



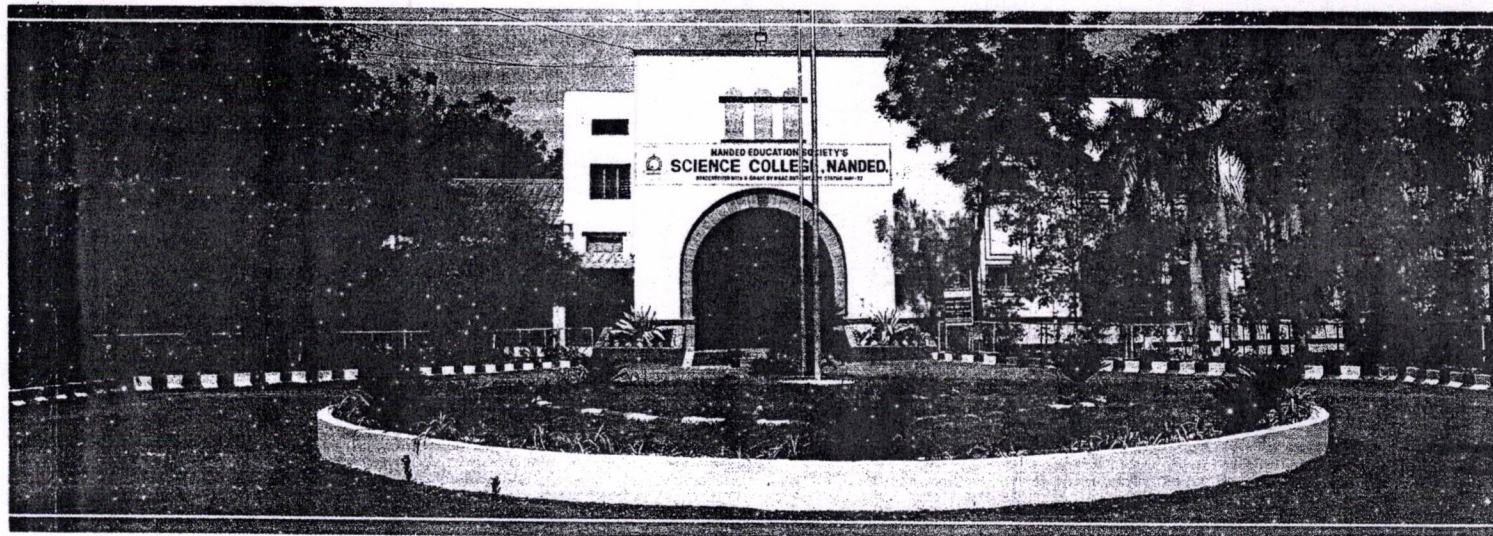
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Environmentally benign Ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate an efficient reaction medium for the one pot synthesis of 2,3-dihydro-2-(2-hydroxyphenyl) quinoline-4(1H)-one

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Abstract:

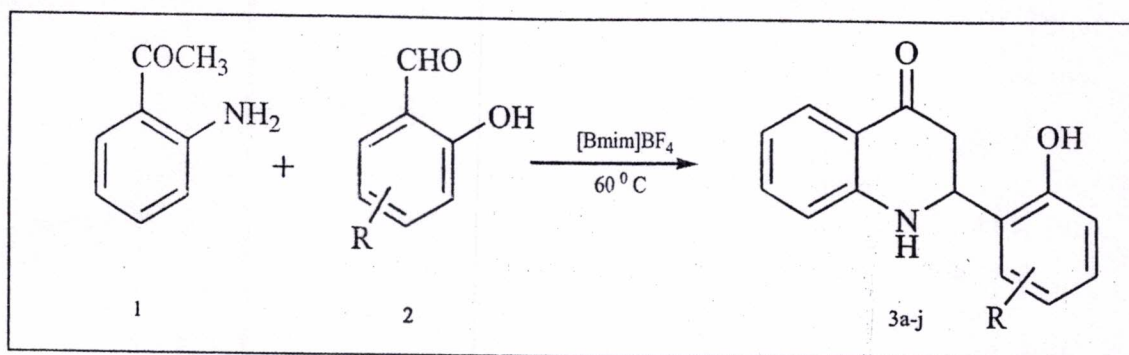
2,3-dihydro-2-(2-hydroxyphenyl)quinolin-4(1H)-one and its derivatives were synthesized via two component one pot reaction of substituted salicylaldehydes, 2-amino acetophenone in presence of 1-butyl-3-methylimidazolium tetrafluoroborate afford the corresponding quinolones derivatives. This method has the advantage of short reaction time, the mild reaction conditions, high yield of product, environmentally-friendly, reusability of the ionic liquids and easy work-up.

Keywords: Quinolones derivatives, one pot synthesis, Solvent Free, [Bmim]BF₄.

INTRODUCTION:

The Mannich reaction is one of the most important carbon-carbon bond and carbon-nitrogen bond forming reactions for the synthesis of optically active nitrogen-containing molecules.¹⁻² In recent years, environmentally-friendly reaction processes have vigorously been considered from the point of view of green chemistry. For example reaction in aqueous media, oxidation reaction with the air etc. Most recently, ionic liquids have attracted as green catalyst for organic synthesis. Among the other ionic liquids based on 1-alkyl-3-methyl imidazolium salts, have drawn significant attention as an efficient and environmentally-friendly reaction media and have found huge application in various organic transformations such as Heck reaction³, Hydrogenation⁴, Bishler-Napieralski reaction⁵, Friedel-Craft reaction⁶, Allylation reaction⁷ etc. [Bmim]BF₄ shows tremendous application in various organic transformation.⁸⁻¹¹ 1-butyl-3-methylimidazolium tetrafluoroborate shows good thermal and electrochemical stability due to weak electrostatic interaction of tetrafluoroborate with the imidazolium cation. 1-butyl-3-methylimidazolium tetrafluoroborate are commercially available & the physicochemical properties like mild and neutral nature, lack of inflammability, low volatility, excellent solubility with many organic compound and environmentally-friendly make this ionic liquid superior than the other.¹²

2,3-dihydro-2-(2-hydroxyphenyl)quinolin-4(1H)-one, which can be considered as aza-analogues of flavanones, have demonstrated a wide range of biological activities and pharmaceutical properties as anticancer and antibiotic agents¹³⁻¹⁴. Conventionally, this reaction was catalyzed by organocatalysts.^{15,16} Other types of organocatalysts such as chiral Brønsted acids,¹⁷ cinchona alkaloids,¹⁸ or phase-transfer catalysts¹⁹ However, some of the reported methods suffered from number of drawback like prolonged reaction time, reagents in stoichiometric amounts, low yield, toxic solvents, and expensive catalysts. Consequently there is scope for further innovation towards shorter reaction time, milder reaction condition, to get high yield of product which is achieved by using 1-butyl-3-methylimidazolium tetrafluoroborate as a reaction media. So we describe herein new synthetic methods by using ionic liquids as reaction media for versatile, simple and environmentally-friendly synthesis of quinolones derivatives (**Scheme 01**).



Scheme 01: Synthesis of quinolones derivatives by using $[\text{Bmim}]\text{BF}_4$ as a reaction medium.

EXPERIMENTAL

Material and Methods:

All chemical were purchased from sigma-aldrich and solvents were used without further purification. Melting point were determined in open capillary tube and are uncorrected. TLC was performed with E. Merck silica gel 60F glass plates. Column chromatography was performed on silica gel (90-140 mesh). $^1\text{H-NMR}$ spectra were recorded on advance 300 MHz spectrometer in CDCl_3 using TMS as an internal standard. Mass spectra were recorded on Polaris Q thermoscientific GC-MS. All products were characterized by comparison of their spectroscopic data ($^1\text{H NMR}$, IR) and physical properties with those reported in the literature. Yields refer to isolated pure products.

General procedure for the synthesis of Quinolones derivatives:

The ionic liquid $[\text{Bmim}]\text{BF}_4$ (1-butyl-3-methylimidazolium tetrafluoroborate) (2 ml) was added to a mixture of substituted salicylaldehyde (1.5 mmol) and 2-amino acetophenone (1 mmol). This reaction mixture was heated at 60°C for the appropriate time as mentioned in **Table 1**. After the completion of the reaction monitored by TLC, the reaction mixture was cooled at room temperature, thereafter this reaction mixture was poured on 30 ml of ice cold water. This reaction mixture was

stirred for 15 minutes in order to dissolve ionic liquid. The resulting solid was filtered, washed with cold water and recrystallized in ethyl alcohol. Then the aqueous layer was distilled at 80 °C under vacuum to eliminate water, leaving behind ionic liquid was dried under reduced pressure and reuse successively. The crude product was purified by column chromatography to give the corresponding compounds 3a-3j, the product were characterized by ¹H-NMR, C¹³ NMR, and IR.

The spectral and analytical data for the known compounds are as follows:

1) 2-(2-Hydroxyphenyl)-2,3-dihydroquinolin-4(1H)-one 3a

IR (KBr disk) ν : 3539, 3310, 1606, 1538, 1389, 1243, 1095, 768 cm⁻¹

¹H NMR (400 MHz, CDCl₃) δ 7.93–7.95 (m, 1H), 7.76 (s, 1H), 7.40–7.44 (m, 1H), 7.16–7.24 (m, 1H), 6.90–6.95 (m, 1H), 6.83–6.88 (m, 4H), 4.87–4.92 (m, 1H), 4.72 (s, 1H), 3.06–3.13 (m, 1H), 2.82–2.86 (m, 1H);

¹³C NMR (100 MHz, CDCl₃) δ 193.6, 155.3, 150.6, 135.5, 129.9, 128.0, 127.8, 124.8, 120.7, 120.6, 120.5, 117.4, 117.3, 57.6, 43.6.

2) 2-(4-Hydroxyphenyl)-2,3-dihydroquinolin-4(1H)-one 3b

IR (KBr disk) ν : 3548, 3067, 1653, 1527, 1498, 1267, 1103, 957, 898, 768 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) δ 7.94–7.96 (m, 1H), 7.22–7.26 (m, 3H), 6.77–6.80 (m, 4H), 5.16–5.21 (m, 1H), 4.64 (br s, 2H), 3.03 (dd, J = 15.4, 5.6 Hz, 1H), 2.81–2.84 (m, 1H);

¹³C NMR (100 MHz, CDCl₃) δ 192.4, 156.5, 149.6, 135.6, 131.0, 127.9, 127.1, 123.3, 117.9, 117.1, 116.1, 55.5, 42.6.

RESULT AND DISCUSSION:

An environmentally benign protocol was used for the synthesis of Quinolones derivatives via two component process from the reaction of substituted salicylaldehyde and 2-amino acetophenone in 1-butyl-3-methylimidazolium tetrafluoroborate which act as an eco-friendly green medium.

To take away the drawback like toxicity and volatility which exist in various organic solvent, the ionic liquid was employed in this reaction as a green solvent medium. Firstly a model reaction was carried out using 2-amino acetophenone (1) and salicylaldehyde (2) in different solvent including 1-butyl-3-methylimidazolium tetrafluoroborate. However the effect of reaction temperature and solvent were evaluated from the model reaction and results are summarized in **Table 1**.

From the duration of optimization of reaction condition, it was observed that the solvent like ethanol, methanol, acetonitrile, acetone acetic acid were used and their effect was only moderate (**Table 1, entry 1-5**). On the other hand when ionic liquid [Bmim]BF₄ were used, it was observed that the shorter reaction time and better yield compare to those of conventional solvents. The yield of product 3a was enhanced and the reaction time was minimized from room temperature to 60 °c, there is no further development in the product yield was observed, when temperature was increased to 80 °c (**Table 1, entry 6-9**). As a result 60 °c was selected as an optimum reaction temperature for all reactions.

Table 01 : Optiization of reaction condition for the synthesis of 3a

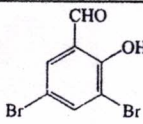
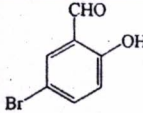
^a Entries	Solvents	Temperature (°C)	Time	^b Yields (%)
1	Ethanol	60	24 Hrs	72
2	Methanol	60	22 Hrs	65
3	Acetone	60	23 Hrs	52
4	Acetonitrile	60	20 Hrs	60
5	Acetic acid	60	22 Hrs	68
6	[Bmim]BF ₄	60	12 Hrs	94
7	[Bmim]BF ₄	80	12 Hrs	94
8	[Bmim]BF ₄	40	14 Hrs	78
9	[Bmim]BF ₄	R.T.	18 Hrs	61

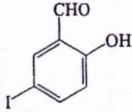
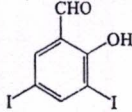
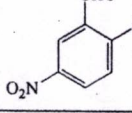
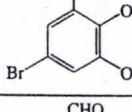
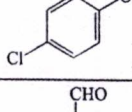
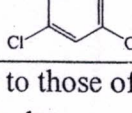
^aReaction condition: 2-Amino Acetophenone (1mmol), salicylaldehyde (1.5mmol), [Bmim]BF₄ (2 ml). ^bYields of the isolated products

Again from the duration of optimization of reaction condition, it was observed that the various substituted salicylaldehyde and 2-amino acetophenone were reacted to each other. All the reactions carry on well with wide range of substituted salicylaldehyde gives excellent yields of corresponding products (Table 2, entry 1-10).

Simplicity of recycling is a useful feature of ionic liquids. For the reaction of 2-amino acetophenone and salicylaldehyde (model reaction), no significant loss of the product yield was observed when [Bmim]BF₄ was reused, even after four times recycling (see Figure 1).

Table 02: Synthesis of Quinolones derivatives by using [Bmim]BF₄ as a reaction medium.

Entry	Salicylaldehydes	2-Amino Acetophenone	Products	Time (Hr)	^a Yield (%)
1	o-OHC ₆ H ₄ -	2-Amino Acetophenone	3a	12	90
2	p-OHC ₆ H ₄ -	2-Amino Acetophenone	3b	12.30	88
3		2-Amino Acetophenone	3c	12.40	84
4		2-Amino Acetophenone	3d	13.15	88

5		2-Amino Acetophenone	3e	13.00	84
6		2-Amino Acetophenone	3f	13.15	82
7		2-Amino Acetophenone	3g	13.30	83
8		2-Amino Acetophenone	3h	12.55	83
9		2-Amino Acetophenone	3i	13.10	86
10		2-Amino Acetophenone	3j	12.50	88

^aYields refer to those of pure isolated products characterized by IR, ¹H NMR, and ¹³C NMR spectroscopic data.

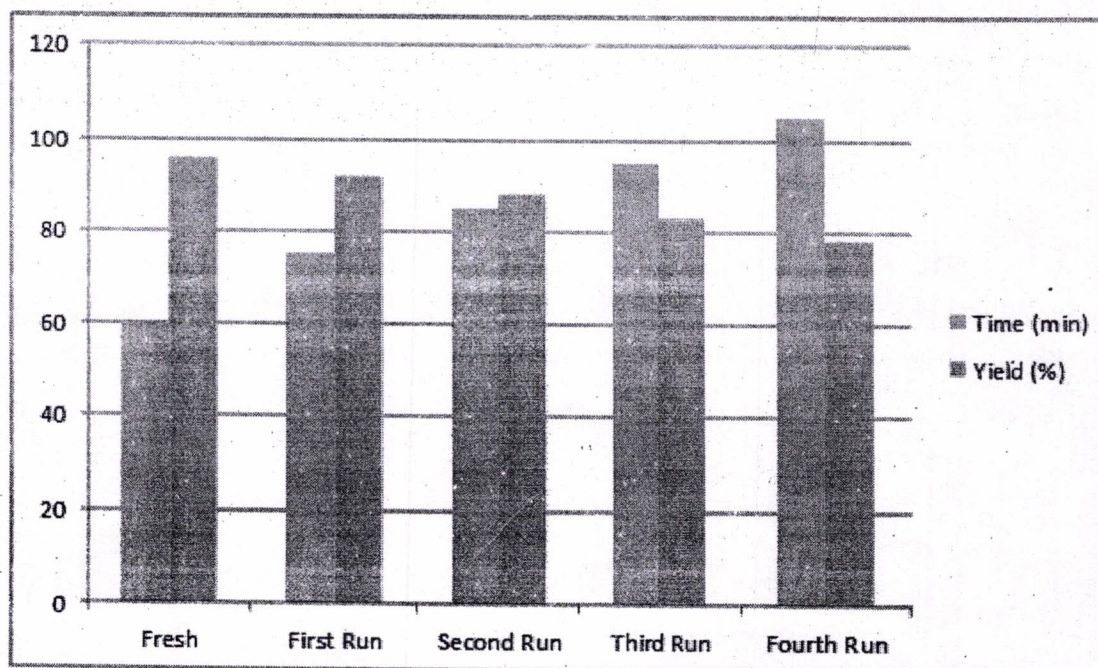


Figure 1 : Synthesis of 2,3-dihydro-2-(2-hydroxyphenyl)quinolin-4(1H)-one (Model reaction) derivatives by using recycled [Bmim]BF₄

CONCLUSION

In conclusion, we have developed a efficient and straightforward method for the preparation of Quinolones derivatives by one pot reaction of substituted salicylaldehyde and 2-Amino Acetophenone in presence of 1-butyl-3-methylimidazolium tetrafluoroborate. [Bmim]BF₄ as a reaction medium and are commercially available ionic liquid. In addition to this, high yields of the products, short reaction times, recyclability of the ionic liquid, catalyst-free nature of the reaction, easy work-up and clean procedure, will make this method an efficient and significant compare to the existing methodologies for the synthesis of Quinolones derivatives.

Acknowledgment:

The authors are grateful to the Principal, N.E.S. Science college Nanded for providing the research facilities and thankful to IICT Hyderabad for providing spectral data. Again we express our deep sense gratitude to respected Director, UGC (WRO), Pune for sanctioning Teacher Fellowship under faculty development programme, (F. No. 31-02/12 Dated 17 Nov. 2016).

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