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Author: E. Rajanarendar K. Thirupathaiah S. Ramakrishna D. Nagaraju

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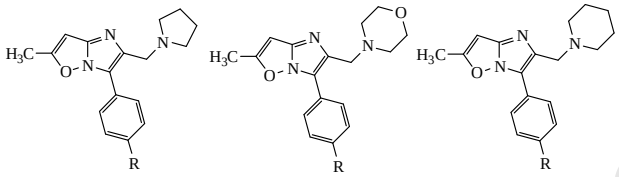
Graphical Abstract

A facile and convenient synthesis of novel imidazo[1,2-*b*]isoxazoles and their Mannich bases as potential biodynamic agents

E. Rajanarendar*, K. Thirupathaiah, S. Ramakrishna, D. Nagaraju
Department of Chemistry, Kakatiya University, Warangal, TS 506 009, India



4 **5** **6**

A series of novel imidazo[1,2-*b*]isoxazoles **3** and their Mannich bases **4**-**6** were synthesized *via* convenient reactions. The reaction of 3-aminoisoxazole **1** with substituted phenacyl bromides **2** in dry ethanol afforded the corresponding 6-methyl-3-arylimidazo[1,2-*b*]isoxazoles **3** in good yields. Compounds **3** on treatment with 37% formaline and secondary amines furnished the corresponding novel Mannich bases *viz*., 6-methyl-3-aryl-2-(morpholine/pyrrolidin-1-yl/piperidin-1-yl)-methyl-imidazo[1,2-*b*]isoxazoles **4**-**6**.

Original article

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E. Rajanarendar*, K. Thirupathaiah, S. Ramakrishna, D. Nagaraju

Department of Chemistry, Kakatiya University, Warangal, TS 506 009, India

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ABSTRACT

A series of novel imidazo[1,2-*b*]isoxazoles **3** and their Mannich bases **4-6** were synthesized *via* convenient reactions. The reaction of 3-aminoisoxazole **1** with substituted phenacyl bromides **2** in dry ethanol afforded the corresponding 6-methyl-3-aryl imidazo[1,2-*b*]isoxazoles **3** in good yields. Compounds **3** on treatment with 37% formaline and secondary amines furnished the corresponding novel Mannich bases *viz.*, 6-methyl-3-aryl-2-(morpholine/pyrrolidin-1-yl/piperidin-1-yl)-methyl-imidazo[1,2-*b*]isoxazoles **4-6**.

1. Introduction

The development of new synthetic methods leading to hybrid structures, which consist of different biologically active moieties in a single molecule has attracted much attention. The heterocyclic pharmacophores are selected on the basis of their known bio profiles, so that the successive hybrid molecules may exhibit synergistic or additive pharmacological activities [1,2]. Imidazoles are quite attractive due to their biological activities [3-5]. Fused imidazoles are described to have antibacterial, current antiviral therapy for chronic hepatitis C, antifungal and perspectives of drug design that targets RNA [6]. Moreover, the structural features of these compounds are found in nature and are incorporated as key structural fragments in many biological and chemical systems [7]. Broad range of therapeutic drugs has also been developed like Zolmidine, Zolpidem, Alpidems and Kifunersine [8]. Temozolomide is used for the treatment of refractory brain tumors [9-11]. Isoxazole derivatives are reported with diverse structural features and versatile biological properties such as antitumor [12], CNS–active [13], analgesic [14], antimicrobial [15], relaxant [16], for the treatment of hypercholsteremia and hyperlipidemia [17], as synthetic muscle intermediates [18], and as chemotherapeutic agents [19]. Based on the bio activities of imidazole and isoxazole ring systems, we proposed to construct a system that combine these bio-labile rings together in a single molecular frame work. The synthesis of imidazo[2,1-*b*]thiazoles are reported earlier and these compounds showed promising biological activity [20,21]. Based on these reports, and as a sequel to our work on the synthesis of fused isoxazoles [22], we herein, wish to report the synthesis of novel imidazo[1,2-*b*]isoxazoles and their Mannich bases as potential biodynamic agents.

2. Experimental

All the melting points were determined on a Cintex melting point apparatus and are uncorrected. Analytical TLC was performed on Merck precoated 60 F_{254} silica gel plates. Visualization was done by exposing to iodine vapour. IR spectra (KBr pellet) were recorded on a PerkinElmer BX series FT-IR spectrometer. ^{1}H NMR spectra were recorded on a Varian Gemini 300 MHz spectrometer. ^{13}C NMR spectra were recorded on a Bruker 75 MHz spectrometer. Chemical shift values are given in δ ppm with tetramethyl silane as an internal standard. Mass spectral measurements were carried out by EI method on a Jeol JMC-300 spectrometer at 70 eV. Elemental analyses were performed on a Carlo Erba 106 and Perkin-Elmer model 240 analyzers.

2.1. General procedure for the synthesis of 6-methyl-3-aryl imidazolo[1,2-b]isoxazoles **3a-d**

A solution of 3-amino-5-methylisoxazole **1** (0.01 mol), and ω-bromoacetophenone **2** (0.01 mol) in dry ethanol (20 mL) was refluxed for 8 h. After completion of the reaction (monitored by TLC), the reaction mixture was poured on to 25 mL of saturated $NaHCO_3$

* Corresponding author.
E-mail address: rajanarendareligeti@gmail.com (E. Rajanarendar)

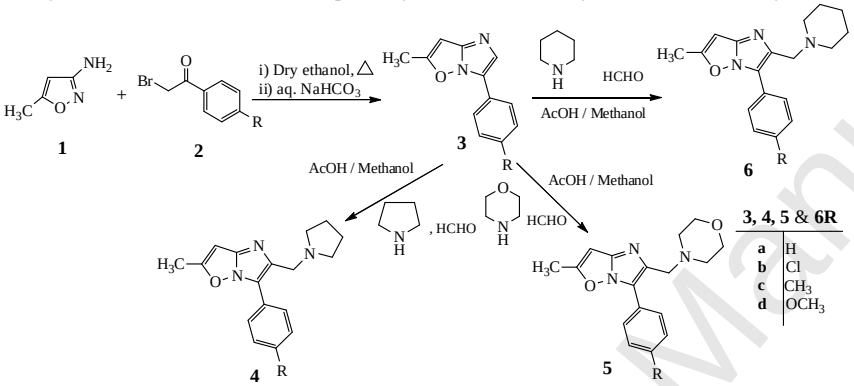
solution with stirring. This mixture was extracted with chloroform (3× 20 mL), and the combined organic layers were distilled under reduced pressure. The resulting solid was purified by recrystallization from ethyl acetate.

2.2. General procedure for the synthesis of 6-methyl-3-aryl-2-(morpholino/pyrrolidin-1-yl/piperidin-1-yl-methylimidazo[1,2,-b] isoxazoles ***4a-d, 5a-d*** *and* ***6a-d***

A solution of 6-methyl-3-aryl imidazo[1,2-*b*]isoxazoles **3** (0.01 mol) in acetic acid (20 mL) was added drop wise to a stirred solution of morpholine (0.01 mol)/pyrrolidine (0.01 mol)/piperidine (0.01 mol), 37% formaline (0.01 mol) and acetic acid (15 mL) in methanol (20 mL). Termination of the reaction was monitored by TLC. The reaction mixture was then poured onto 20 mL of 10% Na_2CO_3 solution with stirring. This mixture was then extracted with chloroform (3×20 mL), and the combined organic layers were distilled under reduced pressure. The resulting solid was purified by recrystallization from ethanol.

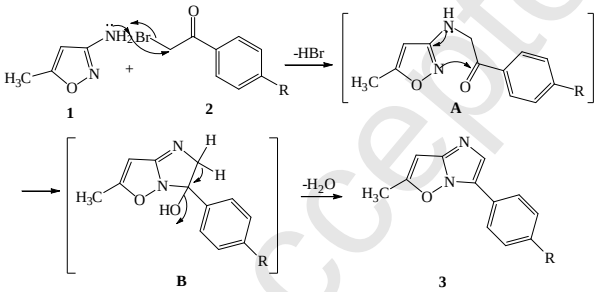
3. Results and discussion

The synthesis of title compounds *viz*., 6-methyl-3-aryl imidazo[1,2-*b*]isoxazoles **3** were achieved by the reaction of 3-amino-5-methylisoxazole **1** with substituted phenacyl bromides **2** in dry ethanol followed by treatment with aqueous $NaHCO_3$.



Scheme 1. Synthesis of 6-methyl-3-aryl imidazolo[1,2-*b*]isoxazoles and their Mannich bases.

Mannich reaction of 6-methyl-3-aryl imidazo[1,2-*b*] isoxazoles **3** with 2°-amines like morpholine / pyrrolidine / piperidine, and formaline resulted in the formation of Mannich bases 6-methyl-3-aryl-2-(morpholino/pyrrolidin-1-yl /piperidin-1-yl)-methylimidazo[1,2,-*b*]isoxazoles **4, 5** and **6** in excellent yields (Scheme 1).



Scheme 2. Plausible mechanism for the formation of 6-methyl-3-aryl imidazo[1,2-*b*]isoxazoles.

The plausible mechanism for the formation of 6-methyl-3-aryl imidazole[1,2-*b*]isoxazoles **3** is depicted in the Scheme 2. The amino group of isoxazole makes a nucleophilic attack on bromine bearing carbon there by displaces HBr to give intermediate **A**. The C=N group of isoxazole activated by NH group attacks carbonyl group and undergoes intramolecular cyclization to give compound **B**, which then undergoes spontaneous dehydration by the action of $NaHCO_3$ to afford the title compounds. The structures of the products **3-6** have been elucidated on the basis of (IR, ^{1}H NMR, and MS) and micro analytical data.

4. Conclusion

The present study offers a facile and convenient method for the synthesis of imidazo[1,2-*b*]isoxazoles and their Mannich bases using inexpensive and commercially available materials. The title compounds may act as drug candidates based on the pharmacological activity of isoxazole and imidazole moieties.

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