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One-pot two-step facile synthesis of 2,3,4,5-tetra substituted dihydrooxazoles and their antimicrobial activity

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ABSTRACT

New 2,3,4,5-tetra substituted dihydrooxazoles derivatives were efficiently synthesized starting from benzaldehyde, aryl thiosemicarbazide and benzoin using designed synthetic route. Newly synthesized 2,3,4,5-tetra substituted dihydrooxazole derivatives were screened for their antibacterial and antifungal activities against different strains of pathogenic bacteria and fungi. The minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBC) and minimum fungicidal concentration (MFC) were determined for the test compounds using positive and negative control. Compounds **4b**, **4d**, **4f**, **4i**, **4k** and **4m**, have shown good antibacterial activity whereas compounds **4e**, **4g**, **4h**, **4j**, **4l** and **4n** have displayed better antifungal activity.

One pot synthesis of drug-like small molecules has been interest for medicinal chemists and chemical biologists because, this provide the important scaffolds in fewer steps and these molecules play very important role in drug discovery processes.[1] Several bacterial infections such as diarrhea, food poisoning, rheumatic salmonellosis, extraintestinal and intestinal wall infections are caused by gram-positive and gram-negative pathogens.[2] The resistance of pathogens bacteria towards available antibiotics is rapidly becoming a major threat to human health world- wide.[3] In addition, fungal infections continue to increase dramatically because of growing number of immunocompromised hosts such as AIDS patients or those undergoing anticancer chemotherapy and transplantation.[4–6] Resistance to known antibiotics is becoming great concern in scientific community and big challenge to develop new scaffold as biologically active molecules. Therefore, design of new antimicrobial compounds to deal with these problems is of prime interest.

Oxazoles are class of compounds that are believed to occur in nature from post-translational modification of serine and threonine residue in peptides. They are the key building blocks of natural products, pharmaceuticals and synthetic intermediates. Oxazoles have not only attracted great interest due to their appearance as subunit of various biologically active natural products but also because of their appearance as subunit of valuable precursors in many useful synthetic transformations. Among the numerous heterocyclic moieties of biological and pharmacological interests, the oxazole ring is endowed with a vital role in the manufacture of various active drugs as brain-derived neurotropic factor induced,[7] analgesic,[8] trypanocidal activity,[9] antimitotic agents with pro-apoptotic activity,[10] antifungal activity,[11] anti-inflammatory,[12] antidepressant,[13] pesticidal,[14] and antimicrobial activity.[15]

Thiourea and its derivatives have found extensive applications in the field of medicine, agriculture and analytical chemistry. They are known to exhibit a wide variety of biological activities such as antiviral, antibacterial, antifungal,[16] The union of heterocyclic ring with thiourea linkage often results compounds with enhanced biological performance.[17]

In light of the above literature and abundance on bio-potentials of oxazoles and thiourea analogues, we designed 2,3,4,5-tetra substituted dihydrooxazoles having thiourea as one of the appendages and were confident that these framework would provide the important structural motifs for the discovery of new antimicrobial agents. In continuation of our research on efficient synthesis of biologically active small molecules,[18] we developed one-pot synthesis of 2,3,4,5-tetra substituted dihydrooxazole derivatives and demonstrated their antimicrobial activity.

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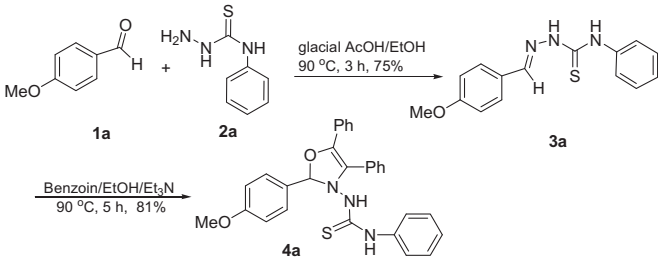


Scheme 1. Synthesis of **4a**.

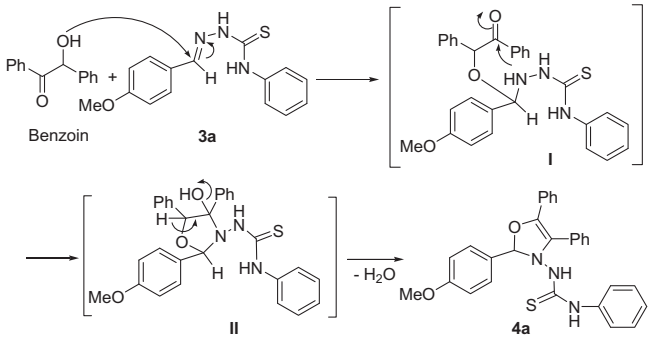


Figure 1. Proposed Mechanism.

Chemistry

For the development of efficient and facile synthesis of new 2,3,4,5-tetra substituted dihydrooxazole derivatives, we identified substituted benzaldehyde **1a** and 4-phenyl thiosemicarbazide **2a** and benzoin as the key starting materials that can be transferred to our designed molecules in two step via Schiff's base intermediate **3a**. We initiated our synthetic protocol with 4-methoxy benzaldehyde **1a** refluxing with 4-phenyl thiosemicarbazide **2a** in ethanol in the presence of catalytic amount of acetic acid which furnished corresponding Schiff's bases **3a** as reported in literature in good yields.[19–22] The Schiff's bases **2a** were purified by crystallization and characterized using spectroscopic data. All the NMR and IR data of the Schiff's bases **2a** were found consistent with the reported analytical data. After obtaining Schiff's base **2a**, it was refluxed with benzoin under various reaction conditions using different solvents (MeOH, EtOH Toluene, THF etc) under reflux for 4–5 h, where ethanol in basic condition was found superior with the formation of clean product **4a** (TLC). Reaction mixture was cooled to room temperature, after work-up and purification it furnished compound **4a** in very good (81%) isolated yield (Scheme 1).

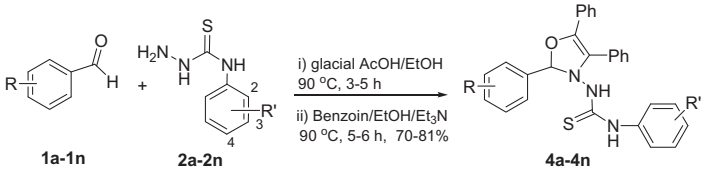
Once reaction condition was standardized, it was decided to perform same transformation in one-pot two-step manner which may furnish the designed 2, 3, 4, 5-tetra substituted dihydrooxazole derivatives **4a**. Thus 4-methoxy benzaldehyde **1a** was refluxed with 4-phenyl thiosemicarbazide **2a** in ethanol in the presence of catalytic amount of acetic acid for 5 h with careful reaction monitoring (TLC) then benzoin was added to same reaction mixture along with little excess of triethyl amine. Resulting mixture was stirred continuously at high temperature (90 °C) for another 5 h which shows the formation of desired product **4a** (TLC). The reaction mixture was cooled to room temperature and after usual workup compound **4a** was obtained in overall 80% isolated yields (Table 1). On optimization of one-pot two-step condition a series of 4-aryl thiosemicarbazides **2b-2n** were successfully transformed into corresponding 2, 3, 4, 5-tetra substituted dihydrooxazole derivatives **4b-4n** using similar reaction protocol in good to very good yields (Table 1). Two different benzaldehydes, viz 4-methoxy benzaldehyde and 4-hydroxy benzaldehyde, along with seven different 4-aryl thiosemicarbazides **2a–2n** were used in this synthetic study and results are summarized in Table 1.

The mechanism of this transformation can be postulated as follows. The hydroxyl group of benzoin (in the presence of triethyl amine at elevated temperature) attacked on imine carbon moving imine double bond towards nitrogen to form an unstable intermediate **I** (Fig. 1). Intramolecular attack of thiosemicarbazide N-atom to carbonyl carbon of benzoin formed intermediate **II** which under high temperature reaction conditions lost a water molecule and furnished stable 2,3,4,5-tetra substituted dihydrooxazoles derivatives **4a**. All the compounds and intermediates were confirmed by spectral analysis.[23]

Biology

The synthesized pure compounds were screened for antibacterial and antifungal activities adopting standard protocols.[24] The antibacterial activity, of prepared final pure compounds **4a–4n** was performed against *Staphylococcus aureus, Bacillus subtilis, Escherichia coli and Klebsiella pneumoniae* using Ciprofloxacin as

Table 1
Synthesis of 2,3,4,5-tetra substituted dihydrooxazoles derivatives.



Compounds	R	R′	Yield%	Compounds	R	R′	Yield%
4a	4-OMe	H	80	**4h**	4-OH	H	79
4b	4-OMe	2-OMe	75	**4i**	4-OH	2-OMe	76
4c	4-OMe	4-OMe	76	**4j**	4-OH	4-OMe	74
4d	4-OMe	2-Me	81	**4k**	4-OH	2-Me	80
4e	4-OMe	4-Me	70	**4l**	4-OH	4-Me	69
4f	4-OMe	2-Cl	65	**4m**	4-OH	2-Cl	63
4g	4-OMe	4-Cl	68	**4n**	4-OH	4-Cl	62