# Environmentally Benign Ionic Liquid 1-Butyl-3-Methylimidazolium Tetrafluoroborate an Efficient Reaction Medium for the One Pot Synthesis of Quinazoline Derivatives

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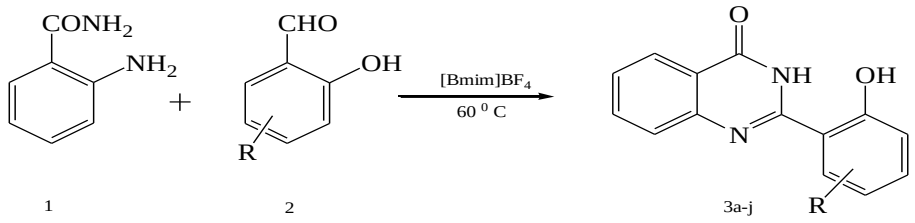
***Abstract:*** Quinazoline derivatives were synthesized via two component one pot reaction of substituted salicylaldehydes, o-amino benzamide in presence of 1-butyl-3-methylimidazolium tetrafluoroborate afford the corresponding quinazoline derivatives. This method has the advantage of short reaction time, the mild reaction conditions, high yield of product, environmentally-friendly, reusability of the ionic liquids and easy work-up. Here the need of catalyst is avoided through the use of catalytically active ionic liquid as a solvent.

**Keywords:** Quinazoline drivatives, one pot synthesis, Catalyst-free, [Bmim]$BF_4$.

## I. INTRODUCTION

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 reaction solvents 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 reaction[3], Hydrogenation[4], Bishler-Napieralski reaction[5], Friedel-Craft reaction[6] , Allylation reaction[7] etc. [Bmim]$BF_4$ 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 inflammablity, low volatility, excellent solubility with many organic compound and environmentally-friendly make this ionic liquid superior than the other.[12]

Quinazoline based derivatives represent an significant class of heterocyclic compounds which contain two nitrogen in their nucleus and being the main constituents of many naturally occurring products, and have been of interest in recent years due to their useful biological and pharmacological features [13]. They possesses a number of biological and therapeutic activities[14-22] such as anticancer, antiviral, antitubercular, anticonvulsant, anti-HIV, antioxidant, anti-inflammatory, antimicrobial, analgesic. Conventionally, this reaction was catalyzed by a acidic catalyst such as $InCl_3$ using acetonitrile as a reaction solvent[23]. Recently, there are number of procedures[24-27] reported in literature for the synthesis of these heterocycles using variety of catalysts and solvent. 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 quinazoline derivatives **(Scheme 01)**.




Scheme 01: Synthesis of quinazoline drivatives by using [Bmim]$BF_4$ as a reaction medium.

## II. EXPERIMENTAL

### 21. 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. Coloumn chromatography was performed on silica gel (90-140 mesh). $^1$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 ($^1$H NMR, IR) and physical properties with those reported in the literature. Yields refer to isolated pure products.

**2.2 General procedure for the synthesis of quinazoline derivatives**

The ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate [Bmim]$BF_4$ (2 ml) was added to a mixture of substituded salicylaldehyde (1 mmol) and o-amino benzamide (1 mmol). This reaction mxture was heated at 60 $^0$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 $^0$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 $^1$H-NMR, C$^{13}$ NMR, and Mass GC-MS.

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

**1] Compound 3f : 2-(2-hydroxy-3,5-diiodophenyl)quinazoline-4(3H)-one**
MP = 244-248$^0$C : $^1$H NMR (300 MHz, $CDCl_3$): □ 5.49 (s, 1H), 7.03-7.11 (m, 2H), 7.6-7.9 (m, 4H), 10.7 (br s, 1H)
$^{13}$C NMR (300 MHz, $CDCl_3$) □ 93.5, 98, 108.2, 114.7, 19.5, 124, 127.8, 130 133.1, 142, 148.9, 154.2, 160.4, 168.
GC-MS, m/z: 490 ($M^+$).

2] **Compound 3d: 2-(5-bromo-2-hydroxyphenyl)quinazoline-4(3H)-one**
MP= 222-226 $^0$C : $^1$H NMR (300 MHz, $CDCl_3$): δ 5.37 (s, 1H), 6.98-7.12 (m, 3H), 7.45-7.75 (m, 4H), 10.6 (br s, 1H)
$^{13}$C NMR (75 MHz, $CDCl_3$) δ 112.4, 116, 120, 124.1, 126.8, 130.2, 130.8, 132.5, 134.1, 136.8, 150.2, 154.5, 159, 163.8.
GC-MS, m/z: 317($M^+$).

## III. RESULT AND DISCUSSION

An environmentally benign protocol was used for the synthesis of quinazoline derivatives via two component process from the reaction of substituted salicylaldehyde and o-amino benzamide 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 o-amino benzamide (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]$BF_4$ 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 $^o$c, there is no further development in the product yield was observed, when temperature was increased to 80 $^o$c **(Table 1, entry 6-9)**. As a result 60 $^o$c was selected as a optimum reaction temperature for all reactions.

**Table 1:** Optimization of reaction condition for the synthesis of 3a

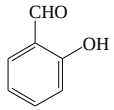
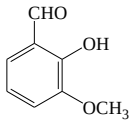
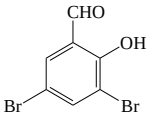
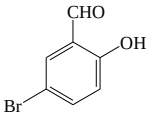
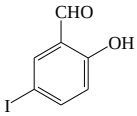
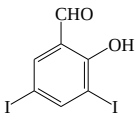
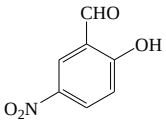
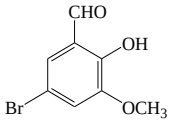
| [a]Entries | Solvents | Temperature ($^o$C) | Time | [b]Yields (%) |
|---|---|---|---|---|
| 1 | Ethanol | 60 | 4 Hrs | 72 |
| 2 | Methanol | 60 | 4 Hrs | 65 |
| 3 | Acetone | 60 | 10 Hrs | 52 |
| 4 | Acetonitrile | 60 | 6 Hrs | 60 |
| 5 | Acetic acid | 60 | 14 Hrs | 68 |
| 6 | [Bmim]$BF_4$ | 60 | 2.5 Hrs | 94 |
| 7 | [Bmim]$BF_4$ | 80 | 2.5 Hrs | 94 |
| 8 | [Bmim]$BF_4$ | 40 | 3 Hrs | 78 |
| 9 | [Bmim]$BF_4$ | R.T. | 3.5 Hrs | 61 |

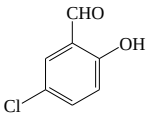
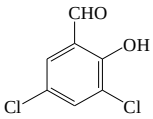
[a]Reaction condition: o-amino benzamide (1mmol), salicylaldehyde (1mmol), [Bmim]$BF_4$ (2 ml). [b]Yields of the isolated products

Again from the duration of optimization of reaction condition, it was observed that the various substituted salicylaldehyde and o-amino benzamide 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 o-amino benzamide and salicylaldehyde (model reaction), no significant loss of the product yield was observed when [Bmim]$BF_4$ was reused, even after four times recycling (**see Figure 1**).

**Table 2:** Synthesis of Quinazoline derivatives by using [Bmim]$BF_4$ as a reaction medium

| Entry | Salicylaldehydes | O-Amino benzamide | Products | Time (Hr) | [a]Yield (%) |
|---|---|---|---|---|---|
| 1 |  | O-Amino benzamide | **3a** | 2.35 | 94 |
| 2 |  | O-Amino benzamide | **3b** | 2.55 | 92 |
| 3 |  | O-Amino benzamide | **3c** | 2.40 | 87 |
| 4 |  | O-Amino benzamide | **3d** | 3.15 | 92 |
| 5 |  | O-Amino benzamide | **3e** | 3.00 | 88 |
| 6 |  | O-Amino benzamide | **3f** | 3.15 | 86 |
| 7 |  | O-Amino benzamide | **3g** | 3.30 | 87 |
| 8 |  | O-Amino benzamide | **3h** | 2.55 | 88 |
| | | O-Amino | | | |

| | | | | | |
|---|---|---|---|---|---|
| 9 |  | benzamide | **3i** | 3.10 | 89 |
| 10 |  | O-Amino benzamide | **3j** | 2.50 | 91 |

[a]Yields refer to those of pure isolated products characterized by IR, $^{1}H$ NMR, and $^{13}C$ NMR spectroscopic data.

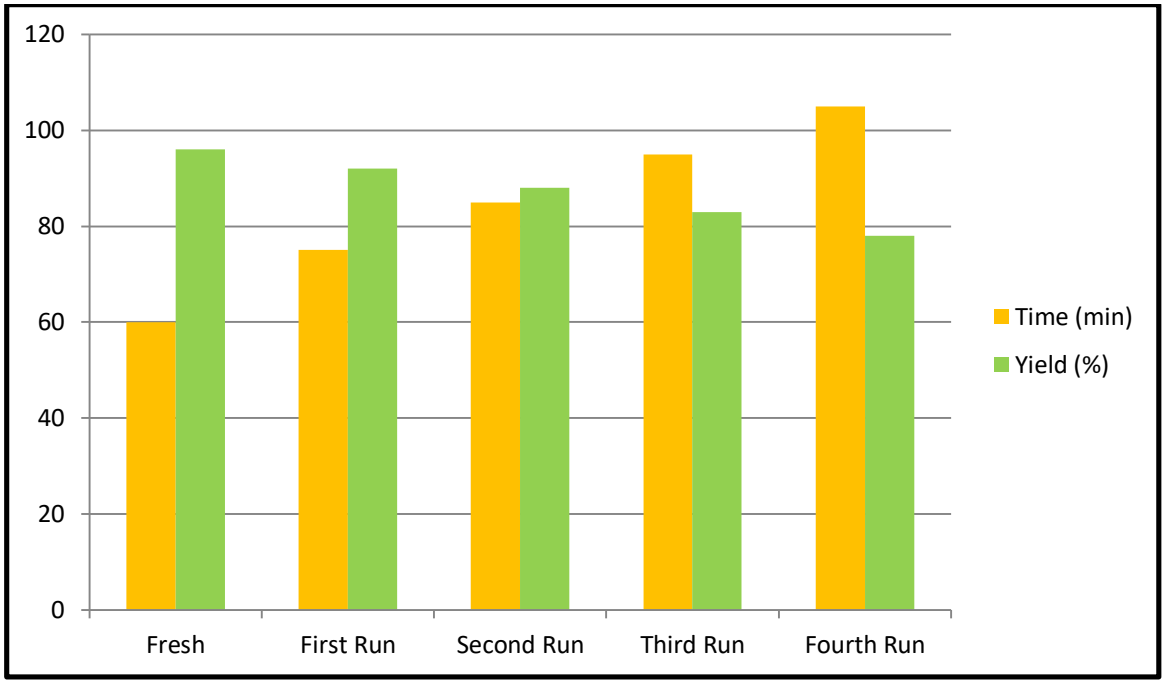



**Figure 1:** Synthesis of 2-(2-hydroxyphenyl)quinazoline-4(3H)-one (Model reaction) derivatives by using recycled [Bmim]$BF_4$

## IV. CONCLUSION

In conclusion, we have developed a efficient and straightforward method for the preparation of quinazoline derivatives by one pot reaction of substituted salicylaldehyde and o-amino benzamide in presence of 1-butyl-3-methylimidazolium tetrafluoroborate. [Bmim]$BF_4$ 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 quinazoline derivatives.

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