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Research article

Green chemistry approach for the synthesis of 2,4,5-triaryl-1*H*-imidazole derivatives using lemon juice as a bio-catalyst

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Abstract

The use of green chemistry is crucial for organic synthesis to protect the environment from hazardous and toxic substances. Lemon juice is a promising candidate for a green chemistry catalyst because it is widely available, inexpensive, biodegradable, and non-toxic. This study reports a simple and highly effective one-pot synthesis of 2,4,5-triaryl-1*H*-imidazole derivatives 4(a-l) using lemon juice as a biocatalyst. The method involves a three-component condensation reaction of benzil, aromatic aldehydes, and ammonium acetate in ethanol using lemon juice as a catalyst, and offers several benefits such as short reaction time, easy work-up, low-cost catalyst, and good yields. Additionally, in silico prediction of ADME properties suggests that the synthesized compounds 4(a-l) have the potential to exhibit favourable oral drug-like properties.

Introduction

With growing concern about environmental contagions, the use of greener and more eco-friendly synthetic methodologies has emerged as a critical area of research. The use of hazardous organic solvents and metal catalysts is a major concern in organic synthesis. Metal catalysts are toxic, often expensive, and result in metal contamination at the end of the reaction. As a result, the development of alternative reaction media and the search for more environmentally friendly forms of catalysis drew insatiable interest in the fields of organic transformation and fine chemical synthesis [1, 2]. Multicomponent reactions (MCR) have become important tools for the rapid generation of molecular complexity and diversity with predefined functionality in chemical biology and drug discovery [3-5]. MCRs, a powerful and virtually reliable target-guided synthetic approach, has extensively been used and applied for the rapid construction of molecular-level complex architectures, and interest from different branches of science is expanding exponentially [6].

Imidazole is a heterocyclic ring molecule with five members that includes two nitrogen atoms within the ring. One of the nitrogen atoms has a pyrrole-like behavior, while the other resembles a pyridine-like nitrogen. The imidazole ring system is an essential substructure present in numerous natural products and biologically active compounds [7, 8]. Triarylimidazole derivatives have many biological activities, for example, herbicidal [9], fungicidal [10], anti-inflammatory [11], and antithrombotic activities [12]. Previous studies have reported several approaches for synthesizing these derivatives, mainly using nitriles and esters as starting materials [13-16]. However, some of these methods have limitations, such as high-temperature requirements, highly acidic conditions, and the use of metal

cyanides, which restrict their practical application [17, 18]. Therefore, it is still important to develop a mild, efficient, and versatile method for this crucial heterocycle.

Recently, there has been a lot of interest in naturally occurring lemon juice as a biocatalyst due to its excellent reactivity and selectivity, as well as its ability to produce less waste than traditional chemical methods [19]. Lemon juice is readily available, water-soluble, environmentally friendly, affordable, non-toxic, and can serve as a substitute for several metallic and non-metallic toxic acid catalysts. These properties align with the principles and measures of green and sustainable chemistry [20]. In continuation of our previous research on one-pot synthesis using lemon juice as a biocatalyst [21], we present our findings on the synthesis of 2,4,5-triaryl-1*H*-imidazole derivatives using lemon juice as a natural, cost-effective, eco-friendly, efficient, and biodegradable catalyst under mild reaction conditions.

Material and methods

The reagents and solvents used in the experiments were purchased from Sigma and Avra synthesis. A fresh lemon was purchased from local market, thoroughly washed with water, cut with a knife, and then pieces were pressed manually. To get clear lemon juice, which was used as a catalyst, the juice was filtered through muslin cloth to remove solid material. The homogeneity of the compounds was monitored by ascending thin layer chromatography (TLC) on silica gel-G coated (Merck) aluminium plates and visualized by iodine vapour. The melting points were measured in open capillary tubes. The 1H NMR spectra were recorded using a 400 MHz Varian-Gemini spectrometer and reported in parts per million (ppm) relative to a tetramethylsilane internal standard. The following abbreviations are used; singlet (s), doublet (d), triplet (t), quartet (q), multiplate (m) and broad (br). The mass spectra were obtained with a Micromass-QUATTRO-II of WATER mass spectrometer.

General procedure for the synthesis of 2,4,5-triaryl-1H-imidazoles 4(a-l)

A mixture of benzil (1.0 mmol), aromatic aldehydes (1.0 mmol), ammonium acetate (4.0 mmol), and lemon juice (4 mL) in ethanol (25 mL) was heated to 50 °C while stirring. The completion of the reaction was checked with TLC (n-hexane: ethyl acetate 4:1). After the reaction was completed, the mixture was cooled to room temperature and poured onto ice water (50 mL) to isolate the solid precipitate. The precipitate was collected by filtration, washed with water, and dried to produce the corresponding 2,4,5-triaryl-1*H*-imidazoles. All the synthesized compounds were purified by recrystallisation using ethanol as a solvent.

Spectral data for some 2,4,5-triaryl-1H-imidazole derivatives

*2,4,5-Triphenyl-1H-imidazole (**4a**)*

1H NMR (400 MHz, DMSO): δ = 7.45-7.58 (m, 6H), 7.65-7.79 (m, 3H), 7.83-7.93 (m, 6H), 8.67 (br, 1H); MS (EI, 70 eV): m/z = 296.35 $[M+H]^+$.

*2-(4-Methoxyphenyl)-4,5-diphenyl-1H-imidazole (**4b**)*

1H NMR (400 MHz, $CDCl_3$): δ = 3.7 (s, 3H), 7.23 (d, J = 8.1 Hz, 2H), 7.42–7.62 (m, 4H), 7.73 (m, 2H), 7.81–7.94 (m, 6H), 8.65 (br, 1H). MS (EI, 70 eV): m/z = 326.44 $[M + H]^+$.

*2-(4-Nitrophenyl)-4,5-diphenyl-1H-imidazole (**4l**)*

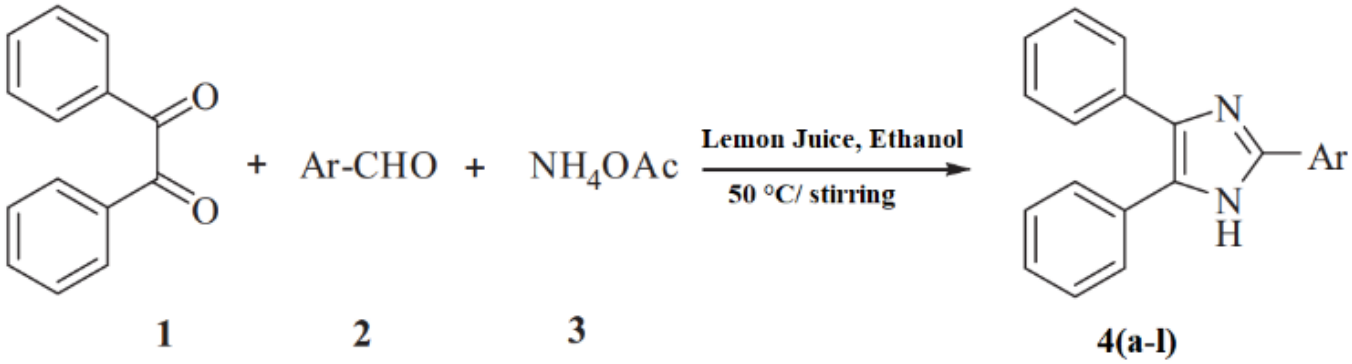
1H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.61 (m, 4H), 7.66–7.75 (m, 4H), 7.88–8.02 (m, 4H), 8.25 (d, J = 8.1 Hz, 2H), 8.85 (br, 1H). MS (EI, 70 eV): m/z = 341.25 $[M + H]^+$.

In silico ADME properties

We conducted an in silico ADME prediction study on the synthesized compounds **4(a-l)**. During the study, we calculated several parameters including molecular volume (MV), molecular weight (MW), logarithm of partition coefficient (miLog *P*), number of hydrogen bond acceptors (n-ON), number of hydrogen bond donors (n-OHNH), topological polar surface area (TPSA), number of rotatable bonds (n-ROTB), and Lipinski's rule of five [22] using Molinspiration online property calculation toolkit [23]. We also calculated the % absorption (% ABS) using the formula: % ABS= 109- (0.345×TPSA) [24].

Results and discussion

This study aimed to develop a sustainable and effective method for synthesis of 2,4,5-triaryl-1*H*-imidazoles **4(a-l)**. Using lemon juice as a catalyst, the compounds were synthesized in good yields from benzil, aromatic aldehydes, and ammonium acetate in ethanol (**Scheme 1**). This research is the first to report the use of lemon juice as a catalyst for the synthesis of 2,4,5-triaryl-1*H*-imidazoles. Lemon juice is an advantageous catalyst due to its low cost, easy availability, mildness, and ease of handling, in addition to being effective in various organic reactions and syntheses. Initially, the effect of catalyst loading on the product yield was investigated (**Table 1**). Using lemon juice in various loads, including 10 mL, 6 mL, 4 mL, and 2 mL, we carried out the reaction for compound (**4a**). The results showed that using 4 mL lemon juice as catalyst is the most effective, yielding up to 95% of the product. Thus, our results make the process under study more attractive and interesting from the viewpoint of economy and simplicity.



Scheme 1. Synthesis of 2,4,5-triaryl-1*H*-imidazoles 4(a-l).

Table 1. Effect of catalyst loading on the yield of 2,4,5-triphenyl-1*H*-imidazole (4a).

Sr. No.	Catalyst	Quantity (mL)	Yield (%)
1	Lemon juice	10	95
2	Lemon juice	6	95
3	Lemon juice	4	95
4	Lemon juice	2	85

To assess the generality of this approach, various aromatic aldehydes were reacted with benzil and ammonium acetate under optimized conditions to obtain 2,4,5-triaryl-1*H*-imidazoles **4(a-l)**. Aldehydes containing either electron-withdrawing or electron- releasing groups produced the corresponding 2,4,5-triaryl-1*H*-imidazoles in high yields (**Table 2**). Furthermore, electron-releasing (-CH_3, -OCH_3, -OH, and -$N(CH_3)_2$) containing aryl aldehydes reacted very smoothly in short reaction times and higher yields (**Table 2**, **4b-4f**), whereas electron-withdrawing (-Cl, NO_2, and -CN) substitutions (**Table 2**, **4g-4l**) showed less reactivity in this condensation reactions. It should be noted that the products **4(a-l)** were obtained simply by filtering from the reaction medium. The compounds were obtained in high yields (90-98%). TLC was used to monitor the reactions, and the time required for completion was 30-50 minutes. The physical data of the synthesised compounds are presented in **Table 2**.

A computational study of synthesized compounds **4(a-l)** was performed for prediction of ADME properties. The value obtained is depicted in **Table 3**. It was found that all of the synthesized compounds displayed a favourable % ABS, with values ranging from 83.29% to 99.10%. However, with the exception of **4d**, all of the synthesized compounds violated at least one of Lipinski's parameters, specifically miLog *P*. For a molecule to be considered a viable orally active drug candidate, it should not violate more than one of the following criteria: miLog *P* (octanol-water partition coefficient) ≤ 5, molecular weight ≤ 500, number of hydrogen bond acceptors ≤ 10, and number of hydrogen bond donors ≤ 5 [30]. All the synthesized compounds followed the criteria for orally active drug and therefore, these compounds may have a good potential for eventual development as biologically active oral agents.

Table 2. Physical data of 2,4,5-triaryl-1*H*-imidazoles 4(a-l).

Entry	Ar	Time (min)	Yield (%)	Melting point (°C)	
				Observed	Reported
4a	C_6H_5	40	95	270-272	274-275 [25]
4b	4-$OCH_3C_6H_4$	35	96	230-232	230-231[25]
4c	4-$CH_3C_6H_4$	30	96	224-226	227-229 [25]
4d	4-OHC_6H_4	30	98	262-264	265-267 [25]
4e	2-OHC_6H_4	35	95	204-206	204–205 [26]
4f	4-$N(CH_3)_2C_6H_4$	40	96	252-254	256-258 [27]
4g	2-ClC_6H_4	50	90	186-188	186-190 [25]
4h	4-ClC_6H_4	45	92	254-256	260-262 [25]
4i	4-BrC_6H_4	45	91	244-246	248-249 [26]
4j	2-BrC_6H_4	45	90	204-206	201-202 [26]
4k	4-CNC_6H_4	50	92	244-246	248-250 [28]
4l	4-$NO_2C_6H_4$	45	93	232-234	235–238 [29]

Table 3. Pharmacokinetic parameters important for good oral bioavailability of 2,4,5-triaryl-1*H*-imidazoles 4(a-l).

Entry	% ABS	TPSA (A^2)	n-ROTB	MV	MW	miLog *P*	n-ON acceptors	n-OHNH donors	Lipinski's violations
Rule					<500	≤5	<10	<5	≤1
4a	99.10	28.68	3	279.10	296.37	5.39	2	1	1
4b	95.91	37.92	4	304.64	326.40	5.44	3	1	1
4c	99.10	28.68	3	295.66	310.40	5.84	2	1	1
4d	92.12	48.91	3	287.12	312.37	4.91	3	2	0
4e	92.12	48.91	3	287.12	312.37	5.12	3	2	1
4f	97.98	31.92	4	325.00	339.44	5.49	3	1	1
4g	99.10	28.68	3	292.63	330.82	6.02	2	1	1
4h	99.10	28.68	3	292.63	330.82	6.07	2	1	1
4i	99.10	28.68	3	296.98	375.27	6.20	2	1	1
4j	99.10	28.68	3	296.98	375.27	6.15	2	1	1
4k	90.89	52.48	3	295.96	321.38	5.14	3	1	1
4l	83.29	74.51	4	302.43	341.37	5.35	5	1	1

% ABS: percentage absorption; TPSA: topological polar surface area; n-ROTB: number of rotatable bonds; MV: molecular volume; MW: molecular weight; miLog *P*: logarithm of partition coefficient of compound between n-octanol and water; n-ON acceptors: number of hydrogen bond acceptors; n-OHNH donors: number of hydrogen bonds donors.

Conclusion

The development of economical and environmentally friendly catalyst has a massive importance in the field of organic synthesis and is extensively needed for industrial processes. In light of this. we have developed a simple, efficient and eco-friendly one-pot three-component method for the synthesis of medicinal and biologically significant 2,4,5-triaryl-1*H*-imidazole derivatives from benzil, various aromatic aldehydes, and ammonium acetate in ethanol using lemon juice as a bio-catalyst. The advantages of this method include high yield, simple workup procedure, economical, easy product purification, short reaction time, and avoid the use of hazardous metals.

Disclosure of conflict of interest

The authors declare no conflicts of interest.

Author contributions

All the authors have contributed equally in designing, drafting the manuscript as per the journal submission format. All authors read and approved the final manuscript.

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