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Lewis Acid Promoted Synthesis of Imidazopyridinyl-1,3,4-Oxadiazole Hybrids with Antibacterial Potential

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ABSTRACT

A simple and efficient Lewis acid–assisted synthetic strategy has been developed for the preparation of a new series of imidazopyridinyl-1,3,4-oxadiazole derivatives. The approach involves cyclodehydration of 2-phenylimidazo[1,2-a]pyridine-3-carbohydrazide with various aromatic and heteroaromatic acid chlorides using boron trifluoride diethyl etherate ($BF_3 \cdot Et_2O$) as a cyclization promoter. The reactions proceed smoothly under mild conditions to afford the desired heterocyclic hybrids in good to excellent yields (79–86%). All synthesized compounds were structurally characterized by IR, ^1H NMR, ^{13}C NMR, and mass spectrometry. The antibacterial activity of the synthesized derivatives was evaluated against *Escherichia coli* and *Staphylococcus aureus* using the cup plate diffusion method. Several compounds exhibited appreciable antibacterial activity compared with streptomycin. Preliminary structure–activity relationship studies indicate that electron-donating and halogen substituents significantly influence antibacterial potency. The present study highlights imidazopyridinyl-1,3,4-oxadiazoles as promising scaffolds for antimicrobial drug development.

Keywords: Imidazopyridine; 1,3,4-Oxadiazole; $BF_3 \cdot Et_2O$; Lewis acid; Antibacterial activity

INTRODUCTION

Heterocyclic compounds constitute one of the most significant classes of organic molecules due to their widespread occurrence in natural products and therapeutic agents [1]. Nitrogen- and oxygen-containing heterocycles are particularly important in medicinal chemistry because of their diverse biological activities and favourable pharmacokinetic profiles [2,3]. Oxadiazoles are five-membered heterocyclic systems containing two nitrogen atoms and one oxygen atom, existing in four regioisomeric forms, namely 1,2,3-, 1,2,4-, 1,2,5-, and 1,3,4-oxadiazoles [2]. Among these, the 1,3,4-oxadiazole ring has gained considerable attention as it acts as a bioisostere of carboxylic acids, esters, and amides, often resulting in enhanced metabolic stability and biological activity [4,5]. A wide range of 1,3,4-oxadiazole derivatives have been reported to exhibit antibacterial, antitubercular, anti-inflammatory, anticancer, antiviral, and enzyme inhibitory activities [6–13].

The imidazopyridine nucleus is another privileged heterocyclic scaffold widely explored in drug discovery. Compounds containing this moiety are known to display antimicrobial, anticancer, and central nervous system activities [21–25]. Hybridization of imidazopyridine with other biologically relevant heterocycles has been shown to enhance pharmacological profiles by increasing molecular rigidity and improving interactions with biological targets. Several synthetic approaches for imidazopyridinyl-1,3,4-oxadiazole conjugates have been reported [22–27]; however, many of these methods require harsh reaction conditions, multistep procedures, or strong dehydrating agents. Therefore, the development of a mild, efficient, and operationally simple synthetic protocol remains desirable.

In continuation of our ongoing efforts toward the synthesis of biologically important heterocycles [28,29], we report herein a Lewis acid–mediated cyclodehydration approach for the synthesis of novel

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

imidazopyridinyl-1,3,4-oxadiazoles using $BF_3 \cdot Et_2O$ and the evaluation of their antibacterial activity.

MATERIALS AND INSTRUMENTATION

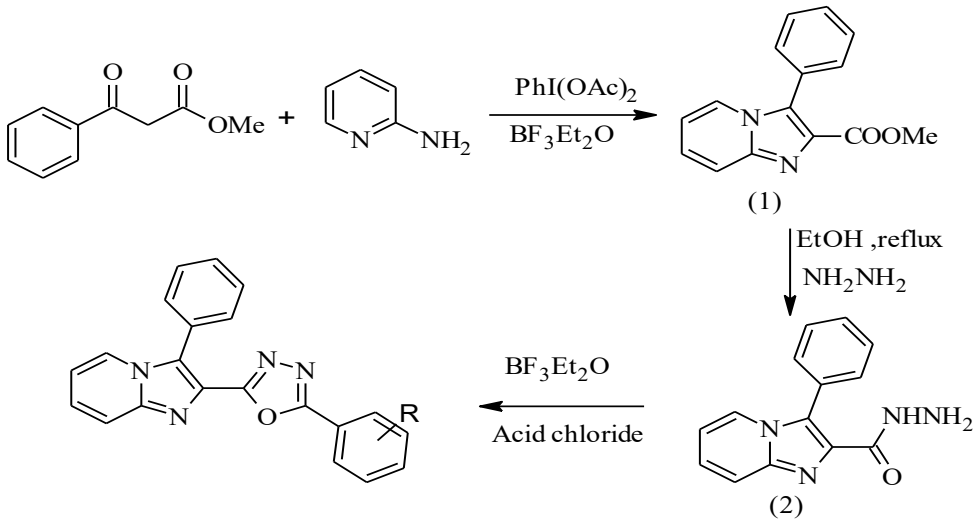
All chemicals were obtained from commercial suppliers and used without further purification. Reaction progress was monitored by TLC. IR spectra were recorded using KBr pellets. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as an internal standard. Mass spectra were obtained using GC–MS. Melting points were determined by open capillary method.

EXPERIMENTAL PROCEDURE

GENERAL PROCEDURE FOR THE SYNTHESIS OF IMIDAZOPYRIDINYL-1,3,4-OXADIAZOLES (3A–3K)

To a solution of 2-phenylimidazo[1,2-a] pyridine-3-carbohydrazide (1.0 mmol) in chloroform (20 mL), the appropriate acid chloride (1.1 mmol) was added and stirred for 30 min. $BF_3 \cdot Et_2O$ (0.5 mmol) was then added, and the reaction mixture was refluxed for 3–4 h. After completion, the reaction mixture was poured into ice-cold water and extracted with chloroform. The organic layer was dried over anhydrous Na_2SO_4, concentrated, and purified by column chromatography.

REACTION SCHEME



SCHEME: Lewis acid–mediated cyclodehydration of 2-phenylimidazo[1,2-a] pyridine-3-carbohydrazide with aromatic/heteroaromatic acid chlorides to afford imidazopyridinyl-1,3,4-oxadiazoles.

SPECTRAL CHARACTERIZATION

All synthesized compounds were characterized by IR, ^1H NMR, ^{13}C NMR, and mass spectrometry. The IR spectra showed characteristic absorption bands corresponding to >C=N stretching vibrations of the oxadiazole ring and C–O–C linkages, confirming cyclization. The NMR spectral data were consistent with the proposed structures, and molecular ion peaks observed in the mass spectra further supported the assigned molecular formulas.

With the optimized reaction conditions in hand, the generality of the protocol was explored using various acid chlorides and orthoformates. The results are summarized in **TABLE 1**.

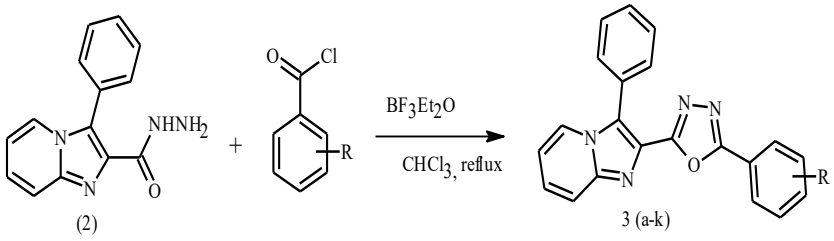
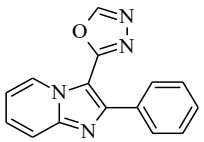
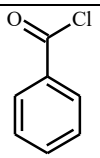
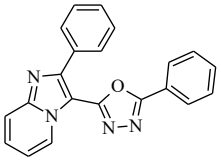
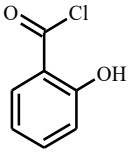
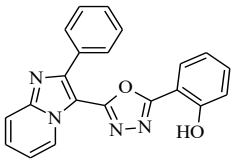
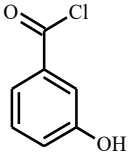
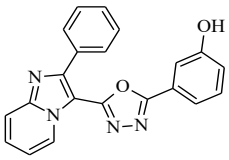
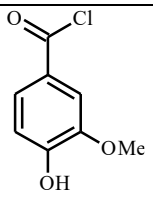
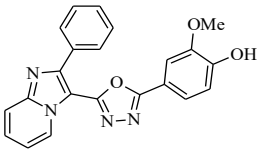
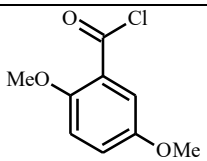
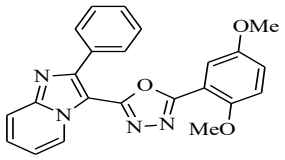
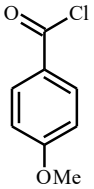
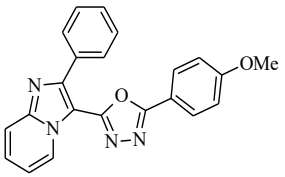
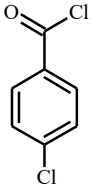
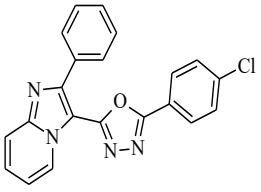
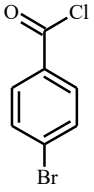
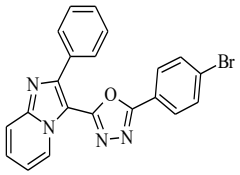
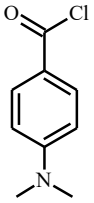
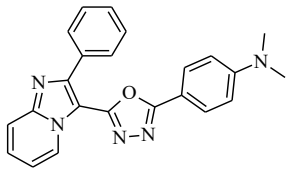
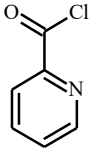
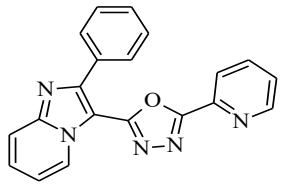


Table 1. Synthesis Of 2-[5-(Aryl)-1,3,4-Oxadiazol-2-Yl]-3-Phenylimidazo [1,2-A]Pyridine (3a-3k)[A]:

Sr.No.	Acid Chloride (R)	Product (3)	Yield[b](%)	MP(^{0}C)
1	$HC(OEt)_3$	 **(3a)**	80	114-120
2		 **(3b)**	85	178-180
3		 **(3c)**	86	200-202
4		 **(3d)**	85	250-252
5		 **(3e)**	82	208-212
6		 **(3f)**	83	176-178
7		 **(3g)**	80	182-184
8		 **(3h)**	82	258-260

9		 **(3i)**	83	252-254
10		 **(3j)**	81	204-206
11		 **(3k)**	79	220-222

[a]Reaction condition**:** (**2**) (1.0mol), acid chloride/orthoformate(1.1mol), $BF_3.Et_2O$ (0.5mol), chloroform (20mL) were fluxed for 3-4 hrs.

[b]Isolated yields after chromatography

RESULTS AND DISCUSSION

The synthetic pathway employed for the preparation of imidazopyridinyl-1,3,4-oxadiazole derivatives is illustrated in **SCHEME 1**. Methyl-2-phenylimidazo[1,2-a]pyridine-3-carboxylate was synthesized according to a reported method [30]. Subsequent hydrazinolysis afforded the key intermediate, 2-phenylimidazo[1,2-a]pyridine-3-carbohydrazide. Cyclodehydration of the hydrazide intermediate with various aromatic and heteroaromatic acid chlorides was carried out using $BF_3 \cdot Et_2O$ as a Lewis acid catalyst. Reaction optimization studies revealed that chloroform is the most suitable solvent and that 0.5 equivalents of $BF_3 \cdot Et_2O$ are sufficient to promote efficient cyclization. Under the optimized conditions, the desired imidazopyridinyl-1,3,4-oxadiazoles were obtained in good to excellent yields (79–86%), demonstrating broad substrate scope and good functional group tolerance.

The antibacterial activity of compounds 3a–3k was evaluated against *Escherichia coli* (Gram-negative) and *Staphylococcus aureus* (Gram-positive) using the cup plate diffusion method at a concentration of 100 µg mL^{-1} [31,32]. Streptomycin was used as the standard drug.

Table 2: Antibacterial Activity Of Synthesized Imidazo- Pyridinyl-1,3,4-Oxadiazoles (3a–3k).

(Zone of inhibition measured in mm using the cup plate diffusion method at 100 µg mL^{-1}.)

Compound	Substituent (Ar)	*E. coli* (mm)	*S. aureus* (mm)
3a	–OEt	15	15
3b	Phenyl	17	20
3c	2-Hydroxyphenyl	17	18
3d	3-Hydroxyphenyl	17	15
3e	2-Methoxy-4-hydroxyphenyl	19	15
3f	2,5-Dimethoxyphenyl	18	19
3g	4-Methoxyphenyl	20	17

3h	4-Chlorophenyl	20	18
3i	4-Bromophenyl	18	19
3j	4-(N,N-Dimethylamino)phenyl	14	20
3k	Pyridin-2-yl	19	18
Streptomycin	Standard	22	23

Although cytotoxicity was not evaluated in the present study, the observed antibacterial activity at moderate concentrations suggests a favorable selectivity profile, warranting further biological investigation.

STRUCTURE–ACTIVITY RELATIONSHIP (SAR)

Preliminary SAR analysis indicates that electron-donating substituents such as methoxy and dimethylamino groups enhance antibacterial activity, possibly by increasing lipophilicity and membrane permeability [6,8]. Halogen-substituted derivatives also exhibited improved activity, which may be attributed to favorable hydrophobic and halogen-bonding interactions with bacterial targets [33]. The imidazopyridine core appears to play a crucial role in biological activity by facilitating π–π stacking and hydrophobic interactions.

The structure–activity relationship analysis **(TABLE 3)** reveals a strong correlation between lipophilicity (logP) and antibacterial activity. Compounds possessing moderate to high logP values (2.5–3.3) exhibited enhanced antibacterial activity, particularly against *E. coli*, suggesting improved membrane penetration. Electron-donating substituents such as methoxy and dimethylamino groups increased activity by optimizing lipophilicity and electronic distribution. Halogen-substituted derivatives (3h and 3i) displayed superior activity, likely due to favorable hydrophobic and halogen-bonding interactions with bacterial targets. Compounds bearing polar substituents showed balanced activity, indicating that an optimal lipophilicity range is critical for antibacterial efficacy.

Table 3. Structure–Activity Relationship (Sar) Analysis With Estimated Logp Values

Relationship between aryl substitution, lipophilicity (logP), and antibacterial activity of imidazopyridinyl-1,3,4-oxadiazoles (3a–3k).

Compound	**Aryl Substituent (Ar)**	**Substituent Nature**	**Estimated logP***	***E. coli* Activity**	***S. aureus* Activity**	**SAR Interpretation**
3a	–OEt	Moderately electron-donating	2.3	Moderate	Moderate	Moderate lipophilicity supports membrane permeation
3b	Phenyl	Neutral hydrophobic	2.8	Good	Very good	Balanced lipophilicity enhances activity
3c	2-Hydroxyphenyl	Electron-donating, polar	2.1	Good	Good	H-bonding improves interaction but slightly lowers lipophilicity
3d	3-Hydroxyphenyl	Electron-donating, polar	2.0	Good	Moderate	Positional effect reduces activity
3e	2-Methoxy-4-hydroxyphenyl	Strong EDG, polar	2.4	Very good	Moderate	Optimal balance of polarity and lipophilicity

3f	2,5-Dimethoxyphenyl	Strong EDG	2.7	Good	Very good	Increased lipophilicity enhances Gram-positive activity
3g	4-Methoxyphenyl	Electron-donating	2.9	Excellent	Good	High lipophilicity favors Gram-negative penetration
3h	4-Chlorophenyl	Electron-withdrawing, halogen	3.1	Excellent	Good	Halogen bonding and hydrophobic interaction
3i	4-Bromophenyl	Strong hydrophobic	3.3	Good	Very good	Higher logP enhances membrane interaction
3j	4-(N,N-Dimethylamino)phenyl	Strong EDG, basic	2.6	Moderate	Excellent	Cationic nature favors Gram-positive binding
3k	Pyridin-2-yl	Heteroaryl, polar	2.2	Very good	Good	Heteroatom improves target interaction

* *Estimated logP values based on substituent hydrophobicity trends and comparable heterocyclic systems.*

Compared to previously reported imidazopyridinyl and oxadiazole derivatives [22–27], the present compounds demonstrate comparable or improved antibacterial activity under milder synthetic conditions, highlighting the efficiency of the Lewis acid–mediated approach.

In early-stage drug discovery, assessment of drug likeness is commonly performed to evaluate the suitability of bioactive compounds for further development. Lipinski's rule of five is a widely accepted empirical guideline used to predict oral bioavailability based on key physicochemical parameters such as molecular weight, lipophilicity (logP), hydrogen bond donors, and hydrogen bond acceptors. Since the present study focuses on small-molecule heterocyclic compounds intended for antimicrobial applications, Lipinski's rule was applied to synthesized imidazopyridinyl-1,3,4-oxadiazoles which possess comparatively higher antibacterial activity and structural diversity for drug-likeness evaluation in order to identify promising candidates for further development. The results of this analysis are given in TABLE 4.

Table 4. Drug-Likeness Evaluation Of Selected Imidazo Pyridinyl-1,3,4-Oxadiazoles

Compound	MW	logP	HBD	HBA	Lipinski Compliance
3b	<500	2.8	≤5	≤10	Yes
3g	<500	2.9	≤5	≤10	Yes
3h	<500	3.1	≤5	≤10	Yes
3i	<500	3.3	≤5	≤10	Yes

All selected compounds complied with Lipinski's rule of five, suggesting favourable oral drug-likeness.

CONCLUSION

In summary, a mild and efficient Lewis acid–mediated protocol has been developed for the synthesis of novel imidazopyridinyl-1,3,4-oxadiazole derivatives using $BF_3 \cdot Et_2O$. The methodology offers good yields, operational simplicity, and broad substrate scope. The synthesized compounds exhibited promising antibacterial activity against both Gram-positive and Gram-negative bacteria. These findings suggest that imidazopyridinyl-1,3,4-oxadiazoles represent a valuable scaffold for further antimicrobial research. Further optimization of substituent patterns and evaluation against resistant

bacterial strains are underway to improve potency and selectivity.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

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