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ORIGINAL ARTICLE

Synthesis and crystal structure analysis of 2-(4-fluorobenzyl)-6-phenylimidazo[2,1-*b*]-[1,3,4]thiadiazole and its chlorophenyl derivative

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C–H···F;
π–π Interactions

Abstract Preparations of 2-(4-fluorobenzyl)-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazole (**3a**) and its chlorophenyl derivative (**3b**) are described. Preliminary analysis was done spectroscopically by means of ^{1}H NMR, ^{13}C NMR spectra, mass spectra and elemental analyses. Further the structures were confirmed by X-ray crystal structure analyses. The compound (**3a**) has crystallized in a triclinic P-1 space group with three independent molecules in the asymmetric unit, while the compound (**3b**) belongs to $P2_1/c$ space group with one molecule in the asymmetric unit. The molecule (**3b**) differs from molecule (**3a**) by the presence of chlorine substituent. Additionally, the imidazo-thiadiazole entity is as usual planar. Intramolecular C–H···N hydrogen bonding between the imidazole and the phenyl ring of the molecule can be observed in (**3a**) & (**3b**). The molecules of (**3a**) are linked into two dimensional supramolecular hexagonal hydrogen bonded network sustained by C–H···F interaction, while those of (**3b**) are linked by bifurcated C–H···N interactions. Further, the molecular packing of both the compounds is stabilized by π–π stacking interactions between the benzene and imidazo-thiadiazole ring systems.

1. Introduction

A large number of imidazo[2,1-*b*][1,3,4]thiadiazole derivatives have been reported to possess diverse medicinal properties which can be classified as anthelmintic, antimicrobial, anti-inflammatory, antipyretic, analgesic and they also have other characteristics of therapeutic significance (Khazi et al., 2004; Palagiano et al., 1995). 1,3,4-Thiadiazoles are known for their promising biological and pharmacological activities, possibly due to the presence of pharmacophoric isothioamide (S–C═N–) unit (Banu et al., 2010) in the thiadiazole nucleus.

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Secondly, the thiadiazole ring is bioisosteric with the thiazole moiety of the novel broad spectrum anthelmintic tetramisole (Kumar et al., 2010). Some thiadiazole derivatives are reported to possess anti-cancer properties (Sanff et al., 2004; Rzeski et al., 2007). They appeared to be the most feasible route to fused imidazo[2,1-*b*][1,3,4] thiadiazole rings of interest in potential applications (Amery et al., 1984).

Apart from this, fluorinated compounds in general and fluorinated heterocyclic compounds in particular, are the focus of much interest in modern medicinal chemistry. In other classes of antitumour compounds, e.g. the anthracycline antibiotics (Miller and Stoodley, 2013), the substitution of a hydrogen atom for a fluorine atom in the tetracyclic ring system was found to possess better antitumour properties (Animati et al., 1996).

Moreover the presence of a fluoro substituent in the molecule enhances its biological activity. Accumulation of fluorine (Strunecka et al., 2004) on carbon leads to increased oxidative and thermal stability. Further it leads to increased lipid solubility which enhances the rate of absorption and transport of the drug *in vivo*. These findings prompted the synthesis of the title compounds. A single crystal X-ray diffraction analysis was carried out to establish the crystal structure and to understand the self-aggregation in terms of possible intermolecular interactions.

In the course of our structural studies of the family of imidazo-thiadiazole derivatives, we report here the structures of two such compounds, namely 2-(4-fluorobenzyl)-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazole and its 6-(4-chlorophenyl) derivative. The syntheses of these compounds were followed by measurement of their analytical data and subsequent spectroscopic analyses using ^{1}H NMR, ^{13}C NMR spectra, mass spectra and elemental analyses techniques to confirm the presence of the supposed ring systems, presence of fluoro and chloro substituents as well as the signals for the existence of various protons. A single crystal X-ray diffraction analysis was carried out for the two compounds in order to establish the crystal as well as molecular structures and to understand the self-aggregation in terms of possible intermolecular interactions. The analyses revealed structural features such as the orthogonal orientation of the fluorobenzyl group to the rest of the molecule, presence of various intermolecular interactions involving the hexagonal hydrogen bond network and π–π interactions.

2. Experimental

2.1. Materials

All reagents were obtained from commercial sources. Solvents were dried and purified with known conventional methods.

2.2. Analytical methods

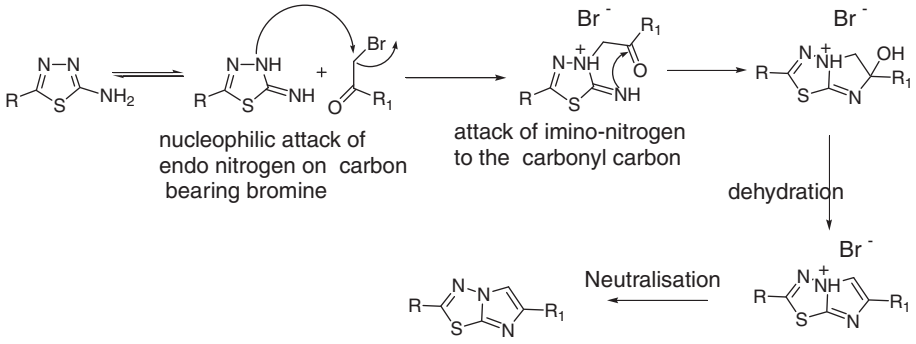
The melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded as KBr discs using a Nicolet FT-IR 410 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian RXZ-300 MHz spectrometer using TMS as internal reference compound. C, H and N were estimated on a Heraus CHN rapid analyzer at Karnatak University, Dharwad, India. The title compounds were prepared following the procedure given below and as shown in Scheme 1.

2.3. Procedure for the preparation of 2-(4-fluorobenzyl)-6-phenylimidazo[2,1-b][1,3,4]thiadiazole (**3a**) and its chlorophenyl derivative (**3b**)

A mixture of 5-(4-fluorobenzyl)-1,3,4-thiadiazol-2-amine (**1**) (Khazi et al., 2004) (2.69 g, 0.01 mol) and phenacyl bromide (**2a**) (0.01 mol) was refluxed in dry ethanol for 12 h. 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 the free base (**3a**). It was filtered, washed with water, dried and recrystallized from ethyl acetate to afford white needles with good yield of 75% (2.98 g).

The same procedure was followed to obtain (**3b**) wherein (**1**) was treated with *p*-chloro phenacyl bromide (**2b**). The crystals of (**3b**) were obtained by recrystallization using ethanol solvent. Yield 70% (3.08 g).

2.3.1. Mechanism



2.3.2. 2-(4-Fluorobenzyl)-6-phenylimidazo[2,1-b][1,3,4]-thiadiazole (**3a**)

Brown crystalline Solid (ethanol + dioxan), yield 75%, m.p. 168–170 °C; IR (KBr) ν cm^{-1}: 3124 (=CH), 2923, 2853 (–CH), 1602, 1507 (C=N); ^{1}H NMR (300 MHz, $CDCl_3$) δ: