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Synthesis, X-ray crystallographic, spectroscopic and computational studies of aminothiazole derivatives

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ABSTRACT

Aminothiazole organic compounds have diverse biological applications. Herein we report the synthesis of two aminothiazole derivatives: 4-(biphenyl-4-yl)thiazol-2-amine (**1**) and 4-(2′,4′-difluorobiphenyl-4-yl)thiazol-2-amine (**2**) *via* Suzuki-Miyaura cross coupling reaction. The chemical structures of **1** and **2** are confirmed using ^{1}HNMR, ^{13}CNMR, FT-IR, UV–Vis and single crystal x-ray studies. The XRD study reveals that the both solid state structures (**1**) and (**2**) are diffused to form poly chain structures due to presence of intra molecular hydrogen bonding (H.B). Furthermore, these compounds were analysed by density functional theory (DFT) at M06-2X/6-311G(d,p), B3LYP/6-31G(d) B3LYP/6-31G(d,p) and B3LYP/6-311G(2d,p) level of theories to obtain optimized geometry, electronic and spectroscopic properties. DFT optimized geometry supports the experimental XRD parameters. Natural bond orbital (NBO) calculation predicted the hyper conjugative interaction and hydrogen bonding in all derivatives. The FT-IR and thermodynamic studies also confirm the presence of hydrogen bonding network in the dimers which agrees well with the XRD results. Moreover, UV–Vis analysis reveals that maximum excitations take place in **1** and **2** due to HOMO → LUMO(98%) and HOMO → LUMO(97%) respectively which show good agreement to experimental data. The first order hyperpolarizability of both molecules is remarkably greater than the value of urea. The global reactivity parameters which are obtained by frontier molecular orbitals disclose that the molecules might be bioactive.

1. Introduction

The thiazole ring consists of both sulphur and nitrogen are available in different and diverse molecules and they have extensive applications in agriculture and medicinal chemistry [1,2]. Thiazole heterocycles containing amine moiety have found applications in material science and these are used as building blocks in organic synthesis [3]. Varieties of biologically active molecules accommodate this interesting scaffold, aminothiazoles [4]. Aminothiazoles are used as important fragments in different drugs related to anti-tuberculosis,5 anti-inflammatory [5,6,7] anti-allergic [8], anti-hypertensive [9], schizophrenia [10], anti-bacterial, HIV infections [5,11] and human lymphatic filarial parasites [12].Aminothiazoles are known ligands of estrogen and adenosine receptors antagonists [13]. Various aminothiazole derivatives are used as fungicides and herbicides and have numerous applications in agricultural field [14].

Alkyllated and arylated aminoacetyl derivatives of 2-amino-4-phenylthiazolyl [15], 2-aminobenzothiazolyl [16], substituted 2-amino-benzothiazolyl [17], 2-phenylamino-4-phenylthiazolyl [18], 2-amino-4-methylthiazolyl [19], as well as 3-aminobenzo[*d*]isothiazole derivatives [20] are found to have a potent local anaesthetic, anti-inflammatory, analgesic, and antipyretic activities [21]. Similarly, sulfonamides of aminothiazolesare used to treat bacterial infections, inflammations, tumours [22] and play a vital role in insulin release [23].

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Although various aminothiazoles derivatives related to the substitution pattern and 4-(biphenyl-4-yl)thiazol-2-amine were synthesized and reported elsewhere [15–21]. However, according to the best of our knowledge, no studies regarding the title aminothiazole derivatives have been reported *via* Suzuki-Miyaura cross-coupling reaction. Herein, we report the synthesis of 4-(biphenyl-4-yl)thiazol-2-amine and 4-(2',4'-difluorobiphenyl-4-yl) thiazol-2-amine employing Suzuki-Miyaura cross-coupling reaction (Scheme 1). The structures of synthesized compounds (**1**) and (**2**) were determined experimentally using ^{1}HNMR, ^{13}C NMR, and single crystal x-ray studies. Moreover, both compounds were studied by density functional theory (DFT) [24,25]. DFT is broadly used to determine the molecular geometry, electronic properties including frontier molecular orbitals (FMOs), natural bond orbital (NBO), non-linear optics (NLO), and molecular electrostatic potential (MEP) and spectroscopic analysis such as FT-IR, FT-Raman, UV–Vis, and non-linear optics of organic molecules [26–29].

The main focus of the current study is to provide a detail structural and spectroscopic insight of the 4-(biphenyl-4-yl)thiazol-2-amine and 4-(2',4'-difluorobiphenyl-4-yl) thiazol-2-amine with the aid of experimental and theoretical techniques.

2. Experimental and calculation section

2.1. Reagents and instruments

All reagents were obtained from Acros Organics and in analytically pure grade. NMR spectra were recorded using a Bruker-Advance spectrometer operating at 400 MHz for ^{1}HNMR and 100 MHz for ^{13}C NMR with tetramethylsilane as the internal standard. Chemical shifts are given in ppm (δ-scale). The experimental FT-IR spectra of both compounds were performed by Perkin Elmer spectrum version 10.4.3. Melting points were measured on a digital melting point apparatus, Stuart, SMP10, U.K. and uncorrected.

2.2. XRD studies

X-ray diffraction data was collected at room temperature by using Bruker Kappa APEX II CCD diffractometer with a graphite monochromator MoKα radiation (λ = 0.71073 Å). This X-ray diffraction data was used to determine structures of compounds (**1**) and (**2**). All crystallographic parameters, structure refinement and conditions for data collections are given in Table 1. Several different programs like *APEX 2* used for data collection, *SAINT* for cell refinement and *SAINT* was used for data reduction. *SHELXS97* program was used to solve structures. *SHELXL97* program was used to refine structures. For molecular graphics *ORTEP-3 for Windows*, *PLATON* and Mercury 3.6 software were used. All the H atoms were positioned geometrically (C–H = 0.93 A) and refined as riding with iso(H) = *x*Ueq(C), where *x* = 1.2 for aryl H atoms. All non-hydrogen atoms were refined anisotropically. The positions of all hydrogen atoms were generated geometrically (C*sp*2-H = 0.93 Å), assigned isotropic thermal parameters, and allowed to ride on their respective parent carbon atoms before the final cycle of full-matrix least-squares refinement including 169 and 175 variable parameters for **1** and **2** respectively. Supplementary crystallographic data are deposited as CIF files at Cambridge Crystallographic Data Centre (CCDC = 1483070 for **1** and 1483071 for **2**).

2.3. Computational procedures

Theoretical studies were executed with Gaussian 09program package [30] employing density functional theory (DFT) [31–35].The initial geometry for the both derivatives (**1**) and (**2**) was retrieved from the single crystal structures. Full optimization of **1** and **2** was carried out by B3LYP/6-31G(d), B3LYP/6-311 + G(2d, p) and M06-2X/311G (d, p) level of theories. All frequencies of the two compounds are found real (positive) ensuring the optimized geometries corresponding to the true minimum in the potential energy surface. NBO, FMOs and MEP analysis of the thiazol derivatives were calculated at M06-2X/6-311G(d,p) level of theory. The FT-IR, FT-Raman, NLO properties and thermodynamic parameters were examined at B3LYP/6-311G(d,p) level of theory. An empirical scaling factor of 0.9627 [36] was used to counterpoise the systematic defects due to basis set deficiency, inconsideration of electron correlation and vibrational anharmonicity. Photophysical properties of these compounds were calculated by time dependent density functional theory (TD-DFT) at B3LYP/6-311G(d,p) level. The input files were organized utilizing Gauss View 5.0. [37] The Avogadro [38], Chemcraft [39] and Gauss View 5.0 programs were used to analyze the output files.

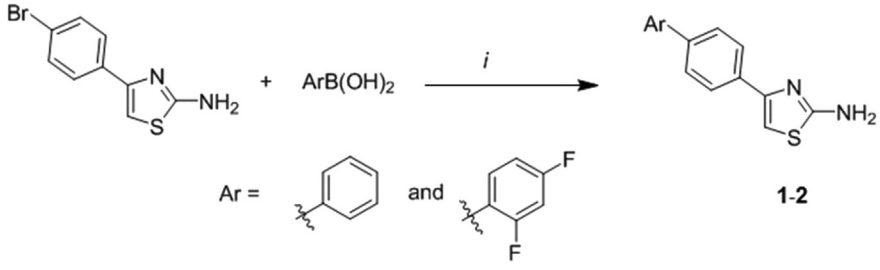
3. Results and discussion

3.1. Synthesis of 4-(biphenyl-4-yl)-1,3-thiazol-2-amine ***(1)***

In a screw capped reaction tube, 4-phenyl-1,3-thiazol-2-amine (100 mg, 0.48 mmol), $Pd(PPh_3)_4$ (8 mg, 1.5 mol%), phenyl boronic acid (136 mg, 0.531 mmol) and K_3PO_4 (153 mg, 0.724 mmol) were added to 3 mL of dioxane solvent. The resulting reaction mixture was flushed with dry nitrogen gas for few minutes. The reaction mixture was heated at 90–100 °C for 8 h. After the completion of the reaction, 20 mL of water was added. After cooling at room temperature, organic and the aqueous layers were separated and the latter was extracted with ethyl acetate three times (3 × 15 mL). The obtained residue was then purified through column chromatography and compound (**1**) was isolated as dark yellow crystalline solid (95 mg, 85%).

3.2. Synthesis of 4-(2,4-difluorobiphenyl-4-yl)-1,3-thiazol-2-amine ***(2)***

In a screw capped reaction tube 4-phenyl-1,3-thiazol-2-amine (100 mg, 0.48 mmol), 4-phenyl-1,3-thiazol-2-amine, $Pd(PPh_3)_4$



Scheme 1. (*i*)$Pd(PPh_3)_4$, dioxane, K_3PO_4, 90–100 °C, H_2O.