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Synthesis and Characterization of Mannich Bases of Imidazo[2,1-b][1,3,4]Thiadiazoles

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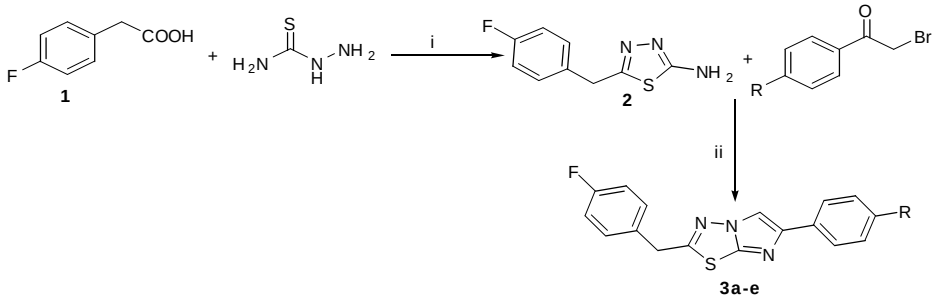
Abstract: Mannich bases of Imidazo[2,1-b][1,3,4]thiadiazles have been reported. These derivatives are prepared by condensing Imidazothiadiazles with secondary cyclic amines viz. pyrrolidine, piperidine and morpholine. Structure of the synthesized compounds have been confirmed by IR, 1H NMR, 13C NMR and Mass spectral studies.
Keywords: Thiadiazole, Imidazothiadiazole, pyrrolidine, piperidine and morpholine

I. INTRODUCTION

Mannich reaction [1]is one of the most fundamental carbon-carbon bond formation reaction that enables synthesis of molecules with diverse functional groups. Variety of molecules, drugs and bioactive molecules have been synthesized using this well established reaction. The widespread literature also supports diversity and application of this reaction[2-5]. Thus mannich reaction and its variants offer diverse range of biological, analytical and industrial applications. Also, heterocyclic compounds have great applicability in pharmaceuticals because they have specific chemical reactivity and provide false synthons in biosynthetic process. In particular, Nitrogen-bridgehead fused heterocycles containing imidazole ring is a quite common structural entity in many pharmacologically active molecules that can exhibit a wide range of diverse activities. One of the most widely studied heterocyclic system is Imidazo[2,1-b][1,3,4]thiadiazole. Imidazothiadiazoles are known to exhibit wide range of biological properties such as antibacterial[6], antifungal[7], antitubercular [8] and anticancer[9-10].
In the light of above facts, it was envisaged to synthesize condensed fluorobenzyl imidazo[2,1-b][1,3,4] thiadiazoles and their Mannich bases.

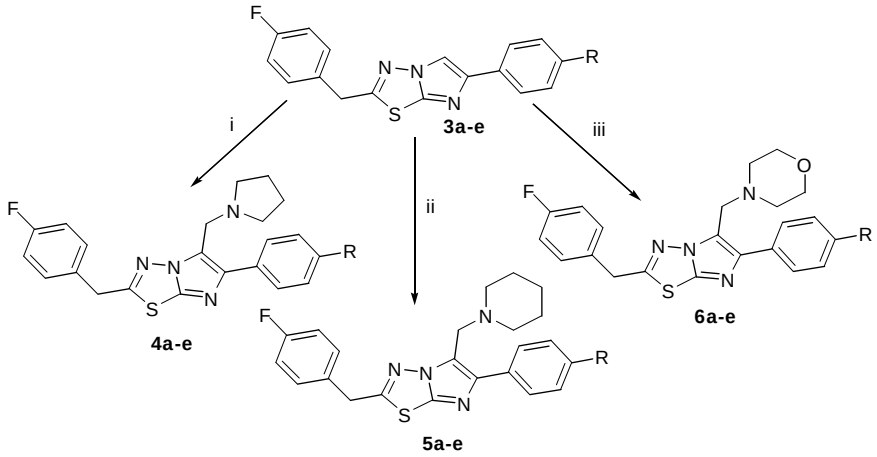
II. PRESENT WORK

The work carried out in the present investigation in synthesizing Mannich bases of imidazothiadiazoles having fluoro substituent is outlined in the following schemes.



a, R = H; b, R = Cl; c, R = NO_2; d, R = Br; e, R = OMe
Reagents and Conditions: i. $POCl_3$, reflux, 45 min, KOH. ii. dry ethanol, 18hr, Na_2CO_3
Scheme I

The required 2-amino-(4-fluorobenzyl)-1,3,4-thiadiazole **2** was prepared by phosphorous oxychloride cyclisation of 4-fluorophenyl acetic acid with thiosemicarbazide. Further imidazo[2,1-b] [1,3,4]thiadiazoles **3a-e** were prepared by the reaction of equimolar quantities of 2-amino-(4-fluorobenzyl)-1,3,4-thiadiazole **2** and appropriately substituted phenacyl bromides in dry alcohol. The respective free bases were obtained by neutralization of the hydrobromide salts with aqueous sodium carbonate solution in good yields (**Scheme I**). By this method the required substituents at 2 & 6 positions have been obtained by starting with suitably substituted synthons.
Imidazo[2,1-b][1,3,4]thiadiazole **3a-e** were then subjected to mannich reaction with three secondary cyclic amines (pyrrolidine, piperidine and morpholine) to yield corresponding Mannich bases **4a-e**, **5a-e** and **6a-e** respectively(**Scheme II**).



a, R = H; b, R = Cl; c, R = NO_2; d, R = Br; e, R = OMe

Reagents and Conditions: i. pyrrolidine, HCHO, AcOH, MeOH, reflux. ii. piperidine, HCHO AcOH, MeOH, reflux. iii. morpholine, HCHO, AcOH, MeOH, reflux.

Scheme II

III. RESULT AND DISCUSSION

During the present investigation required imidazo[2,1-*b*][1,3,4]thiadiazoles were prepared **(Scheme I)** by the reaction of 2-amino(4-fluorobenzyl)-1,3,4-thiadiazole **2** with appropriately substituted α-haloketones (phenacylbromides) in dry ethanol as hydrobromides which on neutralization with aqueous sodium carbonate solution gave corresponding free bases (**3a-e**) in good yields. The absence of ν_{N-H} band in IR spectra of the resulted compounds confirms the formation of product, which exhibits imidazole (C_5-H) proton around δ 7.97 in ^{1}H NMR spectra. The ^{13}C NMR spectrum of compound **3d** is in total agreement with the structure.

Further imidazo[2,1-*b*][1,3,4]thiadiazoles **3a-e** were subjected to Mannich reaction with three different cyclic secondary amines *viz.* pyrrolidine, piperidine and morpholine to afford corresponding Mannich basses (**4a-e**, **5a-e** and **6a-e**). In general the ^{1}H NMR spectra of the products showed the absence of imidazole proton and a singlet is observed between δ 3.8-4.02 depending upon substitution, which is assigned to methylene protons bridged to cyclic amines and the aliphatic protons of the cyclic amine substituent resonated in the expected region along with rest of the protons. Mass spectrum compound of **3b** displayed molecular ion peak at 343.9 which corresponds to molecular weight (343) of the compound.

In ^{1}H NMR spectra of morpholine derivatives (**6a-e**), two triplets (each for 4 protons) were observed at δ 2.58 (C_3, C_5-H; N-CH_2) and δ 3.72 (C_2, C_6-H; O-CH_2). For pyrrolidine derivatives (**4a-e**), two multiplets (in few cases two broad singlets) each for 4 protons were observed at δ 1.7 (C_3, C_4-H *i.e.* -CH_2-CH_2-) and δ 2.6 (C_2, C_5-H; N-CH_2). For piperidine derivatives (**5a-e**), N-CH_2 (C_2, C_6) protons resonated at δ 2.4 as triplet or broad singlet for 4 protons and C_3, C_4 and C_5 protons resonated in the region δ 1.4-1.7 as multiplets for 6 protons.

Formation of Mannich bases was further evidenced by their ^{13}C NMR and mass spectra. In ^{13}C NMR spectra the characteristic methylene carbon (spacer carbon between imidazothiadiazole ring and cyclic amine substitution) resonated around at δ 53.47. Mass spectrum of pyrrolidine derivative **4e** displayed molecular ion peak at 421.2 which corresponds to molecular weight (422) of the compound.

IV. EXPERIMENTAL

Required phenacyl bromides *viz.* *p*-chlorophenacyl bromide (m.p. 95-96°C), *p*-bromophenacyl bromide (m.p.108-109°C), *p*-methoxy phenacyl bromide (m.p. 68-70°C), phenacyl bromide (m.p. 48-49°C), *p*-nitrophenacyl bromide (m.p. 97-98°C) were prepared according to literature methods.

4-Fluorophenyl acetic acid was purchased (Sigma Aldrich) and directly used for the preparation of 2-Amino-5-(4-fluorobenzyl)-1,3,4-thiadiazole.

1) *Preparation of 2-Amino-5-(4-fluorobenzyl)-1,3,4-thiadiazole (2) :* A mixture of 4-Fluoro phenyl acetic acid (15.4g, 0.1mol) and thiosemicarbazide (9.3g, 0.1mol) in phosphorous oxychloride (30ml) was refluxed gently for 45 minutes. The reaction mixture was cooled and quenched (highly exothermic) with cold water (90ml). The resulting solution was refluxed for additional 4 hrs and filtered hot. The filtrate was cooled and basified with aqueous potassium hydroxide solution. The solid that separated was filtered, washed with water, dried and rectystallized from ethanol. Yield 73%, m.p 212-213°C (lit.210°C).

2) Preparation of 2-(4-Fluorobenzyl)-6-arylimidazo[2,1-b][1,3,4]thiadiazoles (3a-e)

a) General Method: A mixture of equimolar quantities of 2-Amino-(4-fluorobenyl)-1,3,4-thiadiazole **2 (**2.69, 0.01mol) and bromoacetyl compound (0.01mol) was refluxed in dry ethanol for 18 hrs. The excess of solvent was distilled off and the solid hydrobromide salt that separated was collected by filtration, suspended in water and neutralized by aqueous sodium carbonate solution to get free base (**3a-e**). It was filtered, washed with water, dried and recrystallized from suitable solvent. The newly synthesized imidazothiadiazoles (**3a-e**) were confirmed by spectral data. These were utilized as the intermediates for the synthesis of corresponding Mannich bases.

3) Preparation of Mannich bases (4a-e, 5a-e & 6a-e)

a) General Method: A mixture of 2-(4-Fluorobenzyl)-6-arylimidazo[2,1-b]- [1,3,4]thiadiazoles **3a-e** (0.005mol), corresponding cyclic amines (pyrrolidine, piperidine, morpholine) (0.71g, 0.01mol), formalin (1mL) and acetic acid (1mL) in methanol (20mL) was refluxed for 10 hrs (monitored by TLC). Reaction mixture was diluted with water and extracted with chloroform (3x30mL). The combined chloroform extract was washed with water (3x30mL) and dried over anhydrous sodium sulfate. The solvent was removed under vacuum and the residue was recrystallized from benzene and hexane mixture.

V. CONCLUSION

In summary, series of pyrrolidine, piperidine, morpholine mannich bases of Imidazo[2,1-b][1,3,4]thiadiazole derivatives were prepared. Structure of all the derivatives were thoroughly confirmed by spectral studies

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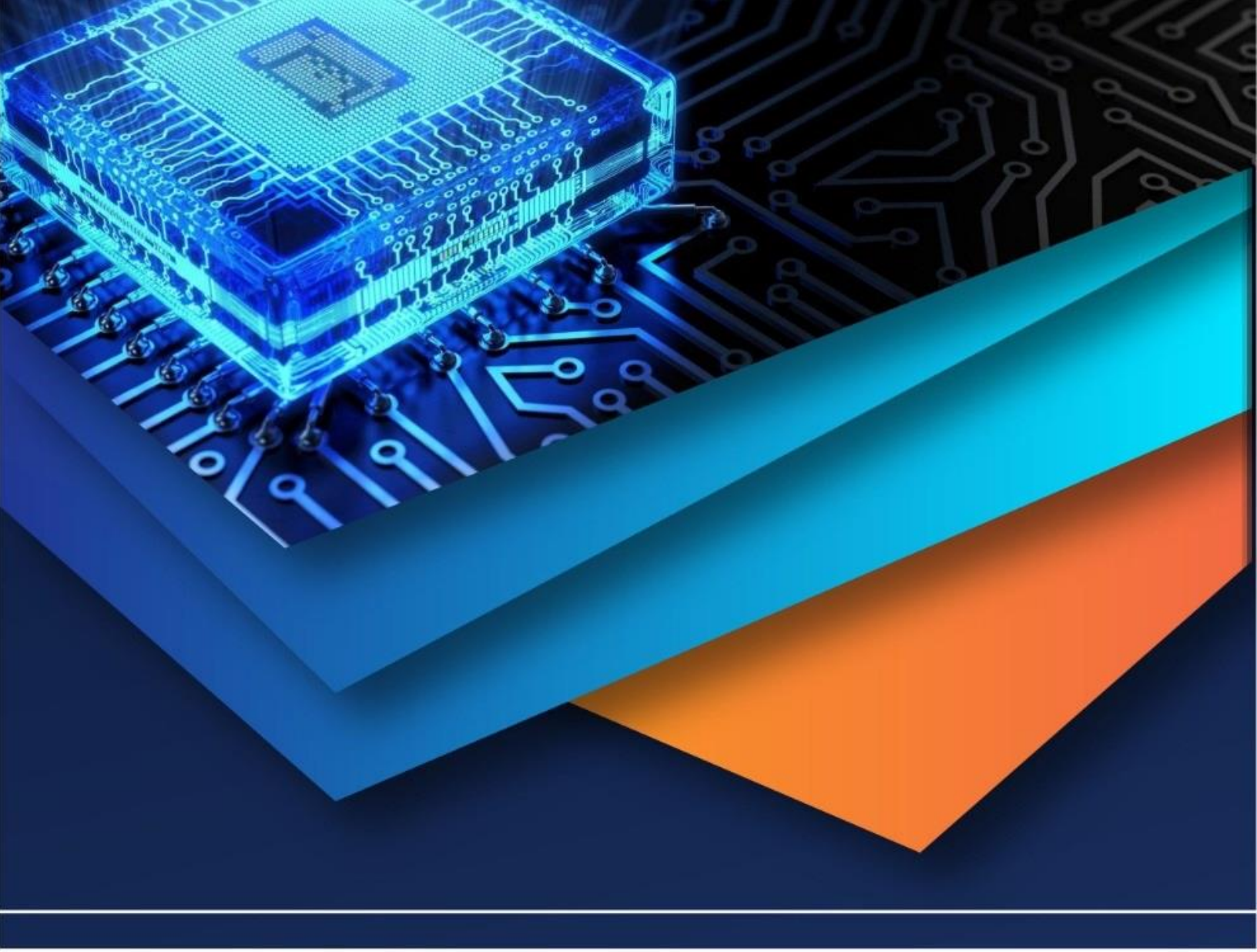

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