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# Micellar-Mediated Phosphomolybdic Acid: A Highly Effective Catalyst for the Synthesis of 1,5-Benzodiazepine Derivatives Via A One-Pot Three-Component Reaction

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## ABSTRACT

*Benzodiazepines are an important class of heterocyclic compounds with diverse pharmacological activities, including anticonvulsant, anti-inflammatory, analgesic, hypnotic, sedative, and anxiolytic properties. Beyond their therapeutic relevance, 1,5-benzodiazepine derivatives serve as intermediates for the synthesis of fused heterocyclic systems and find industrial applications as dyes and in photographic processes. Conventional synthetic methods often suffer from harsh conditions, long reaction times, and limited yields, highlighting the need for greener alternatives.In this study, phosphomolybdic acid (PMA) was employed as a recyclable and environmentally benign catalyst for the one-pot, three-component synthesis of ethyl 4-methyl-2-phenyl substituted-2,3-dihydro-1H-1,5-benzodiazepine-3-carboxylate derivatives. The method proved operationally simple, affording excellent yields (97–98%) within short reaction times (30–50 minutes) under mild conditions. Spectral characterization (FT-IR, $^1H$ NMR) confirmed the structures, while antibacterial screening revealed promising activity, particularly for the 2-phenyl derivative (1a), which showed inhibition zones approaching ciprofloxacin against both Gram-positive and Gram-negative strains.The antibacterial activity observed for compounds 1a–1c suggests potential pharmacological applications, positioning benzodiazepine scaffolds as promising leads for new antimicrobial agents. Recent advances in micellar catalysis and phosphomolybdic acid applications further validate the efficiency and sustainability of this approach, offering a green and practical route to biologically relevant benzodiazepines with pharmaceutical potential.*

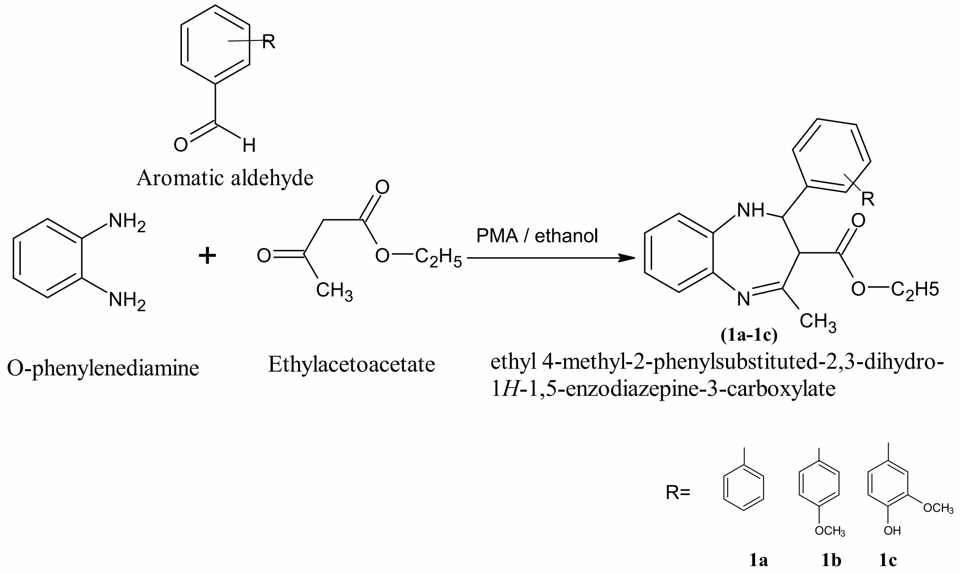
**Keywords:** *1,5-benzodiazepine derivatives; phosphomolybdic acid; one-pot synthesis; multicomponent reaction; recyclable catalyst.*

## 1. Introduction

Benzodiazepines constitute an important class of heterocyclic compounds that have attracted considerable attention in medicinal chemistry owing to their broad spectrum of pharmacological activities. These compounds exhibit diverse biological properties, including anticonvulsant, anti-inflammatory, analgesic, hypnotic, sedative, and anxiolytic effects, making them valuable therapeutic agents in modern medicine [1]. In addition to their pharmaceutical significance, 1,5-benzodiazepine derivatives possess notable industrial applications, particularly as dyes for acrylic fibers and as intermediates in photographic materials [2-3].The unique structural framework of benzodiazepines also enables their utilization as versatile building blocks for the synthesis of fused heterocyclic systems such as triazolo-, oxadiazolo-, oxazino-, and furano-benzodiazepines, many of which exhibit enhanced biological and pharmacological properties [4-5]. Consequently, the development of efficient and environmentally sustainable synthetic methodologies for benzodiazepine derivatives continues to be an active area of research.

1,5-benzodiazepines are synthesized through the condensation of *o*-phenylenediamine (OPDA) with α,β-unsaturated carbonyl compounds, β-haloketones, or ketones in the presence of acidic catalysts. Numerous catalytic systems have been reported for this transformation, including $BF_3{\cdot}Et_2O$, polyphosphoric acid, $NaBH_4$, $MgO/POCl_3$, $Yb(OTf)_3$, $Ga(OTf)_3$, lead nitrate, L-proline, molecular iodine, ionic liquids, and microwave-assisted acetic acid protocols. More recently, heterogeneous catalysts such as sulphated zirconia, $Al_2O_3/P_2O_5$, $Ag_3PW_{12}O_{40}$, PVP–$FeCl_3$, and zeolites have been explored to improve reaction efficiency and catalyst recovery [6].Despite these advances, many of the reported methodologies suffer from limitations such as harsh reaction conditions, prolonged reaction times, low product yields, difficult work-up procedures, and the use of environmentally undesirable reagents, certain solid oxide catalysts exhibit reduced catalytic performance due to their relatively low surface area and limited pore volume, restricting substrate accessibility and catalytic efficiency.In response to these challenges, increasing emphasis has been placed on the development of green and sustainable catalytic processes [7-9]. Among the emerging approaches, micellar catalysis and mesoporous materials with tunable pore architectures have demonstrated significant potential owing to their enhanced catalytic activity, selectivity, and recyclability, phosphomolybdic acid (PMA), a heteropoly acid catalyst, has emerged as an attractive alternative because of its strong Brønsted acidity, high catalytic efficiency, ease of recovery, and environmentally benign nature.The present study describes the application of phosphomolybdic acid as an efficient and recyclable catalyst for the one-pot, three-component synthesis of 1,5-benzodiazepine derivatives [10]. This methodology provides a simple, rapid, high-yielding, and environmentally friendly approach for the preparation of benzodiazepine scaffolds of considerable pharmaceutical and industrial importance.

**Scheme 1**



## 2. Experimental Work

### 2.1 Materials and Methods

All chemicals and reagents employed in the present investigation were obtained from commercial sources and used as received without further purification. The progress of the reactions was monitored by thin-layer chromatography (TLC) on aluminum plates precoated with silica gel 60 F254. The chromatographic spots were visualized under ultraviolet (UV) light and by exposure to iodine vapors.Melting points of the synthesized compounds were determined in open capillary tubes and are reported uncorrected. Structural characterization and functional group identification were carried out using Fourier Transform Infrared (FTIR) spectroscopy on a Shimadzu FTIR-8400S spectrophotometer employing KBr pellet techniques. Elemental composition analyses were performed using a PerkinElmer elemental analyzer to confirm the purity and molecular composition of the synthesized products.The majority of the chemicals, solvents, and analytical-grade reagents used throughout the study were procured from Aldrich Chemical Corporation and other standard commercial suppliers. All reactions were conducted under appropriate laboratory conditions, and the obtained products were isolated and purified using conventional procedures before characterization.

### 2.2 General Procedure for the Synthesis of Ethyl 4-Methyl-2-Phenyl Substituted-2,3-Dihydro-1H-1,5-Benzodiazepine-3-Carboxylate Derivatives (1a–1c)

A mixture of *o*-phenylenediamine (1 mmol) and ethyl acetoacetate (1 mmol) was dissolved in ethanol, and phosphomolybdic acid (PMA) (1 mol%) was added as the catalyst. The reaction mixture was stirred at room temperature for 15 min to ensure complete mixing and activation of the reactants.

Subsequently, the appropriate aromatic aldehyde (1 mmol) was introduced into the reaction mixture, and the resulting solution was refluxed for the duration indicated in Table 1. The progress of the reaction was monitored periodically by thin-layer chromatography (TLC) using silica gel 60 F254 plates. Upon completion of the reaction, the mixture was allowed to cool to room temperature. The phosphomolybdic acid catalyst was then recovered by simple filtration, thoroughly washed with ethyl acetate to remove any adsorbed organic materials, dried, and reused in subsequent reaction cycles.The combined filtrate was concentrated under reduced pressure using a rotary evaporator to remove the solvent [11]. The resulting crude product was purified by recrystallization from ethanol to furnish the corresponding 1,5-benzodiazepine derivatives in high purity. The synthesized compounds were subsequently characterized by melting point determination, FTIR spectroscopy, and elemental analysis.

The synthesized compounds (1a–1c) were characterized by melting point determination and spectral analysis.

*Table 1: Synthesis of 1,5-Benzodiazepine Derivatives*

| C.NO | Aromatic aldehyde | 1,5-Benzodiazepine Derivatives | Time (min) |
|---|---|---|---|
| 1a | Benzaldehyde | Ethyl 4-methyl-2-phenyl-2,3-dihydro-1H-1,5-benzodiazepine-3-carboxylate | 45 |
| 1b | Anisaldehyde | Ethyl 2-(4-methoxyphenyl)-4-methyl-2-phenyl-2,3-dihydro-1H-1,5-benzodiazepine-3-carboxylate | 50 |
| 1c | Vanillin | Ethyl 2-(4-hydroxy-3-methoxyphenyl)-4-methyl-2-phenyl-2,3-dihydro-1H-1,5-benzodiazepine-3-carboxylate | 30 |

## 3. Physical, IR and 1H NMR Spectral Characterization of Synthesized Compounds

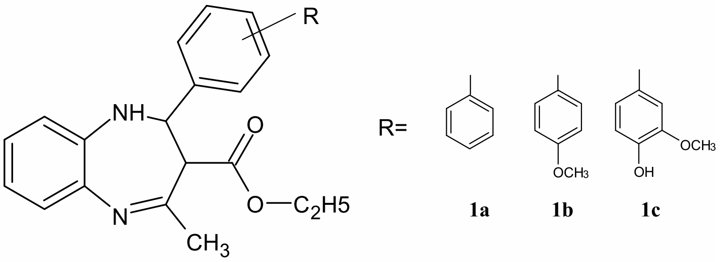


*Table 2: Physical Characterization of Synthesized 1,5-Benzodiazepine Derivatives*

| Parameters | Compound 1a | Compound 1b | Compound 1c |
|---|---|---|---|
| Colour | Yellow | Yellow | Yellow |
| Percentage Yield | 97 % % w/w | 97 %w/w | 98 % w/w |
| Melting Point | 129-132 °C | 142-145 °C | 137-140°C |
| Solubility | Soluble in ethanol and chloroform | Soluble in ethanol and chloroform | Soluble in ethanol and chloroform |
| Mobile Phase | Ethyl acetate: Hexane (7:3) | Ethyl acetate: Hexane (7:3) | Ethyl acetate: Hexane (7:3) |
| Rf Value | 0.52 | 0.54 | 0.51 |
| Molecular Formula | $C_{19}H_{20}N_2O_2$ | $C_{20}H_{22}N_2O_3$ | $C_{20}H_{22}N_2O_4$ |
| Molecular Weight | 308.37 | 338.40 | 354.40 |
| Elemental Composition | C (74.00%), H (6.54%), N (9.08%), O (10.38%) | C (70.99%), H (6.55%), N (8.28%), O (14.18%) | C (67.78%), H (6.26%), N (7.90%), O (18.06%) |

*Table 3: IR Spectral Data of Ethyl 4-Methyl-2-Phenyl Substituted-2,3-Dihydro-1H-1,5-Benzodiazepine-3-Carboxylate Derivatives (1a–1c)*

| Absorption Frequency Region ($cm^{-1}$) | Functional Group | Compound 1a ($cm^{-1}$) | Compound 1b ($cm^{-1}$) | Compound 1c ($cm^{-1}$) |
|---|---|---|---|---|
| 3200–3600 (broad) | O–H Stretching | 3385.84 | 3371.78 | 3471.61 |
| 3300–3500 (medium, sharp) | N–H Stretching | may overlap with OH | may overlap with OH | may overlap with OH |
| 3000–2800 | C–H (aromatic)Stretching | 2926.44 | 2925.02 | 2926.07 |
| 2860–2800 | C–H (alkyl)Stretching | — | 2840.95 | 2860.95 |
| 1616–1600 | C=O Stretching | 1600.81 | 1600.04 | 1596.91 |
| 1300–1050 | C–O stretch | 1129.93 | 1245.60 | 1260.95 |

*Table 4: 1H NMR spectrum data of Ethyl 4-Methyl-2-Phenyl Substituted-2,3-Dihydro-1H-1,5-Benzodiazepine-3-Carboxylate Derivatives (1a–1c)*

| Proton group | Approx. δ (ppm) | Splitting pattern | Integration | Compound 1a (δ ppm) | Compound 1b (δ ppm) | Compound 1c (δ ppm) |
|---|---|---|---|---|---|---|
| **Ethoxy $CH_3$** | 1.2–1.3 | Triplet | 3H | 1.25 | 1.25 | 1.25 |
| **Methyl on a heterocycle** | 2.2–2.6 | Singlet | 3H | 2.35 | 2.35 | 2.30 |
| **Methoxy group** | 3.7–3.9 | Singlet | 3H | – | 3.85 | 3.80 |
| **Ethoxy $CH_2$** | 3.9–4.2 | Quartet | 2H | 4.20 | 4.15 | 4.20 |
| **Aromatic/heterocyclic protons** | 6.5–8.5 | Multiplets | 4–6H | 7.0–7.8 | 7.2–8.0 | 7.1–7.9 |
| **NH proton** | 9–12 | Broad singlet | 1H | 10.5 | 10.3 | 10.4 |

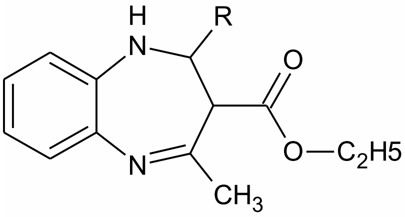
## 4. *In vitro* anti-bacterial screening

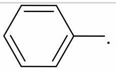
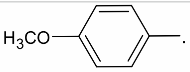
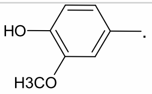
The anti-bacterial activity of synthesized ethyl 4-methyl-2-phenyl substituted-2, 3-dihydro-1H-1, 5-benzodiazepine-3-carboxylate derivatives against both Gram +ve (*Staphylococcus aureus, Bacillus subtilis*) and Gram – ve (*Klebsiella, Pseudomonas, Escherichia coli*) bacteria was carried out by the cup plate method.

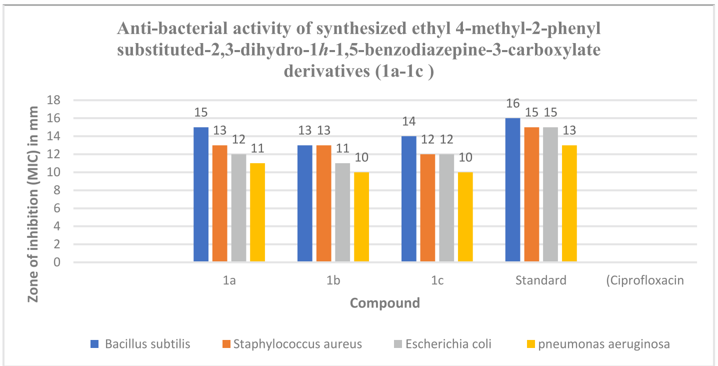
### Procedure

The antibacterial activity of the synthesized 1,5-benzodiazepine derivatives was evaluated using the standard disc diffusion method against selected Gram-positive and Gram-negative bacterial strains. The test microorganisms included the Gram-positive bacteria *Bacillus subtilis* and *Staphylococcus aureus*, and the Gram-negative bacteria *Escherichia coli* and *Pseudomonas aeruginosa*.Nutrient agar medium was prepared by dissolving beef extract (1.0 g), peptone (1.0 g), and sodium chloride (0.5 g) in 100 mL of double-distilled water. The medium was sterilized by autoclaving and allowed to cool before being poured into sterile Petri dishes. The agar plates were left undisturbed for approximately 30 min to ensure complete solidification.Fresh overnight bacterial cultures were uniformly spread over the surface of the solidified nutrient agar plates using sterile cotton swabs to obtain a confluent lawn of growth. Sterile paper discs (5 mm diameter) prepared from Whatman filter paper were impregnated with solutions of the synthesized compounds at a concentration of 20 µg/disc and carefully placed on the inoculated agar surface. Discs containing the standard antibacterial drug ciprofloxacin (20 µg/disc) were used as positive controls, while solvent-impregnated discs served as negative controls where appropriate.

*Table 5: Anti-bacterial activity of synthesized ethyl 4-methyl-2-phenyl substituted-2,3-dihydro-1h-1,5-benzodiazepine-3-carboxylate derivatives (1a-1c)*



| C.NO | Compound | Zone of inhibition (MIC) in mm | | | |
|---|---|---|---|---|---|
| | | Gram +ve | | Gram – ve | |
| | | *Bacillus subtilis* | *Staphylococcus aureus* | *Escherichia coli* | *pneumonas aeruginosa* |
| 1a |  | 15 | 13 | 12 | 11 |
| 1b |  | 13 | 13 | 11 | 10 |
| 1c |  | 14 | 12 | 12 | 10 |
| Standard | Ciprofloxacin | 16 | 15 | 15 | 13 |



## 5. Results and Discussion

The synthesis of ethyl 4-methyl-2-phenyl substituted-2,3-dihydro-1H-1,5-benzodiazepine-3-carboxylate derivatives (1a–1c) was successfully achieved via a one-pot, three-component cyclocondensation of o-phenylenediamine, ethyl acetoacetate, and aromatic aldehydes in ethanol using phosphomolybdic acid (PMA) as a catalyst. The reactions proceeded smoothly under mild conditions, affording yields of 97–98% within 30–50 minutes, which highlights the efficiency of PMA as a recyclable and eco-friendly catalyst.Physical characterization confirmed the purity of the compounds: all derivatives were yellow solids, soluble in ethanol and chloroform, with melting points ranging between 129–145 °C. TLC analysis showed consistent Rf values (~0.51–0.54), indicating reproducibility of the method.

FT-IR spectra exhibited characteristic absorption bands for O–H stretching (3385–3471 $cm^{-1}$), N–H stretching overlapping with O–H (~3370–3385 $cm^{-1}$), aromatic C–H stretching (~2925–2926 $cm^{-1}$), alkyl C–H stretching (~2840–2860 $cm^{-1}$), C=O stretching (~1596–1600 $cm^{-1}$), and strong C–O stretches (~1129–1260 $cm^{-1}$).

$^1$H NMR spectra revealed the expected signals: ethoxy $CH_3$ triplet (~1.25 ppm), ethoxy $CH_2$ quartet (~4.15–4.20 ppm), methyl singlet (~2.30–2.35 ppm), methoxy singlet (~3.80–3.85 ppm in 1b and 1c), aromatic multiplets (7.0–8.0 ppm), and broad OH/NH signals (~9–11 ppm).

Antibacterial activity was evaluated against Gram-positive (*Bacillus subtilis, Staphylococcus aureus*) and Gram-negative (*Escherichia coli, Pseudomonas aeruginosa*) bacteria using the cup-plate diffusion method at 20 µg/ml. All compounds exhibited moderate to strong inhibition zones compared to ciprofloxacin. Notably, compound 1a (2-phenyl derivative) displayed the highest activity (against *B. subtilis*,against *S. aureus*, against *E. coli*, and against *P. aeruginosa*), approaching the standard drug. Compounds 1b and 1c also showed significant activity, particularly against Gram-positive strains [12-22].

## Conclusion

This study demonstrates that phosphomolybdic acid (PMA) is a highly effective, recyclable, and environmentally benign catalyst for the synthesis of 1,5-benzodiazepine derivatives. The method is operationally simple, provides excellent yields in short reaction times, and aligns with the principles of green chemistry. The synthesized compounds were well characterized and exhibited promising antibacterial activity, with the 2-phenyl derivative (1a) showing maximum inhibition across both Gram-positive and Gram-negative bacteria.

The antibacterial activity observed for compounds 1a–1c, particularly 1a, which approached ciprofloxacin in inhibition zones, suggests potential pharmacological applications. Given the global challenge of antibiotic resistance, benzodiazepine scaffolds with demonstrated antibacterial properties may serve as promising leads for new antimicrobial agents. Recent advances in micellar catalysis[10] and phosphomolybdic acid applications [21,22]further validate the efficiency and sustainability of our synthetic approach, positioning these derivatives as candidates for future drug development pipelines.

This approach offers a sustainable route to biologically relevant benzodiazepines with potential pharmaceutical applications.

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