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Microwave-assisted rapid synthesis of substituted oxazoles in a non-ionic liquid medium and their antimicrobial evaluation

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Abstract
A rapid and sustainable microwave-assisted protocol has been established for the synthesis of substituted oxazole derivatives employing polyethylene glycol (PEG-600) as a non-ionic green reaction medium. A series of oxazole derivatives (3a-3m) were obtained via catalyst-free cyclo-condensation of α-bromoacetophenone with substituted amides. The reactions were completed within one minute, providing excellent isolated yields ranging from 80-90%. PEG-600 was efficiently recovered and reused, confirming the eco-friendly nature of the process. Structural elucidation was carried out using melting point determination, TLC, IR, ^{1}H NMR, ^{13}C NMR, Mass spectrometry, and elemental analysis. The synthesized compounds were evaluated for *in vitro* antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*. Several derivatives exhibited noteworthy antibacterial efficacy, indicating their potential relevance in pharmaceutical research.

Keywords: Oxazole, microwave synthesis, PEG-600, Green chemistry, antimicrobial activity

1. Introduction
Oxazoles and their derivatives represent an important class of five-membered heterocyclic compounds that have attracted significant attention due to their wide range of biological and pharmaceutical applications. Oxazole frameworks are present in numerous natural products and synthetic drug molecules, and they serve as key structural motifs in medicinal chemistry. A variety of oxazole derivatives have been reported to exhibit potent antibacterial, antifungal, antitubercular, anticancer, anti-inflammatory, analgesic, antitumor, and antibiotic activities [4-9].Because of their biological relevance, oxazole derivatives are extensively used as intermediates for the synthesis of pharmacologically active compounds and advanced functional materials [1]. Several synthetic strategies have been developed for the preparation of substituted oxazoles, including cyclization reactions involving α-halogenated ketones with urea or amides, as well as transition-metal-catalyzed and multicomponent reactions [1-3]. However, many of these methods suffer from limitations such as the use of toxic or expensive catalysts, hazardous solvents, harsh reaction conditions, longer reaction times, and moderate product yields, which restrict their large-scale and environmentally sustainable applications.
In recent years, green chemistry approaches, particularly microwave-assisted organic synthesis, have emerged as powerful tools for reducing reaction time, energy consumption, and waste generation. Microwave irradiation often leads to enhanced reaction rates, cleaner reactions, and improved yields compared to conventional heating methods. Additionally, the use of environmentally benign reaction media plays a crucial role in sustainable chemical synthesis. Polyethylene glycol (PEG-600) has gained importance as a non-toxic, biodegradable, non-volatile, and recyclable non-ionic liquid, making it an attractive green solvent for organic transformations. Earlier studies have demonstrated the successful synthesis of oxazole derivatives in non-ionic liquids under catalyst-free conditions, emphasizing their efficiency and environmental compatibility [1].
Motivated by these considerations and in continuation of efforts toward sustainable heterocyclic synthesis, the present work describes a catalyst-free, microwave-assisted synthesis of substituted oxazoles using PEG-600 as a green solvent. The method offers

Advantages such as short reaction time (1 minute), excellent yields, easy work-up, and solvent recyclability. Furthermore, the synthesized oxazole derivatives were evaluated for their *in vitro* antimicrobial activity against *Staphylococcus aureus* and *Escherichia coli* to assess their potential pharmaceutical significance.

2. Experimental Section

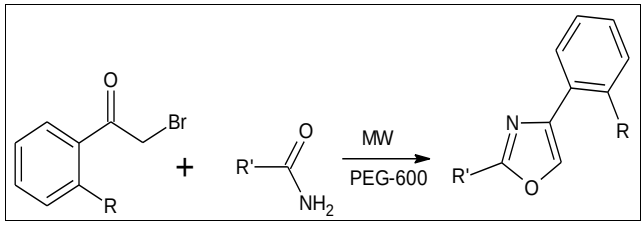
2.1 Materials and Methods

All chemicals used were of analytical grade and procured from commercial suppliers. Melting points were determined using the open capillary method and are uncorrected. Reaction progress and purity were monitored by thin-layer chromatography (TLC) using silica gel plates. Infrared (IR) spectra were recorded on a Perkin-Elmer spectrophotometer using KBr pellets. ^{1}H NMR spectra were recorded on a 300 MHz NMR spectrometer using $CDCl_3$ as solvent and tetramethylsilane (TMS) as the internal standard. Mass spectra were recorded on a GC-MS spectrometer. Elemental analysis (C, H, N) was performed using a Carlo Erba elemental analyzer.

2.2 General Procedure for the Synthesis of 2-Substituted-4-Phenyl Oxazoles

A mixture of α-bromoacetophenone (0.01 mol), substituted amide (0.01 mol), and PEG-600 (sufficient quantity) was taken in a glass beaker and subjected to microwave irradiation in a domestic microwave oven for 1 minute. The completion of the reaction was monitored by TLC. After completion, the reaction mixture was poured into ice-cold water. The resulting solid product was filtered, washed with water, dried, and recrystallized from a suitable solvent to afford pure oxazole derivatives (3a-3m). PEG-600 was recovered from the aqueous filtrate and reused in subsequent reactions as per Scheme.

Reaction Scheme



3. Results and Discussion

3.1 Chemistry

The microwave-assisted cyclo-condensation of α-bromoacetophenone with substituted amides in the presence of PEG-600 as a non-ionic liquid afforded a series of 2-substituted-4-phenyl oxazole derivatives (3a-3m) in excellent yields (80-90%) within one minute (Table 1). The reactions proceeded smoothly under catalyst-free conditions, highlighting the efficiency of PEG-600 as a green reaction medium.

Table 1: Physical Data and Yields of Synthesized Oxazole Derivatives (3a-3m)

Compound	Substituent (R)	Melting Point (°C)	Reaction Time (min)	Yield (%)
3a	C_6H_5	60	1	86
3b	$COCH_3$	40	1	85
3c	p-$CH_3C_6H_5$	80	1	80
3d	2, 4-$Cl_2C_6H_5$	98	1	89
3e	m-FC_6H_5	56	1	82
3f	3, 5-$(NO_2)_2C_6H_5$	54	1	81
3g	o-IC_6H_5	58	1	80
3h	o-OHC_6H_5	66	1	82
3i	o-$CH_3C_6H_5$	52	1	83
3j	p-$OCH_3C_6H_5$	75	1	83
3k	2, 4-$Cl_2C_6H_5$ (OH)	112	1	87
3l	p-$CH_3C_6H_5$ (OH)	160	1	82
3m	p-$NH_2C_6H_5$ (OH)	180	1	80

Compared with conventional synthetic routes for oxazoles, which typically require strong acids, metal catalysts, ionic liquids, or prolonged heating [2, 3], the present method significantly reduces reaction time and avoids hazardous reagents. Previous reports on oxazole synthesis using ionic liquids or copper catalysts required reaction times ranging from several hours to days [2, 3], whereas the current protocol completes the transformation in 60 seconds under microwave irradiation (Table 2).

Table 2: Comparative Yield and Reaction Efficiency with Reported Oxazole Syntheses

Method	Catalyst / Solvent	Time	Yield (%)	Drawbacks	Reference
Conventional heating	Strong acids	6-12 h	50-70	Harsh conditions	[2]
Cu-catalyzed cyclization	CuI, base	4-8 h	65-85	Metal residue	[2]
Ionic liquid method	[BMIM]BF_4	2-4 h	70-88	Cost, toxicity	[3]
Non-ionic liquid	PEG-400	30-60 min	75-85	Longer time	[1]
Present work	PEG-600, microwave	1 min	80-90	Catalyst-free, green	This work

Microwave irradiation enhances molecular collisions and uniform heating, leading to rapid cyclization and improved yields, consistent with earlier reports on microwave-assisted heterocyclic synthesis [1]. The use of PEG-600 further contributes to reaction efficiency due to its high dielectric constant, thermal stability, and ability to solubilize both organic and inorganic species. Notably, the nature of substituents on the amide (electron-donating or electron-

withdrawing) had no significant influence on reaction time or yield, indicating the general applicability and robustness of the methodology. The formation of oxazole derivatives was confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass spectral data, and elemental analysis. The IR spectra showed characteristic absorption bands at 1620 cm^{-1} corresponding to >C=N stretching of the oxazole ring and 1200 cm^{-1} for C-O-C stretching, confirming ring formation.^{1}H NMR spectra displayed a singlet at δ 6.70-6.78 ppm attributed to the oxazole proton, along with multiplets corresponding to aromatic protons. Mass spectra showed molecular ion peaks (M^{+}) consistent with calculated molecular weights, further supporting structural assignment and elemental analysis values closely matched theoretical values, confirming compound purity.

4. Antimicrobial Activity

All synthesized oxazole derivatives (3a-3m) were evaluated for *in vitro* antibacterial activity against *Staphylococcus aureus* (Gram-positive) and *Escherichia coli* (Gram-negative) strains (Table 3).

Table 3: Antibacterial Activity (MIC, µg/mL) of Oxazole Derivatives

Compound	*Staphylococcus aureus*	*Escherichia coli*
3a	-	1.6
3b	-	-
3c	-	2.1
3d	1.5	2.0
3e	-	1.6
3f	-	2.2
3g	0.4	1.5
3h	-	1.4
3i	-	-
3j	-	-
3k	1.5	1.8
3l	1.8	1.7

(-) No significant activity observed.

Structure Activity Relationship Analysis (SAR)

The compounds (3d, 3k) containing halogen substituents exhibited enhanced antibacterial activity, which may be attributed to increased lipophilicity and improved membrane penetration. The compound (3f) showed significant activity against *E. coli*, consistent with literature reports highlighting the role of electron-withdrawing groups (-NO_2) in enhancing antimicrobial potency. The compounds bearing hydroxyl groups (3h, 3k, 3l) demonstrated moderate activity, possibly due to hydrogen-bonding interactions with bacterial enzymes. Simple unsubstituted or alkyl-substituted derivatives (3b, 3i, 3j) exhibited weak or negligible activity, indicating the importance of aromatic and electron-withdrawing substituents for biological activity. Overall, the SAR study suggests that electron-withdrawing and halogen substituents on the aromatic ring enhance antibacterial activity, in agreement with previous studies on oxazole-based antimicrobial agents.

Conclusion

The present study demonstrates an efficient, catalyst-free, and environmentally responsible microwave-assisted approach for the synthesis of substituted oxazole derivatives using PEG-600 as a green solvent. The methodology affords high yields within a remarkably short reaction time and allows solvent recyclability. Biological evaluation revealed that selected derivatives possess promising antibacterial activity. Overall, the developed protocol provides a practical and sustainable route for the preparation of pharmaceutically relevant oxazole scaffolds.

As compared to previously reported methods, the present protocol offers

- Shortest reaction time (1 minute)
- High and consistent yields
- Elimination of catalysts and toxic solvents
- Excellent green chemistry compliance

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Declaration

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