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Solvent Influence on Yield and Selectivity in the Synthesis of 2,4,5-Triaryl-1H-imidazoles

Sajal Jain[1], Dr. Neelu Jain[2]

[1]Research Scholar, Department of Chemistry, Mansarovar Global University, Sehore, Madhya Pradesh, India
[2]Supervisor, Department of Chemistry, Mansarovar Global University, Sehore, Madhya Pradesh, India

In this study Taurine is utilized as an effective and environmentally friendly organocatalyst for one-pot multi component synthesis of 2,4,5-Triaryl-1H-imidazoles in an aqueous ethanol medium. The synthesis was monitored via thin-layer chromatography (TLC) using silica gel plates, and product formation was confirmed through Fourier Transform Infrared (FT-IR) spectroscopy and NMR spectroscopy, with the latter performed in $CDCl_3$ on a Bruker Avance Neo 500-MHz spectrometer. The reaction involved the reflux of a mixture of benzil, various aromatic aldehydes, and ammonium acetate in a 1:1 ethanol-water solvent system, yielding products after cooling, filtration, and recrystallization. The optimization of solvent conditions revealed that different solvents influenced the yield significantly, with the highest yield (90%) achieved using the ethanol-water mixture. Furthermore, the methodology demonstrated robustness across various substituted aldehydes, resulting in good to excellent yields for all synthesized compounds. The study highlights the effectiveness of taurine as a catalyst and emphasizes the importance of solvent choice in enhancing product yields in the synthesis of 2,4,5-Triaryl-1H-imidazoles.

Keywords: Taurine, Aqueous, Ethanol, Aromatic, Yield.

1. Introduction

Thanks to their wide range of biological activities and applications, imidazole derivatives have attracted a lot of interest in medicinal and organic chemistry as a result of their synthesis. A number of pharmacological activity, such as anti-inflammatory, antibacterial, and anticancer actions, have made 2,4,5-triaryl-1H-imidazoles stand out among these derivatives as potentially useful chemicals. These compounds have the ability to treat diseases and improve biological functions because of their structural distinctiveness, which is marked by the presence of numerous aryl groups. Therefore, it is critical to find effective synthetic methods to produce 2,4,5-triaryl-1H-imidazoles so that they can be studied and used in drug discovery.

Choosing the right solvent is an important part of synthesis since it affects the yield and selectivity of the final product. Chemical processes rely heavily on solvents because they modify reactant solubility, intermediate stability, and reaction kinetics. For example, the total

yield can be affected by the solvent's polarity, which in turn affects the reaction rate and the efficiency of intermolecular interactions. The solvent plays an important role in 2,4,5-triaryl-1H-imidazole synthesis by influencing the solubility of the starting materials and, more importantly, by directing the production of certain products by modulating the reaction environment.

Imidazole derivative synthesis can be carried out using a wide variety of solvents, including polar and nonpolar solvents as well as protic and aprotic solvents. Hydrogen bonding allows polar protic solvents like water and alcohols to stabilize charged intermediates, which may result in increased yields. On the other hand, imidazole rings can be more selectively formed in aprotic solvents such as dimethyl sulfoxide (DMSO) and dimethylformamide (DMF) due to the favorable environment they create for reactions involving nucleophiles. Also, by reducing the solvation of reactive intermediates, nonpolar solvents such as toluene can increase selectivity by favoring some pathways over others.

Solvent choice in organic synthesis has been further impacted by recent developments in green chemistry. Researchers have begun to investigate solvent-free settings and ionic liquids as potential alternative reaction media due to the focus on ecologically friendly solvents. These methods have the potential to improve reaction efficiency and product selectivity while simultaneously decreasing the environmental effect of chemical operations. Because there are usually several reaction stages involved in the synthesis of 2,4,5-triaryl-1H-imidazoles, the solvent choice is crucial for optimising the whole synthetic process.

2,4,5-TRIARYL-1H-IMIDAZOLES

2,4,5-Triaryl-1H-imidazoles are a class of heterocyclic compounds characterized by the imidazole ring, which is substituted at the 2nd, 4th, and 5th positions with aryl groups. These compounds have garnered significant attention in organic and medicinal chemistry due to their versatile pharmacological properties and their utility in various chemical reactions. The imidazole ring, a five-membered system containing two nitrogen atoms, is an essential structural motif in numerous bioactive molecules, including natural compounds such as histidine and synthetic pharmaceuticals. The triaryl substitution pattern enhances the electronic and steric properties of the imidazole core, further expanding its range of applications in drug design, materials science, and catalysis.

The synthesis of 2,4,5-triaryl-1H-imidazoles has been widely explored due to the demand for these compounds in both academic and industrial settings. One of the most common methods for their preparation is the multicomponent reaction (MCR) involving aldehydes, ammonium acetate, and benzil or benzoin. This reaction is often catalyzed by acids or bases and proceeds efficiently under mild conditions, making it an attractive and environmentally friendly approach. The simplicity of the reaction, coupled with its high yields, allows for the rapid generation of a diverse array of triaryl imidazole derivatives by varying the aryl groups attached to the imidazole ring. Microwave-assisted synthesis and solvent-free protocols have also been developed to further enhance the efficiency of this process, highlighting the continuing advancements in synthetic methodologies for these compounds.

The unique structural features of 2,4,5-triaryl-1H-imidazoles confer them with a broad spectrum of biological activities. They have been reported to exhibit anti-inflammatory,

antimicrobial, anticancer, and antiviral properties. Their ability to interact with various biological targets, such as enzymes and receptors, makes them valuable scaffolds for the development of new therapeutic agents. For instance, certain triaryl imidazole derivatives have shown promising anticancer activity by inhibiting key enzymes involved in cancer cell proliferation, such as kinases. Other derivatives have been explored as potential anti-inflammatory agents due to their ability to modulate inflammatory pathways, thereby offering potential treatments for conditions like rheumatoid arthritis and asthma.

2. REVIEW OF LITERATURE

Sedrpoushan, Alireza et al., (2014) An effective method for the efficient synthesis of 2, 4, 5-triaryl-1H-imidazole derivatives is investigated. This method involves the reactions of hexamethyldisilazane and arylaldehydes with N-bromosaccharin (NBSa) as a catalyst. Among the many benefits of this novel approach are its straightforward technique, low response times, easy workup, and high yields.

Mohammadi, Ali et al., (2012) Under solvent-free conditions, a novel polymeric catalyst called poly(AMPS-co-AA) allows for the efficient synthesis of 2,4,5-trisubstituted imidazoles through a three-component cyclocondensation of benzil or benzoin, aldehyde, and ammonium acetate. The process's main benefits include reusability of the catalyst, quick reaction durations, fast work-up, and high yields purified by non-chromatographic methods. Visual Summary With the use of a new polymeric catalyst called poly(AMPS-co-AA), we were able to successfully produce 2,4,5-trisubstituted imidazoles in a solvent-free environment through a three-component cyclocondensation process including benzil or benzoin, aldehyde, and ammonium acetate.

Veisi, Hojat et al., (2012) Hexamethyldisilazane, arylaldehydes, benzyl alcohols, and benzyl halides, in the presence of molecular iodine, form a one-pot efficient process that may synthesize 2,4,5-triaryl-1H-imidazole derivatives in good to outstanding yields. High product yields, easy access to reagents, and a straightforward workup approach are the method's notable features.

Niralwad, K.S. et al., (2012) Silica sulphuric acid was found to be an efficient catalyst for the green synthesis of 2,4,5-Triaryl-1H-Im- idazoles by the coupling of Benzil/Benzoin, aldehyde and ammonium acetate under microwave-irradiation at ambient temperature for appropriate time to furnish the desired product in good to excellent yield. The catalyst provides clean conversion; greater selectivity and easy workup make this protocol practical and economically attractive. 3 are imidazole derivatives. Many fungicides, herbicides, medicinal medicines, and inhibitors of p38 MAP kinase are some of the names given to the imidazoles that have been substituted 4–7. The synthesis of imidazoles has gained significant attention in recent years due to their diverse biological and pharmacological activities.

Shelke, Kiran et al., (2009) In a one-pot three-component condensation of benzil/benzoin, an aldehyde, and ammonium acetate in aqueous media under ultrasonography at room temperature, 2,4,5-triaryl-1H-imidazoles can be synthesized in excellent yields using boric acid (BO_3H_3) as a gentle, efficient, and economical catalyst. Green catalyst, gentle reaction conditions, easy processes, significantly faster reactions, and great product yield are some of

the outstanding benefits of this approach.

Parveen, Arshia. (2007) Under solvent-free circumstances, a variety of 2,4,5-triaryl substituted imidazoles were successfully produced by grinding 1,2-diketones, aromatic aldehydes, and ammonium acetate with molecular iodine as a catalyst. This technique is practical and economically advantageous because to its rapid reaction time, cleaner response, and easy workup.

3. MATERIAL AND METHODS

The chemicals and solvents utilized in this study were all of AR grade and did not undergo any additional purification processes. We used uncorrected measurements of melting points taken in open capillary tubes. The chemicals' formation was verified using thin-layer chromatography (TLC) on aluminum sheets coated with 0.5 mm thick silica gel 60 F254 plates. The KBr pellet approach was used to record infrared (FT-IR) spectra using a Shimadzu FT-IR-8400 device. Bruker Avance Neo 500-MHz spectrometer NMR data were acquired in CDCl3 solvent.

Typical Procedure for the synthesis of 2,4,5-Triaryl-1H-imidazoles derivatives (4a-h)

The following was refluxed in a 20 mL round bottom flask (RBF): 1.0 mmol benzil, 1.0 mmol aromatic aldehyde, 4.0 mmol ammonium acetate, and 20 mol% taurine in 5 mL of a 1:1 mixture of ethanol and water. By utilizing TLC, the advancement of the reaction might be monitored. Once the reaction was finished, the mixture was allowed to settle down to room temperature. Then, after whisking for three minutes, ice water was added. After that, the liquid was filtered and then rinsed with a water-ethanol mixture. The final products were obtained by drying the material and then recrystallizing it using ethanol.

4. RESULTS AND DISCUSSION

In our investigation, we explored the impact of solvents on the cyclization process by using various solvent ratios, such as acetonitrile, ethanol: water, dimethylformamide, methanol, and dichloromethane, in the presence of taurine (20 mol%) as a catalyst under reflux conditions (Table 1). Notably, we observed an 80% yield of the product (4a) within three hours when using methanol under reflux (Table 1, entry 1). However, the use of tetrahydrofuran as the solvent resulted in a lower yield of the product after three and a half hours (Table 1, entry 3). Additionally, the use of The yields were 72% for dimethylformamide, 79% for acetonitrile, and 76% for dichloromethane, as shown in Table 1, entries 2, 4, and 5, respectively. Table 1, entry 6 shows that the product was successfully produced within three hours when the reaction was carried out in ethanol. Table 1, entry 7, 92% shows that the product yield increased when the ethanol and water were mixed in a 1:1 ratio. Nevertheless, we found that the optimal results were obtained with a 1:1 water-to-ethanol ratio (Table 1, entry 7), as increasing the ratio by a factor of two reduced the product yield (Table 1, entry 8).

Table 1 Influence Of The Solvent On The Synthesis Of 2,4,5-Triaryl-1h-Imidazoles

Entry	Solvent	Condition	Time (h)	Isolated Yield (%)
1	Methanol	reflux	3	81
2	DMF	reflux	4	74
3	THF	reflux	3.5	47
4	Acetonitrile	reflux	3.5	78
5	DCM	reflux	3	75
6	Ethanol	reflux	3	89
7	Ethanol:Water(1:1)	reflux	3	92
8	Ethanol:Water(1:2)	reflux	3	88

We tested the applicability of the recently established taurine-catalyzed technique in aqueous ethanol for the synthesis of 2,4,5-Triaryl-1H-imidazoles after optimising the reaction conditions. In order to create the appropriate compounds (4a-h), this investigation included using various substituted aldehydes. Amazingly, the matching compounds were produced in good to outstanding yields by all of the aromatic aldehydes, regardless of the type of the substituents (Table 3, entries 1-8).

Table 3 Synthesis Of 2,4,5-Triaryl-1 H-Imidazoles (4a-H)

Entry	Product	R	Reaction time (h)	Melting point (mp,oC)	Isolated Yield %
1	4a	4-CH3O	3	228-230	90
2	4b	4-CH3	4	226-229	89
3	4c	4-Cl	3.5	266-278	90
4	4d	2-Cl	4	196-198	79
5	4e	2-OH	5	259-262	77
6	4f	4-NO2	4.5	306-308	83
7	4g	H	2.5	268-271	85
8	4h	4-OH	3	260-263	78

5. CONCLUSION

Using taurine (2-aminoethanesulfonic acid) as a stable organic catalyst and an aqueous ethanol medium, the one-pot multicomponent synthesis of 2,4,5-Triaryl-1H-imidazole derivatives (4a-h) was effectively accomplished under eco-friendly circumstances. The metal-free catalyst, short reaction durations, excellent yields, benign reaction conditions, easy workup, and avoidance of hazardous organic solvents are only a few of the noteworthy benefits of this study compared to previously reported methods. Solvent selection is an important step in the synthesis of physiologically active chemicals since it affects reaction efficiency, product selectivity, and the final result. Future advancements in the discipline and the development of novel pharmaceutical drugs will be greatly aided by the incorporation of solvent effects into the development of synthetic strategies. Insight into the complex interplay between solvent characteristics and reaction dynamics will open doors to new methods of imidazole synthesis

and beyond, which will have far-reaching implications for many areas of pharmaceutical R&D.

References

1. H. Tran-Trung, V. Dung, N. Chung, and D. Duc, "Recent Achievement in the Synthesis of Imidazoles," Curr. Org. Chem., vol. 27, no. 16, pp. 1–10, 2023, doi: 10.2174/0113852728259414231010050749.
2. S. M. Bagwan and M. Asif, "An Efficient and One Pot Synthesis of 2,4,5-Trisubstituted Imidazole Derivatives Catalyzed by Silver Nanoparticles," Asian J. Chem., vol. 34, no. 4, pp. 889–893, 2022, doi: 10.14233/ajchem.2022.23589.
3. B. Maleki and S. Ashrafi, "N-Bromosuccinimide Catalyzed Three Component One-Pot Efficient Synthesis of 2,4,5-Triaryl-1H-imidazoles from Aldehyde, Ammonium Acetate, and 1,2-Diketone or α-Hydroxyketone," J. Mex. Chem. Soc., vol. 58, no. 1, pp. 76–81, 2014, doi: 10.29356/jmcs.v58i1.159.
4. A. Sedrpoushan, Z. Joshani, and L. Fatollahi, "Efficient Synthesis of 2,4,5-Triaryl-1H-Imidazoles from Aromatic Aldehydes with HMDS Catalyzed by N-Bromosaccharin (NBSa)," Lett. Org. Chem., vol. 11, no. 2, pp. 1–10, 2014, doi: 10.1002/chin.201443121.
5. H. Veisi, A. Khazaei, L. Heshmati, and S. Hemmati, "Convenient One-Pot Synthesis of 2,4,5-Triaryl-1H-imidazoles from Arylaldehydes, Benzyl Alcohols, or Benzyl Halides with HMDS in the Presence of Molecular Iodine," Bull. Korean Chem. Soc., vol. 33, no. 4, pp. 22–29, 2012, doi: 10.5012/bkcs.2012.33.4.1231.
6. A. Mohammadi, H. Keshvari, R. Sandaroos, H. Rouhi, and Z. Sepehr, "A novel polymeric catalyst for the one-pot synthesis of 2,4,5-triaryl-1H-imidazoles," J. Chem. Sci., vol. 124, no. 2, pp. 1–10, 2012, doi: 10.1007/s12039-012-0248-y.
7. K. S. Niralwad, I. B. Ghorade, I. B. Ghorade, and M. Shingare, "Synthesis of 2,4,5-Triaryl-1H-imidazoles Using Silica Sulfuric Acid is an Inexpensive, Efficient and Mild Catalyst Under Microwave Irradiation," Int. J. Sci. Res., vol. 3, no. 2, pp. 58–60, 2012, doi: 10.15373/22778179/JAN2/20.
8. L. Wu, X. Jing, H. Zhu, Y. Liu, and C. Yan, "One-pot synthesis of polysubstituted imidazoles from arylaldehydes in water catalyzed by nhc using microwave irradiation," J. Chilean Chem. Soc., vol. 57, no. 3, pp. 1204–1207, 2011, doi: 10.4067/S0717-97072012000300002.
9. K. Shelke, S. Sapkal, S. Sonal, B. Madje, and M. Shingare, "An Efficient Synthesis of 2,4,5-Triaryl-1H-Imidazole Derivatives Catalyzed by Boric Acid in Aqueous Media Under Ultrasound-Irradiation," Bull. Korean Chem. Soc., vol. 30, no. 2, pp. 1057–1060, 2009, doi: 10.5012/bkcs.2009.30.5.1057.
10. X. Wang, H. Gong, Z. Quan, L. Li, and H. Ye, "PEG-400 as an efficient reaction medium for the synthesis of 2,4,5-triaryl-1H-imidazoles and 1,2,4,5-tetraaryl-1H-imidazoles," Chin. Chem. Lett., vol. 20, no. 1, pp. 44–47, 2009, doi: 10.1016/j.cclet.2008.10.005.
11. M. Adib, S. Ansari, S. Feizi, J. Damavandi, and P. Mirzaei, "A One-Pot, Four-Component Synthesis of N-Substituted 2,4-Diarylimidazoles," Synlett, vol. 2009, no. 20, pp. 3263–3266, 2009, doi: 10.1055/s-0029-1218381.
12. F. Bellina, S. Cauteruccio, and R. Rossi, "Efficient and Practical Synthesis of 4(5)-Aryl-1H-imidazoles and 2,4(5)-Diaryl-1H-imidazoles via Highly Selective Palladium-Catalyzed Arylation Reactions," J. Org. Chem., vol. 72, no. 22, pp. 8543–8546, 2007, doi: 10.1021/jo701496p.
13. N. Kokare, J. Sangshetti, and D. Shinde, "One-Pot Efficient Synthesis of 2Aryl1-arylmethyl-1 H -benzimidazoles and 2,4,5-Triaryl-1 H -imidazoles Using Oxalic Acid Catalyst," Synthesis-stuttgart, vol. 2007, no. 18, pp. 2829–2834, 2007, doi: 10.1055/s-2007-983872.
14. A. Parveen, "Efficient synthesis of 2,4,5-triaryl substituted imidazoles under solvent free conditions at room temperature," Arkivoc, vol. 2007, no. 12, pp. 1–10, 2007, doi: 10.3998/ark.5550190.0008.g02.
15. M. Kidwai, S. Saxena, and S. Rastogi, "An Efficient Synthesis of 2,4,5-Trisubstituted and 1,2,4,5-Tetrasubstituted-1H-imidazoles," Bull. Korean Chem. Soc., vol. 26, no. 12, pp. 2051–2053, 2005, doi: 10.5012/bkcs.2005.26.12.2051.