Orbital: The Electronic Journal of Chemistry
journal homepage: www.orbital.ufms.br
ISSN 1984-6428

| Vol 7 | | No. 3 | | July-September |

*Full Paper*

# Microwave-induced One-pot Synthesis of 2,4,5-trisubstituted Imidazoles Using Rochelle Salt as a Green Novel Catalyst

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*Article history:* Received: 08 March 2015; revised: 20 March 2015; accepted: 01 June 2015. Available online: 20 September 2015. DOI: http://dx.doi.org/10.17807/orbital.v7i3.720

**Abstract:** Rochelle Salt is used as an efficient catalyst for the synthesis of 2,4,5-triaryl-1*H*-imidazoles via condensation of benzil, ammonium acetate, and aromatic aldehydes. The key advantages of this process are the usage of an inexpensive and readily available catalyst, simple procedure, shorter reaction time, and high yield of products.

**Keywords:** Rochelle salt; 2,4,5-triarylimidazoles; one-pot; solvent-free synthesis; microwave irradiation

## 1. INTRODUCTION

Imidazole and their derivatives are unavoidable in the field of medicinal chemistry for their biologically active properties as they have been synthesized and evaluated for their potential as herbicides [1] and therapeutic agents [2]. Imidazole chemistry, because of its use in ionic liquids [3] and in *N*-heterocyclic carbenes (NHCs) [4], opened a new dimension in the area of organometallics and ‘‘Green Chemistry’’. In addition, the imidazole ring system is one of the most important substructures found in a large number of natural products and pharmacologically active compounds, such as the hypnotic agent etomidate [5].

Owing to the wide range of pharmacological and biological activities, the synthesis of imidazoles has become an important target in current years. In 1882, Radziszewski and Japp [6, 7] reported the first synthesis of a highly substituted imidazole from a reaction among 1,2-dicarbonyl compound, aldehydes, and ammonia. In addition, Grimmett et al. proposed the synthesis of the imidazole using nitriles and esters [8]. Another method is the four-component one-pot condensation of a glyoxals, aldehydes, amines, and ammonium acetate in refluxing acetic acid, which is the most desirable and convenient method [9]. Very recently, literature survey reveals several methods for synthesis of 2,4,5-triaryl imidazoles using ionic liquid [10], iodine [11], $ZrCl_4$ [12], $NH_4OAc$ [13], $Yb(OTf)_3$ [14], scolecite [15], PEG-400 [16], L-proline [17], HOAc [18], $CuCl_2.2H_2O$ [19], silica sulfuric acid [20], $SO_4/CeO_2$ [21], and $SbCl_3$ [22]. However, many of these methodologies suffer from one or more disadvantages, such as low yields, high temperature requirement, prolonged reaction time, highly acidic conditions, requirement of excess of catalysts, and the use of solvents. Therefore, there is a strong demand for a simple, highly efficient, environmentally benign, and versatile method for the one-pot synthesis of 2,4,5-triarylimidazole derivatives. Very recently, Rochelle salt (RS) has been used for the synthesis of substituted chromenes and benzochromenes [23]. However, there are no examples of the use of RS as a catalyst for the synthesis of 2,4,5-triarylimidazoles.

The use of microwave for the synthesis of organic compounds under solvent-free conditions proved to be an efficient, safe, and environmentally benign technique, with shorter reaction time, high yields, and easier manipulation. Additionally, it can also avoid the use of hazardous and expensive solvents and can be environmentally benign to make manipulations much easier [24].

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## 2. MATERIAL AND METHODS

The chemicals used, namely benzil, aldehydes, and ammonium acetate, were of analytical reagent grade. Microwave method was used for the syntheses of 2,4,5-trisubstituted imidazoles and their derivatives. 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 $CDCl_3$ 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 (3a-m)

A mixture of benzil (1 mmol), aldehyde (1 mmol), ammonium acetate (2 mmol), and Rochelle salt (10 mol%) was taken in a beaker (50 mL). The reaction mixture was mixed properly with the help of a glass rod and exposed in a microwave oven at the power of 450W and irradiated for a period of 10 seconds. After each irradiation, the reaction mixture was removed from the microwave oven for shaking. The total period of microwave irradiation was 9-13 minutes. After TLC (petroleum ether: ethyl acetate = 9:1 as eluent) indicated that the starting material of benzil and aldehyde had disappeared. After completion of the reaction, the reaction mixture was cooled to room temperature and poured in ice water, the resulting solid was filtered, washed with water, and the crude product was obtained. For further purification, it was recrystallized from ethanol 97%. The experimental data, reaction times, yields and melting points of compounds were presented in Table 3.

### Spectroscopic data of synthesized some principal compounds

**2,4,5-Triphenyl-1*H*-imidazole(3a):** FT-IR (KBr): 3415 (N-H), 2980 (C-H), 1622 (C=C), 1580 (C=N) cm$^{-1}$. $^1$H NMR ($CDCl_3$/DMSO-*d*6, 400 MHz δ, ppm): 7.15-8.00 (m, 15H, Ph), 9.20 (br s, NH). EIMS (m/z, %): 297 (M+1).

**2-(3,4-Dimethoxyphenyl)-4,5-diphenyl-1*H*-imidazole (3b):** FT-IR (KBr):3411 (N-H), 1611 (C = C), 1515 (C = N). $^1$H NMR ($CDCl_3$/DMSO-*d*6, 400 MHz, δ ppm): 3.62 (s, 6H, 2$OCH_3$) 7.35-7.54(m, 3H), 7.20-7.70 (m, 10 H, Ar-H) 12.16 (1 H, brs, NH). ES-MS (m/z): 357 (M $^{+1}$).

**4-(4,5-Diphenyl-1*H*-imidazol-2-yl)phenol (3c):** FT-IR (KBr): 3412 (N-H), 3222 (-OH) 1574 (C=N) cm$^{-1}$. $^1$H NMR ($CDCl_3$/DMSO-*d*6, 400 MHz δ,ppm): 7.13-7.66 (m, 10H, Ph), 7.87-8.32 (d, 2H, J =8.4 Hz, Ar) 7.77-8.06 d, 2H, J= 8.4Hz, Ar) , 12.12 (s N-H) ,9.6 (s OH). EIMS (m/z, %): 313 (M+1).

**2-Methoxy-4-(4,5-diphenyl-1*H*-imidazol-2-yl)phenol (3d):** FT-IR (KBr): 3412 (N-H), 1622 (C = C), 1533 (C = N). $^1$H NMR ($CDCl_3$/DMSO-*d*6, 400 MHz, δ ppm):3.62 (s 3H,-$OCH_3$), 9.43 (S H, OH), 7.11 (d, 2 H, *J* = 8.4 Hz, Ar-H), 7.32 (d, 2 H, *J* = 8.4 Hz, Ar-H) 7.23-7.53 (m, 10 H, Ar-H) 12.10 (1 H, brs, NH). ES-MS (m/z): 343 (M $^{+1}$).

***N,N*-Dimethyl-4-(4,5-diphenyl-1*H*-imidazol-2-yl)benzenamine(3e):** FT-IR (KBr):3450 (N-H), 1622 (C = C), 1556 (C = N).$^1$H NMR ($CDCl_3$/DMSO-*d*6, 400 MHz, δ ppm):2.62 (s 6H,- $CH_3$), 9.33 (S H, OH), 7.55 (d, 2 H, *J* = 8.4 Hz, Ar-H), 7.07 (d, 2 H, *J* = 8.4 Hz, Ar-H) 7.43-7.73 (m, 10 H, Ar-H) 12.10 (1 H, brs, NH). ES-MS (m/z): 340 (M$^{+1}$).

**2-(4-Chlorophenyl)-4,5-diphenyl-1*H*-imidazole (3f):** FT-IR (KBr): 3435 (N-H), 1612 (C = C), 1582 (C = N). $^1$H NMR ($CDCl_3$/DMSO-*d*6, 400 MHz, δ ppm): 7.35 (d, 2 H, *J* = 8.4 Hz, Ar-H), 7.85 (d, 2 H, *J* = 8.4 Hz, Ar-H) 7.20-7.70 (m, 10 H, Ar-H) 12.16 (1 H, brs, NH). ES-MS (m/z): 331 (M $^{+1}$).

**2-(4-Nitrophenyl)-4,5-diphenyl-1*H*-imidazole (3g):** FT-IR (KBr): 3412 (N-H), 1572 (C=N), 1541 ($NO_2$), 1332 ($NO_2$) cm$^{-1}$. $^1$H NMR ($CDCl_3$/DMSO-*d*6, 400 MHz δ,ppm): 7.11-7.61 (m, 10H, Ph), 7.90-8.25 (d, 2H, J =10 Hz, Ar) 7.72-8.12 (d, 2H, J= 10Hz, Ar) , 11.90 (s N-H). EIMS (m/z, %): 342 (M+1).

**3-(4,5-Diphenyl-1*H*-imidazol-2-yl)phenol (3h): FT-**IR (KBr): 3426 (N-H), 3212 (-OH) 1556 (C=N) cm$^{-1}$. $^1$H NMR ($CDCl_3$/DMSO-*d*6, 400 MHz δ,ppm): 7.10-7.53 (m, 10H, Ph), 7.80-8.32 (m, 4H ) , 11.11 (s N-H) ,9.12 (s OH). EIMS (m/z, %): 313 (M+1).

**2-(4-Fluorophenyl)-4,5-diphenyl-1*H*-imidazole (3i): FT-**IR (KBr): 3431 (N-H), 1611 (C=C), 1522 (C=N) cm$^{-1}$. $^1$H NMR ($CDCl_3$/DMSO-*d*6, 400 MHz, δppm): 7.14-7.47 (m, 10H, Ph), 7.00 (d, 2H, J =8.4 Hz, Ar), 7.10 (d, 2H, J =8.4 Hz, Ar), 12.12 (s, N-H) . EIMS (m/z, %):315 (M+1).

**2-(4-Methylphenyl)-4,5-diphenyl-1*H*-imidazole (3j):** FT-IR (KBr): 3450 (N-H), 1600 (C=C), 1585 (C=N) cm$^{-1}$. $^1$H NMR ($CDCl_3$/DMSO-*d*6, 400 MHz, δppm): 2.30 (s, $CH_3$), 7.11-7.40 (m, 10H, Ph), 7.50 (d,

2H, J =10 Hz, Ar), 7.20 (d, 2H, J =10 Hz, Ar), 12.39 (s, N-H) . EIMS (m/z, %):311 (M+1).

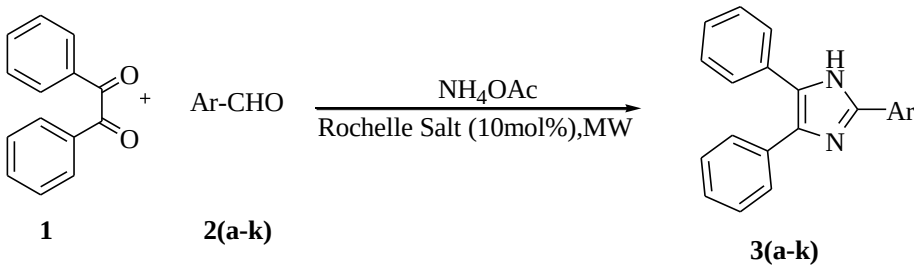
**2-(4-Methoxyphenyl)-4,5-diphenyl-1*H*-imidazole (3k):** FT-IR (KBr): 3420 (N-H), 1613 (C=C), 1565 (C=N), 1377 (C-O) $cm^{-1}$. $^1H$ NMR ($CDCl_3$/DMSO-*d*6, 400 MHz, δppm): 3.75 (s, $OCH_3$), 7.03 (d, 2H, J =8.8 Hz, Ar), 7.90 (d, 2H, J =8.8 Hz, Ar), 7.31-7.82 (m, 10H, Ph), 11.65 (s N-H) . EIMS (m/z, %): 327 (M+1).

**2-(Furan-2-yl)-4,5-diphenyl-1*H*-imidazole(3l):** FT-IR (KBr): 1210 (C-O), 1532 (C=N), 1660 (C=C), 2993 (C-H), 3316 (C=N) cm-$^{1}$. $^1H$ NMR ($CDCl_3$/DMSO-*d*6, 400 MHz, δ, ppm): 11.21 (s, 1H, NH), 7.60–7.70 (m, 3H, Ar), 7.01–8.02 (m, 10H, Ar). EIMS (m/z, %): 287 (M+1).

**4,5-Diphenyl-2-(thiophen-2-yl)-1*H*-imidazole (3m):** FT-IR (KBr): 1556 (C=N), 1672 (C=C), 2997 (C-H), 3332 (C=N) $cm^{-1}$. $^1H$ NMR ($CDCl_3$/DMSO-*d*6, 400 MHz δ, ppm): 11.31 (s, 1H, NH), 7.60–7.70 (m, 3H, Ar), 7.01–8.02 (m, 10H, Ar). EIMS (m/z, %): 303 (M+1).

## 3. RESULTS AND DISCUSSION

In continuation of our work concerning the synthesis and biological evaluation of new heterocycles [25], here we wish to report a very simple, fast and general method for the syntheses of 2,4,5-triarylimidazoles (**3a-m**) in the presence of a catalytic amount of Rochelle salt (RS) under microwave at 450W and solvent-free conditions (Scheme 1) considered as a standard model reaction. As an example, we examined the reaction among 4-chlorobenzaldehyde, benzil, ammonium acetate, and RS (10 mol%) under solvent free conditions. The reaction mixture was irradiated in the microwave oven at different power for appropriate time (8-12 min). The corresponding product was obtained in excellent yield.




**1** **2(a-k)** **3(a-k)**

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

Initially, we examined the reaction without catalyst at different power for 15 min, which did not result in formation of the expected product shown in Table 1.

**Table 1.** Optimization of catalyst amount in synthesis of 2,4,5-trisubstituted imidazole derivatives under microwave irradiation.

| Entry | Power (W) | Catalyst (mol %) | Time (min)[b] | Yield (%)[c] |
|---|---|---|---|---|
| 1 | 100 | None | 15 | No reaction |
| 2 | 180 | None | 15 | No reaction |
| 3 | 300 | None | 15 | No reaction |
| 4 | 450 | None | 15 | No reaction |
| 5 | 600 | None | 15 | No reaction |
| 6 | 900 | None | 15 | No reaction |
| 7 | 100 | 10 | 15 | 45 |
| 8 | 180 | 10 | 15 | 50 |
| 9 | 300 | 10 | 15 | 75 |
| 10 | 450 | 10 | 10 | 96 |
| 11 | 600 | 10 | 10 | 96 |
| 12 | 900 | 10 | 10 | 96 |

To determine the appropriate concentration of the catalyst Rochelle salt, we investigated the model reaction at different concentrations of the catalyst like 2.5,5, 10, and 15 mol%. The product formed in 40, 60, 85, 96, and 96% yield respectively. This indicates that 10 mol% of Rochelle salt is sufficient for the best result by considering the reaction time and yield of product (Table 2).

To study the generality of this process, variety of examples were illustrated for the synthesis of 2,4,5-triaryl imidazoles and results are summarized in Table 3. The reaction is compatible for various substituents such as $CH_3$, $OCH_3$, OH, $N(CH_3)_2$, Cl and F, $NO_2$. This method is also effective for the heteroaromatic aldehydes which form their corresponding 2,4,5-triarylimidazole derivatives in 90~97% of yields. The formation of the desired products was confirmed by $^1$H-NMR, FT-IR and mass spectroscopic analysis techniques.

**Table 2.** Effect of concentration of Rochelle salt[a].

| Entry | Concentration (mol%) | Yield (%)[b] |
|---|---|---|
| 1 | 2.5 | 40 |
| 2 | 5 | 60 |
| 3 | 7.5 | 85 |
| 4 | 10 | 96 |
| 5 | 12 | 96 |

[a]*Reaction conditions:* 1 (1 mmol), (1 mmol), ammonium acetate (2 mmol) and Rochelle salt (10 mol %) at 450W.; [b]Isolated yields.

**Table 3**. Synthesis of 2,4,5-triaryl-1*H*-imidazoles (3a-m) using (10 mol%) Rochelle salt[a].

| Entry | Product | Ar-CHO | Time (min) | Yield[b] (%) | M. P. (°C) | |
|---|---|---|---|---|---|---|
| | | | | | Found | Literature |
| 1 | 3a | $C_6H_5$ | 10 | 93 | 275-276 | 276-277 [19] |
| 2 | 3b | 3,4 $OCH_3$-$C_6H_3$ | 11 | 92 | 220-221 | 220-221 [19] |
| 3 | 3c | 4-$OHC_6H_4$ | 9 | 94 | 269-270 | 268-270 [19] |
| 4 | 3d | 3-$OCH_3$ 4-$OHC_6H_3$ | 10 | 91 | 255-256 | 255-256 [18] |
| 5 | 3e | 4-$N(CH_3)_2C_6H_4$ | 11 | 94 | 258–259 | 260–261[22] |
| 6 | 3f | 4-$ClC_6H_4$ | 10 | 96 | 270–271 | 272–273 [22] |
| 7 | 3g | 4-$NO_2C_6H_4$ | 12 | 90 | 231-232 | 232-233 [19] |
| 8 | 3h | 3-$OHC_6H_4$ | 11 | 97 | 251-253 | - |
| 9 | 3i | 4-$FC_6H_4$ | 11 | 95 | 189-190 | 190 [19] |
| 10 | 3j | 4-$CH_3C_6H_4$ | 12 | 95 | 227–229 | 226–227 [22] |
| 11 | 3k | 4-$OCH_3C_6H_4$ | 11 | 94 | 229-231 | 228-230 [19] |
| 12 | 3l | 2-Furfuryl | 11 | 92 | 198-200 | 198-200 [20] |
| 13 | 3m | 2-Thienyl | 12 | 93 | 259-260 | 261-262 [20] |

[a]*Reaction conditions:* 1 (1 mmol), (1 mmol), ammonium acetate (2 mmol) and Rochelle salt (10 mol%) at 450W.; [b]Isolated yields.

## 4. CONCLUSION

In conclusion, Rochelle salt can catalyze the one-pot synthesis of a large number of multi-substituted imidazoles under microwave conditions very efficiently. Microwave-promoted solvent-free solid acid reactions are environmentally benign methods, usually with improved selectively, enhanced reaction rates, cleaner products, and manipulative simplicity. Rochelle salt is also an excellent catalyst for microwave-assisted organic synthesis. We expect that this method will find extensive applications in the fields of combinatorial chemistry, diversity-oriented synthesis, heterogeneous catalytic systems, and drug development.

## 5. ACKNOWLEDGMENTS

We are thankful to the University Grants Commission, New Delhi, for financial support, which is gratefully acknowledged, and the Sophisticated Analytical Instrument Facility, Punjab University, Chandigarh for providing spectroscopic data.

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