.69 %; Found: C, 67.05; H, 4.41; N, 8.68 %.

2.4.10. *2,6-Dimethyl-4-phenyl-quinoline-3-carboxylic acid ethyl ester* (**3i**): Yield 89 %. M.P. 119 °C. 1H NMR (300 MHz, $CDCl_3$):δ 8.86 – 8.91 (*m*, 2H, ArH), 7.81 – 7.85 (*m*, 2H, ArH), 7.21 – 7.49 (*m*, 5H, ArH), 3.90 – 3.94 (*m*, 2H, OCH_2), 2.54 (*s*, 3H, $NCCH_3$), 1.16 – 1.19 (*t*, 3H, CH_3); ESI-MS: *m/z* 306.247 [M+H]; Anal. Calcd. for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59 %; Found: C, 78.68; H, 6.25; N, 4.62 %.

2.4.11. *6-Chloro-2-methyl-4-phenyl-quinoline-3-carboxylic acid ethyl ester* (**3j**): Yield 87 %, M.P. 107 °C. The compound **3j** was confirmed by comparing melting with those reported in literature [44 – 45].

2.4.12. *2-Methyl-4-phenyl-quinoline-3-carboxylic acid ethyl ester* (**3k**): Yield 88 %, M.P. 100 °C. The compound **3k** was confirmed by comparing melting with those reported in literature [44 – 45].

2.4.13. *2-Methyl-6-nitro-4-phenyl-quinoline-3-carboxylic acid ethyl ester* (**3l**): Yield 83 %. M.P. 138 °C. 1H NMR (300 MHz, $CDCl_3$):δ 8.80 – 8.90 (*m*, 4H, ArH), 7.01 – 7.18 (*m*, 5H, ArH), 3.91 – 3.98 (*m*, 2H, OCH_2), 2.54 (*s*, 3H, $NCCH_3$), 1.18 – 1.19 (*t*, 3H, CH_3); ESI-MS: *m/z* 337.331 [M+H]; Anal. Calcd. for $C_{19}H_{16}N_2O_4$: C, 67.85; H, 4.79; N, 8.33 %; Found: C, 67.88; H, 4.77; N, 8.35 %.

3. Result and discussion.

The protic ionic liquid, tri-(2-hydroxyethyl)ammonium formate (TEAOHF) has been synthesized from known literature pathways [38-40]. The formation of ionic liquid TEAOHF has been confirmed from spectroscopic data and other techniques. It is found that spectroscopic studies, TGA and electrical conductivity of TEAOHF is well in agreement with those documented earlier.

3.1. NMR spectroscopy

The proton NMR spectra were recorded on a Bruker Avance-500 spectrometer in $CDCl_3$ solvent (Figure **1**). 1H NMR spectra of TEAOHF shows multiplates at 2.71 ppm and 3.37 ppm which are obtained due to NCH_2 and OCH_2 respectively. A singlet at 5.16 ppm confirms the presence of OH proton from triethanolamine moiety. Another broad singlet at 7.28 ppm is due to presence of NH proton which confirms the transfer of proton from formic acid. A signal for single proton from formate ion gives a sharp signal at 10.11 ppm. (presence of single proton can be assured from the signal intensity of ionic liquid with that of formic acid in figure **1** [43].

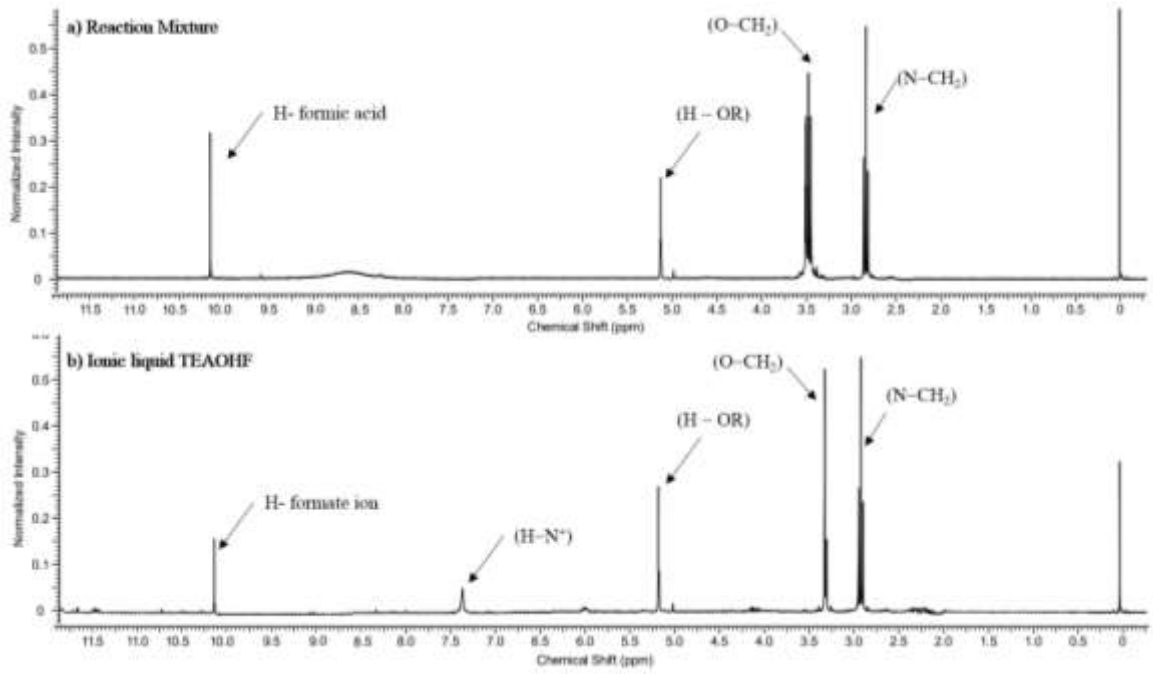


Figure 1. 1H NMR spectra for **a**) reaction mixture; **b**) ionic liquid TEAOHF

3.2. FTIR-Spectra

Further, we have recorded and studied IR spectra for synthesized ionic liquid as shown figure **2**. In the IR spectra a broad spectrum is obtained for vibration band at 3350 cm^{-1} for hydroxyl group (-OH) of ionic salt. Another vibration band at 3080 cm^{-1} indicate presence of protonated ammonium ion (N^+-H). Number of small peaks obtained in the range 2640-2910 cm^{-1} are due to hydrogen bonding interaction between oxygen and hydrogen from quaternary nitrogen, which confirms protonation of amine.

Figure 2. FTIR spectrum of TEAOHF

A broad vibration band obtained at 1750 cm^{-1} is credited to presence of carbon – oxygen bond from formate ion. Signals appeared at 1350 and 1510 cm^{-1} are due to deformation vibrations of alkyl groups [N-$(CH_2)_2$-OH] of TEAOHF. The indication of C-N stretching vibrations can be seen at 1090 cm^{-1}. [46]

3.3 Thermogravimetric analysis

Thermogram as indicated in figure **3**, gives thermal properties associated with ionic liquid TEAOHF. As can be seen from plot of weight loss against temperature, initial loss up to 110 -130 °C is due to loss of water and unreacted formic acid and other solvents. No weight loss is observed up to 230 °C which show that ionic liquid is thermally stable and can be operated up to 230 °C. Decomposition of ionic liquid started around 230 °C, which showed decomposition temperature of synthesised ionic liquid (literature 233 °C) [42]. A

sharp decrease in the region between 230 °C to 360 °C can be assumed because of decomposition of acidic fractions of the ionic liquid. A break appears in weight loss at 360 °C which is attributed to the departure of amino alkyl chain present in ionic liquid within the structure of the ionic liquid B. No weight loss was observed after 510 °C as complete decomposition occurred.

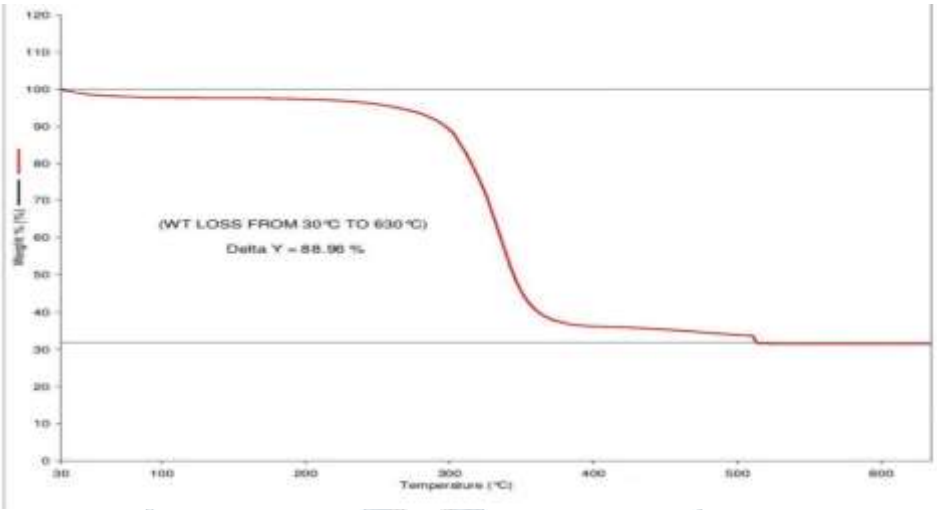


Figure 3. Thermogrametric curve for TEAOHF

3.4 Electrical conductivity of TEAOHF

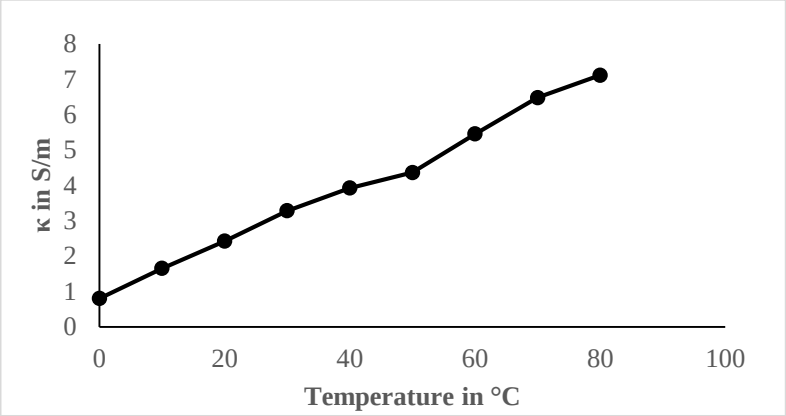
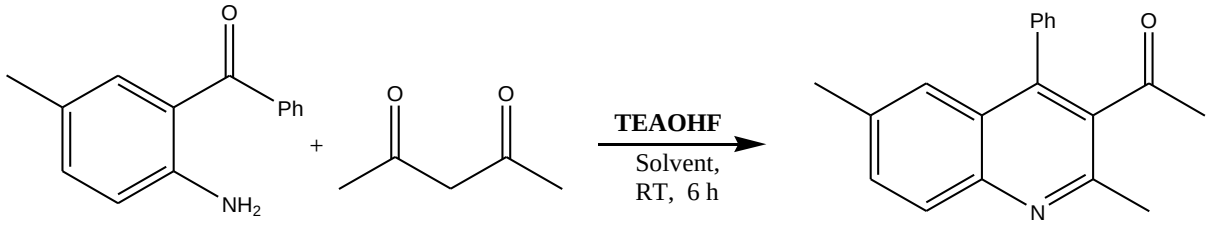


Figure 4. Variation of electrical conductivities of TEAOHF with temperature

Figure **4**, gives relation between conductivity and temperature. Conductivity of the liquid, at 30 °C is 2.42 Sm^{-1} which is satisfactorily high. The ionic conductivity increases with temperature, as the temperature increases. The maximum temperature studied in present work is 80 °C and corresponding value is 6.48 Sm^{-1}. The increased conductivity with increased temperature is due to increase in kinetic energy of ions resulting in fast movements of ion [47].

3.5 Catalytic evaluation.

The catalytic activity of ionic liquid TEAOHF was evaluated in the reaction between (2-Amino-5-methyl-phenyl)-phenyl-methanone (**1a**) and acetyl acetone (**2a**) (Scheme **1**). The reaction was studied using various solvents and various catalytic lodgings of TEAOHF. The reaction time for all reaction was 6 hours irrespective of reaction parameters. The results obtained are collected in Table **1**.



1a **2a** **3a**

Scheme 1: The Friedlander synthesis of 1-(2,6-Dimethyl-4-phenyl-quinolin-3-yl)-ethanone **3a**.

Initially, the reaction was screened with various catalytic loadings of TEAOHF at room temperature using ethanol solvent. At lower catalytic loading of 5 mole %, reaction yielded very low 38 % product **3a** (Table **1**, entry 1). When catalytic loading was increased to 10 mole %, improved 67 % yield was observed for desired product **3a** (Table **1**, entry 2). At 12 mole % catalytic loading reaction gave 71 % of **3a** (Table **1**, entry 3). Further increase in catalytic loading (15 mole%) did not show much influence on yield (73%) of product (Table **1**, entry 4). Thus, 12 mole % was chosen to be suitable catalyst loading for the reaction and perused further studies with same 12 mole % catalyst loading. Next, we performed reaction in aqueous medium in order to replace ethanol with green solvent. The reaction in water proved to be disastrous and failed to give product in good yield (Table **1**, entry 5). It was believed that these unfavourable resulted because of insolubility of reacting substrate in solvent medium. In the pursuit of greater yield aprotic polar solvent acetonitrile was used Which furnished 69 % yield for the reaction product (Table **1**, entry 6). Results led us to conclusion that protic solvents have no effect on performance of reaction in terms of yield. Thus, taking account of solubility nature of reacting species, reaction was studied with non-polar solvents dichloromethane and chloroform. These solvents were not helpful to draw higher yields of product **3a**. The reaction afforded 43 % and 51 % yield for **3a** in dichloromethane and chloroform solvents respectively (Table **1**, entries 7 and 8). The reaction was also studied in absence of solvent. To our surprise, the reaction under solvent free conditions produced higher 81 % yield for desired product **3a** (Table **1**, entry 9).

Table 1. Effect of catalyst loadings and various solvents on synthesis of **3a**.[a]

Entry	Catalytic loadings Mole %	Solvents	Yield [b] in %
1	5	Ethanol	38
2	10	Ethanol	67
3	12	Ethanol	71
4	15	Ethanol	73
5	12	Water	41
6	12	Acetonitrile	69
7	12	Dichloromethane	43
8	12	Chloroform	51
9	12	Solvent free	81

[a] = Reaction conditions: (2-Amino-5-methyl-phenyl)-phenyl-methanone (**1a**) (1mmol), acetyl acetone (1mmol) (**2a**), RT, 6 hrs stirring.
[b] = Isolated yields.

Although, delighted from above result our aim was to achieve more yield for product, we further experimented on effect of temperature on the reaction. Figure **5**, shows effect of temperature on the yield of product **3a**. It can be seen from the plot of temperature and product yield as temperature increases yield of product also increases. When temperature is elevated up to 70 °C, best results are obtained. The increasing yield with temperature may be due to melting point (68 °C) of TEAOHF. As further temperature increase did not increase yield of product for product **3a**.

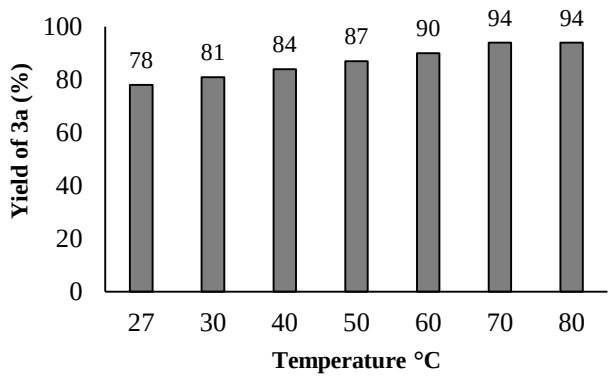


Figure 5. Effect of temperature on yield of the product **3a**.

Having achieved best reaction conditions, the reaction was monitored with respect to time to find out time required for completion under obtained optimized conditions. The reaction was monitored by using thin layer chromatographic method in laboratory conditions. As depicted in Figure **6**, yield of product **3a** increase up to 94 % at 90 min and show constant nature after it.

The above reaction conditions were exploited using various 2-aminoaryl ketones with active methylene compounds to get quinoline derivatives **3** (**a-l**). The results are gathered in Table **2**. All reactions under solvent free conditions using catalyst protic ionic liquid TEAOHF performed exceptionally well to produce high yields for all products. It can be pointed from Table **2**, Reaction favoured aromatic compounds with electron donating effect than electron withdrawing substituent on aromatic ring. The effect of negative inductive effect lowered the rate of reaction with comparatively low yields for corresponding products.

Table 2. The synthesis of quinoline derivatives.[a]

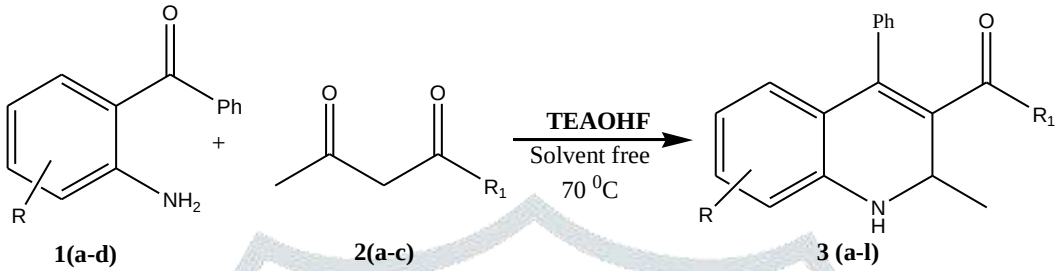


Figure 6. Variation of yield of 3a with respect to time.

Entry	R	R1	Product	Time (min)	Yield (%)
1	5-CH_3	Me	3a	90	94
2	5-Cl	Me	3b	120	91
3	H	Me	3c	110	89
4	5-NO_2	Me	3d	150	84
5	5-CH_3	OCH_3	3e	70	95
6	5-Cl	OCH_3	3f	80	87
7	H	OCH_3	3g	80	90
8	5-NO_2	OCH_3	3h	120	85
9	5-CH_3	OC_2H_5	3i	60	89
10	5-Cl	OC_2H_5	3j	90	87
11	H	OC_2H_5	3k	80	88
12	5-NO_2	OC_2H_5	3l	120	83

[a] = Reaction conditions: (2-Amino-aryl)-phenyl-ketone (1mmole), α-methylene carbonyl compound (1mmole), 12 mole % protic ionic liquid TEAOHF, stirring at 70 °C. [b] = Isolated yields.

Based on obtained results and literature [48], the probable route for the Friedlander synthesis of quinoline derivatives using TEAOHF is given in Figure **7**. The protic nature of TEAOHF activate α-carbonyl compound to generate nucleophile followed by attach on electron deficient carbonyl carbon, which is formed due to aryl ketone and ionic liquid interaction. This reaction between nucleophile and electrophile gives intermediate III. The intermediate III undergo cyclization and intramolecular transformation to give desired quinoline product.

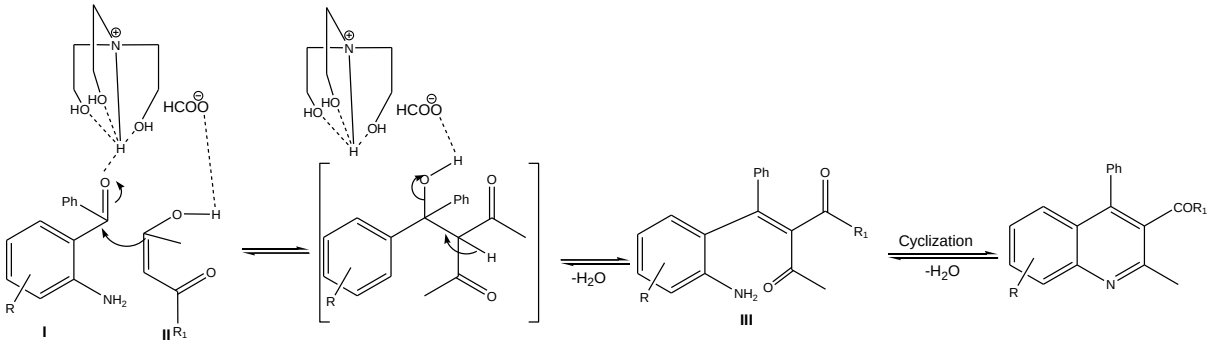


Figure 7. Plausible mechanism for reaction.

4. Conclusion:

In summary, we have synthesized protic ionic liquid tris-(2-hydroxy-ethyl)-ammonium formate (TEAOHF) and characterised by 1H NMR, FTIR, Thermogravimetric method and electronic conductivity. The synthesized ionic liquid was well in agreement with literature data. The catalytic ability of ionic liquid TEAOHF was also evaluated in the Friedlander synthesis of quinoline derivatives. The reaction performed well under solvent free condition at 70 °C temperature affording excellent yields for desired products. The present catalytic system has advantages of having neat reaction conditions, simple procedure, easy workup, excellent yields, high reaction rate and eco-friendly to nature.

Acknowledgments:

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Supplementary Information (SI)

Detailed procedures and spectral data of synthesized compounds is submitted in supplementary data file.

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