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# One-Pot Synthesis of 2,4,5-Triaryl-1*H*-imidazoles Using Glutamic Acid as Catalyst

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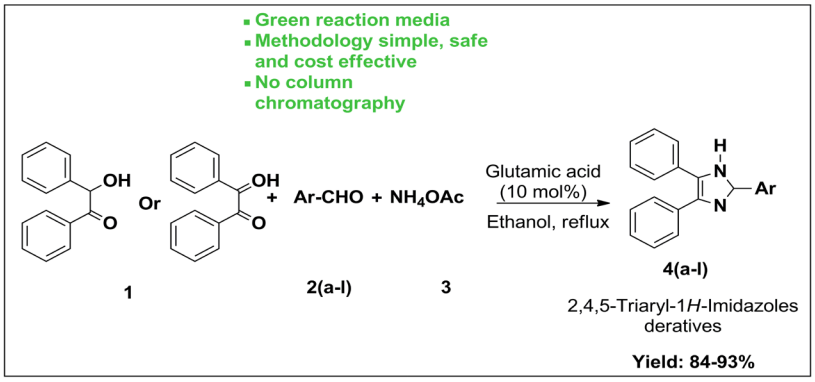
**Glutamic acid has been found to be an efficient organocatalyst for one-pot synthesis of 2,4,5-triaryl substituted imidazole by using a mixture of an aromatic aldehyde, a benzil or benzoin and an ammonium acetate in ethanol as solvent. The cleaner reaction, and easy workup make this protocol practical and economically attractive.**

## Graphical abstract




## Keywords

Benzil or benzoin
Glutamic acid
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## Article history

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## 1. Introduction

Multicomponent reactions (MCRs) refer to a reaction in which two or more ingredients are combined within a single process and the products they create, which is part of all the components are present [1]. 2,4,5-Triphenylimidazoles have widespread biological activities and their use in synthetic chemistry. The imidazole ring system is one of the most important substructures found in a large number of natural products and pharmacologically active compounds hence its can be used as fungicides, herbicides, plant growth regulators and inhibitors of some kinases [2], antibacterial [3], glucagon receptors [4], and antitumor [5]. In recent years, substituted imidazole are substantially used in ionic liquids [6] that has been given a new approach to 'Green Chemistry'. They are used in photography as photosensitive compound [7].

Due to their great importance, many synthesis strategies have been developed such as the hetero-cope rearrangement [8], and four-component condensation of arylglyoxals, primary amines, carboxylic acids and isocyanides on Wang resin [9]. These are some following methods reported in the literature for the synthesis of 2,4,5-trisubstituted imidazole has been catalyzed by zeolite HY [10], ionic liquid [11], ytterbium triflate [12], silica sulfuric acid [13], $InCl_3.3H_2O$ [14], L-proline [15], DABCO [16], $InF_3$ [17], $SbCl_3$ [18], Rochelle Salt [19], magnetic nanoparticle supported Lewis acidic [20]. However, most of the reported methodologies still have certain limitations such as expensive catalysts, toxicity of solvents, restrictions for large scale applications, critical product isolation procedures, difficulty in recovery of high boiling solvents, excessive amounts of catalysts. Thus, the development of a simple and efficient method for the synthesis of 2,4,5-triaryl-1*H* imidazole derivatives would be highly desirable.

Glutamic acid is an α-amino acid that is used by almost all living beings in the biosynthesis of proteins. It is non-essential in humans, meaning the body can synthesize it. In recent year,

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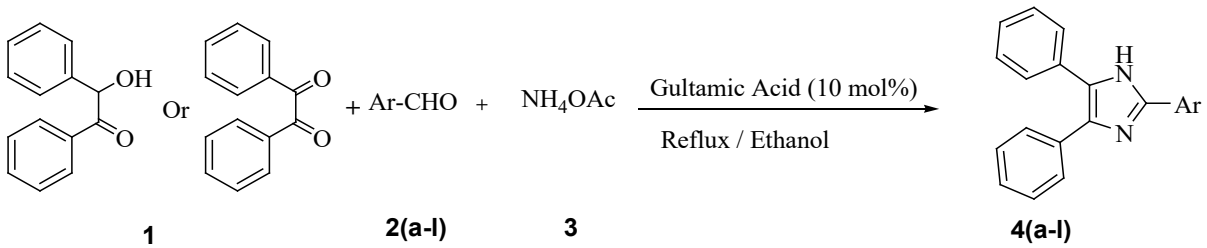
glutamic acid has received considerable attention as an efficient Corrosion Inhibitor for Aluminum in HCl Solution [21]. Glutamic acid occurs naturally in many foods, the flavor contributions made by glutamic acid and other amino acids were only scientifically identified early in the twentieth century. The substance was discovered and identified in the year 1866, by the German chemist Karl Heinrich Ritthausen [22]. When glutamic acid is dissolved in water, the amino group (-$NH_2$) may gain a proton ($H^+$), and/or the carboxyl groups may lose protons, depending on the acidity of the medium [23-25]. By considering this activity of glutamic acid, we described an efficient method by employing glutamic acid as an efficient catalyst for the synthesis of 2,4,5-triaryl-1*H*-imidazoles.

## 2. Results and Discussion

As part of our on-going investigation in developing a versatile and efficient method for synthesis of heterocyclic compounds, we report here an efficient synthetic method for the synthesis of 2,4,5-triarylimidazoles from benzil/benzoin, aldehydes, and ammonium acetate in the presence of glutamic acid (Scheme 1). We initially studied the reaction of 4-chlorobenzaldehyde (**2a**) as a representative aldehyde, compound 1 benzil and ammonium acetate (**3**) in the presence of glutamic acid in ethanol was considered as a standard model reaction for the optimization of reaction condition.




**Scheme 1**. Synthesis of 2,4,5-triaryl-1*H*-imidazoles.

To evaluate the effect of solvent on model reaction was explored and obtained results are shown in Table 1. The we have screened different solvents such as acetonitrile, chloroform, dioxane, methanol, water, water: ethanol (1:1) and ethanol at reflux temperature.

**Table 1.** Screening of solvents for the synthesis of **4g**[a].

| Entry | Solvent | Time (hr) | Yield [b] |
|---|---|---|---|
| 1 | Acetonitrile, | 6 | 27 |
| 2 | Dioxane, | 6 | 15 |
| 3 | Chloroform | 6 | 26 |
| 4 | Methanol | 6 | 76 |
| 5 | Water | 6 | 20 |
| 6 | Water: ethanol (1:1) | 6 | 55 |
| 7 | Ethanol | 6 | 93 |

[a] Reaction conditions: **1** (1 mmol), **2a** (1 mmol), **3** (2 mmol), glutamic acid (10 mol %) at reflux temperature. [b]Isolated yields

To determine the exact concentration of catalyst, we have investigated the model reaction at 2.5, 5, 7.5, 10, 12.5 mol% of glutamic acid in ethanol at reflux temperature. The product was obtained in 22, 47, 78, 93 and 93% of yield respectively. This indicates that the use of just 10 mol% of glutamic acid is sufficient to push the reaction forward (Table 2).

**Table 2.** Effect of concentration of catalyst.[a]

| Entry | Concentration of catalyst in Mole (%) | Time (hr) | Yield[b] |
|---|---|---|---|
| 1 | 2.5 | 10 | 22 |
| 2 | 5 | 10 | 47 |
| 3 | 7.5 | 10 | 78 |
| 4 | 10 | 06 | 93 |
| 5 | 12.5 | 06 | 93 |

[a]Reaction conditions: **1** (1 mmol), **2a** (1 mmol), **3** (2 mmol) and glutamic acid (10 mol %) at reflux temperature. [b]Isolated yields.

With the optimized conditions in hand, to explore the scope of this procedure, we extended our study with wide range of aryl aldehydes containing either electron withdrawing or electron-donating substituent's (Table 3). However, the electronic nature of the aryl substituents in the aldehydes did not show strong effects in terms of yields. Thus, the electron withdrawing substituted aromatic aldehydes and the aromatic aldehydes bearing electron donating groups on the aromatic ring underwent clean conversion under the reaction conditions to produce the corresponding products in good yields. The reaction is equally good with heteroaromatic aldehyde (Table 3, entries 4k and 4l), resulting in good yields of 2,4,5-triaryl-1*H*-imidazoles.

**Table 3.** Glutamic acid catalyzed synthesis of 2,4,5,-triaryl substituted imidazole (**4a-l**).

| Entry | Ar- | Time (h) | | Yield (%) | | M.P °C | |
|---|---|---|---|---|---|---|---|
| | | Benzil | Benzoin | Benzil | Benzoin | Found | Literature |
| **4a** | $C_6H_5$ | 6 | 8 | 90 | 89 | 274-276 | 272-273 [18] |
| **4b** | 4-$OHC_6H_4$ | 7 | 9 | 91 | 90 | 269-270 | 269-270 [19] |
| **4c** | 3-$OCH_3$4-$OHC_6H_4$ | 6 | 7.5 | 91 | 90 | 253-255 | 255-256 [19] |
| **4d** | 4-$OCH_3C_6H_4$ | 5.5 | 8.5 | 85 | 84 | 226-227 | 227-228 [18] |
| **4e** | 4-$NO_2C_6H_4$ | 7.5 | 10 | 90 | 87 | 231-232 | 231-232 [19] |
| **4f** | 4-$CH_3C_6H_4$ | 6.5 | 7.5 | 91 | 88 | 228-229 | 226-227 [18] |
| **4g** | 4-$ClC_6H_4$ | 6 | 7 | 93 | 89 | 270-271 | 270-271 [19] |
| **4h** | 4$(CH_3)_2NC_6H_4$ | 5.5 | 6 | 90 | 88 | 258-259 | 260-261 [18] |
| **4i** | 4-$FC_6H_4$ | 4.5 | 6.5 | 92 | 91 | 191-192 | 189-190 [19] |
| **4j** | 2-$ClC_6H_4$ | 5.5 | 8 | 90 | 87 | 194-195 | 194-195 [15] |
| **4k** | $C_4H_3O$ | 6 | 8 | 91 | 89 | 199-200 | 198-200 [19] |
| **4l** | $C_4H_3S$ | 7.5 | 10 | 90 | 89 | 260-261 | 259-260 [19] |

## 3. Material and Methods

The chemicals used, namely benzil or benzoin, aldehydes and ammonium acetate, were of analytical reagent grade. Melting points were determined in open capillary tubes in a paraffin bath. The progresses of the reactions were monitored by TLC (Thin Layer Chromatography). FT-IR spectra were recorded on Perkin-Elmer FT spectrophotometer in KBr discs.$^1$H NMR spectra were recorded on a 400 MHz FT NMR spectrometer in DMSO-d6 as a solvent and chemical shift values are recorded in units δ (ppm) relative to TMS as an internal standard.

**General Procedure for the synthesis of 2,4,5-triarylimidazoles (4a-l)**

A mixture of benzil or benzoin (1 mmol), aldehyde (1 mmol), ammonium acetate (2 mmol), and glutamic acid (10 mol%) in ethanol (15 ml) stirred at reflux temperature for 6 to 10h. The progress of the reaction was monitored by TLC. After completion of reaction conversion, the reaction mixture was cooled to room temperature and poured on crushed ice. The obtained crude solid product was filtered, dried and crystallized from ethanol to get the corresponding 2,4,5-triaryl-1H-imidazoles 4(a-l)

**Spectroscopic data of synthesized some principal compounds**

***2,4,5-triphenyl-1H-imidazole (4a)*:** IR (KBr, cm$^{-1}$):3052, 1472, 1451, 1121, 697. $^1$H-NMR (400 MHz, DMSO-$d_6$, δ ppm): 12.41 (brs, 1H, NH), 7.30–8.12(m, 15H, Ar-H). EIMS (m/z, %): 297 (M+1). Elemental analysis.,$C_{21}H_{16}N_2$: C, 85.11; H, 5.44; N, 9.45. Found: C, 85.02; H, 5.42; N, 9.42.

***4-(4,5-diphenyl-1H-imidazol-2-yl) phenol (4b)*:** IR (KBr, cm-1): 3266, 3037,1689, 1601, 1492, 687. $^1$H NMR (400 MHz, DMSO-d6, δ ppm): 12.38 (s, 1H, NH), 9.61 (s, 1H, OH), 7.87 (d, 2H, J = 8.4 Hz, Ar-H), 7.54 (d, 2H, J = 7.6 Hz, Ar-H), 7.66 (m, 10H, Ph), EIMS (m/z, %): 313 ($M^{+1}$) Elemental analysis. $C_{21}H_{16}N_2O$: C, 80.75; H, 5.16; N, 8.97. Found: C, 80.61; H,5.17; N, 8.19.

***2-(4-methoxyphenyl)-4,5-diphenyl-1H-imidazole(4d)*:** IR (KBr, cm$^{-1}$): 3028, 1618, 1490, 1253, 1031, 692. $^1$H-NMR (400 MHz, DMSO-$d_6$, δ ppm): 12.51 (brs, 1H, NH), 7.90 (d, 2H, J =8.8 Hz, Ar), 7.31-7.82 (m, 10H, Ph), 3.71 (s, 3H, $CH_3$). EIMS (m/z, %): 327 ($M^{+1}$). Elemental analysis. $C_{22}H_{18}N_2O$: C, 80.96; H, 5.56; N, 8.58. Found: C,80.89; H,5.39; N, 8.42.

***2-(4-Nitrophenyl)-4,5-diphenyl-1H-imidazole (4e)*:** FTIR (KBr, cm-1): 3396, 1582, 1561, 1334 cm-1 $^1$H NMR (400 MHz, DMSO-$d_6$, δ, ppm): 11.90 (brs N-H), 7.16-7.81 (m, 10H, Ph), 7.92-8.36 (d, 2H, J =10 Hz, Ar) 7.61-8.11 (d, 2H, J= 10Hz, Ar), EIMS (m/z, %): 342 ($M^{+1}$). Elemental analysis. $C_{21}H_{15}N_2O$: C,73.89; H,4.43; N, 12.31. Found: C, 73.19; H,4.21; N, 12.01.

***2-(4-chlorophenyl)-4,5-diphenyl-1H-imidazole (4g)*:**IR (KBr, cm-1): 3044, 1621, 1444, 1069, 760, 691. $^1$H`NMR (400 MHz, DMSO-$d_6$, δ ppm): 12.69 (brs, 1H, NH), 8.05 (d, 2 H, J = 8.4 Hz, Ar-H),8.33 (d, 2H, J = 8.4 Hz, Ar-H), 7.21–7.50 (m, 10H, Ar-H). ES-MS (m/z): 331 (M + 1). Elemental analysis. $C_{21}H_{15}N_2Cl$: C, 76.24; H, 4.57; N, 8.47. Found: C, 76.10; H, 4.39; N, 8.46.

***N,N-Dimethyl-4-(4,5-diphenyl-1H-imidazol-2-yl)benzene amine(4h)*:** FTIR (KBr, cm$^{-1}$): 3441, 1623, 1557. 1H NMR (400 MHz, DMSO-d6, δ, ppm): 12.10 (1H, brs, NH), 7.71 (s 6H,- $CH_3$), 2.31 (S H, OH), 7.51 (d, 2 H, J = 8.4 Hz, Ar-H), 7.12 (d, 2 H, J = 8.4 Hz, Ar-H) 7.51-7.82 (m, 10 H, Ar-H) ES-MS (m/z): 340 ($M^{+1}$). $C_{23}H_{21}N_3$: C,81.38; H,6.24; N, 12.38. Found: C, 81.18; H,6.10; N, 12.11.

***2-(4-fluorophenyl)-4,5-diphenyl-1H-imidazole (4i)*:** IR (KBr, cm$^{-1}$): 3021, 1490, 1221, 827, 755, 685. $^1$H-NMR (400 MHz, DMSO-d6, δ ppm): 12.31 (brs, 1H,NH), 7.17-7.49 (m, 10H, Ph), 7.01 (d, 2H, J =8.4 Hz, Ar), 7.17 (d, 2H, J =8.4 Hz, Ar). EIMS (m/z, %):315 (M+1). Elemental analysis. $C_{21}H_{15}N_2F$: C, 80.24; H, 4.81; N, 8.91,. Found: C,80.01; H,4.19; N, 8.47.

***2-(2-chlorophenyl)-4,5-diphenyl-1H-imidazole (4j)*:** IR (KBr, cm-1): 3423, 3032, 1619, 1512, 1496. $^1$HNMR (400 MHz, DMSO-$d_6$, δ ppm): 12.39 (brs, 1H, NH), 7.21–7.41 (m, 14H, Ar-H). ES-MS (m/z): 331 (M + 1). Elemental analysis., $C_{21}H_{15}N_2Cl$: C, 76.24; H, 4.57; N, 8.47. Found: C, 76.14; H, 4.42; N, 8.41.

***2-(Furan-2-yl)-4,5-diphenyl-1H-imidazole(4k)*:** FTIR (KBr, cm$^{-1}$): 3322, 2995, 1667, 1532, 1210 $^1$H NMR (400 MHz, DMSO-d6, δ, ppm): 12.11 (brs, 1H, NH), 7.61–7.70 (m, 3H, Ar), 7.21–8.12 (m, 10H, Ar). EIMS (m/z, %): 287 ($M^{+1}$). Elemental analysis. $C_{19}H_{14}N_2O$: C,79.70; H, 4.93; N, 9.78. Found: C, 79.41; H,4.26; N, 9.52.

***4,5-Diphenyl-2-(thiophen-2-yl)-1H-imidazole (4l)*:** FTIR (KBr, cm$^{-1}$):3342, 2999, 1682, 1546 $^1$H NMR (400 MHz, DMSO-d6, δ, ppm):12.11 (brs, 1H, NH), 7.62–7.73 (m, 3H, Ar), 7.11–8.12 (m, 10H, Ar). EIMS (m/z, %): 303 ($M^{+1}$). Elemental analysis. $C_{19}H_{14}N_2S$: C,75.47; H, 4.67; N, 9.26. Found: C, 75.40; H,4.19; N, 9.01.

## 4. Conclusions

In conclusion, glutamic acid can catalyze the one-pot synthesis of a large number of multisubstituted imidazoles under reflux conditions very efficiently. The reactions are environmentally benign methods, usually with improved selectively, enhanced reaction rates, cleaner products, and manipulative simplicity. We expect that this method will find extensive applications in the fields of combinatorial chemistry, diversity-oriented synthesis, heterogeneous catalytic systems, and drug development.

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## Author Contributions

Bhaskar B. Ankush: He performed reference work and all laboratory work. Balasaheb V. Shitole: He performed reference work and spectroscopic data analysis. Nana V. Shitole: He is research supervisor.

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