



New series of aromatic/ five-membered heteroaromatic butanesulfonyl hydrazones as potent biological agents: Synthesis, physicochemical and electronic properties

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ABSTRACT

The aromatic/five-membered heteroaromatic butanesulfonylhydrazone derivatives; 5-bromosalicylaldehydebutanesulfonylhydrazone(**1**), 2-hydroxy-1-naphthaldehydebutane sulfonylhydrazone(**2**), indole-3-carboxaldehydebutanesulfonylhydrazone (**3**), 2-acetylfuran- carboxyaldehydebutanesulfonylhydrazone(**4**), 2-acetylthiophenecarboxyaldehydebutane- sulfonylhydrazone(**5**) and 2-acetyl-5-chlorothiophene carboxyaldehydebutanesulfonyl hydrazone (**6**) were synthesized by the reaction of butane sulfonic acid hydrazone with aldehydes/ketones and characterized by using elemental analysis, ¹H NMR, ¹³C NMR and FT-IR technique. Their geometric parameters and electronic properties consist of global reactivity descriptors were also determined by theoretical methods. The electrochemical behavior of the butanesulfonylhydrazones were investigated by using cyclic voltammetry (CV), controlled potential electrolysis and chronoamperometry (CA) techniques. The number of electrons transferred (n), diffusion coefficient (D) and standard heterogeneous rate constants (k_s) were determined by electrochemical methods.

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1. Introduction

Hydrazone compounds have interesting biological properties, such as antibacterial [1], antidepressant [2], antiinflammatory, analgesic [3,4] and antipyretic [5]. Hydrazones are important compounds for drug design, as possible ligands for metal complexes, organocatalysis and also for the syntheses of heteroaromatic compounds. It is discovered that sulfones containing heteroaromatic moieties exhibit interesting antibacterial and antifungal bioactivities. Due to this, synthesis of sulfones has attracted considerable attention in pesticides and medicinal formulations [6]. Sulfonylhydrazones derived from sulfonamides have pharmacological properties such as antibacterial, anticancer, antiviral, antinociceptive activity and enzyme inhibition especially to carbonic anhydrase species [7–10]. Many of the physiologically active hydrazones have applications in the treatment of illness like tuberculosis, leprosy and mental damage. For these reasons, the

electrochemical behaviour of the hydrazones may be very helpful for their efficient uses. The enlightening of the electroreduction mechanism can serve as models for the biological pathway of the hydrazones, because their activities depend on reductive processes in the body [11]. The chemical and biological activities of the hydrazones vary in different media. Accordingly, the knowledge of the electrochemical reduction (EC) of these compounds is useful to understand their mechanism in chemical and biological processes. Due to the widespread usage of the hydrazones in the drug industry, the redox properties of these compounds are thought to be useful to understand the metabolic fate of the drug containing hydrazones and the pharmacological activities [12,13]. Electrochemical reduction mechanism of these sulfonylhydrazones have also proposed that hydrazones have electrochemical reduction mechanism corresponding to semireversible two electron transfer steps and that a radical anion formed in the first step followed rapid proton abstraction and a second electron transfer. Electrochemical reduction mechanism contributes to understand the biochemical behavior of the hydrazones [14,15].

In this paper, six aromatic/five-membered heteroaromatic

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butanesulfonylhydrazone derivatives; 5-bromosalicylaldehydebutanesulfonylhydrazone (**1**), 2-hydroxy-1-naphthaldehydebutanesulfonylhydrazone (**2**), indole-3-carboxaldehydebutanesulfonylhydrazone (**3**), 2-acetylfurancarboxaldehydebutanesulfonylhydrazone (**4**), 2-acetylthiophene carboxaldehydebutanesulfonylhydrazone (**5**) and 2-acetyl-5-chlorothiophenecarboxaldehydebutanesulfonylhydrazone (**6**) have been synthesized by the reaction of butane sulfonic acid hydrazide (bsh: C₄H₉SO₂NHNH₂) with aromatic aldehydes and ketones. Their structure were characterized by using elemental analysis, ¹H–¹³C NMR and FT-IR spectrum [16–20]. Theoretical calculations invoking geometry optimization, geometrical and electronic parameters were done using DFT/B3LYP/6-311G(d,p) method in Gaussian 09 software program [21]. The electrochemical behaviors of aromatic/five-membered heteroaromatic butanesulfonylhydrazones were evaluated by cyclic voltammetry (CV), controlled potential electrolysis and chronoamperometry (CA) techniques.

2. Experimental section

2.1. Physical measurements

Elemental analysis was performed according to standard microanalytical procedures. ¹H–¹³C NMR spectra of dimethylsulfoxide-d₆ (DMSO-d₆) solutions of the compounds were registered on Agilent VNMRS 500 MHz spectrometer using tetramethylsilane as internal standard. D₂O-exchange was applied to confirm the assignment of the NH- and OH-signals (compounds **1**, **2**). The infrared spectra of the compounds were taken in a Perkin Elmer Spectrum-One FT-IR instrument with ATR accessory. Melting points of butanesulfonylhydrazone derivatives were determined with a Buchi B540 melting point apparatus. All the solvents used were HPLC grade solvents distilled prior to use in a Innovative Solvent Purification System with special molecular sieves and catalysts (activated alumina) which eliminates traces of water. Butanesulfonylchloride, hydrazine hydrate, 5-bromosalicylaldehyde, 2-hydroxynaphthaldehyde, indol-2-carboxaldehyde, 2-acetylfuran carboxaldehyde, 2-acetylthiophenecarboxaldehyde, 2-acetyl-5-chlorothiophenecarboxaldehyde were commercial products (purum).

2.2. General procedure for the synthesis

The nucleophilic substitution reaction of the hydrazine hydrate with butane sulfonyl chloride was carried out butane sulfonic acid hydrazide (bsh) as procedure [7,16]. Compounds (**1–6**) were synthesized according to the following general procedure: The solution of (0.02 mol) butane sulfonic acid hydrazide in 5 ml of ethanol was mixed with hot solution of 0.03 mol of the corresponding carbonyl compounds (5-bromosalicylaldehyde, 2-hydroxynaphthaldehyde, indol-2-carboxaldehyde, 2-acetylfurancarboxaldehyde, 2-acetylthiophenecarboxaldehyde, 2-acetyl-5-chlorothiophenecarboxaldehyde, respectively) in 10 mL of ethanol and stirred for

20 min. Ethanol was removed in vacuum and the residue was washed three times with n-hexane and yield was dried in vacuum over P₂O₅.

2.3. Computational section

Computational studies were performed by density functional theory (DFT) using Becke's three-parameter hybrid functional combined with the Lee–Yang–Parr correlation functional (B3LYP) and 6-311G(d,p) basis sets with Gaussian 09 software [22,23]. The geometry optimizations were performed for the ground states of butanesulfonylhydrazones and these ground states were assumed to be a singlet state [24]. Geometrical parameters such as bond length, bond angles, dihedral angles and global reactivity descriptors such as electronegativity, chemical potential, global hardness, global softness and electrophilicity index were calculated using this quantum set with Gaussian 09 program package [25]. Global reactivity descriptors consisting of electronegativity (χ) = $-1/2(\epsilon_{\text{LUMO}} + \epsilon_{\text{HOMO}})$, chemical potential (μ) = $1/2(\epsilon_{\text{LUMO}} + \epsilon_{\text{HOMO}})$, global hardness (η) = $1/2(\epsilon_{\text{LUMO}} - \epsilon_{\text{HOMO}})$, global softness (S) = $1/2\eta$ and electrophilicity index (ω) = $\mu^2/2\eta$ are highly successful in predicting global reactivity trends. The frontier molecular orbital energy levels and derived parameters were related not only to the spectral properties, but also to the reactivity properties [26].

2.4. Electrochemical studies

Voltametric measurements were carried out with IVIUM Stat Electrochemical Analyzer. Glassy carbon electrode (BAS MF-2012) and 11 μm -ultramicro carbon electrode (BAS MF-2007) were used as working electrode. The electrodes were polished with 1 μm , 0.3 μm and 0.05 μm alumina slurries made from dry Buehler alumina and ultra pure water (16 M Ωcm) on polishing microcloth before each use. A platinum wire was used as the auxiliary electrode (BAS MW-1032). The reference electrode was a silver wire in contact with 0.01 M AgNO₃ in dimethylsulfoxide (BAS MF-2052). All solutions were deaerated for 15 min with pure nitrogen. All the measurements were taken at room temperature, 20 \pm 1 $^\circ\text{C}$. In all voltammetric measurements, the background currents were automatically subtracted from originally obtained currents. The number of electrons transferred and diffusion coefficients were determined by ultramicro electrode CV technique of Baranski [27] and the heterogeneous rate constants were calculated according to Klingler-Kochi method [28]. The data obtained from bulk electrolysis were also used to calculate the number of electrons transferred.

3. Results and discussion

Analytical data and some physical properties of the aromatic/five-membered heteroaromatic butane sulfonylhydrazone are summarized in Table 1. The general synthetic route used to prepare

Table 1
Analytical and physical data of aromatic/five-membered heteroaromatic butanesulfonylhydrazones

Compound	Empirical Formula (Formula weight)	Colour	m.p. ($^\circ\text{C}$)	Yield (%)	Found (calculated)			
					%C	%H	%N	%S
1	C ₁₁ H ₁₅ BrN ₂ O ₃ S 335 g/mol	Pale yellow	117–119	90	38,95 (39,41)	4,01 (4,51)	8,06 (8,36)	9,12 (9,57)
2	C ₁₅ H ₁₈ N ₂ O ₃ S 306 g/mol	Yellow	133–135	88	57,95 (58,80)	5,56 (5,92)	8,98 (9,14)	10,40 (10,47)
3	C ₁₃ H ₁₇ N ₃ O ₃ S 279 g/mol	White	167–169	84	54,98 (55,89)	5,96 (6,13)	14,95 (15,04)	11,04 (11,48)
4	C ₁₀ H ₁₆ N ₂ O ₃ S 244 g/mol	White	102–105	75	48,89 (49,16)	6,38 (6,60)	11,39 (11,47)	12,98 (13,12)
5	C ₁₀ H ₁₆ N ₂ O ₃ S ₂ 260 g/mol	White	129–131	82	45,89 (46,13)	5,87 (6,19)	10,05 (10,76)	24,05 (24,63)
6	C ₁₀ H ₁₅ ClN ₂ O ₃ S ₂ 294 g/mol	White	145–147	72	40,56 (40,74)	5,01 (5,13)	9,08 (9,50)	21,35 (21,75)

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